● PERSPECTIVE

Need for multiple biomarkers to adjust parameters of closed-loop deep brain stimulation for Parkinson's disease

Closed-loop deep brain stimulation (DBS): DBS has been established as a surgical therapy for movement disorders and select neuropsychiatric disorders. Various efforts to improve the clinical outcomes of the procedure have been previously made. Several factors affect the DBS clinical outcomes such as lead position, programming technique, and surgical complications (Morishita et al., 2010). Currently, there are two approaches for improving DBS: directional DBS lead (Contarino et al., 2014) and closed-loop DBS (Rosin et al., 2011). The directional DBS is a straightforward approach that delivers the electrical stimulation accurately to the treated target area. Despite the more complicated programming paradigm in comparison with conventional programming, directional DBS offers an easier stereotactic procedure in terms of lead positioning. On the other hand, the notion of the basic closed-loop DBS system involves automatically adjustable DBS programming parameters including on/off switching based on the physiological condition of the patient. Typically, this programming procedure requires three to six months until achieving the optimal setting for existing open-loop DBS system, even for an expert DBS practitioner. Moreover, the parameters need to be adjusted to address the clinical symptoms at various stages of Parkinson's disease (PD) (Bronstein et al., 2011). An ideal closed-loop DBS system has been considered to address this issue. In a recent animal study, Rosin et al. (2011) proposed a delayed feedback closed-loop DBS paradigm as an effective system. However, the clinical efficacy of the closed-loop DBS has not been tested yet.

Even though the concept of closed-loop DBS system seems intriguing and promising, a powerful biomarker indicating the clinical conditions of PD has yet to be identified. Currently, the most investigated potential biomarker is beta-band oscillation. Recent studies have demonstrated an abnormal synchronization of the beta-band oscillation activities between the basal ganglia and the motor cortex (de Hemptinne et al., 2015). Therapeutic DBS is reportedly considered to disconnect the abnormal coupling; thus, most closed-loop DBS concepts are designed to modulate the electrical stimulation parameters by beta-band oscillation. A recent study using a computational model indicated that delayed feedback may not suppress the abnormal synchronization (Dovzhenok et al., 2013). In an animal study, closed-loop DBS that delivered electrical stimulation only when beta activity was elevated in the subthalamic nucleus was not as effective as continuous DBS (Johnson et al., 2016).

Feedback and feedforward: Yamamoto et al. (2013) reported a concept of on-demand DBS system and successfully suppressed essential tremor (ET) using their original closed-loop DBS system. It should be noted that this group addressed the importance of combining feedback and feedforward DBS. For example, applying a simple feedback DBS for a tremor disorder encounters a situation whereby the tremor is not suppressed until the DBS turns on. Subsequently, once the tremor is suppressed, the DBS turns off, which results in the tremor appearing again. Therefore, a feedforward system that predicts the symptoms, particularly motor fluctuations, may need to be incorporated in the closed-loop circuit to suppress the movement disorder symptoms continuously (**Figure 1A**). Although the symptoms in patients with PD are not as visually prominent as ET, a closed-loop DBS incorporating both feedforward and feedback systems would be desirable to maximize the clinical outcomes for PD (**Figure 1B**). Switching on and off does not necessarily have to be on-demand, but the ideal closed-loop DBS for PD would be a personalized system for the condition of each patient, which is affected by various factors including on/off motor fluctuations. It is worth noting that DBS have an after effects that persist for minutes to hours in PD cases after turning off. Therefore, a mere on and off switching may not be sufficiently effective to improve activities of daily living. We propose that the ideal closed-loop DBS requires fine tunings of the parameters rather than simple on/off switching.

