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Review

Large-scale, closed-loop interrogation of neural circuits underlying cognition

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Cognitive functions are increasingly understood to involve coordinated activity patterns between multiple brain regions, and their disruption by neuropsychiatric disorders is similarly complex. Closed-loop neurostimulation can directly modulate neural signals with temporal and spatial precision. How to leverage such an approach to effectively identify and target distributed neural networks implicated in mediating cognition remains unclear. We review current conceptual and technical advances in this area, proposing that devices that enable large-scale acquisition, integrated processing, and multiregion, arbitrary waveform stimulation will be critical for mechanistically driven manipulation of cognitive processes in physiological and pathological brain networks.

Highlights

Cognitive processes require coordinated communication between multiple brain regions. Physiological activity patterns governing such interactions may represent an effective focus for manipulating these processes.

The diversity of network disruptions that occur in patients with neuropsychiatric disorders remains incompletely characterized and may necessitate personalized therapeutic approaches.

Neural interface devices that enable large-scale acquisition and multiregion, arbitrary waveform stimulation will be critical to test hypotheses about mechanisms of cognition.

Advances in materials science and engineering increase the information that can be derived from neural interface devices without increasing potential for implantation-related morbidity.

Concurrent advances in architecture for signal processing, data communication, and power management are necessary to permit real-world implementation of closed-loop devices in both animal models and human subjects.

Approaches to neural network modulation

The healthy brain and environment form a closed-loop system that integrates perception and action to enable adaptive behavior. Neural networks responsible for this computational coupling must respond efficiently to changing external stimuli and an organism's dynamic goals. Therefore, the response of neural networks is strongly dependent upon the timing of incoming signals relative to the organism's state, previous experiences, and ongoing information processing. Although highly simplified responsive behaviors can be mediated by a network composed of a sensory neuron, a motor neuron, and the synapse between them, cognitive functions are increasingly appreciated to require cooperative activity of distributed regions.

Attempts to interact with these networks, with the goal of probing their underlying mechanisms or changing their operation, are often performed in an 'open-loop' fashion that does not take these pre-existing spatial and temporal dynamics of the system into account. Although such approaches have led to advances, substantial challenges have arisen due to poorly understood intra- and inter-individual variability and modest effect sizes. Transitioning to 'closed-loop' approaches, whereby a stimulus is delivered to the network only upon detection of a specific brain signal, can increase temporal precision and enhance understanding of the underlying causal relationships. However, questions regarding which signals to use, and from which brain regions, typically remain. We posit that for closed-loop interventions targeting cognitive and affective functions to be maximally interpretable and effective, they should additionally take into consideration the spatial features of the involved networks. Such an approach could require distributed monitoring of brain activity, real-time decision-making based on multiregional signal integration, and capacity for tunable spatially targeted stimulation.

In this review, we investigate the conceptual and technological foundation for large-scale closed-loop modulation of higher-order brain functions. We begin with examining the physiological basis of network-based computations required for these functions, focusing on signals that indicate functional communication between regions and could be amenable to directed manipulation. We then discuss the dysregulation of these signals that occurs in neuropsychiatric disorders

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and identify opportunities for intervention, comparing such strategies with those currently employed for clinical therapeutics. The guiding principles for design of devices capable of performing this closed-loop modulation are proposed, from sensors to analytics, based on current and emerging technologies. We concentrate on electrical signals and stimulation, but the approach is likely to apply to other modalities capable of detecting cognitive biomarkers and affecting neural network activity.

Edges and nodes of neural networks of cognition

Investigation into the anatomical substrates of cognition was initially framed by lesion studies in human subjects or animal models, wherein loss of a constellation of brain regions was correlated with a pattern of deficits [1]. The importance of coordination across brain areas for the emergence of these complex processes has been highlighted by functional electrophysiology and neuroimaging [2,3]. Such approaches propose to identify mutual participation of multiple regional 'nodes' during cognitive tasks, joined by anatomical 'edges' representing synaptic connectivity [4,5]. Although methods to define these networks in a consistent manner across investigational modalities remain challenging, the necessity of communication between multiple brain regions for execution of cognitive functions is clear.

The cellular and synaptic mechanisms that underlie functional network operation are proposed based on the notion that creating windows of excitability facilitates communication between brain regions despite anatomic segregation [6]. At the level of individual synapses, the correlation of presynaptic and postsynaptic potentials can result in spike timing-dependent plasticity, which modulates synaptic strength and contributes to learning processes [7]. Communication by coherence may result from coupling of oscillation frequencies and phases between areas, establishing transient directional flow of information [8]. Evidence for such mechanisms has been observed across a variety of cognitive domains (including attention, memory sequencing and retrieval, reward processing, and decision-making) and involves multiple cortical and subcortical structures [9–12]. However, the degree to which these coherent oscillations are requisite for communication or arise as a byproduct of population spiking activity within synaptically connected networks remains debated [13]. Oscillatory activity has also been observed to track across the cortex in the form of traveling waves that modify excitability, with their propagation linked to functions such as memory consolidation and complex perceptual processing [14–16]. Closed-loop techniques in combination with high spatiotemporal resolution electrophysiological monitoring are poised to directly perturb such large-scale interactions and clarify their contribution to cognition.

What closed-loop approaches have been effective in modulating cognitive processes? Given the well-established role of the hippocampus in memory, many studies have targeted this structure. Hippocampal sharp wave-ripples are high-frequency oscillations that sequence neural firing and replay activity patterns relevant to previous experience across mammalian species [17]. Closed-loop disruption of sharp wave-ripples in rodent models during either non-rapid eye movement (NREM) sleep or wakeful decision-making impaired task performance and indicated a causal relevance to memory [18,19]. Similarly, detecting sharp wave-ripples and extending their duration during tasks improved memory-dependent behavior [20]. These studies highlight one strategy for responsive neuromodulation: identify a specific detectable activity pattern in a particular brain region, develop a stimulation protocol to locally manipulate it, and observe the effects on cognitive behaviors. This modular approach could be interpreted to imply that an activity pattern in one region is sufficient for the cognitive process, seemingly at odds with the large-scale network interactions identified by monitoring the brain during execution of the process. However, properties of sharp wave-ripples suggest a link to these distributed networks. Sharp wave-ripples are the most synchronous output pattern of the mammalian brain, influencing multiple cortical

and subcortical structures [21,22]. Through their temporal coupling with other oscillations, such as thalamocortical sleep spindles and cortical ripples, they are implicated in information transfer from the hippocampus to connected brain regions (Figure 1A–C) [23–25]. In keeping with this notion, a closed-loop protocol in rats that artificially increased the coupling between hippocampal sharp wave-ripples and spindles in frontal cortex, without modifying the ripples themselves, enhanced memory consolidation such that an initially subthreshold spatial learning experience was transformed into long-term memory (Figure 1D) [23]. In a separate study, disrupting such coupling using a neuromodulatory intervention (stimulation of the locus coeruleus) disrupted memory [26].

