Anterior Cingulate Implant for Obsessive-Compulsive Disorder

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Key words
- Addiction
- Alcohol
- Cingulate
- Obsessive-compulsive disorder
- Y-BOCS

Abbreviations and Acronyms
dACC: Dorsal anterior cingulate cortex
EEG: Electroencephalography
OCD: Obsessive-compulsive disorder
pgACC: Pregenual anterior cingulate cortex
SD: Standard drink
sLORETA: Standardized low-resolution brain electromagnetic tomography
TMS: Transcranial magnetic stimulation
Y-BOCS-II: Yale-Brown Obsessive Compulsive Drinking Scale

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BACKGROUND: **Obsessive-compulsive disorder (OCD) is a brain disorder with a lifetime prevalence of 2.3%, causing severe functional impairment as a result of anxiety and distress, persistent and repetitive, unwanted, intrusive thoughts (obsessions), and repetitive ritualized behavior (compulsions). Approximately 40%–60% of patients with OCD fail to satisfactorily respond to standard treatments. Intractable OCD has been treated by anterior capsulotomy and cingulotomy, but more recently, neurostimulation approaches have become more popular because of their reversibility.**

OBJECTIVE: **Implants for OCD are commonly being used, targeting the anterior limb of the internal capsula or the nucleus accumbens, but an implant on the anterior cingulate cortex has never been reported.**

METHODS: **We describe a patient who was primarily treated for alcohol addiction, first with transcranial magnetic stimulation, then by implantation of 2 electrodes overlying the rostrodorsal part of the anterior cingulate cortex bilaterally.**

RESULTS: **Her alcohol addiction developed as she was relief drinking to self-treat her OCD, anxiety, and depression. After the surgical implant, she underwent placebo stimulation followed by real stimulation of the dorsal anterior cingulate cortex, which dramatically improved her OCD symptoms (decrease of 65.5% on the Yale-Brown Obsessive Compulsive Drinking Scale) as well as her alcohol craving (decrease of 87.5%) after 36 weeks of treatment. Although there were improvements in all the scores, there was only a modest reduction in the patient's weekly alcohol consumption (from 50 units to 32 units).**

CONCLUSIONS: **Based on these preliminary positive results we propose to further study the possible beneficial effect of anterior cingulate cortex stimulation for intractable OCD.**

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a brain disorder causing severe functional impairment as a result of anxiety and distress, persistent and repetitive, unwanted, intrusive thoughts (obsessions), and repetitive ritualized behavior (compulsions).[1,2] It has a lifetime prevalence in the United States of 2.3%.[3] Individuals with OCD are likely genetically vulnerable to the impact of environmental factors such as perinatal events, stress, trauma, and neuroinflammatory processes, which in combination may alter glutamate, serotonin, and dopamine gene expression through epigenetic mechanisms.[1] In turn, these modifications result in an OCD-specific imbalance between the direct and indirect loops of the cortico-striatothalamocortical circuit, associated with expression of heterogeneous OCD phenomenology in 4 main dimensions[1]: symmetry aspirations, taboo thoughts, contamination, and hoarding. Symmetry aspirations result in obsessions of symmetry and repeating, ordering, and counting compulsions (accounts for 26.7% of the variance). Taboo thoughts involve aggressive, religious, sexual, and somatic obsessions and checking compulsions (21.0%). Contamination obsessions result in cleaning compulsions (15.9%), and hoarding obsessions and compulsions account for 15.4% of the variance.

Approximately 40%–60% of patients with OCD fail to satisfactorily respond to standard treatments[4] such as cognitive-behavioral therapy, multiple serotonin re-uptake inhibitors, clomipramine, and addition of antipsychotics, and for those patients, neurosurgical interventions can offer some relief.[5] Two main approaches have been used, lesioning and neurostimulation. In stereotactic lesioning for OCD, 2 main targets are used, the dorsal anterior cingulate cortex (dACC) (cingulotomy) and the internal limb of the anterior capsula (anterior capsulotomy), with equally good results.[4] Based on modern structural imaging with tractography, it has become evident that these targets functionally converge at the pregenual anterior cingulate, extending into the orbitofrontal cortex,[6] which could

explain the similar outcomes for cingulotomy and anterior capsulotomy in OCD. In deep brain stimulation, electrodes are implanted in variable striatal areas, namely the anterior limb of the internal capsule, the ventral capsule and ventral striatum, the nucleus accumbens, and the ventral caudate.[7] Alternative targets include the subthalamic nucleus and inferior thalamic peduncle. In the case of deep brain stimulation, no significant differences are detected in efficacy between targets.[7]

