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Anterior Cingulate Implant for Alcohol Dependence: Case Report

Dirk De Ridder, MD, PhD*
Patrick Manning, MD, PhD‡
Paul Glue, MD, PhD§
Gavin Cape, MD, PhD§
Berthold Langguth, MD, PhD¶
Sven Vanneste, PhD‖

*Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; ‡Section of Endocrinology, Department of Internal Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; §Department of Psychological Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; ¶Department of Psychiatry and Psychotherapy, University Regensburg, Regensburg, Germany; ‖School of Behavioral and Brain Sciences, The University of Texas, Dallas, Texas

Correspondence:
Sven Vanneste, PhD,
Brai²n,
Department of Surgical Sciences,
Section of Neurosurgery,
Dunedin School of Medicine,
University of Otago,
Dunedin, New Zealand.
E-mail: sven.vanneste@utdallas.edu

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BACKGROUND AND IMPORTANCE: Alcohol dependence is related to dysfunctional brain processes, in which a genetic background and environmental factors shape brain mechanisms involved with alcohol consumption. Craving, a major component determining relapses in alcohol abuse, has been linked to abnormal brain activity.

CLINICAL PRESENTATION: We report the results of a treatment-intractable, alcohol-addicted patient with associated agoraphobia and anxiety. Functional imaging studies consisting of functional magnetic resonance imaging and resting-state electroencephalogram were performed as a means to localize craving-related brain activation and for identification of a target for repetitive transcranial magnetic stimulation and implant insertion. Repetitive transcranial magnetic stimulation of the dorsal anterior cingulate cortex with a double-cone coil transiently suppressed his very severe alcohol craving for up to 6 weeks. For ongoing stimulation, 2 "back-to-back" paddle electrodes were implanted with functional magnetic resonance imaging neuronavigation guidance for bilateral dorsal anterior cingulate cortex stimulation. Using a recently developed novel stimulation design, burst stimulation, a quick improvement was obtained on craving, agoraphobia, and associated anxiety without the expected withdrawal symptoms. The patient has remained free of alcohol intake and relieved of agoraphobia and anxiety for over 18 months, associated with normalization of his alpha and beta activity on electroencephalogram in the stimulated area. He perceives a mental freedom by not being constantly focused on alcohol.

CONCLUSION: This case report proposes a new pathophysiology-based target for the surgical treatment of alcohol dependence and suggests that larger studies are warranted to explore this potentially promising avenue for the treatment of intractable alcohol dependence with or without anxiety and agoraphobia.

KEY WORDS: Agoraphobia, Alcohol craving, Brain stimulation, Burst, Functional magnetic resonance imaging, Standardized low-resolution brain electromagnetic tomography, Substance abuse

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Alcohol intake is prevalent in the Western world. Almost every adult (92%) has used alcohol in his or her life.[1] Whereas most people can control their alcohol intake, 8.5% of US citizens demonstrate problem alcohol consumption, with 3.8% demonstrating alcohol dependence[2]; ie, they will manifest a constellation of symptoms and signs such as compulsive behavior, dyscontrol, salience, preoccupation, and a biological adaptation to alcohol. Alcohol dependence thereby qualifies as a psychiatric disease, as described in the *Diagnostic and Statistical Manual of Mental Disorders*. Thus, in alcohol dependence there is a persistent use of alcohol despite problems related to the use of the substance. Alcohol abuse, on the other hand, with a prevalence of 4.7%,[2] is a condition that is characterized by failure to fulfill major role

ABBREVIATIONS: ACC, anterior cingulate cortex; **BOLD,** blood oxygen level dependent; **dACC,** dorsal anterior cingulate cortex; **DBS,** deep brain stimulation; **EEG,** electroencephalogram; **fMRI,** functional magnetic resonance imaging; **rTMS,** repetitive transcranial magnetic stimulation; **SMA,** supplementary motor area; **TMS,** transcranial magnetic stimulation

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obligations at work, school, or home, interpersonal social and legal problems, and/or drinking in hazardous situations (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*).

It has been proposed that people will drink alcohol for at least 2 reasons: to feel better (reward drinking), or not to feel bad (relief drinking).[3-5] It is therefore not surprising that alcohol dependence is associated with one or more simultaneously present comorbidities, especially mood disorders (27.6%), anxiety disorders (23.5%), and personality disorders (39.5%).[6,7]

One of the major problems with alcohol dependence is relapse. It is estimated that 85% of patients with alcohol dependence relapse.[8] The 3 main reasons for relapse are alcohol craving,[9-11] alcohol cues, and stress.[12] Therefore, by suppressing craving, relapses should be preventable.

Transcranial magnetic stimulation (TMS) is a noninvasive technique used to modulate activity and connectivity in the brain.[13] Repetitive TMS (rTMS) has been shown to suppress alcohol craving transiently.[14] These studies were performed by using a figure-of-eight coil targeting dorsolateral prefrontal cortex.[15] rTMS of the dorsolateral prefrontal cortex is known to increase the release of dopamine in the nucleus accumbens[16] and caudate nucleus[17] and to modulate dopamine release in the subgenual anterior cingulate cortex (ACC) and the orbitofrontal cortex.[18] However, a recent study using positron emission tomography revealed that frontal TMS using a double-cone coil can modulate both dorsal anterior cingulate cortex (dACC) and subgenual ACC, as well as a number of more distal cortical areas.[19] Thus, this coil can be used in an attempt to suppress alcohol craving transiently as well, by potentially targeting the dACC more directly.[20]

In view of the genetic vulnerability related to alcohol dependence (dopamine receptor D2) and craving (dopamine receptor D3), it is to be expected that rTMS will only result in a temporary improvement of craving-related activity. The dopaminergic reward deficiency will resume after the effect of the rTMS wears off. This effect could potentially be remediated by a more permanent modulation of the dACC via the implantation of an electrode.

