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A proof-of-principle simulation for closed-loop control based on preexisting experimental thalamic DBS-enhanced instrumental learning

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ABSTRACT

Deep brain stimulation (DBS) has been applied as an effective therapy for treating Parkinson's disease or essential tremor. Several open-loop DBS control strategies have been developed for clinical experiments, but they are limited by short battery life and inefficient therapy. Therefore, many closed-loop DBS control systems have been designed to tackle these problems by automatically adjusting the stimulation parameters *via* feedback from neural signals, which has been reported to reduce the power consumption. However, when the association between the biomarkers of the model and stimulation is unclear, it is difficult to develop an optimal control scheme for other DBS applications, i.e., DBS-enhanced instrumental learning. Furthermore, few studies have investigated the effect of closed-loop DBS control for cognition function, such as instrumental skill learning, and have been implemented in simulation environments. In this paper, we proposed a proof-of-principle design for a closed-loop DBS system, cognitive-enhancing DBS (ceDBS), which enhanced skill learning based on *in vivo* experimental data. The ceDBS acquired local field potential (LFP) signal from the thalamic central lateral (CL) nuclei of animals through a neural signal processing system. A strong coupling of the theta oscillation (4–7 Hz) and the learning period was found in the water reward-related lever-pressing learning task. Therefore, the theta-band power ratio, which was the averaged theta band to averaged total band (1–55 Hz) power ratio, could be used as a physiological marker for enhancement of instrumental skill learning. The on-line extraction of the theta-band power ratio was implemented on a field-programmable gate array (FPGA). An autoregressive with exogenous inputs (ARX)-based predictor was designed to construct a CL-thalamic DBS model and forecast the future physiological marker according to the past physiological marker and applied DBS. The prediction could further assist the design of a closed-loop DBS controller. A DBS controller based on a fuzzy expert system was devised to automatically control DBS according to the predicted physiological marker *via* a set of rules. The simulated experimental results demonstrate that the ceDBS based on the closed-loop control

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architecture not only reduced power consumption using the predictive physiological marker, but also achieved a desired level of physiological marker through the DBS controller.

1. Introduction

Deep brain stimulation (DBS) is an effective therapy to help patients with movement disorders, such as essential tremor, dystonia, and Parkinson's disease (PD) [1]. Motor, mood and cognitive activities can be modulated through DBS [2]. Several studies have shown that DBS could significantly improve cognitive tasks such as sequence learning [3] and spatial reversal learning [4]. Furthermore, it has been found that DBS could increase neural oscillations and enhance instrumental learning [5]. While there has been over a decade of clinical research, the optimization of DBS parameters, i.e., voltage, pulse duration, and frequency, is still challenging because the mechanisms underlying the neural behavior remain unknown. Most existing neuro-stimulation systems are performed as an open-loop where the stimulation is applied without feedback from the patients' clinical status. In contrast, a closed-loop neuro-stimulation system that controls the stimulation *via* feedback from physiological changes could provide more effective and efficient therapy with fewer side effects [6]. However, the enhancement of the instrumental learning has not been investigated in the present stage of development of closed-loop DBS systems. Thus, the development of a closed-loop neuro-stimulation system is important for real-time control of DBS.

Indeed, several circuits in the brain are malfunctioning across various disease states such as Alzheimer's disease, depression, and schizophrenia. We are now beginning to understand the circuits in the areas of the brain that are responsible for the clinical signs and the symptoms of those diseases. It is known that DBS can not only change the activity, but also harvest some of the operational functions of the brain [7]. Furthermore, previous research has indicated that stimulation applied to the central lateral (CL) nuclei of the thalamus and related central thalamic structures might improve the cognitive disabilities and enhance directed awareness in damaged brains [8,9]. Therefore, it has been suggested that DBS can be applied to CL nuclei in the thalamus because of their key role in general regulation of arousal and sustained attention [10,11]. On the other hand, electrical stimulation in CL thalamic nuclei can enhance exploratory motor behaviors and cognitive performance in the novel object recognition task. Hence, DBS can help to reinforce the learning ability and instrumental learning related to memory and behavior learning in animals, such as sensory stimuli coding, perceptual binding, attention, and working memory [12]. Evidence from electrophysiology has shown that applying DBS in CL thalamic nuclei could affect instrumental learning [13]. However, most existing DBS systems for cognition function modulation are open-loop and do not control the stimulation based on feedback from physiological signals. Only a few closed-loop DBS systems function have been built for locomotion with open-source hardware [14,15]. Two closed-loop approaches have been proposed to improve the etiology of motor symptoms in PD patients through DBS [16] and transcranial electrical stimulation [17].