Recently, a theoretical model was proposed that considered addiction and OCD as "uncertainty disorders."[8] Uncertainty is defined as a state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing,[9] in other words, Shannonian entropy or informational uncertainty.[10,11] A way to reduce the uncertainty, which is encoded by the rostral anterior cingulate, is to make multiple predictions about the environment that are updated in parallel by sensory inputs.[12] The prediction/behavioral strategy that fits the sensory input best is then selected, becomes the next percept/behavioral strategy, and is stored as a basis for future predictions. Acceptance of predictions (positive feedback) is mediated via the accumbens,[13] and switching to other predictions is mediated by the dACC (negative feedback).[12,13] Maintenance of a prediction is encoded by the pregenual anterior cingulate cortex (pgACC).[12] The balance between acceptance of the current behavioral strategy and switching to an alternative behavioral strategy depends on the balance between the pgACC and dACC. The pgACC encodes that enough input is present to reduce uncertainty, whereas the dACC is activated when more input is required to reduce uncertainty. This same principle has been applied to chronic pain as well, where chronic pain is considered a homeostatic emotion[14] based on a balance between pain suppression and pain input encoded by the pgACC and dACC, respectively.[15]

The pgACC is involved in the descending pain inhibitory (antinociceptive) pathway both for physical[16,17] and mental pain[18] by preventing further input of pain/noxious stimuli at the periphery,[17] and a similar mechanism has been proposed for sound,[19-22] vertigo,[23] and aggression,[24-27] suggesting that this type of suppression of further information input could be a fairly universal nonspecific mechanism. The pgACC is also causally implicated in OCD, as shown by spectroscopic[28,29] and meta-analytic structural (voxel-based morphometry),[30] functional magnetic resonance imaging,[30] and multimodal imaging.[30]

The dACC is also involved in OCD, as shown by functional imaging,[31] structural imaging,[32] theoretical neurobiological,[8] and cingulotomy[4] data. Furthermore, functional[31] and structural[32] imaging of the dACC in OCD can predict therapeutic outcomes, both for medication[31] and for surgical[32] approaches, suggesting a causal involvement. Prospective responders show significantly lower brain perfusion in the dACC and higher brain perfusion in the right caudate when compared with nonresponders, and this occurs only during symptom provocation.[31] Decreased gray matter in the right dACC as well as increased structural connectivity between the right dACC and caudate nucleus predicts improved response to cingulotomy.[32] Thus, based on functional, structural, pathophysiologic, and cingulotomy data, the dACC might be a good candidate for neurostimulation as well. We present a case of a patient with OCD successfully treated with surgical implantation of 2 paddle electrodes on the dACC for intractable OCD, using a simple open surgical approach.

CASE DESCRIPTION

A 47-year-old woman with alcohol addiction and OCD presented at the multidisciplinary neuromodulation group in Dunedin, New Zealand to participate in a study for alcohol addiction. The study involves the implantation of an electrode on the rostral to dorsal part of the anterior cingulate cortex to suppress craving if the patient the patient was deemed eligible (ie, has failed all nonsurgical treatments and has shown reductions in craving in a placebo-controlled transcranial magnetic stimulation [TMS] using a double-cone coil).[33]

The patient had been alcohol dependent since the age of 35 years and consumed at least 2 bottles of wine (16 standard drinks [SD]) per day, qualifying as a continuous heavy drinker, without real binging. At the baseline assessment, using the Yale-Brown Obsessive Compulsive Drinking Scale (Y-BOCS-II), she scored 25 (a score $\geq$7 discriminates between social drinkers and alcohol-dependent drinkers). Her γ-glutamyl transpeptidase level at baseline assessment was increased at 265 (normal range, 10–45 U/L) as was her alanine transaminase level at 43 (normal range, 10–40 U/L) signifying some liver involvement. Based on a retrospective estimate, the patient consumed 56 SDs per week (1 SD = 100-mL glass of wine) in the past 7 days before the interview. Her urge for alcohol was 47/56, and her alcohol craving was 8/10.

The maximum period she had been off alcohol was 3 consecutive weeks since she was diagnosed at the age of 35 years. Since then, she had had 2 residential treatments in a specialized addiction hospital, 5 separate outpatient treatments, 5 medication-assisted treatments (naltrexone, acamprosate; last use 2014 for longer than 3 months), but she always relapsed because of her high craving, which she scored at 8 out of 10. Her drinking pattern could be characterized as relief drinking.[34-36] She started drinking to find relief from her depression, anxiety, and OCD, which were all diagnosed when she was 15 years old. For her comorbidities, the patient took medications: quetiapine 25 mg once daily; alprazolam 0.25 mg 4 times daily; venlafaxine 75 mg once daily; and olanzapine 10 mg once daily.

She had severe OCD, with a Y-BOCS-II of 29/50, predominantly related to obsessions, more so than compulsions. She spent between 3 and 8 hours per day on obsessive thoughts, with only short symptom-free intervals, less than 1 hour per day. Eventhough she had some control over her obsessive thoughts, which she was sometimes even able to stop, the obsessive thoughts were perceived as disturbing, leading to a significant impairment in major areas of daily functioning. Compulsions were clearly present for 1–3 hours per day, and she made some effort to resist the compulsions, over which she had some control. However, that strategy led to a marked anxiety if compulsion was prevented, thereby still causing some interference with daily life. Her anxiety could be considered relatively mild (16/56 on the Hamilton Anxiety Rating Scale), predominantly related to inability to relax, depression, fears, and insomnia).

