

Chemically Reconfigurable Neuromorphic Electronics for Neurochemical Homeostasis

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Abstract

Neuromorphic devices excel at emulating synaptic and neuronal computation, yet their states are predominantly programmed by electrical signals, limiting their ability to directly perceive and adapt to the molecular signals that govern biological neural function. Here we introduce chemical reconfiguration into neuromorphic electronics and develop a chemically reconfigurable neuromorphic healer (CR-NeuroHealer), in which molecular inputs directly reprogram synaptic plasticity to couple neurochemical perception with adaptive regulation. The CR-NeuroHealer responds distinctly to dopamine (DA) and Fe^{3+} , enabling the chemical environment to reconfigure the device between healthy-like and pathological synaptic states. When interfaced with neuron-like PC-12 cells, the device establishes a biohybrid synapse through molecular communication, sensing presynaptic DA while providing adaptive chemical feedback. Pathological iron accumulation weakens synaptic transmission and triggers deferiprone (DFP) release, which chelates excess iron and restores dopamine-responsive plasticity, completing a chemically reconfigurable regulatory cycle. We further demonstrate this chemical perception *in vivo* using a miniaturized neuromorphic OECT implanted in a 6-hydroxydopamine-induced Parkinsonian mouse model. The implanted devices respond to endogenous DA modulation and pathological iron accumulation with distinct synaptic-like outputs that discriminate neurochemical states and guide DFP-mediated intervention, accompanied by recovery of motor performance and device responses. These results establish chemical reconfiguration as a neuromorphic design principle for therapeutic brain-computer interfaces that operate through the molecular language of the nervous system.

Introduction

Neuromorphic electronics emulate both the features and structure of biological neural systems by integrating sensing, processing, and memory functions within compact hardware^{1,2}. This co-location of multiple functional elements enables parallel computation, adaptive learning, and fault tolerance³⁻⁵, mimicking the brain's low-energy ability to simultaneously perceive⁶, process⁷⁻⁹, and respond to environmental stimuli¹⁰. Recent advances have extended neuromorphic electronics from individual synaptic and neuronal functions to integrated sensory and afferent neural circuits¹¹⁻¹³, enabling closed-loop feedback^{14,15} and adaptive neuromodulation^{16,17} through electrical interfaces with biological tissues¹⁸⁻²². More recently, neuromorphic electronics have expanded beyond purely electrical signal processing towards chemically responsive systems²³⁻²⁹, in which neurotransmitters and other molecular cues can directly modulate device states. Such systems provide an important route towards molecular communication with biological neural networks³⁰. However, chemical signals in existing neuromorphic systems primarily serve as inputs for sensing or synaptic modulation, rather than as cues that reconfigure device function in response to changing physiological or pathological states.

Biological neural systems, however, do more than transmit and process information: they continuously adapt to chemical perturbations to preserve homeostasis³¹⁻³⁴. Replicating this capability requires neuromorphic devices whose functional states can be reconfigured by their surrounding molecular

environment, enabling them not only to perceive chemical imbalance but also to initiate an appropriate regulatory response. Such state-dependent chemical reconfiguration remains largely absent from current neuromorphic electronics. Iron–dopamine homeostasis provides a representative neurochemical context in which to explore this capability³⁵⁻³⁷. Iron is essential for normal neuronal function, but its dysregulation and accumulation in dopaminergic regions can promote oxidative stress, dopamine oxidation and neuronal dysfunction³⁸⁻⁴⁰. In Parkinson's disease (PD), disruption of iron and dopamine homeostasis is particularly intertwined⁴²⁻⁴⁷: excessive iron can accelerate dopamine oxidation and oxidative damage, while progressive dopaminergic dysfunction further perturbs the local neurochemical environment, contributing to a pathological feedback loop.⁴⁸⁻⁵¹ Reproducing this dynamic chemical interplay electronically therefore requires a neuromorphic system capable of interpreting distinct molecular cues, transitioning between functional synaptic states and coupling pathological-state recognition to corrective chemical feedback. Neuromorphic devices capable of such chemically reconfigurable homeostatic regulation have yet to be established (Supplementary Table 1).

Here, we introduce chemical reconfiguration into neuromorphic electronics through a chemically reconfigurable neuromorphic healer (CR-NeuroHealer) that couples molecular perception, synaptic-state adaptation and chemical regulation. In the CR-NeuroHealer, molecular cues dynamically and reversibly program the neuromorphic functional state, with dopamine (DA) and Fe^{3+} inducing distinct changes in the synaptic plasticity of the organic electrochemical transistor (OECT). Under DA-dominant conditions, the device maintains robust synaptic plasticity and supports molecular communication with neuron-like cells. Pathological Fe^{3+} accumulation weakens this plasticity and activates deferiprone (DFP) release; subsequent iron chelation restores dopamine-responsive synaptic behavior, completing a reversible chemical reconfiguration cycle. We validate this concept through biohybrid communication with PC-12 cells and further demonstrate its *in vivo* chemical perception using miniaturized neuromorphic OECTs implanted in a 6-hydroxydopamine (6-OHDA)-induced Parkinsonian mouse model. The implanted devices respond to endogenous DA modulation and pathological iron accumulation with distinct synaptic-like responses, providing device-level signals that discriminate neurochemical states and guide DFP-mediated intervention. Together, these results establish chemical reconfiguration as a neuromorphic design principle for translating molecular states into adaptive electronic and therapeutic responses, extending neuromorphic electronics from chemical perception towards homeostatic regulation and chemically integrated brain–computer interfaces.

Design and fabrication of a CR-NeuroHealer

In healthy dopaminergic neurons of the substantia nigra, DA serves as the primary chemical messenger for synaptic transmission. However, pathological iron accumulation disrupts this communication, driving neurodegeneration in PD (Fig. 1a). To address this challenge, we developed a CR-NeuroHealer that autonomously senses chemical imbalances and restores homeostasis (Fig. 1b).

The CR-NeuroHealer integrates two functional modules: (1) a poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) based neuromorphic transistor for chemical perception, and (2) dual

thermally controlled release modules containing DA and DFP. In the healthy state, DA oxidation under the gate voltage of the transistor induces robust long-term conductance change (ΔG), indicating the long-term plasticity (LTP). As Fe^{3+} concentration increases, it progressively complexes with DA, thereby altering the electron transfer pathway for DA oxidation, leading to a progressively weakened LTP. The CR-NeuroHealer continuously monitors ΔG to evaluate the neuronal health. When ΔG falls below a critical threshold—indicating pathological iron accumulation—the system triggers a state transition (Fig. 1c). This decision-making logic orchestrates the localized sense-and-respond paradigm illustrated in Fig. 1d. To execute the therapeutic intervention, the head-mounted synaptic organic electrochemical transistor (OECT) generates decision-making signals that guide exogenous interventions via intraperitoneal (i.p.) injection: the blue pathway represents AMPH administration for DA release enhancement, while the orange pathway represents DFP administration for brain iron chelation. To verify the chemical sensing capability of this strategy, we performed *in vivo* device responses recordings in the 6-OHDA -induced Parkinsonian mouse model. As shown in the post-synaptic current change (ΔPSC) traces of Fig. 1d, the device captured robust LTP in the Saline control group, reflected by prominent ΔPSC amplitudes and substantial ΔG . In sharp contrast, both the ΔPSC amplitudes and ΔG were severely attenuated in the untreated 6-OHDA pathological state, manifesting as weakened LTP. Notably, upon implementing DFP-mediated therapeutic intervention, the ΔPSC signals were effectively rescued to near-healthy levels, confirming that the system can precisely sense iron-overload-induced neural dysfunction. Within the device itself, the processing circuitry redirects thermal activation from the DA release module to the DFP release module. Released DFP chelates excess Fe^{3+} into neutral complexes, liberating DA and restoring normal oxidation pathways. This molecular intervention recovers LTP, completing the chemical reconfiguration cycle *in vitro*.

Chemical reconfigurability of the neuromorphic transistor

The neuromorphic transistor was fabricated through layer-by-layer deposition on flexible substrates, utilizing thermal evaporation for electrode patterning, inkjet printing for the PEDOT:PSS channel, and polydimethylsiloxane (PDMS) to integrate microfluidic channels (Fig. S1). The device can respond to chemical composition in the electrolyte, exhibiting distinct synaptic behaviors based on molecular interactions (Fig. 2a). The device modulates electron transfer pathways and ion doping effects according to the presence of Na^+ , DA, and Fe^{3+} , enabling chemical control of synaptic plasticity.

In a pure NaCl solution (100 mM), the device exhibits short-term plasticity (STP), characterized by a rapid decay of channel conductance to its initial state upon removal of the gate pulse stimulation (Fig. 2b). This behavior results from transient Na^+ ionic doping in the channel, which causes temporary conductance change. The introduction of 1 mM DA fundamentally alters the synaptic behavior of the neuromorphic transistor (Fig. 2c, left), inducing a LTP with a ΔG of 1.61 mS. This transition arises from DA oxidation at the gate interface, which generates protons and electrons that persistently dedope the PSS^- component, thereby creating long-term conductance modulation. Interestingly, the subsequent addition of Fe^{3+} impairs this DA induced LTP behavior in a concentration-dependent manner (Fig. 2c,

middle; Fig. S2). As the Fe^{3+} concentration increases from 5 to 100 μM , the device's LTP is progressively impaired, transitioning from a healthy state (100 mM Na^+ + 1 mM DA) to a severely pathological one. At 100 μM Fe^{3+} , the LTP is almost completely suppressed, with ΔG dropping from the initial 1.61 mS to only 0.24 mS.

We systematically verified that Fe^{3+} modulates DA induced LTP by measuring synaptic responses to varying pulse width (T_w), frequency and number. For instance, extending T_w from 280 to 1280 ms increases ΔG by 3.69 mS in the healthy state but only 0.44 mS in the pathological state (+ 100 μM Fe^{3+}) (Fig. 2d). The impairment of DA induced LTP was Fe^{3+} concentration-dependent (Fig. 2e and S3). Furthermore, increasing stimulation frequency (0.5-3.0 Hz) enhances ΔG by 1.49 mS in healthy state but only 0.03 mS in pathological state, indicating a loss of LTP (Fig. 2f and S4). Multiple pulse stimulation increases ΔG by 1.92 mS in healthy state versus 0.33 mS with pathological state, demonstrating compromised synaptic capability (Fig. 2g and S5).

