



Chronic subdural cortical stimulation for phantom limb pain: report of a series of two cases

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Abstract

Phantom limb pain is a complex, incompletely understood pain syndrome that is characterized by chronic painful paresthesias in a previous amputated body part. Limited treatment modalities exist that provide meaningful relief, including pharmacological treatments and spinal cord stimulation that are rarely successful for refractory cases. Here, we describe our two-patient cohort with recalcitrant upper extremity phantom limb pain treated with chronic subdural cortical stimulation. The patient with evidence of cortical reorganization and almost 60 years of debilitating phantom limb pain experienced sustained analgesic relief at a follow-up period of 6 months. The second patient became tolerant to the stimulation and his pain returned to baseline at a 1-month follow-up. Our unique case series report adds to the growing body of literature suggesting critical appraisal before widespread implementation of cortical stimulation for phantom limb pain can be considered.

Keywords Motor cortex stimulation · Cortical stimulation · Phantom limb pain · Intractable pain · Surgical treatment of pain

Abbreviations

CT	Computed tomography
DBS	Deep brain stimulation
DREZ	Dorsal root entry zone
GABA	Gamma-aminobutyric acid
ICU	Intensive care unit
IASP	International Association for the Study of Pain
MRI	Magnetic resonance imaging
PNS	Peripheral nerve stimulation
PLP	Phantom limb pain
rTMS	Repetitive transcranial magnetic stimulation
SCS	Spinal cord stimulation
VNRS	Verbal numerical rating scale

Introduction

According to the latest definition by the International Association for the Study of Pain (IASP), phantom limb pain is pain perceived as arising from the missing limb. Phantom limb pain is a type of neuropathic pain that most commonly includes tingling, throbbing, piercing, and pins and needles sensations [11]. In 2005, an estimated 1.6 million people in the USA suffered from limb loss with the prevalence expected to double by 2050 [52]. Phantom limb pain occurs in approximately 70% of amputees [1] and in a national survey by Ephraim et al., the number of patients with severe phantom limb pain was 39% [11]. Severe phantom limb pain can lead to suicidality, functional disability, and opioid dependence [11].

Due to scarcity of evidence to guide treatment of phantom limb pain, guidelines for other neuropathic pain conditions are likely the most helpful. First-line therapies include anticonvulsant drugs, antidepressants, and conventional analgesics [2, 13, 30]. However, pharmacotherapy is often ineffective with neuropathic pain response rates of only 40–60% [7, 8, 26]. For severe pharmacologically refractory cases of neuropathic pain, neuromodulatory methods using electrical stimulation provide an alternative approach and have included peripheral

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nerve stimulation (PNS), spinal cord stimulation (SCS), deep brain stimulation (DBS), and cortical stimulation [10].

Cortical stimulation involves permanently implanted electrodes to provide chronic electrical stimulation from either the epidural [3, 9, 18, 29, 32, 36, 37] or subdural space [6, 12, 39]. The indications for cortical stimulation have significantly expanded since its original description pain in the early 1990s by Tsubokawa et al. for central post-stroke pain [48, 49]. Since then, cortical stimulation has been tried for treatment of neuropathic pain, including facial pain [16, 20–23, 31, 41, 45], brachial plexus avulsion [24], post-herpetic neuralgia [50], phantom limb pain [38, 40, 41], complex regional pain syndrome [14, 27, 43], traumatic brain [42], and spinal cord injury [35, 46].

Little is known about the overall efficacy in individual neuropathic pain disorders due to small and heterogeneous patient cohorts with variable follow-up. A combined success rate of cortical stimulation for all chronic pain disorders is reported as 65% from meta-analyses [25, 33]. Despite a long history of cortical stimulation for treating chronic pain, there is no consensus regarding a criteria for patient selection, a surgical technique, stimulation parameters, or electrode implantation site (epidural vs subdural) [19]. Here, we describe our experience with our two initial cases of upper extremity phantom limb pain treated with chronic subdural cortical stimulation.

Methods

This retrospective two-patient case series study was approved by the Institutional Review Board (IRB) of our institution (ID # 18-006449). Following our practice of subdural cortical stimulation [47], the patients underwent a two-step procedure that involved implantation of a trial electrode array followed by permanent spinal leads and an internalized pulse generator (Fig. 1).

