First In-Human Experience With Complete Integration of Neuromodulation Device Within a Customized Cranial Implant

Chad R. Gordon, DO[*‡]
Gabriel F. Santiago, MD[*‡]
Judy Huang, MD[‡]
Gregory K. Bergey, MD[§]
Shuya Liu, MS[¶]
Mehran Armand, PhD[¶‖]
Henry Brem, MD[‡]
William S. Anderson, PhD, MD[‡]

[*]Department of Plastic and Reconstructive Surgery, Johns Hopkins University School of Medicine, The Johns Hopkins Hospital, Baltimore Maryland; [‡]Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland; [§]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; [¶]Department of Mechanical Engineering, Johns Hopkins University, Baltimore, Maryland; [‖]Johns Hopkins University Applied Physics Laboratory, Laurel, Maryland

Correspondence:
Chad R. Gordon, DO,
Department of Plastic and Reconstructive Surgery,
The Johns Hopkins University School of Medicine,
JHOC, 8th Floor,
601 N Caroline Street,
Baltimore, MD 21287.
E-mail: cgordon@jhmi.edu

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BACKGROUND: Neuromodulation devices have the potential to transform modern day treatments for patients with medicine-resistant neurological disease. For instance, the NeuroPace System (NeuroPace Inc, Mountain View, California) is a Food and Drug Administration (FDA)-approved device developed for closed-loop direct brain neurostimulation in the setting of drug-resistant focal epilepsy. However, current methods require placement either above or below the skull in nonanatomic locations. This type of positioning has several drawbacks including visible deformities and scalp pressure from underneath leading to eventual wound healing difficulties, micromotion of hardware with infection, and extrusion leading to premature explantation.

OBJECTIVE: To introduce complete integration of a neuromodulation device within a customized cranial implant for biocompatibility optimization and prevention of visible deformity.

METHODS: We report a patient with drug-resistant focal epilepsy despite previous seizure surgery and maximized medical therapy. Preoperative imaging demonstrated severe resorption of previous bone flap causing deformity and risk for injury. She underwent successful responsive neurostimulation device implantation via complete integration within a clear customized cranial implant.

RESULTS: The patient has recovered well without complication and has been followed closely for 180 d. Device interrogation with electrocorticographic data transmission has been successfully performed through the clear implant material for the first time with no evidence of any wireless transmission interference.

CONCLUSION: Cranial contour irregularities, implant site infection, and bone flap resorption/osteomyelitis are adverse events associated with implantable neurotechnology. This method represents a novel strategy to incorporate all future neuromodulation devices within the confines of a low-profile, computer-designed cranial implant and the newfound potential to eliminate contour irregularities, improve outcomes, and optimize patient satisfaction.

KEY WORDS: Customized cranial implant, Neuromodulation, Epilepsy, Epilepsy surgery, Functional surgery, Neurosurgery, Craniofacial surgery, Medical device

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Neuromodulation devices have the potential to transform modern day treatments for patients with medicine-resistant neurological disease. One example includes patients with seizures that are resistant to drug therapy, also known as drug-resistant epilepsy (DRE). It is estimated that nearly 1 out of every 3 epilepsy patients will have

ABBREVIATIONS: BFO, bone flap osteomyelitis; **CCI,** customized cranial implants; **CNC,** computer numerical control; **CT,** computed tomography; **DOF,** degrees of freedom; **DRE,** drug-resistant epilepsy; **ECoG,** electrocorticographic; **FDA,** Food and Drug Administration; **IRB,** Institutional Review Board; **PMMA,** polymethyl methacrylate; **RNS,** responsive neurostimulation; **WSI,** wound site infection

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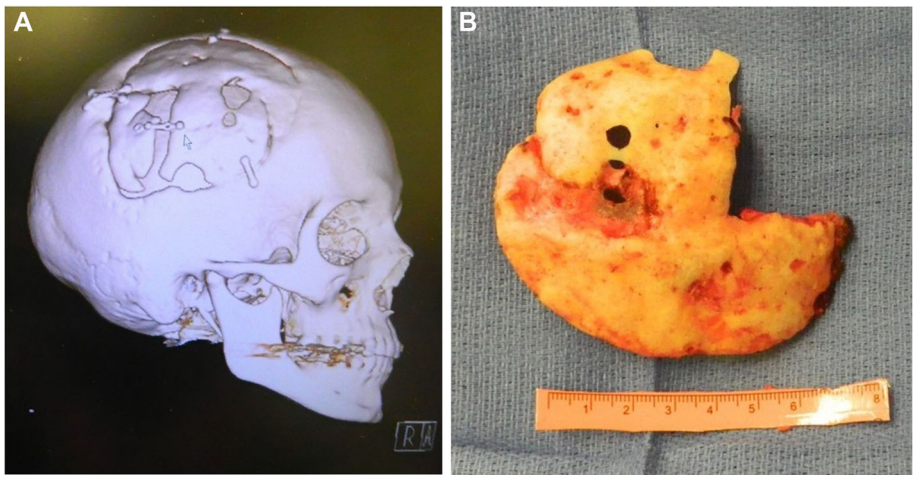

