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Can optogenetics decode human-specific hyperexcitability circuits?

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A closed-loop optogenetic platform is developed for adaptive control and precise modulation of neuronal activity in epilepsy, with real-time spike detection triggering optogenetic silencing, alongside immunohistochemistry staining for HcKCR1-eYFP to mark the optogenetic construct's expression in excitatory neurons.

For over 50 million people with epilepsy globally, the harsh reality is that nearly one-third find no lasting relief from existing drugs or surgery.[1–3] This therapeutic impasse stems largely from discontinuities between preclinical models and human pathophysiology. Human brain network dynamics are pivotal for unraveling epileptic hyperexcitability, where seizures arise from imbalanced glutamatergic excitation and GABAergic inhibition, coupled with aberrant synaptic plasticity and ion channel dysregulation.[4] While rodent models have illuminated seizure mechanisms including interictal spikes, high-frequency oscillations, and spreading depolarization,[5] their translational relevance is constrained by species-specific divergences in neuronal architecture and circuit behavior. Human pyramidal neurons exhibit 5× greater dendritic length than rodents (Table 1), enabling nonlinear synaptic summation that amplifies hyperexcitability[6–8]; theta-gamma phase-amplitude coupling, a hippocampal seizure hallmark, is organized distinctly through human-specific HCN1 channel distributions and astrocytic gap junctions[9,10]; and over 60% of antiseizure drugs effective in rodents fail clinically, compounded by human-specific CYP3A4/CYP2C9 metabolism and P-glycoprotein efflux at the blood–brain barrier.[11] These microarchitectural divergences, alongside species variations in receptor kinetics and glial signaling, create unique spatiotemporal signatures of human hyperexcitability that evade rodent replication. Additionally, human-specific features like a higher proportion of excitatory neurons in certain cortical layers, differences in astrocyte-neuron signaling, and *N*-Methyl-d-Aspartate (NMDA) receptor subtypes with distinct activation/deactivation kinetics shape seizure dynamics in ways that rodent models fail to replicate.[12] These disparities extend to pharmacological responses, and drugs effective in suppressing rodent seizures often underperform in humans due to variations in drug metabolism, blood–brain barrier permeability, and target expression.[2,13–16] These gaps underscore the necessity of human-derived models to decode the interplay of molecular, cellular, and network-level pathologies driving epilepsy, ensuring therapeutic strategies address the clinical complexity of the disorder.

Traditional open-loop neurostimulation exacerbates this disconnect by applying fixed parameters across heterogeneous networks.[17–19] Closed-loop optogenetics could pivot this paradigm through real-time biomarker detection (theta coherence, wave propagation) paired with cell-type-specific inhibition,[20–25] yet 3 barriers impede progress: Rodent-optimized CaMKIIα promoters show <20% specificity in human excitatory neurons (viral targeting)[26,27]; commercial neurostimulators cannot resolve microdomain-specific hyperactivity (eg, dentate gyrus versus CA3, biomarker blindness)[28,29]; and broad-spectrum inhibition disrupts interneuronal plasticity essential for memory encoding (network destabilization).[30] Prior work in human brain tissue has been limited to acute slices or single-cell analyses, which fail to capture the synchronized network activity central to epilepsy.[31] Moreover, existing models often rely on pharmacological induction of hyperexcitability, which may not fully mirror the intrinsic pathology of human epileptic networks.

A recent work published in *Nature Neuroscience* addresses these gaps by establishing a robust ex vivo platform to evaluate optogenetic interventions in surgically resected human hippocampal tissue under clinically relevant epileptic conditions.[30] The organotypic slices (300 μm thick) from hippocampal tissue donated by patients with drug-resistant epilepsy were cultured at the air–liquid interface in serum-free media to model human epileptiform activity (Figure 1A). Slices were transduced with adeno-associated virus serotype 9 (AAV9) carrying the inhibitory potassium-conducting channelrhodopsin, HcKCR1, under the CAMK2A promoter, which restricts expression to excitatory neurons, alongside the enhanced yellow fluorescent protein (eYFP) for visualization. Bicuculline, a $GABA_a$ receptor antagonist, was used to pharmacologically elevate neuronal firing by blocking inhibitory signaling, thereby modeling seizure-like network activity.

