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Neuroelectronics and Biooptics:

Closed-Loop Technologies in Neurological Disorders

Esther Krook-Magnuson, PhD, **Jennifer N. Gelinas, MD, PhD**, **Ivan Soltesz, PhD**, and **György Buzsáki, MD, PhD**

Department of Neuroscience, University of Minnesota, Minneapolis (Krook-Magnuson); New York University Neuroscience Institute, Langone Medical Center, New York (Gelinas, Buzsáki); New York University Center for Neural Sciences, New York (Gelinas, Buzsáki); Department of Anatomy and Neurobiology, University of California, Irvine (Soltesz)

Abstract

Brain-implanted devices are no longer a futuristic idea. Traditionally, therapies for most neurological disorders are adjusted based on changes in clinical symptoms and diagnostic measures observed over time. These therapies are commonly pharmacological or surgical, requiring continuous or irreversible treatment regimens that cannot respond rapidly to fluctuations of symptoms or isolated episodes of dysfunction. In contrast, closed-loop systems provide intervention only when needed by detecting abnormal neurological signals and modulating them with instantaneous feedback. Closed-loop systems have been applied to several neurological conditions (most notably epilepsy and movement disorders), but widespread use is limited by conceptual and technical challenges. Herein, we discuss how advances in experimental closed-loop systems hold promise for improved clinical benefit in patients with neurological disorders.

Closed-loop systems incorporate feedback between output and input signals to effectively exert control over the system. The benefits of closed-loop feedback are most significant when symptoms fluctuate rapidly depending on external or internal conditions or when symptoms occur in time-limited episodes with periods of intervening normal function. In these cases, the development of automated or programmable closed-loop systems that operate in real time is advantageous. Clinical efficacy for such systems has already been demonstrated for several categories of neurological disease.[1] However, effective closed-loop

systems for clinical applications require the following key components:(1) salient pathologic signals to serve as inputs; (2) appropriate sensors to capture these signals; (3) real-time, computationally manageable algorithms to process inputs; and (4) appropriate effectors and actuators to deliver interventions with the correct parameters to the target.

A diverse combination of physiological signals and intervention approaches can be used in a closed-loop fashion. For instance, patient motion captured by an accelerometer has been used to guide the display of virtual visual stimuli to improve gait impairment in patients with Parkinson disease.[2] Furthermore, drug dosing based on monitored physiological parameters in certain patient populations could be seen as on-demand treatment, and such an approach is effectively used in anesthesiology to ensure maintenance of stable, appropriate levels of anesthesia during operative procedures.[3,4] However, most well-established closed-loop devices for neurological applications have used intervention strategies that provide greater temporal precision, typically in the form of on-demand electrical stimulation of the central nervous system, and we focus our discussion on such strategies herein.

Perhaps the earliest closed-loop experiment in an animal model was performed by Delgado and colleagues[5] on a chimpanzee named Paddy. Paddy was fitted with a telemetric device ("stimoceiver"), and when spindle patterns were detected from presumed amygdala circuits, feedback stimulation was delivered to the central gray area. The aversive effects of the stimulation reduced the occurrence of spindles, and Paddy became quieter, less attentive, and less motivated during behavior altesting.[5] Delgado et al[6] envisioned that such closed-loop feedback stimulation could be used to reduce seizures, panic attacks, or other neurological symptoms and explored the feasibility of such potential therapy in humans. Many technical hurdles prevented the practicality of the closed-loop method in clinical use at that time, but neurostimulation is now an established therapy for several neurological disorders. Patients with intractable neuropathic pain experience improved pain relief and quality of life when body position information acquired by an accelerometer is used to adjust the parameters of spinal cord stimulation (RestoreSensor; Medtronic, Inc[7]). Progress has also been made in automated triggering of deep brain stimulation (DBS) based on local field potentials recorded from the basal ganglia in patients with Parkinson disease[8] (Activa PC + S; Medtronic, Inc [clinicaltrials.gov identifiers NCT02115802, NCT01934296, NCT01990313, and NCT02235792]). Two closed-loop options are currently available as adjunctive therapy for patients with refractory epilepsy. Closed-loop therapy in epilepsy requires early seizure detection and effective feedback selectively at the time of seizures. This method is in stark contrast to traditional approaches in which treatment is irreversible (eg, surgical removal of tissue), constantly applied, or applied without regard to the current brain state (Figure). The NeuroPace system (NeuroPace, Inc), which uses abnormal electrocorticography signals to trigger focal cortical stimulation, is approved by the US Food and Drug Administration and has demonstrated clinical safety and efficacy in reduction of seizure frequency in a select patient population.[11] Closed-loop vagal nerve stimulation (AspireSR; Cyberonics, Inc [clinicaltrials.gov identifier NCT01325623]) is approved for use in Europe, although the trigger for stimulation is ictal tachycardia rather than brain-derived electrophysiological signals.

