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Citation for the original published paper (version of record):
Grill, W., Chestek, C., Wang, Y. et al (2026). A roadmap to navigate the future of neural engineering. Journal of Neural Engineering, 23(4). http://dx.doi.org/10.1088/1741-2552/ae78c2

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To cite this article: Warren M Grill *et al* 2026 *J. Neural Eng.* **23** 041501

Journal of Neural Engineering

Check for updates

RECEIVED
13 June 2025

REVISED
28 May 2026

ACCEPTED FOR PUBLICATION
4 June 2026

PUBLISHED
27 July 2026

ROADMAP

A roadmap to navigate the future of neural engineering

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Keywords: neural engineering, neuroengineering, consensus, roadmap

Abstract

A group of leaders in neural engineering collaborated to develop a roadmap to navigate the future of neural engineering. We covered a range of themes, including brain machine interfaces, neural modeling, artificial intelligence and machine learning, neural interfaces, neural imaging, augmented rehabilitation, and neuromaterials. For each topic we reviewed the current status, identified current and future challenges, and speculated on the emerging and necessary advances in science and technology to meet these challenges. Neural engineering will continue to yield the approaches and insights that advance the diagnosis and treatment of nervous system disorders, as well as provide new understanding of neural function.

Contents

1. Introduction

On the occasion of the 20th Anniversary of the Journal of Neural Engineering, we gathered leaders across the topics that constitute neural engineering to develop a roadmap to navigate the future of neural engineering. Twenty years ago there were no implanted human brain machine interfaces (BMIs) that made use of single neuron recordings, while today there are tens of individuals, some with multiple arrays, implanted brain computer interfaces that enable high performance speech decoding, and a burgeoning industry working to commercialize and provide high-resolution brain computer interface products. This transformation of fundamental knowledge to practical use and translation from preclinical testing to clinical applications will continue across the full spectrum that constitutes neural engineering.

High-channel count implanted devices enabling high-resolution and robust closed loop neural interfaces will benefit from advances in neuromaterials, as well as developments in machine learning to advance decoding and interpretation of neural signals. Novel physical modalities, including light and ultrasound, will enable less invasive means to manipulate and potentially to monitor neural activity, thereby reducing the barriers to translation. Multimodality imaging will enable integrated measurements of neural connectivity, neuron activity, and neurochemical dynamics.

We are in the early stages of a neural data revolution, where vast quantities of data are being generated, and increasingly openly shared. New approaches to develop and parameterize complex models where only input-output data may be available, as well as large scale integrated models of neural circuits and systems are required for this abundance of data to yield new understanding. Improved understanding of pathophysiology, enabled by these data, will enable development of new therapeutic approaches, including biohybrid approaches combining devices with cells, as well as further personalization of existing therapies.

Although we have seen tremendous advances in neurotechnology, the translation of these innovations to clinical application has been slow. Challenges of translation exist throughout our field, and these are well exemplified by augmentive neurorehabilitation, where, for example, advances in robotics have been slow to impact clinical practice, even though there are strong anticipated gains in outcomes. Ongoing development of neural engineering science and technology is thus critical, as many of continued advances will further enable discovery, diagnosis, and ultimately, treatment planning and novel therapies to improve human life.

2. BMIs

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Status

A BMI involves recording and interpreting electrical activity directly from the brain and using it to control assistive technology. BMIs have the potential to assist persons with an injury to any lower part of the nervous system, for example in injury related paralysis. In the late 1990s, there were several compelling early examples of BMIs [1, 2]. By 2002, there were simultaneous papers in science and nature in which a monkey was able to control a shaky computer cursor with an ensemble of neurons [3, 4]. These early experiments were conducted in neuroscience labs, and had a major role in improving our understanding of motor cortex. Although the recording of neural ensemble activity can be accomplished through various modalities, including invasive single-cell and multi-electrode array recordings, electrocorticography (ECoG), as well as non-invasive techniques such as electroencephalography (EEG), magnetoencephalography (MEG), and imaging modalities like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), invasive techniques significantly enhance both spatial and temporal resolution, as well as signal-to-noise ratios. These improvements provides more reliable signal foundations for accurately determining the mechanisms of information transmission within the brain and for real-time control over external devices. Consequently, this enabled BMIs to transition over the next few decades from a basic science discipline to an engineering discipline, with a primary focus on restoring human function.

Today, there are numerous ongoing human experiments using BMIs to restore function. BMIs targeted to motor areas can achieve near able bodied levels of 2-dimensional control of computer cursors [5]. Bringing useful motor control to the physical world is challenging, but there are demonstrations of users controlling a variety of physical devices, including prosthetic hands [6, 7] and drones [8]. There have also been exciting demonstrations of restoring movement to the participant's own body using BMI-controlled functional electrical stimulation (FES) of paralyzed limbs [9, 10]. Within the past few years, speech decoding has emerged as a very effective way for a BMI to restore function. First demonstrated by decoding handwriting at high speeds in a person with an motor implant [11], later implants were done in speech areas of persons who had severe aphasia. Within only the past year, we have seen direct speech decoding of the entire English language at close to conversational speeds [12]. Providing a communication channel for someone who is locked in, for example due to ALS, is an important application [13, 14], and this may become the first commercially available treatment, with multiple companies pursuing this approach.

Challenges

These achievements are particularly remarkable when we consider the limitations of current tools. The primary electrode array used in human BMI studies is the Utah array [15], which has a matrix of 64–100 silicon shanks, 1.5 mm in length. Surface grids, similar to those used for epilepsy mapping, can also be used for some applications [16]. Multiple devices can be implanted, such that 256 channels is now common [11, 12]. These electrode arrays have enabled tremendous results to date, but they more commonly have 20 useful channels than 100 [17, 18]. This number then declines in quality over the course of years [19], likely due to the foreign body response and materials degradation. Also, studies to date have used wires passing through the skin, with signals processed on a computer cart. While processing could all be done on an implanted device, the required power consumption and exotic packaging with large hermetic feedthroughs are still beyond todays technology. As a result, 20 years have passed since the first human array implant, without eliminating the percutaneous wires [20].

