



Combining BMI stimulation and mathematical modeling for acute stroke recovery and neural repair

Sara L. Gonzalez Andino^{1*}, Celia Herrera-Rincon², Fivos Panetsos² and Rolando Grave de Peralta¹

¹ Electrical Neuroimaging Group, Department of Neurology, Geneva University Hospital, Geneva, Switzerland

² Neurocomputing and Neurorobotics Research Group, Complutense University of Madrid, Madrid, Spain

Edited by:

Niels Birbaumer, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale San Camillo, Italy

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*Correspondence:

Sara L. Gonzalez Andino and Rolando Grave de Peralta, Electrical Neuroimaging Group, Department of Neurology, Geneva University Hospital, 24 Rue Micheli du Crest, 1211 Geneva 14, Switzerland.
e-mail: sara.gonzalezandino@hcuge.ch; rolando.grave@electrical-neuroimaging.ch

Rehabilitation is a neural plasticity-exploiting approach that forces undamaged neural circuits to undertake the functionality of other circuits damaged by stroke. It aims to partial restoration of the neural functions by circuit remodeling rather than by the regeneration of damaged circuits. The core hypothesis of the present paper is that – in stroke – brain machine interfaces (BMIs) can be designed to target neural repair instead of rehabilitation. To support this hypothesis we first review existing evidence on the role of endogenous or externally applied electric fields on all processes involved in CNS repair. We then describe our own results to illustrate the neuroprotective and neuroregenerative effects of BMI-electrical stimulation on sensory deprivation-related degenerative processes of the CNS. Finally, we discuss three of the crucial issues involved in the design of neural repair-oriented BMIs: when to stimulate, where to stimulate and – the particularly important but unsolved issue of – how to stimulate. We argue that optimal parameters for the electrical stimulation can be determined from studying and modeling the dynamics of the electric fields that naturally emerge at the central and peripheral nervous system during spontaneous healing in both, experimental animals and human patients. We conclude that a closed-loop BMI that defines the optimal stimulation parameters from *a priori* developed experimental models of the dynamics of spontaneous repair and the on-line monitoring of neural activity might place BMIs as an alternative or complement to stem-cell transplantation or pharmacological approaches, intensively pursued nowadays.

Keywords: neuroprotection, plasticity, neuroprostheses, rat, trigeminal, peripheral nerve

INTRODUCTION

Ischemic stroke is the major cause of adult disability (including paralysis) and cognitive deficits (Burns et al., 2009) and the third main cause of death after heart disease and cancer. While approximately 75% people survive their initial stroke, just one-third of them recover completely. According to the World Health Organization (2007) 15 million people suffer stroke worldwide each year. Of these, five million die and another five million remain permanently disabled. This long-term disability implies that most of the costs of stroke are incurred in supporting stroke survivors whose number is expected to increase due to the natural aging of the population.

Although stroke damage can be devastating, some patients survive the initial event and undergo a certain level of spontaneous recovery that can be further augmented by rehabilitative therapies (Murphy and Corbett, 2009; O'Dell et al., 2009; Johansson, 2011). Rehabilitation exploits neural plasticity to adapt the undamaged neural circuits to undertake the functionality of the circuits damaged by stroke (Johansson, 2011). Neurorehabilitation aims to partial restoration of the neural functions by circuit remodeling rather than by the regeneration of damaged circuits. It is based on the observation that cortical representation areas and cortical maps, can be modified by sensory input, experience, and learning. However, while the juvenile brain exhibits a high capacity for plasticity and repair, this capacity considerably declines with age whereas the risk for stroke increases (Popa-Wagner et al., 2007). Rehabilitation usually begins

immediately in the hospital once a patient is medically stable, and can continue on for months to years depending on the severity of the disability. Complete rehabilitation becomes an arduous, expensive and often impossible task as shown by the high proportion of patients that remain permanently disabled.

Brain machine interfaces (BMIs) are gaining increasing importance within stroke rehabilitation (Popovic et al., 2009). Current research and proposed devices are focusing within three major lines of application: (1) Improving the rehabilitation outcome through functional electrical stimulation (FES) of limbs (Barreca et al., 2003) and or spinal cord that helps to regain mobility (Yan et al., 2005), stabilize gait (Kesar et al., 2009), or regulate bladder and bowel functionality (Peckham and Knutson, 2005); (2) Retraining reaching and grasping functions (Popovic et al., 2005), and (3) Transforming neural commands representing subjects intentions into effective motor commands transmitted to robotic arms or other prostheses as reviewed in (Chae and Hart, 2003; Birbaumer and Cohen, 2007; Mak and Wolpaw, 2009).

Due to the difficulties inherent to rehabilitation in the elderly and the relatively low success rate of current techniques, research in stroke is gradually moving into the direction of neural repair (Murphy and Corbett, 2009; Carmichael, 2010). This is a new trend supported by relatively new experimental results (Gross, 2000) showing that the mature nervous system is able to create new neurons (neurogenesis), and that newly formed neurons are able to grow (sprouting) and extend their axons to form new synapses (synaptogenesis).