Following comprehensive characterization of Fe^{3+} induced impairment, we investigated therapeutic reversal using DFP, a clinically approved iron chelator, which coordinates iron ions in a 3:1 molecular ratio^{36, 52, 53}. Introduction of DFP to Fe^{3+} loaded neuromorphic transistor demonstrates remarkable functional recovery through competitive chelation (Fig. 2c, right; Fig. S6). The recovery also exhibits clear concentration dependence: 1 mM DFP partially restores ΔG to 0.63 mS, while increasing concentrations progressively enhance recovery—2 mM yields 0.88 mS, 3 mM reaches 1.05 mS, and 5 mM achieves near complete restoration at 1.39 mS (86.34% of original LTP). The gradual response to DFP concentration provides a tunable mechanism for therapeutic intervention, essential for the device's homeostatic regulation capabilities.

We further quantified synaptic plasticity through comprehensive characterization of channel ΔG (Fig. 2h). The upper panel shows representative synaptic responses to 20 consecutive pulses (0.7 V, 1.2 Hz, $T_w = 550$ ms) across different chemical states: robust LTP in DA solution (blue), progressively weakened LTP responses with increasing Fe^{3+} (5-100 μM , red gradient), and dose dependent recovery with DFP addition (1-5 mM, blue gradient). Comprehensive parametric analysis (Fig. 2i) maps the therapeutic landscape across multiple variables. The three-dimensional response surface reveals antagonistic effects of Fe^{3+} and DFP on synaptic plasticity as a function of stimulation intensity (pulse number). Conversely, pathological iron accumulation (50-100 μM) progressively deepens the response valley across all pulse numbers, with profound suppression of synaptic plasticity that mandates aggressive therapeutic intervention (3-5 mM DFP) to achieve clinically meaningful recovery. Notably, the surface topology reveals that therapeutic effectiveness improves with increasing stimulation intensity (higher pulse numbers), suggesting that the topology of the response surface identifies an optimal therapeutic window where intervention is most effective.

In short, we have developed a chemically reconfigurable neuromorphic transistor that transitions between a healthy state with robust LTP and pathological states with weakened LTP based solely on

electrolyte composition. Unlike conventional electrically programmed neuromorphic devices, our device achieves the chemical reconfigurability of synaptic functionality through molecular interactions, enabling both the emulation of normal synaptic behaviors and the modeling of neurodegenerative changes. This chemical responsiveness expands neuromorphic applications from computational elements to active participants in biological systems requiring homeostatic regulation.

Chemical reconfiguration mechanisms

To shed light on the chemical reconfiguration mechanism of the neuromorphic transistor, we conducted a series of characterizations including electrochemical, spectroscopic, and electrical measurements. Firstly, linear sweep voltammetry confirmed $[\text{Fe}(\text{DA})]^{2+}$ complex formation through concentration-dependent positive shifts in DA oxidation potential. Compared to blank DA solution, the addition of 100 μM Fe^{3+} , leads to a positive shift of the oxidation peak by 0.130 V, indicating that Fe^{3+} coordination thermodynamically stabilizes DA and reduces its electrochemical activity for channel modulation (Fig. S7).

Furthermore, time-resolved UV-vis spectroscopy is employed to directly visualize the impact of Fe^{3+} on the channel's operating mechanism (Fig. 3a and S8). In the healthy state, voltage pulses induced strong, periodic increases in absorbance ($\Delta \text{Norm. Abs.} = 0.062$) appearing as bright spectral bands in the 550-650 nm region. These bands correspond to $\pi\text{-}\pi^*$ transitions indicating PEDOT doping state changes—from neutral to polaron forms—confirming efficient cation driven dedoping. Upon introducing 100 μM Fe^{3+} , these bright bands vanished and absorbance modulation dropped to 0.019, providing direct visual confirmation that $[\text{Fe}(\text{DA})]^{2+}$ complex formation suppresses crucial electron transfer and reduces the cation dedoping process. Crucially, DFP addition restored the system's responsiveness, with bright bands and high absorbance modulation (0.067) reappearing. This demonstrates an “ON/OFF/ON” switch of the device's neuromorphic mechanism, controlled entirely by chemical environment. We further quantitatively analyze the optical density, details given in Supplementary Note 1. Systematic analysis shows progressive suppression of optical response, while DFP treatment enabled dose dependent recovery (Fig. S9).

X-ray photoelectron spectroscopy (XPS) further reveals molecular level changes in channel composition (Fig. 3b). The $\text{S}(2p)$ core level spectra showed distinct binding energies: pristine PSS^- (168.787 eV)⁵⁴, H^+ dedoped PSS-H (169.184 eV with DA), and partially restored PSS^- (168.861 eV with DA + Fe^{3+}). This progression indicates that Fe^{3+} -DA complexation reduces H^+ generation and incorporation during the dedoping process, maintaining higher hole concentrations in the channel.

Transient hole mobility (μ_h) measurements confirmed functional impacts: μ_h decreased from $14.218 \times 10^{-3} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ (healthy state) to $7.369 \times 10^{-3} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ (pathological state), then recovered to $13.860 \times 10^{-3} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$ in the therapeutic state (Fig. S10). This mobility suppression in the pathological state reflects changed hole distribution, which might be due to the reduced cation (such as H^+) dedoping⁵⁵. At

high hole concentrations, charge carriers become trapped in localized states, reducing mobility. DFP treatment restores normal dedoping process, reducing hole density and recovering charge transport efficiency essential for synaptic function.

Based on these characterizations, we propose a chemical reconfiguration mechanism for our neuromorphic device (Supplementary Note 2). In the healthy state, DA oxidation generates electrons, where the electron reduces PEDOT, leading to a decrease in conductivity and high doping level. The H^+ compensate the negative charge of the sulfonate group on PSS (Fig. 3c and Fig. S11). We hypothesize that in the pathological state (low doping level), Fe^{3+} coordinates with DA to form $[Fe(DA)]^{2+}$ complexes, diverting the electron transfer pathway from the PEDOT channel to dissolved oxygen, thus impairing synaptic function (Fig. 3d). In the therapeutic state (high doping level), DFP competitively chelates Fe^{3+} due to its superior binding affinity, liberating DA to restore normal electrochemical processes and recover LTP (Fig. 3e).

The chemical reconfiguration mechanism of neuromorphic transistor is reversible, which can be experimentally verified through multiple Fe^{3+} loading/DFP recovery cycles (Fig. 3f). Over three complete cycles spanning 750 seconds, the device maintained consistent synaptic responses without obvious degradation. Each Fe^{3+} addition suppressed LTP, while DFP treatment consistently restored function, confirming robust chemical reconfiguration for sustained therapeutic applications. This reversible chemical reconfiguration establishes the foundation for autonomous therapeutic neuromorphic systems.

Integrated CR-NeuroHealer system for Fe^{3+} -DA homeostatic regulation

Building on the neuromorphic transistor with chemical reconfigurability, we designed an integrated CR-NeuroHealer system that autonomously maintains Fe^{3+} -DA homeostasis through closed loop regulation (Fig. 4a). The system integrates an OECT based neuromorphic transistor, transimpedance amplifier (TIA) circuitry, and dual thermally controlled release modules (DA and DFP) (Fig. 4b and Fig. S12). In the CR-NeuroHealer, a peristaltic pump enables controlled solution delivery to the transistor, where microfluidic inlet/outlet ports facilitate real time chemical perception and molecular release for bio-integration (Fig. S13). The upper heater module contains DFP releaser for therapeutic iron chelation (orange flow path), while the lower module holds the DA releaser for maintaining normal synaptic communication (blue flow path). The TIA circuitry converts the preprocessing current output of the neuromorphic transistor into a voltage signal, thereby controlling the activation of the thermally controlled release modules. The overall device demonstrates the mechanical flexibility essential for biocompatible applications (Fig. S12c).

The release modules employ phase change material nanoparticles (PCM-NPs) with precisely engineered thermal properties for controlled molecular delivery. We optimized the PCM-NPs composition using a 4:1 lauric acid to stearic acid ratio, achieving a sharp melting transition at 39 °C as confirmed by differential scanning calorimetry (Fig. S14). To create drug loaded nanoparticles, we synthesized PCM-NPs in the

presence of either DA or DFP, yielding DA-PCM-NPs or DFP-PCM-NPs through co-encapsulation methods during nanoparticle formation.

Upon reaching the 39 °C activation threshold, these nanoparticles exhibit rapid and quantitative release: DA-PCM-NPs deliver approximately 130 µM DA within 200 s (Fig. S15), while DFP-PCM-NPs release 0.4-1.3 mM DFP sufficient for chelating 50-100 µM Fe³⁺ given DFP's 3:1 binding stoichiometry (Fig. S16). The drug loaded PCM-NPs are embedded within polyvinyl alcohol hydrogel matrices positioned directly above resistive heaters, which provide precise localized heating to trigger release. The heater design (L/W = 5) achieves the target temperature at a heating voltage of 4.0 V, ensuring reliable thermal activation without overheating (Fig. S17). This thermally-gated release mechanism enables the CR-NeuroHealer to deliver therapeutic molecules only when synaptic signals indicate pathological conditions, maintaining molecular cargo stability at physiological temperatures until needed.

Real-time thermal imaging illustrates the system's adaptive response to pathological iron accumulation (Fig. 4c). Under healthy state, the left heater is activated, corresponding to DA release. With the introduction of Fe³⁺ (25 µM and 75 µM), the system transitions as the right heater becomes illuminated, triggering the release of the therapeutic agent DFP. Upon successful intervention, the device restores the left heater's activity based on the transistor's response, returning to the normal DA releasing state. This reversible thermal pattern demonstrates the device's capacity for autonomous chemical reconfiguration and recovery. This selective activation results from the preprocessing result of the neuromorphic transistor (inset Fig. 4d and Fig. S18): decreasing ΔPSC from iron overload generates reduced voltage to the DA heater (preventing it from reaching 39 °C) while increasing voltage to the DFP heater (enabling 39 °C activation). The actual molecular release profiles (Fig. 4d) confirm concentration-dependent delivery: DA-PCM-NPs maintains ~130 µM release below 10 µM Fe³⁺, while DFP-PCM-NPs progressively activates above ~75 µM Fe³⁺, reaching maximum release at pathological concentrations.

Subsequently, we demonstrated autonomous homeostatic regulation over extended operation (Fig. 4e). The system preprocesses chemical stimulations through 20 consecutive pulses (1.2 Hz, 0.7 V) every 120 s, with ΔPSC converted to heating voltages for selective thermal actuation. During the initial healthy phase (0-1160 s), the DA releaser maintains regular pulsatile activity essential for normal synaptic function. Upon iron challenge (75 µM Fe³⁺), the system enters a self-adaptation phase where DA release progressively diminishes while DFP release activates to combat iron accumulation. Remarkably, successful iron chelation enables spontaneous recovery of DA release function (4525-6000 s), demonstrating true homeostatic regulation without external intervention.