Here, we report the immediate and long-term abolishment of alcohol craving in a treatment-intractable, alcohol-addicted person, who has comorbid agoraphobia and anxiety, by an implant onto the dACC/supplementary motor area (SMA). The patient has been selected for this procedure by a dramatic but transient beneficial response to noninvasive double-cone coil frontal rTMS, targeting cue-evoked blood oxygen level-dependent (BOLD) activation on functional magnetic resonance imaging (fMRI) and resting-state electroencephalogram (EEG).

CLINICAL PRESENTATION

Case Report

A 38-year-old man presented at the former BRAI^{2}N clinic (Brain Research Center for Innovative & Interdisciplinary Neuromodulation) at the University Hospital in Antwerp, Belgium, with a history of intractable alcohol dependence associated with anxiety and agoraphobia. Before he became alcohol-dependent, the patient consumed large amounts of amphetamines and had gambling problems. Alcohol-related problems started when he was 17 years old to curb panic attacks related to, but not limited to, agoraphobia. He could only leave his house after drinking sufficient amounts of alcohol to reduce his anxiety. His main focus of attention became alcohol, making sure it was accessible in case he might require it, but simultaneously hiding his alcohol use from others.

In an attempt to control his drinking problem, he had episodes of restricted drinking, in which he consumed no more than 4 beers with the highest alcohol content (10°, 500 mL can) he could find per day. When he lost control over his alcohol intake he sought help from Alcoholics Anonymous and visited a psychologist and, later, a psychiatrist specialized in addiction. He tried mindfulness and meditation and resorted to disulfiram (Antabuse) implants, which were renewed 10 times. Although the Antabuse implants helped initially, when they were removed from the market he relapsed again, worse than before. He had episodes of binge drinking until he lost consciousness and woke up at night only to restart drinking. Because outpatient treatment failed, he subsequently had several psychiatric inpatient admissions for rehabilitation. Although these were temporarily effective, he eventually relapsed on each occasion soon after discharge. Fearing that his alcohol dependence might prove fatal, he sought a last resort and applied for a treatment with neuromodulation, attracted by media attention following the publication of a case report on rTMS for alcohol addiction.[20] When he presented to the BRAI^{2}N outpatient clinic, his craving intensity score was 9.5 of 10 on a numeric rating scale (0 = no craving, 10 = maximally imaginable craving).

Functional Magnetic Resonance Imaging

fMRI on a 3T MRI scanner (ACHIEVA, Philips Medical Systems, Best, the Netherlands) was performed during a blocked paradigm involving alcohol-specific cues as well as nonalcoholic drinks, and was designed to map cortical areas involved in alcohol craving, as based on a previous study.[21] At each session, 4 sets of images (gradient echo-echo planar imaging; 120 dynamic scans, repetition time = 3000 ms; echo time = 33 ms; voxel size = 2.9 × 2.9 × 4.0 mm; field of view = 230 × 230 mm) were collected during 24 alternating epochs. Each epoch consisted of 5 randomized picture cues lasting 3 seconds, which could be classified into 4 conditions: an alcohol condition (images of alcohol beverages), a beverage condition (images of nonalcoholic beverages), a control condition (scrambled images of alcoholic and nonalcoholic beverages so that it cannot be discerned anymore whether the presented drink is alcoholic in nature or not), and a rest condition (a fixation cross). The patient was instructed to focus on the visually presented stimuli throughout the entire experiment.

Data were analyzed with SPM99 software (Welcome Institute of Neurology, London, England). Preprocessing of the data

included motion correction, image realignment, rigid body normalization, and spatial smoothing. Functional activation was modeled in a standard general linear model, in which a reference boxcar function was convolved with a standard hemodynamic response function to represent the expected signal time course associated with the functional activation. Statistical testing consisted of voxel-by-voxel cross-correlation with the reference function. The threshold for significant functional activation was set at $P < .001$ uncorrected.

EEG Data Collection

EEG recordings were obtained with the participant sitting upright on a small but comfortable chair. The actual recording lasted approximately 5 minutes. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) in the standard 10-20 international system placement referenced to linked ears, and impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 1024 Hz, band passed 0.15-200 Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2 to 44 Hz, and subsequently transposed into Eureka! Software,[22] plotted and carefully inspected for manual artifact rejection. All episodic artifacts were removed from the stream of the EEG. Average Fourier cross-spectral matrices were computed for bands delta (2-3.5 Hz), theta (4-7.5 Hz), alpha1 (8-10 Hz), alpha2 (10-12Hz), beta1 (13-18 Hz), beta2 (18.5-21 Hz), beta3 (21.5-30 Hz), and gamma (30.5-45 Hz).

Data were collected for the patient before the patient was implanted as well as 18 months after treatment, during stimulation on and off.

Normative Database

Exclusion criteria were known psychiatric or neurological illness, psychiatric history of drug/alcohol abuse in a participant or any relative, current psychotropic/central nervous system active medications, history of head injury (with loss of consciousness) or seizures, headache, and physical disability. About 3 to 5 minutes of EEG was continuously recorded while the participant sat with the eyes closed on a comfortable chair. EEG data were acquired at the 19 standard leads prescribed by the 10-20 international system (FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6, O1, O2) using both earlobes as reference and enabling a 60-Hz notch filter to suppress power line contamination. The resistance of all electrodes was kept below 5 kΩ. We removed all biological, instrumental, environmental, and stimulation artifacts, paying particular attention to biological artifacts generated by the eyes, the heart, and the muscles of the neck, face, and jaw via independent component analysis followed by visual inspection on a high-resolution screen. Epochs containing visible artifacts were marked and ignored for ensuing analysis. The control group consisted of 15 males of the same age.

sLORETA Imaging

Standardized low-resolution brain electromagnetic tomography (sLORETA)[23] was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the 7 frequency bands. sLORETA computes electric neuronal activity as current density (A/m^2) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size: $5 \times 5 \times 5$ mm) and is restricted to cortical gray matter and hippocampi, as defined by the digitized Montreal Neurological Institute probability atlas. To reduce confounds that have no regional specificity, such as total power intersubject variability, a global normalization of the sLORETA images was performed before statistical analyses. A comparison was made between the patient stimulation on vs off.

