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Magnetically Induced Deep Brain Stimulation of Neuronal Firing for Pain Relief

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Abstract—**Pain, either acute pain or chronic pain, is usually treated/relieved by chemical means, in which nociceptive signals are blocked from transmitting into the pain registration sites in the brain. However, besides their side effects, chemical means of pain relief are not always effective, causing some serious clinical incidents like anesthesia awareness and chronic pains that are not treatable. A physical means of pain relief that physically modifies pain perception at the brain sites responsible for pain registration could be more effective, for both acute pain and chronic pain. In this paper a novel approach of magnetically induced deep brain modulation of neuronal firing is proposed for pain treatment/relief, in which pain treatment/relief is bioelectronics based and is non-invasive and free of side effects. A novel pulse magnetic field projector has been developed for pain relief through modulation of neuronal firing at the anterior cingulate cortex (ACC). It is based on the neuroscience findings that pain registration in the brain is closely related to the excitation of nociceptive neurons at the ACC , in which the nociceptive neuronal firing rate increases as pain gets more intense. The mechanism of pain relief in the proposed approach is to modify the nociceptive neuronal firing rate at the ACC by magnetically inducing a pulse electric field applying on the neurons in the ACC, hyperpolarizing the neurons that are firing at high frequency during pain perception, resulting in a low level firing rate associated to no pain. A parametric study has been carried out to determine the physical and technical parameters of the proposed approach. The feasibility of the approach has been verified by simulation with the modulation implemented on a reconstructed ACC LV pyramidal cell using Hodgkin-Huxley style model. Action potentials recorded in the soma indicated that the firing frequency can be modulated by the applied pulse electric field.**

I. Introduction

Pain, as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, if insufficiently controlled or inadequately treated, can seriously interfere with a person's normal functioning and impair the quality of life. Although the medical community has always been making great efforts to improve pain management, pain due to inadequate treatment or insufficient control is still widespread across all demographic groups. According to the estimation of the World Health Organization in 2008, about 80% of the world population suffers from moderate to severe pain due to either inadequate or even no access to treatment. Especially, with the ageing world population, there are increasing needs for effective pain control in the elderly who tend to suffer from medically unexplained chronic pain. An effective pain relief device can improve the quality of life for individuals, and largely reduce the financial burden of the society.

In view of the large number of world's population suffering from pain as well as a lack of a device for physical relief of pain, the proposed pain relief approach is expected to have broad applications with huge market potential. The proposed device can be used in hospitals for the management of intraoperative and postoperative pain as well as the treatment of chronic neuropathic pain. As a physical means of pain relief, it has no side effect as compared to the chemical means with analgesics. Furthermore, by directly modulating neuronal firings of nociceptive neurons in the brain, it provides a possibility to deal with the pain conditions when medical treatment is not effective, such as anesthesia awareness and especially the medically unexplained pain symptoms.

II. Neurophysiological Basis

It has been well studied and concluded that the neural excitation or firing of nociceptive neurons in the anterior cingulate cortex (ACC) plays a critical role in pain perception, which forms the basis of modifying pain perception by modulation of nociceptive neuronal firing in the ACC. Pain perception involves multiple brain regions. The regions most consistently reported to be involved in pain perception include the primary (S1) and secondary (S2) somatosensory cortices, the ACC, the prefrontal cortex and the insula [1]. The choice of ACC as the target region for pain relief has the support from substantial evidence in the literature. On one hand, nociceptive neurons have been identified in the ACC by single-unit recordings in both animals and humans [2, 3]. On the other hand, it has been shown by many studies that ablation of the ACC can alleviate the affective components of pain, producing a state without pain unpleasantness [4-7]. It has also been well studied and concluded that the neuronal activity (e.g. the number of responsive neurons, the firing rates, the mass spike counts) of the ACC nociceptive neurons significantly increased during pain perception and is positively correlated with the level of pain [3, 8-10]. For example, it has been reported [9] that the nociceptive neuronal firing rate at the ACC increases from around 21 Hz at no pain to 38 Hz at tolerable pain, and reached as high as 50 Hz at intolerable pain. Therefore, it is reasonable to assume that pain perception can be inhibited by modifying the neuronal firing rate downwards at the ACC.