Detailed temporal analysis (Fig. 4f) captures the complete therapeutic cycle at three critical stages. The healthy state exhibits robust synaptic responses with strong conductance changes (ΔG = 2.67 mS) and regular DA release pulses ($T_{\text{DA releaser}} = 44$ °C). The pathological state simulates age-related accumulation, shows severely compromised synaptic function with minimal conductance changes (ΔG = 0.01 mS) and ceased DA release ($T_{\text{DA releaser}} = 25$ °C), while DFP activation provides therapeutic

intervention ($T_{\text{DFP releaser}} = 44\text{ }^{\circ}\text{C}$). The recovered state demonstrates restoration of both synaptic plasticity and neurotransmitter release ($T_{\text{DFP releaser}} = 39\text{ }^{\circ}\text{C}$), confirming successful therapeutic efficacy.

In brief, this integrated system achieves complete sensing-computation-feedback functionality through chemical perception, and thermally-controlled molecular release, contributing to Fe^{3+} homeostasis

Validation of the connection of CR-NeuroHealer with neuron-like cells for homeostatic regulation

The CR-NeuroHealer operates as a biohybrid neuron that bridges artificial and biological neural components through bidirectional chemical-electrical transduction. Our NeuroHealer responds distinctively to both DA and Fe^{3+} , enabling real-time monitoring and intervention in neurodegenerative pathologies (Fig. 5a). To validate this, we established functional interfaces between CR-NeuroHealer and PC-12 dopaminergic cells by culturing neurons directly on the device electrodes. Optical and fluorescence microscopy confirmed successful cell adhesion and viability on both electrodes and synaptic channel regions, creating the physical foundation for biohybrid connections (Fig. 5b and c).

The CR-NeuroHealer demonstrates robust bidirectional communication with neuron-like cells through DA mediated signaling. When PC-12 cells were stimulated with 120 mM KCl, they released endogenous DA that was detected by the CR-NeuroHealer as time-dependent synaptic responses (Fig. 5d). Prior to KCl stimulation, the device exhibited only STP. However, within 30-90 minutes of incubation, responses transitioned to LTP with ΔG increasing from 0.85 to 1.99 mS after 25 pulses. This enhancement reflects increasing DA accumulation in the cell-device synaptic cleft, with both temporal dynamics (Fig. S19a) and quantitative analysis (Fig. S19b) confirming the successful neurotransmitter perception. The therapeutic drug release mechanism of CR-NeuroHealer exhibits pulse-dependent activation (Fig. 5e). Specifically, DA release is enhanced upon exceeding the threshold of 15 electrical pulses, with approximately 75 μM DA released after 25 pulses. Calcium imaging experiments confirmed bidirectional chemical communication between CR-NeuroHealer and neurons (Fig. 5f). When PC-12 cells were stimulated with 120 mM KCl following 1.5 h incubation, they released endogenous DA that was detected by the CR-Neurohealer. In response, CR-NeuroHealer released its own DA cargo, which activated the cells as evidenced by enhanced calcium fluorescence. This reciprocal signaling demonstrates that the device not only senses neurotransmitter levels but also provides appropriate chemical feedback to maintain synaptic function.

A pivotal characteristic of CR-NeuroHealer lies in its capacity to detect pathological iron accumulation and monitor cellular dysfunction. When PC-12 cells were exposed to Fe^{3+} (0-50 μM) for 12 hours, the cellular DA excretion ability was impaired. It was found that the conductance of device also exhibited Fe^{3+} concentration-dependent decreases in response (Fig. 5g). This reduced conductance translates to lower control voltages, preventing thermal activation of DA release, which further results in reduced cellular activation, as confirmed by calcium imaging showing diminished fluorescence intensity (Fig. 5h). Detailed characterization shows that the synaptic monitoring revealed progressive degradation of both ΔPSC amplitude (Fig. S20a) and ΔG (Fig. S20b) with increasing Fe^{3+} concentration. ΔG systematically

decreased from 4.01 to 1.18 mS as Fe^{3+} increased from 0 to 50 μM . Importantly, this neuromorphic sensing mechanism amplifies the distinction between healthy and pathological states through pulse dependent plasticity enhancement. With 5 pulses, the ΔG between healthy and 50 μM Fe^{3+} states is only 0.92 mS, but this difference increases to 2.83 mS after 25 pulses, demonstrating that activity dependent synaptic plasticity enhances state classification capability. This synaptic degradation directly correlates with cellular dysfunction, as visualized by calcium imaging showing decreased fluorescence (Fig. S20c) and quantified by CCK-8 viability assays demonstrating dose dependent toxicity from 85% (5 μM) to 69% viability (50 μM Fe^{3+}) (Fig. S20d).

To demonstrate autonomous therapeutic capability, we conducted a 24-hour protocol monitoring complete disease treatment cycles (Fig. 5i). The experimental timeline involved: (1) initial KCl stimulation establishing baseline DA release, (2) Fe^{3+} addition at 3 hours inducing pathological conditions, and (3) monitoring at 9 distinct time points throughout the 24-hour experiment to capture the complete progression from healthy through pathological to therapeutic states. The CR-NeuroHealer successfully tracked cellular deterioration and initiated therapeutic intervention (Fig. 5j, k and S21). Under normal conditions, ΔG is 3.12 mS (healthy state). Within 12 hours of iron exposure, ΔG progressively decreased to 1.74 mS (pathological state), triggering autonomous DFP release. By 24 hours, ΔG recovered to 3.03 mS (therapeutic state), demonstrating successful homeostatic restoration.

Multimodal assessments confirmed comprehensive cellular recovery. Calcium imaging revealed restoration of fluorescence intensity from minimal signals in Fe^{3+} exposed cells to robust activity following device mediated DFP treatment (Fig. 5j and l). Most significantly, patch-clamp recordings validated functional recovery at the single cell level (Fig. 5m and S22). Calcium currents, severely suppressed from 1600 pA (healthy) to 469 pA (pathological), recovered to near-baseline levels (~1400 pA) after therapeutic intervention. This electrophysiological restoration, coupled with morphological recovery, confirms that CR-NeuroHealer not only detects pathological states but effectively reverses cellular dysfunction through autonomous chemical intervention.

These results validate CR-NeuroHealer as the first neuromorphic system capable of forming functional biohybrid synapses that autonomously maintain cellular health. By integrating real-time chemical perception with therapeutic feedback, CR-NeuroHealer achieves closed-loop homeostatic regulation at the bio-electronic interface, opening new possibilities for treating neurodegenerative diseases through intelligent, self-regulating therapeutic systems.

***In vivo* validation of neuromorphic OECT devices as a chemical decision-making interface for Parkinsonian therapy**

To comprehensively validate the *in vivo* chemical sensing capability of the miniaturized neuromorphic OECT devices, we designed two complementary *in vivo* experiments to examine its responses to endogenous DA modulation and pathological iron accumulation, respectively (Fig. 6a). To enable precise implantation into the targeted brain regions, we miniaturized the device by reducing the channel length to

10 μm and the substrate width to 1.5 mm (Fig. 6b, c and Fig. S23). The miniaturized devices were stereotactically implanted into the DLS and SNc along the nigrostriatal dopaminergic pathway (Fig. 6a and b).

Before *in vivo* implantation, we evaluated the response of the miniaturized device under a DA-containing environment (40 mM Na^+ + 10 μM DA) with varying Fe^{2+} concentrations. The ΔG progressively decreased with increasing Fe^{2+} concentration (Fig. S24a to f). Specifically, as the Fe^{2+} concentration increased from 5 to 50 μM , ΔG decreased from 0.27 to 0.05 mS under 5 gate pulses and from 0.44 to 0.14 mS under 20 gate pulses. The increased signal contrast with accumulated gate pulses further demonstrates the ability of the miniaturized device to distinguish different iron states (Fig. S24g).

We next considered whether these device responses were relevant to the neurochemical changes associated with the 6-OHDA-induced Parkinsonian state^{35, 56}. Previous studies have consistently reported reduced dopaminergic activity together with increased iron accumulation following unilateral 6-OHDA lesioning^{57, 58}, which is consistent with the DA/iron-dependent response range of the device (Fig. S25). Rather than relying on reported quantitative values^{57, 59}, we experimentally verified these pathological changes in our own model. Unilateral 6-OHDA injection resulted in a pronounced loss of tyrosine hydroxylase (TH)-positive neurons in the ipsilateral nigrostriatal pathway (Fig. S25b and c), while inductively coupled plasma optical emission spectrometry (ICP-OES) analysis confirmed significantly elevated iron levels in the midbrain tissue (containing the SNc) (Fig. S25d). Consistent with these pathological changes, 6-OHDA-treated mice exhibited significant motor deficits in both open-field and rotarod tests compared with Saline controls (Fig. S26). Together, these histological, biochemical, and behavioral results confirmed the successful establishment of the Parkinsonian state used for subsequent device evaluation.

We then evaluated the feasibility and surgical impact of brain implantation. The miniaturized devices were stereotactically implanted into the targeted brain regions and connected to a head-mounted recording apparatus (Fig. 6b and Fig. S27a). Open-field locomotor activity showed no significant difference from the pre-implantation baseline (Fig. S26a) at day 3 post-surgery (Fig. S27b), while progressive wound healing was observed over the following four weeks (Fig. S27c). Histological analysis further confirmed electrode localization within the DLS and SNc, with preserved TH-positive neurons surrounding the implantation sites (Fig. 6d), supporting the feasibility of the implantation procedure.

We first examined whether the implanted neuromorphic OECT devices could respond to endogenous DA modulation *in vivo* (Fig. 6e to g). In this experiment, mice received saline injection into the medial forebrain bundle (MFB), followed by device implantation and AMPH administration (2.5 mg/kg, i.p.)⁶⁰ according to the timeline shown in Fig. 6e. AMPH treatment increased locomotor activity and rotarod performance (Fig. S26c), consistent with enhanced dopaminergic activity. Correspondingly, at 1.5 h after AMPH administration, the implanted devices exhibited significantly increased ΔPSC and ΔG in both the DLS and SNc compared with the saline condition ($P < 0.001$) (Fig. 6f and g). ΔG increased from 0.30 to approximately 0.36 mS in the DLS and from 0.21 to approximately 0.36 mS in the SNc. Representative

recordings from the same implanted region before and after AMPH administration further illustrate this DA-responsive change (Fig. S28). These results demonstrate that the miniaturized neuromorphic OECT devices can detect changes associated with endogenous dopaminergic modulation in the living brain.