Congruent observations have been made for other activity patterns. Hippocampal theta rhythm plays a role in online memory encoding and retrieval by precisely organizing the timing of hippocampal action potentials during navigation [27]. Closed-loop optogenetic stimulation during the local hippocampal theta oscillation was capable of alternately enhancing encoding or retrieval, depending on the phase at which stimulation was applied [28]. This oscillation also drives theta rhythm in primate orbitofrontal cortex, and their interaction is thought to contribute to a

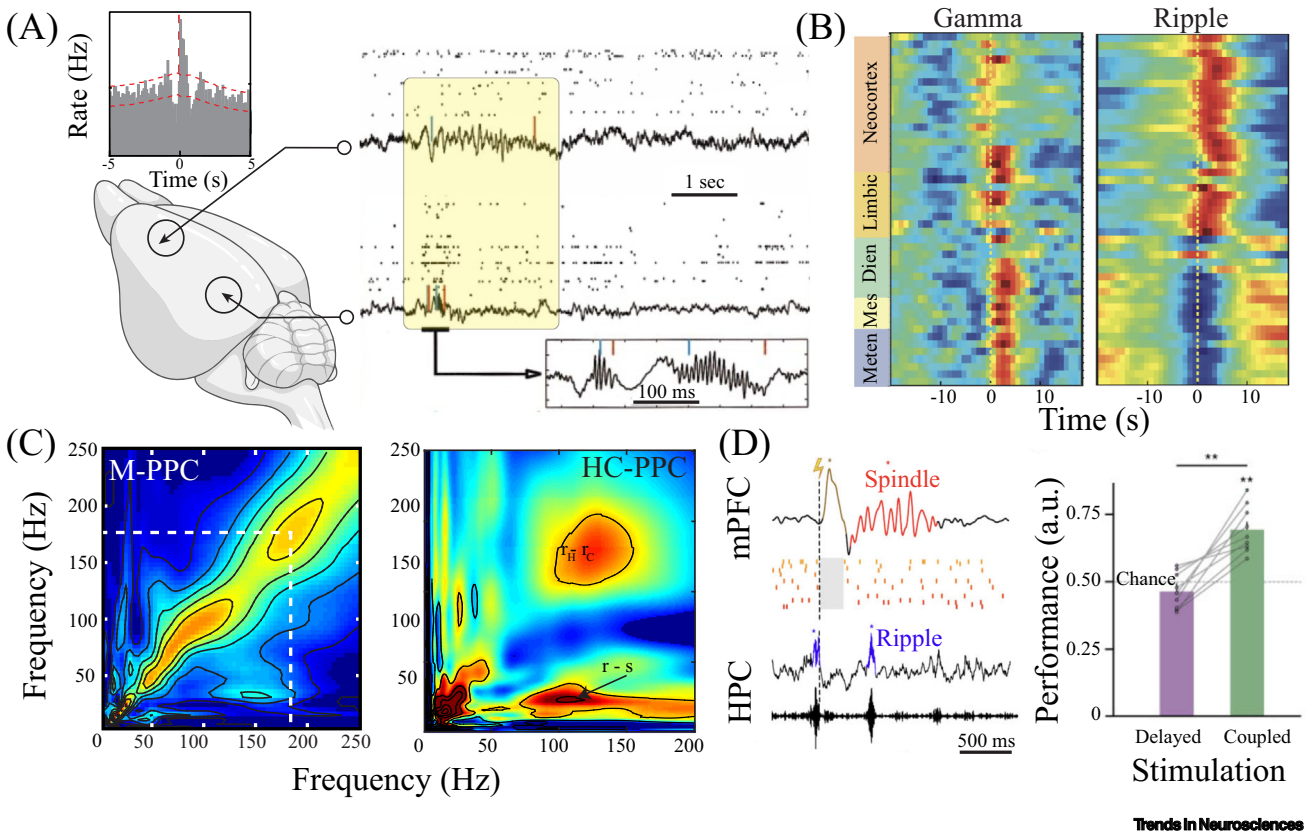

Figure 1. Functional communication across brain regions. (A) Sample local field potential (LFP) traces and spiking raster from the hippocampus and the medial prefrontal cortex (mPFC), along with a diagram of the rat brain indicating the recording sites. The highlighted box illustrates temporal co-occurrence of hippocampal ripples and cortical spindles, which can be quantified using a cross-correlogram (top) [24]. (B) Gamma and ripple triggered population blood oxygenation level-dependent (BOLD) response. Note the sign change in the transition from cortical to subcortical areas during ripple-triggered events. (C) Cross frequency amplitude coupling between midline (M) and posterior parietal cortices (PPC) (left), as well as hippocampus (HC) and PPC highlight the temporal co-occurrence of hippocampal and cortical ripples [25]. (D) Closed-loop detection of hippocampal ripples and induction of sleep spindles in neocortex (left) results in improved memory performance compared to open-loop (with random delay) stimulation (right) [23]. Abbreviations: dien, diencephalon; mesen, mesencephalon; meten, metencephalon [22].

representation of value during specific types of tasks. Disruption of theta synchronization and the locking of neural spiking to particular phases of the theta oscillation by closed-loop microstimulation impaired response to changing value contingencies and resulted in decreased reward obtained by the animal [29]. Local perturbation of gamma oscillations has analogously caused impairment in spatial, object, and emotional memory, depending on which frequency of oscillatory communication was targeted [30,31]. Electrophysiological monitoring revealed disturbance of synchronization between regions, with associated deterioration of information content coded by downstream neurons.

By contrast with these highly spatially focused approaches, interventions that affect large-scale network synchronization also hold promise for cognitive modulation. NREM sleep is important for memory and executive function, and enhanced coupling between NREM oscillations (slow waves and sleep spindles) is mechanistically implicated [32]. Exogenous stimuli timed to the phase of the cortical NREM slow oscillation can increase the amplitude of slow waves and their coupling with spindles [33]. These effects are observed using electroencephalography, which represents summated activity across large neural populations. Acoustic stimuli employed in this manner have been linked to improved memory retention, though inconsistent results across different populations suggest the existence of unrecognized variables that drive outcome [34–36]. Sleep oscillations exhibit a propensity to travel across the cortex and create temporal relationships between distributed brain regions over extended epochs (up to seconds in the human brain), raising the possibility of manipulating this propagation to affect sleep-dependent cognitive processes [37,38]. Thus, an activity pattern that critically shapes network communication may represent an effective focus for manipulation of cognitive processes.

