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COMMENTARY

Toward long-term and high-precision multimodal intracranial biomarker monitoring

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Abstract

Long-term and high-precision intracranial biomarker monitoring is crucial for the diagnosis, prevention, and prognosis of various diseases. However, existing technologies are associated with several issues of poor measurement accuracy, inability to monitor long-term and inadequate biocompatibility. To address these, minimally invasive implantable ultrasound metagel sensors have been developed for monitoring intracranial pressure, temperature, pH, and blood flow velocity. The sensor can quickly respond to changes in ultrasound frequency for high-precision monitoring of key physiological signals compared to current clinical gold standards. Additionally, the hydrogel exhibits excellent biocompatibility and can degrade almost completely within 18 weeks, without causing hematological disorders or systemic inflammatory responses.

Highlights

- Significance, challenge, and existing technologies of intracranial biomarker monitoring.
- Design and characterization of ultrasound-sensitive metagel sensors for multimodal intracranial biomarker monitoring.
- Conclusions and perspectives on the future development of intracranial biomarker monitoring.

Keywords Intracranial monitoring · Wireless monitoring · Ultrasound sensing · Metagel sensor · Implantable devices

Intracranial biomarker monitoring can identify the onset and progression of brain diseases such as brain tumors, cerebral edema, brain injuries, and encephalitis at an earlier stage. This allows for timely therapeutic interventions and effective prognostic evaluations. These biomarkers primarily include electroencephalography (EEG), intracranial pressure (ICP), oxygen levels, cerebral blood flow (CBF), glucose, and pH, which encompass bioelectrical, chemical, and physical physiological signals (Fig. 1a). Typically, normal intracranial pressure ranges from 5.0 to 13.5 mmHg, intracranial temperature ranges from 36.1 to 40.9 °C, and intracranial pH ranges from 7.35 to 7.45, indicating narrow ranges with minimal variation (Fig. 1b) [1, 2]. However, these physiological signals are crucial parameters for normal body function and their precise monitoring is clinically important for diagnosing and treating cranial-related diseases, particularly in critically ill patients.

Soft brain tissue is the core part of the human body and effectively protected by the skull and the blood–brain barrier. Its various accessory components also show marked differences in physiochemical properties such as Young's

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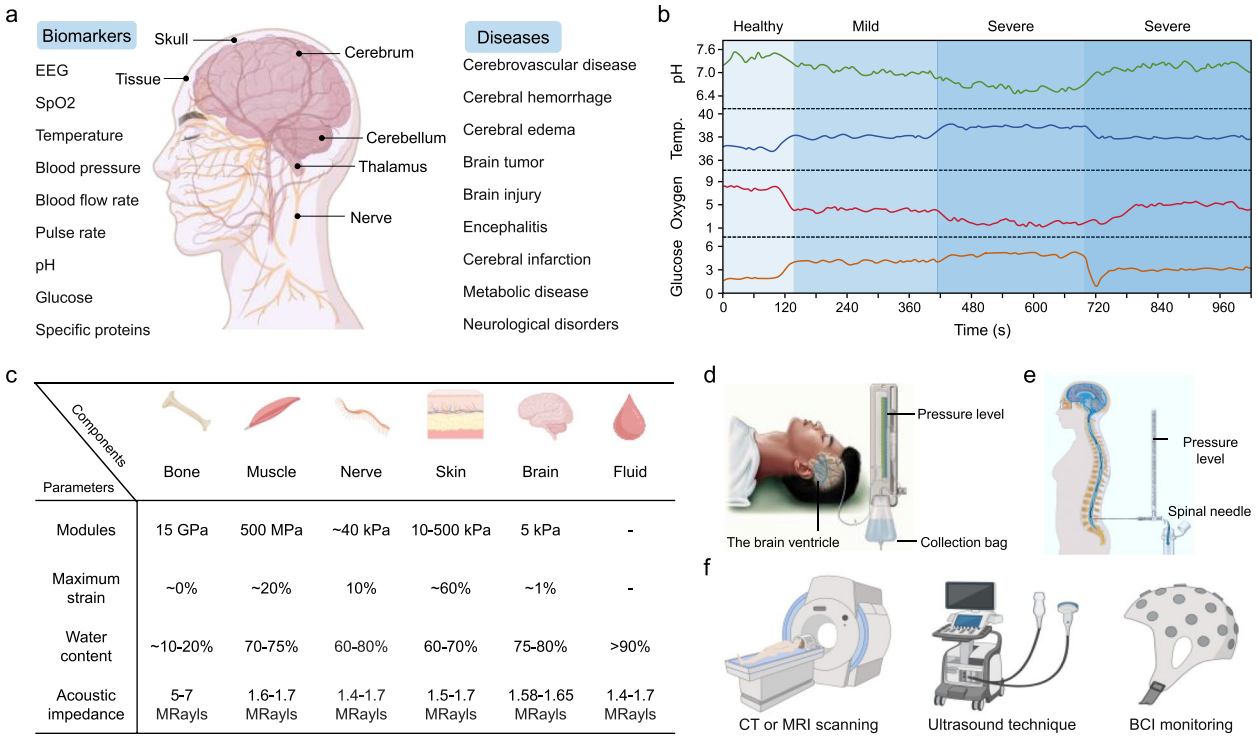