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III. Mechanism

The proposed approach intends to induce quasi-uniform high frequency pulse electric fields in the ACC on both left and right hemispheres of the brain, as shown in Fig. 1. The electric field is induced by a pulse magnetic field projected onto the brain by a novel magnetic field projector. Two magnetic flux projectors are placed on the forehead with the coils in parallel with the scalp surface so that the induced electric field will be along with the direction of the axons of the well aligned pyramidal neurons in the ACC, as shown in Fig. 2.

The neural excitation of the nociceptive neuron at the ACC can be influenced by an applied pulse electric field. As shown in Fig. 2, as the extracellular potential distribution, provided by the pulse electric field, E, is applied along the axon direction of the nociceptive neuron at the ACC, the cell membrane of the neuron at different positions receives different value of applied potential due to the potential distribution, resulting in different membrane potentials. When the electric field is applied in the direction from axon to soma, under the influence of the applied pulse electric field, the neuron will be hyper-polarized and will not fire.

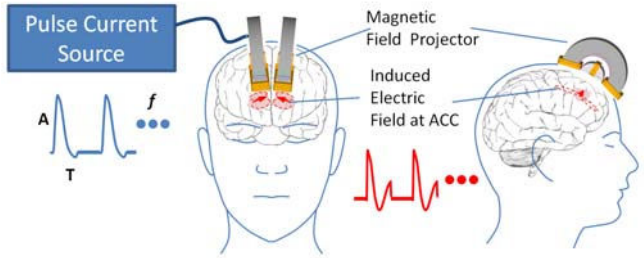


Fig. 1. Illustration of the proposed approach for pain relief by modulation of the neuronal firing at the ACC with two applied electric fields induced by two pulse magnetic fields that are projected into the left side and right side, respectively, of the ACC by two novel pulse magnetic field projectors based on an invention [11]. The two magnetic field projectors are placed on the forehead with the coils parallel to the scalp surface. The waveform of the magnetic pulse is shown in blue on the left with parameters of amplitude, A, duration, T, and frequency, f. The fall time, T_f, of the pulse is 5 times of the rise time, T_r, so that the induced electric pulse (shown in red on the right) has a much larger positive value than the following negative value.

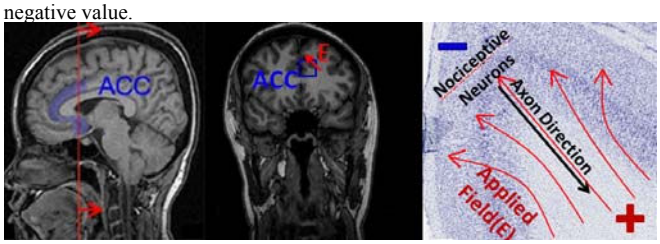


Fig. 2. Modifying the neuronal firing rate at the ACC with an applied pulse electric field on the axons of the neurons along the axon direction.

IV. Device

The key components of the system of magnetically induced deep brain modulation of neuronal firing include a pulse current supply and an array of magnetic field projectors, as shown in Fig. 1. The pulse current supply can be a capacitor discharge circuit, similar to that with most transcranial magnetic systems [12]. The magnetic field projector consists of three square coils and two ferromagnetic cores. The magnetic flux density along the projection axis decreases to zero at a distance and then increases to a local maximum. This local maximum flux density can be characterized for the penetration depth, which can be adjusted in a range of 1 to 5 cm by configuring the structure parameters of the magnetic field projector. For modulation of neuronal firing at the ACC the needed penetration depth from the scalp is about 3 cm. The device was modeled and simulated using an FEM software (ANSYS 12.1, ANSYS Singapore). The amplitude of the pulse current used in the simulation was 6 kA.