The potential for such an approach has been established by behavior-driven stimulation. In this set-up, the timing of stimulation is dictated by various parameters related to task performance rather than electrophysiological biomarkers. Electrical stimulation delivered to temporal lobe structures during encoding was found to modulate memory in an anatomy-dependent manner and in some cases resulted in cognitive improvement [39–43]. External stimuli are therefore required to drive the stimulation, limiting its applicability outside of monitored and rigid experimental regimes. However, it has also been possible to refine the timing of stimulation based on advanced features extracted from individual subject behavior or electrophysiological activity patterns, allowing intervention only when a potential cognitive lapse is detected [44,45]. This type of experimentation is foundational for the development of protocols that can generalize beyond a specific task by using intrinsic biomarkers that are indicative of cognitive processing.

Closed-loop protocols that (i) directly modify properties of such activity patterns (e.g., amplitude, frequency, phase) or (ii) manipulate the ability of the activity pattern to functionally interact with downstream regions are both effective in achieving this goal. The optimal timing of such interventions is often determined by the temporal relationships between activity in connected network ‘nodes’. Enhancing activity patterns linked to cognition in one brain region may actually impair the cognitive process if the manipulation employed disrupts coupling across the network. We suggest that surveillance of the distributed network, at least when closed-loop approaches are being designed, is important to assess functionally relevant large-scale effects. Furthermore, the spatial location of an activity pattern targeted for detection need not necessarily overlap with the stimulated area. Multiple nodes of a network could be stimulated synchronously or sequentially to direct flow of activity. Indeed, artificially creating meaningful neural spiking patterns that encode information related to a cognitive task in a key brain region is likely more technically difficult than influencing the likelihood that downstream brain regions will respond to endogenously generated activity. These theoretical considerations are supported by observations in

human subjects that neurostimulation applied during cognitive tasks is more likely to facilitate performance when targeted to white matter pathways connecting brain structures compared to the structure itself [40,42,46]. However, the effects of different types of stimulation on neuronal somata and axonal projections remain incompletely defined, and additional investigation will be necessary to understand how to optimally modulate functional connectivity [47,48].

Intercepting pathological network propagation

Cognitive and affective dysfunction severely impact quality of life in patients with neuropsychiatric disorders, and therapeutics that aim to ameliorate these deficits have high translational potential. How can closed-loop neuromodulation be leveraged in cognitive neural networks affected by pathology? Current approaches can be classified into several categories: (i) targeting epochs of disease-related network dysfunction, such as seizures, and monitoring for associated cognitive changes [49,50], (ii) modulating structures implicated in execution of a cognitive or affective task during specific phases of this task performance [43,45,46], (iii) deriving neural activity-based biomarkers for cognitive/affective symptoms and implementing disruptive stimulation [51], and (iv) enhancing biomarkers linked to physiological cognitive/affective function [52].

NeuroPace is a closed-loop modulation system designed to detect the onset of seizures in patients with medically refractory, unresectable focal epilepsy and to deliver stimulation aimed at terminating the seizure [53–55]. The anatomic locations of the sensors and stimulators are based on the localization of an individual patient's theorized seizure onset zone, and stimulation parameters are empirically tuned after implantation. This therapy can substantially reduce seizure frequency in a subset of patients. Data derived from patients implanted with NeuroPace devices have been critical in establishing activity patterns that occur in the human brain during real-world experiences and determining translational potential of approaches tested in animal models [56–58]. Many of these patients also have comorbid cognitive and affective dysfunction, and modest improvements in these domains were observed with chronic stimulation [49]. These improvements were not correlated with the degree of seizure reduction, suggesting an independent but unknown underlying mechanism [59]. In contrast, open-loop deep-brain stimulation for motor symptoms of Parkinson's disease has been associated with small decrements in some areas of cognitive processing compared to medical management [60]. Although this impairment could be exacerbated by the open-loop nature of the intervention, these examples suggest that in the absence of directed sensing and targeted stimulation, significant cognitive improvement is unlikely, and adverse effects are possible [39–41,44].

Fully integrated closed-loop strategies rely upon identification of brain activity patterns that are causally related to neuropsychiatric disease symptoms. In animal models, different experimental paradigms can be explored during electrophysiological monitoring of candidate brain regions (Figure 2A,B). This type of approach has revealed putative neural correlates for analogs of such symptoms in rodent models, including impulsivity, chronic pain, and memory dysfunction [61–63]. State-space model-based decoding has been used in these approaches, and feasibility for effective closed-loop intervention in rodents and humans has been shown [61,62]. Major questions arising are whether these neural correlates will be conserved from rodents to humans, and even from human to human [64]. It is possible that the complex combination of intrinsic and environmental factors that contribute to human cognitive and affective symptoms will lead to unique network disruptions. Indeed, clinical trials for open-loop stimulation of depression demonstrate a high degree of inter-subject variability in response to the intervention [65]. Large-scale monitoring and stimulation capacity in an individual patient offer a potential solution to this issue by enabling detection of a personalized, symptom-specific biomarker and testing multiple targets for symptom-suppression efficacy (Figure 2C,D) [66,67].