In terms of algorithms, for the first decade or more, BMI algorithms used primarily Kalman filters [5, 21], despite several unsuccessful attempts to outperform this approach with neural networks (e.g. [22]. But with modern anti-overfitting techniques and faster computers, all recent high-performance results used neural network architectures such as LSTMs, CNNs, and others [12, 23, 24]. Frequent retraining, often daily, is still important for achieving the highest performance, as information from individual electrodes can change significantly from day to day. This is likely dominated by changing neural waveforms due to micromovements of neural tissue. For example, waveforms from single neurons can change amplitude by an average of 35% from day to day [19]. There may also be effects related to learning and adaptation over longer time periods [25, 26]. Such fluctuations pose a challenge for maintaining stable performance in functional prosthetics, which is a fundamental requirement for the clinical applications. To address this issue, researchers have experimented with various methods to recalibrate decoder parameters or extract consistent features, aiming to sustain stable high performance [27, 28, 29]. While these methods often yield relatively consistent results in simplified performance evaluations, they have notable limitations. Currently, decoder performance assessments are reduced to tightly controlled testing conditions, usually in a laboratory environment. This simplification contrasts sharply with the complexities of movement generation in tasks of daily life. Moreover, recalibration methods often rely on predetermined movement trajectories or assumptions about the shortest path to achieve specific movement goals. This approach is unrealistic for subjects with compromised motor function. Additionally, the need for skilled personnel who are well-trained in sophisticated algorithms further complicates the process, creating a significant barrier to the widespread clinical adoption of BMIs.

Another challenge for BMI functionality is sensory feedback, the absence of which makes true closed-loop control difficult. Users of BMIs may benefit from artificial sensory feedback to effectively control their neuroprosthetics [30, 31, 32, 33] There have been preliminary positive results from stimulating sensory cortical areas during prosthetic hand control [34] and deep brain area [35] in improving walking. However, unlike intuitive sensory feedback, the design of the stimulation patterns is generally empirical and may require adaptation and learning from the subjects, necessitating further exploration of optimal stimulation strategies. Feedback is continuously processed by the brain, allowing for adjustments in subsequent movements or decisions. Designing a truly intelligent decoder may also require predicting the dynamics of the neural signals upon the feedback in order to detect unexpected perturbations and alleviate reliance on the adaptation capabilities of the user. Additionally, such computations must meet real-time requirements, ideally within one hundred milliseconds, or even tens of milliseconds. Finally, a substantial challenge is that each of the applications currently being explored for treatment using a BMI involves a relatively small number of potential users. Implantable electronic devices have strict requirements for safety and reproducibility and have to date only been produced by medical device companies for larger populations, such as persons with deafness, chronic pain, or Parkinson's disease.

Advances

The next few decades are likely to be a period of rapid advancement for BMIs. Over the past five years multiple companies have invested in developing wireless implantable hardware to create a BMI with no percutaneous leads (e.g. Neuralink, Paradromics). These systems have higher channel counts and smaller electrodes than devices to date, and they may be immediately useful for restoring speech and enabling direct brain control of a computer. In rodent studies, we have seen demonstrations of many new 'ultramicroelectrodes' that are smaller than neuron cell bodies ($<15\ \mu$m). While difficult to make using traditional silicon lithography, these can be made from metals [36], polymers [37], and pure carbon [38]. They do create additional challenges related to insertion and dissolution, but there are numerous examples of electrodes that show minimal if any scarring response or loss of neurons immediately adjacent to the electrode in chronic implants. At some point in the next few years, the primary source of the foreign body response might be the base holding the electrodes that sits on the top of the brain. This will further motivate neural 'dust' style implants where the signal is transmitted wirelessly from tiny devices on the surface of the brain to a receiver. There are sub-mm proof of concept devices in the literature that could go below the pitch of wired device bases within the next decade [39, 40].

With the advent of advanced recording systems, we are poised to acquire significantly improved training data for BMI algorithms. These systems may enable us to access data from a broader range of brain regions and to intervene in brain activity with greater precision in both temporal and spatial resolution. By collecting data from various cortical areas, we can move beyond merely decoding the movement parameters for a few degrees of freedom at a time to investigating and harnessing the pathways of neural information transmission. Furthermore, the development of these systems may allow for simultaneous microstimulation across many channels, enabling us to intervene at the millisecond level within small clusters of neurons. By employing a population coding strategy, we may be able to create more natural sensations. One could imagine that electrical stimulation could even induce the formation of new functional connections among neurons, artificially stimulating plasticity and producing the desired behaviors. These systems may not be limited to the motor cortex but could also extend to other damaged neural pathways, perhaps restoring functional connections. Looking ahead we can envision a future where BMIs will continuously learn and accumulate new functions, ultimately leading to more seamless integration into daily life.

The first clinical application for implantable BMI will likely be restoring speech, which simply requires a computer speaker. However, to become economically sustainable, BMIs will need to expand to other applications. A near term approach could be expanding into brain controlled FES for paralysis. FES has been around for decades, but has only activated a small number of muscles due to a small number of control signals. Higher channel count systems controlled by BMIs could restore many more simultaneous degrees of freedom. With BMIs first becoming available for a few pilot applications, the next few decades could also see numerous research studies in which these devices are used for other emerging applications. Deep brain stimulation (DBS), uses quite simple stimulation to treat Parkinson's or epilepsy. However, it is already being explored for treating psychiatric disorders [41] and dementia [42]. Single neuron recording has even begun to be used for a wide variety applications, for example in memory [43], visual processing [44], cognition [45], and mood [46], which may reveal future applications of BCIs. There has also been work attempting to use BCIs to treat ADHD and Autism with non-invasive techniques. It is possible that we will see BMI devices deployed as a platform technology to address a wide range of medical applications, bringing about a new age of bioelectronic medicines.

3. Neural modeling

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Status

Neural modeling has played a critical role in advancing our understanding of the nervous system and developing technologies to interface with and emulate its functions. Broadly, neural models were developed with either a focus on integrating biophysical details or on capturing higher-level computational or algorithmic functions. The former, biophysically grounded models often represent ionic current flow through membrane conductances (figure 1(A)), as exemplified by the Hodgkin–Huxley model [47]. This Nobel prize winning work was instrumental in explaining the genesis of action potentials, the main unit of information transmission in the nervous system. It also provided a framework still in use today to simulate the vast array of voltage-gated ion channels that provide diverse signaling properties to different neuron subtypes. Alternatively, models using more simplified representations of neuronal function omit these low-level details (figure 1(B)), such as the McCulloch & Pitts binary neurons [48]. These models were the building block of early artificial neural networks (ANNs) leading to the deep neural networks that exploded in recent years, yielding impressive performance on artificial intelligence applications from computer vision to natural language processing (NLP) and beyond.

Neural modeling remains important to understanding mechanisms underlying brain functions. Models allow us to quantitatively link biological processes across scales and identify potential mechanisms that explain experimental data, as developed in the next section.

