Noninvasive deep brain stimulation using focused energy sources

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A non-invasive methodological possibility for brain stimulation through the simultaneous use of an external energy beam and an existing brain imaging system such as functional magnetic resonance imaging (fMRI) is herein proposed; the main advantage is to confine the stimulation into a single brain area, avoiding unintentional stimulation of adjoining brain regions, thus, allowing for deep brain stimulation. The methodological possibility is to be used for research, treatment and diagnosis of neurological, cognitive and neurophysiologic disorders. The method includes the simultaneous steps of applying focused thermal energy stimulation within a living brain, and monitoring such stimulation using MRI thermometry images; in addition, it includes the detection of stimulated neuronal impulses by its potentially effects in the blood oxygenation level (BOLD) fMRI response signal.

Medical research based on recent brain imaging techniques is placing a lot of attention on the brain as a role player in the pathophysiology of many medical disorders. In particular, the improper functioning of specific brain areas (centre or circuit) is shown to be correlated with illness. For example, social anxiety disorder and panic spectrum disorders seem to be associated with the abnormal functioning of the area involving orbital-frontal cortex, amygdala, cingulum and hippocampus. Psychotic disorders seem to have a relation with prefrontal cortex thalamic striatum and occipital cortex area. Parkinson disease, and tick syndromes seem to have abnormalities in corticothalamic straitum area. Medical conditions such as obesity and stress are related to temporal hypothalamic area. Even though the brain is composed of different but connected areas, each one related to specific functions and conditions, its mechanism of operation is still unclear. Therefore, in the past decade we have seen a rapid increase in the application of noninvasive brain (proper functioning) stimulation to study brain–behaviour relations and treat a variety of neurologic and psychiatric disorders. Noninvasive brain stimulation is a promising treatment for a variety of medical conditions, and the number of applications continues to increase with the large number of ongoing clinical trials in a variety of diseases. Thus, the potential significance of noninvasive brain stimulation is huge, affecting a large number of patients with debilitating conditions[1]. Novel methods of treatment of mental and neurological disorders directed at specific brain areas have been introduced. These include deep brain stimulation by implanted electrodes, successfully used in obsessive compulsive disorders (OCD), Parkinson's disease and epilepsy (Figure 1). Brain surgery is also used in the treatment of depression and OCD. These two last methods are reserved for the treatment resistant conditions where other treatments fail because of the invasiveness and possible complications. The success of these treatments underlines the importance of specific brain areas in the pathophysiology of mental and neurological disorders. Furthermore, it underlines the importance of developing noninvasive methods of intervention at the neuronal level. It has been proposed that brain areas can be assessed noninvasively using transcranial magnetic stimulation (TMS). TMS uses the principle of electromagnetic induction to focus induced currents in the brain (Figure 2). These currents can be of sufficient magnitude to depolarize neurons, and when these currents are applied repetitively (repetitive transcranial magnetic stimulation, rTMS) they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, beyond the duration of the train of stimulation[1]. The signal from the brain after the TMS stimulation can be read using a common brain imaging technique such as structural magnetic resonance imaging (MRI, Figure 3). Functional MRI (fMRI) is an existing neuroimaging technique that permits assessment of rapid changes in the activity of the brain; it is performed carrying out some changes such as fast scanning techniques under common structural MRI scanners. fMRI is capable of producing real time three-dimensional maps of brain activity. This technique allows scientists to study brain areas involved in pathology of different neurological, cognitive and

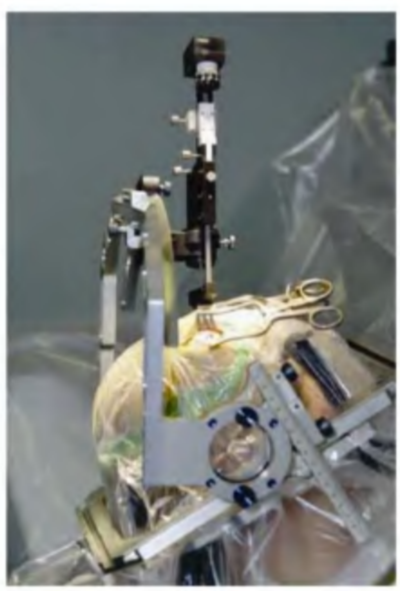

Figure 1. Insertion of an electrode during deep brain stimulation for Parkinson's disease.

