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Electronic Dura Mater Meddling in the Central Nervous System

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IMPORTANCE A growing number of neurologic treatments rely on neural implants capable of delivering electrical and chemical stimulation to targeted regions of the central nervous system for extended periods.

OBJECTIVE To assess the potential of a novel class of multimodal neural implants, termed *electronic dura mater* or *e-dura*, to fulfill this need.

EVIDENCE REVIEW Results from preclinical applications of e-dura implants and clinical evidence.

FINDINGS The silicone-based implant e-dura embeds interconnects, electrodes, and chemotrodes that are entirely stretchable. These unique mechanical properties allow e-dura to conform to the circumvolutions of the brain and spinal cord without damaging neural tissues or triggering foreign body reactions.

CONCLUSIONS AND RELEVANCE Although challenges lie ahead to reach clinical fruition, the unique mechanical properties and integrated modalities of e-dura provide future opportunities to treat or alleviate neurologic deficits.

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The central nervous system (CNS) is the most sophisticated organ of the human body—orchestrating vegetative, motor, and cognitive behaviors involved in daily living. This control center is equipped with a battery of protections against mechanical aggression, viral attacks, chemicals, and cerebrospinal fluid (CSF) leakage.

The dura mater is the toughest bodyguard. This outermost layer of the meninges confers a mechanical and structural protection to the CNS. Below the dura mater, the arachnoid mater is a fragile and thin layer that hosts the vessels and seals the CSF compartment. The most extensive and softest layer is the pia mater, which conforms to the circumvolutions of nervous tissues and provides the brain and spinal cord with their shiny appearance. Finally, the blood-brain barrier establishes a firewall protecting the CNS from undesirable toxic or infectious attacks. The blood-brain barrier forms a network of tightly interconnected endothelial cells that constitute a highly selective, permeable barrier isolating the circulating blood from the extracellular matrix and CSF.

Although neurosurgeons and neurologists recognize the crucial role of the meninges and blood-brain barrier in protecting the CNS, they daily transgress these guardians to treat patients. Neurosurgeons routinely open the meninges to remove brain tumors or clip aneurysms and meticulously seek to repair these protective membranes to avoid CSF leakage and infections. Neurologists and neuro-oncologists continuously seek new molecules that cross the blood-brain barrier to treat neuropathologic disease. Through different angles, these physicians share the common goal of establishing new strategies to meddle in the intimate structures of the CNS to deliver next-generation treatments.

Electronic Dura Mater and Next-Generation Neural Implants

Electronic dura mater (e-dura) implants are a novel class of soft yet resistant neural interfaces that mimic the mechanical properties of the dura mater.[1] The implants are fabricated in a transparent silicone substrate. The leads are made of elastic thin metal films[2] or a metal that is liquid at body temperature.[3] The electrodes are coated with a compliant platinum-silicone composite[4] that transmits electrical stimulation and transfers electrophysiologic signals. Moreover, the silicone embeds a compliant fluidic microchannel termed a *chemotrode* that delivers drugs locally. Consequently, every constituent of e-dura is stretchable (**Figure 1**A). The mechanical match between the silicone and dura mater confers e-dura with unprecedented biointegration in the CNS (Figure 1B-C). Long-term implantation of e-dura over spinal tissues does not upregulate activated astrocytes and microglia. Instead, these standard cellular markers for foreign body reaction were markedly upregulated in animals with implants consisting of polyimide-based thin films. Both cell types accumulate near these stiff implants, causing macroscopic damage of the spinal cord structures.

The e-dura implants thus embody the ideal benevolent "secret agent" that infiltrates the CNS gently and discretely, with the mission to read from and write into the CNS through electrical and

chemical communication channels. For example, e-dura has been implanted over the motor cortex of rats to decode cortical states underlying locomotion.[1] This interface has also been inserted into the subdural space of lumbar segments to deliver electrochemical neuromodulation therapies that restored locomotion in paralyzed rats.[5] In both applications, e-dura exhibited reliable functionality over extended periods.

