Brain Stimulation 17 (2024) 335–338

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

Prestimulation neuronal activity predicts visual awareness of phosphene elicited by intracranial electrical stimulation

Dear Editor:

Visual perception is more than just a passive process of receiving environmental stimuli. It arises from the complex interaction with sensory input and the brain's pre-existing state [1–4]. The pre-stimulation state, particularly the cortical excitability, plays a crucial role in how we consciously perceive stimuli with near-threshold intensity [5]. One of the most direct methodologies to assess cortical excitability is to measure neurons' spontaneous firing rates prior to stimulus presentation [4]. However, in human subjects, non-invasive investigations have predominantly utilized field potential measurements, deducing cortical excitability in an indirect manner [1–4]. Specifically, the pre-stimulation neuronal states within the human cortex that forecast visual awareness remain unknown. Here, we employed intracranial electrical stimulation (iES) alongside microwire recording techniques to investigate the direct impact of pre-stimulation neuronal activity on visual awareness. This exploration was conducted on a unique case of a patient with electrodes implanted in the right ventral V1 area.

Patient D.Q. was implanted with four macro-micro electrodes (**Supplementary Methods**). The tip of one macro-micro electrode, named electrode X, including microwires and first two macro-contacts, was in the right ventral V1 (Fig. 1A). Both the patient and his legal guardian had a comprehensive understanding of the experimental procedures and provided their written, informed consent. All experimental procedures were approved by the Ethics Committee of the Sanbo Hospital of Capital Medical University and the Human Subject Review Committee of Peking University.

We utilized a near-threshold iES approach to explore the neural underpinnings of visual awareness [4]. As a well-established clinical technique, iES can generate artificial visual experiences without altering the external environment [6–8]. The experimental procedure encompassed three stages: (1) assessing the visual receptive fields of the microwires; (2) measuring the phosphene threshold induced by iES; and (3) conducting near-threshold iES and electrophysiological recordings simultaneously.