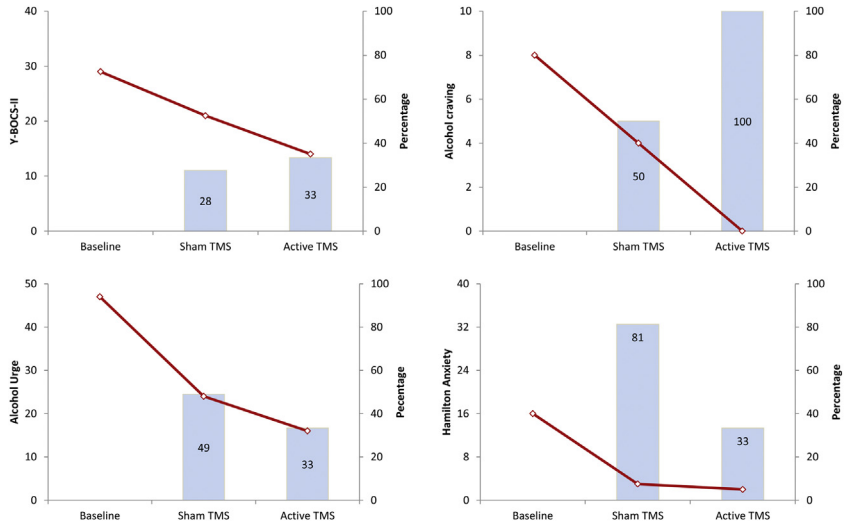

Figure 1. Transcranial magnetic stimulation (TMS)-induced changes in obsessive-compulsive disorder severity (*upper left*, Yale-Brown Obsessive Compulsive Drinking Scale [Y-BOCS-II]), alcohol craving (*upper right*, numeric rating scale), alcohol urge (*lower left*), and anxiety (*lower right*, Hamilton Anxiety score). The *red lines* indicates the raw score on the questionnaire, and the blue bars indicate the percentage improvement.

TMS

The patient underwent a placebo-controlled TMS session, using a double-cone coil TMS,[33] as a prognostic test to verify whether an implant could be beneficial, according to a protocol already used for tinnitus and neuropathic pain, both at the auditory cortex (for tinnitus),[37-41] somatosensory cortex (for neuropathic pain),[37,42,43] and dorsolateral prefrontal cortex (for tinnitus).[44] The double-cone coil is capable of reaching the dACC, as shown by positron emission tomography scan and source-analyzed electroencephalography (EEG).[33]

TMS was performed using a super rapid stimulator (Magstim Co. Ltd., Whitland, Wales, UK) with a double-cone coil (P/N 9902–00; Magstim Co. Ltd.) placed over the medial frontal cortex (1.5 cm anterior to one third of the distance from the nasion-inion).[45] The resting motor threshold to TMS was first determined by placing a figure-of-eight coil over the motor cortex using electromyography. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at a 45° angle from the midsagittal line. The patient's motor threshold was 45%. The intensity of the stimulation was set at 90% of the motor threshold. The patient received repeated stimulation at 1 Hz, each stimulation session consisting of 600 pulses. The presence of a control procedure (ie, placebo effect) was tested by placing the coil perpendicular to the frontal area at the frequencies that yielded maximal suppression rates.

After 1 week (5 sessions) of sham TMS with the double-cone coil, the patient improved on her alcohol-related scores. Her numeric rating scale craving score improved from 8/10 to 4/10 after sham TMS and alcohol intake was dramatically reduced to 6 SD. The urge for alcohol decreased from 47/56 to 24/56. Her OCD scores were also improved by sham TMS. Her Y-BOCS-II score improved from 29 (severe OCD) to 21/50 (moderate OCD). She spent less time per day on obsessive thoughts, between 1 and 3 hours per day instead of between 3 and 8 hours per day, with only very short symptom-free intervals, less than 1 hour per day. She continued to have some control over her obsessive thoughts, which she was now often able to stop. The obsessive thoughts were still perceived as disturbing but led only to some impairment in major areas of daily functioning. Compulsions were less present (<1 hour per day instead of 1–3 hours per day), and she made some effort to resist the compulsions, over which she had some control. That situation led to a moderate amount of anxiety, causing little interference with daily life. Her anxiety had virtually disappeared (3/56 on the Hamilton Anxiety Rating Scale). See Figure 1 for overview.

After real double-cone coil TMS her alcohol scores improved even more. The numeric rating scale for craving was reduced to 0/10, the alcohol intake was very low (5 SD), and the urge for alcohol was further reduced from 56 at baseline to 24 after sham TMS to 16 after real TMS. Also her OCD scores further improved. Her Y-BOCS-II score improved further from 29 (severe OCD) to 21/50 after sham TMS (moderate OCD) to 14/50 (mild OCD) after real TMS. She spent even less time on obsessive thoughts (<1 hour per day with moderately long symptom-free intervals of 3–8 hours per day). She had much control over her obsessive thoughts, which she was now usually able to stop. The obsessive thoughts were still perceived as disturbing but led only to a minor impairment in major areas of daily functioning. Compulsions were also less present, at less than 1 hour per day instead of 1–3 hours per day, and she made little effort to resist the compulsions, over which she had more control than with sham TMS. That situation led to only a mild amount of anxiety, causing little interference with daily life. Her anxiety had virtually disappeared (2/56 on the Hamilton Anxiety Rating Scale). See Figure 1 for overview.