Region of Interest Analysis

The log-transformed electric current density was averaged across all voxels belonging to the region of interest Brodmann Area 24 separately across all frequency bands for the normative database, during baseline (before implantation), and 18 months after treatment during stimulation and when the stimulation was turned off.

For additional information on the methods, please see **Methods**, **Supplemental Digital Content**, http://links.lww.com/NEU/A854.

The patient was investigated by functional imaging looking at both his resting state and cue-evoked activity, using techniques previously described.[20] In short, his resting-state EEG was compared with a group of healthy controls, age- and sex-matched, using the same EEG system and same recording methods under similar circumstances. The fMRI BOLD signal was generated by subtracting the BOLD activity from seeing alcoholic beverages from nonalcoholic beverages (see **Methods**, **Supplemental Digital Content**, http://links.lww.com/NEU/A854). The target for neuromodulation was thus identified by high-resolution cue-evoked fMRI and confirmed by low-resolution resting-state LORETA EEG (Figure 1).

First, noninvasive neuromodulation was performed, using double cone coil transcranial magnetic stimulation[20] as a prognostic test to verify whether an implant could be beneficial, according to a protocol already used for tinnitus and neuropathic pain at the auditory cortex (for tinnitus),[24-28] somatosensory cortex (for neuropathic pain),[24,29,30] and dorsolateral prefrontal cortex (for tinnitus).[31] The double-cone coil is capable of reaching the dACC, as demonstrated by positron emission tomography scan and source-analyzed EEG.

rTMS was performed, targeting the BOLD area and resting-state beta activity, consisting of 600 pulses at 1 Hz tonic stimulation at 50% machine output. His motor threshold was 64%. After 2 weeks of rTMS with the double-cone coil he improved dramatically to an numeric rating scale craving score of 2 of 10, but after 6 weeks the beneficial effect wore off as