A closed-loop neuro-stimulation system acquired electrical signals from the brain *via* an electrode and then adjusted the stimulation parameters to drive the brain signals to a desired range. This system primarily involved two techniques: biomarker detection and DBS control [18–20]. Biomarker detection identifies key bioelectrical signals that represented the severity of symptoms or physiological states. Many physiological signals have been adopted as the biomarker, such as electroencephalography, electrocorticography, and single- and multi-unit activity. Local field potentials (LFPs), one of the physiological signals, have been widely used for biomarker identification and extraction [21,22]. LFPs-based adaptive DBS could be more efficient and efficacious than conventional DBS in terms of power consumption. Furthermore, it does not need additional electrodes or neurosurgical procedures [23]. Several closed-loop stimulation studies have adopted the LFP beta-band peaks to correlate motor behavior in the subthalamic nucleus (STN) in PD patients [6,24–26]. One of these studies has shown that the beta-band oscillatory activity in the basal ganglia was considered as a biomarker for closed-loop control of DBS [27,28]. Another study has suggested that the motor cortex phase amplitude coupling also served as a potential biomarker for DBS control [29]. Furthermore, coupling between the beta band phase and amplitude of broadband gamma was identified as a biomarker to guide closed-loop DBS [30]. Recently, hippocampal LFP was used as a biomarker to manipulate the exploratory walking of rodents [14]. Meanwhile, theta oscillation was highly correlated with learning and memory, including event maintenance, plasticity induction during encoding, memory consolidation, memory retrieval, and novelty assessment of hippocampus in response to the external environment [5,12]. Womelsdorf et al. [31] suggested that inter-areal temporal theta synchronization is crucial for decision making and choice-relevant memory retrieval. Our previous study demonstrated that CL-thalamic DBS not only enhanced the water reward-related behavior learning, but also potentiated the power and inter-areal synchronization of theta oscillations [5]. A brain-wave sub-band power ratio was further considered as a biomarker, where a significant pattern was correlated with behavioral states [32,33].

For DBS control schemes, existing closed-loop DBS systems used various control strategies to adjust the stimulation parameters for the reduction of symptoms, such as traditional proportional plus integral control [34], iterative learning control [35], and variable universe fuzzy control [36]. Nevertheless, these controllers were based on an ideal mathematical model and may not be feasible for practical application. Furthermore, the stability and the design of the stimulation protocol were the most important consideration and challenge. Thus, it was critical to propose a control scheme based on an actual model.

The aim of this study was to develop a proof-of-principle closed-loop DBS control scheme. The control scheme involved first acquiring LFPs from the CL thalamic nuclei by an implanted microelectrode array that performed DBS in the bilateral CL thalamus. Then a physiological marker was identified through spectrum analysis, and was extracted to reveal the central thalamic DBS-enhanced instrumental learning for further design of the predictor and the controller. An autoregressive with exogenous inputs (ARX)-based predictor was designed to forecast the neuro-behavioral dynamics according to the past physiological markers and applied DBS. Finally, the cognitive-enhancing DBS (ceDBS) based on the closed loop control architecture was achieved through a DBS controller based on a fuzzy expert system that automatically switch DBS ON/OFF command via the feedback of the predicted physiological marker from the ARX-based predictor through a set of