Implantation

Based on these results, a more permanent treatment was offered, consisting of an implant of paddle electrodes on the anterior cingulate cortex, using a technique previously described.[8] An open neurosurgical approach was performed, consisting of a small right-sided frontal craniotomy for an infrafalcine approach inserting 2 electrodes for bilateral dACC stimulation.[46]

After induction of anesthesia, intubation, and ventilation, the patient was fixed in the Mayfield head rest in a supine position, with her neck slighted flexed with 0° rotation. After registration of the preoperatively administered skin fiducials for neuronavigation with the Stealth (Medtronic, Minneapolis, Minnesota, USA) frameless

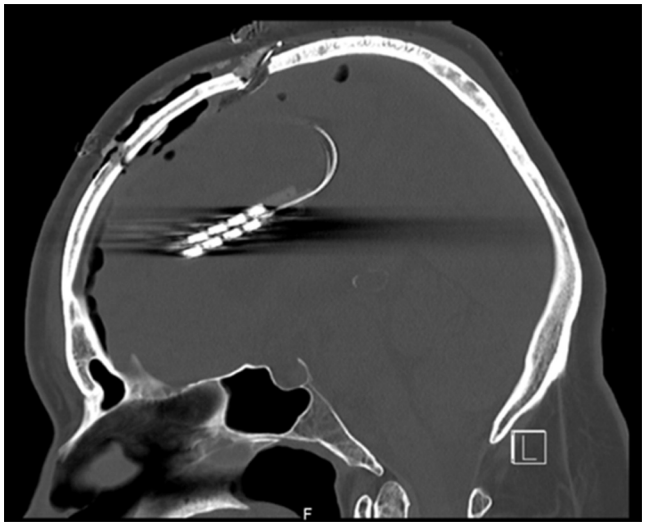

Figure 2. Computed tomography scan showing the electrode location targeting the dorsal anterior cingulate cortex.

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, based on the neuronavigated trajectory. The craniotomy was entirely anterior of the coronal suture, as can be appreciated from Figure 2. Two burr holes were made, 1 left and 1 right of the superior sagittal sinus, anterior of the coronal suture, and 2 more, 4 cm more anterior. One burr hole was made 4 cm lateral of the midline. Subsequently, a square craniotomy was performed crossing the midline. Subsequently the dura was incised in a U shape and the dura reflected across the midline. This procedure was followed by a neuronavigated approach between the right frontal lobe and the falx. The implant target was located at the interface between the dorsal and rostral anterior cingulate cortex, based on a study showing the anatomic difference between responders and nonresponders to cingulotomy, which is the border area between the dACC and the rostral anterior cingulate cortex.[47] Using neuronavigation, the electrode was positioned so that this area was in the middle of the lamitrode 44 poles, and surgical and navigational inaccuracies could be compensated for by programming the adjacent poles on the electrodes. The 2-lamitrode 44 (SJ Medical, Neurodivision, Plano, Texas, USA) electrodes, sutured back to back, were positioned resting on the corpus callosum, inferior of the falx. The electrodes were sutured with prolene 4.0 to the falx with 2 anchor points, 1 at the anterior side of the paddle lead and 1 posteriorly, preventing postoperative migration both anteroposteriorly but also 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 is further tunneled to the anterior side of the upper thorax. Here, it was connected to a Prodigy internal pulse generator (SJ Medical) which is buried in an infraclavicular subcutaneous pocket. The skin on the skull and thorax was closed and the patient relieved from the headrest and woken up from anesthesia (Figure 2).

Behavioral Data

On the second postoperative day, once craving set in, the electrodes were not activated because the patient was randomized to a delayed start. Her alcohol addiction–related and OCD scores were again taken after 2 weeks of placebo stimulation.

Both her alcohol addiction–related and OCD scores had worsened dramatically during these 2 weeks of sham stimulation. Her craving had increased again to 7/10, her alcohol intake to 40 SD, and her medication needed to be increased to control her anxiety: alprazolam was increased from 0.25 mg 4 times a day to 1 mg 4 times a day. Her OCD scores also worsened dramatically, to a state worse than before TMS and the implantation of the electrodes. She now had very severe OCD, with a Y-BOCS-II score of 32/50, predominantly related to obsessions more than compulsions. She spent between 8 and 12 hours per day on obsessive thoughts, with only very short symptom-free intervals, less than 1 hour per day, and had no more control over her obsessive thoughts, which she was no longer able to stop. The obsessive thoughts were perceived as highly disturbing, leading to a significant impairment in major areas of daily functioning. Also, the compulsions had become more severe, present for 3–8 hours per day compared with 1–3 hours per day before any treatment; she made some effort to resist the compulsions, over which she had some control. However, that situation led to a marked anxiety if compulsion was prevented, thereby still causing some interference with daily life. Her anxiety was considered moderate (22/56 on the Hamilton Anxiety Rating Scale), even although her medication was increased, again predominantly related to inability to relax, depression, fears, and insomnia.