A key area where neural modeling is essential is the understanding of how neural activity links to neural signals recorded experimentally. Neural models are necessary to predict how brain signals are generated by neural activity (also called the 'forward problem') and to estimate what neural activity gives rise to brain signals ('inverse problem'). Examples include relating changes in blood oxygen levels measured by fMRI to neural activity [49] and understanding how neurons generate the electric fields recorded via EEG or implanted electrode arrays [50]. Neural models are useful not only to understand these brain signals but also to design and optimize new methods for estimating brain activity.

Neural models are also crucial for predicting and controlling neural activity in response to external stimulation. Indeed, neural modeling is involved directly in some experimental techniques, such as dynamic voltage clamping—where a computational model and a neuron interact in real time [51]. Neural models capturing the coupling between extracellular electric fields and neural activity are increasingly used to generate mechanistic hypotheses and predict dose-response relationships for various brain stimulation techniques, including DBS [52] and transcranial magnetic stimulation (TMS) [53]. These biophysical models can be used to optimize stimulation parameters to enhance precision, selectivity, or functional effects of stimulation therapies. For example, models of peripheral nerve stimulation were used to optimize stimulation amplitudes for spatial selectivity [54] or pulse shape for energy-efficiency [55].

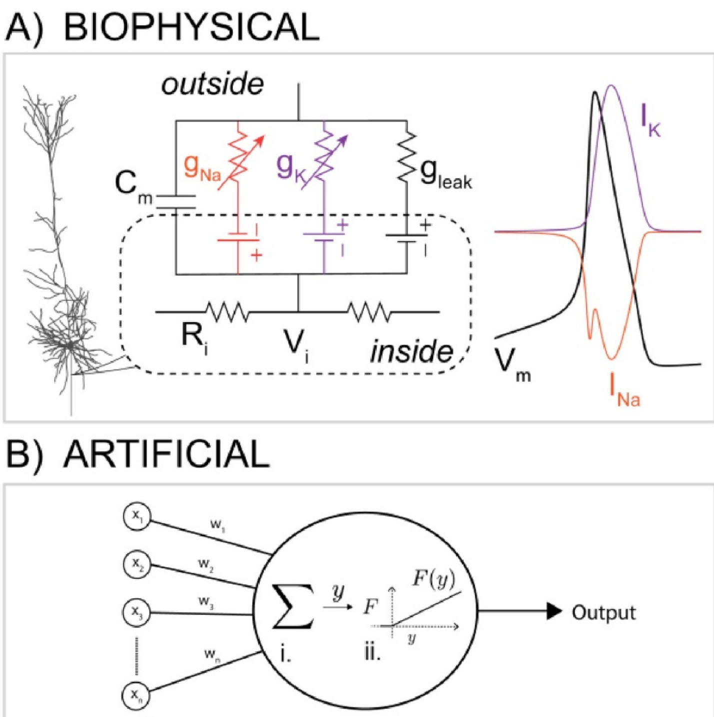
Additionally, recent work explored training ANNs to perform specific tasks [56, 57] or to reproduce recordings of task-related neural activity [58, 59]. These efforts are part of a broader dynamical systems approach to modeling neural population activity, which has yielded insights into how populations of neurons encode information and implement computations [60].

Finally, models of neurons and their synaptic interactions provide the foundation for neuromorphic computing, where dedicated circuits are built to perform neural computations more efficiently by directly implementing spiking neuron models in hardware circuits [61].

Current and future challenges

One of the main challenges in neural modeling is linking between spatial scales to understand how cellular or molecular mechanisms lead to the emergence of brain functions, sometimes involving large regions or even the whole brain. For example, an important goal is understanding the genesis of specific and well-identified brain activity patterns, such as gamma-frequency oscillations. Although the neuronal generators of the oscillations are known [62], it is not clear how the oscillations organize and synchronize between brain areas or what role they play in information processing. Aberrant oscillatory activity has been linked to multiple neurological and psychiatric disorders, like Parkinson's disease and schizophrenia [63], and therefore serves as a potential target for neural stimulation therapies. Here, computational models are needed to explore possibilities and make testable predictions.

Accomplishing this goal will require advances in our theoretical and computational approaches, as well as vast quantities of data. Biophysical neuron models can use Hodgkin–Huxley-like ionic conductances with cable theory to link cellular and molecular properties to electrical activity, e.g. by clarifying how dendritic morphology and ion channel



i. $y = \sum_{i}^{n} w_i \cdot x_i = w_1 \cdot x_1 + w_2 \cdot x_2 + w_3 \cdot x_3 + \ldots w_n \cdot x_n$

ii. $F(y) = max(0, y)$

Figure 1. Canonical biophysical and artificial neuron models. (A) Multicompartmental model (top) of a neocortical pyramidal neuron capturing its morphology (left) and electrical dynamics using a circuit model (middle) with Hodgkin–Huxley-like sodium (Na_v) and potassium (K_v) channels. Example simulation of an action potential, demonstrating the membrane voltage (V_m) and sodium (I_{Na}) and potassium (I_K) current dynamics. (B) Neuron model unit used in many artificial neural networks. The output of this model is the result of (i) a linear summation of activity levels of inputs x_i scaled by their synaptic weights and (ii) a nonlinear activation function—in this case, the commonly used rectified linear function.

expression influence excitability. However, these models have thousands of unconstrained parameters governing complex, nonlinear membrane dynamics. Building and constraining these models remains labor-intensive and relies on *in vitro* experimental data, as the necessary *in vivo* data are typically not available. Connecting these models into large networks increases exponentially the computational cost and requires extensive data on synaptic connectivity and physiology. While significant strides have been made in certain model organisms, primarily in rodents [64, 65], obtaining these data in humans is still beyond our reach.

Alternative approaches using reduced models of neurons or populations of neurons can circumvent the lack of low-level data and computational cost associated with biophysical models. For example, mean field models represent the activity of neural populations rather than individual neurons and have been used for whole brain simulations [66]. These models can be constrained by fMRI or EEG data from humans, potentially allowing simulation of specific individuals and disorders. However, they may rely on unfounded assumptions or neglect important biological details.

In general, the level of detail necessary depends on the specific goal of the model, as assumptions and simplifications are inherent parts of the modeling process. Integrating experimental data with neural models at different scales will enable us to test which details are important for explaining and predicting specific processes.

