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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

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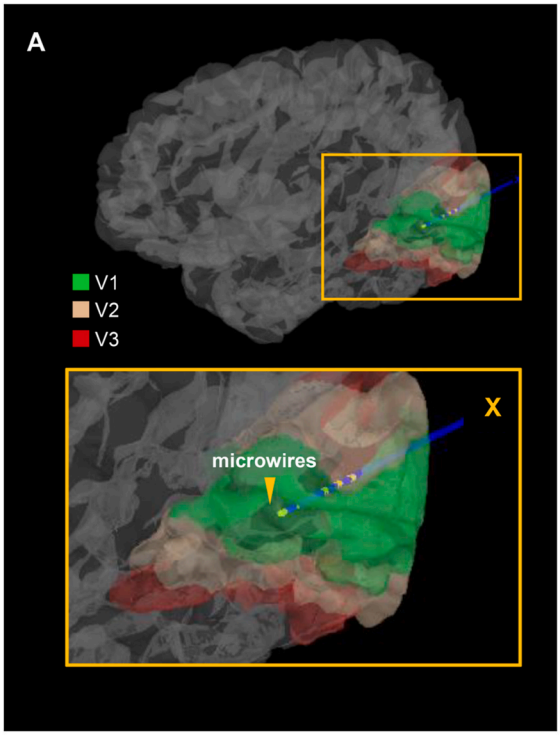

