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STIMULATION METHODS

A method to quantitatively evaluate tremor during deep brain stimulation surgery

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Keywords Deep brain stimulation · Parkinson's disease · Essential tremor · Tremor quantification · Accelerometer

Purpose

Deep brain stimulation (DBS) of basal ganglia using surgically implanted electrodes is now an effective and widely-used method to treat neurological movement related disorders such as Parkinson's Disease (PD) and Essential Tremor (ET). The mechanism of action of DBS is not fully understood; optimal target definition is difficult and thus most groups use complementary intraoperative methods. Intraoperative stimulation tests are performed along the predetermined trajectories to evaluate the clinical effects on tremor while gradually increasing the stimulation parameters (voltage/current), determining the thresholds for clinical effects (subjective threshold) and side effects at each anatomical measurement position. Currently, these evaluations are performed semi quantitatively by the neurosurgeon or the neurologist. Our method intends to improve the targeting procedure and make it more objective by measuring the acceleration of the patient's wrist.

Methods

Under the on-going clinical study at the University Hospital Clermont-Ferrand, France, accelerometer data recordings have been performed during 6 bilateral DBS implantations for PD (n = 2) and ET (n = 4). A 3-axis accelerometer (±2/±4/±8 g digital output evaluation board based on LIS331DLH accelerometer, ST Micro), placed inside a non-conductive printed plastic case (FullCure 830 VeroWhite, Objet Geometries Ltd - Belgium) slightly bigger than a wrist watch, is tied to the patient's wrist during intraoperative test stimulation. At each test stimulation position, while the intensity of electric current used for stimulation is slowly increased, data from the accelerometer is recorded using in-house developed software - Lemur. In addition, the moment and the kind of side effect occurrence are noted. The electrophysiology system responsible for the stimulation is synchronized with the accelerometer system. The final surgical target in which the chronic stimulation electrode is implanted afterwards is chosen by the neurosurgeon by mentally integrating the multitude of anatomical, electrical and clinical data, including clinical efficacy, therapeutic stimulation thresholds and side effects. The above procedure is performed for DBS implantation on both sides of the brain.

Currently, the recorded accelerometer data is analysed postoperatively with plans to do it online during the surgery. As a first step of analysis, the accelerometer data is detrended using smoothness priors method. This data is then low pass filtered and statistical features like standard deviation, signal energy, entropy, main frequency component and amplitude are calculated from it in a windowed manner. These statistical features are then divided into two groups a) the time period before reaching the subjective threshold and b) at the subjective threshold, and they are compared statistically (Wilcoxon two-sided signed rank test) to confirm changes in relation to the subjectively defined threshold. In addition to recording data during stimulation, data was also recorded without any stimulation to set a baseline for comparison. The data recorded at all the stimulation amplitudes is normalized to the baseline value and then used to find the therapeutic thresholds (Fig. 1b). Based on the percentage change from the baseline, 3 different accelerometer thresholds are calculated (25, 50 and 75 %) and are compared to subjective thresholds. We also used the accelerometer threshold and the side effect threshold to decide a final implant site.

Results

The Wilcoxon two-sided signed rank test has identified a statistical significant change in tremor ($p < 0.01$) for signal entropy, energy and standard deviation and peak frequency amplitude. The signal energy and peak frequency amplitude seem to be the most sensitive statistical features showing a higher percentage change compared to baseline (Fig. 1b). Out of the 3 different accelerometer thresholds, the 75 % threshold matched closely to the ones found subjectively during the surgery. In most cases (>90 %), the accelerometer threshold was found at a lower stimulation amplitude than the subjective threshold (Fig. 2).

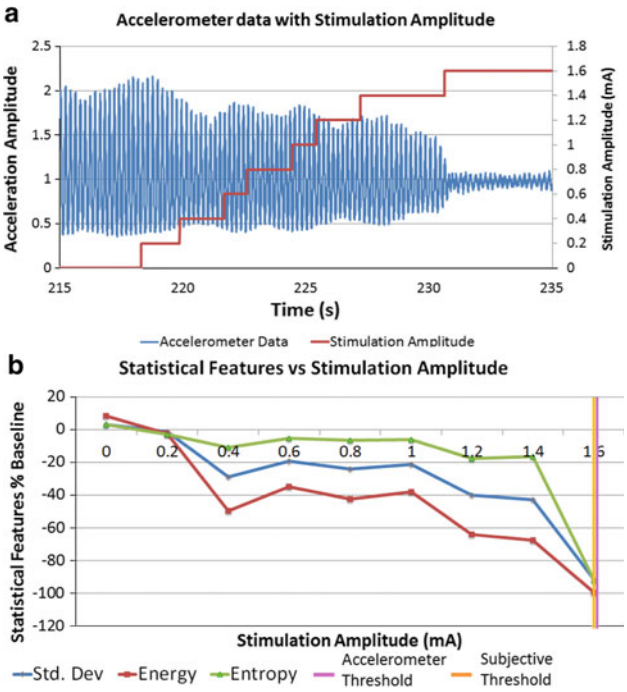

Fig. 1 Stimulation amplitudes (**a**) and statistical features (**b**)