Advances in science and technology to meet challenges

Several advances are needed to meet these challenges. First, we need appropriate digital infrastructure to support close interaction between experimental data and neural models. This is needed not only for model development, which is often motivated directly by experiments, but also for model simulation, by providing computational resources, i.e. simulators, high performance computing (HPC) time, etc. An example of such infrastructure in Europe is EBRAINS [67], an open-access digital infrastructure for brain research, which includes access to HPC and neuromorphic computers.

Second, large scale efforts to collect data with standardized protocols will enable increasingly detailed models capturing the cellular and molecular

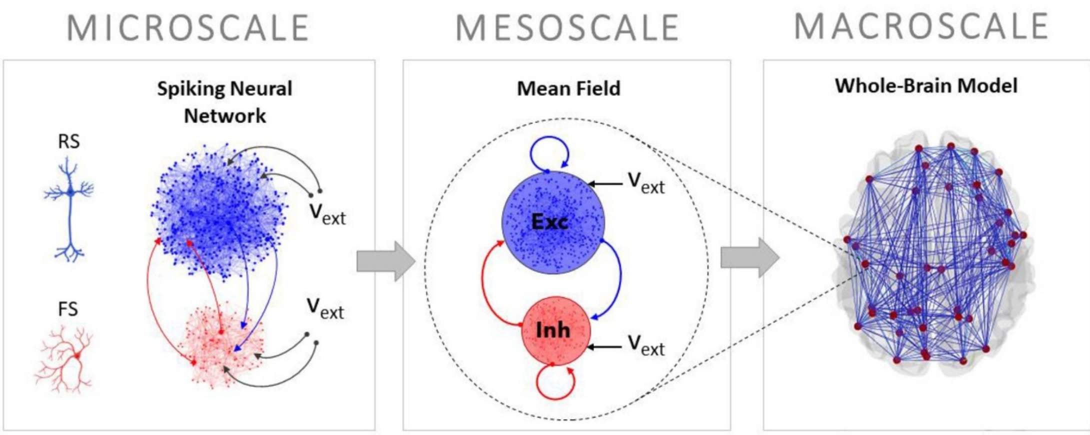


Figure 2. Scheme to illustrate the linking between scales. Spiking network models (Microscale) are used to model some neural function and are then formulated as mean-field models (Mesoscale) to yield a population-level description of the network [66]. Mean-field models are then integrated in large-scale networks (Macroscale) to investigate large-scale dynamics up to the whole-brain level [73]. Reproduced from [74]. CC BY 4.0.

diversity in the nervous system. For example, the Allen Institute for Brain Science in the US is collecting electrophysiological, morphological, and transcriptomic data from neurons in mice and human brain slices. Moreover, optical approaches to recording neural activity, for example using genetically encoded fluorescent reporters of calcium or voltage, now enable recording activity of large neural populations with cell-type specificity during behavior and in response to various stimuli. However, these approaches are currently limited to animal models. Continued improvements to invasive electrical recording technologies, like multielectrode arrays and stereotaxic EEG, have increased substantially the number of neurons or local field potentials, respectively, that can be simultaneously recorded in humans. Further technological advances enabling minimally invasive recordings of neuronal population activity at cellular level resolution will be important for building models of human brain circuits.

Additionally, volumetric electron microscopy has been used to reconstruct up to a cubic micron of mouse [68] and human cortex [69] containing thousands of neurons, and providing unprecedented data on the structural organization of the brain down to the nanoscale. In parallel, large-scale efforts to label and reconstruct single neurons in whole brain samples enabled reconstructions of single morphologies and more detailed cellular level wiring diagrams in the fly, mouse, and non-human primates [70]. These connectomic data have yet to be integrated into models of brain activity and may require new multiscale modeling approaches and optimization techniques to capture key biophysical processes across scales (figure 2). AI and machine learning tools have already been useful in segmenting and analyzing these large petabyte datasets; further advances will facilitate processing and extracting relevant parameters as datasets continue to grow. AI tools will also be useful in neural simulations; ANNs can be trained to reproduce the input–output properties and activation thresholds of biophysical neuron models with orders of magnitude speedup [71, 72], providing a potential strategy for accelerating large-scale simulations of brain activity.

Concluding remarks

Neural modeling is at a stage where many cellular and network mechanisms underlying neural activity have been worked out, but building models that connect these mechanisms across scales and explain the genesis of specific behaviors is an active area of research, still in its infancy. Thus, there is an acute need for multiscale models bridging spatial scales, and a particular effort is needed to transport the findings at the scale of circuits up to the whole brain. This will likely require parallel efforts building models at varying levels of biophysical detail and abstraction to link the neurophysiology to neural computations and behavioral outputs. Armed with more detailed anatomical and physiological data, powerful computational resources, and advanced theoretical frameworks, neural models will progress in their ability to reproduce faithfully and explain the mechanisms of brain function. Critically, the development of accurate neural models across scales will also facilitate the analysis and design of technologies to modulate and record brain activity as well as therapeutic interventions to treat brain disorders.

Acknowledgements

ASA is funded by the Neukom Institute for Computational Science at Dartmouth College. AD is supported by the CNRS and the European Union (Human Brain Project H2020-945539, VirtualBrainTwin project, 101137289; FLAGERA BrainAct project).

4. AI and machine learning

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Status

The convergence of AI and neural engineering has opened a new era of possibilities for emotion, cognition, and human health. Machine learning algorithms have significantly advanced the ability to decode complex neural signals [75], enabling more precise control of neuroprosthetics and natural interaction of brain-machine interfaces. Deep learning models are enhancing the understanding of certain brain functions [76], and some are leading to more effective treatments for neurological disorders [77]. These advances have translated into tangible improvements in neural interface performance [78, 79]. Although current models capture merely a tiny fraction of the brain's complexity, they represent a significant leap in technological capabilities. Consequently, recent advancements in AI have improved neural signal decoding accuracy and enabled more responsive neural interfaces, while also enhancing the ability to model complex neural processes and design targeted neuromodulation therapies.