After 2 weeks, the stimulation was activated at 10-Hz burst mode. Burst stimulation is a new stimulation design, which has shown superiority both in cortex auditory,[47,48] somatosensory, dorsolateral prefrontal, and anterior cingulate, spinal cord, and peripheral nerve stimulation. Her alcohol addiction–related scores and OCD scores again improved dramatically. Eventhough her craving (7/10) and urge scores (31/56) were still high she had not drunk alcohol, and her OCD scores improved dramatically. Her Y-BOCS-II score decreased to 16/50, in a similar way to real TMS, and her anxiety scores again decreased to 8/56, slightly lower than with TMS. Furthermore, these scores remained constant during further follow-up, irrespective of the burst frequency that was selected. For her alcohol

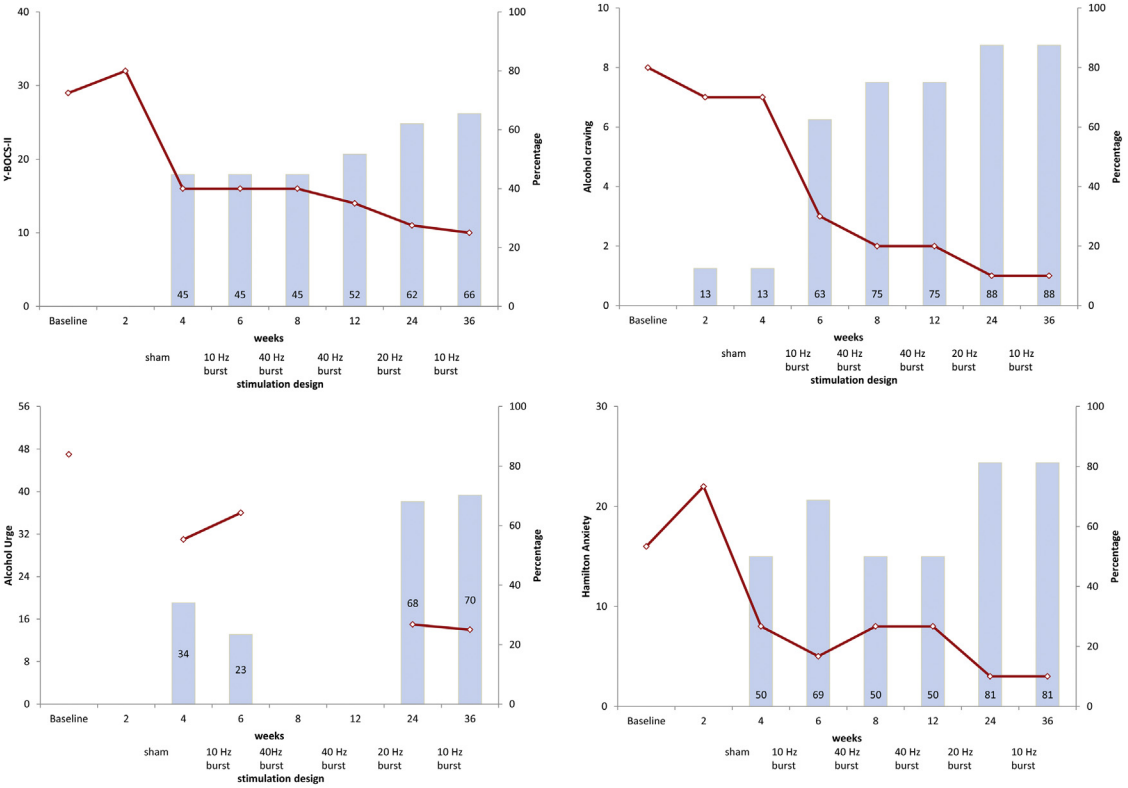

Figure 3. Dorsal anterior cingulate cortex implant—induced changes on obsessive-compulsive disorder (*upper left*, Yale-Brown Obsessive Compulsive Drinking Scale [Y-BOCS-II]), anxiety (*upper right*, Hamilton Anxiety score), alcohol craving (*lower left*, numeric rating scale), and alcohol urge (*lower right*). The *red lines* indicates the raw score on the questionnaire, and the *blue bars* indicate the percentage improvement.

addiction scores, a progressive decrease was seen with regards to the craving score, which decreased to 2/10, as did her urge score to 25/56, but her alcohol consumption was still relatively high, at 37 SD per week. This situation was explained by the patient that eventhough she no longer craved alcohol, she drank wine out of habit. When she was thirsty, she would open a bottle of wine rather than drink water, out of habit.

At week 24, her score on the Y-BOCS-II decreased to 11/50 and on the anxiety scale to 3/56. The patient also scored 1/10 on alcohol craving and her alcohol urge was 15/56. However, she estimated retrospectively that she had 40 SD of wine. For comparison, her intakes during week 6 and week 8 were 21 and 27 standard units, respectively.