We next examined the device response to the pathological state induced by unilateral 6-OHDA lesioning (Fig. 6h to j). The 6-OHDA-lesioned hemisphere and the contralateral saline-treated hemisphere provided pathological and internal control conditions, respectively. Device recordings showed a pronounced attenuation of synaptic-like responses in both the DLS and SNc of the lesioned hemisphere. ΔG decreased from 0.16 to approximately 0.03 mS in the DLS and from 0.14 to approximately 0.03 mS in the SNc ($P < 0.001$) (Fig. 6i and j), consistent with the pathological dopaminergic and iron alterations established above. Representative ΔPSC recordings further confirmed the attenuated device response in the 6-OHDA-lesioned hemisphere relative to the contralateral control (Fig. S29).

Having established that the implanted devices could distinguish the 6-OHDA-induced pathological state, we further investigated whether therapeutic iron chelation could reverse this altered device response. Based on the DFP-mediated iron-chelation and recovery mechanism⁶¹ established in the preceding *in vitro* studies, DFP was administered systemically for 5 consecutive days (20 mg/kg, i.p.) following detection of the pathological state. Device recordings before treatment confirmed a marked reduction in ΔG in the lesioned hemisphere, from 0.49 to 0.21 mS in the DLS and from 0.48 to 0.10 mS in the SNc ($P < 0.05$) (Fig. S30).

Following DFP treatment and a 1-week recovery period, the mice showed significant improvements in locomotor activity and motor coordination compared with the untreated 6-OHDA condition (Fig. S31). We then re-evaluated the device responses in the same targeted brain regions. ΔG recovered to 0.44 mS in the DLS and 0.43 mS in the SNc (Fig. 6k and l), representing a significant recovery from the 6-OHDA-induced pathological state ($P < 0.01$) and approaching the corresponding Saline control levels. Although absolute baseline ΔG values varied among animals, likely because of inter-animal variability, the relative response changes within each experiment were consistent and pronounced. Representative ΔPSC recordings similarly showed recovery of the previously attenuated synaptic-like responses following DFP treatment (Fig. S30). Together, these results demonstrate that DFP-mediated iron chelation reverses the 6-OHDA-associated pathological state and restores the chemical responsiveness of the implanted devices *in vivo*. The correspondence between disease-associated neurochemical alterations and device responses (Fig. S32) further supports the ability of the devices to distinguish healthy and pathological chemical states through pulse-dependent ΔG modulation.

Conclusion

In this work, we have developed a CR-NeuroHealer that addresses the critical challenge in maintaining iron–dopamine homeostasis. In healthy conditions, the system operates as an artificial dopaminergic synapse, exhibiting LTP and maintaining neural communication through DA release. Upon detecting pathological iron accumulation, Fe^{3+} binding alters its synaptic properties, triggering a state transition

that activates therapeutic DFP release while suppressing DA output. The CR-NeuroHealer integrates sensing, computation, and therapeutic feedback modules. This closed-loop operation enables real-time homeostatic regulation in a cell-based biohybrid environment: the system autonomously detects and process iron overload, and releases DFP at therapeutic concentrations (0.4–1.3 mM) to maintain physiological balance.

Validation in PC-12 neuronal models confirmed that CR-NeuroHealer forms functional biohybrid synapses with living cells. The system not only detected endogenous DA release from neurons but also reversed Fe^{3+} -induced cellular dysfunction through autonomous device-triggered therapeutic intervention at the single-cell level, as corroborated by the near-complete restoration of calcium channel function in patch-clamp recordings.

Building on this, we evaluated the *in vivo* chemical sensing capability of the miniaturized neuromorphic OECT devices in a 6-OHDA induced PD mouse model. The system successfully generated decision-making signals in response to two complementary chemical cues: endogenous DA modulation and pathological iron accumulation. *In vivo* device response revealed that severely attenuated ΔPSC and ΔG signals in the 6-OHDA-lesioned brains were effectively distinguished from healthy controls. Guided by the device's signal output, the administration of DFP *in vivo* was associated with significant recovery of spontaneous locomotion and motor coordination, corroborating the device's ability to detect and guide therapeutic intervention.

Despite these promising results, several challenges remain for clinical translation. Long-term biocompatibility, channel stability upon chronic implantation, and precise DFP release kinetics in the complex *in vivo* environment require further optimization. Future iterations could integrate wireless power/data transmission and automated on-demand therapeutic release modules to fully realize autonomous closed-loop operation in clinical settings. Overall, this work establishes a generalizable design principle for neuromorphic bioelectronics—from passive signal processing to active chemical intervention. By integrating sensing, computation, and therapeutic decision-making in a system that responds to molecular inputs rather than electrical programming, the CR-NeuroHealer opens new possibilities for adaptive bioelectronic therapeutics that can potentially guide the treatment of neurodegenerative diseases.

Declarations

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Author contributions

M.W., T.W., and L.W. (Lianhui Wang) conceived the project; S. P., Q.X., H.Z., W.H., and R.Z. developed the methodology; Z. C., G.S., F.Z., L.X., and Z.T. conducted the investigation; T.L., X.Z., L.G., and L.W. (Lixing Weng) contributed to visualization; M.W., T.W., and L.W. (Lianhui Wang) supervised the study; S.P., M.W., and T.W. wrote the original draft; and J.J., M.W., T.W., and L.W. (Lianhui Wang) reviewed and edited the manuscript.

Data and materials availability:

All data, code, and materials used in the manuscript are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare no competing interests.

Methods

Synthesis of PCM-NPs

To control the melting point at 39 °C, lauric acid and stearic acid were mixed at a 4:1 ratio to form the oil phase, while lecithin and PEG-2000 were combined at a 3:1 ratio to form the aqueous phase. The oil phase and aqueous phase were mixed at a 1:5 ratio and separately combined with a 1:75 v/v, 10 mM solution of DA and DFP under ultrasonic stirring (Detailed in Supplementary Note 3). The mixture was then filtered under vacuum and freeze-dried to form nanoparticles.

Preparation of CR-NeuroHealer

A device pattern was fabricated by depositing 3 nm Cr/50 nm gold (Au) onto a 0.125 mm double-sided pre-coated PET substrate using mask-assisted electron beam evaporation (Detailed in Fig. S1). The channel length-to-width ratio (L/W) was defined as 150 μm /2000 μm , and the resistance length-to-width ratio was set to 6.5/1. PEDOT:PSS ink (BASE-CD01, Shanghai Mifang Technology Co., Ltd.) was patterned into the channel via a 60 μm dispensing printing process, with an injection pressure of 10 kPa. Subsequently, the device was placed on a hotplate at 130 °C and annealed for 15 minutes. The encapsulation layer was patterned using photolithography. A mixture of PDMS (base agent to curing agent ratio of 10:1) was spin-coated at 500 rpm for 60 seconds, followed by 3000 rpm for 30 seconds. The device was then annealed at 80 °C for 12 hours. After curing, it underwent oxygen plasma treatment for 2 minutes.

Electrical characterization of the device

Transistor performance and synaptic properties were characterized using a dual-channel probe testing system equipped with a pulse generator (Model 2616b, Keithley). The sampling interval for measurements was set to 10 ms.

Time-resolved UV-vis spectra characterization

A probe station coupled with a Time-resolved UV-vis spectrophotometer was used for characterization. The absorption of the thin film was monitored in transmission/reflection mode using a spectrophotometer (OCEAN-HDX-UV-VIS, Ocean Insight, America). The spectrophotometer was controlled by Ocean view software. The sample was fabricated on an Indium Tin Oxide (ITO)/PEDOT:PSS-coated glass substrate with a gold thickness of 50 nm. An Au wire was used as the working electrode, and the ITO substrate was grounded. A halogen white light source was employed. Reflection spectra were fitted and analyzed in real-time using the Ocean view software.

XPS characterization

XPS spectra of the thin films after 60 s of potential doping were acquired using a Shimadzu AXIS-Supra instrument equipped with a monochromated Al K α X-ray source (spot size $\sim$ 500 μ m). The PEDOT:PSS thin film samples for XPS analysis were prepared by cutting out the channel region of the device.

Electrochemical testing

Cyclic voltammetry was performed using a CHI760 electrochemical workstation. For the CV measurements, a Au electrode served as the working electrode, an Ag/AgCl (saturated KCl) electrode as the reference electrode, and a Pt wire as the counter electrode. For channel testing, a PEDOT:PSS thin film was spin-coated onto a gold-coated PET substrate. The working electrode was connected to the bottom gold layer, while the reference and counter electrodes were placed in a PDMS chamber on top of the substrate. The electrolyte consisted of a mixture of DA and iron ions in phosphate buffered saline (PBS) solution.

Electrical measurements of the integrated CR-NeuroHealer neuromorphic system

Electrical measurements on the integrated CR-NeuroHealer neuromorphic system were conducted with a test board comprising an OECT and two release electrodes on the PET substrate, along with the necessary peripheral circuits, interconnected by a 1.0 mm pitch FPC cable. The peripheral circuits mainly consisted of a microcontroller unit (MCU), a digital-to-analog converter-DAC 8563, an analog-to-digital converter-ADC7606, and a TIA. The TIA was used to convert the drain currents to voltages with a gain of 800. The microcontroller unit used in our experiment was an STM32, which was responsible for reading voltage signals from TIA through the ADC. Subsequently, based on the signal received at the 33.5 s after the gate pulse onset, the microcontroller unit performs a linear mapping and subtraction to generate two voltages (V_1 and V_2 to release electrodes-DA and DFP heater, respectively) through the DAC and set both

V_1 and V_2 to 0 V after 60 s. A user interface was coded in Python to load, process, and save the data, and display the drain current results.

PC-12 cell culture

PC-12 cells (purchased from ATCC) were cultured in high-glucose DMEM medium supplemented with 10% fetal bovine serum FBS in a humidified atmosphere with 5% CO₂ at 37 °C. The medium was replaced every day throughout the lifetime of all cultures.

Characterization of the functionality of PC-12 cells by calcium imaging

Calcium signal changes were used to assess the functionality of PC-12 cells before and after treatment with CR-NeuroHealer under pathological iron accumulation conditions. PC-12 cells pre-incubated with different iron concentrations for 24 hours were loaded with 2 μM Fluo-4 AM probe (40704ES, YEASON, China) for 30 minutes at 37 °C in a 5% CO₂-95% O₂ atmosphere. The probe solution was then removed, and dishes were washed with Hanks' solution three times before calcium imaging of cells under 100 μM DA stimulation using laser scanning confocal microscopy. Similarly, for treatment validation, iron-poisoned PC-12 cells were incubated with DFP solution released by CR-NeuroHealer for 6 hours and subsequently imaged under 100 μM DA stimulation.

