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Fiber-optic photoacoustic enables targeted neuromodulation and stress reduction in mice

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Abstract: Ultrasound neuromodulation offers a non-invasive approach to modulate neural activity in the central nervous system. Precise, minimally invasive devices capable of targeted stimulation remain limited. A 200 μm diameter fiber-optic photoacoustic emitter (FPE) was developed, coated with a MXene ($Ti_3C_2T_x$) and polydimethylsiloxane composite to generate controllable, broadband ultrasonic waves with high spatial precision. Using this FPE to stimulate the medial prefrontal cortex in mice, it was observed marked alleviation of acute social defeat stress-induced emotional stress, evidenced by reduced anxiety-like behavior and increased social interaction. This approach enables near-field, broadband, and tunable ultrasound neuromodulation with potential applications in treating neuropsychiatric disorders involving emotional regulation.

Keywords: ultrasound neuromodulation; fiber-optic photoacoustic emitter; MXene composite; transcranial focused ultrasound

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Ultrasound neuromodulation, focused or unfocused ultrasound waves, has been applied to non-invasively modulate neural activity in the central or peripheral nervous system[1–7]. In a recently published study in *Opto-Electronic Science* by Li JP, Liu XH, Xiao ZH,… and ZY Li has demonstrated a new innovative technique to modulate *in vivo* emotional stress by a broadband ultrasound generator over a fiber-optic tip[8]. The photoacoustic has been shown to modulate mood and emotional states in both preclinical and clinical studies by targeting specific brain regions such as the prefrontal cortex and dorsal raphe nucleus[9,10]. This is achieved by coating the distal tip of an optical fiber with a photoacoustic material —such as gold nanocomposite, carbon nanotube-polymer composite, or patterned carbon films, which absorbs pulsed laser light delivered through the fiber and converts it into ultrasonic waves via the thermoelastic effect[11–13]. The fiber-optic approach allows for probes with diameters as small as 200–800 μm, facilitating access to deep or confined anatomical regions with minimal trauma[13–15]. The generated ultrasound can achieve pressures up to several MPa and bandwidths exceeding 20 MHz, supporting detailed imaging and discrimination of tissue microstructure[11,13–15]. In addition to cognitive, behavioral, and pharmacological treatment for a variety of psychological and psychiatric disorders, the use of neural stimulation[16,17], transcranial focused ultrasound for mood and emotional regulation, has been widely investigated and applied.

Researchers[8] engineered a tiny (200 μm diameter) fiber-optic photoacoustic emitter (FPE). This device uses a composite of MXene ($Ti_3C_2T_x$) and polydimethylsiloxane (PDMS) to generate controllable and broadband ultrasonic waves with high spatial precision through deposition on the distal facet of a 200 μm optical fiber. $Ti_3C_2T_x$ possesses excellent photothermal stability after repeated near-infrared (1064 nm) radiation, which makes it possible to continuously apply laser pulses to the FPE that can consistently emit ultrasound. Using an ultrasound generator over a fiber-optic tip enables highly miniaturized, directional, and broadband ultrasound generation for imaging and sensing applications, particularly in minimally invasive procedures. This current

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work[8] integrates several technologies: *in situ* ultrasound generation at the fiber tip, shrinking the source-to-target distance to hundreds of micrometers, and naturally reducing far-field energy accumulation and off-target risks (Fig. 1). Under nanosecond optical excitation, plasmon-enhanced photothermal absorption in MXene couples to the high thermoelastic coefficient of PDMS, enabling efficient photoacoustic conversion at the fiber tip. The emitter delivers broadband ultrasound with a center frequency of ~4 MHz and a −6 dB fractional bandwidth of ~162%. At an incident optical fluence of 10 mJ·cm^{-2}, the peak-to-peak acoustic pressure reaches ~0.7 MPa (positive peak≈0.4 MPa). Near-field mapping indicates lateral/axial full width at half maximum (FWHM) of ≈163/207 μm and ~50% amplitude after ~400 μm propagation in water, evidencing rapid spatial roll-off favorable for focal stimulation. In addition, TetTag (cfos-mCherry) labeling shows robust neuronal recruitment within the medial prefrontal cortex (mPFC) following stimulation. *In vivo* fiber photometry confirmed that the photoacoustic stimulation successfully induced an activation of mCHERRY expression (indicating an increased activity), as well as substantial calcium transients (a sign of activation) in the targeted mPFC neurons. The current study confirmed that photoacoustic stimulation of the mPFC using the FPE markedly decreased acute social defeat stress (SDS)-induced emotional stress behavior in mice, resulting in reduced anxiety-like behavior and enhanced social interaction.

