Received: 14 December 2021 | Revised: 29 December 2021 | Accepted: 14 January 2022

DOI: 10.1111/aor.14200

PIONEER EDITORIAL

Artificial Organs WILEY

Jose Delgado: A controversial trailblazer in neuromodulation

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Funding information
National Institutes of Health, Grant/Award Number: U01-NS113198

Abstract

Dr. Jose Delgado performed audacious demonstrations utilizing brain stimulation to instantly change behavior in animals. These feats spark ethical debates to this day. However, behind his controversial career is an important legacy of neurological discoveries and technological innovation. Delgado pioneered techniques in causally manipulating brain patterns and behavior with electrical stimulation and developed innovative, closed-loop neural devices. His inventive devices and techniques were ahead of his time and remain relevant to the field of neuromodulation today.

In 1963, Dr. Jose M. Delgado stepped into the bullring on a ranch in Cordoba, Spain. He taunted the bull in the ring so it would charge at him. Then, he calmly took a couple of steps back, and, as the bull nearly arrived, he pressed a button on the metal box in hand, and watched as the charging bull came to an abrupt stop only feet from him (Figure 1). This audacious demonstration of using electrical brain stimulation to control behavior captured the attention and imagination of the public.[1] It sparked fierce ethical debates while fueling an already controversial reputation surrounding Dr. Delgado. However, behind this attention-grabbing feat lay a career of neurological discoveries and technological innovation that were ahead of their time and remain relevant to this day.[2]

In recent decades, researchers and clinicians have utilized brain stimulation for a wide variety of purposes. Brain stimulation can be a mapping and research tool to better understand the networks involved in different behaviors. Additionally, direct brain stimulation holds enormous potential as a treatment for a range of neurological and psychiatric disorders. Deep brain stimulation first showed reliable clinical results in the treatment of Parkinson's disease and since then researchers and clinicians have rapidly developed new stimulation protocols and implantable brain stimulators that will provide clinicians with the means to treat a range of neurological, neuropsychiatric, and cognitive disorders.[3,4] Delgado's work provided the basis for these contemporary advances in brain stimulation, and thus understanding his career is useful for understanding the origin of current neuromodulation devices and their potential future paths.

Delgado was born in Ronda, Spain in 1915, and he initially pursued a medical degree with the intention of becoming an eye doctor. While he was in medical school, the Spanish Civil War began, and Delgado enlisted as a member of the medical corp. After the war, Delgado resumed

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medical school, but after learning of Ramon y Cajal's work in neurophysiology[5] and Walter Rudolf Hess's work in brain stimulation,[6] Delgado dedicated the rest of his career to learning about the brain. He completed his medical degree and doctorate at the University of Madrid and began performing brain stimulation experiments in animals. During a fellowship at Yale School of Medicine in the early 1950s, Delgado published early papers on a series of experiments where he optimized the implantation of electrodes into the brains of mice, cats, dogs, and monkeys.[7] The technique he describes with implanting needle electrodes for deep brain recording and plate electrodes for surface recordings allowed for between 14 and 40 individual direct recording sites from the animal brain. He quickly expanded upon this early experiment and in the same year published an article describing a technique for brain implantation in humans.[8] One of Delgado's hopes for these implants was to develop methods for the treatment of epilepsy and neuropsychiatric disorders.[1] Rather than the then-standard approach of lobotomizing and removing entire brain regions, Delgado hoped to use specific localized stimulation to stop a seizure or treat another neurological condition, which has recently become the subject of intense interest.[3] Over the course of his career, Delgado began to expand his vision of the possible uses of brain stimulation beyond the treatment of neurological disorders. He even began contemplating the use of stimulation to provide functional improvements to healthy humans with the hope of creating a more civilized society.[9]

Working towards his vision of harnessing brain stimulation to implement societal improvements, Delgado made substantial advances in two critical areas that remain relevant to neuromodulation to this day. First, Delgado significantly advanced brain implantation technology by exploring closed-loop brain stimulation designs and allowing for freedom of movement with long-term, wireless implantable devices. Namely, Delgado invented the "stimoceiver," which was a wireless device that used bidirectional radio waves to transmit brain recording data and stimulation pulses between the implanted device and the device used by the physician or researcher[10] (Figure 2). One of his first studies using these devices was

