APPARATUS FOR TREATING NEUROLOGICAL DISORDERS BY MEANS OF CHRONIC ADAPTIVE BRAIN STIMULATION AS A FUNCTION OF LOCAL BIOPOTENTIALS

Technology object:
Apparatus for treating neurological disorders by means of adaptive electro-stimulation retroacted by biopotentials.

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Application:
Deep Brain stimulation for neurological and neurodegenerative disorders

Novel aspects and advantages:
- Optimization of the therapy for the patient, (e.g.: in Parkinson in controlling fluctuations, and adverse effects, without additional work for the patient or the caregiver).
- Optimization of the device performances, in terms of battery life, and possibility to switch to different waveforms.
- Adaptive DBS can be implemented on the current DBS architecture and devices, without specific changes of neurosurgical or neurological practices.
- The technology is applicable also to new generation electrode arrays, with more than 4 contacts.
- Stimulators based on this technology will be fully compatible with existing implants and will allow patients with old impulse generators to upgrade their implant when replacing it for battery depletion.

Current development stage:
External system prototype

Intellectual propriety rights:
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**Invention at a glance**

The invention relates to a system for treating neurological disorders by means of adaptive electro-stimulation, which is able to detect biopotentials from the stimulating electrode, cleaning the stimulation artifact, to correlate such signals to the stimulation effects and feedback the stimulus parameters.

The system proposed is able to optimize deep brain stimulation (DBS) therapy that was introduced almost fifteen years ago to treat Parkinson’s disease and essential tremor, and it is now an established neuromodulatory strategy for several neurological and neuropsychiatric disorders, including dystonia, Tourette syndrome, and obsessive compulsive disorders.

*In the current situation*, whatever adverse event or fluctuation experienced by the patient during stimulation delivery, parameters are fixed and the doctor or the patient can adjust them only through a manual procedure. Fast variation, like movements, freezing, ecc... are not controllable.

*The innovation introduced* by the invention is that stimulation parameters are adapted on-line on the bases of the signals recorded in the area around the electrode (namely local field potentials, LFPs), and the amount of charge exchanged with the tissue is not constant but it is calculated on the patient’s specific need.

**Innovative aspects of adaptive brain stimulation**

Adaptive brain stimulation represents the necessary advance in neuromodulation therapies.

- The idea is innovative because it changes completely the philosophy of neurostimulation, starting to use neurological signals for optimizing therapies, instead of using them only to understand brain functions.
- Another innovative point resides in the use of the neuronal signals directly recorded through the electrodes implanted for DBS. This implies that no adjunctive hardware is required to apply adaptive brain stimulation instead of normal DBS.
- Also, the algorithms that control the adaptation of stimulation parameters have been already tested in LFP research.
- The proposed invention can be directly applied to the present neurosurgical procedures and settings.
- The design proposed by the invention is also suitable for any kind of electrode implanted for brain stimulation, because it requires only the presence of at least one electrode for stimulation and two electrodes for recording.

**Clinical Benefits from adaptive brain stimulation**

Adaptive stimulation will produce benefits for the patient and also for the caregiver:

- Fluctuations are controlled by means of the feedback algorithm;
- Adverse effects are controlled by means of the feedback algorithm;
- The risk of cognitive and behavioral impairment following stimulation is reduced because the total amount of electrical stimulation is under control.

Adaptive stimulation also optimizes the device performances in terms of battery life, possibility to switch to different waveforms, and it is open to other developments such as telemonitoring for homecare.
Stimulators incorporating this technology will be fully compatible with existing implants and will allow Patients with old impulse generators to upgrade their implant when replacing their IPG when battery depletes.

**Marketing benefits from adaptive brain stimulation**

The device will help increasing the knowledge of brain mechanism, thus increasing the understanding of physicians about the huge limitation of traditional non-adaptive stimulation: the market is waiting for it.

The more financial resources for healthcare are undergoing cut, the more Evidence Based Medicine approach is gaining application: in this scenario EBM in DBS can be achieved only by much more sophisticated devices able to both increase patient outcome and give additional information during therapy (e.g. by means of analysis of in-impulse generator recorded signals) for a better knowledge of DBS. Adaptive DBS is such device.

Owners of this technology will not only breakthrough the market of new implants, but they will also boost the replacement market where thousands of patients are waiting for better treatment options.

*Existing market leaders* find in this technology a great opportunity for maintaining their leadership and opening a huge gap in front of competitors whose products will become suddenly old stuff.

*New players* can find in this technology the opportunity of a very fast growth based on exclusive products. For new players the price of the Patent will be paid back in a short tim and will also reduce the marketing effort that they would in any case afford in trying to penetrate the market.