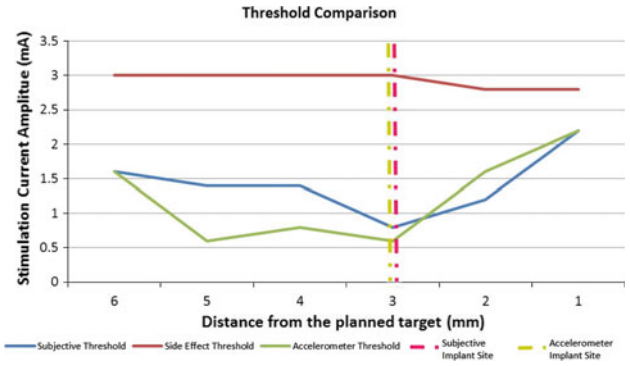

Fig. 2 Subjectively defined stimulation threshold

Conclusion

The present study describes a method to perform tremor assessments using mathematical parameters extracted from the acceleration signal of the wrist. The accelerometer recording in the OR does not increase the duration of the surgery or interfere with any other procedure. The subjectively defined stimulation threshold was confirmed by the acceleration measurements, and it seems that the measurements were more sensitive than the neurologist's evaluation (Fig. 2). Further research is planned with the recorded data. The data will be correlated with the anatomical brain structures stimulated during the surgery. This might bring new information related to the mechanism of action of DBS.

Unlearning pathological neuronal synchrony by coordinated reset neuromodulation

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Keywords Deep brain stimulation · Desynchronization · Coordinated reset · Computational neuroscience

Purpose

A number of brain diseases, e.g. Parkinson's disease (PD) and tinnitus, are characterized by abnormal neuronal synchronization. To specifically counteract neuronal synchronization we have developed Coordinated Reset (CR) stimulation, a spatio-temporally patterned desynchronizing stimulation technique. According to computational studies, CR stimulation induces a reduction of the rate of coincidences and, mediated by synaptic plasticity, an unlearning of abnormal synaptic connectivity, so that a sustained desynchronization is achieved. Computationally it was shown that CR effectively works no matter whether it is delivered directly to the neurons' somata or indirectly via excitatory or inhibitory synapses.

Methods

Pre-clinically as well as in an early clinical proof of concept trial invasive deep brain CR stimulation of the subthalamic nucleus (STN) was used for the treatment of Parkinson's disease. In a randomized single blind placebo-controlled proof of concept trial non-invasive acoustic CR neuromodulation was applied to patients suffering from tinnitus.

Results

Unlike standard high-frequency DBS, electrical CR stimulation delivered to the STN in parkinsonian (MPTP) monkeys has sustained long-lasting aftereffects of up to 30 days after cessation of CR stimulation (with only 2 h CR/day during 5 days). Accordingly, electrical CR stimulation of the STN in externalized PD patients caused a significant cumulative clinical and electrophysiological aftereffects as assessed by motor scores and power analysis of LFP recordings.

Acoustic CR neuromodulation delivered during 4–6 h/day during 12 weeks led to a significant decrease of tinnitus loudness and annoyance (as assessed by visual analogue scale scores) and a significant decrease of the tinnitus questionnaire. Furthermore, power and functional connectivity analysis of EEG recordings demonstrated that acoustic CR therapy caused a significant decrease of pathological neuronal synchrony in a tinnitus-related network of auditory and non-auditory brain areas along with a normalization of tinnitus characteristic abnormal interactions between different brain areas, especially between the posterior cingulate cortex and the primary auditory cortex as well as between the dorsolateral prefrontal cortex and the primary auditory cortex.

Conclusion

In the pre-clinical and clinical settings tested so far, CR neuromodulation causes a sustained long-lasting desynchronization of pathologically synchronized neuronal populations, as predicted theoretically. Accordingly, the CR approach appears to be a promising novel therapeutic option for the therapy of PD and tinnitus and possibly other brain diseases characterized by pathological neuronal synchrony. While different technical realizations are required for the invasive vs. non-invasive CR approach, the underlying stimulation algorithm, however, remains the same.