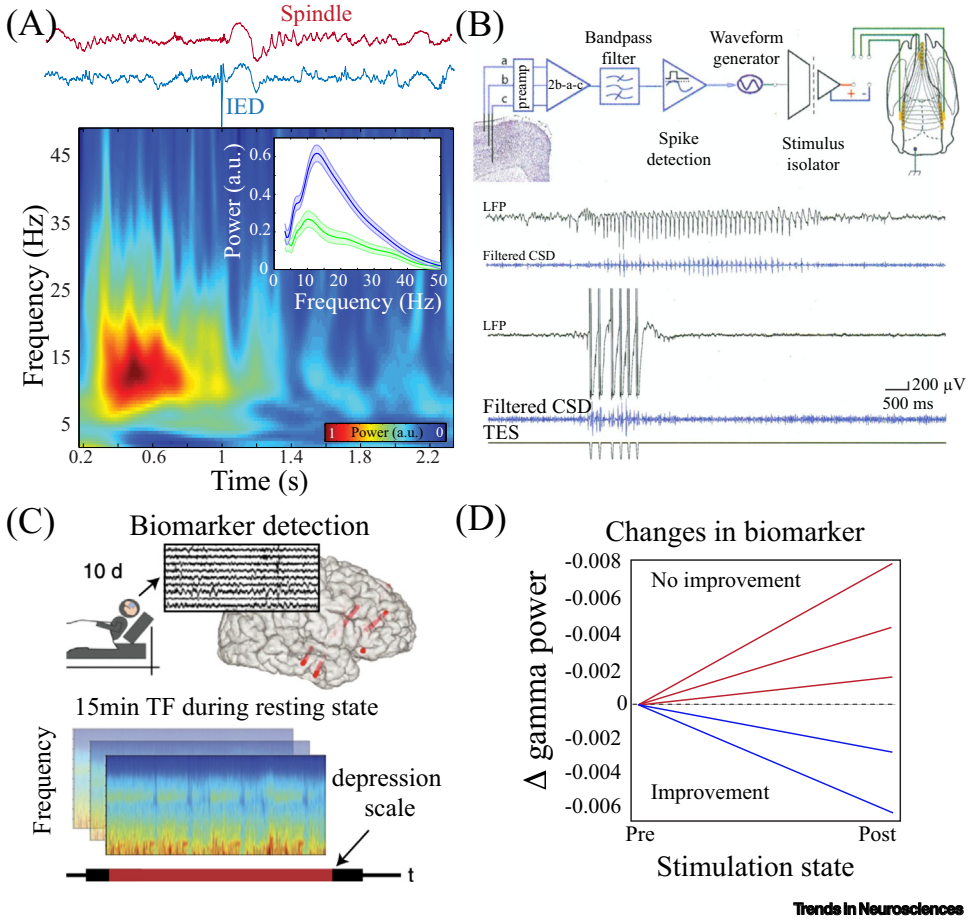

Figure 2. Intercepting pathological network activity in neuropsychiatric disorders. (A) Sample local field potential (LFP) traces of pathologic activity patterns – hippocampal interictal epileptiform discharges (IEDs), blue trace – inducing an oscillation critical for memory (thalamocortical sleep spindle) in an anatomically remote cortical region [medial prefrontal cortex (mPFC)]. Inset, averaged mPFC power spectrum before (green) and after (blue) IED (error bars are means ± s.e.m.) [63]. (B) Schematic of the closed-loop recording and stimulation system to precisely detect and abort epileptic spike and slow wave (SW) episodes in rodents (top). Sample SW episodes: LFP and spatially filtered by current source density (CSD) traces, unstimulated and stimulated. The closed-loop electrical stimulation (bottom traces) significantly shortens the duration of seizures compared to no stimulation (top traces) [99]. (C) Overall approach for identifying neural biomarkers of treatment-resistant depression in amygdala in human subjects [66]. (D) Change in gamma biomarker after a period of continuous stimulation for those trials that led to a reduction in symptom severity (blue) and those that did not reduce symptom severity (red) [66].

Similar to approaches leveraged by brain computer interfaces (BCIs) for motor control, integration of neural spiking data with extracellular potentials has the potential to improve decoding of complex brain states [68,69]. However, this high temporal resolution should be balanced with the ability to survey multiple network nodes simultaneously. Because the goal of closed-loop neuromodulation for neuropsychiatric disorders is the best individual patient outcome, personalization of the approach becomes critical. These disorders are inherently heterogeneous in their clinical presentation, and perhaps similar diversity of neural network dysfunction could be expected. Personalized biomarkers, conceivably incorporating signals from different brain regions, could improve predictive power in an individual network. Similarly, the capacity to explore stimulation of multiple areas and evaluate symptomatic response could optimize individualized efficacy and minimize side effects.

Implementation of large-scale, high spatiotemporal resolution closed-loop devices

How can we implement closed-loop neuromodulation devices that are both high spatiotemporal resolution and large-scale? Current closed-loop devices struggle to combine these features because they incur mechanical, signal processing, power and data management requirements that are challenging to integrate into an implantable design. However, fully implantable closed-loop devices can generally be broken down into simplified functional blocks, and advances in materials and technologies for each block are poised to address these challenges. Here, we discuss these advances and highlight opportunities for integration that could enable the next generation of closed-loop devices capable of efficiently modulating large-scale neural networks during cognitive processes.

Large-scale, multiregional neural acquisition

Communication between brain regions occurs across a wide bandwidth, ranging from slow oscillations (0.1–2 Hz) to action potentials of individual neurons (waveforms with 1–3 ms duration, requiring sampling rate of signals to be 10–30 KHz for accurate detection). In addition, cognitive processes are dynamic over the course of seconds to weeks (such as consolidating a memory or learning a new association). Therefore, the form factor, material, minimum number of channels, and the sampling rate of acquisition systems should be optimized for high spatiotemporal resolution, stable recording to maximize yield of potentially modifiable neural signals. In general, higher spatial coverage (including cortical and subcortical structures) corresponds to a more invasive surgical implantation procedure, and increasing the channel count and sampling rate also leads to a larger physical footprint of the device itself, which can add technical and surgical complexity. To alleviate this trade-off between spatiotemporal resolution and invasiveness, several material- and device design-based strategies have been explored.

The first strategy centers around enhancing the efficiency of individual electrodes in converting the ionic signals generated by neural tissue into electronic signals suitable for further processing (quantitatively assessed by the electrochemical impedance spectrum of the electrode, with lower impedance values indicating higher efficacy). This electrode impedance can be lowered by increasing electrode size, but at the cost of spatially summating neural signals in proximity to the electrode and decreasing spatiotemporal resolution. A solution to this issue is to change the electrode material in a manner that increases the effective surface area or charge capacity of the electrode while maintaining its overall macroscopic geometry of the electrode [70–72]. Conducting polymers such as poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) are particularly promising in this regard because extracellular ions can directly penetrate into the bulk of the material, establishing a large volumetric capacitance and consequently low impedance for even micrometer-scale electrodes (Figure 3) [73–77]. Such organic polymer-based electrodes also offer other advantages, including mechanical softness and optical transparency, enabling unique integration opportunities [78–80].

The next approach is to utilize organic transistors that simultaneously sense and amplify neural signals rather than relying on passive electrodes coupled to additional implanted Si-based transistors for amplification (Figure 3B). Si-based transistors require encapsulation in physiological environments to function, whereas organic transistors should be in direct contact with the extracellular space to sample the ionic currents. Such transistors are typically composed of conducting polymers or organic semiconductors, providing biocompatible solutions to signal amplification and increasing the number of sensors that can be used without concomitantly increasing the number of electronic components required [81–83].