To enable precise interrogation of network dynamics, high-density microelectrode arrays (MEAs; 26,400 electrodes) were integrated with a closed-loop system featuring fiber-coupled 530 nm light emitting diodes (LEDs) for spatiotemporally

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Table 1

Comparative analysis of human slices versus rodent models.

Parameter	Human slices*	Typical rodent models	Insights
Optogenetic construct	AAV9-CAMK2A-HcKCR1 (human CAMK2A promoter)	AAV-CaMKIIα-ChR2 (rodent CaMKIIα promoter)	Human CAMK2A promoters ensure excitatory neuron specificity in human tissue
Network activity mapping	High-density MEA (26,400 electrodes) resolves single-cell and network dynamics	MEAs (typically ≤256 electrodes).	Detects propagating theta waves (4–8 Hz) and microcircuit motifs unique to human epilepsy
Hyperexcitability	Endogenous (epileptic tissue) + 0-Mg^{2+}/KA induction	Pharmacologic induction (bicuculline, 4-AP)	Combines intrinsic pathology with provoked activity, modeling clinical TLE heterogeneity
Translational biomarkers	Theta-coherent propagating waves, rhythmic bursting	High-frequency oscillations (ripples, fast ripples)	Theta coherence in human tissue correlates with ictogenic networks, unlike rodent biomarkers
Closed-loop intervention	Real-time spike detection triggers optogenetic silencing	Open-loop electrical stimulation (RNS devices)	Precision targeting reduces off-target effects; mimics adaptive neuromodulation strategies
Control experiments	Nontransduced slices, ChR2 (excitatory opsin) controls	Sham surgeries, saline-injected controls	Validates HcKCR1-specific suppression and rules out light-induced artifacts
Immune response	Limited immune reaction in acute ex vivo culture	Chronic immune activation in rodent AAV models	Requires immune-stealth AAVs in future human in vivo applications
Long-term stability	Short-term viability (5–8 days postculture)	Chronic expression (weeks–months in rodents)	Human tissue models require improved culture systems for prolonged functional studies
Therapeutic specificity	Targets $CAMK2A^+$ excitatory neurons (key drivers of TLE)	Broad-spectrum inhibition (DBS, VNS)	Cell-type specificity minimizes cognitive side effects compared with nonselective methods

*Human slices can retain human-specific pathology (sclerosis, mossy fiber sprouting) absent in rodents.

AAV, adeno-associated virus; AAV9, adeno-associated virus serotype 9; CAMK2A (for the human gene/promoter)/CaMKIIα (for the rodent protein), calcium/calmodulin-dependent protein kinase II alpha; ChR2, channelrhodopsin-2; DBS, deep-brain stimulation; HcKCR1, K^+-selective channelrhodopsin; KA, kainic acid; 0-Mg^{2+}, magnesium-free (solution); RNS, responsive neurostimulation; TLE, temporal lobe epilepsy; VNS, vagus nerve stimulation.

precise illumination (Figure 1B) and 3D-printed inserts for precise light delivery (Figure 1C). Custom software enabled real-time spike detection and adaptive control of light parameters (intensity, duration, and frequency), triggering optogenetic silencing when firing rates exceeded hyperactivity thresholds. This system achieved rapid suppression, with 15% to 40% of bicuculline-treated slices exhibiting near-complete silencing (≥90% reduction in firing rates). Continuous 530 nm illumination (10-second duration) consistently silenced spontaneous hippocampal activity in $CAMK2A^+$ neurons (Figure 1D). In kainate-treated slices, rhythmic bursting emerged alongside theta-frequency (4–8 Hz) local field potential (LFP) coherence (Figure 1E). While optogenetic inhibition suppressed overall firing rates, coordinated bursts persisted in a subset of network activity, suggesting residual synchronization mechanisms resistant to targeted intervention (Figure 1F). Postexperiment immunohistochemistry confirmed CAMK2A-driven eYFP expression in hippocampal neurons, with enrichment observed in dentate gyrus granule cells and pyramidal neurons (Figure 1G). Waveform clustering revealed 12 neuronal subtypes with distinct anatomical and functional profiles. Neurons localized to nongranule cell layer (GCL) regions (CA1/CA3) consistently exhibited lower baseline firing rates (3–8 Hz) and stronger optogenetic suppression (Figure 1H). Conversely, dentate gyrus GCL-localized neurons showed characteristically high baseline activity (10–25 Hz) with attenuated responses to HcKCR1-mediated silencing. This functional-anatomical divergence suggests dentate granule cells drive network hyperexcitability while displaying relative resistance to inhibition, potentially due to compensatory glutamatergic signaling or incomplete transduction efficacy.