Functional imaging as a biomarker of cortical activity: Task-specific brain activity has been investigated by various groups using functional magnetic resonance imaging. Nevertheless, there have been safety concerns and metal artifacts in patients with DBS devices. Therefore, investigation of the functional alteration by DBS may potentially shed light on the current issues in closed-loop DBS. Near infrared spectroscopy (NIRS) is a tool to measure the dynamic changes in the hemoglobin levels in the cerebral cortex by detecting the characteristic absorption spectra of hemoglobin through near-infrared light probes. The increased level of oxyhemoglobin (HbO) and decreased level of deoxyhemoglobin are considered as markers of the local neuronal activity in the cerebral cortex. Given that NIRS measurement is not affected by implanted metals, the procedure has an advantage of safe application to patients following DBS surgery.

In the first study using NIRS in DBS patients (Sakatani et al., 1999), a single-channel NIRS system was used to measure the cerebral oxygenation levels in response to various DBS settings. The findings suggested that, while electrical stimulation of the globus pallidus interna (GPI) increases HbO levels in the prefrontal cortex, the thalamic stimulation decreases HbO levels in the same area. We have recently demonstrated alterations in the cortical activity in association with electrical stimulation of the GPI (Morishita et al., 2016). In this present pilot study, the cortical activity of six patients who underwent unilateral DBS in the GPI was investigated using a multichannel NIRS. We found that the primary motor cortex of the operated hemisphere was more likely to be activated during a motor task performance following DBS. Despite some limitations of NIRS in measuring neuronal activity in the cerebral cortex, the technique offers an excellent time resolution in capturing the dynamic neuronal activity. Measurement of cortical hemoglobin levels by NIRS may be a potential biomarker to adjust the parameters of the closed-loop DBS. An additional advantage of the NIRS measurements is its capability to quantify activity changes. Hence, hypoactivity
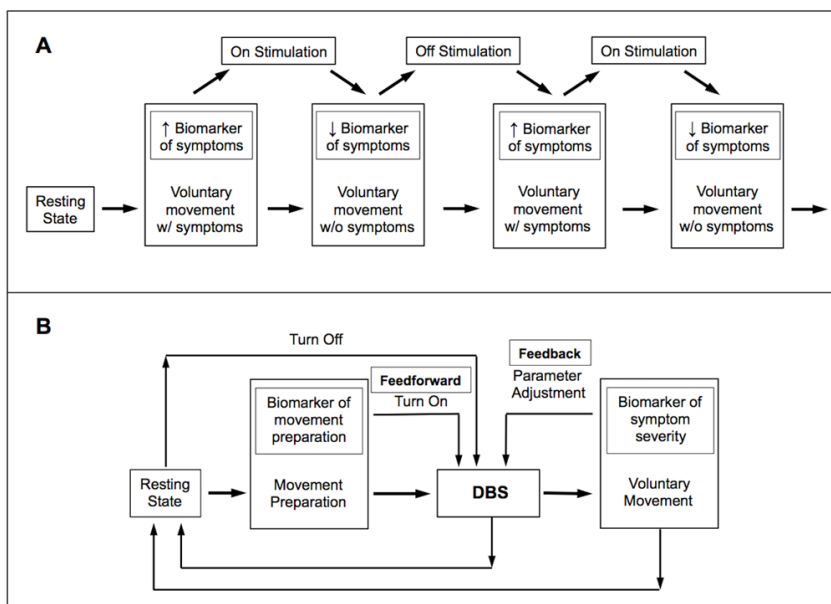
Figure 1 Closed-loop deep brain stimulation (DBS) paradigms.
(A) Concept of simple feedback system. Simple feedback system using single biomarker for on/off stimulation may fail to continuously suppress symptoms. (B) Proposed closed-loop system applying multiple biomarkers.

during a motor task may implicate the severity of the pathological conditions according to previous studies (Sakatani et al., 1999; Morishita et al., 2016).

Conclusion: In this paper, we propose a new type of closed-loop DBS paradigm incorporating a combination of feedforward and feedback systems for the treatment of PD. Applying multiple modalities may address the current issues in closed-loop DBS. Rather than merely switching the electrical stimulation on and off, the stimulation parameters should be adjusted according to the physiological conditions of each patient.

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