6-OHDA-induced Parkinsonian model and behavioral assessments

Adult male and female C57BL/6J mice (18-20 g, 8-12 weeks) underwent stereotaxic surgery for unilateral injection of 6-OHDA (4 μg/μl, 1 μl) into the MFB at the coordinates AP -1.2 mm, ML -1.3 mm (ipsilateral) and +1.3 mm (contralateral Saline control), DV -4.75 mm. For behavioral assessments, locomotor activity was evaluated using the open-field test (10 min recording) and motor coordination via the rotarod test (accelerating from 5 to 45 rpm over 5 min, three trials per mouse, averaged from the two best attempts). AMPH-treated groups were tested at 2 hours post-injection, while 6-OHDA groups were evaluated at 2 weeks post-lesioning (Detailed in Supplementary Note 4). All the animal experiments were conducted with approval and guidance by Animal Ethics Committee of Aniphe Biolaboratory Inc. (Nanjing, China), and the approved number is IACUC-JSAB25012M (Approved on August 7, 2025).

***In vivo* device-guided DFP intervention in 6-OHDA-lesioned mice**

Unilateral 6-OHDA lesions were induced in the MFB as described above. At day 2 post-6-OHDA lesioning (i.e., 48 hours after injection), the synaptic OECT devices were surgically implanted into the SNc and the DLS for *in vivo* testing. After confirming the baseline pathological signal, DFP (Sigma-Aldrich) was freshly dissolved in 0.9% sterile saline and administered via i.p. injection at a dose of 20 mg/kg body weight. The DFP treatment was initiated on the same day as the first device implantation (day 2 post-lesion) and continued once daily for 5 consecutive days. The control group received equivalent volumes of 0.9% sterile saline via the same i.p. injection schedule. Following the 5-day DFP treatment and a subsequent 1-week recovery period, the devices were re-implanted into the same brain regions on day 14 post-lesion

(i.e., day 21 of the experimental timeline in Fig. 6h to assess the device response. All behavioral tests and device response recordings were conducted at the designated endpoints to evaluate the therapeutic restoration.

Fabrication of the miniaturized synaptic OECT devices

Miniaturized OECTs were fabricated on a 2-inch Si/SiO₂ substrate. Source, drain, and gate electrodes were defined by electron-beam lithography and electron-beam evaporation of Cr/Au, followed by a standard lift-off process. The channel region was patterned with a length of 10 μm and a width of 100 μm, and PEDOT:PSS was spin-coated and patterned onto the channel area as the active sensing layer (Detailed in Fig. S23). Individual devices were diced into strips of 1.5 mm × 17 mm, and electrical connections to the electrode pads were established via wire bonding for subsequent *in vivo* (or *in vitro*) testing.

***In vivo* device response of the implanted synaptic OECT**

The miniaturized flexible synaptic OECT arrays were stereotactically implanted bilaterally into the targeted brain regions according to the following coordinates relative to bregma (in mm). For the DLS, the ipsilateral (lesioned/injected side) coordinate was AP +0.5, ML -2.5, DV -2.0; and the contralateral (healthy/saline-injected side) coordinate was AP +0.5, ML +2.5, DV -2.0. For the SNc, the ipsilateral coordinate was AP -3.14, ML -1.42, DV -4.0; and the contralateral coordinate was AP -3.14, ML +1.42, DV -4.0. Prior to the *in vivo* device characterization, a 100 s baseline calibration was performed for each implanted device. During the baseline calibration, the source-drain voltage (V_D) was set to -0.1 V, while the gate voltage (V_G) was maintained at 0 V. After the baseline signal stabilized, a train of 5 continuous gate voltage pulses (0.7 V, 550 ms width, and 100 ms inter-pulse interval) was applied. The I_D was continuously recorded up to 220 s to capture the complete synaptic-like response dynamics.

Immunohistochemistry and TH immunofluorescence staining

Mice were deeply anesthetized and transcardially perfused with ice-cold phosphate PBS followed by 4% paraformaldehyde (PFA). Brains were post-fixed in 4% PFA, equilibrated in 30% sucrose, and rapidly frozen. Coronal slices of the striatum and SNc (30 μm thickness) were obtained using a cryostat. For immunofluorescence staining, frozen sections were subjected to heat-mediated antigen retrieval and then blocked with 3% bovine serum albumin at room temperature. The sections were incubated overnight at 4 °C with rabbit anti-TH primary antibody (dilution 1:500), followed by Alexa Fluor 488-conjugated secondary antibody for 50 min at room temperature in the dark. Cell nuclei were counterstained with 4,6-diamidino-2-phenylindole (DAPI). Finally, the sections were mounted with an antifade mounting medium and imaged using a digital tissue slide scanner (Detailed in Supplementary Note 4).

Measurement of midbrain iron concentration by ICP-OES

To quantify the iron concentration in the midbrain tissue (containing the SNc), approximately 200 mg of the dissected bilateral midbrain sample was collected and homogenized with 0.5 mL of 2 N hydrochloric acid using an ultrasonic homogenizer (Misonix Sonicator). The homogenate was subsequently mixed with 1 mL of 70% nitric acid (HNO_3) and 0.3 mL of hydrogen peroxide, followed by ultrasonication at 60 °C for 1 hour. The mixture was then further digested at 200 °C for 30 minutes using a graphene-assisted ultrasonic digestion apparatus. After the digestion process, the solution was cooled to room temperature and volumetrically adjusted to 5 mL with 5% dilute HNO_3 . The resulting supernatant was filtered through a 0.45 μm membrane filter prior to analysis. For calibration, a 1000 ppm iron standard solution was diluted with 5% dilute HNO_3 to prepare a series of standard solutions at concentrations of 0.1, 0.5, 1, 2, and 5 ppm to establish the standard curve. The iron concentration was analyzed using a ICP-OES (SPECTRO BLUE SOP) system, with the emission wavelength set at 259.94 nm.

Statistical analysis

All data are presented as means $\pm$ standard error of the mean (SEM). For comparisons between two independent groups, statistical significance was assessed using two-tailed unpaired Student's t-test. For comparisons among three or more groups, one-way analysis of variance (ANOVA) was applied, followed by appropriate post hoc tests (e.g., Bonferroni or Tukey's multiple comparisons test). A P-value of less than 0.05 was considered statistically significant ($*P < 0.05$, $**P < 0.01$, $***P < 0.001$). Non-significant differences are denoted as "n.s." Sample sizes (n) for each experiment are specified in the corresponding figure captions.

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Figures

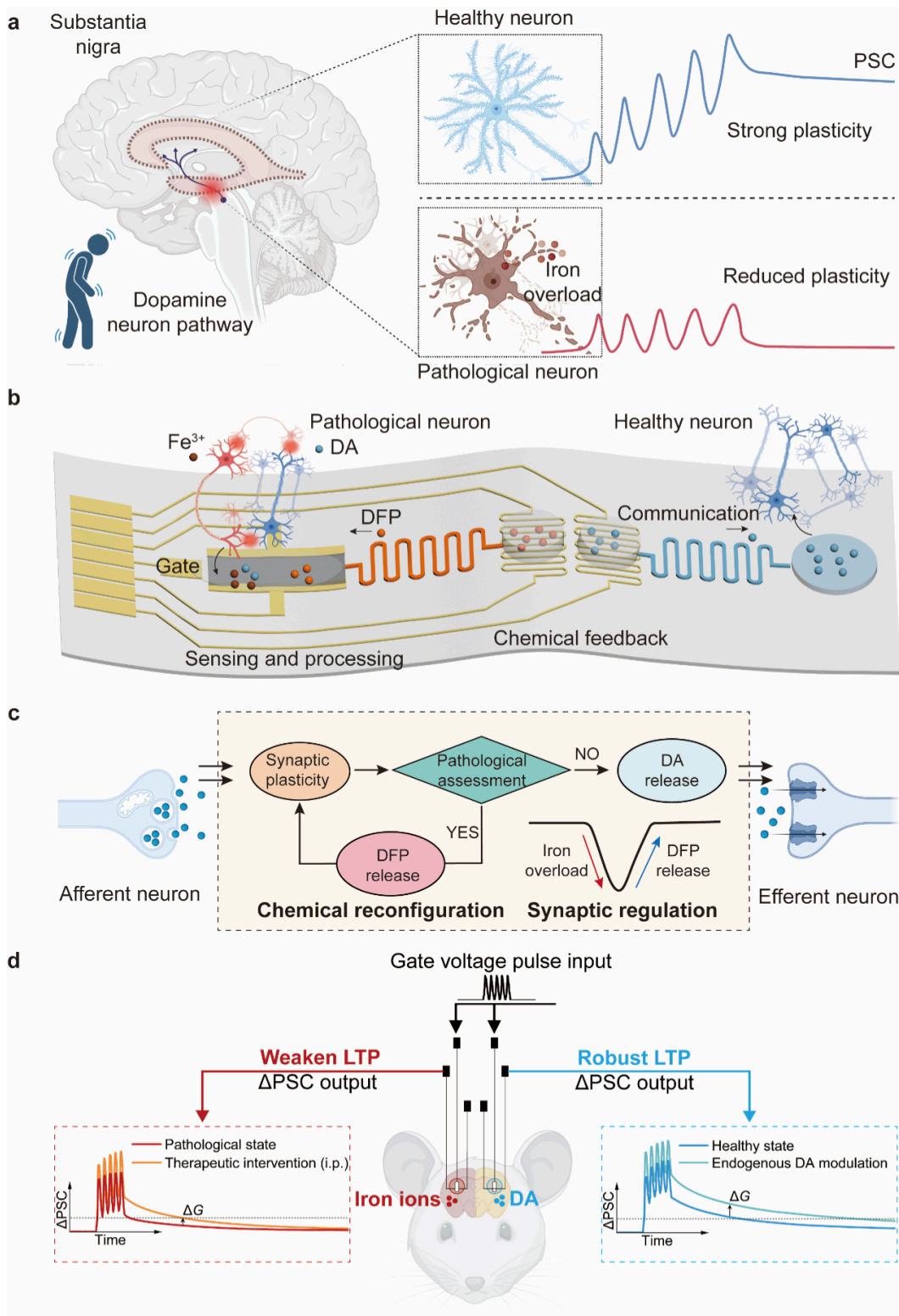


Figure 1

Schematic of CR-NeuroHealer. **a**, Neurodegeneration induced by iron overload in dopaminergic neurons, along with the degeneration of synaptic plasticity. **b**, Schematic illustrations of two interactive state modes between CR-NeuroHealer and biological neurons. CR-NeuroHealer *in-situ* perceives Fe^{3+} or DA signals in the form of weights, judges the pathological state based on the threshold, and feedback, maintaining neuronal iron homeostasis by releasing DFP. **c**, System operation block diagram showing

integrated sensing, synaptic weight computation, and adaptive molecular release. The Δ PSC characteristics generated by DA and Fe^{3+} inputs are transduced into synaptic weights that determine the release pathway. Based on weight thresholds, the system activates either DA release to maintain postsynaptic communication in healthy states, or DFP release to provide therapeutic feedback in iron overload conditions. **d**, *In vivo* bilateral sensing and processing by the CR-NeuroHealer. The device monitors the contralateral healthy and ipsilateral 6-OHDA-lesioned regions through Δ PSC responses. Endogenous DA enhancement by AMPH induces robust LTP in the healthy state, whereas iron overload produces weakened LTP in the pathological state. DFP-mediated iron chelation restores the weakened LTP toward the healthy level, demonstrating device-level discrimination of pathological states and guidance of therapeutic intervention.