Data generated from the use of these devices support the notion that closed-loop therapeutics can offer increased efficacy and clinical benefit of stimulation, as well as decreased stimulation adverse effects, compared with open-loop protocols.[7,12] Despite these potential benefits, it remains difficult to develop new closed-loop technologies and refine stimulation parameters in a clinical setting. Herein, we discuss examples of how studies using cutting-edge techniques and analysis methods in a research setting can facilitate improvements in components of a closed-loop therapeutic system.

Input Signals

Determining the appropriate pathologic signals to use as triggers for closed-loop modulation in various disease states remains a major challenge. For example, various features identified in electromyography recordings and electrophysiological signals from basal ganglia or cortical structures are associated with parkinsonism.[13,14] Without a sufficient understanding of which signals are critically integrated in the pathologic circuit vs merely correlational, selection of 1 or more of these features for incorporation into a closed-loop paradigm becomes a process of trial and error. By inserting recording electrodes in cortical and basal ganglia structures in the nonhuman primate, Rosin et al[12] demonstrated that responsive DBS that was triggered by action potentials in the motor cortex was effective in improving motor function and was associated with a prominent reduction in pallidal oscillatory activity. Conversely, triggering DBS based on action potentials in the pallidum (rather than the motor cortex) increased pallidal oscillatory activity and actually worsened motor activity. These experiments supported the pathologic role of these oscillations and (in concert with other key research and clinical observational studies) helped prompt clinical investigation of closed-loop stimulation in patients with Parkinson disease triggering on oscillatory activity recorded in the basal ganglia.[8]

Experimentation in animal models offers the advantage of recording signals from individual and populations of neurons in brain regions often inaccessible to clinical recording in humans, as well as the possibility of recording from multiple distributed brain regions simultaneously. Such approaches allow for better characterization of network-level mechanisms at the spatiotemporal scale of neuronal interactions, the significance of which is being increasingly recognized in neurological disorders.[15,16] Closed-loop methods have been used successfully to selectively detect and abolish or enhance hippocampal sharp wave ripples by electrical[17] or optogenetic[18] stimulation and to demonstrate that these oscillations have a causal role in memory trace consolidation. However, the successful translation of animal studies results to clinical applications is dependent on the reliability of the animal model used, emphasizing the importance of an ongoing dialogue among researchers involved in animal and clinical studies of any given disorder.

Sensors

Once the relevant signals have been identified, appropriate sensors for acquisition of these signals are required. For electrophysiological signals, sensors should be placed in proximity to the generator of the pathologic signal and be capable of sufficiently high temporal resolution acquisition. For example, changes in neural spiking rates or patterns are linked to

the onset of seizures and worsening of parkinsonian symptoms in humans and could potentially be used for triggering intervention in a closed-loopsystem.[19,20] However, most clinical electrodes placed on the brain surface (electrocorticography electrodes) or within deep structures (depth electrodes) are too large and often transduce signals too inefficiently to capture high-frequency activity in the form of action potentials. Electrodes or arrays with improved spatiotemporal resolution could substantially enhance the sensitivity and specificity of closed-loop therapeutics. Seizure control is a prime example of the potential benefits of improved triggering methods through improved signal selection and recording methods because it has been demonstrated that early intervention improves the success of seizure termination.[21] Evidence from high-density microelectrode arrays (eg, NeuroPort; Cyberkinetics Neurotechnology Systems) inserted into the cortex located in the seizure-onset zone in patients with medically refractory epilepsy revealed microseizures that often preceded detection of seizure activity on the clinical subdural electrodes.[22] Multiunit spiking activity acquired by these research electrodes further showed that there was a discrepancy between the onset of the ictal rhythm as detected by conventional electrodes and the time of hypersynchronous neuronal recruitment.[16] Therefore, it is possible that the use of refined electrodes capable of acquiring spike resolution data could serve as more effective triggers for closed-loop intervention in epilepsy.

