Homeostatic activity regulation as a mechanism underlying the effect of brain stimulation

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Abstract
Hyperexcitability of the neural network often occurs after brain injuries or degeneration and is a key pathophysiological feature in certain neurological diseases such as epilepsy, neuropathic pain, and tinnitus. Although the standard approach of pharmacological treatments is to directly suppress the hyperexcitability through reducing excitation or enhancing inhibition, different techniques for stimulating brain activity are often used to treat refractory neurological conditions. However, it is unclear why stimulating brain activity would be effective for controlling hyperexcitability. Recent studies suggest that the pathogenesis in these disorders exhibits a transition from an initial activity loss after acute injury or progressive neurodegeneration to subsequent development of hyperexcitability. This process mimics homeostatic activity regulation and may contribute to developing network hyperexcitability that underlies neurological symptoms. This hypothesis also predicts that stimulating brain activity should be effective in reducing hyperexcitability due to homeostatic activity regulation and in relieving symptoms. Here we review current evidence of homeostatic plasticity in the development of hyperexcitability in some neurological diseases and the effects of brain stimulation. The homeostatic plasticity hypothesis may provide new insights into the pathophysiology of neurological diseases and may guide the use of brain stimulation techniques for treating them.

Keywords: Homeostatic synaptic plasticity, Hyperexcitability, Brain stimulation, Epilepsy, Neuropathic pain, Tinnitus, Traumatic brain injury, Stroke

Introduction
Hyperexcitability and excessive abnormal activity of the neural network is a common pathophysiological mechanism underlying many neurological disorders such as epilepsy, neuropathic pain, tinnitus, and Alzheimer’s disease (Latremoliere and Woolf 2009; Eggermont 2005; Badawy et al. 2009a; Vossel et al. 2017). The observation of such hyperexcitability naturally leads to a treatment strategy that targets to directly inhibiting neuronal activity so that a normal level of activity and neurological functions will be recovered and maintained. In fact, modern pharmaceutical industry is dominated by efforts to develop drugs to inhibit different components of neural circuits. Many drugs work by inhibiting neuronal activity and excitability. However, this strategy does not always work successfully. Because many patients with neurological disorders are refractory to conventional drug treatments, more radical and invasive therapeutic approaches are often required for symptom control. For example, about one third of patients with neuropathic pain or acquired epilepsy cannot be effectively controlled with the best of existing drug treatments (Finnerup et al. 2015; Yoo and Panov 2019).

Paradoxically, brain stimulation that enhances neuronal activity is also found to be effective for treating these hyperexcitable neurological diseases (De Ridder et al. 2007; Treister et al. 2013; Morrell 2011). How can either inhibiting or stimulating neuronal activity be effective in controlling these diseases? While various hypotheses have been proposed to explain the therapeutic mechanism, the direct effect of brain stimulation on the stimulated network is not well understood. A deep understanding of causes that lead to hyperexcitability may provide novel insight on the...
mechanism and treatment strategy. Because these neurological disorders start with an acute or chronic injury, progressive degeneration of neurons, or loss of afferent input, a homeostatic plasticity mechanism may play a role in the development and maintenance of brain hyperexcitability. This hypothesis also supports that stimulating brain activity can control aberrant hyperexcitability through compensating the lost activity to reduce homeostatic hyperexcitability. Recent studies on diseases such as neuropathic pain, acquired epilepsy, and tinnitus support a role of homeostatic plasticity mechanism and demonstrate the effectiveness of targeting excitatory activity for disease treatment. Here we review observations on neurological diseases that feature circuit hyperexcitability and the effectiveness of brain stimulation on them. We summarize recent progress on using homeostatic plasticity to explain the mechanism and to guide developing novel treatment strategies in the future.

Hyperexcitability is a key neurophysiological change in some neurological diseases

Network hyperexcitability occurs in many neurological disorders such as epilepsy, traumatic brain injury (TBI), chronic pain, migraine, stroke, tinnitus, and Alzheimer’s disease (AD). These conditions involve injuries or pathologies of either the central nervous system (CNS) (e.g. epilepsy) or peripheral nervous system (PNS) (e.g. neuropathic pain). In terms of etiology, there are acute injuries such as TBI, spinal cord injury, and stroke, or chronic damage or neurodegeneration such as AD.