During the postoperative week 24 visit, the patient reported that she was developing the need to "look in the car rearview mirror after passing pedestrians to make sure she had not hit the person while driving past." She reported that the compulsion was mild and she had moderate control over it. The patient was kept on 40-Hz burst mode (Figure 3).

At the end of postoperative week 34, the patient called the investigators, reporting that the compulsion was now "out of control." She had very strong compulsive thoughts that whenever she passed somebody with her car she had to verify that she had not hurt that person by driving into them. She was not willing to be in a car to come in for assessment. Her EEG at 24 weeks showed a pgACC/dACC balance analogous to her pretreatment situation (Figure 4). This finding suggested that the 40-Hz and 20-Hz stimulation was not effective, and that the electrophysiologic measurements might have been a carry-over effect of the beneficial 10-Hz stimulation. Because she did not want to come to the clinic for assessment (because she refused to drive her car), she was asked to change her stimulation program back to 10-Hz burst global; reported over the phone 3 days later that she was feeling a lot better. After 12 days on a 10-Hz burst, the participant presented herself, driving her car, at the clinic for assessment (week 36 postoperatively). At the end of week 36, 2 new stimulation designs were programmed in the internal pulse generator, both in cycle mode (10-Hz burst global, 5 seconds on 10 seconds off and 5 seconds on 15 seconds off). Her score on the Y-BOCS-II decreased to 10/50 and on the anxiety scale to 3/56. The patient's score on alcohol craving was 1/10 and the alcohol urge was 14/56. The patient reported that she had 32 SD of wine during the week. See Figure 3 for overview.

Neuroimaging Data

EEG recordings were obtained in a fully lit room with the participant sitting upright on a small but comfortable chair. The recording lasted approximately 5 minutes.

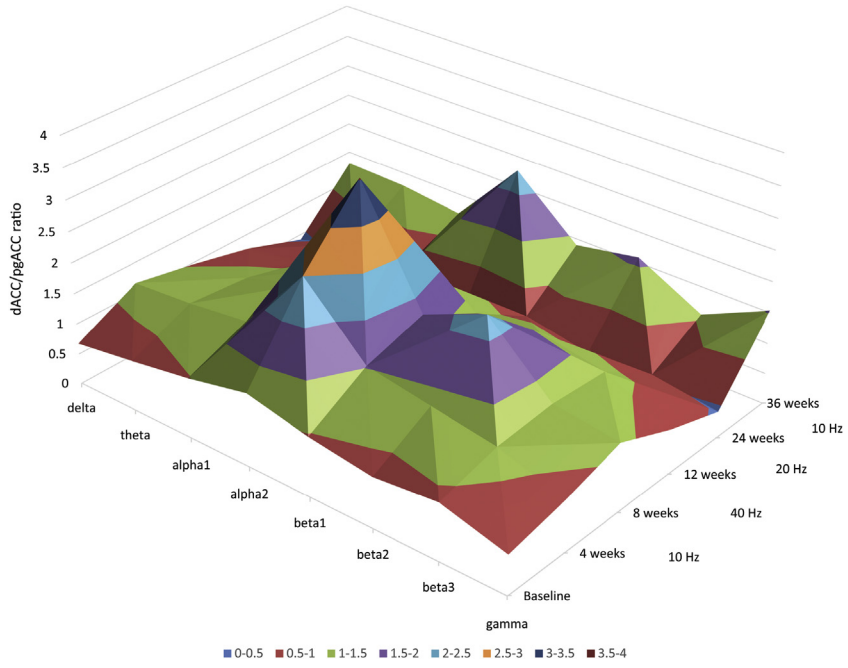

Figure 4. Current density ratio dorsal anterior cingulate cortex (dACC)/pregenual anterior cingulate cortex (pgACC), compared with healthy controls without obsessive-compulsive disorder, between the dACC and pgACC as an electrophysiologic measure for input supporting activity (dACC) and input suppression activity (pgACC). The patient decompensated a couple of weeks after the recording at 24 weeks, which showed a balance analogous to her pretreatment situation. This finding suggests that the 40-Hz and 20-Hz stimulation was not effective, but that the electrophysiologic measurements might be a carry-over effect of the beneficial 10-Hz stimulation.

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 placement referenced to linked ears and impedances were checked to remain lower than 5 kΩ. Data were collected with 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 2–44 Hz and subsequently transposed into Eureka! Software,[49] 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 δ (2–3.5 Hz), θ (4–7.5 Hz), α_1 (8–10 Hz), α_2 (10–12 Hz), β_1 (13–18 Hz), β_2 (18.5–21 Hz), β_3 (21.5–30 Hz), and γ (30.5–45 Hz). Data were collected for the patients before the patient was implanted as well as at 4, 8, 12, 24, and 36 weeks of treatment.