As the field progresses, foundation models [80, 81], previously led by GPT [82] and DeepSeek [83] series, and generative AI are expected to revolutionize all aspects of neural engineering. Recent developments in vertical large models (VLMs) have shown promise in integrating diverse neural data types to enhance our understanding of complex neural processes (figure 3) [84]. VLMs refer to large models that are pre-trained and fine-tuned for specific domains. For instance, Jiang *et al* employed a large volume of unlabeled EEG data—publicly available from diverse research institutions worldwide and collected for various tasks—to pre-train the VLM LaBranM. They subsequently fine-tuned LaBranM using a limited amount of labeled EEG data for downstream tasks such as EEG-based emotion recognition and gait prediction [85]. The integration of various modalities, such as EEG, fMRI, and behavioral data, is crucial for training robust VLMs in neural engineering, allowing for more generalizable insights. Additionally, the application of AI in neuroscience is accelerating discoveries, from simulating biologically realistic neural circuits to investigating dynamics of large-scale brain networks during emotion and cognitive tasks, and even enabling EEG-to-content generation (text, speech, image, video). Concurrently, the on-going construction of large, publicly accessible neural datasets fosters collaboration and scientific innovation, although challenges in data diversity, quality, and standardization persist [86].

The impact of AI extends beyond basic research to practical applications. In virtual rehabilitation, machine learning algorithms personalize therapy regimens by adapting in real-time to patient progress and enhancing the effectiveness of home-based rehabilitation programs [87]. Multimodal affective brain-computer interfaces are opening a new way for objective assessment of depression [88]. Simulation and virtual reality, powered by AI, are creating immersive environments for more effective motor learning.

Meanwhile, the relationship between AI and neuroscience has become increasingly reciprocal. Neuromorphic computing architectures and biologically-inspired algorithms, such as attention mechanisms [89] and graph neural networks, are advancing AI capabilities. As researchers continue to push the boundaries of both AI and neural engineering, the focus is not only on improving the accuracy and efficiency of neural interfaces, but also about discovering neuroscience insights and expanding the limits of human potential.

Current and future challenges

The rapid development of foundation models urgently requires neural engineering to address the following key problems: (1) In comparison with the fields of NLP and computer vision, there is a lack of large-scale neural datasets, especially multimodal ones, for building vertical large models of neural engineering (VLM-NE), thus calling on laboratories, hospitals, and companies around the world to make their data as open as possible. (2) There is an urgent need to establish international standards for invasive and non-invasive neural data collection, annotation, and management so that laboratories, hospitals, and companies around the world can contribute their data to build a public dataset for VLM-NE [90]. (3) Most of the machine learning algorithms used at present are derived from the field of NLP or computer vision, and there are few algorithms designed for neural engineering. (4) On the construction of VLM-NE, how to effectively pre-train VLM-NE on the basis of the existing foundation models while incorporating domain knowledge is an important research topic.

These challenges extend to technical, biological, and population-level domains. At the technical level, particularly for VLM-NE, scalability and computational efficiency are key focus areas as the field advances toward increasingly complex models and real-time neural signal decoding. A significant technical challenge lies in developing high-performance, low-power algorithms capable of processing high-dimensional neural data with minimal latency, essential for responsive and energy-efficient brain-machine interfaces.

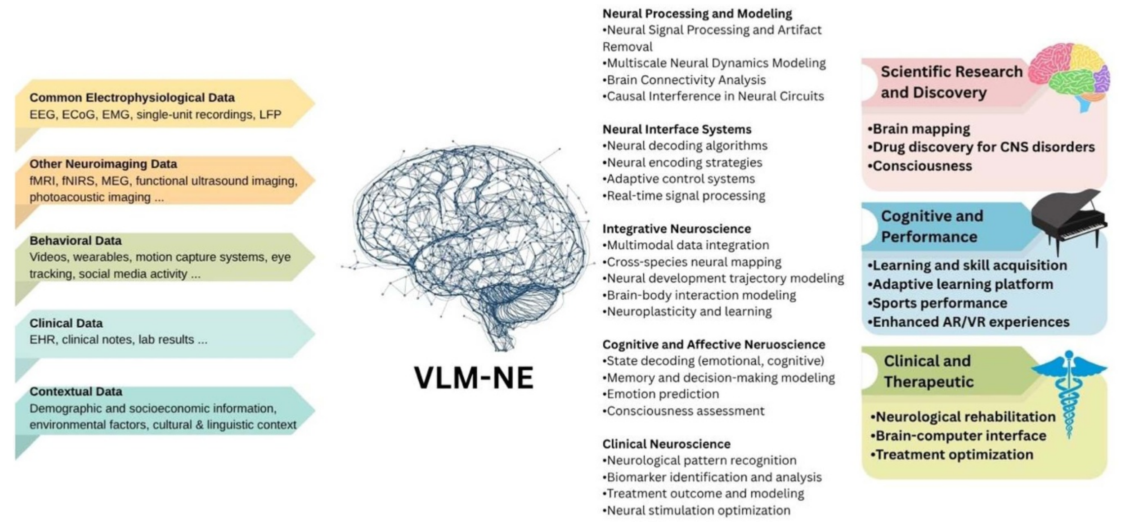

Figure 3. Vertical large models of neural engineering (VLM-NE) from inputs, tasks, to applications. This schematic depicts the flow from diverse input data sources (left; including electrophysiological, neuroimaging, behavioral, clinical, and contextual data) to a central VLM-NE processing core. The VLM-NE underpins core task domains (center-right list; e.g. neural processing and modeling, neural interface systems, integrative neuroscience, cognitive/affective neuroscience, and clinical neuroscience). These tasks, in turn, enable a broad range of applications (right; scientific research and discovery, cognitive and performance, and clinical and therapeutic interventions), highlighting the pathway from foundational analysis to real-world impact in neural engineering.

Beyond technical considerations, biological factors present equally important challenges. Emphasis on explainable AI models is crucial, enabling researchers and clinicians to interpret and validate AI-driven decisions in neural engineering applications [91]. Simultaneously, leveraging neuroplasticity principles remains vital for creating adaptive systems that evolve dynamically [92]. These biological considerations are fundamental to developing AI systems that can effectively interface with and adapt to the complex and dynamic nature of neural systems.

At the population level, challenges emerge in the construction of public datasets, particularly in ensuring representativeness in data distribution. The recent identification of age-amplified sex differences in neural oscillations presents a striking challenge for the future of AI in neural engineering [93]. Looking ahead, as the field pushes toward bigger models and personalized neuromodulation therapies, it must confront the implications of variations across populations. AI systems will need to evolve to integrate multidimensional data to provide a comprehensive understanding of neural dynamics that accounts for individual variability [94].