Patient selection Between January 2016 and June 2018, two patients were referred directly to our institution to be considered for cortical stimulation after multiple other treatment

approaches were unsuccessful in treating their phantom limb pain (Table 1). At our institution, these patients were further screened and evaluated via in-person consultations by board-certified neurologists and neurosurgeons to ensure they were appropriate candidates for further consideration—including accurate diagnosis and no confounding or surgically—excluding factors. Then, an institutional neuromodulation committee consisting of neurosurgery, neurology, psychiatry, and radiology members deemed these patients as likely-to-benefit from chronic subdural cortical stimulation. The selection criteria required that patients with chronic and severe pain have exhausted all other conventional and likely-to-help interventions. Informed consent, including the discussion of off-label use of FDA approved devices for cortical stimulation, was obtained from both patients. Prior to electrode array implantation, these patients were further evaluated by a board-certified psychiatrist to establish realistic expectations, assess emotional stability, and ensure that no untreated confounding psychiatric comorbidities existed.

Operative procedure The motor cortical stimulation procedure was performed under general anesthesia as a planned two-staged operation. Patients underwent brain magnetic resonance imaging (MRI) with three-dimensional surface volume reconstruction, combined with functional MRI, to improve target identification and surgical planning. Using image fusion and neuro-navigation (StealthStation, Medtronic, Minneapolis, MN), a focused, standard frontotemporal craniotomy was performed. The dura was reflected in standard fashion, with care taken not to violate the subarachnoid space (Fig. 2b). Numerous tack holes and stitches were placed around the circumference of the craniotomy (Fig. 2c). Patient 1 was implanted with subdural 6 × 6 cm, 36 plate electrode system (Ad-Tech Medical Instrument Corporation, Racine, WI) over the right perirolandic frontal cortex, ensuring the motor cortex and premotor cortex regions were covered by the electrode array placement (Fig. 2c–d). The electrode array was secured in place with silk sutures to the dura (arrows in Fig. 2c), and the bone flap replaced after meticulous hemostasis was obtained. A ground electrode was placed on the temporalis muscle. All electrodes were secured to the

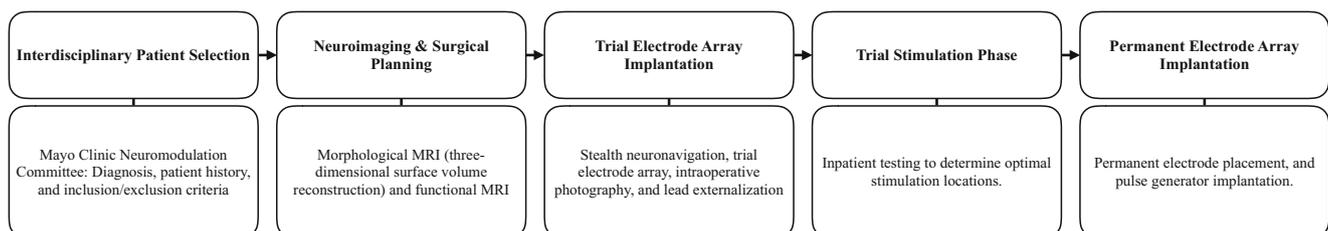


Fig. 1 Treatment algorithm of subdural electrode implantation. Two-step procedure using morphological (three-dimensional surface volume reconstruction) and functional magnetic resonance imaging with image fusion for surgical planning and neuro-navigation guidance for accurate

targeting. Trial electrode array exploration and trial stimulation are followed by permanent implantation of two adjoining spinal leads and internalized pulse generator

Table 1 Characteristics of subjects

Patient no.	Sex/age (year)	Pain distribution	Diagnosis	Triggers	Pain duration (year)	Medications at presentation	Previous failed procedures
1	Male/84	Primarily missing left 4th digit and stump, occasionally radiating to the left arm	PLP after traumatic fourth digit amputation	Left hand movement; non-painful stimuli to the left arm, left side of his face and foot	57	Amitriptyline 50 mg Gabapentin 3600 mg	Stump removal and hand neuroma excision
2	Male/45	Distributed throughout the missing left arm	PLP after traumatic left arm amputation	None identified	6	Gabapentin 600 mg Amitriptyline 10 mg Venlafaxine 225 mg Mirtazapine 30 mg	Dorsal root entry zone surgery

PLP, phantom limb pain

calvarium with a titanium plate and tunneled superomedially and externalized at the midline through the scalp. The operative site was closed in anatomic layers, and a post-operative head computed tomography (CT) was obtained to evaluate for no acute intracranial hemorrhage. Patient 2 underwent an identical operation procedure and stimulation testing, with a modification of using a 6 × 8 cm, 48 plate electrode array system (Ad-Tech Medical Instrument Corporation, Racine, WI) (Fig. 4a).