Within neural repair, one of the major trends is the grafting or injection of multiple types of stem-cells to enhance regeneration and functional recovery (Borlongan, 2009; Carmichael, 2010). However, for the moment and compared to the initial expectatives, stem-cell-based therapy has reached a relatively modest level of success in clinical trials (Kondziolka et al., 2005; Banerjee et al., 2010). Indeed, it is not yet clear if the observed functional improvements are due to a differentiation of the stem-cells in neurons and their integration into the injured CNS or their presence simply provokes secretion of grow factors that contribute to the regeneration of the tissues (Murphy and Corbett, 2009).

A different approach, today considered as the most promising one for the future of stroke patients, is to directly act on the causal molecular mechanisms that control tissue regeneration and on the design of pharmacological approaches to manage them (Carmichael et al., 2005; Benowitz and Carmichael, 2010). It has been recently proposed that a good model to start searching for causal mechanisms in tissue regeneration is the spontaneous or self-healing process that occasionally takes place after stroke in selected groups of patients or animals (Carmichael, 2006; Murphy and Corbett, 2009). Animal studies indicate that genes and proteins important for the three key aspects in neural repair, namely neural growth, synaptogenesis, and neural sprouting, expressed at their highest levels during early brain development (Hattiangady et al., 2005) are also expressed during a short-lived period that opens immediately after stroke (Murphy and Corbett, 2009). Consequently it is hoped that the understanding of the natural recovery mechanisms will help us in the development of therapeutic processes to augment and/or accelerate the self-repair process.

The core hypothesis of the present paper is that – in stroke – BMIs can be designed to target neural repair instead of rehabilitation. To support this hypothesis we first review existing evidence on the role of endogenous or externally applied electric fields on all processes involved in CNS repair. We then describe our own results to illustrate the neuroprotective and neuroregenerative effects of BMI-electrical stimulation on sensory deprivation-related degenerative processes of the CNS. Finally, we discuss three of the crucial issues involved in the design of neural repair-oriented BMIs: when to stimulate, where to stimulate and – the particularly important but unsolved issue of – how to stimulate.

With respect to the use of mathematical models we argue that optimal parameters for the electrical stimulation can be determined from studying and modeling the dynamics of the electric fields that naturally emerge at the central and peripheral nervous system during spontaneous healing in both, experimental animals and human patients.

We conclude that a closed-loop BMI that defines the optimal stimulation parameters from *a priori* developed experimental models of the dynamics of spontaneous repair and the on-line monitoring of neural activity might place BMIs as an alternative or complement to stem-cell transplantation or pharmacological approaches, intensively pursued nowadays.

THE ROLE OF NATURALLY GENERATED ELECTRICAL FIELDS IN NEURAL REPAIR, PLASTICITY, AND NEUROGENESIS

In this section we briefly review some of the evidences that support our hypothesis that neural repair could be artificially induced through an appropriate modulation of intracellular and extracellular fields by means of BMIs.

STROKE DAMAGE AND MECHANISMS FOR NATURAL RECOVERY SUITABLE TO BE PROMOTED BY BMI STIMULATION

Around one-third of stroke patients survive the initial event and undergo partial or complete spontaneous recovery (Murphy and Corbett, 2009; Johansson, 2011). In the initial stage of the recovery (weeks 1–4) different homeostatic mechanisms appear that contribute to the re-activation of the stroke-affected areas through structural and functional changes of the neural circuits.

Stroke-affected tissue is usually divided into a core area, characterized by complete blood deprivation and cells' death, and a peri-infarct area, termed the penumbra, characterized by reduced blood flow and damage of the neural cells and neuropil (axon terminals, dendrites, and glia). In animal models of focal stroke, diaschisis – a sudden loss of function in a portion of the brain connected to but at a distance of a damaged area – is also observed in regions adjacent and connected to the core (Carmichael et al., 2004). While at the core there is a severe and rapid tissue injury, brain cell death evolves more slowly within the penumbra zone (Lo et al., 2005). In acute ischemic stroke in primates the neurons at the penumbra remain structurally intact but functionally inactive (Astrup et al., 1977). Without reperfusion, i.e., restoring nutritional blood flow to threatened tissues before they progress to infarction (Molina and Saver, 2005), the penumbra collapses, brain cells die, and the lesion expands (Lo et al., 2005).

Functional recovery is thought to depend on function remapping from the core to the penumbra area. Indeed, saving of the penumbra has been shown to have definite and predictable benefit on subsequent neurological recovery in man (Guadagno et al., 2003). Recovery of the penumbra impacts both, early and late recovery (Furlan et al., 1996). Remapping depends on reperfusion and on latent subthreshold inputs to the penumbra region combined with a rewiring of the neural connections promoted by axonal sprouting and synaptogenesis (Murphy and Corbett, 2009). Both, remapping and rewiring are promoted by Hebbian-like, activity-dependent, synapse-based learning rules that strengthen and refine the circuits if (and only if) there is some circuitry to route sensory signals to the brain and motor commands out of it (Murphy and Corbett, 2009). Importantly, while the mature brain is able to create new neurons (neurogenesis) this effect is limited to selected brain areas. However, new neurons can migrate to the peri-infarct zone. The necessary condition to facilitate the restoration of circuit activity over days to weeks through compensatory rewiring or remapping seems to be the presence of some of the original connections to provide weak sensory and motor signals, subsequently enhanced through neural plasticity. Rerouting and rewiring for saving the penumbra should also lead to prevention of the diaschisis.