Epilepsy has hyperexcitability as its defining pathophysiological feature, with epileptic seizures resulting from an imbalance between excitation and inhibition. Hyperexcitability has been observed in many different types of epilepsies (Badawy et al. 2009a; Bauer et al. 2014). Enhanced excitation or reduced inhibition is generally regarded as an important basic mechanism in the generation of epileptic seizures (Badawy et al. 2009b; Scharfman 2007) (Fig. 1a). Moreover, most antiepileptic drugs work by enhancing inhibition and/or reducing excitation (Stafstrom 2010; White et al. 2007).

Recovery following stroke or TBI involves development of hyperexcitability. In the peri-infarct region of stroke, transient appearance of low-frequency spontaneous activity (0.1–1.0 Hz) occurs earlier after injury, followed by development of hyperexcitability in the following weeks (Carmichael and Chesselet 2002). High discharge frequency in the perilesional region peaks in 3–7 days post-stroke and maintains higher for up to 4 months (Neumann-Haefelin et al. 1995; Schiene et al. 1996). In a mouse model of permanent ligation of the middle cerebral artery, hyperexcitability of sensorimotor cortex also develops on the intact contralateral cortex in 2–6 weeks after stroke (Barios et al. 2016). Similarly, TBI is known to cause hyperexcitability of neocortex and hippocampus by increasing glutamate signaling, enhancing synaptic bursting, impairing GABAergic inhibition, and inducing epileptiform activity (Nichols et al. 2015; Cantu et al. 2015; Golarai et al. 2001; Hoffman et al. 1994).

Neuropathic pain originates from a primary lesion of the somatosensory nervous system such as nerve or spinal cord injury, which causes peripheral and central sensitization of the nociceptive pathways (Latremoliere and Woolf 2009). The resulting neuronal hyperexcitability and ectopic spontaneous firing of the nociceptive pathways are believed to be its key underlying neurophysiological mechanism. In tibial nerve injury model of neuropathic pain, optical imaging of voltage sensitive

**Fig. 1** A schematic presentation of the homeostatic plasticity mechanism. a. Reduced inhibition (I) and/or enhanced excitation (E) that leads to hyperexcitability is a widely accepted mechanism of acquired epilepsy. b. We propose that the brain needs to not only maintain a balance between E and I, but also maintain a set level of functional output (i.e. neuronal activity, represented here as filling the circle). c. Injuries and other brain pathologies cause loss of neurons and neuronal activity (dotted circle). To compensate for the lost function, the neural network would use the homeostatic plasticity mechanism to scale up excitation (E) (and may simultaneously reduce inhibition (I)) to attempt to reach a set level of neuronal activity, which causes hyperexcitability simultaneously. d. Controlling hyperexcitability may be achieved by stimulating neuronal activity after injuries or degeneration, which will promote functional recovery and suppress intrinsic homeostatic activity regulation, and increase activity-dependent enhancement of inhibition.
and stroke) or during the chronic phase of progressive period following acute injury (e.g. posttraumatic epilepsy excitability at certain specific time points after a latent et al. 2009). Although these mechanisms explain hyperactivity at AMPA receptors and enhanced excitatory synaptic transmission in models of neuropathic pain (Blom et al. 2014; Gao et al. 2016; Yang et al. 2018).

Tinnitus is the perception of a sound in the absence of acoustic stimulation. Cochlear damage and hearing loss can lead to tinnitus and abnormally increased spontaneous firing rates, synchronization of neurons, and elevated AMPA receptor mRNA expression and reduced GABAA receptor mRNA expression in the auditory pathway, including the primary auditory and associated cortices (Bar tels et al. 2007; Elgoyhen et al. 2015; Balaram et al. 2019). Interestingly, in a blast brain injury model in rats, spontaneous activity in auditory cortex in the tinnitus-positive rats show robust hyperactivity at all frequency regions in 3 months after injury (Luo et al. 2017). In a hearing loss model, neurons in the auditory cortex that represent the hearing-loss frequencies have reduced inhibitory synaptic transmission, unaltered excitatory synaptic transmission, and behavioral signs of tinnitus with the pitch in the hearing-loss frequency range (Yang et al. 2011).