Position detection method for ocular movement sensor using Hall effect IC array

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Keywords Ocular movement sensing · Monitoring · Hall effect sensor · Neurosurgery

Purpose

In neurosurgery, analysis of the extraocular muscle electromyogram which is evoked by electric stimulation to cranial nerves in the operative field is a common technique for intraoperative neurophysiological evaluation of ocular movement [1]. However, this method has lower reliability for quantifying cranial nerve damage because of poor reproducibility and instability of placement of electrodes for stimulation. Moreover, it is difficult to secure the cranial nerves for stimulation in many occasions of the surgery.

It is known that electrical stimulation for unilateral frontal eye field produces conjugated horizontal ocular movement to the contralateral side. The frontal eye field may be an alternative stimulation site for intraoperative monitoring of ocular movement. However, electromyograms evoked by transcranial stimulation and obtained from surface electrodes [2] cannot quantify the ocular movement due to noise caused by spreading stimulation current or contraction of orbicularis oculi muscle co-induced by the transcranial stimulation.

In order to solve this problem, the authors have been developing a new device using a magnet system which can detect and quantify ocular movement independently of the electromyogram applicable for the transcranial stimulation.

Methods

The system consisted of a Hall effect IC sensor array (Fig. 1a) and a specially designed thin magnet (Fig. 1b) which can be worn on the cornea just like a contact lens. In this study, the contact-lens-shaped magnet was seated on an experimental model of eyeball mounted in a gimbal (Fig. 2a). The sensor array consisted of thirteen linear Hall effect sensors which were configured to detect changes of intensity of the magnetic field caused by the movement of the magnet on the eyeball model.

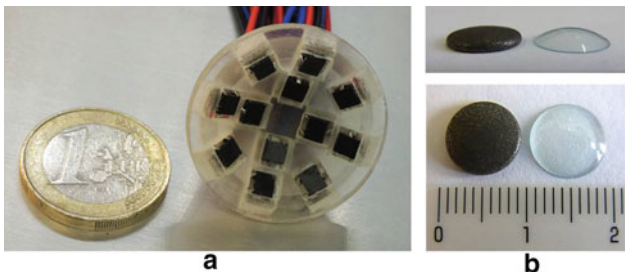

Fig. 1 **a** A magnetic sensor array which consisted of twelve linear Hall effect sensors. A diameter of the sensor array is 30 mm. The footprint of a sensor is 4.4 × 3.6 mm. Each sensor has a resolution of 65 mT/mV and an output range of 0–5 V (0 T = 2.5 V). **b** A concept photograph of sensor array installation. The wired sensor array is placed on the closed right eyelid

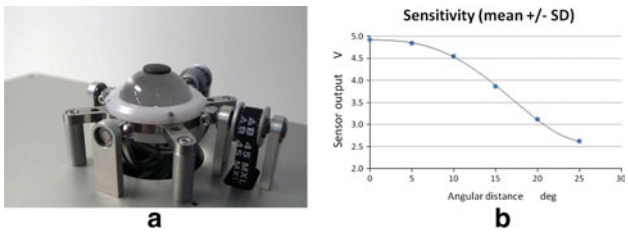

Fig. 2 **a** An experimental model of ocular movement. A one-inch acryl ball resembling an eyeball is mounted in a two-axis gimbal which provides pitching and yawing resembling ocular movement. The contact-lens-shaped magnet is pasted on the top of the acryl ball (*arrow*). **b** A graph exhibiting a relation between angular distance from a linear Hall effect sensor on the sensor array to the center of the contact-lens-shaped magnet on the eyeball model, and output voltage of the sensor. Zero degree means that the magnet is located right below the sensor. Data were collected every 5° and interpolated with a natural *cubic spline curve*. The sensor output was monotonically decreasing throughout the section between zero and 30°. The polarity of lines of magnetic force is inverted at 30°

Thirteen Hall effect sensors were arranged in array, but to detect the rotation angle of the eyeball accurately, it is necessary to estimate the exact angle of the eye ball from plurality sensor values. However, it is difficult to simply estimate the eyeball rotation angle because the spread of the magnetic field from the magnet is non-linear (Fig. 2b), in this study, the following method was used to estimate the position of the magnet.

1. Select the three sensors from the top voltage value of thirteen sensors, and assume the center of the magnet field within the triangle the corners of which are the selected three sensors.
2. Calculate the geometric center of gravity of the triangle.
3. The calculated center of gravity is set as the temporary magnetic field center, and the magnetic field model (Fig. 2b) is adopted to the temporary center to calculate the error between the real sensor value and the computed sensor value from temporary magnetic field.
4. Move the temporary magnetic field center to the direction which decreases the error between the real sensor value and the computed value.
5. Calculate the error value a number of times. This method is repeated until the error is below 0.1 deg.

