Neuromodulation: Technology at the Neural Interface

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CLINICAL LETTERS

Burst Stimulation of the Dorsal Anterior Cingulate Cortex in Addiction: Sustained Benefit Without Continued Stimulation

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To the Editor:

Neuromodulation is generally considered symptomatic, with its effects disappearing soon after stimulation is stopped. In Parkinson disease, deep brain stimulation (DBS) withdrawal leads to rapid recurrence, and tinnitus suppression with cochlear implants also ceases within seconds. Rare exceptions exist, such as sustained remission in a small subset of patients with tardive dystonia after globus pallidus interna DBS, although the causal link to stimulation remains uncertain. For spinal cord stimulation, certain designs such as burst produce short-lived residual inhibition, but effects typically last only minutes to hours.

We report here what we believe is a unique case of complete and sustained remission of alcohol craving, agoraphobia, and anxiety for >three years after cessation of ten years of burst stimulation of the dorsal anterior cingulate cortex/supplementary motor area (dACC/SMA). This long-term benefit suggests a possible shift from purely symptomatic relief toward a lasting effect, potentially mediated by neuroplastic or neuroimmune mechanisms.

A man aged 38 years presented at the University Hospital Antwerp with severe alcohol dependence, anxiety, and agoraphobia (see suppl. mat.). His substance use history began in adolescence with heavy amphetamine use and problematic gambling. At the age of 17 years, he began consuming alcohol to self-medicate panic attacks, which were often linked to agoraphobia and social phobia. Over time, alcohol became the only way he could leave his home, leading to a life structured around constant access to alcohol and concealment of his drinking from others. Attempts to impose self-restrictions, such as limiting intake to four strong beers per day, frequently failed. Despite multiple interventions, including psychotherapy, mindfulness, Antabuse implants, and repeated inpatient rehabilitation, abstinence was short-lived. Outpatient care failed, and repeated inpatient stays gave only brief abstinence before relapse. This study was approved by the Antwerp University Hospital ethics committee, in accordance with the Declaration of Helsinki, with patient consent obtained. Fearing for his life, the patient sought neuromodulation as a last-resort treatment. Preoperative high-resolution functional magnetic resonance imaging (fMRI) and resting-state electroencephalogram (EEG) revealed hyperactivity in the dACC/SMA. Cue-evoked activation localized to this same area. Transcranial magnetic stimulation using a double-cone coil over the dACC temporarily abolished both craving and anxiety, which led to the decision to implant a cortical electrode over dACC/SMA. After obtaining approval from the ethical committee at the University Hospital in Antwerp and informed consent from the patient, two back-to-back lamitrode44 electrodes (SJM, Plano, TX, USA) were sutured to the falx, targeting the area of fMRI blood oxygenation level-dependent activation elicited by stimuli for alcoholic drinks. The electrodes were activated with a custom-made programmer in 3-Hz burst mode, comprising five spikes at 500-Hz spike mode, with a 1000-microsecond pulse width and an amplitude of 1.5 mA. This was later reduced to 0.5 mA. The electrode pole configuration was +-+-+-+- to generate a large stimulation field.

After implantation, the patient's craving score decreased from 9 of 10 on the day of surgery to 4 of 10 by discharge. By one month, it had decreased to 1 to 2 of 10, with complete resolution of anxiety and agoraphobia (Fig. 1a). Functionally, the patient became able to shop alone, navigate crowded stores, and walk through alcohol aisles without compulsion to drink—activities that had previously been impossible. At one year, he stopped smoking. This state of remission persisted for ten years with continuous stimulation.

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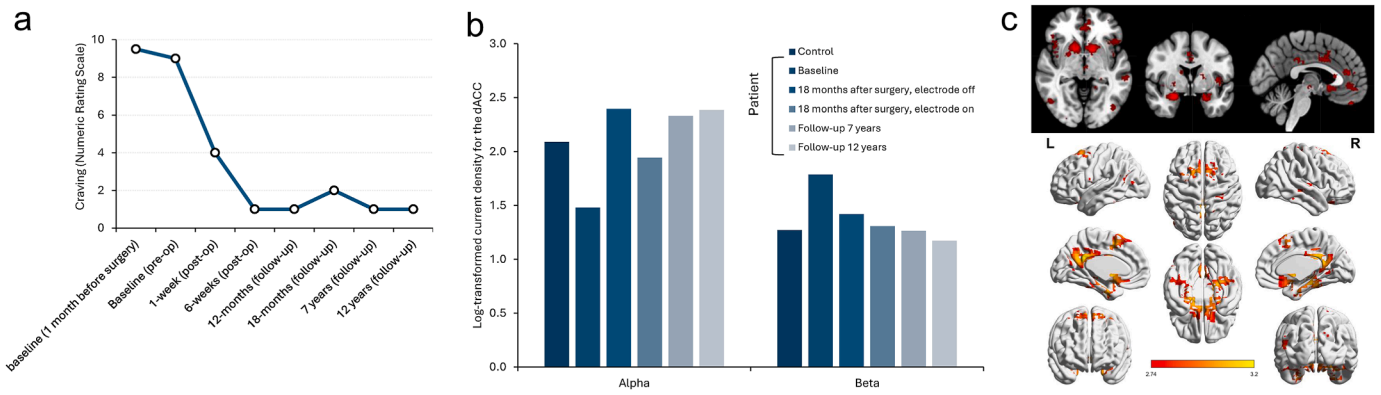

