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News & Views

Chronically monitoring the deep brain rhythms: from stimulation to recording

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Humans have never stopped exploring their brains, one of the most complex systems in nature. A thorough understanding of the brain is the ultimate challenge for neuroscientists. As there is a rapid increase in the aging populations and the number of brain disorders, researchers are much more eager to clarify how the billions of neurons and trillions of neural connections in the brain organize themselves and operate the complex brain circuits to produce a human's behavior and cognition, to provide guidelines for brain disorder therapies. This is also the deep reason for that the U.S. and European Union launched their brain projects relatively.

In the history of brain exploration and intervention, one milestone is the invention of deep brain stimulation (DBS) technique. It is the first technique in the clinic that can directly modulate the brain activities. Since Benabid first applied long-term deep brain stimulation for therapy of essential tremors in 1987, it has developed quickly and has been widely used for therapy of various movement disorders such as Parkinson's disease (PD) [1]. It has benefited more than 100,000 individuals with PD worldwide, as well as patients with other neurologic or neuropsychiatric disorders, although the mechanism for how these stimulations provide symptomatic benefit is still unclear and many phenomena cannot be adequately explained [2]. Usually, for clinical treatment, surgeons implant the leads into a specific nucleus using the technic of magnetic resonance imaging (MRI), stereotactic and microelectrode recording to observe the process. Thereafter, a pulse generator is placed under the clavicle to deliver continuous high-frequency pulses via subcutaneous extension wires to the electrodes to normalize the brain circuits and inhibit the symptoms. Thus fortunately, DBS also provides an opportunity for directly measuring the deep brain activities during the DBS surgery by connecting the extended lead to an electroencephalogram (EEG) amplifier [3].

By this approach, researchers already have a preliminary understanding on certain movement disorders caused by abnormalities of brain networks. More and more evidences show that DBS does more than affecting the target nuclei, but somehow modulates pathophysiological oscillations that reverberate through multiple brain regions [4]. In fact, we have entered the era of human neural-network modulation thanks to DBS [5]. However, such data as evidences have only been temporarily obtained from patients undergoing brain electrode implants prior to the development of the DBS system by Medtronic called Activa PC + S (Medtronic, Inc, Minneapolis, MN, USA), which can sense the local field potential (LFP) around the electrodes as well as apply stimulation [6]. Although its recorded LFP is stored internally first and then transmitted out using close distance transfer with a relatively slow speed of 11.7 kbps [7], it gives *the first time we're really getting a window into the brain* [4]. This long-term monitoring of brain electrophysiological activities, especially for patients with psychiatric diseases,

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including Alzheimer's disease, remains important for uncovering the pathophysiological mechanisms [4].

Since DBS has provided such a valuable opportunity for the implementation of implantable and long-term electrophysiological activity recording, we reported a novel design based on numerous years' of experience developing DBS devices, that not only provides the DBS therapy but also gives concurrent measurements and real-time and high-speed transmissions of brain activities [8]. This paper presented the recent progress. The device, model G102RS developed by the National Engineering Laboratory for Neuromodulation, Tsinghua University and manufactured by Pins-Medical, Inc, Beijing, China, is shown in Fig. 1a. The differential LFP signals between the electrodes on the DBS lead can be recorded at a sampling rate up to 1000 Hz. The recorded LFP signal is transmitted out synchronously within a range of 2 m using radio frequency (RF) communications with a carrier frequency range of 402–405 MHz according to the Medical Implant Communication Service (MICS). The system also has wireless recharging which is a trade-off for the additional power consumption of the LFP recording and transmission functions, ensuring the long service life of the implanted neurostimulator.

A clinical implant has been successfully carried out in a PD patient for obtaining LFP data recorded from the implanted G102RS system in the ON and OFF DBS states. The patient gave informed consent before participating in the study and all the procedures were approved by the ethics committee of the Beijing Tiantan Hospital, Capital