Measurement and calculation was done by QNX 6.5.0. The eyeball model was rotated in front of the magnetic sensor array, and the performance of the system was evaluated.

Results

The eyeball rotation angle was changed 40 patterns, the rotation error between the real value and estimated value was 1.23 ± 0.62°.

Discussion

The cause of the estimated error can be considered an individual difference of the each sensor and the placement error of the array arrangement. But it is considered that the magnitude of the error is no problem because the purpose of the system is to confirm the cranial nerve damage.

In this experiment, the sensor was installed in ideal position on the eyeball model, but in the clinical case, it is easily assumed that a few mm deviations will occur, we have to go on the examination in the situation of miss placement of the sensor system.

Conclusion

In this study, development of an ocular movement sensor and iterative calculation method for estimating the magnet position were illustrated. We plan to use the developed sensor in clinical case in near future.

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Future neuromodulation/deep brain stimulation: advantages of nanoarrays for brain neurotransmitter monitoring

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Keywords Carbon Nanofibers · Deep Brain Stimulation · Nanotechnology · Neuromodulation · Neurotransmitters

Purpose

Brain electrical activity has been monitored for decades using depth electrodes, and more recently has been altered with depth electrodes in deep brain stimulation (DBS). DBS has proven quite effective at treating movement disorders such as Parkinson's disease, but has been much less successful in treating other disorders such as major depression and obsessive–compulsive disorder. Since in Parkinson's disease, as well as in mood disorders, the primary pathophysiology appears to involve neurotransmitter(s) rather than brain electrical activity, it is reasonable to monitor brain neurotransmitter concentrations in real-time to better understand (and treat) these disorders.

The Wireless Instantaneous Neurotransmitter Concentration System (WINCS) is being developed to measure neurotransmitters *in vitro* and *in vivo*. The WINCS uses fast-scan cyclic voltammetry (FSCV) and differential pulse voltammetry (DPV) together with Bluetooth wireless communication to allow free-roaming animals, with the device implanted in the skull, to have remote *in vivo* monitoring of neurotransmitters. WINCS has proved successful in monitoring individual neurotransmitters such as adenosine, dopamine, and serotonin during DBS. However, the traditional carbon microfiber (CMF) electrodes used in FSCV/DPV to measure single neurotransmitters have not been as successful at monitoring more than one neurotransmitter simultaneously under *in vivo* conditions.

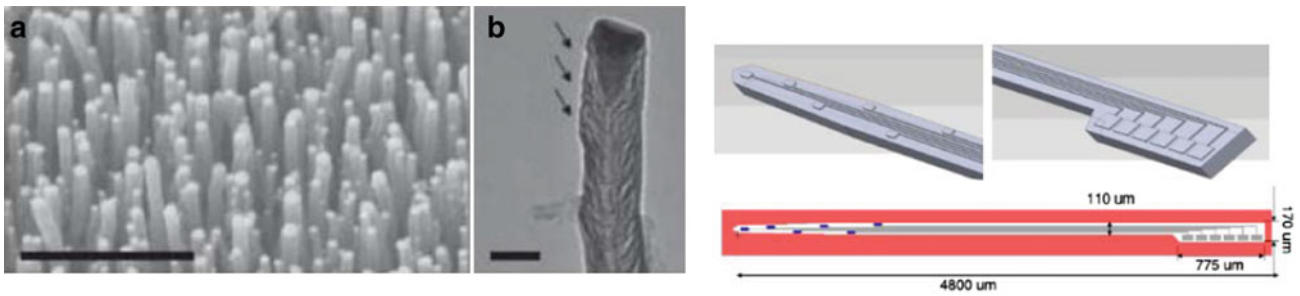

Fig. 1 *Left*: **a** SEM image of an array of vertically aligned CNFs. *Scale bar*—1 mm. **b** TEM image of an individual CNF; *arrows* show active sites. *Scale bar*—0.1 mm. *Right*: *Upper panels* show enlarged views of tip and base of microelectrode with six pads of CNF arrays that is illustrated in the *bottom panel*