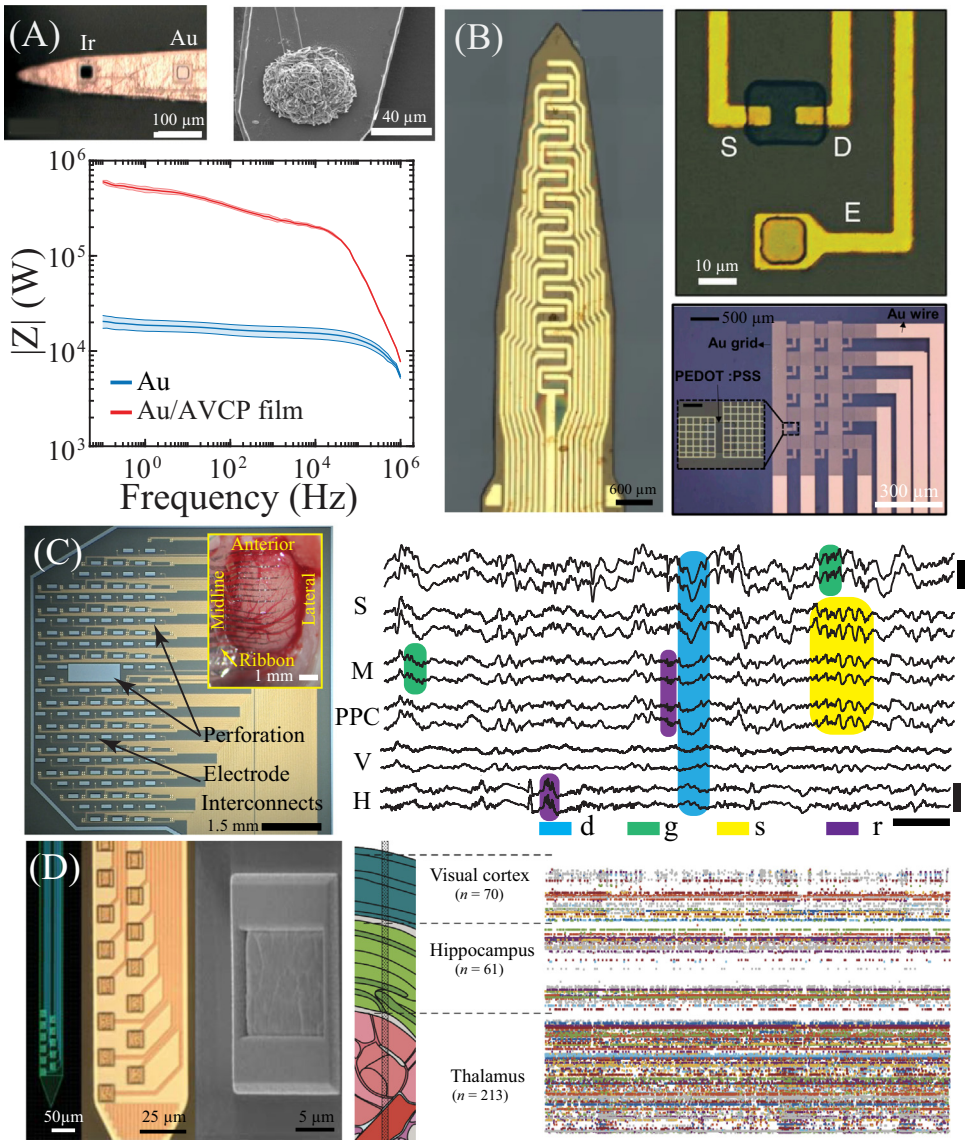

Figure 3. Large-scale, multiregional neural acquisition. (A) Optical micrograph (left) of gold (Au) and iridium electrodes on an implantable Si-based probe. Scanning electron microscopy of a poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) electrode highlighting its high surface area. Sample impedance plot comparing a non-polarizable electrode (Au) to a conducting polymer-coated electrode counterpart with identical geometries (bottom) [113]. (B) Top view of a microelectrode and an organic electrochemical transistor (OECT) microfabricated on a conformable substrate for electrocorticography (top). A multiplexed OECT-based surface array that utilizes an Au grid to provide optical transparency near the recording site [81,114,115]. (C) Highly conformable 4 µm-thick NeuroGrid with visible perforations to facilitate cerebrospinal fluid circulation (left). NeuroGrid conforming on the dorsal surface of a rat cortex (inset). Sample local field potential (LFP) traces acquired by NeuroGrid spanning somatosensory (S), midline (M), posterior parietal (PPC), and visual (V) cortices. It is also possible to combine such probes with implantable probes for simultaneous recording of deeper structures such as hippocampus (H) [25]. (D) Optical and electron micrograph of Neuropixel electrodes (left). Sample raster plot of spiking activity acquired by Neuropixel from multiple brain regions along its silicon shank (right) [70].

Lastly, the material properties and geometry of the acquisition device's substrate layer can be modified to permit large-scale surface recording or multisite implantations with minimal tissue damage (Figure 4). Use of soft organic material a few micrometers thick enables the creation of conformable devices that can follow the curvilinear surface of the brain. High performance micro-scale conducting polymer-based electrodes embedded in conformable <4 μm thick parylene C substrate can record neuronal action potentials from the surface of the brain, allowing for a scalable multiregional neural acquisition at the level of individual action potentials [25,84,85]. Altering the probe substrate from a continuous plane to a perforated sheet or net-like structure significantly improves ease of cerebrospinal fluid circulation. Structural support material for extremely thin surface probes can be used to improve manipulation during implantation, after which the