FIGURE 1. **A**, *Preoperative CT scan image of the patient needing RNS neuromodulation therapy with evidence of significant bone resorption and acquired skull deformity.* **B**, *Intraoperative photograph of resorbed, nonviable bone flap removed as a result of repeated surgery for medicine-resistant epilepsy.*

DRE[1]. In certain cases, drug-resistant focal epilepsy can be treated with surgical resection. However, surgical resection for DRE is not always an option, especially in patients whose seizure foci are located near eloquent areas of the brain. Therefore, in drug-resistant partial seizure patients who have failed and/or are not surgical candidates, vagus nerve stimulation[2] and responsive neurostimulation (RNS)[3,4] represent the 2 remaining options with demonstrated efficacy.

The RNS System (NeuroPace Inc, Mountain View, California), approved by the Food and Drug Administration (FDA) in November 2013 after having undergone testing via a multicenter, double-blinded, controlled clinical trial.[5] It was found to have been successful at reducing the frequency of disabling partial seizures and improving quality of life during this investigation.[5] Indications for RNS include patients who have frequent and disabling partial seizures and less than 2 foci of epileptogenesis. The device both detects and responds via a cortical stimulator to the development of seizure foci by detecting electroencephalographic events.[5]

Despite proven efficacy in seizure control, drawbacks include numerous design flaw-related complications such as scalp dehiscence, device exposure, hardware contamination, wound site infection (WSI), contour irregularities, chronic scalp pain, and/or bone flap osteomyelitis (BFO).[6] From a plastic surgery/wound healing perspective, a logical possible etiology of these complications stems from the fact that the device requires nonanatomic placement above the cranium and/or bone flap, which leads to both pressure and localized ischemia to the overlying scalp as well as to bone flap resorption (Figure 1). Furthermore, this type of nonanatomic placement creates irregular cranial contours and visual deformities that are unappealing to both patients and their families. For example, in situations of male balding or short hair, this drawback is amplified and can accompany negative stigmata of one having an easily visible cranial implant and/or neuromodulation device.[7] Another drawback to the RNS device design is the need for repeated exposure of the pulse generator battery changes every 2 to 3 yr. Each surgery further compromises the scalp, and puts the device at risk for bacterial contamination as well as lead damage during exposure. Previous studies have shown that the risk of WSI may approach 1 out of every 10 patients, with an increased infection risk directly correlating to the number of necessary reoperations.[8-10]

With this in mind, our goal was to re-examine the standard method of implanting neuromodulation devices and hypothesized that we could make use of the valuable dead space found inside commonly used customized cranial implants (CCIs)—in an effort to optimize cranial contour, decrease pressure on the deep aspect of the scalp, decrease risk of device lead damage during battery changes, and improve patient satisfaction.[7,11] Planning for this procedure took place at our institution's Multidisciplinary Adult Cranioplasty Center with the goal of providing the inaugural patient with an ideal solution for RNS integration within a customized polymethyl methacrylate (PMMA) implant.[11,12,13] One new implant design improvement we decided to use was that of completely transparent PMMA (Figure 2). To date, all other implants have been manufactured with an opaque material. We felt that by using a clear implant, we could enhance surgeon visibility, avoid electrocorticographic (ECoG) signal interference, and ensure proper lead placement for uninterrupted lead-device connectivity—which are all critical for proper RNS function via wireless communication.