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by dementia and progressive memory loss. Network hyperexcitability and epilepsy is a feature of AD in patients as well as in numerous mouse models (Palop et al. 2007; Kazim et al. 2017; Garcia-Cab rero et al. 2013). Intercitial spikes are seen in a high percentage of AD patients who have no prior history of clinical seizures (Vossel et al. 2016). Nonictal network hyperactivity has been detected with fMRI in individuals at risk of developing dementia, such as in those carrying the APOE4 allele (Filippini et al. 2009) and in patients with mild cognitive impairment (Dickerson et al. 2005).

Additionally, other neurological disorders feature development of network hyperexcitability such as migraine and autism spectrum disorders including fragile X syndrome (Burstein et al. 2015; Zarcone and Corbetta 2017; Takarae and Sweeney 2017).

The hyperexcitability in these neurological conditions can be induced by various neurophysiological alterations, which include sprouting of excitatory axons, changes in intrinsic excitability of pyramidal neurons, insertion of AMPA receptors and enhanced excitatory synaptic transmission, reduced number of interneurons, impaired inhibitory synapses, impaired efficacy of inhibition due to chloride potassium transporter (Becker 2018; Prince et al. 2009). Although these mechanisms explain hyperexcitability at certain specific time points after a latent period following acute injury (e.g. posttraumatic epilepsy and stroke) or during the chronic phase of progressive neurodegeneration (e.g. AD), they do not elucidate why a damaged brain tends to become hyperexcitable. In this regard, a homeostatic plasticity mechanism may provide a useful model to explain the development of network hyperexcitability.

**Homeostatic plasticity drives the development of network hyperexcitability**

Homeostatic plasticity is the intrinsic capability of the neural network to maintain a relatively constant level of activity in response to an imposed increase or decrease in neuronal activity (Turrigiano et al. 1998). For example, when a cortical network loses activity or afferent input, it responds with enhanced excitatory synaptic strength and intrinsic excitability and/or a reduction in synaptic inhibition to maintain a relatively constant level of activity (Turrigiano et al. 1998; Davis and Bezprozvanny 2001). Although homeostatic plasticity has been extensively studied in cultured neurons, brain slices, and more recently in visual cortex in vivo (Keck et al. 2013; Hengen et al. 2013; Goel and Lee 2007; Ec hego et al. 2007), its role in neurological disorders only begins to be revealed. Based on the homeostatic plasticity mechanism, we hypothesize that neural network must not only keep a dynamic balance between excitation and inhibition, but also maintain a certain level of activity as its functional output (Fig. 1b). Such homeostatic regulation may serve as a compensatory mechanism after brain injuries or neurodegeneration. Because hyperexcitability often develops from an acute (e.g. TBI and neuropathic pain) or chronic (e.g. AD) loss of neurons and synapses, abnormal homeostatic plasticity in response to the lesions and activity loss likely contributes to the development of hyperexcitability that underlies the symptoms (Fig. 1c). Indeed, sensory deprivation due to PNS injury is identical to some classical animal models for inducing homeostatic plasticity.

Homeostatic synaptic plasticity may be a driving force that underlies the development of acquired epilepsy, which usually develops following an initial insult such as TBI or status epilepticus (Houweling et al. 2005; Avramescu and Timofeev 2008; Dinocourt et al. 2011). Brain injury, particularly severe TBI and penetrating TBI, causes neuronal death, tissue damage, and an initial loss of activity in surviving neurons (Ping and Jin 2016; Alves et al. 2005). Lower action potential firing rates are recorded in the lateral fluid percussion and undercut models of TBI in vivo (Alves et al. 2005; Timofeev et al. 2000). Pharmacological blockade of neuronal activity of hippocampal neurons in vitro or in vivo for a few days leads to hyperexcitability with increased glutamatergic transmission, decreased GABAergic synaptic inputs, and epileptogenesis (Trasande and Ramirez 2007). In the hippocampus of developing animals, chronic blockade of activity with tetrodotoxin or a lesion produces chronic
focal seizures accompanied by axon sprouting and increased intrinsic excitability (McKinney et al. 1997; Bausch et al. 2006). Similarly, neuronal activity is also depressed following brain ischemia (Heiss et al. 1976), which is followed by development of hyperexcitability.