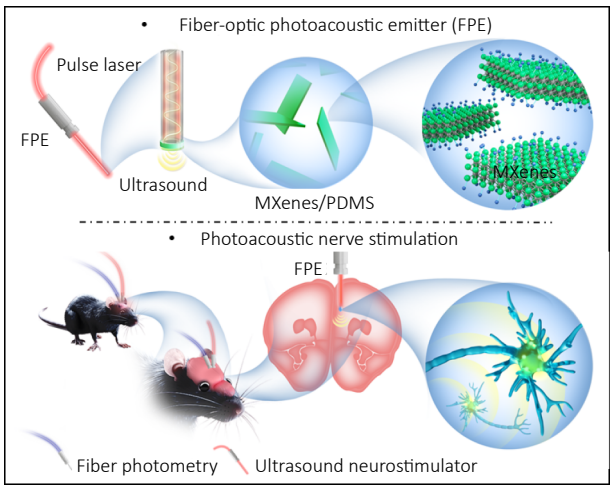


Fig. 1 | An implantable fiber-optic photoacoustic neurostimulator.

Clinically, transcranial ultrasound stimulation (TUS), particularly low-intensity transcranial focused ultrasound (tFUS) has been investigated for modulating neural circuits implicated in neuropsychiatric disorders, including mood, anxiety, and trauma-related disorders, by directly targeting subcortical regions such as the amygdala and cortical areas like the prefrontal cortex[10,18–20]. In emotional stress modulation, tFUS has demonstrated the ability to acutely reduce amygdala activity and alter functional connectivity in emotion regulation networks, leading to improved mood and reduced anxiety symptoms in both healthy volunteers and patients with mood and anxiety disorders[10,18,21]. For example, MRI-guided repetitive tFUS to the left amygdala over multiple sessions showed significant symptom improvement and safety in patients with mood and anxiety disorders[18]. Stimulation of the right prefrontal cortex also improved mood and modulated resting-state networks related to emotional regulation[10,21].

Mechanistically, TUS modulates neuronal excitability through mechanical interactions with neuronal membranes and mechanosensitive ion channels, producing both short-term and lasting changes in neural activity[5,20]. Preclinical studies support its efficacy in ameliorating depression- and anxiety-like behaviors by modulating monoamine neurotransmitters and neuroplasticity markers[9]. Stimulation of the mPFC improves mood disorders by enhancing the activity of neural circuits involved in emotion regulation, reward processing, and adaptive learning. Increased excitability of mPFC pyramidal neurons, particularly those expressing dopamine D1 receptors, produces rapid and sustained antidepressant and anxiolytic effects, in part by modulating downstream targets such as the basolateral amygdala and limbic structures. Neuromodulation of the mPFC normalizes fronto-limbic circuit function and increases serotonergic output to the hippocampus and amygdala, which is critical for antidepressant response[22,23].

In summary, by shrinking the source to the fiber tip while preserving broad bandwidth and tunability, this work shows that selectivity, reversibility, and repeatability can coexist in a compact, integration-ready platform. The implications reach beyond the mPFC: with appropriate safety windows and closed-loop control, miniaturized, programmable acoustic interfaces may become versatile tools for dissecting and correcting neural circuit function in neuropsychiatric disorders. This innovative preclinical fiber-optic tip ultrasound device demonstrates a highly precise, non-genetic, and minimally invasive photoacoustic technology for reversible neuromodulation that holds great potential for future clinical applications in treating neurological and psychiatric disorders, particularly those related to mood disorders (emotional regulation), Parkinson's disease, epilepsy, chronic pain, and cognitive improvement.

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