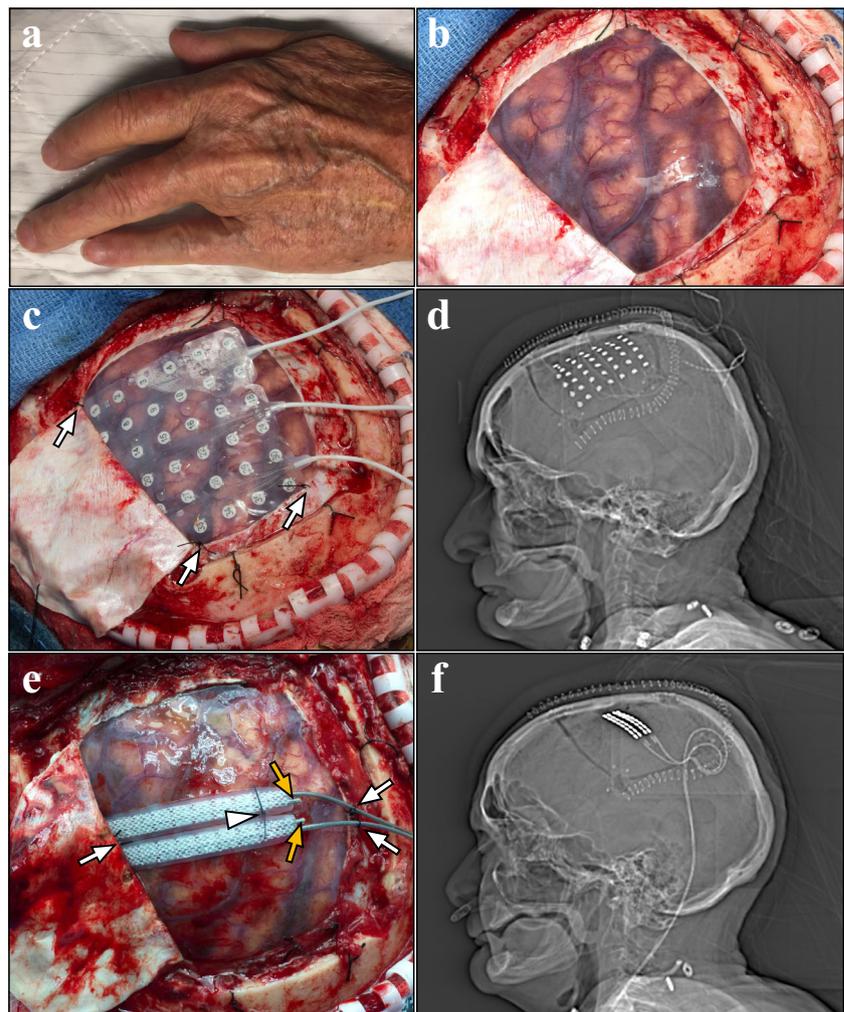
After the stimulation, trials were complete or acute hemorrhage in the case of patient 2, both patients underwent surgical replacements with permanent electric arrays consisting of two 2 × 8 spinal leads (Medtronic Specify SureScan Leads 977c265, Medtronic USA Inc.) adjoined by a silk suture (white arrowhead in Fig. 2e). The two unnecessary middle leads of the permanent electrode array were cut (yellow arrows in Fig. 2e). An implantable pulse generator (Medtronic-Neuro Stimulator 97,702, Medtronic USA Inc.) was placed in the ipsilateral infraclavicular region. Intraoperative impedance testing was used to confirm all contacts to be satisfactory and hardware was tested for functionality. The surgical sites were then closed again in anatomic fashion and a post-operative head CT was again utilized to confirm electrode placement and evaluate for hemorrhage (Fig. 2f).

Stimulation trials Patients were maintained in the ICU for the duration of monitoring and trial electrode stimulations. Verbal numerical rating scale (VNRS) scores were surveyed hourly during wake hours, and after each significant parameter change. Patients were maintained on seizure prophylaxis with levetiracetam throughout the post-operative course. No clinical seizures were observed for either patient during trial stimulations. Each column of the implanted subdural electrode array was tested with cathodal stimulation (biphasic, 1–2 V, pulse width 450 μs, 40 Hz with the patient's pain level monitored) (Fig. 3).

