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Impact of volume-conducted potential in interpretation of cortico-cortical evoked potential: Detailed analysis of high-resolution electrocorticography using two mathematical approaches

Seijiro Shimada [a], Naoto Kunii [a,*], Kensuke Kawai [b], Takeshi Matsuo [c], Yohei Ishishita [a], Kenji Ibayashi [a], Nobuhito Saito [a]

[a] Department of Neurosurgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Department of Neurosurgery, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
[c] Department of Neurosurgery, NTT Medical Center Tokyo, 5-9-22 Higashi-Gotanda, Shinagawa-ku, Tokyo 141-8625, Japan

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H I G H L I G H T S

- Impact of volume-conducted potential on cortico-cortical evoked potentials (CCEP) was evaluated with high-density grid electrodes.
- Volume-conducted potential accounted for the majority of the potential around the stimulation site.
- This study contributes to delineating the CCEP component which reflects true cortical connectivity.

A B S T R A C T

Objective: Cortico-cortical evoked potential (CCEP) has been utilized to evaluate connectivity between cortices. However, previous reports have rarely referred to the impact of volume-conducted potential (VCP) which must be a confounding factor of large potential around the stimulation site. To address this issue, we challenged the null hypothesis that VCP accounts for the majority of the recorded potential, particularly around the stimulation site.
Methods: CCEP was recorded with high-density intracranial electrodes in 8 patients with intractable epilepsy. First, we performed regression analysis for describing the relationship between the distance and potential of each electrode. Second, we performed principal component analysis (PCA) to reveal the temporal features of recorded waveforms.
Results: The regression curve, declining by the inverse square of the distance, fitted tightly to the plots (R^2: 0.878–0.991) with outliers. PCA suggested the responses around the stimulation site had the same temporal features. We also observed the continuous declination over the anatomical gap and the phase reversal phenomena around the stimulation site.
Conclusions: These results were consistent with the null hypothesis.
Significance: This study highlighted the risk of misinterpreting CCEP mapping, and proposed mathematical removal of VCP, which could lead to more reliable mapping based on CCEP.

1. Introduction

Direct electrical stimulation (DES) still remains the gold standard method of human brain mapping, especially in surgery for intractable epilepsy or brain tumors (Ojemann et al., 1989; Lesser et al., 1994; Sanai et al., 2008; Mandonnet et al., 2010; Duffau, 2012), although DES has several well-known limitations such as lack of objective evaluation and a risk of provoking

Abbreviations: DES, direct electrical stimulation; CCEP, cortico-cortical evoked potential; SPES, single pulse electrical stimulation; ALA, anterior language area; PLA, posterior language area; VCP, volume-conducted potential; PCA, principal component analysis; ECoG, electrocorticography; MRI, magnetic resonance imaging; CT, computed tomography; HGA, high gamma activities; EEG, electroencephalography; RMS, root mean square.

* Corresponding author. Fax: +81 3 5800 8655.
E-mail address: nkunii-tky@umin.ac.jp (N. Kunii).

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seizures. Additionally, singular electrical artifacts prevent us from assessing objectively electrophysiological responses during DES. These issues need to be resolved in order to accomplish safer and more reliable functional brain mapping.

Cortico-cortical evoked potential (CCEP), a new method using single pulse electrical stimulation (SPES) to evaluate connectivity between separate cortices, has been first reported in 2004 (Matsumoto et al., 2004). It is expected to be a supportive method or a possible alternative to DES. CCEP can be measured by averaging waves induced by SPES, and is usually free from after-discharges and iatrogenic seizures. Additionally, with much less artifacts than DES, CCEP allows for objective and quantitative evaluation of electrophysiological responses.

CCEP has been first reported in the human language network between the anterior language area (ALA) and the posterior language area (PLA) (Matsumoto et al., 2004). Furthermore, CCEP has now been used for the evaluation of other cortical networks connected by white matter such as the motor-sensory system (Matsumoto et al., 2007, 2012; Swann et al., 2012; Enatsu et al., 2013b), visual system (Matsuzaki et al., 2013), and limbic system (Kubota et al., 2013; Enatsu et al., 2015). Recently, intraoperative real-time CCEP has been reported to be useful for monitoring the language system, resulting in successful resection of brain tumors (Saito et al., 2014; Yamao et al., 2014; Tamura et al., 2016). In this way, CCEP is now utilized both in the clinical setting and various fields of cognitive neuroscience, since it is the only available investigative technique that uses brain stimulation with high quantitative capability and acceptable noise levels.

