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QUANTIFYING THE EFFECTS OF THE ELECTRODE–BRAIN INTERFACE ON THE CROSSING ELECTRIC CURRENTS IN DEEP BRAIN RECORDING AND STIMULATION

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Abstract—A depth electrode–brain interface (EBI) is formed once electrodes are implanted into the human brain. We investigated the impact of the EBI on the crossing electric currents during both deep brain recording (DBR) and deep brain stimulation (DBS) over the acute, chronic and transitional stages post-implantation, in order to investigate and quantify the effect which changes at the EBI have on both DBR and DBS. We combined two complementary methods: (1) physiological recording of local field potentials via the implanted electrode in patients; and (2) computational simulations of an EBI model. Our depth recordings revealed that the physiological modulation of the EBI in the acute stage via brain pulsation selectively affected the crossing neural signals in a frequency-dependent manner, as the amplitude of the electrode potential was inversely correlated with that of the tremor-related oscillation, but not the beta oscillation. Computational simulations of DBS during the transitional period showed that the shielding effect of partial giant cell growth on the injected current could shape the field in an unpredictable manner. These results quantitatively demonstrated that physiological modulation of the EBI significantly affected the crossing currents in both DBR and DBS. Studying the microenvironment of the EBI may be a key step in investigating the mechanisms of DBR and DBS, as well as brain–computer interactions in general.

Key words: local field potentials, computational simulation, finite element model.

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Abbreviations: BP, blood pressure; DBR, deep brain recording; DBS, deep brain stimulation; EBI, electrode–brain interface; ECF, extracellular fluid; FEM, finite element method; GP, globus pallidum; LFP, local field potential; MRI, magnetic resonance imaging; PVG, periventricular gray; STFT, short-time Fourier transform; STN, subthalamic nucleus.

Since the early 1990s, there has been a revival of therapeutic deep brain stimulation (DBS) to treat movement disorders (Benabid et al., 1987, 1994, 2002; Vitek, 2002; Vidailhet et al., 2005; Deuschl et al., 2006; Kupsch et al., 2006), neuropathic pain (Young and Chambi, 1987; Kumar et al., 1997; Bittar et al., 2005), epilepsy (Hodaie et al., 2002; Kerrigan et al., 2004) and psychiatric disorders (Nuttin et al., 2003; Mayberg et al., 2005). This treatment involves the unilateral or bilateral implantation of metal electrode(s) into selected brain areas, through which electrical pulses are delivered to modulate neuronal activity and alleviate abnormal symptoms. Implanted electrodes also provide an invaluable opportunity to obtain high quality information about the synchronized population activity from the depth structures of the brain (deep brain recording, DBR), in the form of local field potentials (LFPs). This can reveal the pathological mechanisms at the population level (Engel et al., 2005; Liu et al., 2006; Wang et al., 2006; Brown et al., 2006), as well as the modulation of this pathophysiology by either medication (Brown et al., 2001; Priori et al., 2004; Doyle et al., 2005; Brown and Williams, 2005; Kuhn et al., 2006; Marceglia et al., 2006), or electrical stimulation (Brown et al., 2004; Priori et al., 2006; Foffani et al., 2006; Wingeier et al., 2006).

It is well established that an exchange of ions and electrons occurs between a metal electrode and the natural or artificial fluid at the electrode–tissue interface, thereby forming an electrical double layer (Rockwood, 1986). However, only recently has the depth electrode–brain interface (EBI) been studied in the case of DBS (Butson and McIntyre, 2005; Xie et al., 2006; Yousif et al., 2007). The functional compartments of a broad depth EBI can be defined as consisting of (1) the implanted depth electrode; (2) the surrounding brain tissue; and (3) a peri-electrode space, which is filled with extracellular fluid (ECF) at the acute stage a few days post-implantation (Thoma et al., 1987), and is replaced by giant cell growth (Moss et al., 2004) or the formation of microglia (Griffith and Humphrey, 2006) at the chronic stage. This encapsulation process is stabilized over a period of 6–8 weeks post-implantation. These observations indicate that the EBI evolves over time.

The clear significance of studying the biophysical properties of the EBI is that the changes in such properties will affect the electric current crossing the interface during both recording and stimulation procedures. This can be a key step in improving the signal to noise ratio of depth recording, investigating the mechanisms of therapeutic DBS, and optimizing the stimulation parameter settings. We previ-

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ously demonstrated (Xie et al., 2006) using LFP recordings, that in the acute stage post-implantation an electrode potential reflecting the electrical charge established following the exchange of ions and electrons, was modulated by physiological brain pulsation. We postulated that this is due to two factors: 1) the relative motion between the pulsating brain and the implanted electrode; 2) the pressure on the electrode which is varying with heart rate. The physiologically modulated electrode potentials could be identified as a specific component in the recorded compound LFP signals that were time-locked with blood pressure (BP) signals (Xie et al., 2006). Further supporting evidence that the electrode potential is modulated by brain pulsation came from another study of the acute after-stimulation effects of subthalamic nucleus (STN) stimulation for the treatment of Parkinson's disease (Priori et al., 2006). This study showed that the magnitude of such electrical charges could be dramatically enhanced during DBS, possibly as the ECF is further polarized by the injected electrical current, and gradually declined following the stimulation being turned off.