History and results: patient 1

Patient 1 is an 83-year-old man who suffered from severe left fourth digit phantom limb pain and residual limb pain, following traumatic amputation related to a motor vehicle collision 57 years prior to presentation. In the 3 years following the accident, he underwent several operations aimed at pain reduction, which included excision of a neuroma and residual soft tissue (Fig. 2a). Unfortunately, he received no sustained pain relief and suffered from debilitating pain over the intervening decades. Pharmacologic interventions with maximally dosed amitriptyline and gabapentin led to a temporary 15–20% reduction in pain severity; however, he was unable to tolerate the medications due to associated side effects.

Fig. 2 Subdural implantation of stimulating electrode array. **a** Patient 1's hand with amputated left fourth digit. **b** Incision and retraction of the dura mater while paying careful attention to keep the arachnoid intact. **c** Implantation of the 6×6 temporary stimulating electrode array secured to dura with silk sutures (white arrows). **d** Post-procedure 1 computed tomography (CT) for position control and exclusion of hemorrhage. **e** Location of a permanent array of two 2×8 spinal leads adjoined by silk sutures (arrowhead) and secured to dura (white arrows); two unnecessary middle leads were cut (yellow arrows). **f** Post-procedure 2 computed tomography (CT)



On presentation, his pain in the missing digit ranged from 4 out of 10 to 10 out of 10, with a median score of 8. His pain also worsened throughout the day and would wake him up at night. The pain was exacerbated with movement, light touch, and wind, and would occasionally migrate proximally into his left upper extremity. Light tactile stimulation distal to the mid-humerus would create sharp, tearing sensations in his amputated left fourth digit. Non-painful stimuli to the left side of his face or foot would also reproduce the left hand pain. He also had developed extreme sensitivity over the dorsal and ulnar side of the hand. Direct stimuli near the site of amputation induced severe pain, often resulting in pre-syncopal and syncopal responses.

According to the available studies of the efficacy and safety of neurostimulation techniques, such as SCS and cortical stimulation, it is still uncertain which of these treatments are best for chronic phantom limb pain [5]. In this patient with decades of phantom pain generated mainly above the cord and evidence of cortical reorganization, our institution's neuromodulation committee preferred cortical stimulation instead of SCS, a more common intervention for phantom pain.

Interestingly, in the post-operative setting prior to initiation of the stimulation trials, patient reported improvement in baseline pain scores. Once his pain had stabilized, and he was cognitively ready to participate, stimulation trials were initiated. The patient then continued to experience promising results during trial stimulation and afterward with chronic stimulation. Further, during stimulation, he was able to engage in volitional movement of his left fifth digit for the first time since his injury; thereafter, volitional movement was observed when stimulation was on but not when stimulation was turned off.

During trial stimulations, the lowest pain levels were found to occur when stimulating the columns perpendicular to Brodmann areas 1–3, 4, and 6 at the level of primary hand area extending from middle frontal gyrus to supramarginal gyrus (Fig. 3, stim 9). Initial cathodal stimulation (biphasic, 1 V, pulse width 450 μ s, 40 Hz) at the location decreased pain level from 8/10 to 2/10 (Fig. 4). Stimulation of the same location with amplitude increased from 1 to 2 V further decreased the pain to 1/10 (Fig. 3). Patient's permanent electrode array (Fig. 5a) was placed at the "stim 9" location (Fig. 3b).