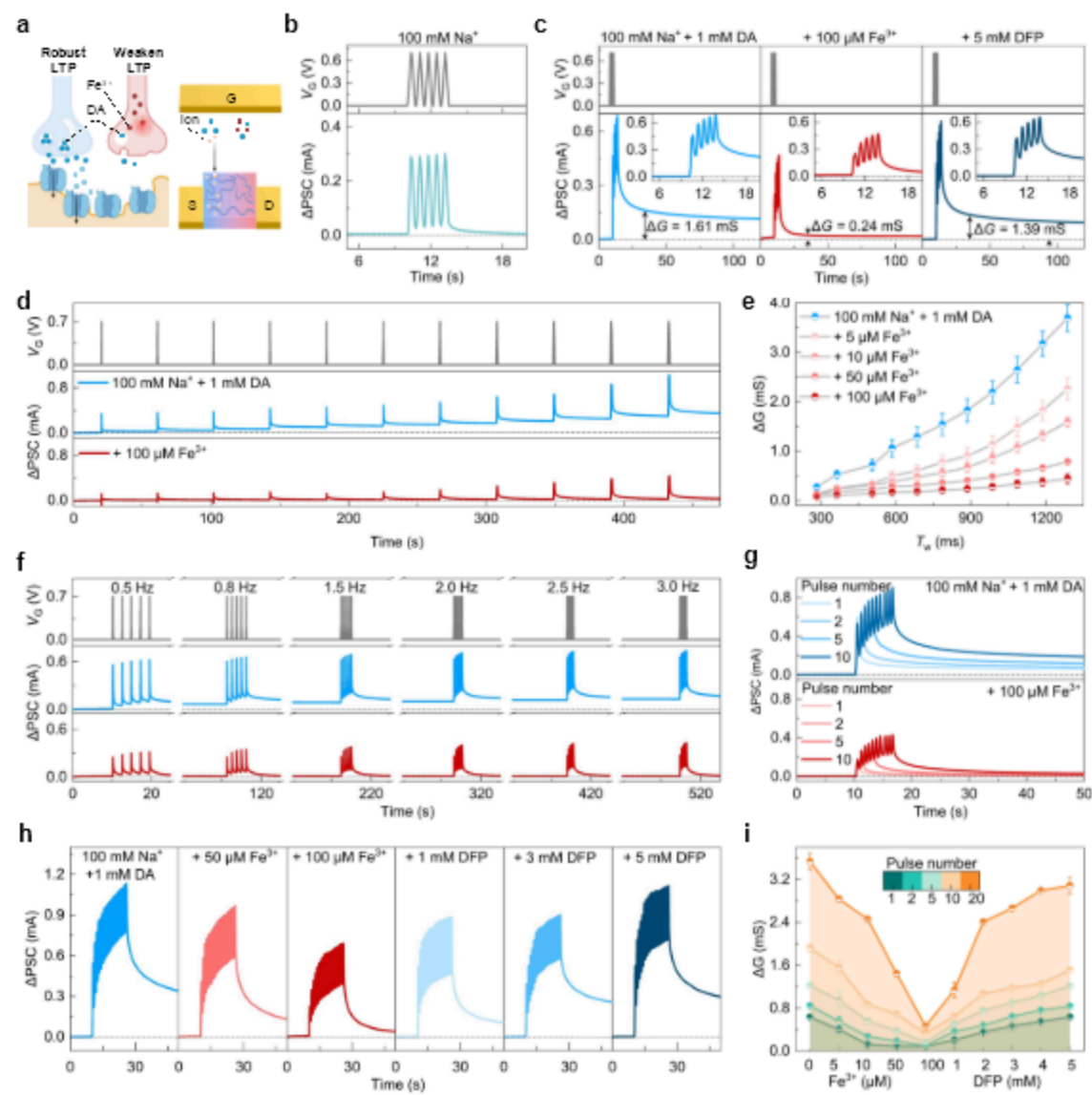


Figure 2

Electrical characteristics and reconfigurable properties of CR-NeuroHealer. **a**, In the process of DA release in biological synapses under normal and iron overloaded neurodegenerative conditions, as well

as in the chemical mediated robust LTP and weakened LTP synaptic plasticity, the neuromorphic transistor demonstrates biomimetic synaptic plasticity of normal (DA mediated robust LTP) and iron overloaded biological synapses (weakened LTP). **b**, The biomimetic STP characteristics of neuromorphic transistor in a 100 mM Na⁺ gate liquid electrolyte. **c**, Δ PSC and Δ G of the postsynaptic terminal. The presynaptic stimulations (V_G) consist of five consecutive 0.7 V pulses with 550 ms width and 100 ms inter-pulse interval. The CR-NeuroHealer exhibits large Δ PSC and plasticity variations. **d**, Duration-dependent responses (11 pulses with T_w incrementally increasing by 100 ms) demonstrate progressive enhancement with longer pulses in healthy state, suppressed by Fe³⁺. **e**, Quantitative analysis reveals linear Δ G duration (20 s after the end of the last pulse.) relationship degrading with Fe³⁺ concentration (0-100 μ M), providing a biomarker for iron overload severity. Error bars represent: mean $\pm$ standard deviation (SD) of Δ G across $n = 5$ devices. **f**, Frequency dependent synaptic responses (0.5-3.0 Hz, five 0.7 V pulses, $t_w = 550$ ms, $V_D = -0.1$ V) in three states: DA baseline (blue) exhibits robust Δ PSC and strong LTP; Fe³⁺ addition (red) reduces responses and converts to weakened LTP; DFP treatment restores function. **g**, Activity-dependent plasticity shows enhanced response with increasing pulse number (1-10, $t_w = 550$ ms) in healthy state, impaired by Fe³⁺. **h**, Concentration-dependent synaptic responses to 20 consecutive pulses (1.2 Hz, 0.7 V, $t_w = 550$ ms) demonstrate progressive plasticity degradation with increasing Fe³⁺ (5-100 μ M, red gradient) and dose-dependent recovery with DFP addition (1-5 mM, blue gradient). **i**, Quantitative surface plot mapping Δ G as a combined function of Fe³⁺ concentration (0-100 μ M, leftward axis), therapeutic DFP intervention (1-5 mM, rightward axis), and pulse number (1-20, color-coded gradient). The surface topology reveals: (1) Fe³⁺-induced depression creating a pathological valley at 50-100 μ M iron; (2) DFP-mediated recovery along the rightward trajectory restoring Δ G toward healthy baseline levels; (3) antagonistic dose-response relationships with Fe³⁺ suppressing and DFP enhancing synaptic plasticity across all pulse numbers. The valley-to-peak transition establishes the therapeutic intervention window where DFP administration automatically corrects iron-induced synaptic dysfunction (measured 20 s after the end of the last pulse). Error bars represent: mean $\pm$ SD of Δ G across $n = 5$ devices.