An electric field is induced by the pulse magnetic field and can be estimated, according to Faraday's law of induction, by

$$E = -\frac{r}{2}\frac{dB}{dt} \tag{1}$$

where r is the radius of the induced circular electric field. Assuming a magnetic field in sinusoidal waveform

$$B = B_0 \sin\left(\frac{2\pi}{T}t\right) \tag{2}$$

with a peak flux density, B_0, and period, T, the induced peak electric field will be

$$E_0 = \frac{\pi r B_0}{T} \tag{3}$$

In checking any possible heating effect of the operation to the brain, for a typical pulse, T = 200 μs, r = 10 mm, and peak magnetic field at surface B_0 =1.7 T, E_0 =267 V/m, consider the scalp conductivity, σ = 0.45 S/m, the maximum current density in the scalp, $J = \sigma E_0$ = 120 A/m^2, then the specific absorption rates (SAR) calculated based on the induced current in the scalp is

$$SAR = \frac{J^2 Tf}{2\sigma\rho} \tag{4}$$

where the pulse frequency, f = 100 Hz, tissue density, ρ = 1000 kg/m^3, SAR = 320 mW/kg, which is well below the limit of IEEE standard safety level, 400 mW/kg [13]. In the targeted brain region ACC, B_0 = 0.13 T, E_0 = 20 V/m, and σ = 0.5 S/m, thus SAR = 2 mW/kg, which is far below the limit of IEEE standard safety level.

V. Simulation

A simulation study of the modulation of neuronal firing by an applied extracellular pulse electric field has been

performed in a 3D pyramidal cell model reconstructed from ACC LV pyramidal neurons in human [14], as shown in Fig. 4 (a). All the segments in the model were rearranged from the morphology data to ensure each segment has no branch.

The neuron was represented by a Hodgkin-Huxley style model which has been calibrated to match LV pyramidal neuron membrane properties including three kinds of potassium channels, two calcium kinetics, and one kind of sodium channel [15] . A 0.1 nA current clamp was attached to neuron soma during the simulation, driving the target neuron to fire at the frequency of the "intolerable pain" state as reported in animal experiments [9].

The stimulation was a pulse electric field in the direction from axon to apical dendrite with amplitude of 20 V/m and duration of 0.1 ms, assuming that the pulse electric field was uniform throughout the space and static within its duration. Therefore, the membrane potential, V, can be approximated by [16]:

$$\frac{\partial^2 V}{r_i \partial x^2} - \frac{V}{r_m} = c_m \frac{\partial V}{\partial t} + \tilde{i}_m \tag{5}$$

where r_i is the cytoplasmic resistance (150 Ωcm), r_m is the membrane resistance, c_m is the membrane capacitance (0.75 μF/cm^2) , and $\tilde{i}_m$ is induced current,

$$\tilde{i}_m = -\frac{1}{ar_i}\left\{\left[E_x^0(x_1 - x_0)\right] + \left[E_y^0(y_1 - y_0)\right]\right\} \tag{6}$$

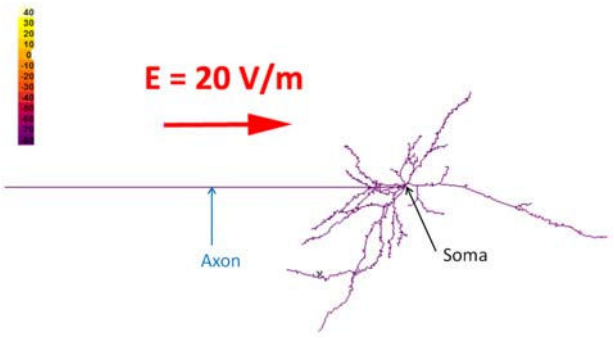
where a is compartment length, E_x^0 and E_y^0 are the x and y components of the electric field at the beginning of the compartment, respectively, (x_0, y_0) and (x_1, y_1) are the coordinates of the compartment beginning and end, respectively. Ions driven by the applied electric field were not allowed to pass through the membranes and were assumed to be accumulated at the segment ends. This magnetically induced current is different from the trans-membrane current in the previous models [16, 17] and is more accurate for quasi-uniform electric field as in this case.

