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Transparent graphene bioelectronics as a new tool for multimodal neural interfaces

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ABSTRACT

A central challenge of neuroscience is to monitor the coordinated activity of neural circuits underlying information processing and behavior. Combining the advantages of electrical and optical modalities can provide unprecedented access to the spatiotemporal dynamics of neural activity. Transparent graphene bioelectronics has emerged as a suitable tool for the seamless integration of electrophysiological recording with optical imaging and optogenetic stimulation, opening up a variety of new opportunities in both neuroscience research and clinical applications.

In the mammalian central nervous system, billions of neurons are interconnected by trillions of synapses to form functional circuits. To understand how brain functions are generated by neural circuits, it is necessary to utilize tools that can record and manipulate the complex spatiotemporal dynamics of neural activity [1,2]. Electrophysiology was among the first neural interfacing techniques. Neuronal activity in the brain gives rise to ionic currents through transmembrane channels. The ionic currents spreading through the extracellular medium can be detected as extracellular voltages by implanted neural probes which transduce ionic signals to electronic signals [3]. Implantable neural probes allow us to explore neural dynamics with high temporal precision (μs) [4]. Furthermore, implantable neural probes have been applied as clinical tools to treat various neurological disorders, including chronic depression and movement disorders, such as Parkinson's disease [5]. Despite many advantages, implantable neural probes are limited in their ability to simultaneously record from a large number of neurons over vast areas. Optical imaging techniques, such as calcium imaging, can provide quantitative optical readouts of neuronal activity with cellular resolution [6]. Action potential firing of neurons leads to calcium influx through voltage-dependent calcium channels, which can be measured by fluorescent calcium indicator dyes [7] or genetically encoded proteins [8]. Rapid advancements in two-photon calcium imaging have now made it possible to simultaneously monitor the activity of hundreds of neurons, as well as to acquire structural information on neural circuits with near-millimeter depth of penetration [9]. However, calcium imaging has limited temporal resolution (ms) due to the slow response kinetics of the calcium indicators.

The development of multimodal neural interfaces that combine the advantages of electrical and optical techniques can introduce a wide range of new opportunities to study the complex spatiotemporal dynamics of neural circuits [10–13]. To this end, transparent graphene bioelectronics have recently been investigated for their potential to integrate electrophysiological recording with optical techniques [14–16]. Due to its large surface-to-volume area and unique electrical properties [17], graphene can monitor cellular bioelectrical activities with high signal-to-noise ratio (SNR) [18,19]. In addition, conventional rigid neural probes based on metals or silicon suffer from a substantial mechanical mismatch with soft neural tissue, which results in inflammatory responses and severe signal degradation in chronic studies [2]. Flexible bioelectronics based on polymer substrates offer improved mechanical compliance and biocompatibility with neural tissues. In particular, graphene is well-suited for use in flexible bioelectronics because of its atomic thickness and high fracture toughness [20–22]. Furthermore, single-layer graphene has high optical transparency [17]. As a result, graphene has been considered as a promising transparent conductive electrode material to complement indium tin oxide (ITO), especially for flexible electronics applications.

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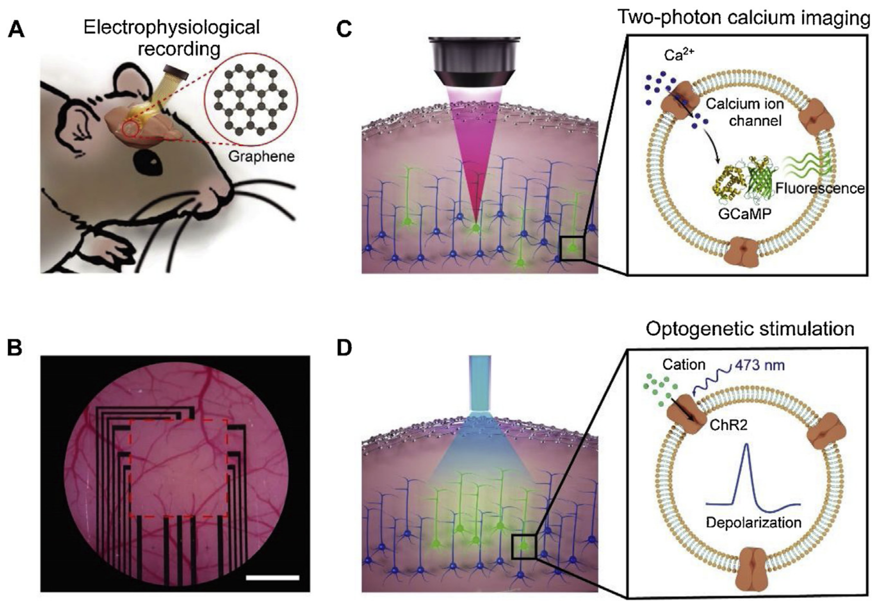