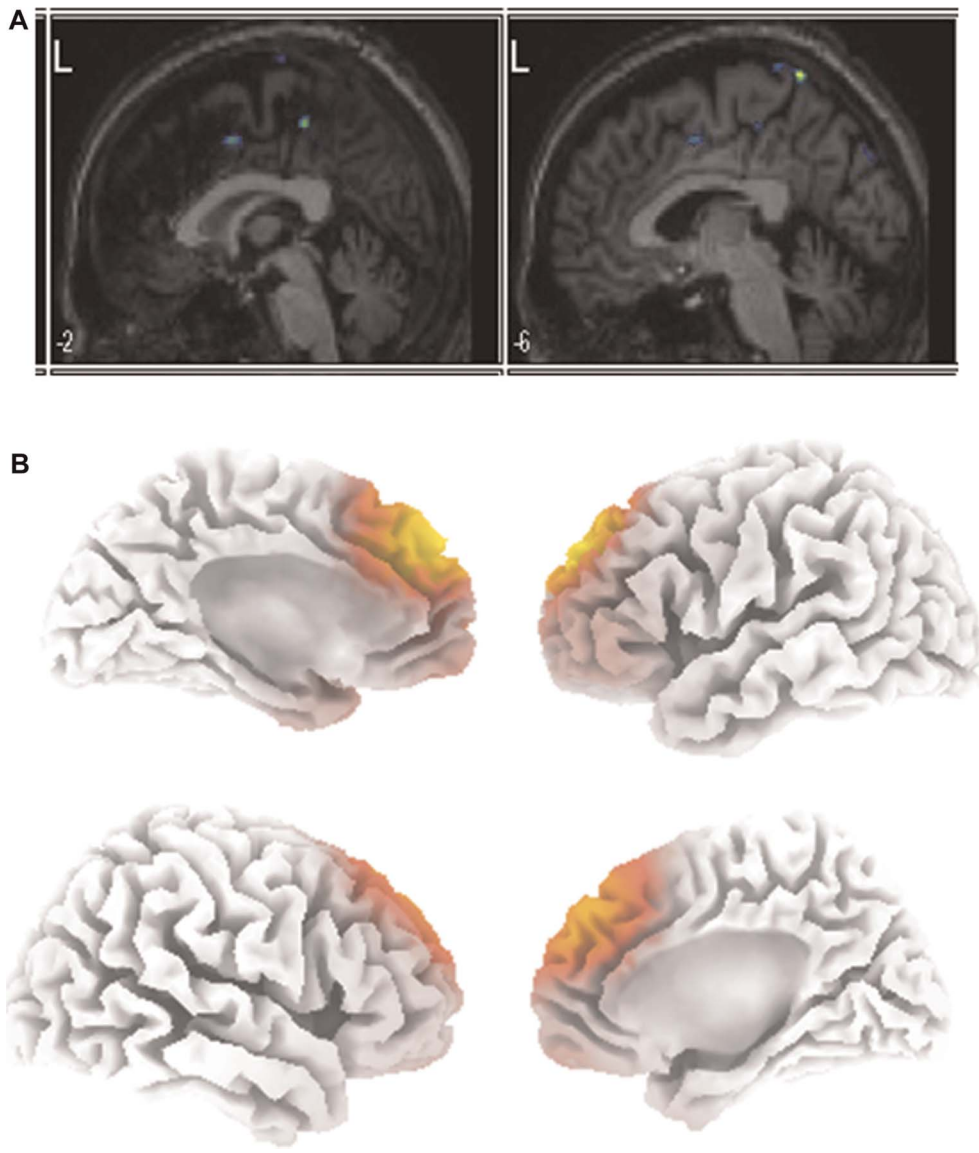

FIGURE 1. **A**, *sagittal fMRI demonstrating BOLD activation in the left dACC/SMA (anterior BOLD spot) and left precuneus (posterior BOLD spot). The BOLD signal is elicited by presenting alcoholic beverages vs nonalcoholic beverages at baseline (1 month before surgery).* **B**, *source-localized (sLORETA) resting-state EEG of alcohol-dependent patient in comparison with healthy subjects (age and sex matched) for the beta frequency (12-30 Hz) indicate an increased spontaneous activity at the anterior cingulate cortex/SMA (left upper and right lower image) extending to frontopolar cortex (Brodmann area 10) (left lower and right upper image) in the alcohol-dependent patient at baseline (1 month before surgery). BOLD, blood oxygen level dependent; dACC, dorsal anterior cingulate cortex; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; sLORETA, standardized low-resolution brain electromagnetic tomography; SMA, supplementary motor area. Color version available online only.*

previously described[20] (Figure 2). We proposed performing a placebo-controlled session so both the patient and the treatment team would be certain the beneficial effect was not placebo-related before continuing with an implant, a proposal the patient refused. He wanted to undergo an experimental treatment with the implant of 2 Lamitrode 44 paddle electrodes targeting the same area of BOLD activation elicited by alcohol cue-evoked craving in the fMRI scan (Figure 3) without a placebo trial, because he felt the effect was so strong it could not be a placebo.

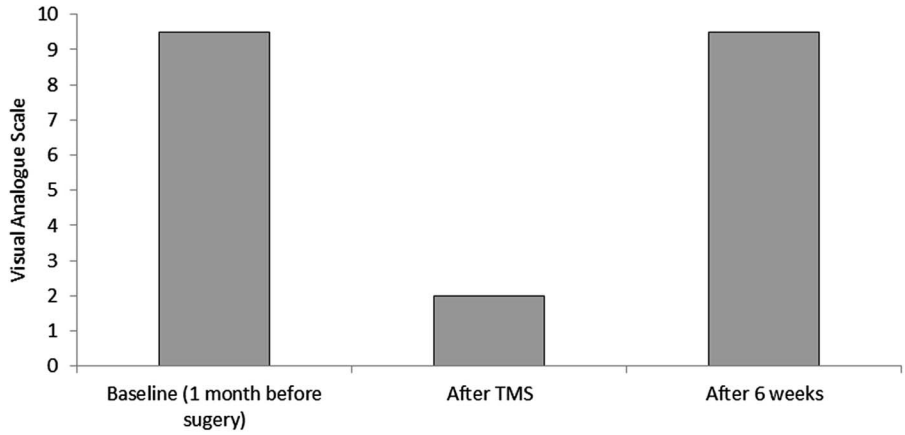

FIGURE 2. *Craving scores on a visual analogue scale for the different time points for the TMS treatment demonstrate only a short-lasting effect of the TMS treatment. TMS, transcranial magnetic stimulation.*

Surgery

After obtaining ethical approval from the ethical committee at the University Hospital in Antwerp, Belgium, and informed consent from the patient, an open neurosurgical approach was performed consisting of a small right-sided frontal craniotomy for a transfalcine approach inserting 2 electrodes for bilateral dACC stimulation.

After induction of anesthesia, intubation, and ventilation, the patient was fixed in the Mayfield head rest in a supine position, his neck slighted flexed with zero degrees rotation. After registration of the preoperatively administered skin fiducials for neuronavigation with the Stealth frameless stereotactic system, the patient's head was disinfected and draped in a sterile fashion. A laterolateral frontal incision was made within the hairline crossing the midline, followed by a 4 cm × 4 cm right frontal craniotomy, crossing the superior sagittal sinus. Subsequently, the dura was incised in U-shaped fashion and the dura reflected across the midline. This was followed by a neuronavigated approach between the right frontal lobe and the falx (Figure 2). Once the target was localized, the falx was incised and 2 Lamitrode 44 (St. Jude Medical, Neurodivision, Plano, Texas) electrodes were positioned resting on the corpus callosum, lateral of the pericallosal arteries, and sutured back-to-back and inserted with the fMRI BOLD activity as the target (Figure 1). The electrodes were inserted as such that the fMRI BOLD spot was located at the middle of the electrodes (pole 2-3-5), to potentially compensate for navigational or intraoperative spatial inaccuracy. The electrodes were sutured to the falx with 2 anchor points, one at the anterior side of the paddle lead and one posteriorly, with Prolene 4.0, preventing postoperative migration both anteroposteriorly and superoinferiorly, to prevent eroding into the corpus callosum. Subsequently, the operative site was thoroughly rinsed, the dura closed in a primary fashion, and the bone repositioned and fixed with a craniofix system. The electrodes were tunneled subcutaneously in a posterior direction to the parietal area, where they were connected to an extension lead, which was further tunneled to the anterior side of the thorax. Here, it connected to a second extension lead and was subcutaneously tunneled to the right abdominal area, where the electrodes are inserted in an EON (St Jude Medical, Neurodivision, Plano, Texas), which is buried in a subcutaneous pocket. The skin on the skull, thorax, and abdomen was closed, and the patient relieved from the headrest and woken up from anesthesia.

On the second postoperative day, once craving set in, the electrodes were activated with a custom-made programmer in 3-Hz burst mode, consisting of 5 spikes at 500-Hz spike mode, with a 1000-microsecond pulse width and an amplitude of 1.5 mA.[32,33] The electrode pole configuration was $+-+-+-+-$ to generate a large stimulation field. The amplitude was titrated to craving reduction. With 1.5 mA he had an immediate but incomplete improvement of his symptoms without any signs of the expected withdrawal symptoms. Because he perceived no side effects, this was not used to adjust stimulation patterns. He was discharged on the fifth postoperative day with a craving score of 4 of 10. At follow-up in the outpatient clinic after 1 month, 3 months, 6 months, and 1 year, he reported that his craving score had reduced to 1 of 10 and that his anxiety had resolved, as had his agoraphobia. He also reported "mental freedom," which he described as a weight having been lifted from his shoulders. He could now go shopping by himself, even in large shops full of people, and his urge and desire for alcohol had completely disappeared. He could now walk through the alcohol section of a department store without filling up his shopping cart, which was impossible before his surgery. Because he was no longer preoccupied by alcohol, he spent a lot more time with his daughter and wife. Subjectively, he experienced no side effects from the stimulation.