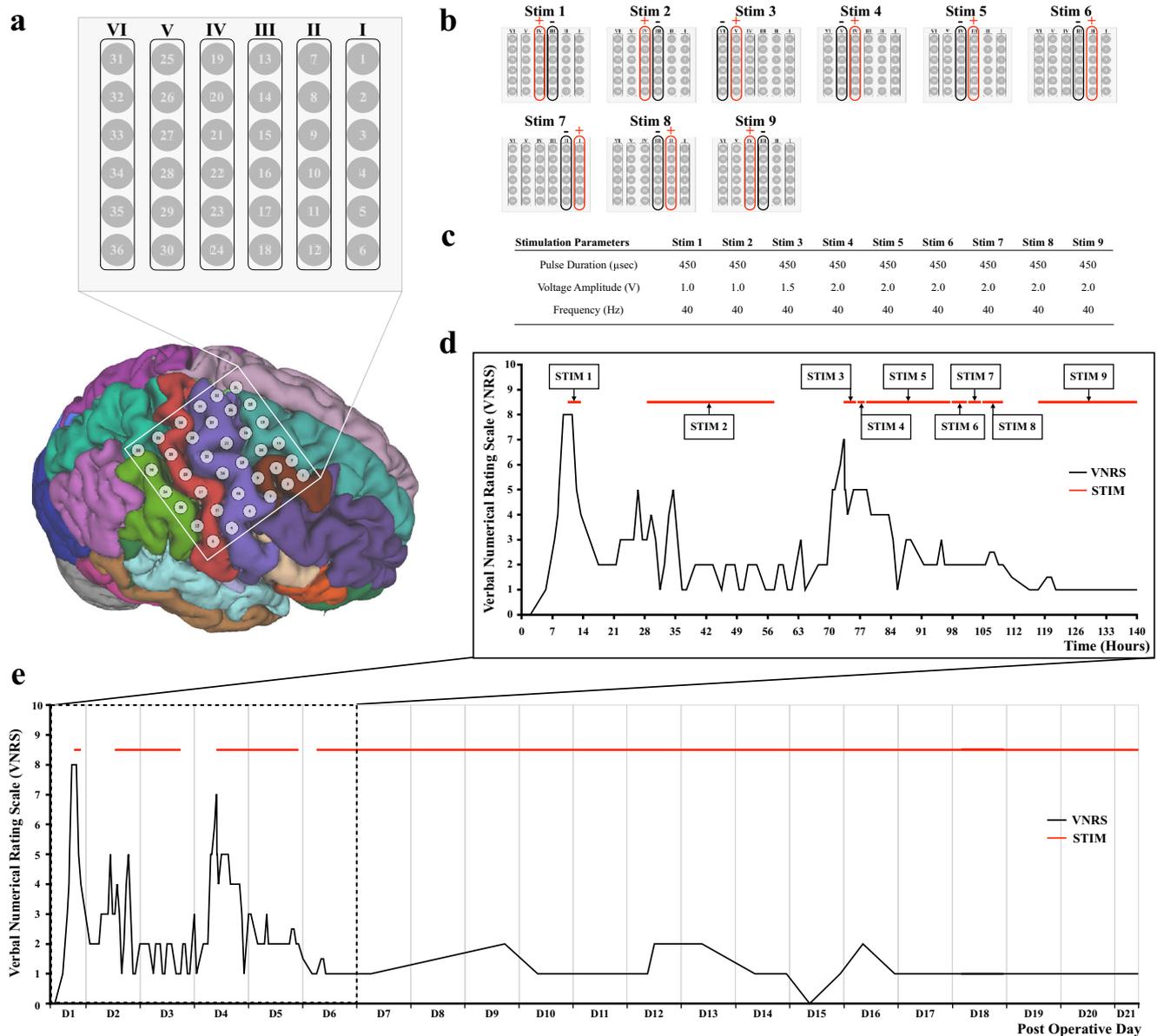


Fig. 3 Patient 1's test stimulation locations, parameters, and pain levels. **a** Representative location of the 6 × 6 electrical array by aligning MRI/CT fusion with a brain atlas [17]. **b** Columns stimulated during trial stimulations. **c** Parameters used for trial stimulations in **b**. **d** Graph documenting

pain using verbal numerical rating scale (VNRS) vs stimulation trials for the post-operative 0–140 h. **e** Graph documenting pain using verbal numerical rating scale (VNRS) vs stimulation trials for the post-operative 0–21 days

Following the initiation of chronic stimulation after discharge, his pain was noted to be 1–2/10 and he continued to receive 80–90% pain reduction 3 weeks later (Fig. 3). At his 3-months follow-up visit, he noted that his pain level was still 1/10 with continued full recovery of his fifth digit function. In addition, he was also able to lift up to 40 pounds in his left hand, whereas prior to surgery he had difficulty lifting a cup of water without spilling. Finally, at 3 months, he was able to wean off his chronic analgesic medications. The patient's improvement was sustained at his 6-month follow-up. Since discharge, the patient has required no further adjustments in his stimulation parameters.