The simulation model was implemented in NEURON 7.1 simulation platform [18] using a time step of 0.025 ms. The modulation of neuronal firing was simulated using a train of electric field pulses at 100 Hz. As shown in Fig. 4 (b) and (c), when the neuron was not driven to fire, under the influence of the applied pulse electric field the soma was gradually hyperpolarized. When the neuron was driven by the current clamp to fire at a high frequency, the application of the pulse electric field significantly reduced the firing frequency (from 46 Hz to 32 Hz).

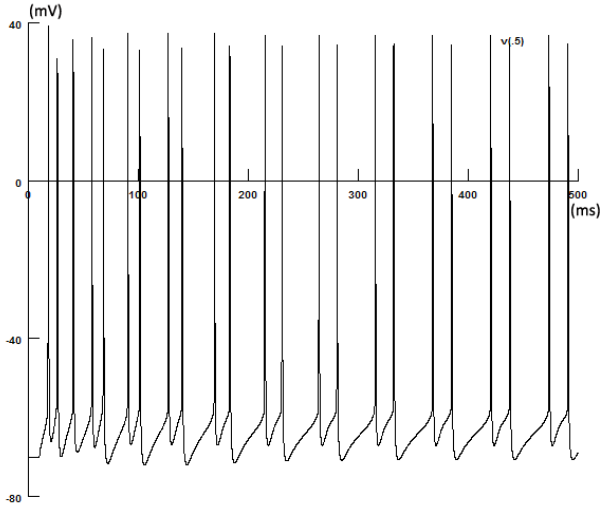
It should also be noted that the applied electric field may have to be different in the direction of the field according to the different neuron morphology. The LV pyramidal neuron used in the current simulation was only a part of the original neuron with a large portion of the apical dendrite in absent. Further investigation will be carried out on more anterior cingulate neurons with full morphological profiles.

VI. Conclusion

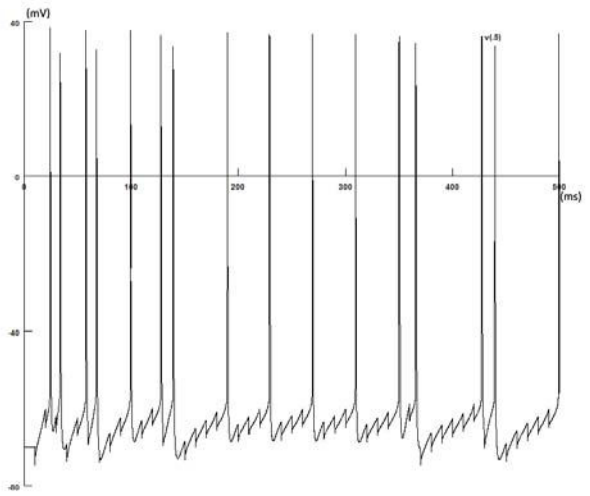
A novel approach for pain relief by magnetically deep brain stimulation of neuronal firing at ACC has been proposed based on a patented magnetic field projector. The magnetic field projector produces a concentrated magnetic field 3 cm deep into the brain and induces a pulse electric field that modulates the neural firing at ACC. The modulation mechanism has been verified by simulation of the membrane potential of a 3D reconstructed ACC pyramidal cell under stimulation of the pulse electric field showing a decrease of the firing rate. The proposed approach will hasten novel noninvasive devices for pain relief with higher efficacy and safety.



(a)



(b)



(c)

Fig. 4. (a) False color plot of the membrane potential in the cell morphology at 0.3 ms after stimulation onset; (b) membrane potential with the clamped current of 0.1 nA showing the neuronal firing at 46 Hz; (c) membrane potential with the pulse applied electric field at 100 Hz the neuronal firing rate reduced to 32 Hz.

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