The translation of this technology into clinical implants faces a series of challenges. These hurdles notably include compliance of all the constituents with regulatory requirements, development of reliable implants for a duration of use that is compatible with human medical devices, and interface of e-dura with implantable stimulation and recording electronics. While we are tackling these technical challenges, we have imagined clinical applications wherein e-dura could be used by physicians to treat and alleviate neurologic deficits.

Key Points

Question What are the advantages and possible applications of the soft, multimodal neural interface electronic dura mater?

Findings Soft neural interfaces limit chronic central nervous system inflammation and conform to the surface of the brain and spinal cord. In this preclinical review, the ability to stimulate and record from the same device was found to offer a range of clinical applications, especially when neuromodulation therapies need to be applied in poorly accessible regions or when the therapy can be titrated based on neural activity recordings.

Meaning The soft neural interface electronic dura mater provides new therapeutic options to treat or alleviate neurologic disorders.

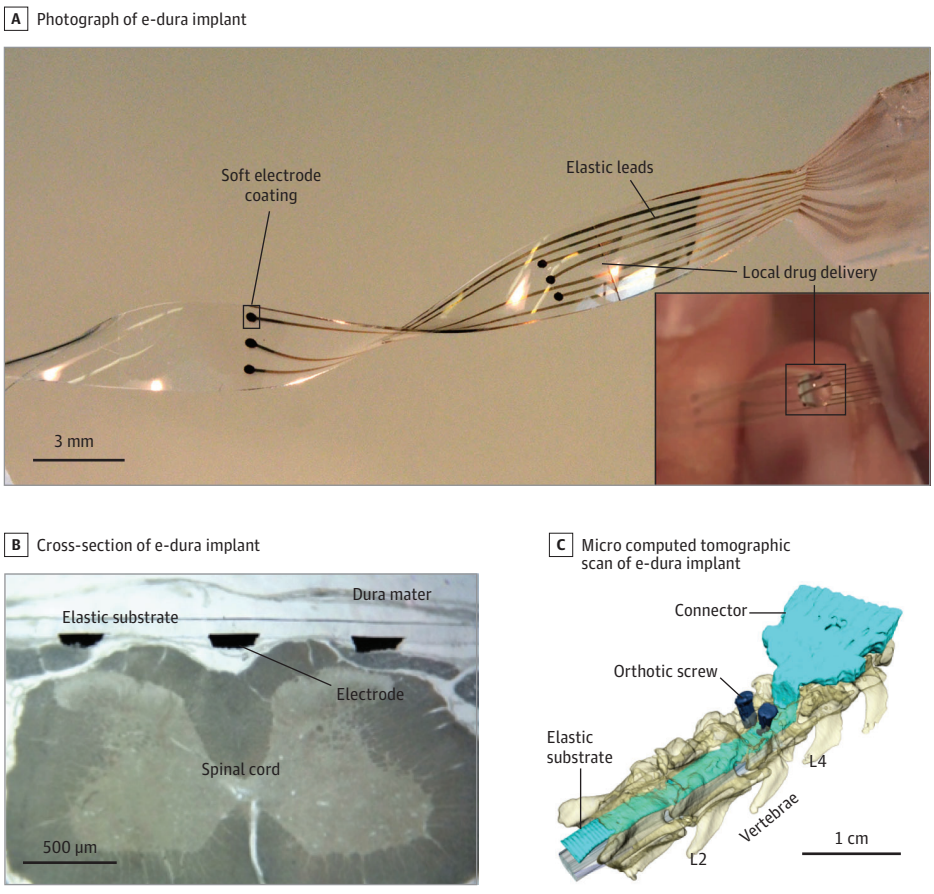
Meddling in the Spinal Cord

Pain Therapies

Epidural electrical stimulation of the spinal cord has become a common medical practice to alleviate neuropathic pain resistant to classic therapies.[6] The electrical current elicits a pleasant sensation that blocks the brain's ability to perceive persistent pain sensations. This treatment allows patients to reduce analgesic medication use and thus improves their quality of life. The more severely affected patients with chronic intractable mechanical pain or pronounced spasticity benefit from the additional intrathecal delivery of morphine derivatives or spasmolytic drugs into the intrathecal space through a catheter attached to an implantable electronic pump.[7]