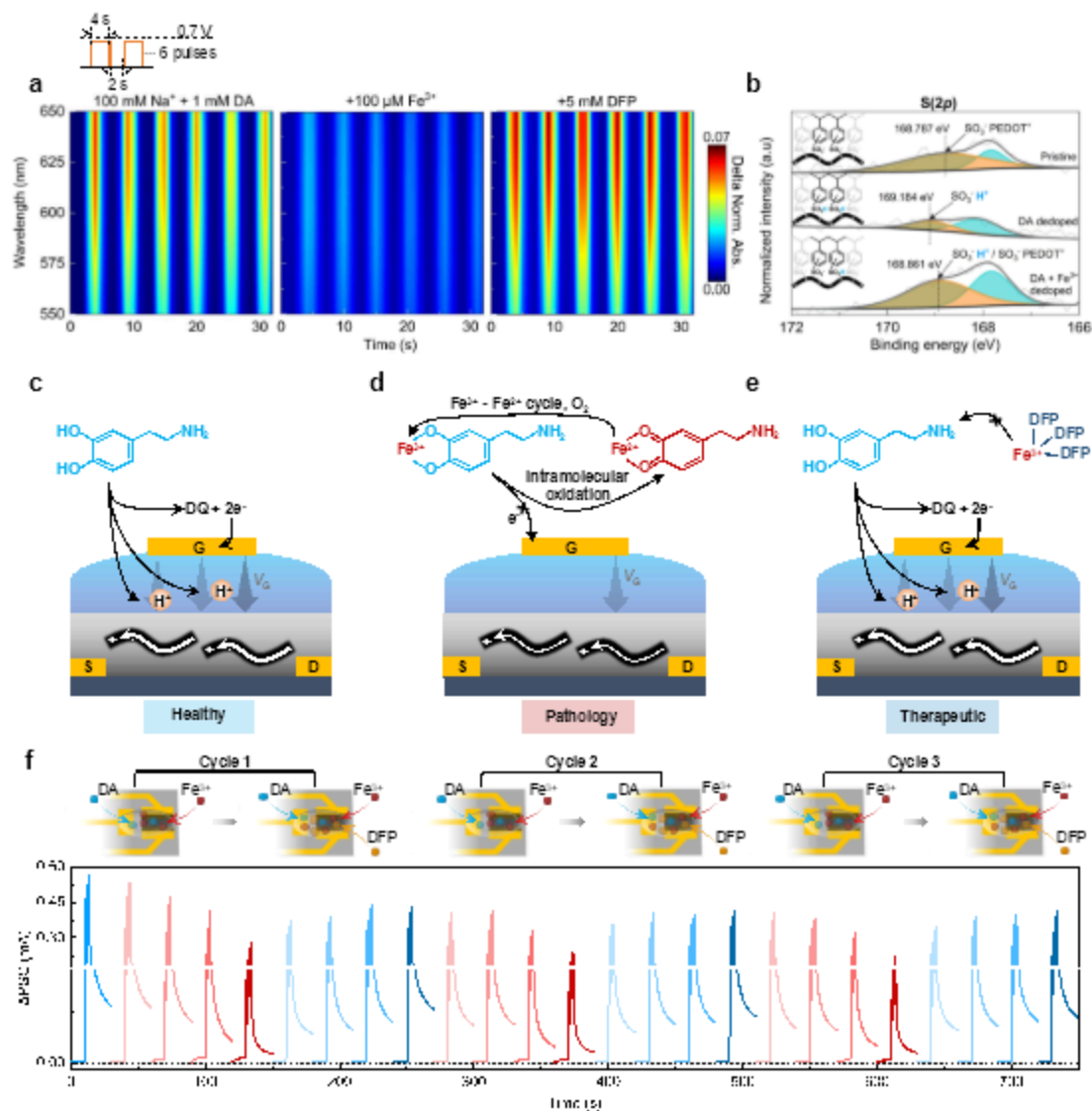


Figure 3

Molecular mechanisms and comprehensive characterization of chemical reconfiguration in CR-NeuroHealer. **a**, Time-resolved UV-vis spectroscopy (550-650 nm) during gate pulsing (six pulses, $t_w = 4$ s, 2 s interval, 0.7 V) shows PEDOT absorption changes correlating with doping states across three chemical conditions. **b**, XPS characterization of S(2p) binding energy following 60 s gate stimulation confirms electronic structure modulation: pristine PEDOT:PSS, dedoped state with DA, and Fe^{3+} induced doping changes. **c to e**, Schematic illustration of reconfiguration mechanism at the electrode-electrolyte interface. **c**, Healthy state: DA oxidation generates electrons and protons under gate voltage, with H^+ dedoping PSS^- groups to create sustained ΔG , the thick and thin white lines correspond to high and low doping levels, respectively. **d**, Pathological state: $[\text{Fe}(\text{DA})]^{2+}$ complexation facilitates electron transfer from DA through Fe^{3+} to dissolved oxygen, bypassing the PEDOT channel. This diverted electron pathway inhibits channel dedoping, resulting in diminished plasticity. **e**, Therapeutic state: DFP chelates Fe^{3+} , liberating DA to restore normal electrochemical oxidation and channel dedoping. **f**, Long term cycling stability demonstrated through three complete Fe^{3+} loading/DFP recovery cycles over 750 s, with

consistent synaptic response amplitudes confirming reversible chemical reconfiguration without degradation.

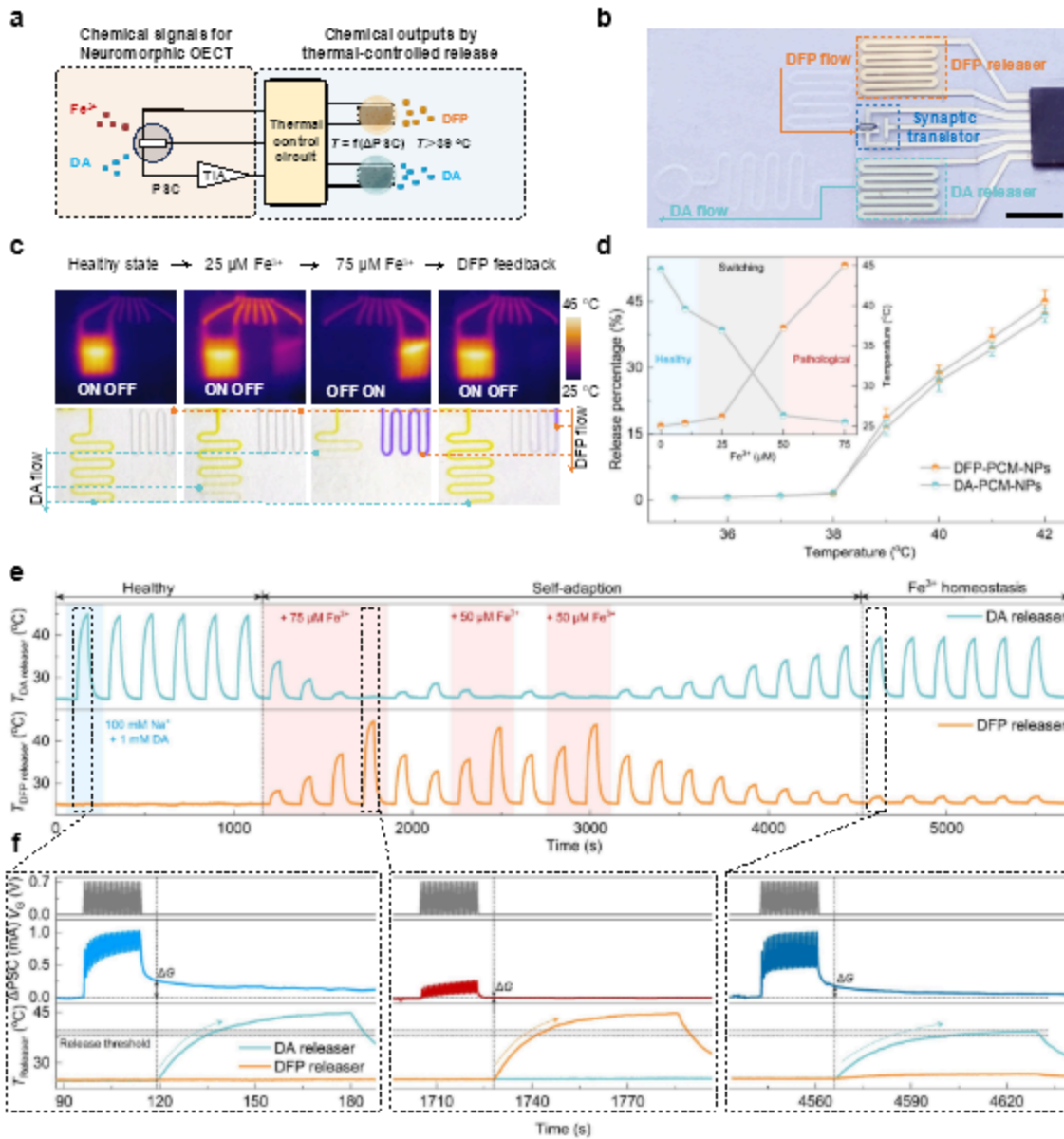


Figure 4

Integrated CR-NeuroHealer system demonstrates autonomous Fe³⁺-DA homeostatic regulation through closed loop chemical feedback. **a**, System architecture showing chemical signal processing through neuromorphic OECT with integrated thermal control circuit. Input signals (Fe³⁺ and DA) are processed via TIA to generate temperature modulation ($T = f(\Delta\text{PSC})$) that triggers drug release when $T > 39^{\circ}\text{C}$, enabling closed loop therapeutic delivery of DFP and DA. **b**, Fabricated microfluidic device photograph showing integrated components: DFP releaser (orange channel, top), central synaptic transistor, and DA releaser (cyan channel, bottom) with scale bar: 5 mm, indicating device dimensions. **c**, Thermal imaging sequence demonstrating state transitions across increasing Fe³⁺ concentrations (Healthy state baseline, then 25 to 75 μM Fe³⁺, followed by DFP feedback). Temperature maps (25-46 $^{\circ}\text{C}$

scale) show progression from healthy through pathological to therapeutic states. **d**, Temperature dependent drug release kinetics. Left inset: Concentration-dependent crossover behavior showing antagonistic control between healthy and pathological states ($0-75 \mu\text{M Fe}^{3+}$). Main panel: Thermal activation profiles ($36-42^\circ\text{C}$) for DFP-PCM-NPs and DA-PCM-NPs systems demonstrating sharp release threshold at 39°C , enabling precise therapeutic control, error bars represent: mean $\pm$ SD, $n = 5$ per sample. **e**, Extended operation over 6000 seconds demonstrating self-adaptive therapeutic response. Top trace: DA releaser (cyan) maintains regular pulsatile activity during healthy phase ($0-1160$ s), progressively attenuates during self-adaptation phase with incremental Fe^{3+} additions ($75, 50, 50 \mu\text{M}$), then recovers during Fe^{3+} homeostasis phase ($4525-6000$ s). Bottom trace: DFP releaser (orange) activates only during pathological iron accumulation ($1160-4525$ s), providing therapeutic iron chelation that enables system recovery. **f**, Detailed temporal analysis at three critical timepoints. Left ($90-180$ s): Healthy state with normal synaptic response, active DA release above threshold, and inactive DFP. Middle ($1700-1790$ s): Pathological state showing suppressed synaptic activity, ceased DA release, and activated DFP release. Right ($4530-4620$ s): Recovered therapeutic state demonstrating restored synaptic function and DA release following successful iron chelation intervention.