*Companies producing impulse generators/components* for industrial customers will find in this technology the opportunity of changing dramatically their position in front of their customers. They will be able to increase their earnings as owners of the technology making the difference to the end market.

**Patent Rationale**

Despite its diffusion, deep brain stimulation (DBS) suffers from the limitation of being delivered with constant stimulation parameters, adjusted only during control visits. Conversely, neurological and neuropsychiatric disease treated with DBS, especially Parkinson's disease that is DBS main indication, are characterized by fluctuations. The current stimulation strategy does not fully control symptoms (Krack et al, NEJM 2003; Deuchl et al, NEJM 2006; Kleiner-Fisman, Mov Disord 2006; Romito and Albanese, J Neurol, 2010), and it could achieve an even better clinical result adapting moment-by-moment to the clinical condition of the patient. In addition, several cognitive and behavioral side effects observed years after stimulation therapy started are thought to be due to the amount of stimulation delivered (Bronstein et al, Arch Neurol, 2011; Kleiner-Fisman, Mov Disord 2006; Romito and Albanese, J Neurol, 2010; Wjtias et al, 2007).

A DBS implant is usually composed by two deep brain electrodes (one for each side), implanted during a stereotactic neurosurgery procedure, and connected, through a cable extension, to a high-frequency neurostimulator implanted in the subclavicular area. The DBS electrode has 4 metal contacts that can
be selected to adjust the stimulation point after the implant. One or two of them are selected for chronic stimulation, the other are unused.

In the last years, DBS electrodes were used to record the electrical activity of neurons in the area around the electrode. The signals so recorded are known as local field potentials (LFPs) and can be interpreted as deep electroencephalographic signals. LFPs are differentially recorded through two of the stimulation metal contacts of the DBS electrode.

LFP analysis helped clarifying basal ganglia pathophysiology and its relationship with the clinical state of patients with movement disorders. LFPs are characterized by oscillations at different frequencies, acting as independent channels for information processing in deep brain structures. For instance, LFP oscillations at specific frequencies were discovered to be modulated by movement preparation, execution, and also imagination and observation (Foffani et al, 2003; Priori et al, 2004 and 2006; Foffani et al, 2005a and b; Brown and Williams, 2005; Foffani and Priori, 2006; Marceglia et al, 2007; Marceglia et al, 2009; Kuhn et al, 2006; Rodriguez-Oroz et al, 2010). In addition, these modulations change when the patient experience severe parkinsonian symptoms (eg bradykinesia, tremor, akinesia), thus showing the existence of an encoding system able to represent the clinical state in the oscillations. Other recent evidence showed that LFPs are recordable during stimulation, and that DBS itself is able to modulate specific oscillations (Rosa et al, 2010 and 2011; Giannicola et al, 2010; Rossi et al, 2008).

Finally, specific LFP oscillations represent the cognitive and behavioral state of the patient (Marceglia et al, 2011; Fumagalli et al, 2010; Kuhn et al, 2005; Brucke et al, 2007; Balaz et al 2008; Rektor et al, 2009). These studies suggested that involvement of LFP oscillations in cognitive and behavioral processes together with the observation that DBS is able to modulate LFP oscillations explain the post-DBS occurrence of behavioral disturbances.

**Adaptive brain stimulation features**

In the adaptive brain stimulation, clinical changes are automatically detected and stimulation parameters are changed accordingly, to give the optimal stimulation in any situation.

In the invention, the control variable, used as feedback to capture the clinical condition and to change stimulation parameters are LFP oscillations.

This choice is supported by several observations.

1. **LFPs are recordable without additional implants**: LFPs are differentially recorded through two of the stimulation metal contacts of the DBS electrode that are unused during current stimulation.

2. **LFPs are easy to capture and to be processed**: through specifically-designed devices (eg, FilterDBS-external device, Rossi et al, 2007; implantable device Avestruz et al, 2008) it is possible to record LFPs during DBS on, without artifacts. The processing algorithms are available from the research conducted in the last years.

3. **LFPs correlate with the clinical condition**: the literature regarding LFP analysis, in the last ten years, showed the existence of LFP oscillations specifically modulated during movement, during cognitive and behavioral tasks, and reflecting clinical changes induced by both electrical and pharmacological therapies.

4. **LFPs could be recorded from any basal ganglia structure selected as DBS target**, not only for Parkinson’s disease but also for other disorders, such as dystonia and Tourette Syndrome.
For these reasons, LFPs have the correct characteristics to be used as control variable of the adaptive brain stimulation system.

References

- Foffani G and Priori A. Deep brain stimulation in Parkinson’s disease can mimic the 300 Hz subthalamic rhythm. Brain 129(Pt 12), e59; author reply e60 (2006).


Sample figure

LFP-based control signal

Parameters adjustment

New parameters

FilterDBS

LFPs