In summary, functional recovery after stroke seems to heavily depend on:

- Saving penumbra cells from death: This is dependent on early reperfusion further promoted by angiogenesis (the growth of new capillary vessels) as well as by insuring sufficient synaptic input to the penumbra area.
- Promoting rewiring and remapping in the penumbra by stimulating synaptogenesis and axonal sprouting. Axonal sprouting (rewiring) and functional remapping are based on

synapse-based learning rules that depends on the existence of synaptic input and the circuitry to route sensory signals to the brain and motor commands out of it.

- Preventing diaschisis. If the circuitry to route sensory signals to the brain and motor commands out of it is altered due to the loss of function in areas connected to the core, synaptic input is interrupted. As mentioned before, synaptic input to the penumbra is essential for rewiring, remapping, angiogenesis, and preventing cellular death.

A BMI aiming to neural repair should target the above mentioned goals rather different from those pursued nowadays in BMI-based stroke rehabilitation. However, to be effective in these directions, BMIs should be capable to effectively modulate electric fields on the CNS given their beneficial effects on neural repair described next.

ELECTRIC FIELDS INFLUENCE ANGIOGENESIS, NEUROGENESIS, AND SYNAPTOGENESIS

Spontaneously emerging intrinsic electric fields

As Maxwell equations predict but for too long ignored in Neuroscience, neurons apart from generating electromagnetic fields are also sensitive to them. There is experimental evidence accumulated over the last 5 years supporting that the weak electric fields generated in a natural way by the physiological activity of neocortical networks are strong enough to (i) significantly modify the excitability of their own cells and (ii) alter the synchronization of the networks themselves (Fröhlich and McCormick, 2010; Mann and Paulsen, 2010; Weiss and Faber, 2010). Moreover, electric fields and biochemical neural processes are deeply intermingled and, therefore, electric fields are likely to also affect dendritic conductances, transmitter release, and the diffusion of ions and charged neurotransmitters (Weiss and Faber, 2010).

Altering excitability and network synchronization are keys to the two synaptic learning rules, known to influence CNS synaptogenesis and plasticity (Murphy and Corbett, 2009): (1) Hebbian plasticity mechanisms that favor the rewiring of neural pathways and (2) homeostatic plasticity mechanisms that ensure that neurons receive an adequate amount of synaptic input. It has been proved that self-repair processes are accompanied by the spontaneous modulation of extracellular fields (Carmichael and Chesselet, 2002; Carmichael, 2003; McCaig et al., 2009; Floel and Cohen, 2010) and the emergence of synchronous activity (Carmichael and Chesselet, 2002). Moreover, the spontaneously appearing synchronous neuronal activity is a signal for axonal sprouting after cortical lesions (Carmichael and Chesselet, 2002).

The appearance of electric fields is not a prerogative of the central nervous system. Direct-current (DC) electric fields naturally arise in all developing and regenerating animal tissues although their existence and potential impact on tissue repair and development remain largely unexplored (McCaig et al., 2005, 2009). Cells undergo a variety of physiological processes including division, migration, and differentiation, under the influence of endogenous electrical cues which are generated physiologically or pathologically in the extracellular and sometimes intracellular space. In almost all systems that have been studied, crucial behaviors such as cell

division, cell migration, and cell differentiation take place within an extracellular milieu in which standing voltage gradients persist for several hours or even days (McCaig et al., 2005, 2009).

THE ROLE OF ARTIFICIALLY INDUCED ELECTRIC FIELDS IN NEURAL REPAIR, PLASTICITY, AND NEUROGENESIS

In ischemic rats, direct invasive electrical stimulation of the cerebral cortex has been shown to exert antiapoptotic, angiogenic, and anti-inflammatory effects (Baba et al., 2009). Electrical stimulation seems to render the ischemic brain as a nurturing microenvironment characterized by robust angiogenesis and diminished microglial/astrocytic proliferation, resulting in the reduction of infarct volumes and promoting behavioral recovery (Baba et al., 2009). The repairing role of peripheral stimulation (further illustrated in the next section) is also crucial: manual stimulation of the whiskers in the ischemic rat promotes angiogenesis and enhances blood flow in the penumbra (Whitaker et al., 2006), enhances neurogenesis, and neural progenitor migration toward the ischemic barrel cortex (Li et al., 2008) and increases the vascular endothelial growth factors (Whitaker et al., 2006). This happens because manual stimulation of the whiskers excites the mechanoreceptors located under the skin which transform these mechanical stimuli to electrical pulses that travel to the central nervous system through the peripheral nerves.

Consequently, physiologically weak electrical fields and ionic currents should be the electrical equivalents to cellular therapies for neural repair, axonal guidance, and chemotropism given their role on neurogenesis, nerve repair, promotion, and orientation of axonal sprouting and even on cell migration in damaged neural tissues (Yao et al., 2008, 2009; Sundelacruz et al., 2009).