The multimodal properties of e-dura support the delivery of electrical and pharmacologic neuromodulation therapies through the same medical device that establishes an intimate interface with spinal tissue. Compared with implants located above the dura mater, the location of the e-dura over the pia mater improves stimulation

Figure 1. Technical Features of the Electronic Dura Mater (e-Dura) Implant



A, Photograph of the e-dura implant tailored for spinal cord repair interventions. The silicone-based membrane combines soft electrodes and a microfluidic channel termed the *chemotrode*. Inset shows a close-up view of in situ drug delivery (droplet diameter, 2 mm). B, Cross-section of the subdural e-dura implant surgically inserted on the surface of the spinal cord 6 weeks after implantation. C, Reconstructed 3-dimensional microcomputed tomography scan of the e-dura implant in the spinal canal at 5 weeks after implantation. Adapted in part from Minev et al.[1]

specificity and allows a substantial decrease in the amount of current that is necessary to mediate therapeutic effects.[1] This feature enhances the life of the battery, supporting the development of more ecological pulse generators that may play a crucial role in augmenting the patient's acceptance of implanted devices.[8] Moreover, the chemotrode provides the opportunity to deliver morphine or baclofen through the same medical device, thus reducing the cost and complexity.

Improving Motor Control After Spinal Cord Injury

Spinal cord damage interrupts the communication between supraspinal centers and lumbar spinal circuits that produce leg movements. Albeit intact, lumbar spinal circuits lack the essential source of modulation and excitation originating from brainstem centers[9] to sustain walking.[10] Neuromodulation approaches have been developed to replace these missing inputs. For example, the combination of serotoninergic agonists and electrical stimulation of lumbar segments restored locomotion in rats with a complete injury.[10] Electrical stimulation also reactivated lumbar spinal circuits in patients with paraplegia.[11,12]

These observations prompted us to study the interactions between this stimulation and spinal circuits for clinical applications. Previous studies[13,14] found that the stimulation engages spinal circuits through the modulation of proprioceptive feedback circuits located in the dorsal roots. This framework guided the design of e-dura implants that integrated spatially selective electrodes. These electrodes target the dorsal roots projecting to spinal segments that contain the circuits that produce extension vs flexion movements.[5] The e-dura implants were positioned subdurally, which enabled the concurrent delivery of electrical and chemical stimulation.[1] Real-time control of stimulation not only activated but also controlled the activity of spinal circuits engaging synergistic muscle groups.[5] Spatiotemporal neuromodulation therapies improved gait quality, endurance, and skilled locomotion.[5] These concepts are directly translatable to strategies to improve motor control in humans.

Meddling in the Brain

The management of neurogenic pain brings a flurry of challenges. Pharmacologic therapies often show limited efficacy.[7] Motor cortex stimulation delivered over the epidural surface has emerged as a potential strategy to treat resistant peripheral and central neurogenic pain resulting from stroke or trigeminal neuropathy.[15] Imaging studies[16] suggest that motor cortex stimulation inhibits the high firing rate of the sensory compartment of the thalamus and increases the activity of the cingulate gyrus, which together diminish pain.

In present applications, electrodes are positioned epidurally. Compared with subdural electrode placement, this location prevents arachnoiditis and mitigates complications. However, this approach has 2 major drawbacks. First, brain atrophy increases the distance between electrodes and targeted cortical regions. Analgesic effects require larger electrical currents, which disrupt nontargeted regions and thus elicit adverse effects. Second, the interhemispheric region is not accessible from the epidural surface, which has restricted the application of motor cortex stimulation to the regions of the face and upper limbs.[17]

The unique biomechanical properties of e-dura afford an intimate apposition of soft electrodes in the vicinity of cortical tissue while preventing inflammation or venous mechanical shearing lesions. Previous studies[18] described the advantages of subdural implants for motor cortex stimulation but also revealed higher complication rates. The insertion of e-dura in the interhemispheric region allows targeting of the leg area that is currently inaccessible with epidural stimulation while potentially reducing nondesired effects. For example, e-dura can be easily slid below the dura mater without damaging tissue or triggering foreign body reaction.[1] Stimulations revealed that e-dura moves together with neural tissue, which contributes to the long-term biointegration.