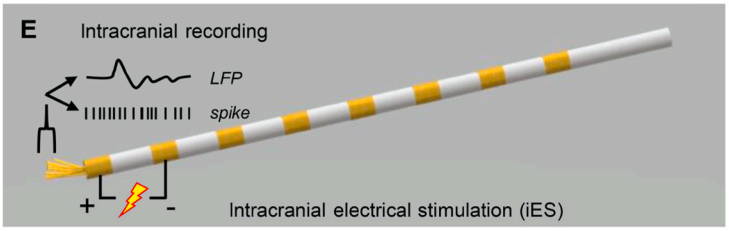

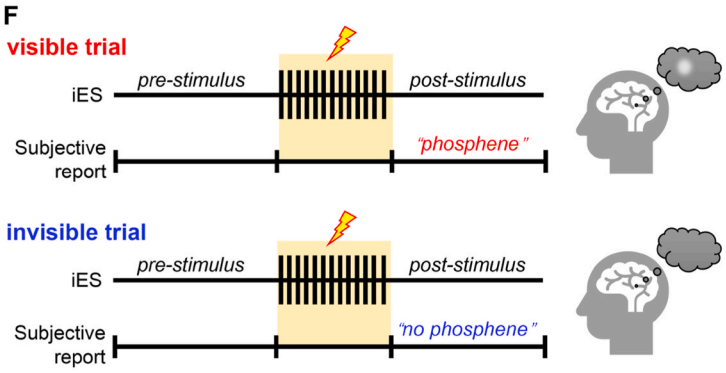

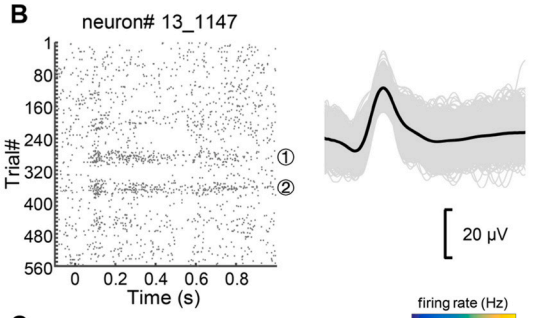

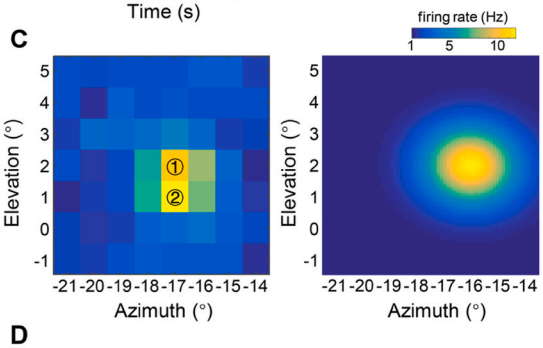

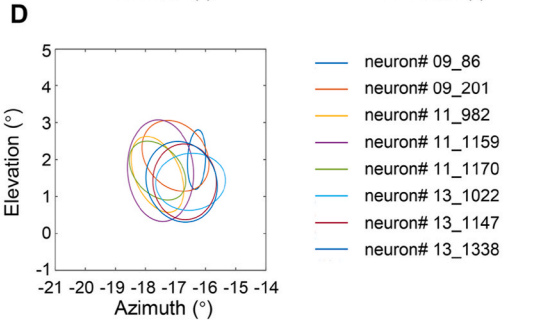

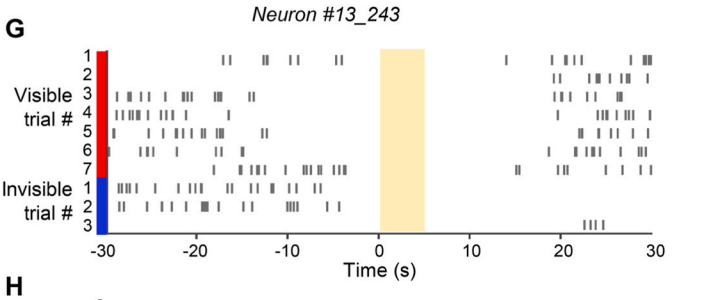

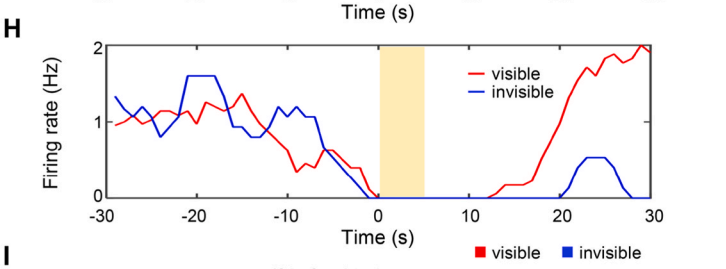

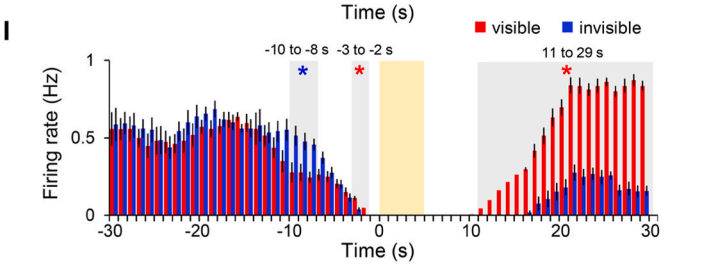

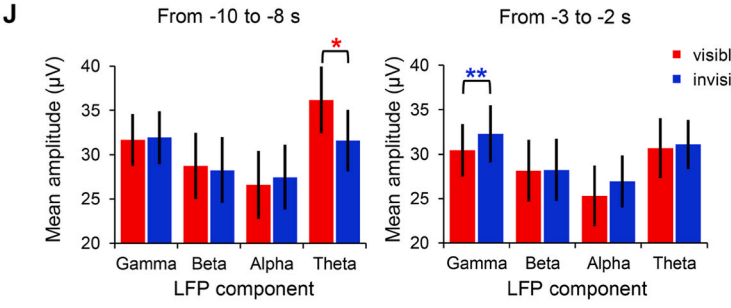

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Fig. 1. **(A)** Location of the implanted macro-micro electrode (Electrode X). Microwires at the tip of the macro-micro electrode (yellow arrowhead) were localized in the ventral part of V1. The colors on the brain indicate different visual areas (*green*: V1; *orange*: V2; *red*: V3). **(B)**, **(C)**, and **(D)** illustrated the RF mapping experiment. **(B)** RF mapping of an example neuron (neuron# 13_1147). A raster plot of spikes around visual stimulus onset (*left*) and the spike waveforms (*right*) are shown. Trials were sorted by RF mapping position. The *black curve* indicates that averaged spike waveform of neuron# 13_1147. **(C)** Activation map of averaged firing rates (*left;* averaged between 100 and 800 ms after stimulus onset) and two-dimensional Gaussian fit (*right*) calculated for neuron# 13_1147. **(D)** RFs of the 8 neurons from three microwires (#9, 11, and 13). **(E)** to **(K)** illustrated the simultaneous iES and electrophysiological recording experiment. **(E)** Rectangular electrical pulses were delivered to the macro-contact pair (X01 – X02) adjacent to microwires and both local field potentials and spike activities were recorded from microwires simultaneously. **(F)** Illustration of example visible and invisible trials. The *transparent yellow areas* indicate the time period of iES. **(G)** A raster-plot of spikes around iES onset of an example neuron (Neuron#13_243). **(H)** Averaged PSTHs in visible and invisible trials of Neuron#13_243. **(I)** Group averaged firing rates ($n_{neuron} = 7$) in visible and invisible trials. Red asterisks denote that the firing rates in visible trials were significantly higher than those in invisible trials, whereas blue asterisk indicate the opposite. **(J)** Comparison of the group averaged pre-stimulation powers in each frequency band between visible and invisible trials in two time windows (*left*, −10 to −8 s; *right*, −3 to −2 s). *Error bar* denote one standard error, *, $p < 0.05$, **, $p < 0.01$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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 Ren:** Investigation, Methodology. **Meng Zhao:** Conceptualization, Investigation, Methodology. **Guoming Luan:** Investigation, Methodology. **Fang Fang:** Conceptualization, Investigation, Funding acquisition, Visualization, Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT-4 to polish the manuscript. After using ChatGPT-4, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from wangqianpsy@pku.edu.cn

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.03.003.

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