NEUROPROTECTIVE EFFECTS INDUCED BY BMI STIMULATION

In this section, we provide evidence that neuroprotective and neuroregenerative effects similar to those provoked by manual stimulation of the whiskers (Angiogenesis, neurogenesis, and migration of progenitor cells toward the ischemic areas) can be achieved by direct electrical stimulation of the peripheral nerves through an implanted BMI.

Indeed, peripheral and central nervous system are completely interrelated. Since Merzenich et al. (1983) proved that transection of a peripheral nerve modifies the cortical representation of the injured limb, many studies have focused on structural and physiological alterations in deafferented central pathways (for reviews see Merzenich et al., 1990; Jain et al., 1998; Kaas, 2000; Blake et al., 2002). Changes in neural activity can be quantified in several ways (histologically, electrophysiologically, etc.). Particularly useful is quantification using cytochrome oxidase (CyO), a critical enzyme whose levels correlate with chronic changes of the synaptic activity. An increase of the sensory stimulation or behavioral training provokes an increase in the energetic demand of the sensory areas and, consequently, an increase in the expression of CyO while a decrease of the sensory stimulation provokes the opposite effect (Wong-Riley, 1989; Bruchey and Gonzalez-Lima, 2008). Also Parvalbumin (PV) and Calbindin (Calb), two calcium-binding proteins (CaBPs) present in cortical interneurons, are indicative of the modifications of the neural activity and their expression levels are altered after peripheral manipulations.

In determining the effects of peripheral manipulations to the central nervous system the trigeminal somatosensory system of the rat has resulted particularly useful due to its highly topographic organization (Waite and Tracey, 1995; Diamond et al., 2008; Panetsos and Sanchez-Jimenez, 2010). This is because in all relay stations information processing is done by groups of neurons spatially distributed in the same manner as the whiskers on the snout on the animal (somatotopic maps) and each group of neurons receives its main input from only one whisker in the periphery. In cortical layer IV these groups of neurons take the shape of barrels forming the cortical “barrel field” (Figure 1, see also Woolsey et al., 1975).

To assess the restoring effects of BMIs on damaged cortical neural networks we compared the barrel cortices of rats with transaction of the peripheral nerve (and a consequent massive deafferentation of the cortex, lesioned, or LES-animals) and the barrel cortices of animals with the same manipulation but to which a stimulating device was implanted immediately after the lesion (whose cortices received artificially generated currents from the BMI, BMI-animals). Electrical stimulation was delivered to the proximal stump of the transected nerve for 4 weeks, 12 h/day, using 100 μ s-long pulses, 3.0 V, and with a frequency of 20 Hz. Animal handling, housing, surgery, and euthanasia were carried out according to current national legislation (R.D. 223/88), and EU Directives (86/609/EC) on this matter. In Figure 1 a schematic presentation of the experiment can be shown. More details on the experimental procedures are given in (Herrera-Rincon et al., 2010a,b).

Effects induced by BMI stimulation were quantified at all levels of the trigeminal sensory pathway, i.e., we estimated the metabolically active volume of whisker-related regions in brainstem, thalamus, and cortex and we estimated the number of cortical interneurons expressing CaBPs in LES- and BMI-animals. In every animal we compared the two hemispheres, manipulated versus control (experimentally affected versus intact). After 4 weeks LES-animals showed a severe decrease in the cortical activity and a reduction in the number of PV- and Calb-positive neurons (Figure 2A) while no BMI-animal displayed differences between control and experimental hemispheres (Figure 2B). Similar results were observed in the lower stations of the somatosensory pathway.

Our results confirm that loss of sensory input from the peripheral nervous system leads to structural and functional changes at the barrel cortex and that such changes can be avoided by the very early use of BMI. Indeed, these results show that chronic electrical stimulation directly applied to the proximal stump of the transected nerve can be used to prevent the significant loss of synaptic activity in the cortex and distant interconnected structures. BMI stimulation displayed a clear neuroprotective and neuroregenerative effect to the affected regions.

WHEN, WHERE, AND HOW TO STIMULATE WITH BMIs TO OPTIMALLY PROMOTE NEURAL REPAIR

In the present paper we defend the idea that, in stroke, functional recovery can be effectively obtained by using BMI stimulation, alone or in combination with other therapeutic techniques. In