Standardized low-resolution brain electromagnetic tomography (sLORETA[50]) 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 × 5 × 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 and intersubject variability, a global normalization of the sLORETA images was carried out before statistical analyses. The log-transformed electric current density was averaged across all voxels belonging to the regions of interest for the different frequency bands δ (2–3.5 Hz), θ (4–7.5 Hz), α_1 (8–10 Hz), α_2 (10–12Hz), β_1 (13–18 Hz), β_2 (18.5–21 Hz), β_3 (21.5–30 Hz), and γ (30.5–45 Hz). The regions of interest selected were the dACC and the pgACC. We then calculated the ratio between the 2 areas by dividing the pgACC from the dACC for each frequency band and for each time point (baseline, 4, 8, 12, 24, and 36 weeks).

Figure 4 shows the ratio for each frequency band for each time point indicating that at week 8 (ie, 10-Hz burst), the balance has changed for the α_2 and β_2 frequency bands. Over weeks 12 (20-Hz burst) to 24 (40-Hz burst), the ratio returned to its original baseline for all frequency bands. However, after week 36 (10-Hz burst), there were changes in the balance for the α_2 and β_2 frequency bands, as well as the γ frequency band similar to baseline. Based on the findings, we had a closer look at α_1 and α_2 frequency bands and conducted a whole-brain analysis comparing the baseline with week 8, 24, and 36 after treatment and the combination of week 8 and 36 with the baseline and week 24. This analysis showed that at 8 weeks, increased activity was shown at the dACC and the left dorsal lateral prefrontal cortex compared with baseline. However, at week 24, the effect at the dACC and the left dorsal lateral prefrontal cortex was not present. Instead, there was decreased activity in the presupplementary motor area compared with baseline. At 36 weeks, there was again increased activity at the left dorsal lateral prefrontal cortex compared with baseline. Comparing weeks 8–36 with baseline and week 24 further confirmed increased activity at the dACC and the left dorsal lateral prefrontal cortex. See Figure 5 for overview.

DISCUSSION

This case report shows the feasibility of implanting 2 paddle leads via a simple open surgical unilateral approach onto the rostral ACC to dACC for the treatment of OCD, analogous to what has been performed for tinnitus[46] and alcohol addiction.[8] Because the patient was discharged on the first postoperative day, this technique seems to be well tolerated. It furthermore has the advantage that no stereotactic frame is required and that any neurosurgeon can perform this technique, if needed even without neuronavigation, because of the large area that is covered by the paddle leads.