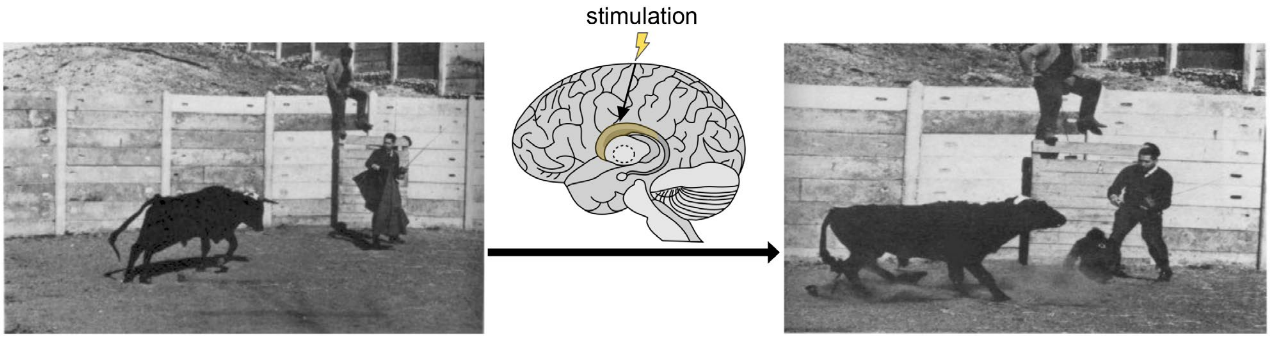

FIGURE 1 Jose Delgado stopped a charging bull with brain stimulation. As the bull charged towards him, Delgado wirelessly transmitted a signal to deliver stimulation to the implanted stimoceiver in the bull's caudate nucleus, causing the bull to immediately come to a stop. Adapted from Ref. [9] [Color figure can be viewed at wileyonlinelibrary.com]

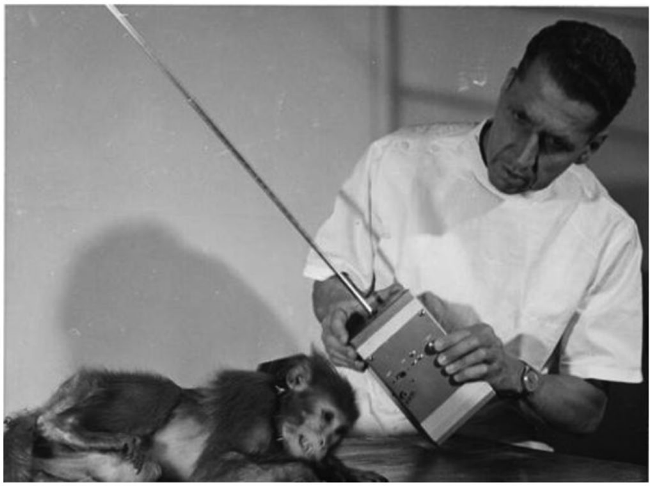

FIGURE 2 Delgado testing an implanted wireless stimulation device in the brain of a macaque with a separate controller device. Adapted from Ref. [41]

his famous bull experiment.[9] The other critical area of research involved experiments in animals by which Delgado uncovered many new findings about the role of specific brain regions in different types of behavior. These fundamental discoveries directly led to the spectacular feat of stopping the charging bull in its tracks. In pursuit of his end goal of using neurological implants to improve mankind, Delgado sought the means to improve motility or decrease aggression, and in the process uncovered many fundamental links between specific brain regions and behavior. Despite Delgado's fantastical vision and unconventional demonstrations, his true legacy lies in the relevance of his basic human neuroscience findings and innovative device design that remain relevant today for designing brain stimulation therapies.

1 | EARLY DISCOVERIES WITH PSYCHIATRIC PATIENTS

Delgado began his research career in Spain working primarily in primates exploring techniques of selective ablation of specific brain regions. Upon starting a fellowship in physiology, he began research in schizophrenic patients. This work involved implanting needle and scalp electrodes to various areas of the brain in an attempt to undergo focal electrical interruption of brain activity rather than conducting an ablation or lobotomy.[8] Viewing brain ablation as a severe form of treatment and pharmacological treatments as too general, Delgado began exploring brain modulation techniques of electrical and chemical stimulation of specific locations in the brain.