Novel Therapeutic Missions

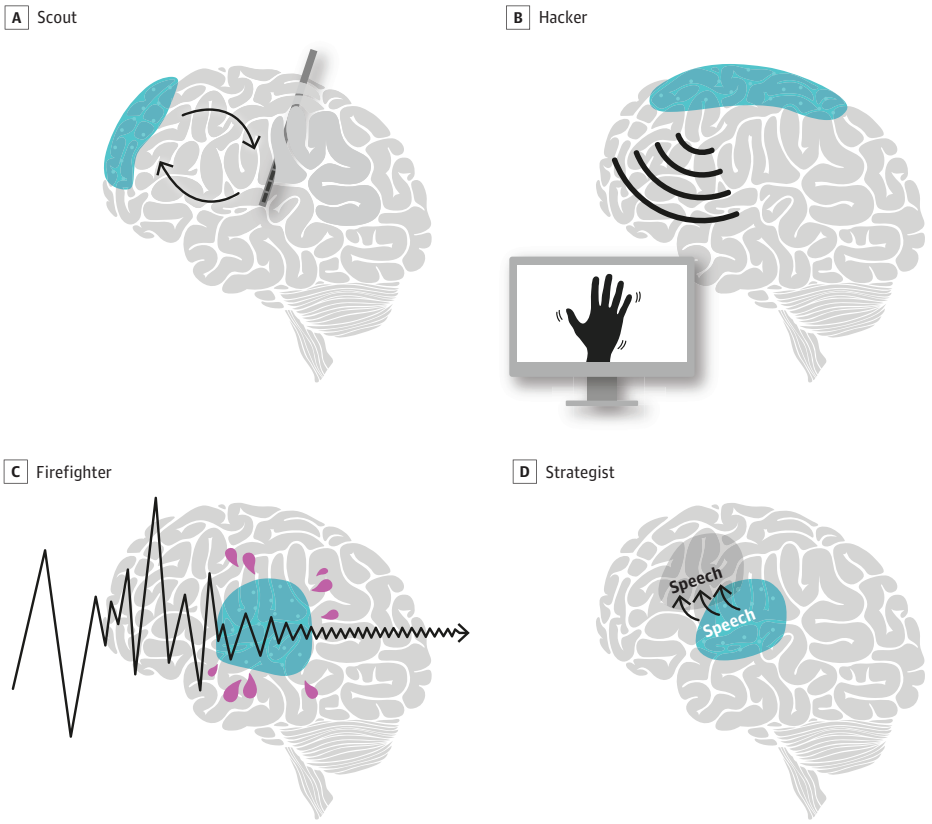
The secret agent e-dura can be inserted below the dura mater incognito. This camouflaged programmable membrane can read from and write into the CNS through electrical and chemical communication channels. These features provide e-dura with a range of therapeutic missions. To understand this potential, we have identified the following 4 capacities in the fight against neurologic disorders: (1) the scout, which explores conflict zones in the brain and provides this information to ground troops (ie, therapeutic agents to regulate brain activity); (2) the hacker, which extracts the patient's intention from neural signal decoding to control of a lost or an impaired function; (3) the firefighter, which extinguishes anarchic behaviors in the brain; and (4) the strategist, which acts for longer periods to reprogram brain functions (**Figure 2**).