With regard to the relation of implant to device, we felt it important to integrate all components of the device below the

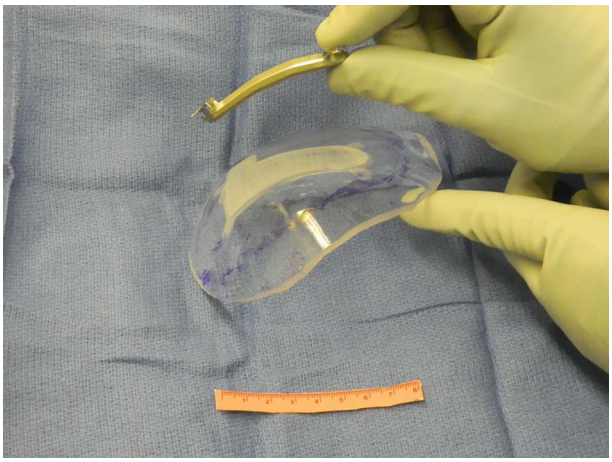

FIGURE 2. *Lateral view of CCI made of PMMA showing parallel curvature relation to the housing unit supplied with the RNS device. One can appreciate here that the dead space within the solid implant provides both an anatomic solution for incorporation (similar curvature) and has adequate dead-space within.*

implant. This was due in part to our experience of finding both lead migration into the scalp and lead extrusion in cases of reoperation of patients with previously placed RNS systems. A new craniofacial implant design described in 2015, by Zhong et al,[14] incorporated strategic bulking for coexisting soft tissue deficiency. Using the newly designed implant, we took advantage of the newfound additional volume to create a space for the RNS device, all the while maintaining the structural integrity important for cerebral protection. We felt it was not only viable for this type of neuromodulation device, but also a suitable vehicle for other implantable neurotechnology currently in development and/or to-be developed.

For cases of patients with bone resorption requiring implantable neurotechnology, placing the technology within and deep to a cranial implant has the ability to replace a nonviable bone flap at the same time of device insertion, prevent an obvious scalp/skull deformity, and treat postneurosurgical temporal hollowing (Figure 1).[7,11,13-15]

METHODS

We report a case involving a patient with DRE evaluated by our institution's multidisciplinary epilepsy team and subsequently offered RNS implantation. The patient is a 54-yr-old female with 4 prior craniotomies from previous seizure surgery and seizure focus monitoring who presented to our clinic with significant bone flap resorption on preoperative computed tomography (CT) scan imaging in the areas of planned RNS insertion. As such, she was offered simultaneous cranioplasty reconstruction with the RNS device fully integrated within a translucent, CCI depicted in Figure 2.

A preoperative virtual plan meeting was conducted with both the functional neurosurgeon (W.S.A.) and the craniofacial plastic surgeon (C.R.G.) to optimize the RNS device placement and implant design. After design and planning, the computer-designed PMMA CCI was sent for processing and fabrication.

The cranial implant was produced from a 3-dimensional printed mold of the patient's skull using an FDA-approved process (Osteosymbionics, Cleveland, Ohio). It was then sent to our medical campus for presterilization as well as implant contour modification specific to the virtual plan approved by the surgical team. This modification process followed the exact size specifications surrounding the stereolithography file matching the neuromodulation device. Three-dimensional orientation/rotation axis of the RNS device in relation to the focus of brain pathology was also decided ahead-of-time during the team's virtual planning session.

Computer-guided laser modification of the implant was performed using a 5-axis robot laser cutter (prior to sterilization),[16] as a way to drastically reduce the prolonged times required to perform intraoperative implant modification. By using a laser cutting technique, this 2-armed robot is able to modify a mirroring cavity with exact dimensions matching the RNS device—which removes the potential to waste up to 80 min for standard hand-carving.[7]

As is the case with many of our CCI-based cranioplasties, this implant was shipped to our hospital's processing center for ethylene oxide sterilization. This process is managed by the hospital. Data collection and review of this case were performed under an active Institutional Review Board (IRB) protocol. The patient was informed preoperatively of the detailed plan and no additional consent was required for the operation since the neuromodulation device and customized cranial implant are both FDA approved; the patient consented to publication of their photograph.