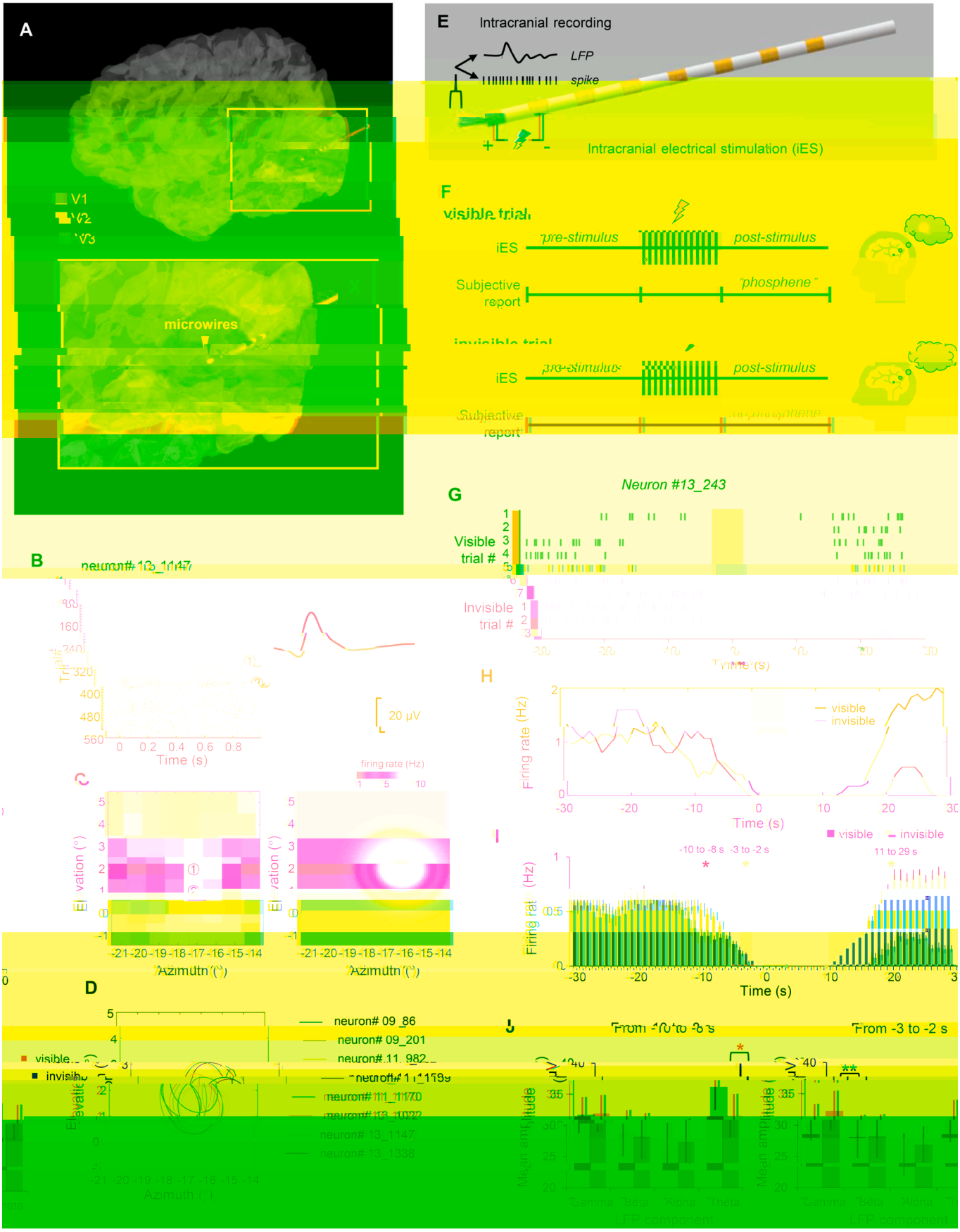
First, we conducted the receptive field (RF) measurement experiment, following the protocol described in our previous study [9] (see Fig. 1B and **C**). We isolated eight visually responsive neurons. As illustrated in Fig. 1D, these neurons exhibited similar RF sizes (1.899 ± 0.242°, mean ± SE) and locations (−17.000 ± 0.181°, 1.663 ± 0.096°; azimuth, elevation) in the upper left visual field (refer to Supplementary Table 1).

Second, we applied iES to the nearest pair of macro-contacts (X01-X02), adjacent to the microwires, to determine the minimum stimulation intensity to induce phosphenes (i.e. near-threshold intensity). The patient was seated in bed and instructed to fixate at a "+" sign displayed on a touch-screen LCD monitor (27-inch, ViewSonic TD2730) at a viewing distance of 66 cm. As shown in Fig. 1E and **F**, rectangular electrical pulses (frequency = 40 Hz, pulse width = 0.3 ms, duration = 5 s) were applied to the macro-contact pair nearest the microwires. Starting from 1 mA, we incrementally increased the current amplitude with a step of 0.1 mA, until the patient reported his first a phosphene at 1.4 mA. Immediately following the disappearance of the phosphene, the patient was asked to freehand sketch the phosphene on the touch-screen monitor. The spatial location of the phosphene closely matched the RFs of neurons identified via microwire recordings, corroborating findings in a prior study [7] (Supplementary Fig. 1). Consequently, we estimated the phosphene threshold level to be approximately 1.3 mA (refer to Supplementary Table 2). Given the clinical imperative to limit electrical stimulation while still fulfilling the objectives of the experiment, the number of iES trials was constrained.