The Scout

Deep brain stimulation (DBS) of the subthalamic nucleus is a common medical practice to alleviate motor and behavioral impairments associated with neurologic disorders such as Parkinson disease, dystonia, essential tremor, obsessive-compulsive disorder (OCD), or even depression.[19] More than 90 clinical trials have probed the ability of DBS to treat neurologic diseases.[19] Clinical studies showed that the stimulation variables not only differ between anatomical targets and therapeutic applications but also from patient to patient. Physicians tune the locations and variables of stimulation empirically based on visual observations. After titration, the patient has very limited control over stimulation features. The amount of injected energy is not adapted to the state of pathogenic circuits.[8] This approach fails to exploit the full potential of these interventions. Instead, closed-loop control systems based on detection of pathologic neural activity could titrate therapies to meet dynamic patient-specific needs.[20] For example, studies in patients with Parkinson disease have shown that motor impairments correlate with the subthalamic nucleus activity in the beta frequency band (13-30 Hz). The power of this band has been exploited to control the amount of delivered current.[21] This closed-loop control policy mediated superior motor improvements compared with continuous or random stimulation. Exaggerated coupling between the beta rhythm and the amplitude of broadband motor cortex activity is an alternative control signal for this application.[22]

These results provide a glimpse at the exciting future: a new era of precision neuroprosthetics. The one-size-fits-all DBS technology is on the track to obsolescence. Next-generation neuromodulation therapies could exploit e-dura implants that are tailored to the surface and geography of a targeted cortical region to record neural states. The e-dura implant is more pliable and better conforms to the gyri and sulci of the brain. This property is likely to enable intrasulcal electrocorticography with minimally invasive neurosurgi-

Figure 2. Different "Secret-Agent" Roles of Electronic Dura Mater (e-Dura)



The e-dura implant (cyan) can read from and write into the central nervous system using electrodes and chemotrodes (purple) to treat neurologic disorders. As the scout, e-dura reads the neural state to adjust deep brain stimulation therapies to the current need of the patient. As the hacker, e-dura reads motor intention from cortical ensemble modulation (illustrated for hand movement). As the firefighter, e-dura detects the onset of an epileptic episode and delivers electrical and chemical stimulation to extinguish the seizure. As the strategist, e-dura delivers stimulation over an eloquent region of the brain to encourage adjacent regions to take over its function, thus allowing the preservation of speech abilities after removal of the brain tumor in the targeted region.

cal protocols.[23] Such e-dura implants would act as scouts that survey circuitopathy to optimize stimulation variables that normalize neural states (Figure 2A).

This approach may translate to various neurologic and psychiatric disorders. For example, OCD affects 2% to 3% of the population. People with OCD exhibit recurrent intrusive thoughts (obsessions), repetitive behaviors, and/or mental acts (compulsions) triggered by anxiety. Obsessive-compulsive disorder was initially linked to altered corticostriatal circuitry, but recent neuroimaging studies[24] uncovered networks of interlinked neuronal systems in patients with OCD. The emergence of symptoms has been associated with excessive prefrontal activity.[24] Nucleus accumbens DBS is a possible strategy to alleviate medically resistant OCD.[19] The nucleus accumbens interfaces the limbic and motor systems. The stimulation thus aims at regulating the disrupted integration of emotional and motor information in the nucleus accumbens. At present, the stimulation is delivered continuously. A potentially more efficacious strategy may exploit e-dura implants to detect abnormal neuronal activity from prefrontal recordings and trigger nucleus accumbens DBS on demand to diminish the amplitude or even prevent the onset of compulsions and obsessions.

The Hacker

The e-dura implants could help the brain deliver commands to disrupted circuits or paralyzed limb muscles. Similar to a hacker meddling in a computer program to take control of its operations (Figure 2B), e-dura can crack the neural code to detect motor intentions.[1,25]

The e-dura implant can be positioned over the leg region of the motor cortex, which is located in the interhemispheric fissure. This location is difficult to access using rigid implants. Leg motor cortex signals allow decoding of gait initiation or gait timing,[1] which provides high-level commands to steer locomotor prosthetics.[26] This decoding may directly adjust spinal cord stimulation to reestablish leg movements after paralysis.[27] When implanted over the arm motor cortex region, e-dura could support the design of a brain-computer interface that links intended hand movements to computers, prosthetic limbs, or arm muscle stimulation.[28,29]

The Firefighter

The e-dura implant could serve as a firefighter that extinguishes anarchic brain behaviors, such as epileptic seizure (Figure 2C). Although this neurologic disorder is generally well controlled with medication, epilepsy is refractory to pharmacotherapy in 20% to 30% of patients. When medically intractable seizures emerge from a well-defined, noneloquent region, ablative surgery of the epileptic focus provides an efficient strategy to treat these patients. Neuromodulation therapies, including vagal nerve stimulation or thalamic DBS, are the only alternative strategies for patients who are not candidates for ablative surgery.