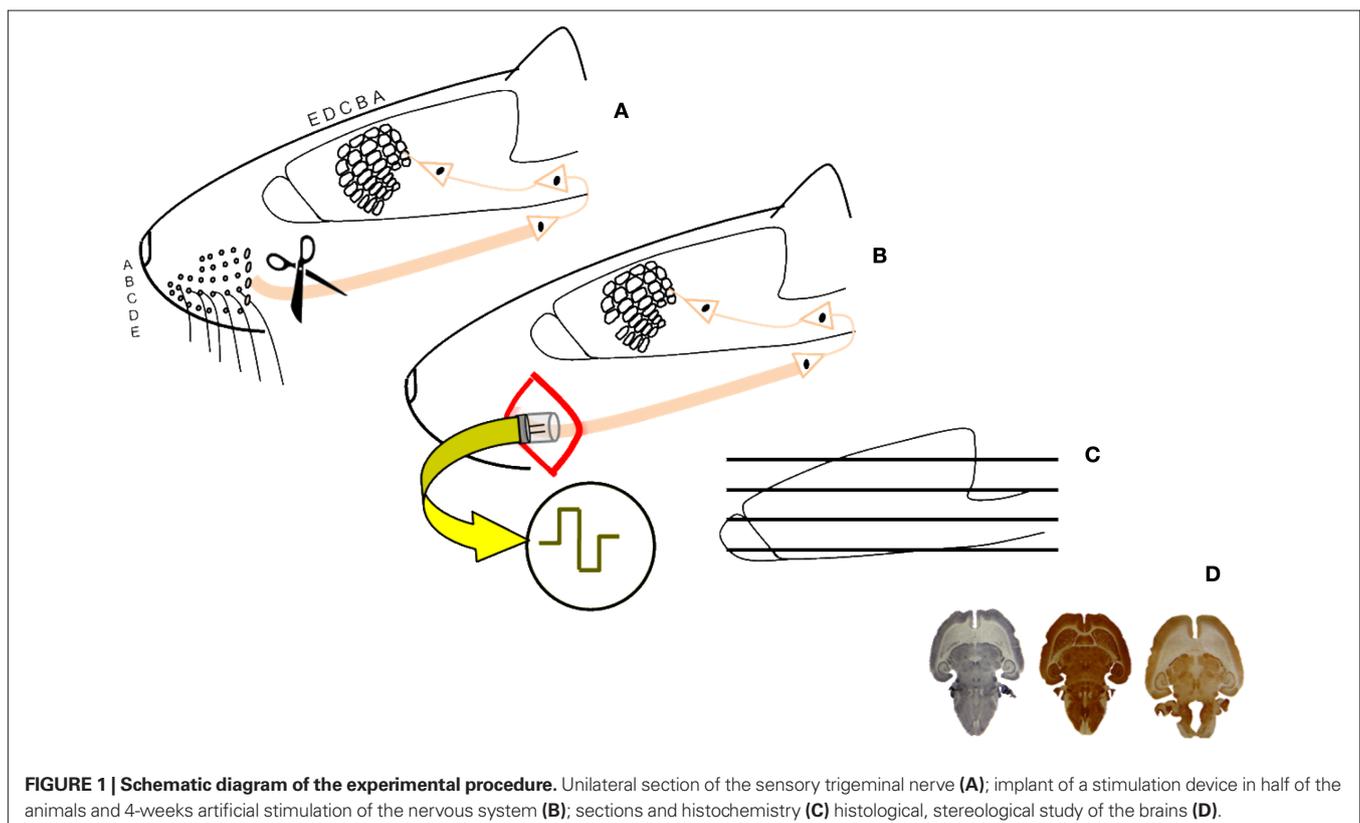


FIGURE 1 | Schematic diagram of the experimental procedure. Unilateral section of the sensory trigeminal nerve (A); implant of a stimulation device in half of the animals and 4-weeks artificial stimulation of the nervous system (B); sections and histochemistry (C) histological, stereological study of the brains (D).