Third, we conducted ten near-threshold iES trials, during which we simultaneously recorded both spiking activities and local field potentials (LFPs) from the microwires (Fig. 1E). The current amplitude was consistently set at 1.3 mA. The patient reported perceiving a phosphene in seven of these trials (referred to as "visible" trials), while in the remaining three trials, no phosphene was reported (referred to as "invisible" trials; see Supplementary Table 2). No phosphenes were reported in response to sham stimuli. We isolated seven neurons. As shown in an example neuron (Neuron #13_243), there was a noticeable variation in pre- and post-stimulation firing rates between visible and invisible trials (Fig. 1G and H). We observed that during the 11–29 s period following the onset of iES, the firing rates were higher in the visible trials compared to the invisible ones (all $ps < 0.05$; paired t-tests), which was consistent with a previous study [8]. During the pre-stimulation period, specifically in the 10 to 8 s before iES onset, firing rates were observed to be higher in the invisible trials compared to the visible ones. (Fig. 1I; −10 s: $t(6) = 2.660$, $p = 0.038$; −8 s: $t(6) = -2.276$, $p = 0.033$; −5 s: $t(6) = -5.415$, $p = 0.002$; paired t-tests). Intriguingly, during the −3 to −2 s period, firing rates were observed to be higher in visible trials compared to invisible trials (Fig. 1I; −3 s: $t(6) = 3.526$, $p = 0.013$; −2 s: $t(6) = 4.076$, $p = 0.007$; paired t-tests). Furthermore, we investigated the variation in LFP across different frequency bands during these two critical periods. We revealed that, in the −10 to −8 s time window, only the averaged theta-band (4–7 Hz) amplitudes were significantly higher in visible trials compared to those in invisible trials (Fig. 1J, $t(6) = 3.284$, $p = 0.017$), whereas in the −3 to −2 s time window, gamma-band (30–59 Hz) amplitudes in visible trials were significantly lower than those in invisible trials (Fig. 1J, $t(6) = -3.774$, $p = 0.009$).

In conclusion, capitalizing on a rare opportunity to combine iES with microwire recording techniques, we discovered that the excitability of V1 neurons during two critical pre-stimulation periods predicts visual

https://doi.org/10.1016/j.brs.2024.03.003
Received 25 February 2024; Accepted 3 March 2024
Available online 4 March 2024



(caption on next page)

awareness. Furthermore, distinct patterns in theta and gamma band amplitudes between visible and invisible trials suggest differential roles in facilitating visual awareness. These findings support a dynamic model for visual perception [10], suggesting that the slow drift of spontaneous neuronal activity modulates subjective experiences in response to physically identical stimuli, thereby enhancing our understanding of the neural underpinnings of consciousness [5].

CRediT authorship contribution statement

Qian Wang: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Guanpeng Chen:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Xiongfei Wang:** Conceptualization, Data curation, Funding acquisition, Methodology, Visualization, Writing – original draft. **Ruolin Yang:** Data curation, Formal analysis, Investigation. **Lu Luo:** Investigation, Methodology. **Haoran Ding:** Conceptualization, Investigation, Methodology. **Pengfei Teng:** Conceptualization, Investigation, Methodology. **Jing Wang:** Investigation, Methodology. **Leijie He:** Conceptualization, Investigation, Methodology. **Jie**

National Key Laboratory of General Artificial Intelligence, Peking University, Beijing 100871, China

Guanpeng Chen[1]
School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China
IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China
Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China

Xiongfei Wang[1]
Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China
Beijing Key Laboratory of Epilepsy, Epilepsy Center, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Ruolin Yang
School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China
IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China
Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China

Lu Luo
School of Psychology, Beijing Sport University, Beijing 100084, China

Haoran Ding
Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China
Beijing Key Laboratory of Epilepsy, Epilepsy Center, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Pengfei Teng
Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Jing Wang
Epilepsy Center, Kunming Sanbo Brain Hospital, Kunming 650100 China

Leijie He
Department of Neurology, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Jie Ren
Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China
Department of Neurology, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Meng Zhao
Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Guoming Luan
Department of Neurosurgery, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China
Beijing Key Laboratory of Epilepsy, Epilepsy Center, Sanbo Brain Hospital, Capital Medical University, Beijing, 100093, China

Fang Fang[**]
School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China
IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China
Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China

[*] Corresponding author. School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China.

[**] Corresponding author. School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China.
E-mail address: wangqianpsy@pku.edu.cn (Q. Wang).
E-mail address: ffang@pku.edu.cn (F. Fang).

[1] Co-first author.