Recently, NeuroPace received a premarket approval from the US Food and Drug Administration for a closed-loop device that controls medically refectory seizures. This device integrates leads targeting the surface of the cortex and deep structures overlying the preidentified epileptic foci. The NeuroPace system automatically senses abnormal neural activity and responds to emerging seizures with electrical shocks that stop the seizure. A double-blind randomized clinical trial[30] reported that NeuroPace decreased mean seizure frequency by 37.9%. A reduction of the delay between seizure detection and electric shock delivery could enhance the efficacy of this treatment. Indeed, the key feature of this strategy is to trigger the electric shock before the spread of the epileptic wave.

The e-dura implants present several advantages in this firefight. This membrane can cover a large cortical surface, integrate dozens of electrodes to provide high-level territory surveillance, and fire electrical shocks over multiple regions simultaneously or sequentially. However, this type of implant will require multichannel connectors, amplifiers, and other complex electronics that are still under development.[31] Moreover, e-dura the firefighter can integrate a second line of defense. The microfluidic channels enable the rapid infusion of antiepileptic drugs at the specific sites of fire. For example, the local cortical infusion of γ-aminobutyric acid agonists has mediated anticonvulsive effects in animal models of epilepsy.[32] The local application allows the drug to reach a high concentration at the target site, while minimizing the secondary adverse effects associated with systemic administration.

The Strategist

A sudden neurologic insult opens a window of opportunity for neuroplasticity, which mediates partial recovery of affected bodily functions. Consequently, the development of strategies to augment neuroplasticity remains a major challenge and priority in public health policies.

Neuromodulation therapies showed the ability to promote anatomical and structural reorganization of neural pathways. For example, long-lasting stimulation of corticospinal axons after spinal cord injury triggered a sprouting of synaptic terminals in the brainstem and spinal cord.[33,34] This remodeling enhanced motor recovery in animal models. Similarly, repetitive transcranial magnetic stimulation and transcranial direct current stimulation enhanced motor learning and cognitive recovery in persons with stroke.[35,36]

These treatments use noninvasive techniques that not only lack specificity but also require specialists who deliver the stimulation during succinct sessions scattered across several weeks. The strategist properties of e-dura are uniquely fitted to improve these approaches. The implantation of e-dura over targeted cortical regions enables delivery of long-term stimulation, which is likely to lead to more pronounced improvements compared with intermittent stimulations. Moreover, the practicality of implantable technology enhances the spectrum of possible combinatorial therapies. Electrical stimulation patterns can be synchronized with virtual reality environments, robotic actuation, and sensory enhancement to augment the cognitive, motor, and sensory rehabilitation experience. The rapid development of bioresorbable electronics[37] may even offer the additional advantage of limiting this strategy to a single surgical intervention.

Removal of a glioma from a dominant cerebral hemisphere may endanger critical brain functions, including the understanding and production of language. Aggressive gliomas lead to irreversible loss of functions encoded in the invaded region. Instead, longitudinal neuroimaging studies revealed that, when gliomas grow slowly, surrounding brain territories progressively take over the operations of invaded regions, which results in unexpected preservation of function. On one hand, this vicarious potential of surrounding brain tissues conflicts with the primary strategy of neurosurgeons, which consists of maximizing total gross tumor resection. On the other hand, this neuroplasticity can be exploited to preserve functions. This awareness has triggered the development of staged surgical treatments whereby gliomas are removed during awake surgery until approaching eloquent areas. A second surgical resection is performed several months later when neuroplasticity has occurred in surrounding tissues.