However, the clinical relevance of microelectrode arrays for closed-loop therapy is currently limited by their small spatial coverage (typically 4×4 mm), instability in recording unit activity over long periods, and cortical damage associated with array insertion.[23,24] These barriers could potentially be overcome by innovations in electrode design. Ongoing mechanical trauma caused by micromotion of implanted electrodes contributes substantially to recording instability and post implantation glial cell activation.[24,25] A sinusoidal probe microfabricated from flexible materials has been designed to minimize this motion and has successfully recorded physiological signals for close to 2 years' duration with decreased neuronal tissue damage in a rabbit model.[26] An alternative approach involves detection of spiking activity from the surface of the human brain using conformable, biocompatible, and scalable electrode arrays based on conducting polymers (NeuroGrid[27]). Further studies are required before such technology could be translated to routine clinical use, but these novel sensors could improve the sensitivity of detection while simultaneously decreasing the potential adverse effects of sensor placement.

Advances in sensors are not limited to electrophysiology. In addition to electrical fields, neurons generate neurochemical signatures in the extracellular space due to neurotransmitter release. Changes in various neuroactive substances are associated with neurological disease. The most well-known is the pallidal dopamine deficiency in Parkinson disease.[28] Fast-scan cyclic voltammetry is a method by which changes in the extracellular concentration of electroactive molecules (eg, dopamine, norepinephrine, serotonin, and adenosine) can be measured in real time by oxidation and reduction reactions at a carbon fiber electrode.[29] In patients with essential tremor, fast-scan cyclic voltammetry has been incorporated into a wireless, instantaneous, neurochemical concentration sensing system that can quantify changes in adenosine release following DBS electrode insertion.[30] Similar sensors could serve as the input component of closed-loop systems that aim to maintain constant extra-

cellular concentrations of a targeted neurochemical, such as dopamine in Parkinson disease.[31]

Detection Algorithms

Fast and reliable pattern detection algorithms with a low incidence of false alarms are needed for making closed-loop stimulation safe and effective in clinical settings. Although such algorithms are required for all closed-loop devices, the inherent difficulties and possibilities for implementation of novel strategies is especially evident for seizure detection in patients with epilepsy and is thus discussed herein.

Seizure detection is a complex issue due to the heterogeneity of seizure characteristics in individual seizures from the same patient and in seizures from different patients. Detection algorithms have been based on features of signals extracted from electroencephalography, electrocorticography, electromyography, electrocardiography, accelerometry, and video recordings,[32] but the only closed-loop device currently approved by the Food and Drug Administration (NeuroPace system) uses signals recorded from electrocorticography or implanted depth electrodes.[33] This device has 3 detection parameters (bandpass, line length, and area) that can be adjusted by the physician to enhance the sensitivity and specificity for each individual patient's electrophysiological seizure pattern. Although this detection algorithm is computationally efficient and can detect events within a fraction of a second, adjustment of detection parameters is fine-tuned by trial and error, requiring significant time for the physician and patient. A potential solution to this issue is to use advanced classification methods or learning algorithms, which are increasingly being used in a wide variety of applications from drug discovery to computer vision. Methods that have been tried for seizure detection include support vector machines, artificial neural networks, fuzzy logic models, and Markov modeling.[32] Such approaches typically involve a training phase, during which previously acquired data are processed and relevant features indicating seizure onset are extracted. A classifier that can be run in real time is then created and used to detect subsequent seizures. Data from many patients can be used during training, with the goal of creating a generalizable classifier; alternatively, a substantial amount of data from an individual patient can be used to derive a patient-specific classifier.[34] A significant challenge to these approaches is to optimize the speed of the real-time classifier to detect seizures within a reasonable latency for closed-loop applications.

Effectors and Actuators

Ideally, effective stimulation parameters for a closed-loop system should revert pathologic neural activity patterns to physiological patterns. Some disorders could benefit from large volume and relatively diffuse stimulation or suppression of cortex-wide activity, whereas others need focal stimulation. In practice, these parameters can be difficult to establish because the effects of electrical stimulation on populations of neurons are often unknown, and various cell types in the brain may be influenced. For example, it may be theoretically advantageous to suppress the firing of pyramidal (excitatory) cells but not interneurons (inhibitory) at the onset of a seizure. Testing the effect of cell type–specific modulation on

pathologic states was not efficiently possible until the application of optogenetic techniques,[35] described in detail below.