One year after the surgery, he also quit smoking, and remains alcohol-, anxiety-, and agoraphobia-free 18 months postimplantation. His numeric rating scale has remained at 1 to

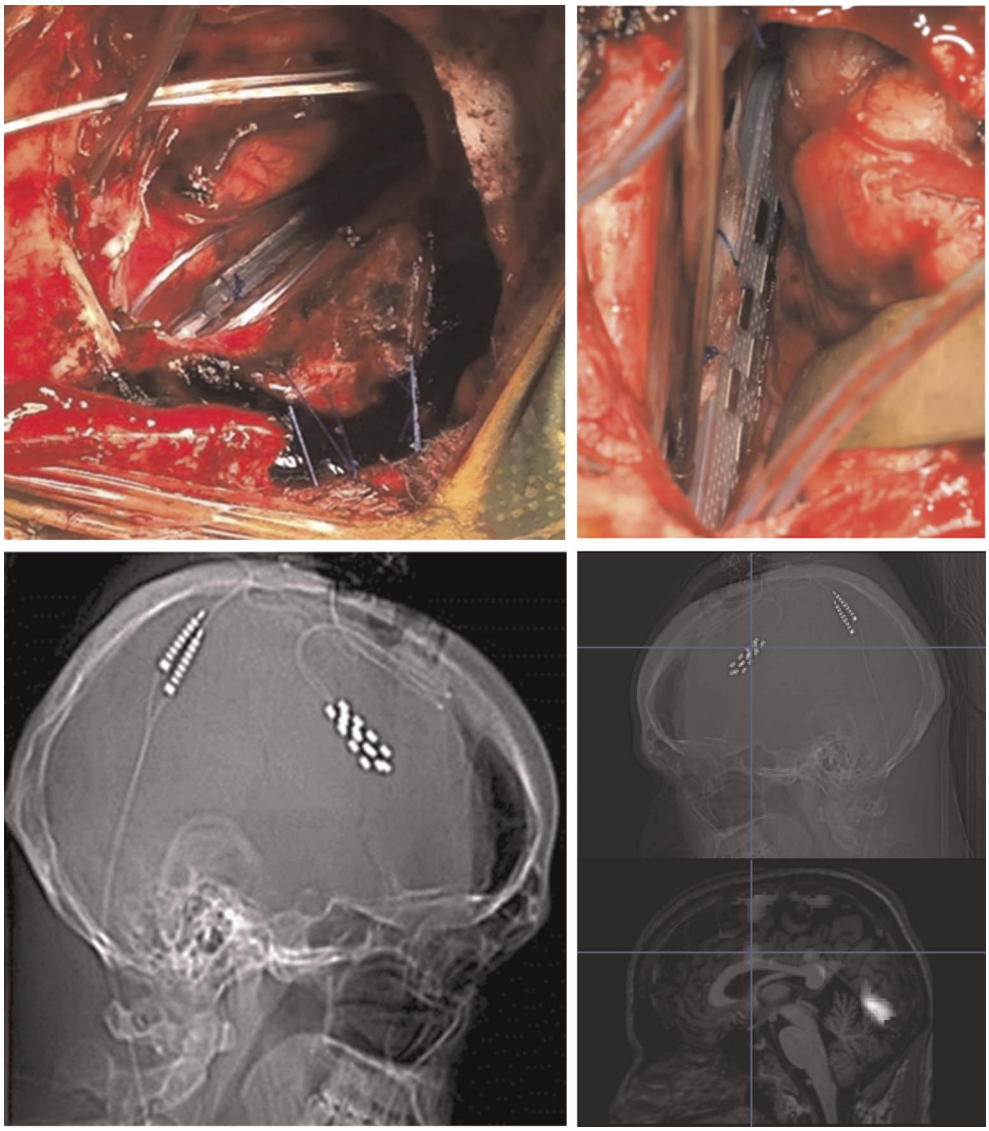

FIGURE 3. *A unilateral right-sided transfalcine approach for bilateral dorsal anterior cingulate cortex stimulation with 2 "back-to-back" paddle sutured electrodes. The right lower image shows the coregistration between CT scan and the fMRI. CT, computed tomography; fMRI, functional magnetic resonance imaging. Color version available online only.*

2 of 10 (Figure 4). An EEG with sLORETA source localization was performed and demonstrated that, at baseline, there were marked differences in delta, alpha, and beta activity in the dACC between the alcohol-dependent patient and healthy controls. Even though, when turning off the stimulator, differences can be seen in the alpha oscillations (Figure 5A), the alpha activity when the stimulator is off is still within normal range (Figure 5B). In fact, when turning the stimulation off after 18 months, all his oscillations except for delta have become normalized in the dACC (target of stimulation) (Figure 5B). For details of the recordings and artefact rejection, see **Methods**, **Supplemental Digital Content**, http://links.lww.com/NEU/A854. The same finding was noted for the dorsolateral prefrontal cortex and inferior temporal cortex. When comparing his on-and-off stimulation with a healthy control group, it is clear that his postoperative resting state brain activity with stimulation on is similar to dACC activity in nonaddicted controls, in contrast to his off status (Figure 4B). He does not experience an immediate change in his craving when the stimulation is turned off for 45 minutes for performing the EEG. This could explain why, 2 1/2 years after the surgery, he has not drunk any alcohol and remains craving-free. He has lost "interest in alcohol."