In the ideal scenario, the neurosurgeon would implant a neuromodulation device during the first resection to accelerate the shift of the eloquent area and thus reduce the interval between the ablation procedures. In the strategist application, e-dura could empower neurosurgeons with the weapon to make this strategy a reality (Figure 2D). A case study reported that high-frequency stimulation applied for 25 days over the surface of a partially resected tumor located in the Broca area produced a mild speech disturbance that forced the brain to shift the location of the speech area away from the stimulation.[38] Therefore, shortly after the first partial resection, a second, more radical resection could be performed without altering the speech abilities of the patient. The versatility of e-dura implants is well suited for this application. Moreover, e-dura provides the opportunity to infuse chemotherapies locally to reduce the growth of the tumor.

Conclusions

We sought to provide a glimpse of the exciting therapeutic opportunities that next-generation implant technology, such as e-dura, may provide for the diagnosis and treatment of neurologic disorders. This technology heralds precision neuroprosthetics. Although challenges lie ahead to pass the various regulatory hurdles and technical issues along the path to clinical fruition, we believe that the pluripotent secret agent e-dura will provide a novel arsenal to help neurologists and neurosurgeons meddle in the intimate and hidden territories of the brain and spinal cord to treat or alleviate neurologic deficits and thus improve a patient's quality of life.

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REFERENCES

1. Minev IR, Musienko P, Hirsch A, et al. Biomaterials: electronic dura mater for long-term multimodal neural interfaces. *Science*. 2015;347(6218):159-163.

2. Lacour SP, Chan D, Wagner S, Li T, Suo Z. Mechanisms of reversible stretchability of thin metal films on elastomeric substrates. *Appl Phys Lett*. 2006;88(20):204103.

3. Hirsch A, Michaud HO, Gerratt AP, de Mulatier S, Lacour SP. Intrinsically stretchable biphasic (solid-liquid) thin metal films [published online February 29, 2016]. *Adv Mater*. doi: 10.1002/adma.201506234

4. Minev IR, Wenger N, Courtine G, Lacour SP. Research update: platinum-elastomer mesocomposite as neural electrode coating. *APL Mater*. 2015;3(1):014701.

5. Wenger N, Moraud EM, Gandar J, et al. Spatiotemporal neuromodulation therapies engaging muscle synergies improve motor control after spinal cord injury. *Nat Med*. 2016;22(2):138-145.

6. Bittar RG, Teddy PJ. Peripheral neuromodulation for pain. *J Clin Neurosci*. 2009;16(10):1259-1261.

7. Yaksh TL, Fisher C, Hockman T, Wiese A. Current and future issues in the development of spinal agents for the management of pain [published online March 7, 2016]. *Curr Neuropharmacol*.

8. Courtine G, Bloch J. Defining ecological strategies in neuroprosthetics. *Neuron*. 2015;86(1):29-33.

9. Jordan LM, Liu J, Hedlund PB, Akay T, Pearson KG. Descending command systems for the initiation of locomotion in mammals. *Brain Res Rev*. 2008;57(1):183-191.

10. Courtine G, Gerasimenko Y, van den Brand R, et al. Transformation of nonfunctional spinal circuits into functional states after the loss of brain input. *Nat Neurosci*. 2009;12(10):1333-1342.

11. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain*. 2014;137(pt 5):1394-1409.

12. Gerasimenko YP, Lu DC, Modaber M, et al. Noninvasive reactivation of motor descending control after paralysis. *J Neurotrauma*. 2015;32(24):1968-1980.

13. Capogrosso M, Wenger N, Raspopovic S, et al. A computational model for epidural electrical stimulation of spinal sensorimotor circuits. *J Neurosci*. 2013;33(49):19326-19340.

14. Moraud EM, Capogrosso M, Formento E, et al. Mechanisms underlying the neuromodulation of spinal circuits for correcting gait and balance deficits after spinal cord injury. *Neuron*. 2016;89(4):814-828.

15. Delavallée M, Abu-Serieh B, de Tourchaninoff M, Raftopoulos C. Subdural motor cortex stimulation for central and peripheral neuropathic pain: a long-term follow-up study in a series of eight patients. *Neurosurgery*. 2008;63(1):101-105.