Optogenetics rests on selective expression of light-sensitive proteins.[36] These engineered proteins (called opsins) are not natively expressed. Therefore, the use of optogenetic techniques has so far been limited to animal research. Through restricted expression of the light-sensitive proteins, selective control of specific neuronal populations is possible. In addition, different light-sensitive proteins exist, including excitatory channels (to increase the firing rate of expressing neurons) and inhibitory pumps and channels (to inhibit the firing of expressing neurons). Therefore, on-demand optogenetics provides not only the temporal specificity of electrical stimulation but also cell-type specificity and direct control over the direction of modulation (ie, excitation or inhibition). For example, it is now possible to selectively inhibit a subclass of neurons in a particular brain region at a particular time, at least in animal studies.[37] The great specificity of intervention achievable with on-demand optogenetics already makes it an extremely powerful experimental tool, and discoveries made can have implications in the clinical setting.

Optogenetic techniques have been applied in several epilepsy models,[38] and on-demand optogenetics specifically has shown success in rodent models of thalamocortical[39] and temporal lobe[9] epilepsy. One recent study[39] reported that experimental cortical stroke could induce thalamocortical epilepsy and examined the potential for on-demand optogenetics targeting the thalamus to stop these cortical stroke–induced seizures. To inhibit thalamic output, an inhibitory opsin (halorhodopsin) was expressed in excitatory cells in the ventrobasal thalamus ipsilateral to the site of induced cortical stroke.[39] Seizures were detected online using line-length threshold crossing, rapidly triggering automatic light delivery. This on-demand optogenetic approach successfully truncated thalamocortical seizures.

Several distinct on-demand optogenetic approaches for temporal lobe seizures have been tested.[40] First, an inhibitory light-activated chloride pump (halorhodopsin) was expressed in excitatory cells.[9] On-demand light delivery to the hippocampus inhibited these cells and dramatically truncated seizures (Figure, C and D). A second approach tested an excitatory light-activated cation channel (channelrhodopsin) expressed in a subpopulation of inhibitory neurons. These neurons comprise less than 5% of the neuronal population.[41,42] On-demand light delivery to the hippocampus excited these inhibitory cells (which in turn inhibited excitatory hippocampal neurons).[9] Despite directly targeting such a limited population of inhibitory interneurons, this approach also effectively inhibited temporal lobe seizures. These findings indicate not only that a temporally precise on-demand intervention can provide seizure control, but also that a cell-type restricted intervention can work. Recently, it was shown that an on-demand optogenetic approach targeting the cerebellum could inhibit temporal lobe seizures, with optogenetic excitation of the midline cerebellum producing a unique long-lasting inhibition of seizure initiation.[43] These studies pave the way for future uses of on-demand optogenetics to study the cell types and networks critically involved in seizures.

Similarly, optogenetics has been used to elucidate cell type–specific output targets in Parkinson disease. Optogenetic activation of direct pathway medium spiny neurons in the striatum of mice with 6-hydroxydopamine–induced parkinsonism improved bradykinesia to prelesion levels, whereas activation of indirect pathway medium spiny neurons generated parkinsonism in mice with previously normal motor behavior.[44] These results provide causal support for the role of these pathways in basal ganglia function and establish that pathway-specific stimulation is sufficient to ameliorate parkinsonian symptoms. A different optogenetic approach revealed that inhibition of subthalamic nucleus firing (the presumed mechanism by which DBS operates) was insufficient to improve parkinsonian symptoms in hemiparkinsonian rats.[35] These authors were then able to photostimulate only afferent fibers arriving from the cortex rather than subthalamic neurons using a transgenic mouse expressing channelrhodopsin under the Thy1 promoter. This specific stimulation was able to replicate the beneficial effects of DBS in these rats, suggesting a new anatomical target for stimulation in this disorder.

Optogenetic techniques are not currently available for humans, in part due to safety concerns arising from the need for gene therapy approaches to achieve opsin expression (because these proteins are not natively expressed).[45,46] However, safety has been demonstrated for a variety of viral vectors for gene therapy for Parkinson disease,[47] and orphan drug status has been given to a viral vector–based channelrhodopsin (RetroSense Therapeutics) as part of the process to potentially establish clinical trials for optogenetic restoration of vision in patients with retinitis pigmentosa. As such, it is conceivable that, in the future, optogenetic techniques may transition from a method to refine output parameters to an actuator in closed-loop therapeutic devices.