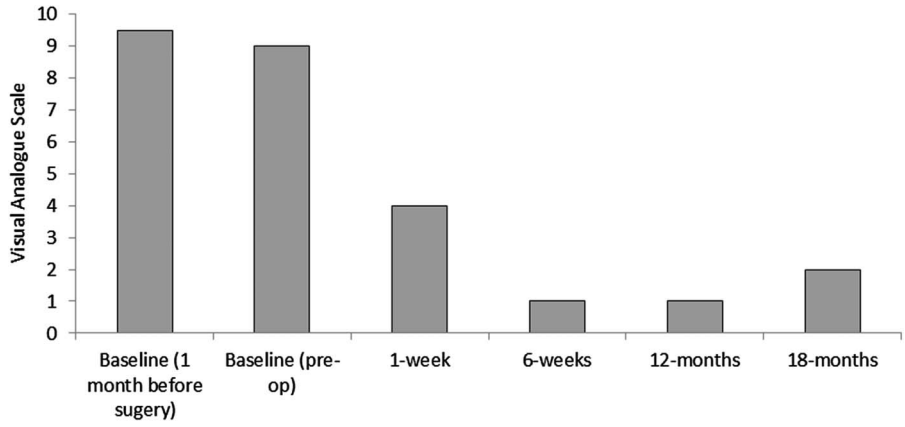

FIGURE 4. *Craving scores on a visual analogue scale for the different time points before and after implantation demonstrate a maintained effect on craving suppression. pre-op, preoperation.*

DISCUSSION

This is the first report demonstrating dACC/SMA stimulation via an electrode implant completely extinguishing craving, agoraphobia, and anxiety in a long-term setting. This is in line with a previous report that rTMS with a double-cone coil targeting the dACC can transiently improve alcohol craving,[20] as well as influence anxiety and negative mood,[34] both of which could be important in explaining the continued beneficial effect in this patient.

The concept behind this case report is relatively simple and is based on 4 principles, as previously described for tinnitus and pain treatment by implanting electrodes on the auditory cortex[26-28] and somatosensory cortex,[24,29] respectively. These include: (1) the knowledge that alcohol-related craving is related to glutaminergic overactivity of the dACC/SMA (and nucleus accumbens); (2) demonstration of this abnormal activity using cue-evoked, high-resolution BOLD fMRI confirmed by low-resolution, resting-state EEG; and (3) transient improvement in craving using double-cone coil rTMS followed by (4) more permanent craving reduction by implanting an electrode in the same area.

A recently published case series described a similar treatment approach for pain by targeting the dACC.[35,36] This was performed via a deep brain stimulation (DBS) approach using transfrontal insertion of wire electrodes, targeting the same area, which is also involved in processing the affective component of pain; in other words, treating the unpleasantness of the pain.[37] Interestingly, at a group level, no improvement was seen on the intensity of the pain, but an improvement was noted on the quality of life, suggesting that the improvement was mediated via the affective or attentional component of the pain. This effect was not immediate, taking 2 to 3 days to develop. This is similar to the development of beneficial treatment effects in the reported patient with alcohol dependence, for whom, after an immediate improvement, the effect further improved in the week following the activation of the electrode (Figure 3B). The stimulation settings for the pain patients were 4 to 6.5 V for amplitude, 130-Hz frequency, and 450-microsecond pulse width, which in the subthalamic nucleus induces electrophysiological silence with intermittent spontaneous bursting,[38] suggesting an inhibitory effect.

We elected to use a paddle electrode instead of a wire electrode. The advantage of a paddle electrode is that it covers a larger area of the cingulate cortex and therefore permits more versatile programming, and a larger electrical field can be generated. Furthermore, by inserting the electrode between the hemispheres, the risk of an intraparenchymal iatrogenic hemorrhage is minimized. Also, the angle of placing the electrode along the corpus callosum is not easy to do with a percutaneous DBS approach. A further advantage is that any neurosurgeon can do this, even without DBS experience.

Stimulation at the same target in the setting of epilepsy with 2 to 8 mA at 50 Hz and 200-microsecond pulse width during diagnostic workup suggested that this area is involved in generating the "will to persevere." These patients also described changes linked to activation of the autonomic nervous system and associated anxiety. It has been shown that, at a neocortical level, 40-Hz stimulation is excitatory,[39] and even though the dACC has a 5-layer structure[40] different from the 6-layer neocortical structure, clinically it appears to exert an excitatory response as well. This is in agreement with recent functional imaging studies that demonstrate this area is also involved in the urge for action.[41] Urges are highly automatic, habitual responses that occur primarily in response to sensory stimulation and are not necessarily conscious. However, when an urge becomes conscious, it can lead to the perception of a desire for action.[41]

The increased dACC/SMA activity in the resting-state EEG of the patient described in this case report with alcohol dependence suggests an ongoing urge for action,[41] resulting in the conscious perception of craving and a strong desire for alcohol, driving him to obtain more alcohol. Through the presentation of alcohol-related