Deprivation of peripheral input by activity blockade, amputation, or nervous lesion may cause homeostatic hyperexcitability of cortical network in developing or adult brain (Xiong et al. 2017; Wang and Thompson 2008). Such homeostatic plasticity regulation may underlie the development of hyperexcitability in neuropathic pain. During the earlier time period after spinal cord injury, slower and more silent overall cortical spontaneous activity is recorded in the deafferented cortex as well as in the neighboring cortex, representing a switch to a slow-wave network activity (Boord et al. 2008). In a spinal cord ischemia model of neuropathic pain, in vivo two-photon imaging demonstrated that initial activity loss occurs in 6 h after injury in cortical layer II/III pyramidal neurons of the primary somatosensory cortex, followed by recovery and hyperactivity in 48 h (Xiong et al. 2017). Because development of neuropathic pain reflects a transition from an initial loss of neuronal activity due to a primary lesion (e.g. nerve or spinal cord injury (SCI)) to a state of hyperexcitability of the affected neural network, this process is identical to the classical model of homeostatic plasticity.

Homeostatic plasticity is also suggested to contribute to hyperexcitability in auditory pathway in tinnitus (Yang et al. 2011) (Auerbach, 2014 #38). A computational study suggested that homeostatic compensation leads to hyperactivity of the model neurons when a normal ratio between mean and spontaneous firing rate of the auditory nerve is decreased due to a loss of outer hair cells or damage to hair cell stereocilia. Homeostasis can also amplify non-auditory inputs, which then contribute to hyperactivity (Schaette and Kempter 2006).

**Homeostatic plasticity supports the effectiveness of brain stimulation**

The idea that pathological hyperexcitability originates from homeostatic plasticity suggests that it is not sufficient to directly suppress hyperexcitability by blocking excitation or enhancing inhibition. If a loss of neuronal activity caused by CNS or PNS injuries induces homeostatic hyperexcitability and neurological disorders, then stimulating activity at an earlier time period following injury should suppress pathological homeostatic regulation/compensation and prevent the development of neurological diseases (e.g. acquired epilepsy after brain injury) (Fig. 1d). Furthermore, because the primary lesion or pathology in the etiology of these neurological disorders is often permanent or progressive, such homeostatic compensation is likely a constant or progressive process so that the deafferented or injured brain circuits can maintain a set level of activity. In that case, stimulating brain activity will relieve the constant burden of homeostatic regulation so that hyperexcitability is reduced and activity of neural circuits is reversed to a relatively normal activity state (Fig. 1d). Therefore, stimulating activity should also be effective in controlling or reversing neurological conditions that have already developed through homeostatic regulation. Below we summarize current evidence that supports this idea (Table 1).

The predicted effectiveness of activity enhancement on disease prevention and treatment is supported by some evidence from previous clinical and animal studies. Electrical stimulation is effective in reducing bursting activity in neuronal culture in vitro (Madhavan et al. 2006; Wagenaar et al. 2005) and in enhancing neuronal plasticity and synaptic reorganization and controlling partial seizures in drug resistant patients in vivo (Ziemann et al. 2002; Demirtas-Tatlıdede et al. 2011). Electrical stimulation of hippocampus has also been demonstrated to be effective and safe for controlling refractory temporal lobe epilepsy (Han et al. 2014). A recent double-blind, randomized, controlled trial in patients with refractory partial-onset seizures suggested that open loop cortical stimulation for 1 month resulted in a significant reduction in mean seizure frequency in the treatment group compared with that in the sham group (37.9% versus 17.3%) (Morrell 2011). However, evidence that specifically supports a role of homeostatic plasticity in preventing acquired epileptogenesis or controlling epileptic seizures is still not available.

Activity enhancement can also be achieved by pharmacologically modulating excitatory or inhibitory components of neural network. Treatment of cultured hippocampal slices with bicuculline for 1 week greatly diminishes the intensity of epileptiform activity that could be induced (Swann et al. 2007). For acquired epilepsy, cannabinoid antagonist SR141716A and alpha (2)-adrenergic antagonist atipamezole are both proconvulsant, but their application immediately after brain insults prevents the development of hyperexcitability or reduces seizure frequency and severity in animal models of epilepsy (Echegoyen et al. 2009; Pitkänen et al. 2004).