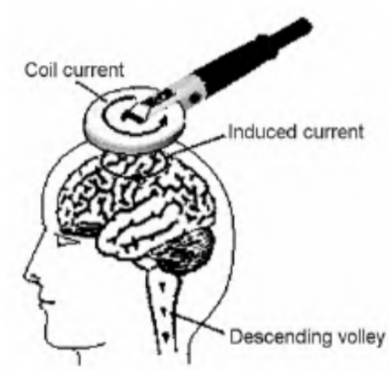

Figure 2. TMS single coil. (Reproduced with permission from Gillian O'Driscoll.)

neurophysiologic disorders. The TMS stimulation guided by fMRI method has been described for therapeutic purposes. This TMS–fMRI neuronavigation system is currently being implemented in psychiatry and neurology for diagnostic and therapeutic purposes. The system, however, has some drawbacks. For example, TMS does not stimulate deep brain areas, because it is incapable of penetrating brain tissue deeper than 1–2 cm. In addition, TMS has a large area of focus, 1 cubic cm or more, which does not permit focused activation of a specific brain location (Figure 4). There is a problem in using TMS together with fMRI, because TMS produces a magnetic signal that interferes with the magnetic field and consequently with the fMRI image. Therefore, another biomedical engineering approach that could lead to a more effective brain stimulation device: to noninvasively confine the stimulation into a single brain area, avoiding unintentional stimulation of adjoining brain regions, and to allow for deep brain stimulation requires absolute consideration. These new approaches would be valuable in research with potential therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry and neurobehavioural research.

Theory and hypothesis

Action potentials or nerve impulses are not created only by electrical stimulation. It has been demonstrated that nerve stimulation by low-intensity pulsed infrared light is possible[2]. In this case, action potentials are created by absorption of infrared energy. In other words, this absorption increases the temperature creating an action potential. It has been calculated that the temperature increase of 6°C (from baseline temperature) is the biophysical mechanism responsible for stimulation of sciatic nerve of rats and frogs[2]. This optical stimulation *in vivo* exhibits advantages over standard electrical means by providing high spatial selectivity, contact-free and artifact-free stimulation for peripheral nerves[3]. The potential of possible human deep brain stimulation *in vivo* using the above mentioned optical means is proposed here. Another possible electromagnetic source for future noninvasive brain stimulation are microwaves. Currently, focused microwaves have been employed for thermal ablation of tumours[4]. However, the brain absorption mechanism of microwave energy, counting for focused microwave brain stimulation is expected to be mediated by similar thermal effect present in infrared laser stimulation. In addition, future techniques concerning focusing microwave beam pulses, that is: microwave amplification through stimulated emission of radiation (maser) pulses can play a major role in localized human deep brain stimulation, eliciting an action potential while increasing the baseline temperature. A mechanical energy source such as high frequency sound is another possibility for noninvasive deep brain stimulation. Currently, focused ultrasound is combined with MRI to perform thermal ablation of tumours[5]. However, it has been recently shown that focused pulse ultrasound excites mouse brain hippocampus area *in vitro* responses[6]. Therefore, we hypothesize that proper localized energy sources such as the ones discussed here: infrared pulse laser, focused pulse microwaves (and/or maser pulse beam) and focused pulse ultrasound guided to specific brain areas will indirectly create an action potential (nerve impulse) within those areas (Figure 5). Brain stimulation mechanism is possible by radiated energy tissue absorption processes within the brain including a prominent thermal effect for electromagnetic waves (infrared and microwave); whereas for ultrasound (mechanical wave) stimulation the mediation by energy absorption is present and high rise in temperature will not be a determinant factor. The consequences are the possibility to noninvasively confine the stimulation into a single brain area, avoiding unintentional stimulation of adjoining brain regions, and to allow for deep brain stimulation (Figure 5). Furthermore, the use of additional noninvasive guided energy sources such as: pulsed infrared laser, focused microwaves (and maser), focused ultrasound, is envisioned for deep brain stimulation. The MRI thermometry using realtime brain temperature maps, common during MRI guidance (or neuronavigation) ultrasound[5] is a practical technique counting for proper monitoring of future electromagnetic brain stimulation sources such as pulse infrared laser and focused microwaves (Figure 6). It is expected that the induced brain current from the stimulating electromagnetic and mechanical sources mentioned here distorts the structural MRI signal in the location of the stimulation, allowing possible control and detection of the stimulation[7]. In addition, it is also expected that the action potential generated by focused energy stimulation modulates or excites a metabolic response in the brain area such as the blood oxygenation level dependent (BOLD) fMRI signal, hence, allowing indirect localization of the brain stimulation.

Figure 3. The MRI scanner facility. (Courtesy: Anita Kuijper.)

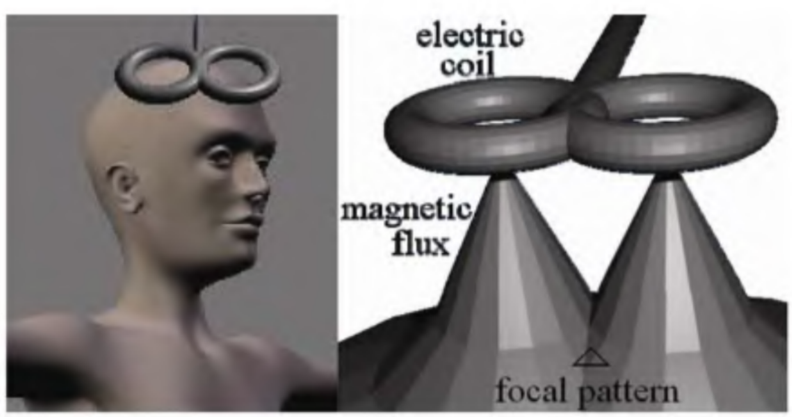

Figure 4. Butterfly TMS coil and its focality limitation.