At present, most actuators in closed-loop neurological systems involve modification of electromagnetic fields in the brain via focal electrical stimulation. Current is injected via depth leads or subdural strips (NeuroPace system) or via a depth electrode with 4 cylindrical contacts (DBS Therapy; Medtronic, Inc). However, there is substantial clinical interest in the development of noninvasive closed-loop actuators, which would likely decrease cost and device adverse effects. Transcranial electrical stimulation (TES) may be an effective noninvasive actuator for paroxysmal neurological disorders due to its great temporal precision. Furthermore, TES does not require the bulky and more expensive equipment needed for trans-cranial magnetic stimulation. The excitement for the potential of TES is evident in the range of applications recently tested in humans, from addiction to stroke rehabilitation, spatial tactile acuity, and reading performance.[48,49] Transcranial electrical stimulation can be applied in a variety of manners, including alternating current or direct current schemes. Transcranial electrical stimulation is reported to be safe, with only limited and minor adverse effects, including itching, tingling, and fatigue.[50] Most important, effects of TES are reported to be brain state dependent.[10,48,51,52] In this regard, combining TES with a closed-loop system may not only reduce unnecessary intervention but also actually improve symptom control.[10]

Indeed, a study[10] examining the use of TES in a rodent model of absence epilepsy (also referred to as thalamocortical epilepsy) indicated that on-demand intervention may provide superior seizure control. Long-Evans rats with spontaneously recurring spike-and-wave

episodes (which are characteristic of absence seizures) were implanted with electrodes to record neuronal activity and these seizure events. Three recording electrodes were placed at equally increasing depths in the neocortex (a, b, and c in Figure, E). The recorded signal was first amplified and filtered, and a current source density (CSD) trace was generated using the following equation: $CSD = 2b − (a + c)$. Then, spike-and-wave episodes were rapidly detected online as voltage crossings of a preset threshold level of the CSD trace, and TES was delivered via transcranial stimulating electrodes implanted on the skull (Figure, E). Effects of constant (not on-demand) 1-Hz sinusoidal stimulation and on-demand stimulation (50-millisecond gaussian waveforms triggered by online seizure detection) were examined. While sinusoidal stimulation was able to entrain the firing of neurons (recorded as multiunit firing) and modulate the amplitude of spike-and-wave episodes, it was unable to reduce the duration of spike-and-wave episodes. In contrast, on-demand TES significantly inhibited seizure duration and thereby reduced the amount of time the animal spent seizing (Figure, F). These findings demonstrate 2 critical points. First, TES can effectively inhibit absence seizures. Second, seizure control can be improved by using an on-demand approach.

A similar approach has been piloted for tremor reduction in patients with Parkinson disease.[53] In this case, TES was applied focally to the motor cortex at the frequency of the patient's tremor, as recorded by an accelerometer on the wrist. Closed-loop stimulation that produced a specific phase alignment of TES and motor tremor was more effective than open-loop stimulation in reduction of tremor amplitude. Although the efficacy of this method has only been demonstrated acutely, it illustrates the potential efficacy of noninvasive technologies when used in a closed-loop fashion.

Despite the success of these TES-based closed-loop paradigms, the mechanisms by which TES affects neural activity acutely and chronically in specific brain regions remain obscure. Therefore, in parallel with the development of TES devices, carefully designed studies should be undertaken to clarify the underlying physiological basis for observed effects. Such studies[10,54] in animal models, where it is possible to couple invasive neural recordings with TES, have already begun to make progress in understanding the modulations of local field potential and spiking activity that occur in behaving animals during TES stimulation.

Conclusions

Closed-loop devices have been successfully used to treat several neurological disorders in severely affected patients for whom noninvasive therapies are insufficient. However, closed-loop technology may improve therapeutic efficacy and reduce adverse effects of treatment in a broader patient population by limiting intervention to specific times when it is required and responding to an individual patient's internal brain dynamics. Currently, the invasiveness of such devices and lack of comprehensive understanding of which pathophysiological signals to modify, as well as how to precisely modify them, preclude widespread use. Experimental models and approaches such as those described herein can help improve all aspects of these technologies and provide a unique opportunity to study the underlying mechanisms of physiological and pathologic neural processes.[18,55] These studies will be critical as closed-loop paradigms are applied to increasingly diverse clinical disorders, including stroke rehabilitation,[56] minimally consciousstate,[57] and a host of

psychiatric disorders.[58,59] Effective closed-loop systems for clinical use require advanced understanding of pathophysiological brain signals combined with sophisticated technology for signal processing and subsequent modulation. Only when advancements in basic science, engineering, and materials science are coupled to clinical need will closed-loop technologies translate efficiently to improvements in therapeutic devices for patients with neurological disorders.