History and results: patient 2

Patient 2 is a 45-year-old right-handed man who suffered from left upper extremity phantom limb pain with likely coexisting pain after root avulsion. Five years prior to presentation, he had a complete amputation of the left upper extremity following a motor vehicle collision. Two months after the amputation, he developed severe, intractable phantom pain. Spine MRI revealed left cervical C6 and C7 nerve root avulsions. After approximately 1 year of uncontrolled and continuous burning paresthesias, he underwent a DREZ rhizotomy, which unfortunately failed to provide any relief. Despite maximal

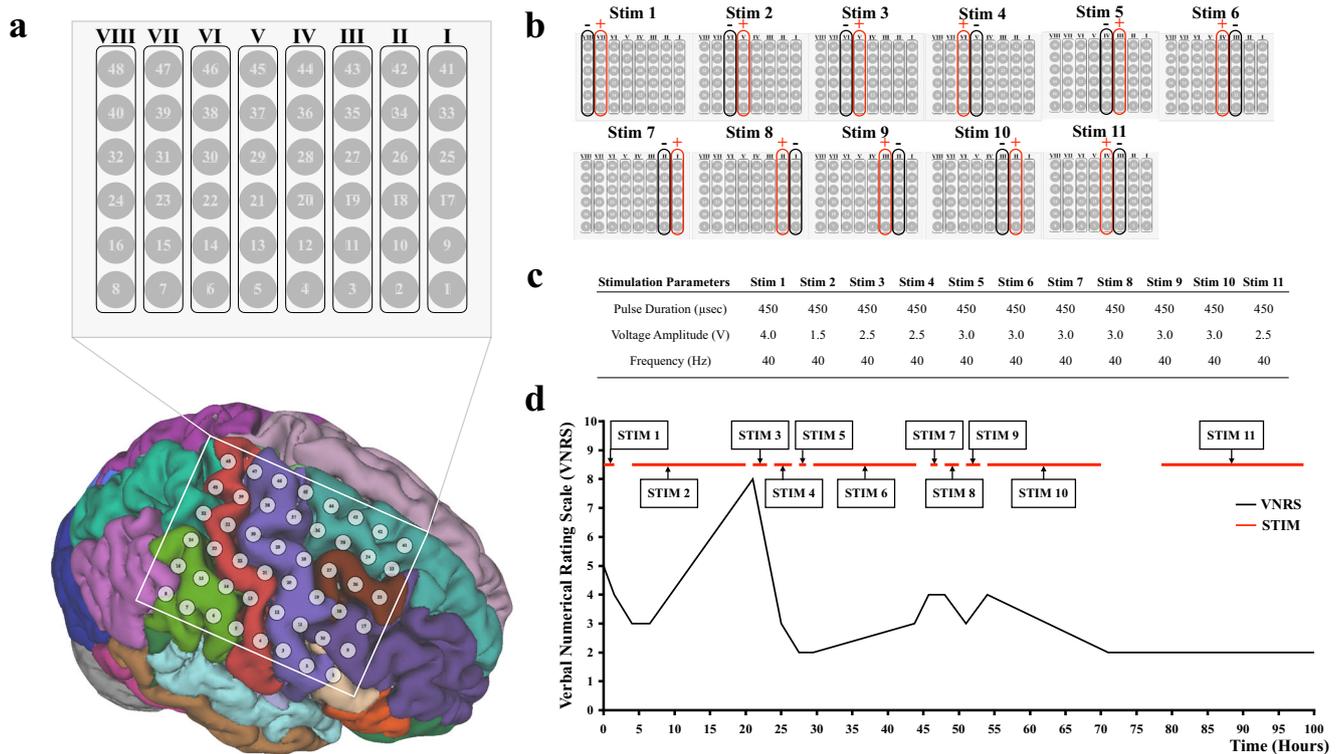


Fig. 4 Patient 2’s test stimulation locations, parameters, and pain levels. **a** Representative location of the 6 × 8 electrical array by aligning MRI/CT fusion with a brain atlas [17]. **b** Columns stimulated during trial

stimulations. **c** Parameters used for trial stimulations in **b**. **d** Graph documenting pain using verbal numerical rating scale (VNRS) vs stimulation trials for the post-operative 0–100 h

medication interventions (Table 1), his pain continued to worsen, progressively spreading proximally into his left shoulder. The burning pain severity score at its baseline was 4/10, but exacerbated frequently to 9/10.

On post-operative day 5, patient experienced progressive confusion that prompted an emergent head CT and identification of both an acute subdural hematoma, with approximately 1 cm of midline shift. The patient was taken to operating room

for hematoma evacuation and permanent electrode placement. There were no adverse peri-operative events following implantation of the permanent system.

The patient initially found stimulation to be helpful, reducing his pain by 60% during the first few weeks of chronic stimulation. Of note, cathodal stimulation (biphasic, 1.5 V, pulse width 450 µs, 40 Hz) overlying Brodmann areas 1–4 and 40 actually increased pain level from 3/10 to 8/10 (Fig. 4).