This work establishes a platform for precision neuromodulation in epilepsy by integrating cell-specific optogenetics, human-derived circuit analysis, and adaptive closed-loop control. Central to its innovation is the use of the CAMK2A promoter to restrict optogenetic inhibition (via HcKCR1) to excitatory neurons, key drivers of seizure propagation, while sparing inhibitory interneurons. This specificity is critical, as inhibitory neurons are often compromised in epilepsy, and indiscriminate silencing risks exacerbating network instability. High-density MEAs enabled the identification of human-specific biomarkers, such as theta-frequency coherence (4–8 Hz) and propagating wave dynamics, which are poorly replicated in rodent models. These biomarkers reflect pathological synchronization and spatial spread of hyperactivity, aligning with clinical seizure phenotypes. A modified Hodgkin–Huxley-based network model revealed that theta coherence facilitates long-range communication between epileptic foci while propagating waves mediate localized signal spread. Theta-phase propagation analysis during epileptiform bursts revealed spatiotemporal wave dynamics across the dentate gyrus, partially disrupted by optogenetic intervention (Figure 1I). This underscores that modulating oscillatory patterns can halt seizures without suppressing healthy activity, aligning with clinical goals of preserving cognitive function.

Conventional neurostimulation devices, such as vagus nerve stimulators, lack cellular specificity and temporal precision, often disrupting both pathological and physiological activities.[17–19] The closed-loop system's targeted approach remained effective even with partial transduction of excitatory neurons (10%–54% efficacy), a realistic clinical scenario given the current limitation in viral delivery. This robustness arises from focusing on hyperactive dentate granule cells rather than requiring full neuronal coverage, highlighting the therapeutic potential of precision targeting. This challenges the assumption that high transduction efficiency is mandatory for therapeutic efficacy. The system dynamically modulated epileptiform activity in 2 distinct models: GABAergic blockade (mimicking disinhibition) and kainate-induced glutamate hyperactivity. Optogenetic suppression proved more potent in GABAergic blockade (Figure 1J), suggesting that disinhibited networks rely disproportionately on excitatory neuron synchronization, whereas glutamate-driven hyperactivity involves diffuse mechanisms requiring combinatorial strategies. This differential efficacy highlights the need to tailor interventions to the underlying circuit pathology, a cornerstone of personalized therapy.