Custom Implant Design Process

The design of the CCI started with CT scan DICOM data of the patient's skull. This data allowed the company to fabricate a 3-dimensional model of the patient's resorbing bone flap and surrounding cranium. Our team also used this process to predefine the extended limits of the planned craniotomy in relation to the epileptic brain foci. The cranial implant, constructed of a fully transparent PMMA material, was fabricated to match the patient's native cranial contour. In order to integrate the RNS device, a laser cutting machine was specifically designed to perform postmanufacture engraving of the implant process via a 5-axis robotic laser machine.[16,17] In this case, the craniofacial plastic surgeon (C.R.G.) only needed to perform minor modification (by hand) with the handheld burr.[7]

Components of the 5-axis Cranial Implant Laser Cutting Robot System

The cranial implant CO_2 laser cutting system is a patent-pending technology developed by an engineering team.[16,17] It has the newfound ability of shaping customized implants with 5 degrees of freedom (DOF). This allows the system to customize the cavity of the skull implant to conform to any type of device such as neural stimulators, hydrocephalus shunt, and/or medicine delivery device. The user interface includes a personal computer, emergency buttons, and various types of switches. The electromechanical hardware includes a 3-axis Cartesian linear stage, a 2-axis rotary table, motor drivers, a circuit board for the 5 moving axes, and the implant mounting plate. The laser components include

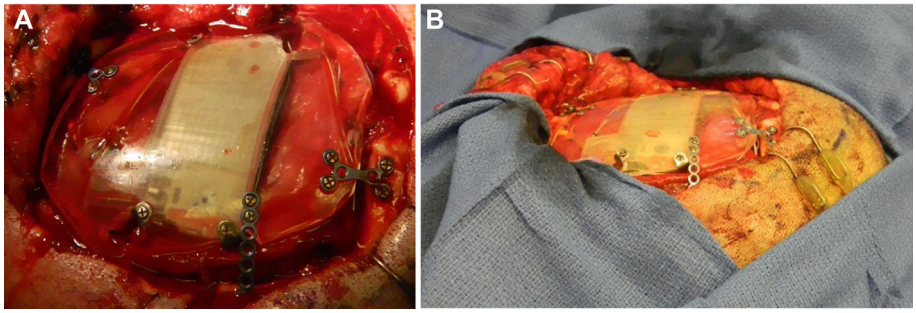

FIGURE 3. **A**, *Photograph shows full integration of the neuromodulation device within the CCI 9.* **B**, *Tangential view demonstrates symmetrical contour in comparison to the patient's nonoperated side thereby preventing any visible deformity.*

a 60W CO_2 sealed laser tube and 3 reflecting mirrors. The electromechanical and laser components are installed within a mobile machine frame built from a combination of aluminum and steel (**Video, Supplemental Digital Content 1**).

The Cartesian linear stage provides 2 DOF planar linear motion for the laser source. An additional translational DOF controls the elevation of the implant mounting plate while the 2 DOF rotary table controls the rotational motion of the implant mounting plate. Each motor is driven by a driver board, which in turn is controlled by a 5-axis breakout board. Placement of the mirror allows the laser beam to be projected onto the rotary table. Linux computer numerical control (CNC), an open-source software that controls CNC machines, is selected for machine control when operating the laser cutting system. The software reads the G-code and instructs the machine to move accordingly by sending control signals from a computer to the controller board in order to drive the motors. Details of the 5-axis cranial implant laser cutting system are described in Liu et al (2017).[16]

Patient Description and Timing of Surgery

Indications for the patient's first craniotomy included a long-standing history of focal partial seizures that began 29 yr prior to this RNS implantation. She had undergone the previous epilepsy surgery with localization of seizure foci and subpial resection of parenchyma. She obtained relief for several years but eventually her seizures recurred. Additional mapping was performed and showed the epilepsy foci to be near the language and motor-swallowing areas. Also, since the patient had undergone previous craniotomies, we used the original incision line to prevent any further vascular compromise to the surrounding scalp. During the surgery, the RNS device was prefixated within the clear implant on a sterile back table. To improve fit of the device, the inner aspect of the implant required slight modification with hand-held burr.[7]

The RNS device was secured to the deep aspect of the cranial implant, and to the surrounding cranium using standard fixation hardware (Figure 3). The implanted leads were then connected to the RNS device and tunneled underneath the clear implant. The translucent medium provided ideal visualization of underlying lead positioning and assisted our efforts in preventing lead misplacement and/or inadvertent device interference.

Prior to scalp closure, the RNS device was interrogated to ensure proper function and to confirm that the clear implant had zero interference related to wireless ECoG transmission. The scalp was then closed tension-free in usual multilayer fashion with closed suction drains.[13] Postoperative CT scan imaging was obtained to confirm proper positioning of both the neuromodulation device and CCI (Figure 4). Epilepsy management following the surgery and device activation was managed by our epilepsy neurology service.

RESULTS

The patient recovered well following the surgery with no complication. Immediately following the surgery, the patient demonstrated a symmetrical contour without any visible deformity (Figure 5). To date, she is completely satisfied and is pleased with her appearance. No complications have been reported with a follow-up of 180 d.