The next study published by Delgado in humans examined long-term dynamics of brain activity following intracranial stimulation using needle and scalp electrodes. Following electrical stimulation, Delgado found that in one schizophrenic patient, brain activity did not normalize until 45 minutes after scalp stimulation.[11] Much of his early work in humans was an attempt to effectively alleviate symptoms with the delivery of electrical current directly to brain tissue.[12] He primarily treated schizophrenic, epileptic, and intractable pain patients due to the invasive surgical techniques that were used to observe and treat these patients. Delgado followed these initial studies with more exploratory work to understand how stimulation on one side of the brain would affect neural activity in the ipsilateral and contralateral hemispheres.[13] Following electrical stimulation deep in the frontal lobe, he observed prolonged changes in brain activity in superficial areas on the same side of the brain as the stimulation. However, electrical activity recorded from the opposite side of the brain was less altered following stimulation (Figure 3). These early studies were some of the first attempts to understand the electrophysiological effects of direct brain stimulation across the brain.

Throughout his career, Delgado showed widely varying behavioral results of brain stimulation in improving patient symptoms and even stated observing unpredictable outcomes in the same patient. This unpredictability in brain stimulation effects remains a challenge in neuromodulation even today.[14–16] Delgado's work in humans was specifically aimed at therapeutic goals whereby electrodes were typically implanted for a couple of days, stimulation was delivered to specific brain regions, and the patients' neural activity and behavior were observed following stimulation. An example of the type of unpredictability he observed came from one patient who felt jaw and tongue sensations following a stimulation event in the left temporal lobe and experienced ideations leading to a lapse in memory or abrupt, out-of-context statements when stimulated in the left frontal lobe.[17] However, his work in humans did produce additional proof that epileptic patients have a central focus of an epileptic episode.[18] Delgado ultimately reported that the most reliable therapeutic outcome he observed in patients was alleviating chronic pain. After much of

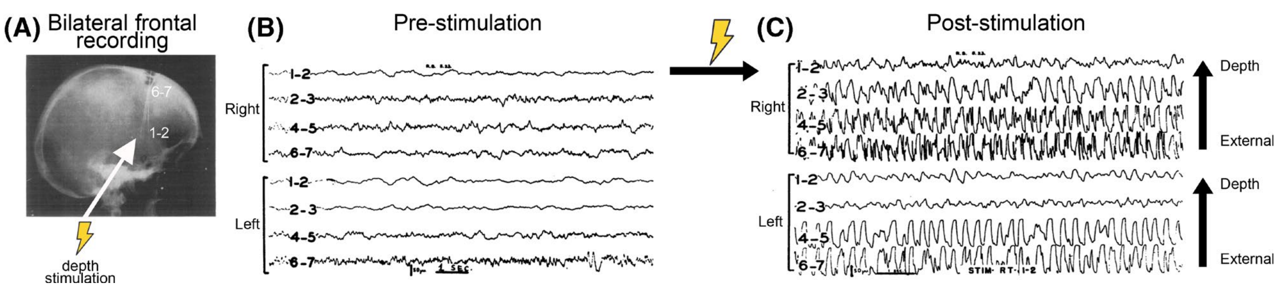

FIGURE 3 Example of the electrophysiological effects of depth stimulation in patient. (A) Diagram of a patient implanted with needle electrodes in their frontal lobe. Stimulation was applied to the deepest contact (1–2) in the right frontal lobe. Adapted from Ref. [12]. (B) Intracranial EEG recordings made directly from depth probes in frontal lobe with electrical activity measured prior to stimulation from both hemispheres. (C) Intracranial EEG recordings following stimulation. Adapted from Ref. [13] [Color figure can be viewed at wileyonlinelibrary.com]

this work, Delgado began to shift his focus to animals where he could more directly examine consistent behavioral changes by stimulating various brain regions. Occasionally, he would return to human subjects to test his latest technologies, which he believed could impact the brain stimulation field.[19]

2 | BEHAVIORAL REGULATION IN ANIMALS

Throughout Delgado's research career, he continuously developed and tested his technologies in animals. His most common procedure was to surgically implant a multi-lead needle electrode into deep brain tissue. This was likely the most reliable and efficient recording and stimulation method, in comparison to his wireless stimoceiver device (see details below), which he used in demonstrations. The goal of the animal studies was to determine how to control various behaviors which could be translated into human studies with the goal of treating mental illness and aggression. He asked his students "What sort of humans would we like, ideally, to construct?... not only our cities are very badly planned; we as human beings are, too. The results in both cases are disastrous".[1] This quote perfectly portrays what motivated his research in animals. By understanding the behavioral effects of stimulating specific brain region, he believed that knowledge could be extended to humans for the improvement of mankind. To achieve this goal, Delgado ran many animal experiments to more fully understand how brain stimulation could drive behavioral changes (Figure 4).