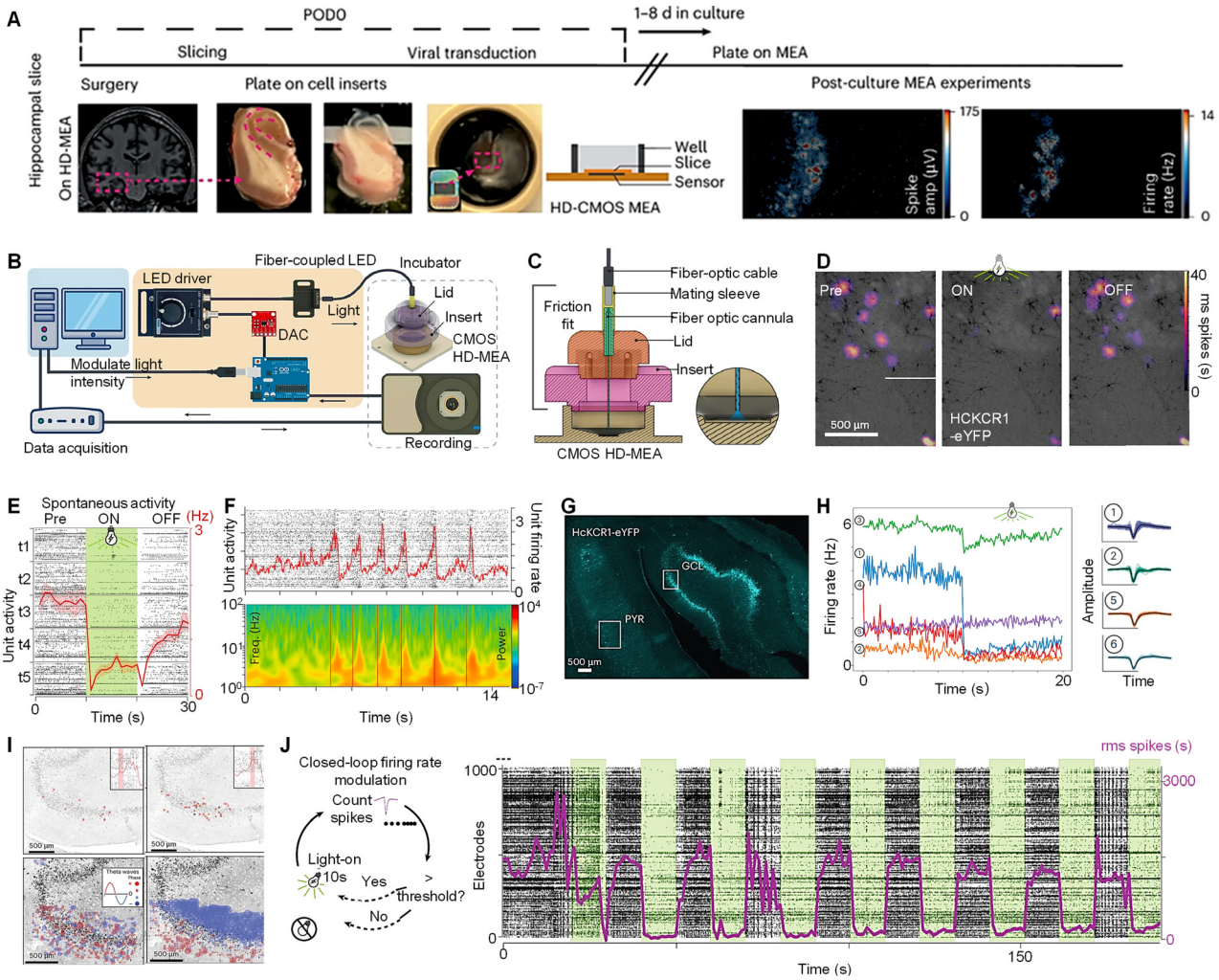

Figure 1. Closed-loop optogenetics for human hippocampal circuit interrogation and adaptive seizure control. (A) Workflow for preparing and recording human hippocampal slices. Resected tissue was sliced, cultured, transduced with AAV9 vectors, and recorded after 5–8 days. (B) Optogenetic hardware integration with HD-MEA system. A custom Arduino-controlled LED driver modulates light delivery (530 nm) synchronized with electrophysiological recordings. (C) Cross-sectional schematic of the 3D-printed optogenetic well insert, ensuring reproducible light delivery to tissue on the MEA. (D) Heat maps representing spike activity (5× RMS threshold) across the HD-MEA during 10-second intervals, highlighting regions of hyperactivity. Black denotes HcKCR1-eYFP staining. (E) Stacked raster plot of single-unit activity during optogenetic silencing trials. The average firing rate (red) shows suppression during illumination (green). (F) Rhythmic bursting activity (top) and theta-band LFP increases (bottom) following kainic acid application. (G) eYFP expression co-localizes with neuron-dense regions in the AAV9-HcKCR1-transduced hippocampal slice. (H) (Left) Average firing rate dynamics across response clusters. (Right) Representative extracellular waveforms for each cluster. (I) Spatiotemporal propagation of theta-phase coherence during epileptiform bursts. Dot size reflects phase magnitude; color indicates phase direction. (J) Closed-loop optogenetic control for bicuculline-provoked activity suppression. Reproduced with permission from Andrews et al.[30] Copyright 2024, Springer Nature.

1. Immune-optimized gene delivery for chronic stability

However, the translation of optogenetic interventions from ex vivo human hippocampal slices to clinical applications presents critical challenges that remain partially unresolved. While acute optogenetic control in cultured slices has been demonstrated, long-term safety and efficacy in intact human brains are unproven.[32] Chronic AAV-mediated opsin expression risks triggering immune responses or losing potency, particularly within the neuroinflammatory environment and gliosis characteristic of sclerotic hippocampal tissue in drug-resistant epilepsy. The incomplete suppression of rhythmic bursts in models, stemming from limited spatial targeting (10%–54% transduction rates) and spectral specificity (inability to fully block theta-frequency coherence), highlights the potential for off-target effects from the CAMK2A promoter or diffuse light scattering disrupting nonpathological circuits.[33] Moreover, current closed-loop systems, often reliant on simple firing rate thresholds, may miss subtler biomarkers like pre-ictal theta-gamma coupling[34] and fail to adapt effectively to evolving seizure dynamics, such as propagation shifts across hippocampal subfields.