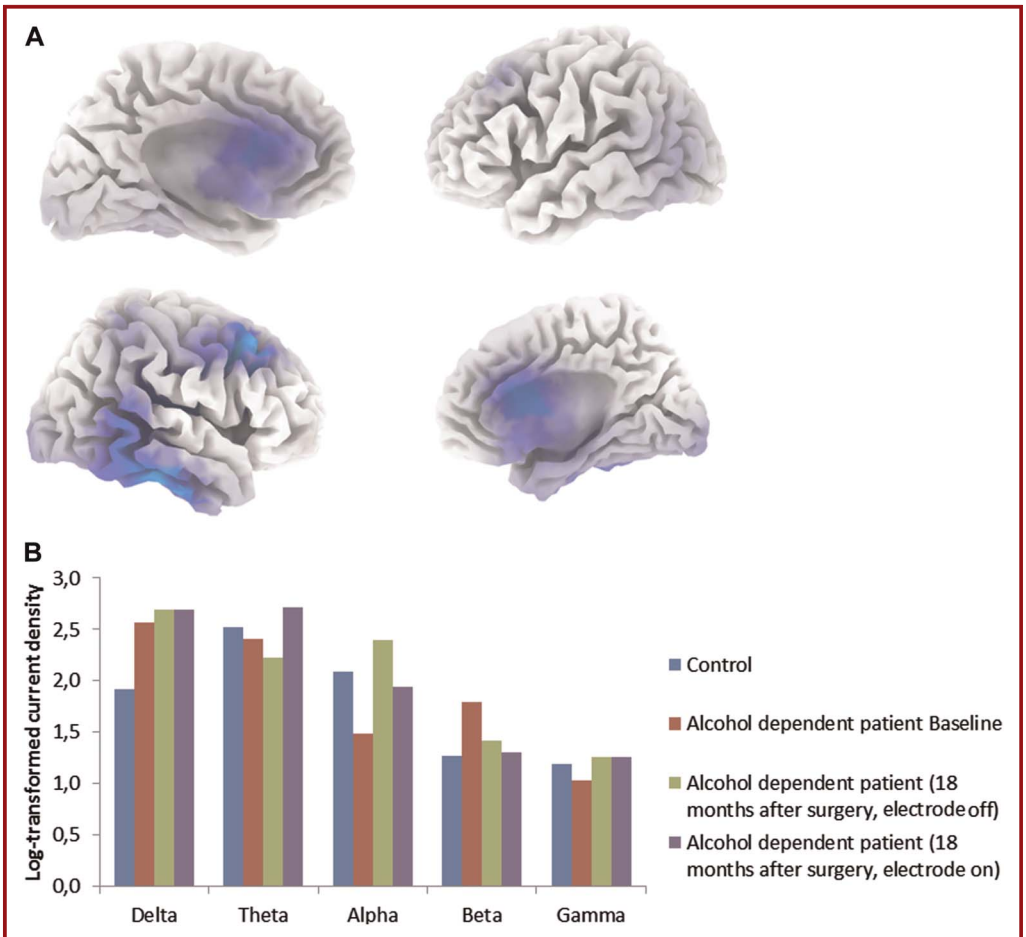

FIGURE 5. **A**, *a comparison between on vs off stimulation at 18-month follow-up revealed a significant decrease in the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, and inferior temporal cortex for the alpha frequency (8-12 Hz).* **B**, *log-transformed current density for the region of interest of the dorsal anterior cingulate cortex for the different frequency bands for a healthy control and an alcoholic patient before the treatment and 18 months during the treatments, when the stimulator is on and off. Before surgery, alpha activity (decreased) and beta activity (increased) are abnormal in the dACC. Postimplant, at 18 months, the beta activity is normalized both in stimulation on and off mode, and the alpha activity is normalized in the stimulation on mode. dACC, dorsal anterior cingulate cortex. Color version available online only.*

cues, this urge was further increased as demonstrated by the fMRI results. Suppressing this activity abolished this urge and desire for alcohol.

The burst stimulation design used here for suppressing dACC/SMA activity has been recently developed[33] and has been used in the brain[32] and on the spinal cord[42] and peripheral nerves.[43] It tries to mimic burst firing in the brain, is a stronger activator of the postsynaptic potential, whether excitatory[44,45] or inhibitory,[46] and appears to be clinically more effective than tonic stimulation.[32,33,42,43,47] The 500-Hz spike mode in burst firing elicits the greatest inhibitory postsynaptic potential[46] and is therefore selected. Low-frequency stimulation (1 Hz, 90 mA, 200 microseconds) at the anterior cingulate cortex inhibits its activity and has behavioral effects in primates.[48] However, because transient coupling between theta- and gamma-frequency brain rhythms coordinates activity in distributed cortical areas[49] in which theta is considered a carrier frequency and gamma contains the information,[50] we opted to use a low frequency (3 Hz), which could disrupt the nesting on the carrier frequency. Based on the data from the dACC stimulation in pain patients, 130 Hz could theoretically be used as well,[35] and based on the primate data, 1 Hz could also be used,[48] but not 40 Hz, because it is expected that this would worsen the anxiety.[51] In addition, burst stimulation appears to be more clinically effective than tonic stimulation,[32,33,42,43,47] explaining our decision to use this stimulation design.

Alternative psychosurgical approaches have previously been used. Cingulotomies have been successfully used for alcohol

dependence.[52] Even though they seem to have few side effects, apart from a decrease in sustained attention,[53-55] they have the disadvantage of being irreversible. Furthermore, neuromodulation by implanted electrodes has the theoretical benefit that, depending on the stimulation design, different brain areas can be modulated,[56] and therefore has the advantage of greater versatility. Nucleus accumbens lesions have been performed for alcohol addiction as well and appear to be a safe method to alleviate alcohol craving, reduce relapse rates, and improve quality of life in patients with psychological dependence on alcohol,[57] but they have the same problem of irreversibility. Accumbens ablation in heroin addicts is better studied and carries a long-term relapse rate of 42% and some important, albeit rare, side effects. Therefore, the authors concluded that "because ablation is irreversible, nucleus accumbens surgery for addiction should be performed with cautiousness, and DBS is an ideal alternative."[58] Nucleus accumbens stimulation has been performed for alcohol dependence in 6 patients,[59,60] 3 of whom attained remission. It is of interest that 1 of these 3 patients had a problem identical to the patient described in this report: agoraphobia with panic attacks improving with alcohol consumption.[59]

The alcohol consumption in our patient was also related to agoraphobia with panic attacks. Thus, one could argue that dACC/SMA stimulation had primarily an effect on anxiety and only indirectly on alcohol abuse. However, this seems highly unlikely, because there was an immediate effect on craving intensity after both rTMS and electrode implantation. Whether the co-occurrence of anxiety is a prerequisite for the therapeutic effect of dACC/SMA stimulation on alcohol craving, or whether dACC/SMA stimulation may also have positive effects on craving in patients without anxiety symptoms, can only be answered by further research.