His early published work compared techniques to implant electrodes in the brains of animals. In one early study, he described the implantation in a cat and the behavioral motor response that occurred following stimulation of a frontal lobe gyrus[7] (Figure 4). In this study, even though a motor response was elicited, Delgado was unable to observe a clear emotional response. This may have motivated his subsequent focus on non-human primates, where emotional responses can better be interpreted from facial expressions, in many following studies because he wanted to modulate higher cognitive processes. As his ideas developed, his methodologies advanced. In subsequent experiments, Delgado examined primate responses to repeated stimulation, and in a parallel study, he examined prolonged stimulation to observe how long the stimulated response could last following cessation of stimulation.[20,21] To run this experiment, he created a transistor timing stimulation collar that would deliver one pulse of electrical current each minute for 1 h. This study demonstrated the long-term robustness of stimulation because throughout this period, for each stimulation pulse, the monkey stopped whatever else it was doing, and opened its mouth and scratched its cheek. Delgado followed this study by then observing how long altered brain activity would last following prolonged stimulation over days. To do this, he stimulated the thalamus and hypothalamus of a monkey for 15 days and observed brain wave patterns every few days. He found that this pattern of stimulation increased the number of slow waves and that this pattern was maintained not only throughout the 15 days of stimulation but also for 5 days following stimulation cessation.[21] The recordings were taken an hour before stimulation each day and thalamus recording, specifically, showed the greatest difference 1 h post-stimulation (Figure 5A). However, both the thalamus and hypothalamus had more slow-wave patterns in the prolonged stimulation days at day 8 and day 15 while maintaining this pattern through 5 days post-stimulation (Figure 5B). He then observed the behavioral patterns of monkeys following prolonged stimulation and did not find any fatigue effects; however, stimulation of the right putamen consistently led to a right head turn (Figure 5C).

These experiments allowed Delgado to further understand the effects of brain stimulation and the best approaches to elicit desired behavioral outcomes. He then examined whether brain stimulation held the potential to decrease aggression in an animal model. His first experiments were based around the social interactions of four monkeys where two had implanted needle electrodes. Delgado implanted electrodes in the brain of the alpha primate of the group, which was one of the monkeys that would usually show aggression to the others. Following stimulation of multiple regions including the caudate nucleus and thalamus, Delgado observed decreased aggression and hand-biting behavior, which led to a change in the power structure of the group.[22] This work directly led to his famous bull experiment, and he later found that repeated stimulation caused even further decreases in the bull's aggression.[9] While the bull demonstration took the world by storm, it is important not to forget the other important preceding and following studies that together comprised a highly impactful line of work.

Delgado's most noteworthy brain stimulation studies in animals followed the bull experiment, allowed him to advance his technology and understand more about behavioral responses to stimulation. He began by stimulating different brain regions at different times in the caudate nucleus of monkeys.[23] The goal was to understand how specific brain areas differed from one another even if they were close in proximity. In line with prior studies conducted by Penfield and colleagues,[24] he found that stimulating adjacent regions could lead to widely varying responses, with some sites causing partial inhibition of behaviors whereas others nearby would lead to total

	1952	1959	1963			1966	1971
Significance	First published study	Repeated stimulation evokes similar response	First decreased aggression animal study	Famous bull study	Stimulate different brain regions at different times in same monkey	Behavior observed before, during, and after stimulation	Repeated stimulation evokes same response
Stimulation Area	Sulcus cruciatus (cat)	Left rhinal fissure (monkey)	Caudate nucleus head, thalamus, central gray, reticular substance (monkey)	Caudate nucleus (bull)	Rostral caudate nucleus (monkey)	Forel's field (monkey)	Amygdala (monkey)
Stimulation Device	Implanted needle electrodes	Transistor timing stimulation collar with needle electrodes	Multi-lead electrodes	Stimoceiver	Implanted needle electrodes	Stimoceiver	Multi-lead electrodes
Behavioral Response	Motor response without emotional disturbance	Ceased current task, opened mouth, scratched cheek	Decreased aggression, biting hand	Stop charging, turn to one side, decrease aggression	Cessation of eating	During stimulation: stand on hind legs After stimulation: take aggressive stance	Ipsilateral retraction of mouth
Publication	Delgado, The Yale journal of biology and medicine, *1952.*	Delgado, *Journal of neurophysiology,* 1959.	Delgado, *Science*, 1963.	Delgado, *World Bank Publications*, 1969.	Rubinstein and Delgado, *American Journal of Physiology-Legacy Content*, 1963.	Delgado, *Integrative and Comparative Biology*, 1966.	Delgado, Rivera, and Mir, *Brain Research*, 1971.