Fig. 1 Intracranial biomarkers and its monitoring technologies. **a** Typical intracranial biomarkers and diseases. **b** Schematic data showing the changes in intracranial biomarkers. **c** Modules, maximum strain, water content, and acoustic impedance of different brain-related components. **d** Intracranial pressure monitoring with EVD. **e** Intracranial pressure monitoring with lumbar puncture. **f** Emerging intracranial biomarker monitoring technologies

modulus, water content and acoustic impedance, making it challenging for clinical intracranial signal monitoring (Fig. 1c). Current clinical methods for monitoring intracranial biomarker monitoring include external ventricular drainage (EVD) and lumbar puncture. EVD is considered the gold standard for the measurement of multiple biomarkers, including ICP and multiple biochemical signals (Fig. 1d). However, it requires the insertion of a catheter into the brain ventricle, potentially causing complications such as edema, hemorrhage, and infection. Lumbar puncture is a less invasive method that can indirectly assess intracranial pressure while monitoring cerebrospinal fluid chemistry, but only provides a snapshot of the data (Fig. 1e). Some emerging methods based on computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and EEG are aimed at finding new routes for long-term and high-precision intracranial biomarker monitoring (Fig. 1f). Unfortunately, physical examinations often provide partial structural information and face technical challenges such as radiation exposure with CT and metal incompatibility with MRI. Multimodal ultrasound techniques with A, B, D, M modes can resolve some issues of CT and MRI but are largely limited by the skull barrier. High-density invasive EEG can accurately record brain electrical activity, which is crucial for monitoring epileptic activity, but has difficulty accessing deep brain information and is susceptible to motion artifacts [3].

To overcome these challenges, wearable electronics incorporating near-field communication (NFC), electromagnetic wave communication, and ultrasound communication have been developed for monitoring deep tissue physiological signals, offering insights for intracranial signal monitoring [4–6]. However, these technologies require implantable devices that are large, non-degradable and can trigger immune responses. Recently, wearable ultrasound patches that conform to the body have shown great potential for long-term monitoring by providing 3D imaging of intracranial vascular networks and parameters like blood flow velocity and volume [7]. But its measurement accuracy and spatial resolution remain limited and vulnerable to external stress, motion artifacts and electromagnetic interference. Therefore, achieving long-term, high-precision, multimodal intracranial biomarker monitoring with minimal brain injury remains a challenging task.

Until recently, a medicine-engineering interdisciplinary research team led by Professors Jianfeng Zang, Xiaodong Chen, and Xiaobing Jiang from Huazhong University of Science and Technology and Nanyang Technological University designed an ultrasound-sensitive metagel sensor [8]. This