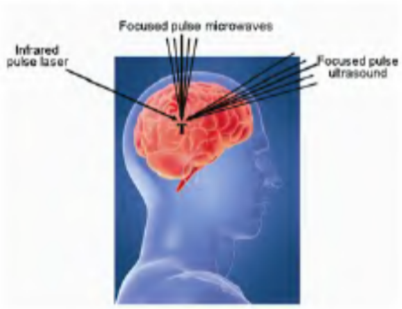

Figure 5. Illustrative scheme of noninvasive thermal brain stimulation using focused energy sources.

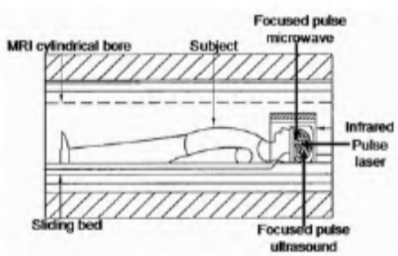

Figure 6. Illustrative scheme of MRI guidance (thermal) brain stimulation.

Experimental validation

Validation comes from an experiment consisting of separately stimulating the brain auditory and visual cortices of human volunteers by three separate sources: infrared pulse laser, focused pulse microwaves and focused pulse ultrasound. These three localized energy sources are expected to separately create an action potential within those brain areas. Since this stimulation is mediated by a rise in temperature, an infrared camera neuronavigation system is to be attached to the stimulating set-up to monitor temperature variations within the brain while a sensing technique will measure evoked potentials for auditory and visual cortices following standard protocols. These sensing techniques include electroencephalography (EEG) or magnetoencephalography (MEG) of the brain auditory and visual cortices respectively. Other interesting experimental possibility is realizing the whole experiment inside the MRI scanner, relying on proper thermometry guidance (MRI neuronavigation) for the three discussed energy sources modalities (Figure 6). However, magnetic compatible stimulating equipment has to be employed while placing humans inside the MRI scanner. In another exciting set-up, magnetic resonance spectrometry (MRS) technique performed with MRI is used to follow certain neurotransmitter localized dynamics and flux, and to follow changes in temperature, allowing indirect brain activation localization. Some MRI scanners already possess low power laser light guiding the patient bed arrangement setup. However, a proper powered stimulating laser is to be guided inside the MRI scanner bore using small diameter but long fibre optic tube, whereas the focused ultrasound with coordinated amplitude and phase array for proper beam delivery system is already developed for MRI compatibility. Adjustments however, in power, design and frequencies should be introduced for the stimulating sources. Current focused microwave technology[4] has to be improved for brain stimulation including an MRI compatible maser pulse. Many techniques should be employed for detecting the evoked potential location by its modulating effects in the MRI image signal[7]. MRI together with MRS could give specific metabolic information right after effective brain area stimulation takes place using the focused energy sources. In addition, a small blood oxygenation level dependent (BOLD) fMRI effect has to be measured right after the stimulation take place, accounting for indirect brain stimulation localization. Finally, special care has to be placed for any response from patients such as hearing or seeing experiences while the experiment is conducted.

Conclusion

The objective of this discussion is to provide methods for stimulating neurons within the human brain. The method includes the simultaneous steps of applying a focused energy source such as: infrared laser, focused ultrasound or focused microwaves (maser) stimulation, within the brain of living person, and monitoring such stimulation using neuronavigation systems based on current neuroimaging modalities. In particular, we propose MRI thermometry images given the availability and precision of this technique; in addition, it includes the detection of stimulated neuronal impulses by its potentially modulating effects in the BOLD fMRI signal. The application of different amplitudes, frequencies and phases of directed energy source to the brain areas will stimulate the brain, therein, exciting the BOLD MRI response signal to be detected by the imaging system. At that time, changes in brain areas will be assessed. This detection in addition to the real time temperature maps of the brain will permit adjustment of the (energy) source beam location, to achieve most effective stimulation of such brain areas. The changes in the brain areas are useful for research, diagnosis and treatment. Further the methods have to diagnose and treat specific psychiatric, neurological and neurophysiologic conditions. Examples of such conditions include, but are not limited to, obsessive compulsive disorder and its spectrum, post-traumatic stress disorder, depression, bipolar disorder, social anxiety disorder, psychotic disorders, panic disorder, ticks, chronic pain syndrome, insomnia, chronic fatigue syndrome, stress, obesity and other similar conditions.

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