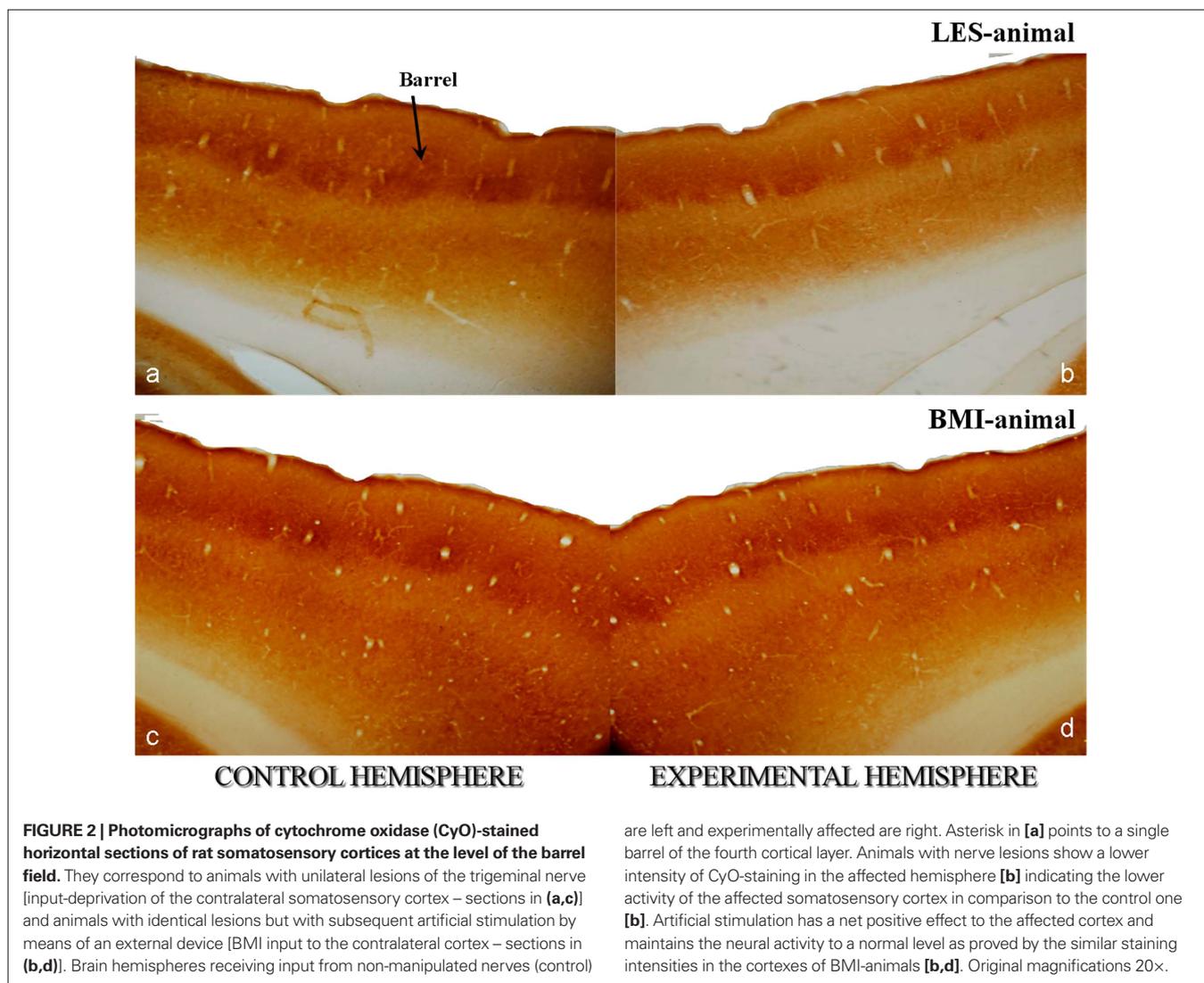


FIGURE 2 | Photomicrographs of cytochrome oxidase (CyO)-stained horizontal sections of rat somatosensory cortices at the level of the barrel field. They correspond to animals with unilateral lesions of the trigeminal nerve [input-deprivation of the contralateral somatosensory cortex – sections in (a,c)] and animals with identical lesions but with subsequent artificial stimulation by means of an external device [BMI input to the contralateral cortex – sections in (b,d)]. Brain hemispheres receiving input from non-manipulated nerves (control

are left and experimentally affected are right. Asterisk in [a] points to a single barrel of the fourth cortical layer. Animals with nerve lesions show a lower intensity of CyO-staining in the affected hemisphere [b] indicating the lower activity of the affected somatosensory cortex in comparison to the control one [c]. Artificial stimulation has a net positive effect to the affected cortex and maintains the neural activity to a normal level as proved by the similar staining intensities in the cortices of BMI-animals [b,d]. Original magnifications 20x.

the previous section we justified our approach using both, the most recent bibliography in this field and experimental data from our labs. However, the mere proposal of a novel approach or technique, although well documented and justified, is not sufficient for future applications or even research if it is not accompanied by precise indications on how to use it. For example electrical stimulation has been used for a while to treat the symptoms in Parkinson disease. Nevertheless, the basic functional mechanisms and, more particularly the optimal stimulation parameters that could allow us to reach a full recovery of the damaged tissues, remain largely unknown the application of BMIs to the treatment of this disorder being far limited by the scarce information available on these issues (Logothetis et al., 2010).

In the present section we describe the way our theory could be tested and, if correct, to be applied for neural repair in stroke patients. We consider that all necessary information is available in the natural healing processes and can be extracted by means of precise experiments and mathematical models.

WHEN BMI STIMULATION MUST BE APPLIED? CRITICAL TIME-WINDOW FOR OPTIMAL RESULTS

Brain machine interfaces should be introduced in the acute/sub-acute period after stroke to exploit and widen the Critical Phase, a spontaneously opening time-window of neural plasticity occurring approximately between the 5th and 20th-day.

Self-repair processes such as self-induced neuroregeneration and self-induced neuroprotection emerge during this Critical Phase. Genes and proteins important for neural repair, the same that are expressed during early brain development, where there is maximal neural growth, neural sprouting, and synaptogenesis, are also expressed at very high levels (Murphy and Corbett, 2009) immediately after stroke. It is during this phase that damaged cells, still alive in the penumbra area, have to be protected and maintained alive. By the end of the Critical Phase is marked by the extinction of the self-repair processes, and the closing of the neuroplasticity window. At this point neural repair becomes impossible and rehabilitation techniques can be introduced to facilitate functional recovery but not neural repair! Indeed, neurorehabilitation fails to exploit both,

the self-repair mechanisms and the preserved functional specialization of the partially undamaged neural circuits, so functional recovery is considerably delayed and hardly ever complete.

We propose that this Critical Phase of heightened neuroplasticity must be both, investigated and exploited to initiate any treatment aimed to neural repair. As the only period during which self-repair mechanisms and structurally damaged, but functionally specialized neural circuits, co-exist, the Critical Phase is the optimal and probably the only period to artificially induce neural repair. Moreover, as shown before, central, or peripheral electrical stimulation exert angiogenic effects and promotes vascular growth factors preserving the functionality of individual neurons and entire regions then it can be potentially used to extend the Critical Phase, i.e., to extend the time limited period of neural survival keeping the optimal conditions for neural repair.