Advances in science and technology to meet challenges

The anticipated impact of VLM-NE, inspired by exponential development of LLMs [95–97], is substantial, with early large EEG models already outperforming previous deep learning benchmarks [85]. Significant effort is dedicated to scaling research, specifically investigating scaling laws for VLM-NE to understand the relationship between data size, model parameters (with models like EEGPT [98] and NeuroLM [80] scaling to over 10 million parameters), and performance emergence, drawing inspiration from LLM research. Concurrently, the development of sophisticated multimodal architectures is underway, creating foundation models capable of integrating diverse neural signals (EEG, ECoG, LFP) with other physiological data (ECG, EMG), imaging (fMRI), behavioral data, and even text (e.g. NeuroLM), potentially revealing deeper insights into neural mechanisms.

Neural engineering is also exploring brain-inspired AI, recognizing the brain as nature's most efficient learning system. AI advancements have deepened our understanding of neural processes, further driving this neuroscience-informed approach. For example, continual learning based on power law dynamics observed in brain connectivity could potentially adapt to new neural data and changing conditions over time [99], mimicking the brain's lifelong learning capacity with a compact model. Similarly, building on complex network theories, community graph topology, which exhibits small-world properties similar to those in the brain, improves representation learning [100]. This approach balances channel interdependence and diversity, potentially leading to more robust feature learning in neural signal decoding and interface applications. These brain-inspired insights are driving current research toward developing compact, efficient models capable of running on limited hardware, a crucial requirement for practical neural interfaces. While still in the research phase, they represent promising directions for brain-machine interfaces, neural prosthetics, and neuromodulation techniques. By further investigating these brain-inspired principles, the field aims to achieve enhanced adaptability, personalization, and improved long-term performance in neural interfaces, ultimately bringing neural engineering closer to learning the brain's capacity for efficient lifelong learning and adaptation.

Concluding remarks

The convergence of neuroscience, machine learning, foundation models, and cybernetic integration has highlighted four key research directions: VLM-NEs, multimodal data acquisition and integration, brain-inspired computational paradigms, and large-scale standardized public datasets. While much of the discussion in this roadmap has used examples in EEG, it is important to note that these challenges and future directions are broadly applicable to other neural signal modalities. As VLM-NEs and brain-inspired architectures progress, they offer potential for integrating diverse neural data types and mimicking the brain's efficient learning mechanisms. Simultaneously, the construction of large, public datasets is becoming increasingly important, addressing challenges of data representativeness and fostering collaborative research. With these advances, addressing model bias becomes crucial for developing equitable and effective NeuroAI systems. Future efforts push the boundaries of generative applications like neural-to-content decoding and pursue ambitious goals such as digital twin brains, potentially integrating foundation models with knowledge graphs for deeper understanding. Achieving this vision requires breakthroughs in model interpretability and robustness, which may be accelerated by techniques like ensemble and federated learning. Through interdisciplinary synergy and a focus on fair and adaptive neural systems, neural engineering advances toward revolutionizing personalized neurorehabilitation, treatment of psychiatric illness, and management of mental health. This progression unlocks new frontiers in decoding neural computations, illuminating both healthy neural function and disease mechanisms. In this emerging AI and cybernetic future, the boundaries between human emotion, human cognition, and artificial systems blur, challenging our fundamental conceptions of intelligence and artificial general intelligence, and potentially redefining the essence of human-machine symbiosis.

Acknowledgements

R H M Chan was supported by a grant from the Innovation and Technology Fund (Project No. ITS/326/21FP) of Hong Kong. Any opinions, findings, conclusions or recommendations expressed in this roadmap do not reflect the views of the Government of the Hong Kong Special Administrative Region, the Innovation and Technology Commission. B. L. Lu was supported in part by grants from STI 2030-Major Projects + 2022ZD0208500, Shanghai Municipal Science and Technology Major Project (Grant No. 2021SHZDZX), Medical-Engineering Interdisciplinary Research Foundation of Shanghai Jiao Tong University 'Jiao Tong Star' Program (YG2023ZD25 and YG2024ZD25), Shanghai Pilot Program for Basic Research—Shanghai Jiao Tong University (No. 21TQ1400203), and Shanghai Jiao Tong University 2030 Initiative.

5. Neural interfaces: current challenges and the road ahead

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Status

Neural interfaces constitute the physical contact that converts neuronal activity into electrical signals and vice versa. This fundamental building block for both implantable and non-invasive systems is key to improving our understanding of brain function and as well as medical diagnostics, therapeutic interventions [101], and augmentative communication systems for individuals with disabilities.

The modern origins of the field date back to the mid-20th century with fundamental studies of electrical recording and stimulation of the nervous system [102, 103] and explorations into high-resolution methods to decode neural signals [104, 105]. These technologies have improved over the decades, driven by advances in microfabrication [106], materials science [107], and nanotechnology [108] that have improved the stability, longevity, and scale of electrical stimulation and recording. Microelectrode arrays capable of recording and stimulating neural activity with high spatial resolution [109, 110] was one critical breakthrough that continues to enable groundbreaking research in neural prosthetics [101] and neural rehabilitation.

Less invasive methods have also been developed in particular sub-dermal [111] and epidermal neural interfaces that interface with the nervous system without deep penetration into brain or spinal tissues. Sub-dermal interfaces, implanted beneath the skin but outside of the brain or nervous tissue, can stimulate and record neural activity with lower resolution than implantable devices but have shown efficacy for pain management and prosthetic device control. Epidermal interfaces, which rest on the skin's surface, are the least invasive and can also record and stimulate electrical signals, but typically with even less precision than sub-dermal technologies.

Both invasive and non-invasive technologies were built on foundational theoretical work to uncover the principles that underlie neuronal stimulation and recording and the electrochemical properties of these interfaces [112–114].

Despite remarkable progress, the field continues to face challenges [105, 115]. Figure 4 summarizes the key technological challenges and enabling strategies for the development of advanced interfaces, highlighting four major challenge domains: **Stability, resolution, power**, and **data delivery**. Stability relies on improved encapsulation, interface materials, and degradation mitigation. Resolution is driven by advances in fabrication techniques such as photolithography, transfer, and ink-jet printing. Power optimization depends on innovations in low-power electronics, batteries, and energy harvesting. Data delivery requires reliable transmission and compression methods. Together, these advances form the foundation for robust, high-performance, and long-lasting bioelectronic systems. Retinal epiretinal and subretinal implants for functional vision exemplify the current limitations of neural interface technology, as existing devices still fall short of achieving the **high spatial resolution, long-term stability**, and **ultra-low-power operation** required for seamless integration, and they lack the capability for **bidirectional data transfer** essential for implementing **intelligent, adaptive stimulation paradigms**.