In OCDs, there is an abnormal functional and structural connectivity between

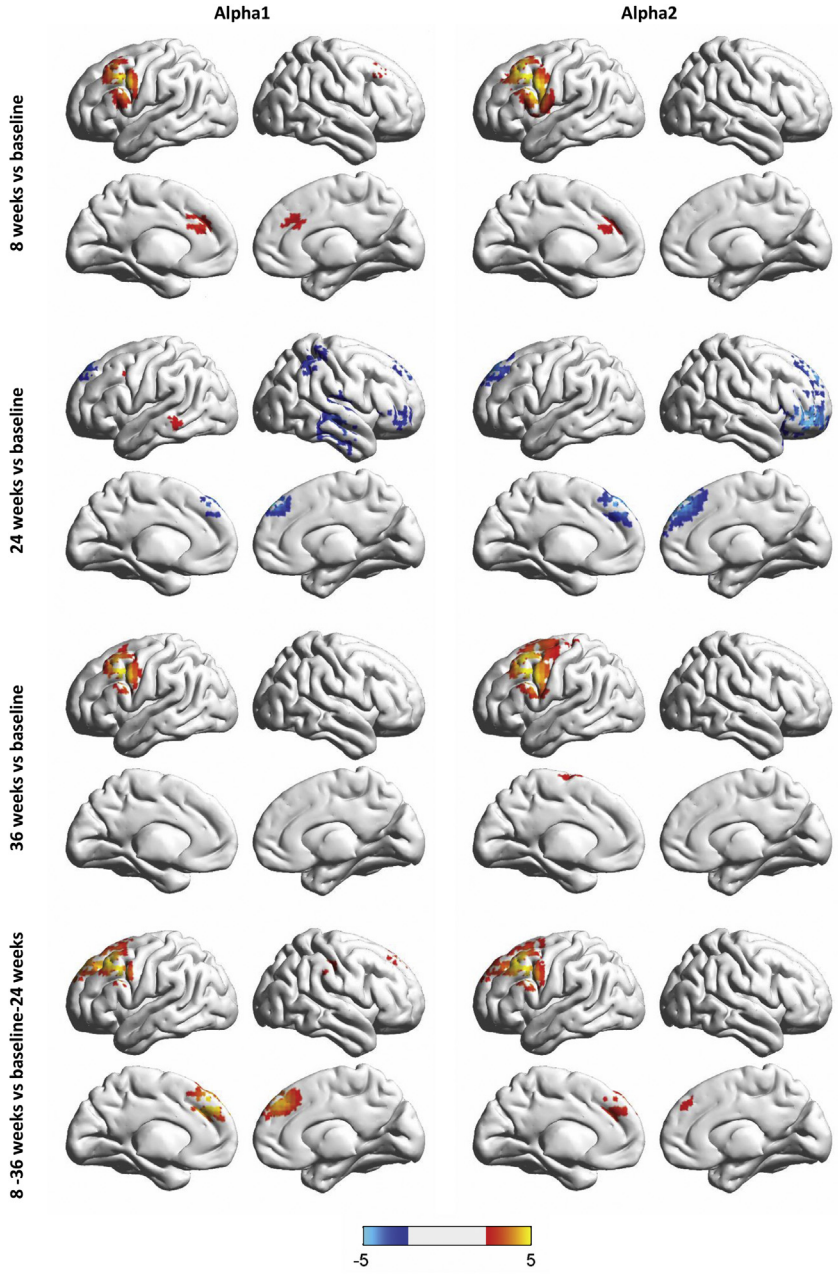

Figure 5. Comparison between baseline and 8 weeks of treatment, baseline and 24 weeks of treatment, baseline and 36 weeks of treatment, and 8–26 weeks of treatment compared with 24 weeks of treatment and baseline for brain activity using source-localized resting-state electroencephalography.

the right dACC and caudate nucleus.[32,51] The major output of the caudate nucleus is sent to the pregenual cingulate cortex, which is under the influence of dopamine, as is the output from the nucleus accumbens to the pgACC,[52] either via the subgenual anterior cingulate cortex[53] or via the posterior cingulate cortex.[13] There is also increased functional connectivity between the caudate and pgACC[54] and between the nucleus accumbens and the pgACC.[55]

Implants for OCD are commonly inserted in the anterior limb of the internal capsula or the nucleus accumbens,[56-58] but to the authors' knowledge, this is the first case of an implant on the anterior cingulate cortex. The anterior limb of the internal capsula is targeted both with lesioning and with stimulation for OCDs.[59] Lesioning has a successful outcome in 50%–70% of patients.[60-62] Chronic anterior capsular stimulation for OCDs has a beneficial effect in 50% of patients.[63,64] It decreases metabolic activity in the subgenual anterior cingulate cortex and preoperative resting metabolic activity in the subgenual anterior cingulate cortex may predict therapeutic response. The therapeutic response correlates with changes in the metabolism of the nucleus accumbens[65]; therefore, it might essentially exert its clinical effect by similar mechanisms to nucleus accumbens stimulation. Combining cingulotomy with accumbens stimulation does not yield better results than cingulotomy alone,[66] which could be explained by the fact that they influence the same final common pathway probably involving the pgACC (the area where all 4 psychosurgical approaches converge in their effects).

Nucleus accumbens stimulation for OCD has a beneficial effect in 60% of patients[56-58] by normalizing the aberrant functional connectivity between the nucleus accumbens and the pgACC,[67] resulting in normalized dopamine release.[68] Cingulotomy for OCDs has a long-term beneficial effect in 30%–69% of patients[60,69] by inducing atrophy in the caudate nucleus,[70] thereby indirectly modulating the pgACC. In a recent comparison of successful versus unsuccessful cingulotomies for OCDs, the critical area seems to be located rostrally rather than dorsally in the anterior cingulate cortex.[47]

Recently, a simplified model was proposed unifying psychosurgical approaches that interfere with flexible decision making.[8] It proposed that the function of the rostral anterior cingulate cortex was related to uncertainty processing, the function of the dACC was to obtain more input, and the function of the pgACC was to suppress further input. Addiction and OCD were proposed to be

"uncertainty disorders," in which the fundamental brain dysfunction was related to an imbalance between input and input suppression, related to positive (nucleus accumbens/pgACC) or negative feedback (habenula/dACC).[13] Modulating this balance can therefore improve OCD either by suppressing the dACC or by activating the nucleus accumbens.

In this case report, we show that the balance between the input suppressing pgACC and the input supporting dACC corresponds to the clinical expression of OCD, albeit that the electrophysiologic signature may change more rapidly than the clinical symptoms. The patient had 2 periods during which she was stimulated at 10-Hz burst mode, which coincided with dramatic electrophysiologic changes (**Figure 4**). It is possible that the clinical delay in worsening after changing to other stimulation frequencies was still a beneficial carry-over effect from the beneficial 10-Hz burst stimulation. Therefore, it could conceptually be used as a way of programming the implanted electrodes with a possibly higher sensitivity than programming based on modifying clinical symptoms.

Eventhough the patient's craving is almost completely abolished and her OCD dramatically improved, she still consumes a lot of alcohol. When questioned about the reason for that the patient states that this is out of habit. When she feels thirsty, she opens a bottle of wine rather than drinking water. This factor suggests that habitual drinking might not respond to this kind of treatment, or at least not to this target, and that dACC stimulation can control craving but not habitual overconsumption of a substance of abuse.

Eventhough the primary indication of the implant was (secondary) alcohol addiction, the results of this case report strongly suggest that a study using dACC implantation for the treatment of OCD is a worthwhile avenue. Burst stimulation at 10 Hz (or lower frequencies) seems to induce significant OCD-relieving effects.

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