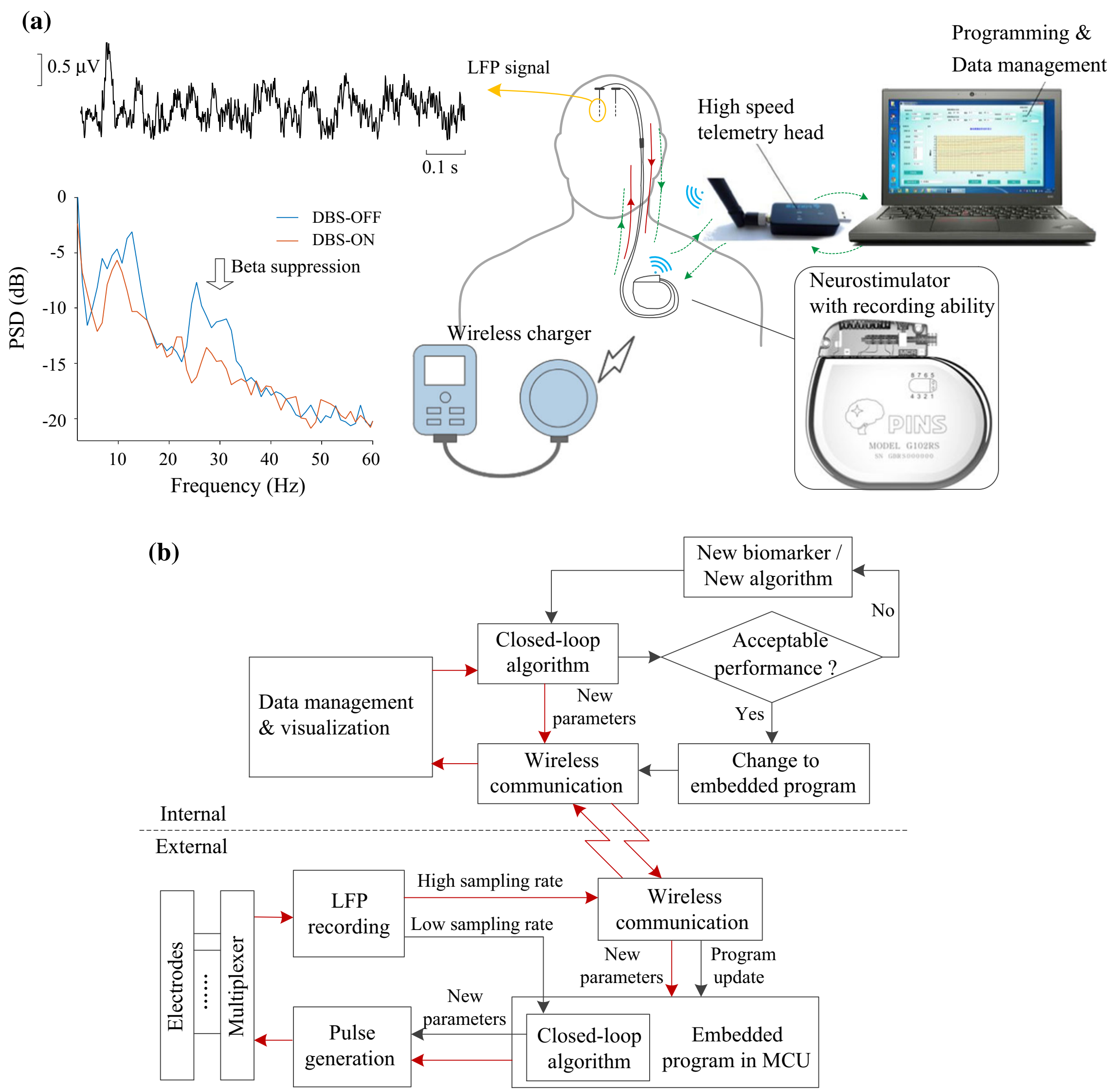

Fig. 1 External PC equipped with a data receiver and the G102RS model neurostimulator with the recording ability (**a**) and an application example of the system (**b**). **a** also shows 1 s time LFP segment recorded from the right STN of the PD patient in the first clinical trial and the frequency spectra during 2V-DBS OFF and ON

Medical University. Figure 1a shows the LFP signal and power spectra of recording from the STN in the PD patient using the implanted neurostimulator during his rest state. Consistent with the previous studies [9], the recorded data show that the STN-LFPs exhibited excessive beta band activity, which has been commonly recognized as a biomarker of PD, and it was suppressed during 2V stimulation, demonstrating that the G102RS was able to record the pathophysiological oscillations as a PD biomarker and subsequent suppression during DBS therapy.

We have integrated the recording and real-time transmission into the traditional DBS system, enabling chronic monitoring of the deep brain rhythms. The G102RS system is just like a brain monitor that provides brain signal measurements that will provide actual information on some types of brain disorders and brain states in combination with behavioral evaluations. The potential advantages of the system are as follows: the long-range RF communication reduces the limitations in patient movement, allowing for simultaneous behavioral experiments. This real-time LFP transmission can be used to support on-line algorithm training for closed-loop DBS therapy of brain disorders, which currently can only be achieved with an external system recording the beta band oscillatory activity from the extended DBS electrodes as a biomarker to trigger the stimulation [10]. An example of potential application of the system is illustrated in Figure 1b. The system, including the internal and external parts, gives a complete platform for biomarker exploration and closed-loop stimulation algorithm development and training. The neural activity is collected and sent into the external element which is designed to determine the biomarkers of a specific disease, such as the beta band oscillation in STN of PD patient. The stimulation parameters can then be modulated according to the algorithm result with feedback and control, which can be continually adjusted according to patient feedback and the physician's evaluation. The algorithm was changed to an embedded program and downloaded into the neurostimulator for validation. In addition, the ability of wireless software updates of the system enables simple upgrades of the embedded algorithm.

In conclusion, the G102RS system could be used as a data collecting platform for chronic recording of deep brain LFP, besides for delivering DBS therapy. It has significant clinical value for guiding DBS parameter programming and finally realizing individualized therapy, and may help us understand a great deal about how the brain works upon the applied electrical stimulation. As the DBS technique is growing fast, the development of new type DBS lead with more electrode contacts for more precise stimulation target [11] and new stimulation modes such as the variable frequency stimulation (VFS) specialized for the advanced PD patients with axial symptoms [12] certainly will make the number of the stimulation parameters much more and their range much larger. Therefore, the DBS programming is likely to become more effective and also complex [13], thus as a result combination with the deep brain rhythms reading turns out to have great advantages. With the chronic monitoring, we will have a clearer understanding of our brain for better treatment of brain disorders.

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Conflict of interest The authors declare that they have no conflict of interest.

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