Invasive implants, while offering high spatial resolution, carry risks such as tissue damage, infection, and immune rejection. Long-term stability of the interface is a major obstacle, and many technologies suffer from performance deterioration over time. Non-invasive techniques, although of lower risk, often lack the spatial and temporal resolution required for precise control of external devices or targeted therapeutics. Moreover, the complexity of neural signals and the variability across individuals pose significant hurdles for decoding and interpreting brain activity accurately.

Current and future challenges

One primary challenge in the field of neural interfaces is long-term, high-resolution stimulation and recording. In the case of implanted microelectrodes, long-term stability is often limited by the longevity and stability of materials in biological environments and the body's response to a foreign object. Addressing these issues will benefit from the development of flexible or biocompatible materials and coatings that minimize the foreign body response, promote neural integration [116], and maintain stable electrical interfaces with neurons over extended periods [117].

Less-invasive interfaces typically provide improved longevity and reduced surgical risks. Electrodes laid across the surface of the brain, implanted in blood vessels in the brain, or over the dura often provide higher resolution than non-invasive wearable devices, better stability than electrodes in the neural tissue, but generally suffer the trade-off: less-invasive technologies provide less resolution. For some applications, however, high-resolution may not be necessary; such as therapeutic neuromodulation for movement disorders, mood disorders, and neurogenerative diseases.

Wearable interfaces are also improving due to advances in microelectronics and signal processing.

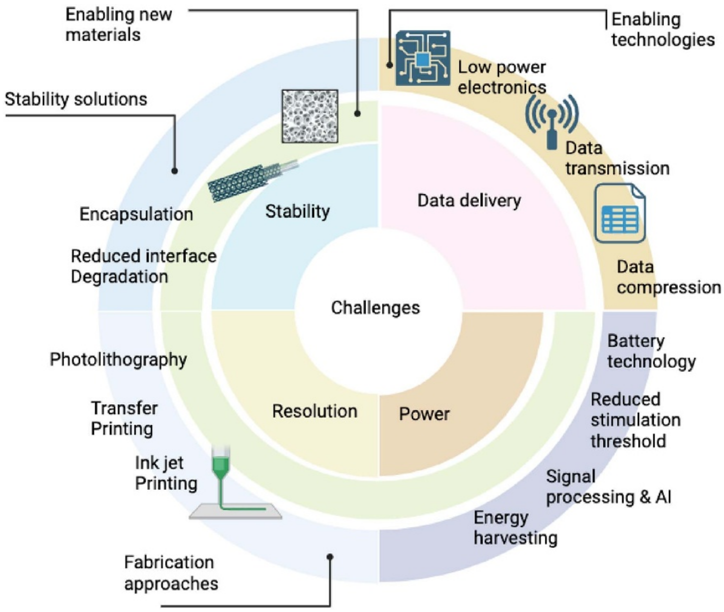

Figure 4. Current challenges in neural span over: stability, data delivery, power supply and management and resolution. In each of these realms innovative technologies are playing a major role. New materials are helping shape new solution for improved stability, resolution and power consumption.

Materials for low-impedance dry electrodes are making EEG easier and more reliable. Consumer friendly wearables with low form factors like EEG-enabled headphones and earbuds may enable entry into consumer markets. On the therapeutic side, implanted devices like DBS, still show higher efficacy for difficult to treat disorders when compared to wearable counterparts, but contemporary efforts may advance wearable approaches, for example using temporal interference and focused ultrasound [118].

In cases where high-bandwidth information transfer is desired, a major research challenge is improving the spatial resolution and specificity of neural recordings and stimulation. While current microelectrode arrays offer impressive capabilities for capturing neural activity, they often lack the spatial precision necessary to distinguish individual neurons or neural populations reliably. Furthermore, the indiscriminate activation of nearby neurons during stimulation can lead to unintended side effects and limit therapeutic efficacy. It is important to note that increasing the density of recording or stimulating channels in neural implants inevitably intensifies mechanical and biological constraints. A challenge is increasing spatial resolution without compromising tissue integrity. Although some degree of neuronal damage is unavoidable, progress in **biocompatible and mechanically compliant electrode materials** may help reduce damage as spatial resolution is improved. In parallel, the **need to wire-out each electrode** poses major scaling challenges that can be partially mitigated by integrating **local active electronics** for multiplexing and signal conditioning. However, such integration introduces additional hurdles in **power delivery, thermal management, and long-term encapsulation**. Addressing these interrelated challenges is essential for achieving scalable, high-density invasive neural interfaces. Altogether, overcoming existing challenges requires the development of advanced electrode designs, signal processing algorithms, and closed-loop control strategies that enable precise targeting and modulation of specific neural circuits. The integration of implanted microelectrodes with external devices presents additional technical hurdles. Ensuring seamless communication between the implanted electrodes and external hardware while minimizing power consumption, size, and weight constraints is essential for practical and scalable neural interface systems.

Advances in science and technology to meet challenges

Meeting the challenges associated with implanted microelectrodes for neural interfaces requires significant advances across multiple fronts to unlock the full potential of neural interfaces for medical and scientific applications (see figure 5). Neural interfaces open transformative opportunities across therapeutic, personalized, and augmentative domains. Applications span movement and sleep disorders, neurodegeneration, mental health, and neuroprosthetics, while also enabling real-time, adaptive, and closed-loop interventions for rehabilitation and mood regulation. Together, these opportunities highlight the growing potential of neural technologies to deliver intelligent, individualized, and responsive solutions for

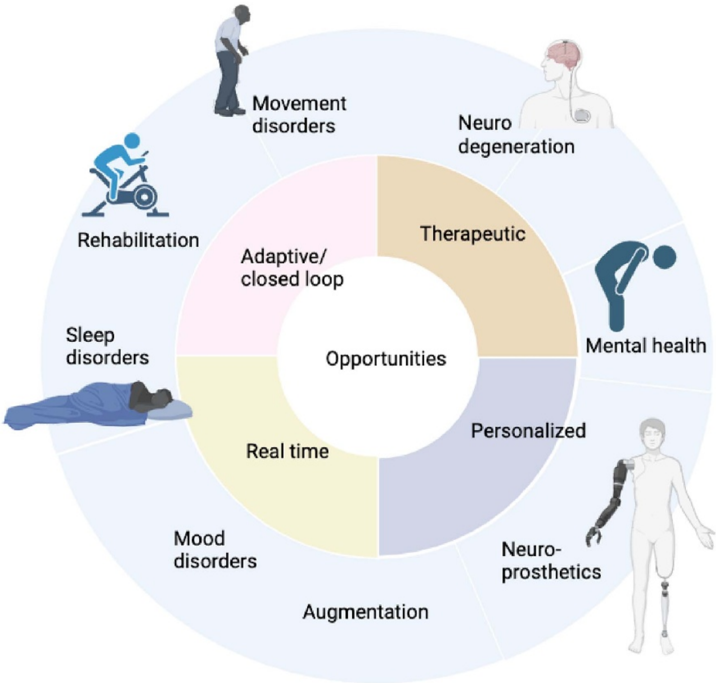

Figure 5. Opportunities in neural interfaces: adaptive closed loop systems, real time data, personalized analysis and new and enhance therapeutics. Those can benefit a wide range of fields including rehabilitation, movement disorders, neurodegeneration, mental health and neuro-prosthetics.

