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Contribution of research on ‘epilepsy and behavior’ to the refinement of functional brain atlas in four dimensions

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Abstract

Intracranial stimulation mapping by Penfield et al. largely contributed to our current knowledge of the functional organization of motor, sensory, and language systems. The functional maps were generated and printed in two dimensions, based on the summary results of direct cortical stimulation of which locations varied across patients. Intracranial measurement of electrocorticographic changes elicited by a task can localize the regions involved in or participating to the given task. Augmentation of high-gamma activity at >80 Hz is considered to reflect *in situ* cortical activation at each moment. In the late 2000s, the spatial-temporal profiles of event-related high-gamma activity began to be published as a video material in journals. We have referred to our animation movie as ‘in-vivo animation of event-related high-gamma activity’, that demonstrates ‘when’ and ‘where’ cortical regions are activated in a self-explanatory fashion. Summation of event-related high-gamma measures derived from a large cohort of patients, as previously performed by Penfield et al, is expected to generate unique four-dimensional functional brain atlas covering the whole cerebral cortex.

Keywords

cognition; language; vision; temporal dynamics; causality; pediatric epilepsy surgery; intracranial subdural electrodes; stimulation; video-EEG; electrocorticography (ECoG); ripples; in-vivo animation of event-related high gamma activity; video movies

Styles of literature review in the past and now

Fifteen years ago, when the first issue of *Epilepsy & Behavior* was published, I just arrived at my current institution as a research fellow. On these days, it was not easy to access to the contents of research articles in general. Few academic journals used to publish electronic articles, and I needed to walk over to the university library to decide if each article suggested

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by PUBMED was relevant to my specific interest. My behavior of literature review has gradually changed over the past 15 years; electronic-form documents currently consist of more than 95% of articles which I read. Today, a more inclusive search engine like Google Scholar suggests what I am looking for; a single mouse click and scrolls can tell me the relevance of each of the suggested articles. I also go through ‘articles in press’ on neurology and neuroscience journal websites on a weekly basis, while eating sushi [1] or working out in a gym [2]. The favorite folder in my computer browser has included *Epilepsy & Behavior* website for years. This journal has focused on the behavioral and cognitive aspects of epilepsy, which are closely related to my research interest: ‘human brain mapping’. Clinicians and neuroscientists, including myself, have attempted to improve the brain mapping techniques to better localize the functionally-important areas for patients who undergo epilepsy surgery, and to better understand how the brain works during behaviors in daily life.

Mapping via craniotomy created functional brain atlas printed in two dimensions

Few would argue that intracranial studies of epileptic patients by Penfield and his colleagues largely contributed to our current knowledge of the functional organization of motor, sensory, and language systems [3,4]. The functional maps were generated and printed in two dimensions, based on the summary results of direct cortical stimulation of which locations varied across patients. These maps still serve as a simple and generalized framework for understanding the roles of brain areas in behaviors and cognition [5,6]. Importantly, the presence of focal epilepsy does not indicate that the rest of brain is all abnormal; as reflected by, for example, the observations that the temporal-spatial dynamics of neural signals during sensorimotor behaviors were quite similar between healthy non-human primates and patients with focal epilepsy [7–10]. The current consensus in the neuroscience community is that intracranial studies including direct cortical stimulation and electrophysiology recording will continue to serve as essential and complementary brain mapping techniques, and bridge the gap between non-invasive neuroimaging and neurophysiology studies [11–14].

Intracranial studies will refine functional brain atlas in four dimensions

The ultimate goals of epilepsy surgery and related research include improving the behavioral outcome and quality of life following epilepsy surgery. Functional MRI (fMRI) is commonly used to localize the areas showing hemodynamic activation during a specific task such as language [15,16]; the results of fMRI studies are presented on two-dimensional slices [17–20] or three-dimensional surface rendered images of individual patients [21]. In case assessment with non-invasive diagnostic modalities fails to confidently presume the boundary between the epileptogenic zone and functionally-important areas, chronic electrocorticography (ECoG) recording with intracranial electrodes is chosen to be performed in a number of epilepsy centers [11,22,23].