innovation allows rapid, highly accurate, long-term monitoring of various intracranial biomarkers, including intracranial pressure, temperature, pH, and flow rate (Fig. 2a). These metagels are only 2 mm × 2 mm × 2 mm containing 25 air columns, and can specifically respond to changes in pressure, temperature, pH, and flow rate by altering the frequency of ultrasonic echoes (Fig. 2b). By simultaneously collecting signals from two metagels, the researchers could decouple these signals to obtain precise measurements (Fig. 2c). Test results indicate that metagels exhibit a high linear ultrasound frequency response to variations in pressure, temperature, and pH, with high precision of 0.1 mmHg, 0.1 °C and 0.0012, respectively (Fig. 2d). In addition, pulsed fluid flow will cause metagel vibrations that allow the detection of brain vascular flow rates far superior to commercial sensors (Fig. 2e). Furthermore, metagels can be implanted into rats and pigs via minimally invasive surgery, facilitating efficient ultrasound transmission and reception (Fig. 2f). In-vivo animal experiments demonstrate that these metagels provide highly precise wireless intracranial biomarker monitoring, surpassing the accuracy of clinical implanted intracranial pressure (ICP) probes (Fig. 2g). Additionally, the shape and position of the ultrasound metagels remain stable for approximately 3–4 weeks, with significant degradation occurring after 5 weeks. Throughout the monitoring and degradation cycle, the implants caused minimal immune response, without inducing blood system disorders or systemic inflammation.

This design transforms difficult-to-access intracranial signals into significant changes in ultrasonic echo frequency, offering new insights for high-precision intracranial signal monitoring. This is particularly beneficial for clinical ICP monitoring, which currently relies on invasive methods such as EVD and lumbar puncture. On the contrary, non-invasive methods such as transcranial Doppler ultrasound and magnetic resonance elastography, are inherently limited to an