DISCUSSION

To our knowledge, this is the first description of a fully integrated neuromodulation device within a CCI. In this particular situation, given the patient's pre-existing bone flap resorption, there were no other options than to perform a simultaneous cranioplasty. As of the time of this writing, our first patient is very pleased to have had successful skull reconstruction performed at the same time as her neuromodulation placement.

While the CCI was chosen in this specific patient who was found to have a nonviable bone flap, several factors may, in the future, dictate that all implantable neuromodulation devices be performed using a CCI, as the ideal delivery vehicle. Firstly, this method allows for avoidance of visible irregularities associated with the standard practice of "above-skull" placement. Secondly, scalp dehiscence, device extrusion, and lead migration into and through the scalp has been identified at our institution on several occasions with standard above-skull placement technique, all

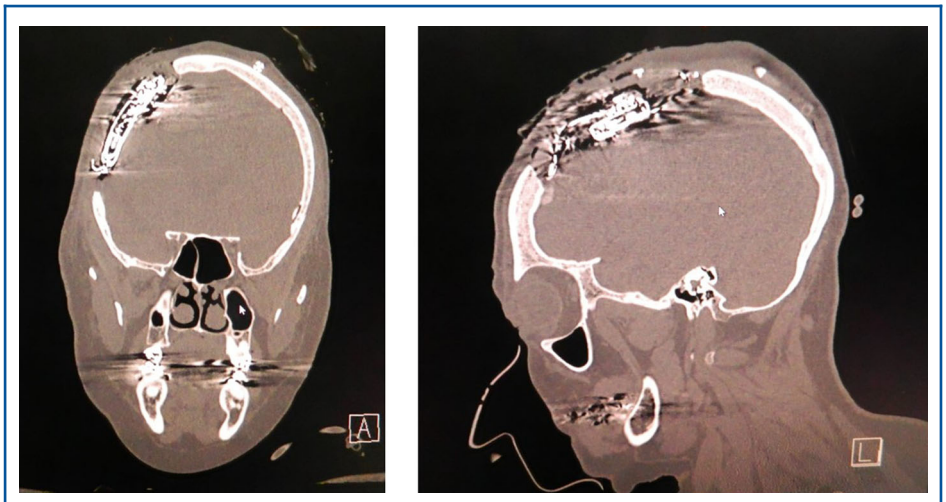

FIGURE 4. *Postoperative coronal (left) and sagittal (right) CT scan images showing the ideal positioning of the neuromodulation device integrated within the CCI.*

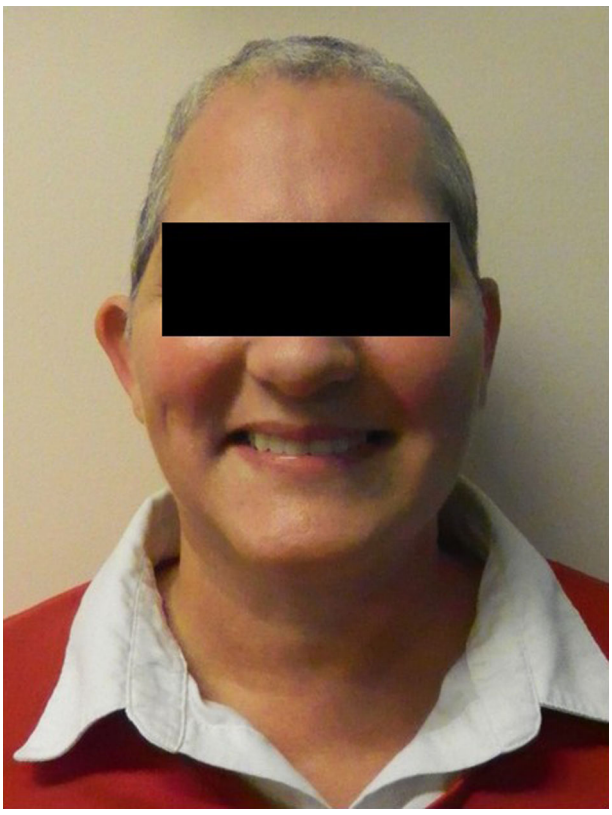

FIGURE 5. *Postoperative frontal view photograph of the patient without any visible contour deformity.*

of which can be avoided by placing these devices deep to a smooth surface implant.[8-10] By attempting more ideal "anatomic positioning" of implantable neurotechnology, we feel this may serve to reduce scalp tension, and prevents undue pressure onto the overlying scalp's sub-dermal plexus, hopefully leading to better wound healing and decreased wound dehiscence—while at the same time, avoiding visible skull deformity occurrence and the associated negative social stigmata and undue apprehension towards having functional neurosurgery.