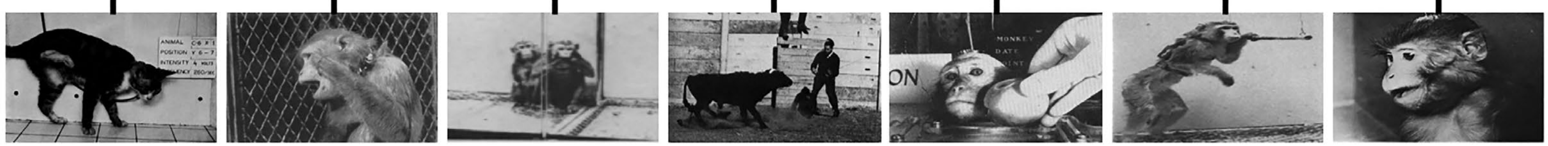

FIGURE 4 Timeline of Jose Delgado's stimulation experiments in animals. His initial experiments led to his most famous bull study where he was able to stop a charging bull. He then continued to determine how electrical stimulation of other brain regions would lead to behavioral changes in animals. Adapted from Refs.[7,9,20–23,42]

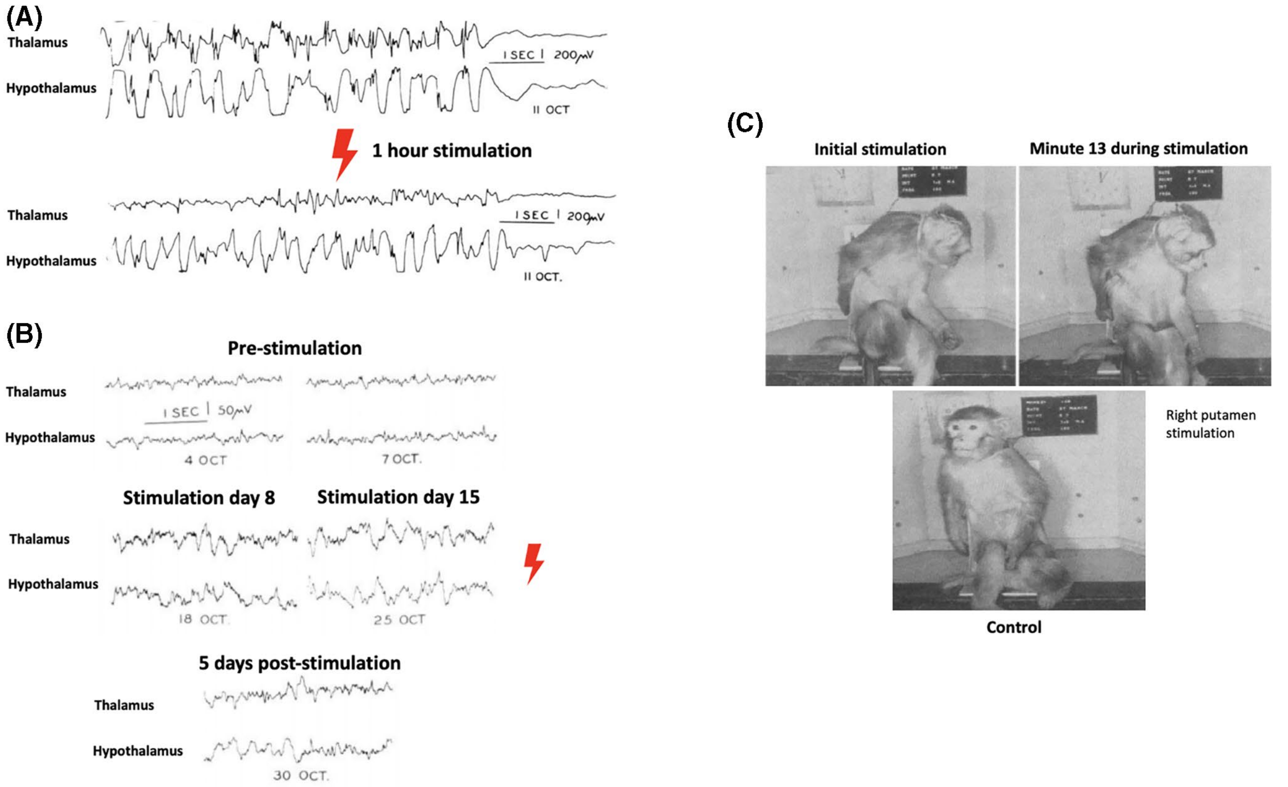

FIGURE 5 Direct modulation of motor behavior with stimulation (A) example of intracranially recorded electrical activity before and after one hour of stimulation. (B) Example of raw traces examining activity over 15 days when repeated stimulation was delivered. Neural activity was also recorded five days following the end of the 15-day repeated stimulation protocol. (C) Prolonged stimulation of putamen area elicited distinct motor response during stimulation in comparison to unstimulated control animal. Adapted from Ref. [21] [Color figure can be viewed at wileyonlinelibrary.com]

inhibition. One of his later studies in animals showed the ability of technological advancements to improve his earlier experiments. Delgado implanted electrodes that could record from up to 28 distinct locations with at least 6 electrodes (per hemisphere) in the amygdala and hippocampus of 11 monkeys. He delivered a variety of repeated stimulation patterns to specific amygdala and limbic locations.[20] Following stimulation in different targets, he observed changes in neuronal activity as well as a range of behaviors from changes in mobility, sensory reactivity, aggression, and even spontaneous smiling. All of these behavioral studies were geared towards understanding how brain stimulation could alter human behavior and lead to more effective treatments for mental illnesses and the suppression of violent and aggressive behaviors.

3 | DEVELOPMENT OF NOVEL BRAIN INTERFACING DEVICES

In addition to making fundamental discoveries about the effects of stimulation and function of brain regions, Delgado excelled as an inventor of numerous innovative stimulation and drug delivery devices. These devices directly interfaced with brain tissue. Delgado conducted many of his studies in animals, as well as a few in psychiatric patients, using a "stimoceiver." The stimoceiver, his most notable device, consisted of a wireless FM radio device that transmitted EEG (electroencephalography) signals recorded intracranially from 14 to 28 electrodes on the surface of the cortex to a separate controller device outside the brain. By also receiving wireless signals, the implanted device was capable of receiving triggers for when to deliver electrical stimulation to the area of the cortex where the device was implanted.