Figure 1. a. Craving scores on a numeric rating scale for the different timepoints before and after implantation indicate a maintained effect on craving suppression. b. Direct comparison of alpha and beta frequency bands showed increased alpha activity and decreased beta activity in the dACC during stimulation at 18 months, observed in both the "on" and "off" settings. c. (Top panel) All areas that are linked to "craving" according to a neurosynth (www.neurosynth.com) automated meta-analysis. (Lower panel) Seed-based connectivity analysis using the dACC as the seed revealed increased alpha-band connectivity at baseline between the dACC and several regions—including the SMA, insula, subgenual anterior cingulate cortex extending into the nucleus accumbens, posterior cingulate cortex, and parahippocampus—compared with a control group. [Color figure can be viewed at www.neuromodulationjournal.org]

When the implanted pulse generator battery depleted after ten years, it was not replaced unless symptoms returned. Two years later, the patient remained free of craving, anxiety, and agoraphobia, and at three years follow-up remained in remission. He has been alcohol-free for >12 years, including >three without stimulation (Fig. 1a). Resting-state EEG was recorded before implantation, 18 months after implantation (with stimulation on and off), and at seven and 12 years after implantation, the latter after ≥two years without stimulation. An age- and sex-matched normative data base of 15participants with no known disease was used for comparison. Data were processed with artifact removal, standardized low-resolution brain electromagnetic tomography current density mapping, and seed-based lagged phase coherence analysis using the dACC as the seed region.

Baseline EEG showed abnormal alpha/beta power (Fig. 1b) and hyperconnectivity between dACC and craving-related regions (Fig. 1c). At 18 months after implantation, alpha power in the dACC increased, whereas beta power decreased toward normative values (Fig. 1b). Functional connectivity also normalized, with resolution of the widespread baseline hyperconnectivity. At both seven and 12 years after implantation, EEG measures remained normal, showing no significant differences from healthy controls in either power or connectivity, even after >two years without stimulation.

To our knowledge, this case is the first to show that long-term cortical stimulation of the dACC/SMA can abolish alcohol craving, anxiety, and agoraphobia, with these effects persisting for years after cessation of stimulation. In the alcohol-addicted state, the dACC hyperconnects to the SMA, the insula, the subgenual anterior cingulate cortex, the amygdala, the posterior cingulate cortex, and the parahippocampus (Fig. 1c, lower panel) in comparison with healthy controls, all areas that are linked to "craving" according to a neurosynth (www.neurosynth.com) automated meta-analysis (Fig. 1c, top panel). The connectivity from the dACC normalizes, that is, it is not different from healthy controls long after stopping the therapy. This suggests that burst stimulation may have induced durable changes in brain networks rather than providing merely symptomatic relief.

At baseline, the patient's EEG indicated both abnormal activity and abnormal connectivity involving a network known to be associated with craving. These abnormalities normalized after stimulation and remained stable for years after cessation. Given that residual effects of burst in spinal cord stimulation are typically transient, the persistent cortical effects observed here likely required structural or synaptic rewiring rather than transient suppression alone.

One possible mechanism is that burst stimulation facilitated Hebbian plasticity. Burst patterns mimic natural burst firing, which is critical for long-term synaptic changes. By imposing a 3-Hz burst rhythm, the hyperactive dACC may have been downregulated, leading to stable reorganization of its network connections. Another hypothesis is that stimulation reduced low-grade neuroinflammation in the dACC. Alcohol addiction has been linked to neuroinflammation, particularly in prefrontal regions, as shown by translocator protein positron emission tomography studies in humans and animals.[1] Modulating the dACC with burst stimulation may have resolved such inflammation, thereby contributing to the sustained remission.

If this finding is confirmed by other studies, an important question raised by one of the reviewers is how long burst stimulation should be minimally maintained for a potentially permanent benefit to result. There is no scientific answer to this question yet, but studies investigating functional and structural neuroplasticity may suggest some estimated guesses. Gray matter changes induced by learning develop and disappear in a three-month time frame,[2] suggesting that a stimulation period may require >three months of stimulation. However, white matter plasticity takes longer to develop, and electrical activity is known to induce adaptive oligodendrogenesis in the brain.[3] This central myelination is associated with improved functioning.[3] Clinical translation of this gray and white matter neuroplasticity, as evaluated in recovery in brain injuries, indicates that most patients with stroke or brain injury reach a recovery plateau after three to six months, associated with functional connectivity changes. However, one in three patients continues to improve up to two years.[4] Thus, on the basis of the clinical link between white matter neuroplasticity and clinical changes, it may require ≥six months, but potentially up to two years, of stimulation for more permanent changes to develop.

A study with burst spinal cord stimulation may be helpful to resolve this question.

It could be argued that alternative explanations might be offered for long-lasting benefit. A lesion effect is very unlikely, given the paddle electrodes do not penetrate the cortex but lie on top of it. Even though in surgical studies the placebo response is large for subjective outcomes, persisting as a time-invariant effect throughout blinded follow,[5] it is unlikely as an explanation because the patient responded well to repetitive transcranial magnetic stimulation of the same target but relapsed. The same relapse could be expected if the response was purely placebo-related.

This case challenges the view that neuromodulation effects end with stimulation. In this patient, burst dACC/SMA stimulation abolished alcohol craving, agoraphobia, and anxiety, with benefits persisting for more than three years after cessation. EEG showed lasting normalization of dACC activity and connectivity. These results suggest cortical burst may induce durable neuroplastic or neuroimmune effects, warranting confirmation in larger studies and other targets.

Authorship Statements

Dirk De Ridder and Sven Vanneste wrote the manuscript, data-analysis, and data collection.

Conflict of Interest

Dirk De Ridder has an impending patent on the burst stimulation design. Sven Vanneste reported no conflict of interest.

How to Cite This Article

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2025.10.064.

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