Future Outlook

We feel that technology-containing cranial implants, such as this, also have the potential to treat brain-related pathologies such as brain tumors, epilepsy, and/or movement disorders.[15,17,18] In parallel, it could also symbolize the ideal delivery vehicle for more futuristic devices such as those designed to provide supra-normal cognition and memory via personalized brain computers, as recently described by Elon Musk.[19]

However, for this type of disruptive innovation to be effective, we as a specialty must identify improved methods of implanting foreign devices within the confines of the scalp and cranium. Although the scalp incision and bone carpentry aspect of implantable technology may seem mundane, it is essential for the long-term safety and success of implantable neurotechnology as it relates to the host environment. For example, numerous studies have shown that WSIs and BFO are significant adverse events associated with "*above*-skull" insertion of various devices regardless of function.[8-10] Therefore, all attempts should be made to decrease stress on the tissues surrounding the implantable neurotechnology.[8]

Other areas for improvement involve decreasing rates of reoperation such as extending device battery life and integrating components capable of transcutaneous wireless (inductive) battery charging technology. In fact, ongoing work by Thimot and Shepard shows great advances in wirelessly powered implants and that electromagnetic energy delivery may help to reduce the size and frequency of battery changes, which is currently required for implantable neurotechnology.[20,21]

Limitations

Of note, there are several drawbacks of this study. First, it is limited to just a single patient. As such, a larger prospective study is undoubtedly warranted. Therefore, we plan to coordinate a prospective, multicenter trial in light of this encouraging result. Secondly, the patient population for whom we sought initially was relatively small—as this option is only offered to those RNS therapy candidates suffering from concomitant bone flap resorption. Third, our institution's annual volume of RNS device insertion is limited to around 3 to 4 cases per year, and lastly, our patient follow-up spans only 6 mo. However, given the significance of this advancement, we felt that it was reasonable to share our early success in hopes of making this novel approach known publicly—mainly for those patients in need of concomitant neuromodulation device placement and cranioplasty. Similarly, we are comfortable reporting the preliminary success keeping in mind our published long-term experience with CCIs made of PMMA (dating back to 2011).[6,11,12-14] Furthermore, this complicated patient had no other alternative other than to have simultaneous skull reconstruction with this much-needed placement of neuromodulation device. As the success of this approach becomes more apparent in the future, it is safe to say that many will consider using this novel approach as a new standard for all types of implantable neurotechnology.[8-10,15,18]

CONCLUSION

The additional surface area provided by solid CCIs with strategic pterional augmentation for coexisting soft tissue deformities like temporal hollowing, may provide optimal and safe integration of various neuromodulation devices.[22] This could one day include medicine-delivery capabilities for brain neoplasms, imaging modules with remote sensing for various brain pathologies, integrated shunts capable of treating hydrocephalus, personalized computers capable of enhancing one's memory or cognition, and/or any combination thereof. Here, we show that a new approach—incorporating a computerized neurostimulation device within the confines of a clear, custom-designed cranial implant—has the distinct advantage of eliminating contour irregularities, protection of the neuromodulation device during battery changes, decreased pain, surgical morbidity, and provide great patient satisfaction.

Disclosures

The Johns Hopkins University and Dr Gordon are entitled to patent-related royalty distributions on technologies described in the article. This arrangement has been reviewed and approved by the University in accordance with its conflict of interest policies.

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COMMENT

Brain-computer interface (BCI) is increasingly considered in movement and cognitive disorders as well as drug resistant focal epilepsy through neuromodulation. BCI devices might be implanted intracranial, inside the calvarium (or an implant), or over the skull underneath the scalp. Complications include infection, pressure sores, wound dehiscence, and device exposure. In this case report the authors of the submission propose housing the neural modulator inside a cranial implant (using laser technology) aimed at preventing some of the above-mentioned complications. The submission is level 5 evidence but is well articulated and written. While I understand the procedure is good if there was an element of bone resorption, potentially the device could be implanted inside the calvarium by a craniotome side cutter.

Bizhan Aarabi
Baltimore, Maryland