Despite its increasing use, CCEP is not yet fully understood. Although the distribution of CCEP have previously been reported in individual cases, the detailed profile of CCEP, especially regarding the relationship to the distance from the stimulation, have not been well described. One possible major confounding factor that may interfere with detailed CCEP analysis is volume-conducted potential (VCP), which spreads from the original signal source and is reduced with distance. Previous reports of CCEP have described bimodal responses: larger responses around the stimulation site and smaller responses in the remote cortices (Conner et al., 2011; Enatsu et al., 2012a, 2013a,b). The majority of studies have used the remote smaller responses to evaluate cortico-cortical connectivity between separate brain areas. On the other hand, the larger responses around the stimulation site, which had amplitude of more than 1000 μV in some reports (Iwasaki et al., 2010; Enatsu et al., 2012b; Swann et al., 2012), have largely been overlooked, presumably because of the technical difficulty of measurement and concerns about the significant contamination of the VCP component. In fact, only one report has referred to VCP (Keller et al., 2014). In the report, they excluded responses within 1.5 cm of the stimulation site to omit the contamination. Despite these concerns, the impact of VCP in the interpretation of CCEP has yet to be studied in detail. To address this issue, we validated the null hypothesis that there is a singular electrical signal source just beneath the stimulation site and VCP yielded by the source accounts for the majority of the recorded potential around the stimulation site. Note that CCEP could have two meanings: "recorded potential" in CCEP mapping and locally-evoked potential just under the recording electrode without VCP. For clarification, "CCEP" hereafter means the latter one.

We utilized 2 different approaches. First, we performed regression analysis to describe the relationship between the distance and potential of each electrode. If VCP significantly affects recorded potential, they are expected to decline in inverse proportion to the square of the distance from the source (Zaveri et al., 2009; Schevon et al., 2010). Second, principal component analysis (PCA) was applied to the averaged waveforms. By calculating the correlation coefficients between the averaged waveform at each electrode and major components of PCA respectively, we obtained a correlation map for each component. VCP theoretically spreads with "zero-time delay", so every recorded potential significantly affected by VCP is supposed to have the same temporal features and highly correlate to the same principal component. To reinforce the validity of these 2 approaches, we used high-density grid electrodes with a center-to-center distance of 5 mm.

This is the first study to focus on the impact of VCP in interpretation of CCEP, which is critical for a detailed understanding of CCEP.

2. Methods

2.1. Subjects

Functional brain mapping, including CCEP mapping, was performed at the University of Tokyo Hospital in 8 patients (5 men, 3 women; mean age 33 years) with intractable epilepsy. In these patients, preoperative workups indicated epileptic foci in the lateral cortices of the language-dominant hemispheres, which were subsequently covered with high-density grid electrodes. Before functional brain mapping, long-term electrocorticography (ECoG) was performed for identification of epileptic foci. Detailed demographic data of the patients are shown in Table 1.

Ictal ECoG indicated epileptic foci on the left hemispheres in 5 patients (Case 2–5, 8), the right hemisphere in 1 patient (Case 6), and bilateral hemispheres in 2 patients (Case 1, 7). Magnetic resonance imaging (MRI) analysis showed no apparent brain lesions in all but 2 patients (Case 2, 8). One had a focal cortical dysplasia in the left superior temporal gyrus and the other had an infarct region in the left temporal tip. All patients had verbal intelligence quotient scores higher than 60.

This study was approved by the ethical review board of our institute (No. 1797). Written informed consent was obtained from all patients and their family before participation in this study.

2.2. Electrode implantation and functional brain mapping

The high-density grid electrodes used in this study consisted of silastic sheets embedded with platinum electrodes (1.5 mm in diameter) with a 5 mm-interelectrode interval (center-to-center, Unique Medical Inc., Tokyo, Japan). These electrodes widely covered the lateral surfaces of the language dominant hemispheres including both the ALA and the PLA. After implantation, we obtained 3D head computed tomography (CT) data that were used to delineate the electrode positions of all patients.

Before the CCEP mapping, we performed extraoperative DES mapping in each patient and also measured language-related high gamma activities (HGA) for the purpose of localizing language areas. During the DES mapping, constant current electrical stimulation was delivered to pairs of electrodes with an electric stimulator (KS-101 or NS-101; Unique Medical Inc) with 5 s trains of 50-Hz 0.2 ms biphasic polarity square wave pulses. When stimulation with an electrode pair reproducibly induced disruption of language-related functions, both electrodes were indicated to be positive. During the HGA mapping, patients were instructed to categorize the visually presented words silently into "abstract" or "concrete" on the basis of the nature of the word. The ECoG were digitally recorded and processed using custom software, and the electrodes with significant HGA were indicated to be positive. Details of this functional brain mapping performed in our institute have been previously described (Kunii et al., 2011, 2013; Kunii et al., 2014).