WHERE BMI STIMULATION MUST BE APPLIED? STIMULATION OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

Stroke damages are not limited to the core or the penumbra area but they can reach distant regions physically connected to the core of the stroke by means of neural pathways. In addition, loss of a limb or its prolonged immobility leads to neurodegenerative processes in the whole somatosensory pathway and in particular in the cortex as a result of the chronic deafferentation/reduction of sensory stimuli and the subsequent drop of direct synaptic input. Consequently, BMI stimulation must be applied in such a way to influence both, the penumbra area and the neural pathways that interconnect the affected regions in the brain. On one hand we have to control the electric fields in the penumbra area to locally promote synaptogenesis and angiogenesis. On the other hand we have to maintain functional all the circuitry that routes sensory signals into the brain and motor signals outside from it to allow Hebbian plasticity to be effective.

As seen before, both, central and peripheral electrical stimulation exert neuroprotective and neurorepair effects in animal models of stroke. To take advantage from both techniques and also to increase their effectiveness in a synergistic approach neural repair should rely on both

- direct brain stimulation to dynamically modulate electric fields in the extracellular space that will influence the extracellular matrix and therefore neurogenesis/sprouting and homeostatic plasticity and
- peripheral stimulation expected to basically impact Hebbian and homeostatic plasticity.

Controlling the dynamic of electric fields at the penumbra area can be achieved by both, invasive and non-invasive BMIs. Neural implants at the penumbra can provide a finely tuned control of extracellular fields but the risk of surgical intervention at the acute and post-acute stages of stroke needs to be carefully weighted. Non-invasive BMIs in the form of central stimulation can be based on transcranial magnetic stimulation (TMS) or transcranial direct-current stimulation (tDCS).

Brain machine interface-originated electric fields must lead to a functional re-activation of the sensory pathway, hence to maintain the organization of the neural circuits by means of the aforemen-

tioned Hebbian rule. Such effects will be mediated by the action of the electrical stimulation on the activity-depending signaling pathways, for example by promoting genes transcription, necessary for synaptic transmission or long-term potentiation (Tan et al., 2008). This way BMIs should contribute to the creation and maintenance of a molecular microenvironment similar to the one that spontaneously arise after stroke in cases of successful self-repair.

The above considerations on the maintenance of functional pathways and the importance of a high neural activity toward and from the affected regions make clear that, due to its neurostimulating nature, neurorehabilitation should complement the BMI approach if we want to achieve real/effective functional restoration after neural repair.

HOW BMI STIMULATION MUST BE APPLIED? THE NEED OF MATHEMATICAL MODELS

The effectiveness of BMI stimulation, as that of every clinical treatment, depends on the knowledge we have on the specific disease and the mechanisms of action of the treatment that define the therapeutic protocol. Unfortunately, while invasive and non-invasive devices for FES are widely used for other neurological diseases (e.g., Parkinson) our limited knowledge hinders the exploitation of the enormous potential of these methods. Indeed most stimulating BMIs rely on fixed stimulation protocols where the stimulation frequency and intensity do not vary over time.

Contrarily to other diseases of the CNS, in stroke, the existence of naturally occurring self-repair processes allows us to determine stimulation procedures for optimal BMI-based neural repair. It is plausible that the same temporal dynamics followed by the electric fields in case of successful spontaneous healing serve to artificially promote neural repair where self-repair does not spontaneously arise or even to increase the effectiveness of the spontaneously arising healing processes. By modeling such processes and then by studying the behavior of the electric fields we will be able to determine the correct way to stimulate and establish the ranges of the parameters to obtain optimal neural repair by means of BMIs. Accordingly, it is necessary to investigate the relationship between the dynamics of spontaneously emerging electrodynamic fields and the self-induced repair processes that lead to a complete recovery of the central nervous system using data from both, animal models and human patients.

The development of mathematical models for the healing processes in stroke can rely on both, experimental data from *in vivo* animal models in rodents and human clinical data from human patients. Information theory and its close cousin Bayesian modeling provides an ideal framework to uncover hidden dependencies between the temporal evolution of healing and the dynamics of spontaneously generated electric fields as these models assume no fixed (e.g., linear) physical relationships between the variables. Rather the dependencies are discovered from repetitions of the observations.

MATHEMATICAL MODELING OF HEALING PROCESSES AFTER STROKE

In animals, we can rely on extracellular measurements of local field potential (LFPs) and single/multi unit activity (SUA/MUA) on one hand and the anatomical-structural changes in the neural tissue on the other to establish specific links between the naturally occurring electric fields and functional/structural recovery. The link between electric field dynamics and neural recovery can be established by

correlating specific changes in the electrophysiological recordings with the diverse histochemical measures of network activity and connectivity: amplitude, frequency, hyperexcitability, synchrony, and different functional connectivity measures in the first case and metabolic activity, number of neurons, axonal sprouting, neurogenesis, etc., in the second.

In humans, scalp EEG can be monitored during the acute/post-acute phase of stroke and after the transfer of patients to the rehabilitation unit. As scalp EEG lacks the spatial resolution to assess the properties of ongoing phenomena within the core/penumbra area one could rely on the non-invasive estimation of field potentials or currents (Grave de Peralta Menendez et al., 2000). With such approach we should be able to correlate frequency specific changes in the core/penumbra with structural/functional and metabolic changes detected from non-invasive neuroimaging techniques such as MRI/PET/fMRI. Furthermore, frequency specific changes in the estimated signals at the core/penumbra can be correlated with electrophysiological measures of local network connectivity.