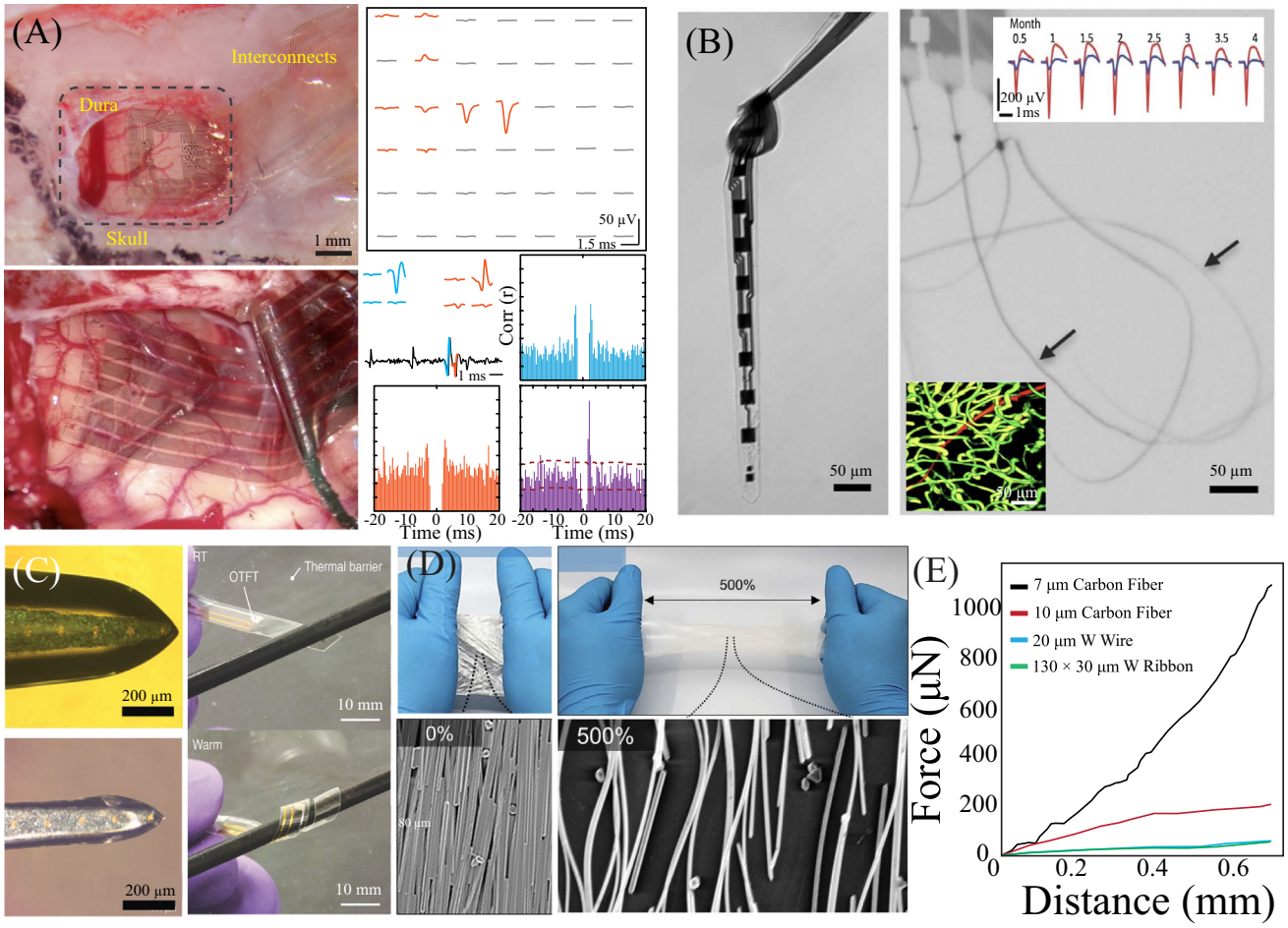

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Figure 4. Material and geometrical strategies to enable high resolution and stable neural interface devices. (A) Conformable polymer-based array following the curvilinear surface of the rat brain (top left) and human brain (bottom left) to improve biocompatibility and spatiotemporal resolution of neural recording at the level of individual neurons (top right). Sample waveforms of two putative single neurons and their corresponding auto- (blue and orange) and cross- (purple) correlograms illustrative a putative monosynaptic connection in human cortex [84,116]. (B) Ultrathin polymer-based implantable probes that can maintain the integrity of the brain–blood barrier (bottom inset), allowing for stable recording of the same neuron for several months (top inset) [117]. (C) A water-soluble dissolvable polymer [polyethylene glycol (PEG)]-coated implantable probe (top left) that is sufficiently stiff to be inserted into the brain, but after insertion and contact with water, the PEG dissolves and leaves a thin probe (bottom left). A thermoplastic-based probe is able to roll and maintain a helical shape without ongoing force (right top and bottom) [113]. (D) Stretchable substrate and embedded conducting gold nanowire-based interconnects patterned at micron scale [118]. (E) Insertion force as a function of the cross-sectional area of shuttle used to assist implantation of ultraflexible probes into the brain [117].

support material dissolves in aqueous medium at the implant site [86,87]. Alternatively, materials that leverage the biological environmental conditions to modulate their stiffness can be used to insert flexible probes into the brain. Examples of such materials are hydrogel-coated microneedles [88–90] and thermoplastics, or thermally reactive copolymers that soften after implantation at biological temperatures [91,92]. These designs permit stable recording from the same neuronal population and structures over months, improving the ability to safely survey multiple network nodes over time and across interventions [93–96].

Time- and location-specific, arbitrary waveform stimulation

Closed-loop protocols typically involve selection of an individual electrode for stimulation delivery due to device power and processing limitations. However, the ability to intervene and stimulate individual or multiple network nodes will likely be critical to effective modulation of functions mediated by distributed neural networks. In addition, pulses and pulse trains have conventionally been used for brain stimulation, but patterns that better mimic endogenous brain activity may be more effective in biasing occurrence and flow of activity across a network [97]. Strategies to achieve these stimulation parameters involve modifications to materials and circuit design.

The electrodes used for electrical stimulation share fundamental properties with electrophysiological sensors, and therefore most design rules and material considerations for the device output are similar to those of its input components (Figure 5A). However, stimulating electrodes are required to pass significantly larger electrical currents compared to electrophysiological recording electrodes. Therefore, it is especially important to develop low-impedance stimulation electrodes to minimize the overall electrical power required to excite neurons, as higher power values may damage electrodes and result in tissue scarring that further elevates the threshold for neural excitation. Material modifications that permit miniaturization of stimulating electrodes while maintaining low impedance will be necessary to make implantation of multiple stimulating electrodes feasible [98]. Customizable stimulating electrode size via selective merging of electrodes could also be beneficial to allow spatial targeting of small and/or irregularly shaped subcortical structures or white matter pathways.

A key approach for multichannel stimulation is time-division multiplexing, which permits creation of circuits capable of delivering different types of stimulation independently to multiple electrodes (Figure 5B,C) [99]. Patterns of stimulation can be reconstructed by a train of short (t_{pulse}) variable amplitude pulses such that the duration of the pulse is significantly shorter than the time constant ($\tau = RC$) of the stimulating electrode. In this manner, it is possible to emulate simultaneous delivery of electrical stimulation to individual channels via fast sequential pulses generated by a single block consisting of an amplifier and digital-to-analog converter (DAC). This design also allows delivery of arbitrary waveforms to different electrodes, enabling use of stimulation patterns that extend beyond conventional square wave pulses (Figure 5D). Although delineating the spatial response of neural tissue to such waveforms (e.g., sine waves, gaussian waves, variable amplitude pulses, or white noise) would likely require dedicated experimentation, such regimes have been shown to lead to more natural neural activation and improved energy efficiency [100]. The feasibility of generating focal electrical stimulation by applying two frequencies that are individually too high to entrain neural firing, but result in a frequency difference at neuronal bandwidth has also been established (Figure 5E,F) [101–103].

Real-time detection and processing of neural signals

Communication between brain regions is dynamic, necessitating adaptive signal processing capacity to guide timing of network manipulation. Because the most effective regions for sensing and modulation may not be known *a priori*, the processing unit must be able to access all