To address these challenges, several potential strategies can be employed. Enhancing tropism for epileptic neurons requires developing engineered AAV capsids through directed evolution in human brain organoids[35,36]; variants like AAV-PHP, exploiting human-specific LY6A receptors, could improve transduction in sclerotic regions. Immune responses might be mitigated by creating stealth capsids with reduced antigenicity and introducing glycosylation sites into opsins like HcKCR1 to mask immunogenic epitopes, paralleling strategies used in therapeutic antibodies.[37] Chronic safety and efficacy should be tested in humanized animal models, “epilepsy-on-a-chip” co-cultures integrating human neurons, glia, and immune cells, or organoids.[38]

Improving specificity necessitates dual-promoter systems, combining CAMK2A with activity-dependent promoters (FOS or NPY), to restrict opsin expression to hyperactive neurons, sparing quiescent cells and reducing off-target effects and immune exposure.[39] Spectral limitations and light scattering could be countered by integrating red-shifted opsins like Jaws for deeper, more focused penetration.[40] Meanwhile, overcoming detection limitations involves training machine learning algorithms on human-derived high-density microelectrode array data to recognize patient-specific epileptiform signatures (propagating wave directionality) and optimize stimulation parameters in real time.[24] These refinements engineered capsids, stealth opsins, dual-promoter targeting, red-shifted tools, and adaptive closed-loop systems can extend optogenetic efficacy from acute slices to chronically seizing networks, aligning with the clinical imperative for lifelong disease management.

2. Adaptive closed-loop architectures for predictive control

Despite suppressing seizure-like events by targeting firing rate thresholds, the closed-loop system failed to fully abolish theta-coherent bursts in kainate models, exposing a critical limitation of biomarker blindness. Current systems lack the sensitivity to detect latent precursors like pre-ictal theta-gamma coupling and cannot adapt to dynamically shifting propagation patterns. Overcoming this, multimodal biomarker detection should incorporate LFPs, intracellular Ca^{2+} imaging via fiber photometry, and astrocytic glutamate sensors into closed-loop algorithms.[24] Crucially, astrocyte-derived glutamate surges precede neuronal hyperactivity by 300 to 500 ms in human tissue, providing a vital predictive trigger for preemptive intervention. Moreover, machine learning-driven adaptation is essential; neural networks should be trained on human-specific seizure signatures using high-density microelectrode array datasets, enabling reinforcement learning to optimize stimulation parameters (wavelength, pulse width) in real time while preserving physiological theta rhythms critical for memory.[23] Meanwhile, deploying red-shifted optoelectronics replacing 530 nm LEDs with far-red light sources paired with opsins like Jaws or ChrimsonR will enable deeper tissue penetration and artifact-free concurrent electrophysiology, which is vital for targeting subcortical foci in intact brains.[22] These strategies would transform closed-loop optogenetics from reactive "firefighters" into adaptive "prevention engines," capable of decoding the spatiotemporal grammar of human seizures.

The convergence of human-derived models and optogenetics has revealed a fundamental principle: effective epilepsy therapy must align with the biological uniqueness of human neural networks. Complementary evidence from rodent and theoretical models reinforces that pathological oscillations, whether arising from cortical-thalamic loops,[41] hypothalamic excitatory surges,[42] or leader neuron-initiated cortical bursts,[43] can be modulated by precise, scalable neurotechnologies. Emerging multimodal platforms further expand this toolkit: Sono-optogenetic systems enable noninvasive deep-brain targeting,[44] while engineered bacterial phytochromes operating in biliverdin-enriched environments achieve cell-specific control with enhanced spectral precision.[45] These advances, combined with our CAMK2A-guided closed-loop platform, signal a transformative shift toward biologically realistic therapeutic strategies. By pairing immune-stealth gene delivery with intelligent neuromodulation systems, we can extend ex vivo success to in vivo durability, evolving therapies alongside the brain's dynamic complexity to realize personalized epilepsy management.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: V.N.N. and S.X.; Writing – original draft: Y.W., N.M.B., Y.Z., and M.G.; Writing – review and editing: Y.W., N.M.B., V.N.N., and S.X.; Visualization: Y.Z. and M.G.; Supervision: V.N.N. and S.X.; Project administration: S.X.

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