Direct electrical stimulation is the current gold-standard procedure to identify the regions essential for a perception, behavior, or cognition of interest, for example, hearing, vocalization, or understanding the meaning of words [11,24–28]. Alternatively,

measurement of ECoG changes elicited by a task can localize the regions involved in or participating to the given task [11,29]. Particularly, event-related high-gamma ECoG activity at >80 Hz has recently received a rapidly growing interest [12]; in short, augmentation of such high-gamma activity is treated as *in situ* cortical activation at a given time [9,30–32]. Studies have suggested that both stimulation and high-gamma mappings are useful to predict the behavioral outcome immediately following cortical resection [24,33,34]. Measurement of event-related high-gamma activity on ECoG illustrates the dynamic changes of cortical activation during a given task with a spatial resolution of <1cm and temporal resolution of 10 milliseconds or so [11,35–38]. Investigators have developed the methods to register the amplitudes of high-gamma activity to a three-dimensional surface rendered image of an individual patient [7,35,39–43] as well as a standardized brain template [44–46]. In the late 2000s, the spatial-temporal profiles of event-related high-gamma activity began to be presented as a video material in selected journals including *Epilepsy & Behavior*. We have referred to our animation movie as ‘in-vivo animation of event-related high-gamma activity’ [7,39], that demonstrates ‘when’ and ‘where’ cortical regions are activated in a self-explanatory fashion.

Measurement of high-gamma activity on ECoG benefits from a much better temporal resolution compared to that of blood oxygen level dependency signals on functional MRI [11,18]. Consideration of the temporal order of cortical activations is one of the criteria to judge the causal significance of a given region activated during a task [47]. Intracranial ECoG recording provides a unique opportunity to directly sample neural signals from deeply located regions such as medial and inferior surfaces of cerebral cortex in case subdural electrodes happen to be placed on such regions. Conversely, scalp EEG and magnetoencephalography recordings may not reliably detect such signals generated by regions distant from sensors [10,48–50], and suffer from a larger degree of artifacts difficult to eliminate [51,52]. Investigation of high-gamma ECoG activity combined with stimulation mapping can further clarify the causal significance of event-related high gamma activity during a task [42,47,53].

Intracranial studies do have several limitations. Brain mapping using ECoG recording inevitably suffers from limited spatial sampling, since the extent of subdural electrode placement is determined purely according to the clinical needs. Interictal epileptiform discharges may alter the amplitude of event-related high-gamma activity in the seizure onset zone [54]; thus, high-gamma measures in the seizure onset zone may not be generalizable. Nonetheless, summation of event-related high-gamma measures derived from non-epileptic cortices of a large cohort of patients, as previously performed in electrical stimulation studies by Penfield et al [3,4], is expected to generate unique four-dimensional functional brain atlas covering the whole cerebral cortex in the future. Thereby, the four dimensions include ‘space’ and ‘time’ in the order of 10 milliseconds. Another measure such as the effect of development [34,55] or aging [56] can be also incorporated according to the purpose of atlas. I hypothesize that such multi-dimensional functional brain atlas would ultimately help in prediction of specific neurological symptoms following focal brain damage.

My congratulations to the editorial team in *Epilepsy & Behavior*

All editors and staff deserve warm congratulations for the success of *Epilepsy & Behavior*. Their efforts at any level should be respected, taking into account that the initial decision has been made, on average, as short as three weeks after manuscript submission and that accepted manuscripts have been published as fully paginated articles within two months after the official acceptance. I particularly appreciate editors' a sentence-by-sentence review on all of our corrected proofs to ensure the accuracy of wording, which certainly increased our confidence and pride in each of our previous works published in *Epilepsy & Behavior*.

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HIGHLIGHTS

Intracranial studies largely contributed to our current knowledge of human brain.

High-gamma activity is sequentially generated by regions involved in a given task.

Event-related high-gamma activity can be presented in a video movie.

We plan to generate a 4D functional brain atlas covering the whole cerebral cortex.