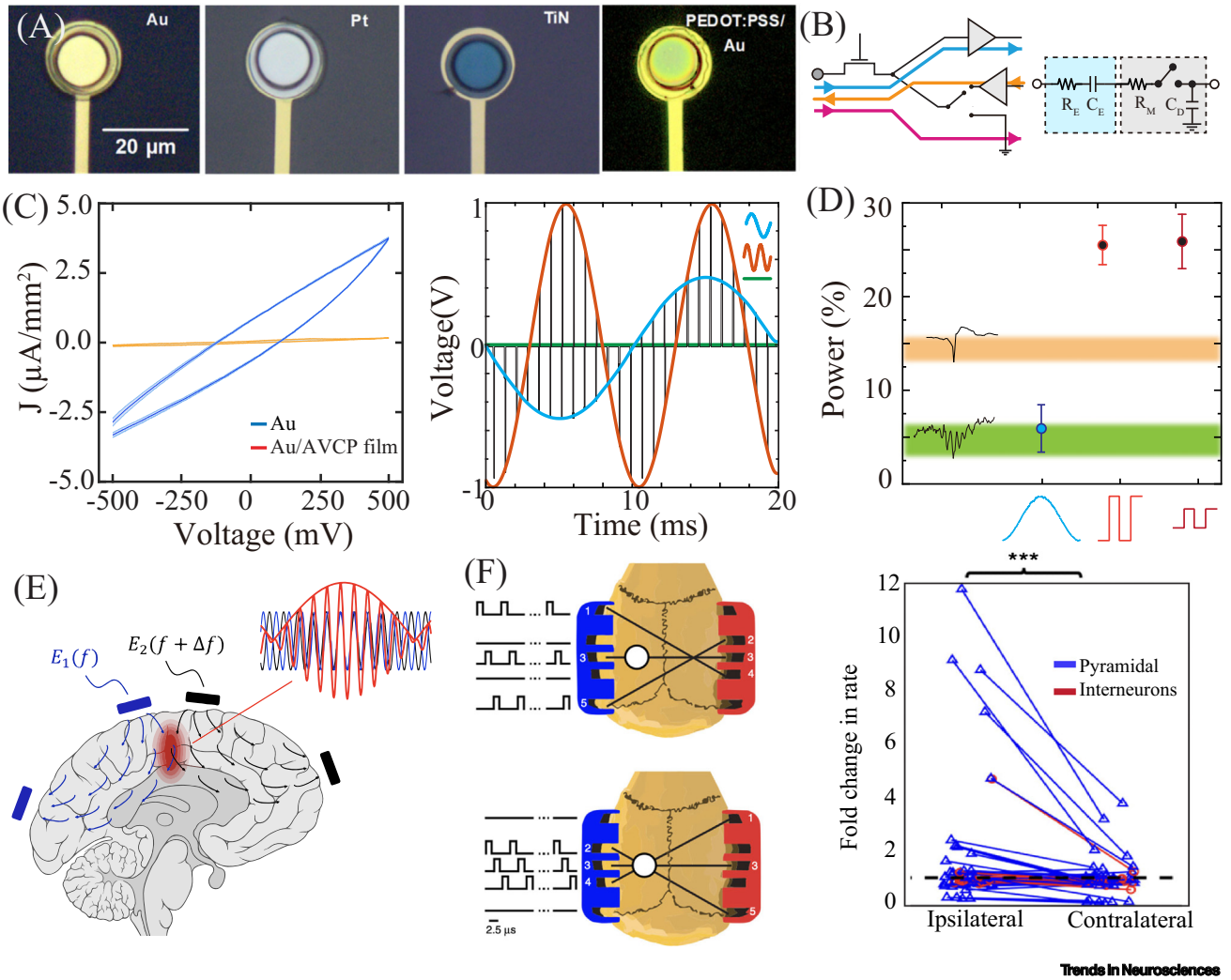

Figure 5. Temporally and anatomically specific arbitrary waveform stimulation. (A) Optical micrograph of commonly used electrode materials for *in vivo* recording and stimulation [118]. (B) Schematic for multiplexing prior to amplification, reducing the number of electronic components required for a closed-loop stimulation device [97]. (C) Cyclic voltammetry of two similar geometry Au and conducting polymer-based electrodes highlighting the larger charge density of the polymer electrode (left) [119]. Simultaneous output voltage traces of stimulation unit delivering multiplexed, multichannel stimulation patterns to two channels at different sine wave frequencies (right, orange channel = 100 Hz at 1 V; blue channel = 50 Hz at 0.5 V). Voltage of remaining channels (green trace) was unchanged [120]. (D) Summary of power changes in spindle band with different closed-loop stimulation waveforms and amplitudes; mean and 95% confidence intervals (95% CIs) are plotted for each group. Gaussian stimulation is most effective in decreasing spindle power, and pulse waveforms are ineffective. 95% CIs for spindle band power after hippocampal interictal epileptiform discharges (IEDs) (orange) and after ripple (green) are plotted as color shaded areas for comparison [97]. (E) Schematic of multiple high-frequency stimulation waveforms for targeting deep brain structures. Both blue and black pairs are delivering electrical stimulation with frequencies beyond capacity for physiological signal integration, but their frequency difference (Δf) results in deep stimulation within the neural bandwidth [103]. (F) High-frequency, spatially multiplexed pulsing enables localized delivery of stimulation (left) characterized by the corresponding firing rates of neurons in both hemispheres during the stimulation (right) [102]. Abbreviation: PEDOT:PSS, poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate).

recording and stimulating electrodes in real time. Conventional data analytics such as line length and power in predetermined frequency bands may need to be bolstered by multiregion measures such as coherence and phase alignment. The analog circuitry required for such complex computations carries a physical footprint that can be prohibitive for a fully implanted device, especially given the bulky and rigid enclosures required to protect the Si-based components from aqueous media. Organic transistors have the potential to overcome some of these challenges because

they are biocompatible, miniaturizable, and can be engineered to operate as independent building blocks for circuits. These components have been used to create digital logic gates, perform cascaded amplification, and detect epileptiform discharges, suggesting a means to reduce the number of Si-based circuits needed while maintaining computational flexibility (Figure 6A).

Computational architectures can also be optimized to enhance speed and complexity of operations possible within an implanted device. In contrast to conventional von Neumann architecture, which involves an exchange of data between the arithmetic logic unit (ALU) and memory unit for every machine code line, use of field program gate arrays (FPGAs) [104] establishes a stream of hardware-based operation blocks that can be operated in parallel. FPGAs can substantially improve the efficiency of computation, especially for high-dimensional matrix correlations commonly used in pattern recognition (Figure 6B) [105]. A parallel effort involves neuromorphic computing, for instance via the use of mixed (ion and electron) conducting transistors to create networks capable of performing computations via mechanisms inspired by function of neurons and synapses (Figure 6C,D). This approach merges memory and arithmetic units within a component, allowing processes to be defined by the anatomy of the network and its physical parameters, rather than by explicit instruction lines [106,107]. Such networks receive analog inputs, in contrast to the binary coding of von Neumann architecture, permitting the magnitude and shape of the input to also encode information. It is anticipated that these computational approaches will advance in parallel and keep pace with encoding and stimulation technologies to permit creation of functional integrated devices with high processing capacity.