Auditory cortical stimulation may be a valuable treatment option for severe intractable tinnitus. In severe cases of intractable tinnitus, 37% of patients were responsive to tonic auditory cortex stimulation via implanted electrodes in the primary auditory cortex or overlying the secondary auditory cortex. A half of the 63% non-responders became responsive after switching to burst stimulation (De Ridder et al. 2011). Burst stimulation is capable of suppressing tinnitus in more patients more effectively than tonic stimulation, especially for noise-like tinnitus (Meng et al. 2011). However, non-
invasive brain stimulation using repetitive transcranial magnetic stimulation (rTMS) have shown mixed results on tinnitus, with some studies showing significant improvement in the severity of tinnitus while the others having no significant effect (Meng et al. 2011; Londero et al. 2018; Landgrebe et al. 2017). Since different stimulation parameters and study designs affect the efficacy of rTMS and treatment outcome, further basic and translational studies are needed to elucidate the efficacy and mechanism of rTMS for tinnitus.

Enhancing brain activity after peripheral lesion can control cortical hyperexcitability and reduce pain. We recently showed that using optogenetic stimulation or a GABA<sub>A</sub> receptor antagonist to enhance cortical layer V pyramidal neuron activity in S1 resulted in reduced pain-like behavior in a transient spinal cord ischemia model and a tibial nerve injury model of neuropathic pain. The stimulation directly reduced hyperexcitability of the S1 through decreasing excitatory synaptic transmission and increasing the threshold of action potential firing of the related cortical neurons (Xiong et al. 2017). Clinical studies demonstrated that stimulating motor cortex or S1 using rTMS (5–20 Hz) is effective in controlling refractory chronic pain including neuropathic pain and phantom pain (De Ridder et al. 2007; Lima and Fregni 2008). Although the underlying mechanisms of brain stimulation on refractory pain are unclear and may involve inhibiting the nociceptive pathway (e.g. thalamus) and activating descending pain modulation (Treister et al. 2013), homeostatic plasticity regulation may provide a novel explanation for the effect.

**Table 1** Effects of activity enhancement on neurological disorders featuring hyperexcitability

| Condition          | Model or patients                                                                 | Treatment                                                                                           | Effect                                                                                              | References                                      |
|--------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Acquired epilepsy  | Multi-electrode arrays recording of neuronal culture in vitro.                    | Electrical stimulation (0.05–50 Hz)                                                                  | Higher stimulation frequency transforms burst activity to dispersed spiking reminiscent of the awake cortex in vivo | (Madhavan et al. 2006; Wagenaar et al. 2005) |
| Temporal lobe epilepsy in rats in vivo | Electrical stimulation of subcubicum after kindling or pilocarpine injection | 1 Hz stimulation retarded progression of kindling seizures and inhibited chronic spontaneous pilocarpine-induced seizures | (Han et al. 2014; Zhong et al. 2012)                                                                |
| 191 patients with refractory partial-onset seizures. A double-blind, randomized, controlled trial | Open-loop responsive cortical stimulation for 1 month | Reduction in seizure frequency in the treatment group (~37.9%) than control group (~17.3%). | (Morrell 2011)                                                                                       |
| Alpha (2)-adrenocceptor antagonist atipamezole | Treatment started 1 week after SE induction and lasted for 9 weeks. | Lower seizure frequency and severity, and milde cell damage and mossy fiber sprouting in treatment group. | (Pitkanen et al. 2004)                                                                            |
| Neuropathic pain   | Spared tibial nerve injury and transient spinal cord ischemia models of neuropathic pain in mice | S1 optogenetic stimulation for 1 week, or S1 activity enhancement by bicuculline. | Reduced pain-like behavior in both models and reduced S1 neuronal [80]excitability. | (Xiong et al. 2017). |
| Eight intractable neuropathic pain patients | TMS (1–50 Hz for 1 h) or electrical stimulation (4–8 Hz) for 1 month. | Significant pain relief in all patients. | (De Ridder et al. 2007)                                                                      |
| Tinnitus           | 43 intractable tinnitus patients                                                  | Implanted electrodes in the primary auditory cortex or secondary auditory cortex                    | 67% of patients improved with average tinnitus reduction of 53%. Burst stimulation has better effect than tonic stimulation. | (De Ridder et al. 2011) (Meng et al. 2011). |
| 163 tinnitus patients | rTMS at 1 Hz (2000 stimuli, 110% motor threshold) or sham stimulation | This protocol has no effect. | (Landgrebe et al. 2017)                                                                |
| Ten tinnitus patients | rTMS at 1 Hz on auditory cortex for 5 consecutive days | Improvement was associated with increases intracortical inhibition, intracortical facilitation, and prolongation of cortical silent period. | (Langguth et al. 2007)                                                                 |
| Tinnitus induced by tone exposure in rats | Auditory cortex electrical stimulation with electrical array. | Tinnitus is suppressed and hearing is improved at the central level. | (Zhang et al. 2011)                                                                 |