The features of this device presented three major advantages to scientists and clinicians that have a legacy in neurotechnologies. Firstly, the wireless abilities of the stimoceiver allowed patients and animals to move freely while signals were being recorded. In Delgado's early studies, he had observed that the bulky, wired devices required to record from patients often restricted their movement. Thus, Delgado designed the stimoceiver so it was lightweight and portable, allowing him to measure brain signals during a wide range of behaviors with unrestricted movement. This remains a relevant consideration even today as intracranial EEG is typically recorded from patients with drug-resistant epilepsy who participate in research by performing virtual tasks using a laptop. Even with the use of advanced computer graphics and virtual reality for studying neural correlates of complex behavior, virtual tasks lack the sensory and proprioceptive information of real-world tasks.[25] Few studies have explored the use of programmable and implantable devices that allow patients to move freely while simultaneously recording and stimulating intracranially.[26,27] Thus given these challenges, Delgado's advances remain highly relevant. Wireless recording and stimulation devices remain at the forefront of this field with much to be optimized for research purposes in wireless communication between components and efficiency in closed-loop stimulation.

Secondly, Delgado demonstrated with the stimoceiver the potential for long-term implantation of recording and stimulation devices. While Delgado only conducted studies with the stimoceiver implanted in humans for a few days at a time, his work in animals showed that these devices could remain safely implanted for years.[1] In fact, Delgado once stated, "There are chimps in our laboratory who have had up to 100 contacts implanted for more than four years; there seems to be no limit to how long they may safely be left in". In recent years, researchers have focused on the development of long-term implants for the purpose of treating patients with intractable neurological conditions. The most commonly used long-term neural interface today is the cochlear implant that transmits auditory information directly to patients' auditory nerves. Additionally, chronically implantable devices in the brain have been used to enable paralyzed patients to move external limbs and utilize thought-to-text communication.[28] With the expansion of the potential of long-term neuromodulation to range of neurological conditions, patients can now be implanted with long-term deep brain stimulation devices for the treatment of Parkinson's Disease, epilepsy, essential tremor, dystonia, chronic pain, or obsessive-compulsive disorder.[29,30]