All data can be obtained under electrodynamic stimulation to characterize electric field dynamics during the acute phase to identify common features of spontaneous recovery. The idea is to establish unambiguous links between electrodynamic fields at the penumbra area and the level of functional and structural recovery derived from specific circuit changes or behavior using information theory mathematical tools.

The use of experimental animal models of stroke in rodents provides crucial information that is impossible to obtain from human subjects:

- Electrophysiological characterization of electrodynamic phenomena within the core and the penumbra area to create the information theoretical models that can guide BMIs to induce optimal repair and recovery.
- Fine quantitative assessment of the effects of artificially induced electrodynamic fields on the neural repair via the electrophysiological (Hebbian and homeostatic plasticity) and histochemical analysis of the neural tissue (metabolic activity, number of neurons, connectivity, axonal sprouting, neurogenesis, etc.).
- Functional assessment of the recovery in terms of behavioral markers.

Rodent models of stroke allow correlating spatially tuned frequency specific changes in the measured fields with the diverse histochemical and electrophysiological measures of the recovery of the neural circuits. It is from these correlations that appropriate models for stimulation that mimic the sequence of natural recovery can be devised. However, realistic models in rodents should be relatively small as survivable human strokes affect 5–15% of the hemisphere. Examples of well established models of small strokes in rodents are the Middle cerebral embolism and the Photothrombosis (Murphy and Corbett, 2009) which bears the additional advantage of being non-invasive. Moreover, rodent models permit the a posteriori assessment of the effectiveness of invasive and non-invasive stimulation directly applied to the penumbra area and the comparison with the less invasive peripheral stimulation if applied alone.

The use of information theory provides an ideal framework to:

- Characterize the dynamics of self-repair processes using concepts such as entropy or mutual information.
- Evaluate which parameters of spontaneous electrodynamic fields influence self-repair, as measured by conventional electrophysiological, histochemical, neuroimaging, or behavioral techniques.
- Model the recovery process, for example as Markov stochastic processes.
- Determine the optimal dynamic for the implementation of BMI devices oriented to artificially promote neural repair.

The self-healing process can be initially modeled as a Markov stochastic process to relate the sequences of measured electrodynamic events to the transitions in the state of the system. Such model could be able to dynamically determine the parameters that determine optimal state transitions (i.e., those that were previously learned as leading to successful self-repair in the animal and human models). Note that the dynamical evaluation of entropy rates during spontaneous and artificial healing could constitute a new clinical prognostic measure of the possibility to repair the nervous system after its acute damage.

Once the characterization of the optimal dynamic changes of the fields is established we will be able to create more advanced models describing the sequence of the stimulating parameters as a function of the state of neural networks inferred from the real time monitoring of the brain electrical activity. This would therefore constitute a closed-loop BMI that defines the optimal stimulation parameters from the on-line monitoring of neural activity and the existing model of the dynamics of neural repair.

CONCLUSIONS

In the present paper we provide theoretical and experimental evidence that conveniently designed BMIs could be used to achieve neural repair in stroke patients. BMI-based stroke therapies, alone or combined with other advanced approaches (e.g., stem-cell therapies) could go far beyond the limits of up-to-day clinical treatments for stroke but in any case, to be effective, they should be followed by neurorehabilitation techniques (classical, virtual, etc.).

Theoretical evidences were given to sustain that (i) natural activity of the neural networks can generate electric fields of sufficient strength to influence themselves (ii) low intensity electric fields arise spontaneously in a short time-period after stroke in the damaged area and (iii) these spontaneously arising low intensity electric fields play a very important role in the effectiveness of after stroke self-repair mechanisms. On this basis, we suggest that it should be equally possible to artificially reproduce (using electrical stimulation) the electrical conditions measured *in vivo* in the extracellular space during the processes of natural healing.

Experimental evidences were presented to support that (i) BMIs can preserve the functionality of brain areas deprived from natural sensory input and (ii) can be used to influence the two plasticity rules that play a crucial role in neural repair and recovery processes: homeostatic plasticity that ensure that neurons receive an adequate

amount of synaptic input and Hebbian plasticity that redistribute synaptic strength to favor the wiring of pathways that are coincidentally active.

The aforementioned evidences suggest that by correctly modulating ionic currents and extracellular electric fields via BMIs we should be able to provoke and guide plastic changes of the CNS.

To achieve this ambitious objective we propose to develop information based mathematical models of natural healing processes that help us to determine the optimal stimulation parameters to induce neural repair by means of a closed-loop BMIs that rely on the on-line monitoring of electrical activity.

Besides, selective electrical stimulation of peripheral nerves innervating the core area affected by stroke should be initiated as soon as the location and extent of the penumbra area has been identified from MRI to increase the chances of neural survival and maximally exploit the Critical Phase. In this way we expect that BMIs can become a novel avenue of research that optimally exploit neural repair and plasticity for improving functional and structural recovery after severe ischemic stroke

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