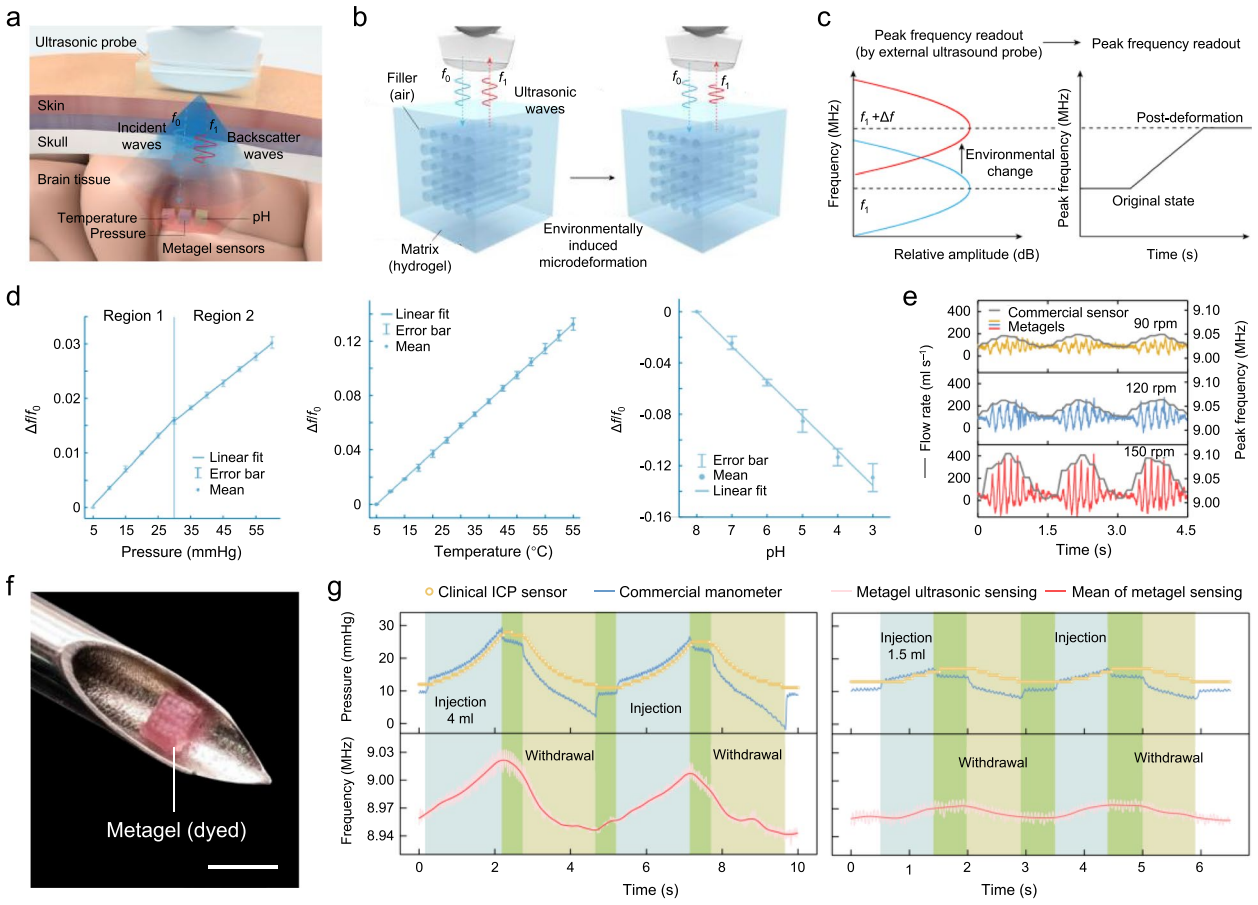

Fig. 2 Ultrasonic metagel for multimodal intracranial biomarker monitoring. **a** Design of an ultrasonic metagel sensing system. **b** Working principle of metagels based on environment-induced microdeformation. **c** Schematic showing peak frequency shifts of metagel with deformation. **d** Ultrasound frequency response to variations in pressure, temperature, and pH. **e** Flow rate assessment with an ultrasonic metagel and a commercial sensor. **f** Photograph of metagel and needle for in-vivo delivery. Scale bar, 2 mm. **g** Real-time assessment of the ultrasonic metagel sensing system during periodic saline injections/withdrawals into/from the spinal canal in pig experiments. From Tang et al. [8]. Copyright the Nature Publishing Group

indirect ICP evaluation through blood flow velocity and tissue mechanical characteristics. By transmitting ultrasound through a small acoustic window made by the implanted progress, energy loss through the skull is minimized, significantly enhancing signal-to-noise ratio and sensitivity. The metagel system requires B-mode imaging only for initial positioning, after which A-mode ultrasound can continuously monitor echo changes. Furthermore, metagels can be combined with wearable ultrasound patch technology for long-term intracranial signal monitoring. A-mode ultrasound reduces data processing requirements, thereby facilitating the miniaturization of backend circuit and power sources [9].

While the movement of the metagel sensors within the cranium may alter ultrasound incident angle, which necessitates repositioning for significant movements for increased operational complexity. Incorporating adhesive design can enable wet adhesion within the intracranial tissue, mitigating errors due to movement. The metagel system can also integrate EEG or functional MRI to comprehensively fuse information, effectively enhancing disease assessment [10]. Despite the minimal invasiveness of a 5.8 mm insertion window, the technique involves inserting a 2 mm hydrogel cube into the cranium, making it better suited for patients undergoing necessary craniotomies. The minimally invasive design could also inspire research areas such as transcranial ultrasound neuromodulation, as the insertion window may provide a pathway for ultrasound energy to penetrate while avoiding the limitations of traditional transcranial windows. The metagel system could also be coupled with wearable ultrasound technology to facilitate continuous bedside monitoring of various intracranial biomarkers, guiding more rational clinical treatment plans and effectively assessing surgical prognosis. The metagel requires accurate positioning via a costly and rare high-field MRI system, suggesting that future clinical applicability could be improved with ultrasound imaging systems. Additionally, this technology may replace traditional wired gastrointestinal monitoring systems, enabling real-time monitoring of heart rate, blood pressure, and oxygen saturation. As such, it can be a major contribution to the assessment of the intestinal environment, nutrient absorption, and post-perforation suture conditions in the gastrointestinal field. The metagel degradation after 5 weeks may limit its use in prolonged clinical applications, and thus the introduction of smart, controllable, degradable materials could be beneficial. Last but not least, comprehensive evaluations of the clinical application effects of biocompatibility and toxicology are essential to obtain ethical approval for medical applications.

As a significant milestone, the conceptual design provides a promising paradigm for long-term and high-precision multimodal intracranial biomarker monitoring with potential for further enhancement in biomedical applications. As would be expected, the metagel technology opens a new chapter in multimodal bioelectrical, chemical, and physical intracranial physiological signals physiological monitoring to update existing wireless implantable sensors. This research is a typical example of interdisciplinary integration, which may also catalyze more collaboration among experts in clinical medicine, materials science, and artificial intelligence to tackle complex clinical challenges.

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Declarations

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