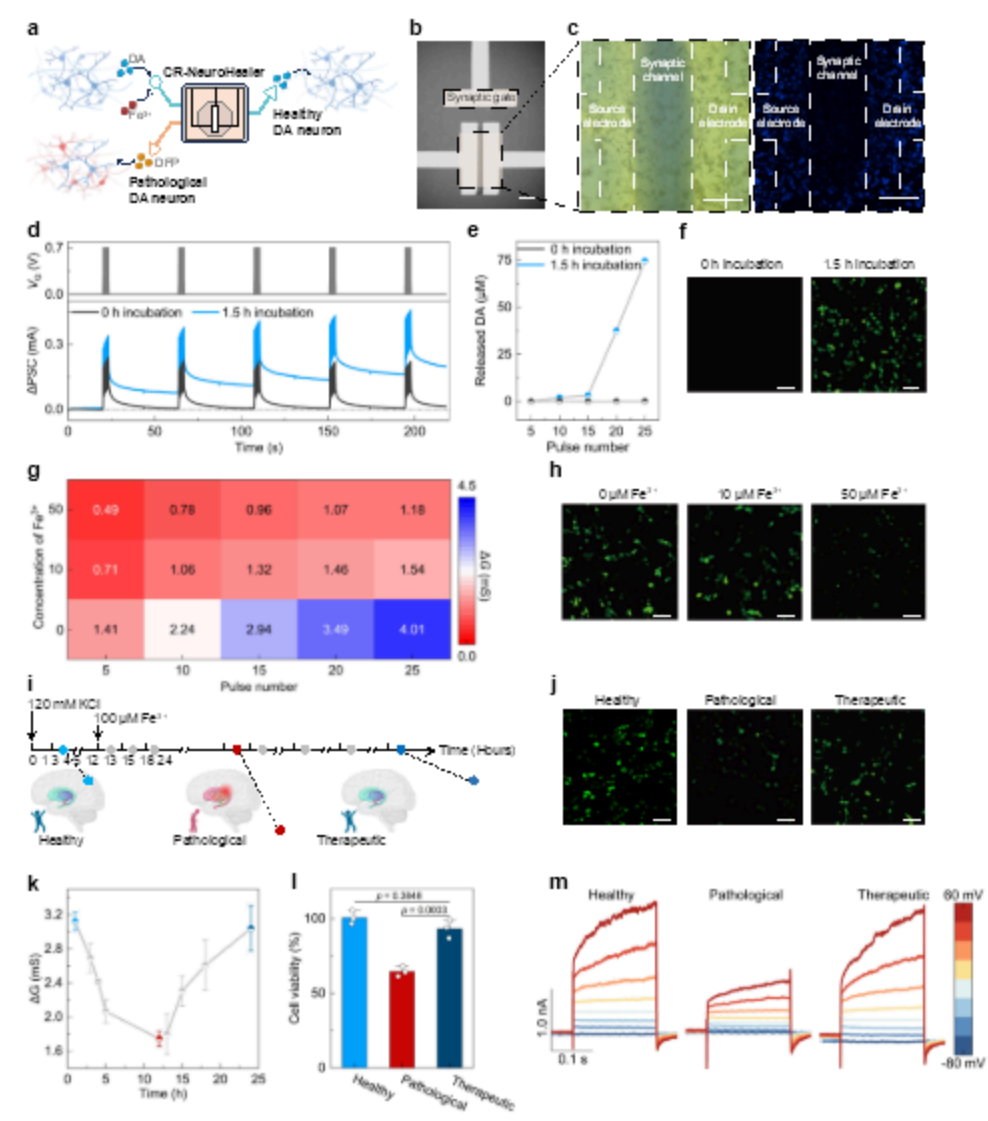


Figure 5

CR-NeuroHealer establishes functional biohybrid synapses with living neurons for autonomous homeostatic regulation.

a, Schematic of bidirectional communication between CR-NeuroHealer and dopaminergic neurons, showing healthy synaptic transmission versus disrupted signaling in PD. **b**, Device configuration with PC-12 cells cultured on electrodes for biohybrid synapse formation. Scale bar: 500 μm . **c**, Optical (left) and fluorescence (right) microscopy of PC-12 cells interfaced with source/drain electrodes. Scale bars: 500 μm . **d**, Time dependent enhancement of synaptic responses to KCl induced dopamine release, showing increased ΔPSC and sustained ΔG after 1.5 h incubation as cells establish stronger device coupling. **e**, Pulse number dependent DA release quantification showing exponential increase from 5 to 25 pulses, with significant release activation above 20 pulses (blue markers indicate active release, black markers indicate baseline). **f**, Bidirectional communication demonstrated through calcium imaging: KCl stimulation (120 mM) triggers cellular DA release detected by the device, which then releases DA to activate cells. Scale bars: 100 μm . **g**, Heat map quantifying Fe^{3+} co-incubation effects on synaptic function, revealing concentration-dependent (0-50 μM) and activity-dependent (5-25 pulses) plasticity degradation. **h**, Calcium imaging shows Fe^{3+} induced cellular dysfunction: normal fluorescence (0 μM), reduced signal (10 μM), and minimal activity (50 μM), Scale bars: 100 μm . **i**, Experimental timeline for inducing iron toxicity and therapeutic intervention over 24 h. **j**, Fluorescence images comparing neuromorphic responses in healthy (baseline DA response), pathological (Fe^{3+} -induced suppression), and therapeutic (DFP-restored) states, demonstrating functional recovery, scale bars: 100 μm . **k**, The ΔG trajectory along the timeline (**i**) reveals the CR-NeuroHealer's autonomous detection and correction of iron-induced pathology. The experiment encompasses two sequential phases: iron accumulation (0-12 hours) and therapeutic intervention (13-24 hours), demonstrating the integrated closed-loop feedback mechanism, error bars represent: mean $\pm$ SD, $n = 3$ per group. **l**, Quantitative assessment of PC-12 neuronal cell viability was performed across three biological states along the timeline (**i**): healthy baseline (1 h), iron overloaded condition exposed cells, (pathological, 12 h) and restored activity following device initiated DFP release (therapeutic, 24 h), error bars represent: mean $\pm$ SD, $n = 3$ per group. Statistical significance was determined by one-way ANOVA followed by Tukey's post hoc test. Exact P values are indicated in the figure. **m**, Patch clamp recordings validate functional recovery with calcium currents recovered from 0.569 nA (pathological) to 1.680 nA (therapeutic), confirming successful homeostatic intervention at single cell level.

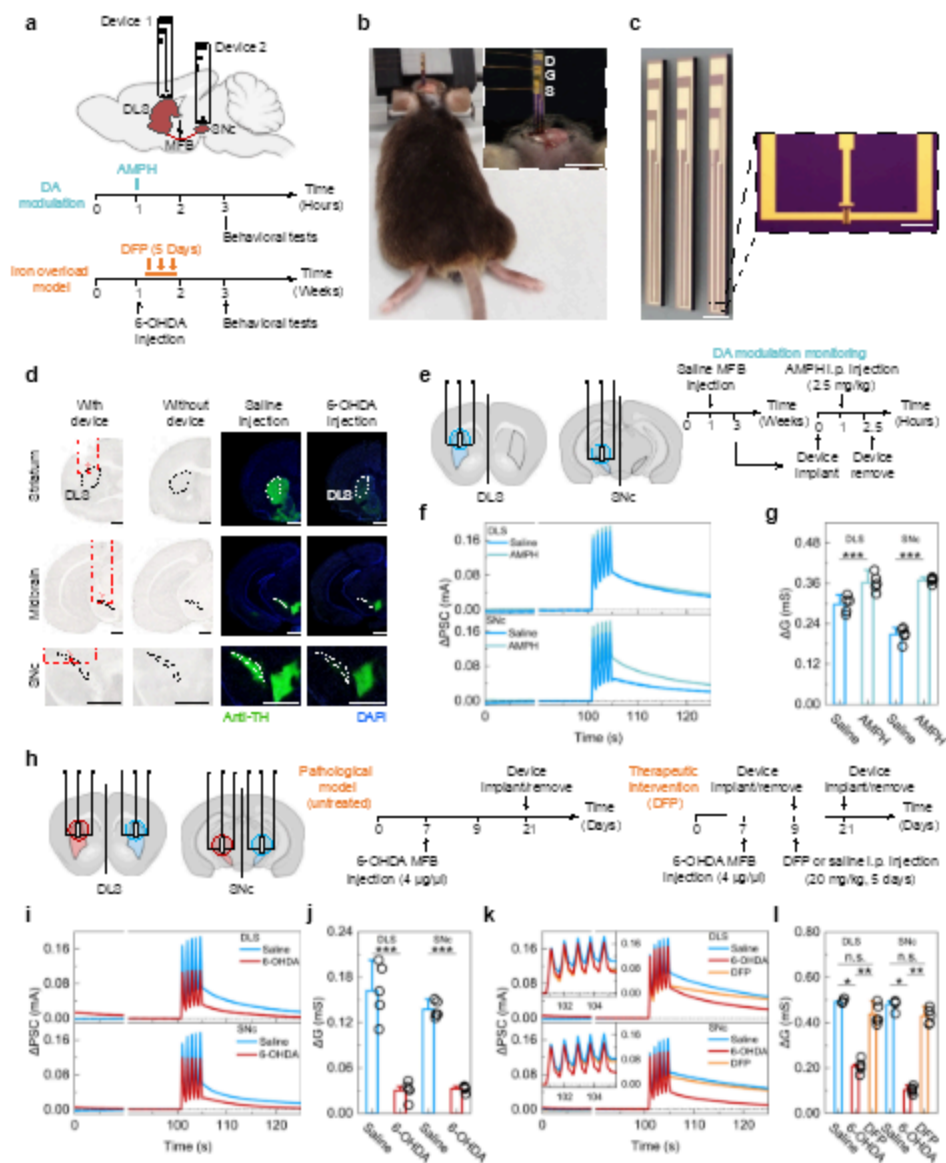


Figure 6

In vivo validation of neuromorphic OECT devices for chemical sensing in a Parkinsonian model. **a**, Top panel depicts the device implantation locations in the DLS and SNc along the dopaminergic nigrostriatal pathway, with the red arrow indicating the injection site in the MFB. Upper timeline: In the DA modulation paradigm, AMPH was administered i.p. at 1 hour, followed by behavioral assessments at 3 hours. Lower timeline: In the iron-overload model with therapeutic intervention, 6-OHDA was injected into the MFB at week 1. A 5-day DFP treatment regimen was administered during weeks 1-2, with behavioral tests performed at week 3. **b**, Photograph of the head-mounted device with chronically implanted microelectrodes. Inset: magnified electrode connector (D: drain, G: gate, S: source). Scale bar: 5 mm. **c**, Optical microelectrodes with the inset showing the magnified active recording sites. Scale bars: 2 mm and 200 μ m. **d**, Representative histological verification of electrode placement and 6-OHDA induced dopaminergic degeneration. Left: bright-field coronal sections of the ipsilateral hemisphere showing the precise stereotaxic implantation of the microelectrode arrays within the targeted DLS and SNc, compared with the non-implanted side. Right: TH/DAPI immunofluorescence images showing intact TH-

positive neurons in the Saline control group and severe unilateral TH depletion in the 6-OHDA model group. Scale bars: 1 mm. **e**, Experimental timeline and schematic of the AMPH-induced DA modulation paradigm with bilateral device implantation. **f and g**, Representative Δ PSC traces (**f**) and quantitative Δ Gcomparison (**g**) in the DLS and SNc for the DA modulation paradigm. (**h**) Experimental timeline and schematic of the 6-OHDA lesion model without and with DFP therapeutic intervention. **i and j**, Representative Δ PSC traces (**i**) and quantitative Δ G comparison (**j**) for the untreated pathological model. **k and l**, Representative Δ PSC traces (**k**) and quantitative Δ Gcomparison (**l**) demonstrating the restorative effect of DFP therapeutic intervention. Data are presented as means $\pm$ SEM ($n = 5$ independent recordings per group for **f, g, i, j, k, and l**). Statistical significance was determined by one-way ANOVA with post hoc tests ($*P < 0.05$, $**P < 0.01$, $***P < 0.001$; n.s., not significant).

Supplementary Files

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