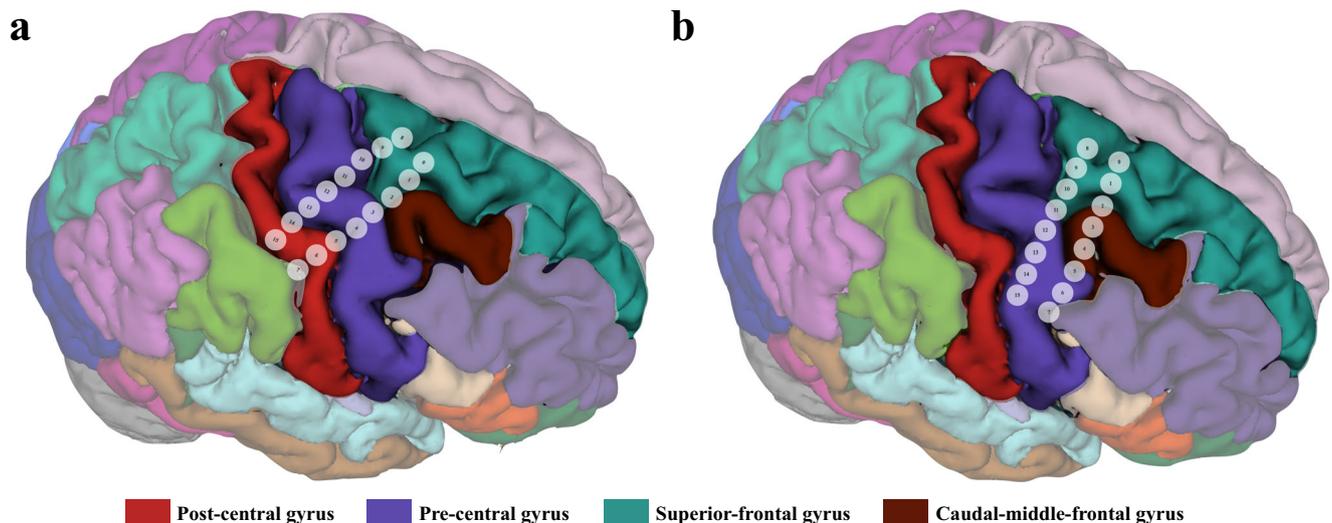


Fig. 5 Representative location of permanent electrode array placement of two adjoining spinal leads. **a** Patient 1 and **b** patient 2

In contrast, the lowest pain levels were initially best maintained at 2/10 with cathodal stimulation (biphasic, 2.5 V, pulse width 450 μ s, 40 Hz) of the columns overlying Brodmann areas 6, 8, and 44 extending from superior parietal lobule to inferior portion of precentral gyrus (Fig. 4). However, at 1-month follow-up, his pain returned to pre-operative baseline. At his 3- and 6-month follow-up visits, he noted his pain to be 3/10 at its best, often 4–5/10 and up to 7–8/10. During in-office stimulation programming (3.2 V, 40 Hz, 450 μ s), he had a witnessed a short, self-resolving focal seizure with maintained awareness and no incontinence or tongue biting. Since the risk-benefit ratio of device removal versus not favors no removal, the cortical stimulation device may be switched off (vs removed) if the pain levels fail to improve after 2 years of optimizing stimulation parameters.

Discussion

We present two patients with persistent pain after amputation, treated with subdural cortical stimulation. For patient 1, his recalcitrant pain lasting for 57 years immediately resolved with pain relief sustained at 6-month follow-up. For patient 2, there was an initial pain improvement response, but his pain returned to pre-operative baseline within 1 month. The difference in response to chronic stimulation in patient 1 versus patient 2 could be related to the multiple factors, including the extent of amputation (the whole limb vs the fourth digit), chronic and permanent electrode array implantation sites, complications (subdural hematoma in case 2), pre-existing traumatic changes in the spinal cord (patient 2), different coexisting pain syndromes (residual limb syndrome in patient 1 and nerve root avulsion pain in patient 2), and, most importantly, the presence of cortical reorganization in patient 1. Given the heterogeneity of phantom limb pain disorder, the subset of patients who may benefit from cortical stimulation may be diluted by the larger group. Far from conclusive evidence, our unique case series report adds to the growing body of

literature that may aid in patient selection for cortical stimulation in patients with phantom limb pain.