Acknowledgments

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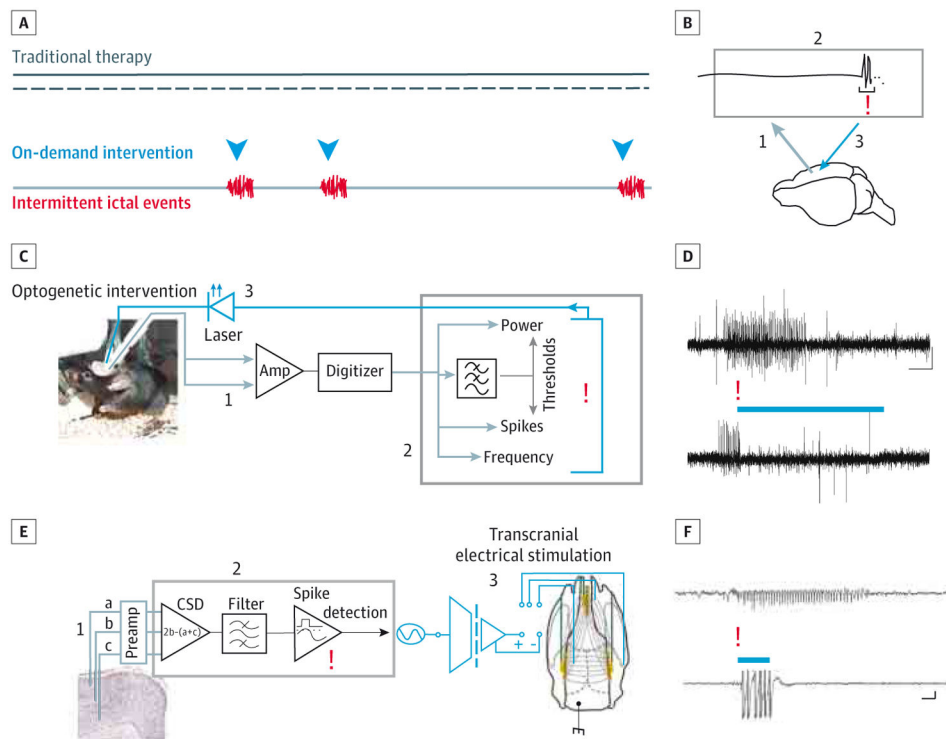
Figure. Closed-Loop Intervention to Inhibit Spontaneous Seizures

A, In contrast to traditional therapeutic approaches (black lines), which are applied in a constant or scheduled manner without regard to brain states or the actual occurrence of pathologic events such as seizures, on-demand intervention is designed to align intervention (blue arrowheads) with events that require intervention (eg, seizures [red]). B, Such closed-loop approaches use information about ongoing brain activity to determine when to provide intervention. Brain activity is recorded (step 1 [gray]) and processed in real time (step 2 [upper rectangle]) to detect events online (red exclamation point). Detection triggers immediate intervention (step 3 [blue]), altering brain activity and closing the loop. C, Closed-loop optogenetic system used to detect spontaneous temporal lobe seizures based on various properties of the signal, including power, spiking, and frequency components. D, On-demand optogenetic inhibition of excitatory cells reduced seizure duration. The top trace shows a spontaneous seizure without intervention, and the bottom trace shows a spontaneous seizure with light intervention. E, Closed-loop transcranial electrical stimulation intervention system used to inhibit absence seizures in rats (described in detail in the Effectors and Actuators section in the main text). CSD indicates current source density. F, On-demand transcranial electrical stimulation intervention shortens absence seizures. The top trace shows a spontaneous seizure recorded without intervention, and the bottom trace shows a spontaneous seizure detected online (red exclamation point), triggering transcranial electrical stimulation intervention (the period of intervention is denoted by a blue bar [the large amplitude signal is a transcranial electrical stimulation–induced artifact and has been truncated]). Scale bars are 500 ms and 0.5 mV (D) and 5 s and 100 μV (F). C and D are modified with permission and in accord with the Creative Commons license (http://

creativecommons.org/licenses/by/3.0/) from Krook-Magnuson et al.[9] E and F are modified with permission from Berényi et al.[10]