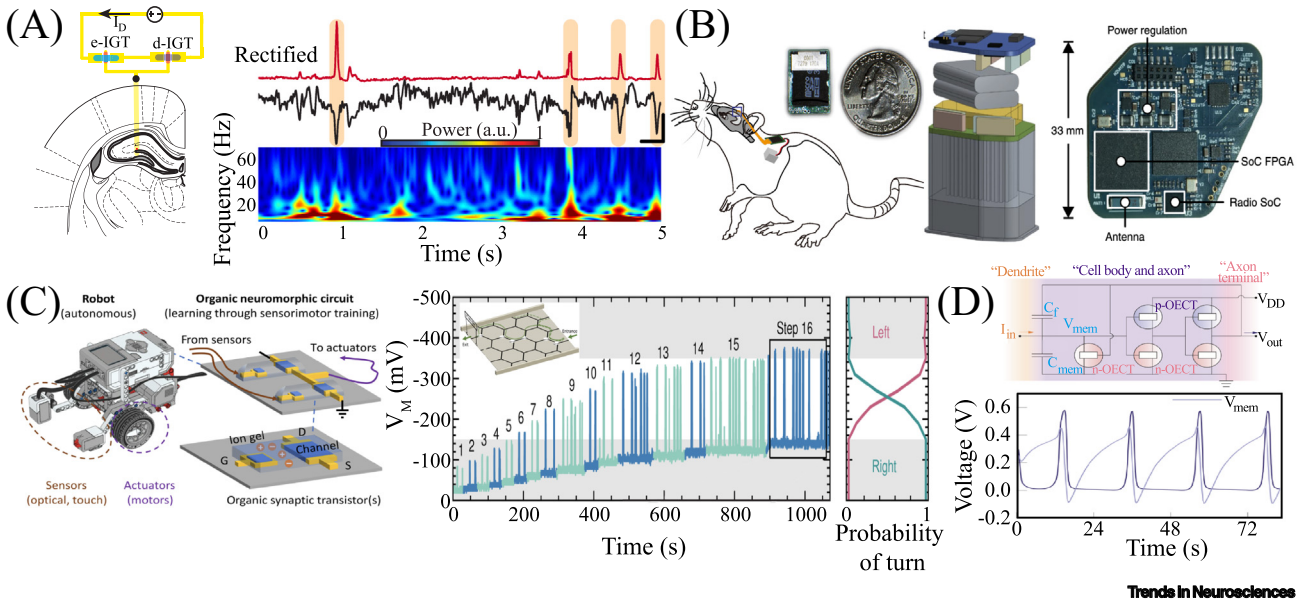

Figure 6. Real-time detection and processing of neural signals. (A) Combination of depletion and enhancement mode organic transistors (schematic, left) enables real-time, high-quality detection of interictal epileptiform discharges (IEDs) [detection signal, top-right; raw local field potential (LFP) and spectrogram, middle and bottom right, respectively] [82]. (B) Fully implantable closed-loop stimulation device with onboard data management and schematic for chronic implantation in a freely moving rodent (left) and non-human primates (right) [104,112]. (C) An autonomous robot gradually learns to navigate a maze by following cues to the exit. Processing and learning of the target task are achieved locally with an organic neuromorphic circuit (left). Temporal evolution of the output membrane voltage during training, in respect to the probability curve of turning. Alternate colors in the membrane voltage graph correspond to sequential training (right) [107]. (D) Schematic of a biological neuron and the analogous organic electrochemical neuron based on an axon hillock circuit (top). Spiking behaviors of the organic electrochemical neurons in response to a ramp function membrane voltage (bottom) [121]. Abbreviations: d-IGT, depletion mode internal ion-gated organic transistor; e-IGT, enhancement mode internal ion-gated organic electrochmical transistor; FPGA, field program gate array; SoC, system on chip.

Power and data management

Because closed-loop devices must have a small physical footprint to be safely implanted in the body, innovative means to broadcast data to the external world are needed. Data transfer is typically accomplished using radio-frequency (RF) communication, which can also be leveraged to deliver power via inductive coupling of coils that can resonate at MHz frequencies. However, RF circuitry is built with rigid and non-biocompatible components and, due to the high ionic conductivity of biological tissue, it requires a high-power budget for reliable data and power exchange [108–110]. These parameters can limit the amount of data stored and transferred, preventing real-time monitoring of signals and network response to modulation. Ultrasound-based devices can use mechanical waves of significantly longer wavelength to provide power to deep structures and mechanically stimulate nearby tissue [111]. This approach still requires rigid elements to convert mechanical to electrical energy, and work is ongoing to combat instability caused by inhomogeneity of intervening tissue layers. It is also possible to use the ions within biological tissue to mediate signal communication and establish MHz range links with fully implantable bioelectronics [112]. More work is required to establish high fidelity, high bandwidth, biocompatible, and wireless methods of communication with implanted devices to accommodate the increased sampling of neural signals required for effective network level interventions.

Furthermore, transient power devices are unlikely to replace implantable batteries for powering of these devices. Closed-loop operations require a continuous source of power to allow real-time detection and responsive interventions. This requirement is a substantial challenge as device complexity increases, because conventional batteries require rigorous encapsulation to prevent tissue toxicity, and they dramatically raise the size and weight of devices. Therefore, advances in biocompatible batteries are key to enable progress in the design of closed-loop devices. Ultimately, the optimal solutions for data and power transfer to an implant should be compatible with, rather than impeded by, the ion-rich environment of neural tissue.

Concluding remarks and future perspectives

Closed-loop approaches have enabled spatially and temporally targeted manipulation of brain activity, identifying physiological signatures that are causally linked to specific functions. Such approaches have also been effective in detecting signatures of neuropsychiatric pathology and delivering stimulation that ameliorates certain symptoms, such as seizures or tremor. However, cognitive processes are increasingly appreciated to require precise communication and coordination of neural activity patterns between multiple brain regions within networks. There is potential to better utilize understanding of these mechanisms to develop novel closed-loop strategies and devices to modulate cognition in health and disease (see Outstanding questions).

Several technological advances are poised to help address these challenges. From biocompatible and conformable materials to organic electronic components for computation, these approaches present the opportunity to increase the amount of information that can be derived from, and input to, distributed neural networks. Focus on integrating components into functional closed-loop devices that can be easily accessed and employed by researchers engaged in experimentation across diverse species, brain regions, and disease states could accelerate progress toward meaningful improvements in our ability to address cognitive disorders and improve quality of life in patients with neuropsychiatric disease.

Outstanding questions

What cellular and connectivity features demarcate activity patterns most likely to enable manipulation of distributed networks?

Does chronic responsive neurostimulation engage mechanisms beyond the acute intended effects that modify the network slowly over time? How can such effects best be examined and quantified in animal models and human subjects?

How can we quantitatively evaluate the added value of using higher dimensional data to operate closed-loop devices relative to the requisite increased device complexity involved?

How can we establish rigorous but efficient experimental processes that permit testing of new materials and device architectures against established benchmarks and focus on immediate systems-level incorporation of promising technologies into functional closed-loop devices?

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Declaration of interests

The authors declare no competing interests in relation to this work.

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