Fig. 1. Transparent GraMEA for multimodal neural interface. **A**) Transparent GraMEA for electrocorticographic recording from mouse brain. **B**) Bright-field image of a GraMEA placed on mouse cerebral cortex [23]. The graphene-based electrodes and interconnects in the center of the array are transparent (red dashed line highlighted the scope). Scale bar, 500 μm. **C**) GraMEA integrated with two-photon calcium imaging. The inset is the schematic of calcium imaging of GCaMP-expressing neurons. **D**) GraMEA integrated with optogenetic stimulation. The inset is the schematic of optogenetic activation of ChR2-expressing neurons. Activated and resting neurons are shown in green and blue, respectively, in C and D.

The unconventional electrical, mechanical, and optical properties of graphene offer unique opportunities to develop multimodal neural interfaces. Large-area, high-quality graphene films grown by the chemical vapor deposition (CVD) method were transferred onto flexible substrates, including Parylene C, Polyimide, and Polyethylene terephthalate, to fabricate flexible and transparent subdural graphene microelectrode arrays (GraMEAs) [14,15]. The flexibility of the GraMEAs allowed them to readily conform to the soft brain surface and record *in vivo* electrocorticographic (ECoG) signals over large cortical surface areas (Fig. 1A). In contrast with conventional metal microelectrodes that are opaque to light, the GraMEAs exhibited high optical transmittance of >90% over the ultraviolet to infrared spectrum (Fig. 1B). This allowed for both fluorescence and optical coherence tomography (OCT) imaging of the anatomical brain structures directly underneath the graphene microelectrode sites with little signal loss [14]. The high infrared transmittance of the GraMEAs further enabled two-photon imaging of both enhanced green fluorescent protein (EGFP)-expressing neurons in transgenic mice down to ~600 μm and vascular structures down to ~1200 μm [23]. In addition, simultaneous calcium imaging of neuronal activity at high spatial resolution and GraMEA-based electrophysiological recording of local field potentials (LFPs) at high temporal resolution have been demonstrated with minimum interference across modalities (Fig. 1C) [15,24]. Such multimodal neural activity recordings can allow us to investigate the correlations between cellular- and circuit-level neural functions.

Understanding how neurons interact with each other in complex circuits requires precise manipulation of neuronal activity. By genetically engineering neuron subtypes to express photosensitive channel proteins, optogenetics provides a powerful means for the targeted control of neuronal activity [13]. The genetically-engineered neurons can be selectively activated or inactivated by optical stimulus with millisecond precision. The high transparency of GraMEAs allows the easy integration of electrophysiological recording with optogenetic stimulation [23]. Flexible GraMEAs were used for subdural ECoG recording from the somatosensory cortex of channelrhodopsin-2 (ChR2) transgenic mice [14,23]. The ChR2-expressing neurons could be quickly activated when exposed to blue light pulses (~473 nm) (Fig. 1D). The simultaneous optical manipulating and electrophysiological recording of neural activity provides a valuable means to study the effects of evoked neuronal activity on the surrounding local neural network.

Decoding the complex spatiotemporal dynamics of neural activity underlying behavior is recognized as one of the most challenging problems in neuroscience. In our opinion, the integration of existing neural interfacing techniques with nanomaterials and devices can open a wide variety of new opportunities to study the neural systems from cellular to circuit scales. Graphene has emerged as a promising material for the development of flexible transparent bioelectronics so as to effectuate the seamless integration of electrical and optical modalities in neural interfaces. However, the merging of flexible transparent graphene bioelectronics and neural systems is still in its infancy, with many challenges yet to be addressed. For example, despite the promising results obtained so far in acute studies, the chronic compatibility and stability of the graphene bioelectronics remain poorly characterized. Moreover, while previous studies primarily used graphene devices for subdural recording of LFPs from the cortical surface [14,15], it is highly desirable for future studies to investigate the capability of graphene bioelectronics for intracortical recording of single-unit activity and integrating with optical modalities. Addressing these challenges will require coordinated efforts involving scientists from different areas, including nanomaterials, engineering, and neuroscience.

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