16. Lefaucheur JP. Cortical neurostimulation for neuropathic pain: state of the art and perspectives. *Pain*. 2016;157(suppl 1):S81-S89.

17. Vargas López AJ, Fernández Carballal C, González Quarante LH, Prieto Montalvo J. Motor cortex stimulation in the interhemispheric subdural space as treatment of neuropathic pain in the lower limbs. *Neurologia*. 2014;29(5):310-311.

18. Tronnier V, Rasche D. Epidural and subdural stimulation. *Handb Clin Neurol*. 2013;116:343-351.

19. Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. *Neuron*. 2013;77(3):406-424.

20. Rosin B, Slovik M, Mitelman R, et al. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron*. 2011;72(2):370-384.

21. Little S, Beudel M, Zrinzo L, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2015.

22. de Hemptinne C, Swann NC, Ostrem JL, et al. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci*. 2015;18(5):779-786.

23. Matsuo T, Kawasaki K, Osada T, et al. Intrasulcal electrocorticography in macaque monkeys with minimally invasive neurosurgical protocols. *Front Syst Neurosci*. 2011;5:34.

24. Nakao T, Okada K, Kanba S. Neurobiological model of obsessive-compulsive disorder: evidence from recent neuropsychological and neuroimaging findings. *Psychiatry Clin Neurosci*. 2014;68(8):587-605.

25. Courtine G, Micera S, DiGiovanna J, Millán JdelR. Brain-machine interface: closer to therapeutic reality? *Lancet*. 2013;381(9866):515-517.

26. Wang S, Wang L, Meijneke C, et al. Design and control of the MINDWALKER exoskeleton. *IEEE Trans Neural Syst Rehabil Eng*. 2015;23(2):277-286.

27. Borton D, Bonizzato M, Beauparlant J, et al. Corticospinal neuroprostheses to restore locomotion after spinal cord injury. *Neurosci Res*. 2014;78:21-29.

28. Wolpaw JR, Winter Wolpaw E. *Brain-Computer Interfaces: Principles and Practices*. New York, NY: Oxford University Press; 2012.

29. Bouton CE, Shaikhouni A, Annetta NV, et al. Restoring cortical control of functional movement in a human with quadriplegia. *Nature*. 2016;533(7602):247-250.

30. Lockman J, Fisher RS. Therapeutic brain stimulation for epilepsy. *Neurol Clin*. 2009;27(4):1031-1040.

31. Viventi J, Kim D-H, Vigeland L, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nat Neurosci*. 2011;14(12):1599-1605.

32. Ramakrishnan L, Dalhoff Z, Fettig SL, et al. Riluzole attenuates the effects of chemoconvulsants acting on glutamatergic and GABAergic neurotransmission in the planarian *Dugesia tigrina*. *Eur J Pharmacol*. 2013;718(1-3):493-501.

33. Carmel JB, Berrol LJ, Brus-Ramer M, Martin JH. Chronic electrical stimulation of the intact corticospinal system after unilateral injury restores skilled locomotor control and promotes spinal axon outgrowth. *J Neurosci*. 2010;30(32):10918-10926.

34. Carmel JB, Kimura H, Martin JH. Electrical stimulation of motor cortex in the uninjured hemisphere after chronic unilateral injury promotes recovery of skilled locomotion through ipsilateral control. *J Neurosci*. 2014;34(2):462-466.

35. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*. 2005;128(pt 3):490-499.

36. Wessel MJ, Zimerman M, Hummel FC. Non-invasive brain stimulation: an interventional tool for enhancing behavioral training after stroke. *Front Hum Neurosci*. 2015;9:265.

37. Yu KJ, Kuzum D, Hwang S-W, et al. Bioresorbable silicon electronics for transient spatiotemporal mapping of electrical activity from the cerebral cortex. *Nat Mater*. 2016;15(7):782-791.

38. Barcia JA, Sanz A, Balugo P, et al. High-frequency cortical subdural stimulation enhanced plasticity in surgery of a tumor in Broca's area. *Neuroreport*. 2012;23(5):304-309.