Recently, a number of computational modeling studies (McIntyre et al., 2004; Hemm et al., 2005a,b; Gimsa et al., 2006; Butson et al., 2007; Sotiropoulos and Steinmetz, 2007) have been carried out using the finite element method (FEM, for a general reference see Zienkiewicz et al., 2005) to compensate for the present impossibility of measuring the spread of current directly in the depth structures of the human brain (Yousif and Liu, 2007a). However, future advances, for example in voltage sensitive dye techniques, may advance our understanding of the effects of stimulation on cortical activity (Hillman, 2007). Using a model of the generic depth EBI which is independent of the cellular structure of the surrounding brain tissue, the neurological disorder treated, and the instrumentation used (Moss et al., 2004; Xie et al., 2006), our quantitative simulations (Yousif et al., 2007) revealed that the peri-electrode space was a significant element of the EBI and was modulated by physiological factors including brain pulsation in the acute stage, and the growth of giant cells in the chronic stage.

A number of questions remain about the EBI. Firstly, no quantitative evidence has been reported on the effect of physiological modulation of the EBI on LFP recordings; and secondly, there is a transitional period within the initial 2–8 weeks post-implantation, during which the peri-electrode space gradually changes from being filled with ECF, to partial encapsulation which occurs as early as 2 weeks, and is followed by the stabilization of the growth of reactive giant cells after 6–8 weeks (Moss et al., 2004). The changes occurring during this transitional period are crucial for adjusting stimulation parameters in DBS, and yet have not been investigated extensively, as neurophysiological examination after the initial acute stage is not possible. This is because LFP recordings can only be made while the implanted electrodes are "externalized" in the first few days post-implantation (Liu, 2003), and magnetic resonance imaging (MRI) of DBS has limited resolution on the peri-electrode space due to significant artifact of the metal electrode contacts (Fig. 1; Pollo et al., 2004). In the current study, we hypothesize that the changes in the peri-electrode space occurring over the acute, transitional, and stabilized chronic stages will have an impact on the electric currents crossing the peri-electrode space in two directions, from the brain to the electrode in DBR procedures, and from the electrode to the brain in DBS procedures. Quantification of these effects would significantly enhance the capacity of investigating the biophysical mechanisms

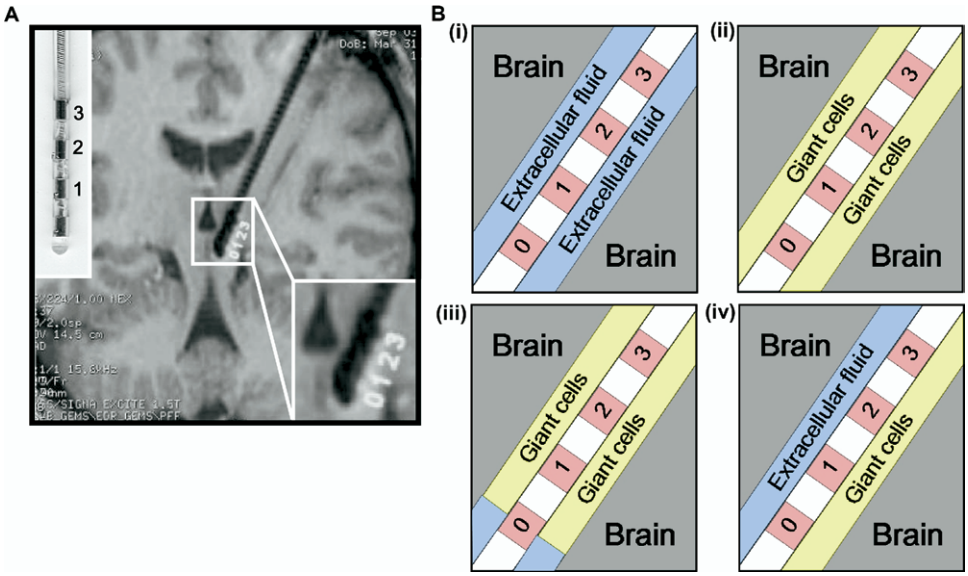

Fig. 1. Structural definition of the EBI: (A) an MRI of the implanted quadripolar DBS electrode *in situ*, with an enlarged photo of the electrode model 3387 (the left upper corner) and an enlargement of the EBI (the right lower corner), and (B) schematic representation of the EBI consisting of three essential elements of the implanted quadripolar electrode (contacts 0–3), the surrounding neural tissue, and the "peri-electrode space" in between, which is filled with ECF in the acute stage (i), with giant cells in the chronic stage (ii), and a mixture of ECF and giant cells in the transitional stages post-implantation. The giant cells grow transversely over all but the tip of the electrode (iii), or longitudinally over the lower half of the electrode (iv).