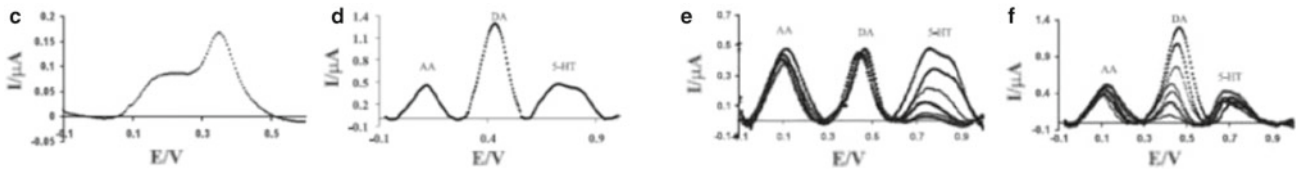

Fig. 2 *Left*: DPV plots of a mixture of 1 mM AA, 10 mM DA, and 10 mM 5-HT. (c) using GC electrode; (d) using CNF electrode. *Right*: DPV plots of a mixture of AA, DA, and 5-HT using a CNF electrode. (e) AA (1 mM), DA (10 mM), and 5-HT (10, 5, 2.5, 1, 0.5, 0.25, 0.1 mM); (f) AA (1 mM), DA (10, 5, 2.5, 1, 0.5, 0.25, 0.1 mM), and 5-HT (10 mM)

Multiplexed carbon nanofiber (CNF) arrays detect small biomolecules such as DNA, proteins, and neurotransmitters with high sensitivity. Integration of the CNF array with WINCS (WINCS nanotrode) has the advantage of sensing at multiple locations for better spatial resolution of neurotransmitter release. We here report progress on developing CNF arrays to monitor multiple neurotransmitters under conditions found *in vivo*.

Methods

For CNF arrays, a multiplexed chip is fabricated on a 4-inch silicon wafer using standard lithographic techniques. For the WINCS nanotrode, vertically aligned CNFs are grown directly on the wafer from lithographically defined nickel catalyst. Silicon dioxide is added to insure that only the CNF tips are exposed as sensing electrodes. Electrode performance is evaluated using FSCV and electrochemical impedance spectroscopy. Figure 1 (left) shows SEM and TEM images of vertically aligned CNFs; Fig. 1 (right) shows a schematic of a microelectrode under fabrication that is $\sim$100 mm in diameter with six individually-addressed pads <50 mm in diameter. This will allow monitoring of one or more neurotransmitters as well as monitoring of electrical activity (and, if desired, the option of electrical stimulation) all in a region of brain tissue less than 100 mm in diameter.

By using a standard triangle-shape FSCV wave, dopamine (or dopamine plus serotonin) are detected; by using an N-shape wave, only serotonin is detected—as we have reported previously. However, ascorbic acid *(present in concentrations 100–1,000 times that of dopamine in brain tissue* in vivo*) presents a particular problem for the electrochemical detection of neurotransmitters such as dopamine and serotonin. Using DPV, a CNF array was compared to a glassy carbon (GC) electrode at distinguishing dopamine (DA) and serotonin (5-hydroxytryptamine—5-HT).*

Results

Figure 2 (left) shows the DPV plots of a mixture of ascorbic acid (AA), dopamine (DA), and serotonin (5-HT), (c) being with a GC electrode and (d) with a CNF electrode. Using the CNF electrode, the peaks for AA, DA, and 5-HT are quite easily distinguished (d), which is not the case with the GC electrode (c). Figure 2 (right) shows the DPV plots, using a CNF electrode, of a mixture of AA, DA, and 5-HT, (e) being where the concentration of 5-HT alone is varied and (f) being where the concentration of DA alone is varied. It is clear that the CNF electrode is capable of detecting changes in the concentration of either neurotransmitter in the presence of ascorbic acid and the second neurotransmitter.

Conclusion

A vertically aligned CNF array can discriminate between AA, DA, and 5-HT and detect variations in concentration of a single neurotransmitter, which a standard GCE cannot do. CNF arrays have excellent stability, selectivity, sensitivity, and spatial and temporal resolution. We have previously demonstrated the integration of CNF electrode arrays with the WINCS for the simultaneous monitoring of dopamine and serotonin. A 100 mm diameter microelectrode with six individually-addressed CNF array pads can be used for precise localized recordings of two neurotransmitters, together with monitoring of electrical activity and focal tissue electrical stimulation if desired. The small size of the CNF array microelectrode (less than 1/10 the diameter of the macroelectrodes used in DBS at present) presents the opportunity for minimally-invasive monitoring and stimulating in various regions of the brain simultaneously. This increased spatial resolution of multiple neurotransmitter monitoring will improve our understanding of both the pathophysiology of various nervous system disorders and the mechanism of DBS efficacy. In time, the monitoring of focal brain electrical activity as well as multiple neurotransmitter concentrations can permit truly "smart" DBS, i.e. where the DBS is guided by the electrochemical deficits (and the electrochemical responses) of the brain itself. The era of "coaching" the brain to correct its own electrochemical disorders will soon be upon us.