The third important feature of Delgado's stimoceiver paved the way for modern-day developments in closed-loop brain stimulation. Even though Delgado's stimoceiver was operated manually via a separate controller device, the two-way nature of communication between the stimoceiver and controller was a necessary first step in closed-loop neurostimulation. The transmission of EEG signals back to the controller device via wireless radio waves meant that Delgado could observe the fluctuations in an animal's brain activity almost in real-time and make a decision about when to stimulate. In particular, Delgado dramatically advanced closed-loop stimulation in one particular experiment where he implanted a stimoceiver in the amygdala of a chimpanzee. He programmed the device to deliver stimulation specifically when spindles were detected in the amygdala, which elicited an aversive behavioral response and further decreased the prevalence of spindles with repeated stimulation.[31] While this process was not systematic at the time, it demonstrated a critical concept whereby stimulation is delivered at specific moments relevant to ongoing brain activity. Closed-loop technology remains an important area of neuromodulation today as researchers seek to determine the relevant neural biomarkers that would signal when stimulation is required as well as learn how to stimulate the brain to bring about the desired outcomes for a wide range of neurological and cognitive disorders.[29,30,32]

In addition to Delgado's work in electrical stimulation, he also designed two implantable devices that could be used to deliver pharmaceutical compounds directly to brain tissue (Figure 6, left). One device, termed the "chemitrode," consisted of an array of electrical contacts and a cannula implanted in the brain with a portion on the surface of the skull. This allowed for two-way passage of chemical and electrical information with a targeted brain area.[33,34] Delgado further improved upon this design in a second device, termed the "dialytrode." Similar to the chemitrode, the dialytrode could be used for perfusing solutions to specific brain regions while also recording electrical activity with the potential to stimulate the brain. Unlike the chemitrode, this device contained a porous membrane at the site of drug delivery that allowed for the delivery of fluids while blocking the passage of microorganisms and cells.[35,36] Delgado tested this device in both monkeys and cats, and later research groups further improved upon the design.[37,38] Today, researchers continue to explore the efficacy of closed-loop implantable neural devices that are capable of recording while delivering electrical stimulation and perfusing drugs[39] (Figure 6, right).

Delgado also pioneered a form of non-invasive brain stimulation decades prior to others' exploration of these methods. Delgado experimented with an electromagnetic helmet where a monkey's brain was placed in the middle of a series of coils, which were used to deliver a field of magnetic stimulation throughout the whole area.[9] This design opened the doors to non-invasive brain stimulation techniques, in particular modern-day transcranial magnetic stimulation (TMS), a commonly used neuromodulation technique in both research and medicine. A number of modern-day devices, particularly long-term brain implants, build upon the concepts and designs pioneered in Delgado's experimental devices.[19]