Mechanism-based treatments of phantom limb pain

Multiple and multifactorial mechanisms may lead to post-amputation pain, a broad term for phantom limb pain, stump pain, and phantom sensations. Supraspinal, spinal, and peripheral categories of post-amputation pain with corresponding treatments are summarized in Table 2. The most commonly cited mechanisms of phantom limb pain belong to the supraspinal category. One such mechanism, cortical reorganization, is where nociceptive, proprioceptive, and tactile inputs from the neighboring cortical areas take over regions of the brain that no longer receive afferent input [44]. For example, as seen in patient 1, stimuli to the face and foot may elicit pain in the missing limb. Functional MRI may localize regions of cortical reorganization [28]. Then, targeting of these regions with cortical stimulation is thought to provide pain relief through an unclear signaling mechanism.

Identifying the discrete category(-ies) of post-amputation pain helps to identify the appropriate treatment options (Table 2). For instance, peripheral category treatments, such as local anesthetic injection, may be an appropriate treatment modality for pain in the peripheral nerve distribution, whereas spinal category treatments, such as spinal stimulation, may be considered otherwise. However, patients with evidence of cortical reorganization should be considered for supraspinal treatment categories, such as cortical stimulation. The difficulty in identifying discrete categories of phantom limb pain may result in barriers to appropriate treatment [51].

Subdural versus epidural placement of electrode array

In the literature, cortical stimulation for phantom limb pain has a handful of reports with epidural stimulation [4, 15, 19, 34, 38, 40], and to the best of our knowledge, only one study with

Table 2 Mechanism-based treatment modalities for post-amputation pain

Categories	Mechanism (s)	Potential procedures
Supraspinal	Cortical reorganization	Deep brain stimulation (DBS)
	Cortical motor-sensory dissociation	Cortical stimulation
		Mirror therapy
Spinal	Spinal cord sensitization	Spinal cord stimulation
Peripheral	Stump and neuroma hyperactivity	Dorsal root entry zone (DREZ) lesioning
		Peripheral botulinum toxin, local anesthetic injections
		Transcutaneous electrical nerve stimulation (TENS)
		Pulsed radiofrequency
		Neuromata excision or stump revision surgeries

the subdural approach that unfortunately, combines outcomes of two phantom limb patients with those of 17 other patients with neuropathic pain [39]. Overall, limited by small and heterogeneous patient cohorts with variable follow-up, these reports are insufficient to quantitatively compare the safety and efficacy of subdural versus epidural placement. Our choice for subdural approach for phantom limb pain is partly based on our experience in treating facial pain. Traditionally, concern for the higher risk of complications, including subdural hematoma, dissuaded US neurosurgeons from the subdural approach. However, at our institution, the epidural approach for facial pain resulted in a universal loss of efficacy. When re-explored, we found significant scarring surrounding epidural electrodes. In these patients, the efficacy was subsequently restored by subdural implantation. Preliminary unpublished results using subdural implantation for facial pain in 23 patients showed success rates of at least satisfactory pain relief in 100% of patients initially and around 80% at 1-year follow-up or more. Thus, despite having higher complication rates, we adopted subdural implantation as our initial approach. Still, the neurosurgeons should be prudent when choosing the subdural approach, especially in the setting of no official approval for cortical stimulation to treat phantom pain in most countries.

Limitations

Cortical stimulation is known to show diminishing results over time. In a meta-analysis of cortical stimulation for chronic pain, Lima et al. report a decline from initial response from 64 to 55% at 1-year follow-up [25] and Fontaine et al. showing a similar decline from 57 to 45% [15]. Therefore, a 6-month (vs 1 year or longer) follow-up in our study is a limitation. Further, the interpretation of our results may be limited by coexisting phantom limb pain with residual limb pain in patient 1 and possibly pain after nerve root avulsion in patient 2.

Conclusion

Subdural cortical stimulation proved to be effective in one of our two patients with phantom limb pain at 6-months follow-up and was associated with functional improvements. Considering that phantom limb pain is notoriously treatment resistant, subdural cortical stimulation may be a reasonable option for some patients that have exhausted all medication options. Further investigation into the long-term safety, efficacy, and patient selection criteria will be critical before widespread implementation is considered.

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Compliance with ethical standards

Conflict of interest Dr. Kendal H Lee served as a consultant to Medtronic Inc. in the past year. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript

Informed consent Informed consent, including the discussion of off-label use of FDA approved devices, was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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