We are well aware that our report is preliminary because it is based on data from a single patient without placebo control. However, the replication of rTMS effects by electrical stimulation via implanted electrodes, the 18-month-long clinical effect in this severely ill patient, and the stimulation-dependent normalizing effects on EEG activity in the dACC argue strongly against a pure placebo effect as an explanation for the favorable clinical course. Furthermore, it is unlikely that the placebo effect can explain the clinical long-term benefit the patient perceives. A recent systematic review and meta-analysis has shown that principally the clinical effect of placebo is rather small[61-63] and induces, on average, a 7% improvement.[61]

Nevertheless, even if it remains unclear whether the reported patient is representative for other patients with alcohol addiction (without anxiety symptoms), our observation demonstrates that alcohol addiction can be improved by focal modulation of dACC activity and underscores the potential of brain stimulation techniques for the treatment of this highly debilitating disorder.

The question remains: how universal is this method? It is known that craving for alcohol is encoded by the dACC,[20,64-67] similar to what has been noted in illegal drugs.[68] However, analogous to other neuromodulation approaches for different diseases, it is unlikely this procedure will be efficacious in 100% of severely addicted alcohol-addicted patients. Biomarkers such as functional connectivity could potentially be useful in determining who might ultimately benefit from this approach.[69] Further studies are required to delineate ideal candidates for this surgical approach.

CONCLUSION

We describe a novel pathophysiological approach to suppress alcohol craving associated with agoraphobia and anxiety by implanting electrodes onto the dorsal part of the anterior cingulate cortex/SMA, an area that is involved in craving in general. This pathophysiological approach consists of 4 principles previously described for tinnitus and pain suppression. (1) Pathophysiologically, alcohol-related craving has been shown to be related to glutaminergic overactivity of the dACC (and nucleus accumbens). (2) Demonstrate this pathological activity by cue-evoked BOLD activation in the fMRI and confirm it with source-localized, resting-state EEG. (3) Target this area noninvasively by double-cone coil rTMS. (4) If the rTMS exerts a transient, clinically meaningful improvement, implant an electrode at the same area for long-lasting effect, associated with normalized alpha and beta activity in the stimulated area. Further studies in a placebo-controlled way should be performed to analyze the clinical potential of this treatment for intractable alcohol-addicted patients.

Disclosures

This study was performed with an unrestricted educational grant from St Jude Medical. Dirk De Ridder has intellectual property on burst stimulation, and is a paid consultant for, and has received speakers fees from, St Jude Medical. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The authors report on the case of a patient with intractable alcohol dependence. The patient initially underwent rTMS and the authors noted a reduction in craving for alcohol with stimulation of the anterior cingulate cortex. Based on these results, he was offered a neurostimulation system and underwent implantation with 2 paddle leads aimed at the cingulate cortex, side-by-side, via an interhemispheric approach. The results are quite impressive because the patient had a dramatic reduction in craving for alcohol. The duration of the effect is equally important, and the patient remained free of alcohol consumption over 18 months. There were notable improvements in associated anxiety and agoraphobia as well. This case report may have implications for the treatment of substance abuse and further investigation with this approach would be reasonable given the encouraging results. The reproduction of rTMS results with electrical neurostimulation is particularly interesting and indicates that rTMS may be a good screening tool. Despite the impressive results in this single patient, we need to be cautious and avoid excess optimism. In addition to the usual limitations related to single-case reports, this was not a blinded study and stimulation titration was limited. There is ample evidence from recent DBS trials for depression and prior studies in neurostimulation for pain that placebo effect can be very strong, even in patients with severe and refractory disorders. Therefore, future studies should not only attempt to reproduce the findings in a cohort of patients but also evaluate the effects of stimulation under a blinded design.

Andre Machado
Cleveland, Ohio

The authors present an uncontrolled case report on the successful application of neuromodulation in the treatment of alcohol abuse. The case report focused on reducing the craving for alcohol by stimulating the dorsal anterior cingulate cortex (DACC). The authors selected the target for stimulation by provocative testing with fMRI, corroboration of abnormal cortical behavior with sLORETA, and confirmed transient efficacy of noninvasive stimulation of the target with double-cone repetitive transcranial magnetic stimulation (rTMS) before electrode implantation. The authors chose a paddle electrode over a wire DBS lead to create a larger field of stimulation and novel stimulation parameters to approximate carrier and informational frequencies.

The DACC has been implicated in disorders of impulse control such as alcohol[1] and cigarette[2] craving, bulimia nervosa,[3] pathological gambling,[4] trichotillomania,[5] and in the impulse control disorder-related Parkinson Disease.[6] Interestingly, the stimulation also controlled the agoraphobia and anxiety that the patient experienced and was suppressing with alcohol, leading to speculation of an anxiolytic effect of DACC stimulation that may be equally effective on this common comorbidity of the Impulse Control Disorders (ICDs) listed above. Because DACC is only one of many brain regions implicated in ICDs, this clinical vignette may elucidate an intervention in the affective branch of the impulse control network, much like DACC stimulation for chronic pain eliminates the misery of the pain state without lowering the pain scores.[7]

Clearly an uncontrolled case report does not establish a therapy. Neurosurgeons are correct to look upon such case reports warily, conscious of the sordid past of psychosurgery. But more importantly, the reader should appreciate the societal and personal devastation wrought by impulse control disorders, the refractory nature of ICDs to medical management, and the recidivism rate of cognitive behavioral therapy before dismissing the notion of reversible neuromodulation in the treatment of impulse control disorders.

Daniel J. Curry
Houston, Texas

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