**Perspectives and conclusions**

Research on homeostatic plasticity has been mainly focused on its basic physiological role and mechanisms, while sensory deprivation is often used as a tool for inducing homeostatic plasticity. Recent studies have extended to various neurological conditions such as neuropathic pain and acquired epilepsy. Because neuronal death and degeneration is a common etiology of many neurological disorders and the CNS cannot compensate for the lost function through regeneration, homeostatic plasticity likely plays a critical role in functional compensation which often leads to pathological...
hyperexcitability. Future study to understand its role and mechanism in different neurological diseases is important for their prevention and treatment, which is particularly true since a high percentage of neurological patients are refractory to current drug treatment.

Establishing the role of homeostatic plasticity in the etiology of neurological diseases has broad and important significance. This mechanism supports that stimulating excitatory activity will be effective in the prevention and treatment of these diseases, which will open a new direction for future research. In vitro and in vivo electrophysiological recording and recent activity imaging techniques, such as calcium imaging in GCaMP6 expressing neurons, will allow us to characterize potential homeostatic activity regulation in different models of neurological diseases. Optogenetic stimulation and chemogenetic stimulation such as designer receptor exclusively activated by designer drugs (DREADD) provide powerful tools to specifically activate excitatory or inhibitory neurons for testing the homeostatic plasticity hypothesis. While much is understood about the molecular mechanisms of homeostatic plasticity (Li, 2019 #37), whether these mechanisms are involved in related neurological conditions needs to be further studied. The homeostatic plasticity hypothesis may guide developing effective brain stimulation protocols for disease treatment or prevention. For example, we found that early optogenetic stimulation of cortical excitatory neurons after brain injury is effective in preventing post-traumatic epileptogenesis (unpublished data). Because the mechanism of the brain stimulation is not clear, there is no theory to guide the development of brain stimulation protocols including the frequency, duration, and target. Treatment based on homeostatic plasticity would require that the frequency and pattern of cortical stimulation be similar to physiological activity and longer duration of stimulation may be more beneficial. It will be important to determine whether using brain stimulating protocols based on homeostatic plasticity hypothesis will be more effective than ones based on experience. The hypothesis also supports that combining cortex stimulation with rehabilitation or peripheral stimulation (Levy et al. 2016) may have good effects by compensating the lost activity and reducing hyperexcitability. For example, pairing electrical stimuli and external stimuli (noise) in tinnitus patients is shown to drive cortical activity more efficiently and improve the outcome (De Ridder et al. 2014). In addition to various brain stimulation techniques, drugs that stimulate the injured neuronal circuit should also be effective in controlling neurological disorders including epilepsy and neuropathic pain. Obviously, research in this direction has important translational significance. Particularly, when a neurological disorder is refractory to conventional treatments that target to directly inhibit hyperexcitability fail, a strategy that aims to enhance excitatory activity for symptom control may be effective. Future study may focus on determining whether activating AMPA or NMDA receptors, or inhibiting GABAergic inhibition will be effective in controlling hyperexcitability and relieving related neurological symptoms. Achieving a balance between enhancing activity and avoiding excitotoxicity and seizures will be a key consideration in this line of study.

In conclusion, homeostatic plasticity regulation can explain why activity enhancement through various techniques of brain stimulation is effective for treating hyperexcitable neurological diseases. The homeostatic plasticity mechanism may also provide guidance on designing protocols for brain stimulation. Such stimulation will enhance and normalize spontaneous activity and improve functional connectivity of the related network, leading to symptom relief and functional improvement. Because the activity stimulation strategy is consistent with the intrinsic need of the body to compensate for lost function, it may be more effective and longer lasting in controlling hyperexcitable neurological disorders, including the refractory ones.

Abbreviations
AD: Alzheimer’s disease; CNS: Central nervous system; PNS: Peripheral nervous system; rTMS: Repetitive transcranial magnetic stimulation (rTMS); S1: Primary somatosensory cortex; SCI: Spinal cord injury; TBI: Traumatic brain injury

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