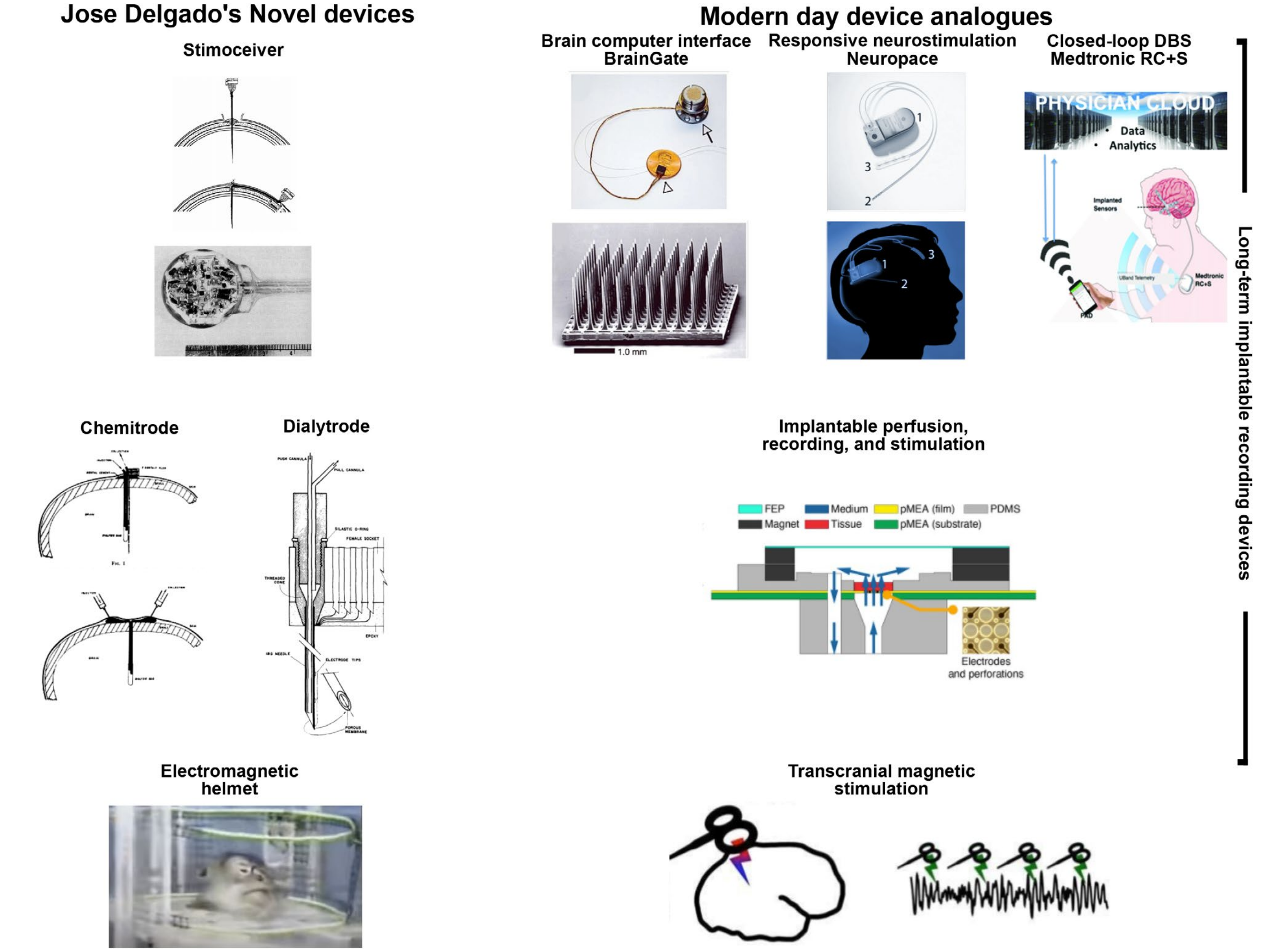

FIGURE 6 Notable devices engineered by Jose Delgado and their modern day analogues. Left: Four most notable devices invented by Jose Delgado. Adapted from Refs. [9,35,36] Right: Modern day analogues, including four notable long-term implantable recording devices. Chronic implant BCI for motor control of neuroprosthesis found in BrainGate device,[28] recording and responsive neurostimulation found in NeuroPace device,[29] and chronic implant from Medtronic for sensing and stimulation,[43,44] an implantable device that perfuses drugs in a closed-loop manner,[39] and transcranial magnetic stimulation[45] [Color figure can be viewed at wileyonlinelibrary.com]

4 | MODERN-DAY LEGACY

The impact of Delgado's innovation and basic neuroscience discoveries were often overshadowed by ethical concerns regarding his idealizations of creating a more civilized society using brain stimulation. Delgado discussed his goal of using brain stimulation to eliminate aggression, criminal tendencies, and mental illnesses in his book *Physical Control of the Mind: Toward a Psychocivilized Society*.[9] His vision, which remains a futuristic possibility to this day, was met with fierce concerns over the possible abuses of neurotechnologies in manipulating identity and free will. Much like his inventions, his philosophical ideas opened the doors to discussions that continue today on the ethics of neural devices.[40] Seeing the potential in stimulation to go beyond lobotomies and pharmacological interventions, Delgado revolutionized stimulation experiments by systematically and causally linking specific brain regions with behavior. This provided basic information about the brain and neuromodulation that are still in use today. In particular, the fundamental concepts in his innovations and techniques are echoed throughout stimulation and long-term recording devices designed for patients in the modern era. Decades later, we can now connect many of the recent advances in neuromodulation research and therapeutics to the original findings and inventions of Dr. Jose Delgado.

ACKNOWLEDGMENT

JJ acknowledges support from National Institutes of Health grant U01-NS113198 and the National Science Foundation.

AUTHOR CONTRIBUTIONS

N.D. and U.M. participated in researching prior works and interpretation. All authors contributed to writing and editing.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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How to cite this article: Lorusso ND, Mohan UR, Jacobs J. (2022). Jose Delgado: A controversial trailblazer in neuromodulation. Artif. Organs. 2022;46:531–540. https://doi.org/10.1111/aor.14200