both clinical and enhancement purposes. One key area of advancement lies in materials and coatings that promote neural integration while minimizing the foreign body response. Novel materials with tailored mechanical, electrical, and biological properties also hold promise for improving the biocompatibility and longevity of neural interface devices, thereby extending their functional lifespan and therapeutic efficacy.

Furthermore, advances in microfabrication techniques are critical for improving the spatial resolution and specificity of neural recordings and stimulation. Novel electrode designs, such as high-density arrays with smaller feature sizes and improved electrode-tissue interfaces, enable more precise targeting and modulation of specific neural circuits. Microscale manufacturing technologies, such as microelectromechanical systems and nanofabrication [119], offer unprecedented control over electrode geometry and surface properties, facilitating the development of next-generation neural interface devices with enhanced performance and functionality.

Low power electronics, wireless data and power transfer, and improved signal processing algorithms are also needed to enable future closed-loop devices [120] and minimally invasive surgical procedures. Improvements in power density via novel wireless technologies and low-power electronic design will help transition neural interfaces from traditional medical device architectures with batteries and long lead wires to fully integrated, to leadless devices that can be delivered laparoscopically via out-patient procedures and operated as distributed wireless networks within the body.

Alternatives to electrodes are also a promising route forward, particularly for stimulating neural activity. Forms of energy like light, magnetic fields, and ultrasound are being explored with and without materials or genetic manipulation as co-factors to facilitate neural stimulation. How to use these modalities for recording to extract information from the nervous system remains an open question. Indeed, future interfaces may include electrodes alongside other forms of energy or even living cells as multimodal brain interfaces with enhanced longevity and specificity.

In summary, neural interfaces are already helping individuals with neurological injuries or degenerative disorders. Future neural interfaces will be capable of adapting to individual needs via closed-loop therapies, operate reliably for years, and improve over time not only by treating disorders, but eventually tracking what each patient needs and preventing further decline in their medical condition.

Concluding remarks

Neural interfaces represent a pioneering convergence of neuroscience and technology, offering unprecedented opportunities for direct communication between the brain and external devices. While the field has made significant strides, challenges persist in the development of implanted microelectrodes, including issues of long-term stability, spatial resolution, and integration with external hardware. However, ongoing advances in materials science, microfabrication, and nanofabrication, as well as understanding the factors that determine the biological responses to implanted device, hold promise for overcoming these challenges and unlocking the full potential of neural interfaces. By leveraging interdisciplinary collaboration and pushing the boundaries of science and technology, researchers are poised to address these challenges and realize the transformative potential of neural interfaces. Together, these efforts herald a future where seamless communication between the brain and technology enables novel therapies, enhances human capabilities, and deepens our understanding of the mind-brain interface.

6. Neural imaging

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Status

Neuroimaging, or the visualization of the nervous system across space and time, is a fundamental tool to map and understand the inner universe within us. The human nervous system is comprised of billions of neurons with trillions of connections operating at millisecond speed. Emerging neuroimaging techniques can be used to investigate brain function and structure at high spatial and temporal resolutions, while remaining largely non-invasive.

The field of neuroimaging evolved rapidly over the past several decades, overcoming technical challenges, enabling discovery and diagnosis, and improving treatment planning and monitoring. Given the current breadth of the field, we simply cannot cover every promising progress, rather we hope to provide a representative sampling of the many exciting advances, as well as promising directions, with an emphasis on those that are being developed and translated to image the human brain.

Current and future challenges

Because of the sheer scale of neurons and neuronal connections, it is a daunting task to fully capture the brain in action at both high spatial and temporal resolution. Yet neuroimaging faces obstacles that go far beyond improving imaging hardware alone. Four key areas stand out: imaging technology, data management, broad accessibility, and integration with other neuroengineering disciplines (figure 6).

While imaging technology has seen marked improvements over the past two decades, it remains a challenge to reach both high spatial and temporal resolution at the same time in a non-invasive manner. For example, PET and fMRI can spatially map cerebral blood flow and oxygenation changes as the result of neuronal activation, but their temporal resolution is constrained by hemodynamics; EEG and MEG arrays can detect neuronal activity at the rate of neuronal firing, but they lack sufficient spatial localization. Even pre-clinical imaging modalities that use genetically encoded indicators of neural activity are ultimately limited by the dynamics of the biological signal, the indicator, and the microscope. To date, there still is not a neuroimaging technique that can directly and non-invasively measure neuronal activities at both high spatial and temporal resolution across the human brain.

Despite this, advances in imaging technology have led to an explosion in the size and volume of neuroimaging data collected around the world. The vast amount of neuroimaging data has had a transformative effect on scientific discovery, but the management of those data has emerged as a significant challenge. With the diverse array of neuroimaging techniques, features of data management such as standardization, curation, processing, and sharing have been a central focus within the neuroimaging community in recent years. Improved ability to harmonize the diverse and large amount of neuroimaging data is in urgent need so that the collective big data can be used to enable data-driven and AI-assisted analysis to harness its power.

While large publicly available datasets begin to address democratization of scientific inquiry, accessibility to emerging neuroimaging tools remains a challenge. As most of the development effort has been invested to reach higher resolution, stronger hardware, and faster speed, the costs of modern neuroimaging devices have been steadily increasing, and are often out of reach in under-served regions and populations. Addressing this challenge will ensure the benefits of neuroimaging meet the needs of the community more fully.

Finally, neuroimaging has traditionally focused on discovery and diagnosis, rather than treatment. Integration with other neuroengineering disciplines, such as artificial intelligence, brain-machine interfaces, and neuromodulation, for treatment and rehabilitation has been nascent. Closing this gap is critical for using neural imaging to improve treatment planning, implementation, and monitoring.

Advances and opportunities

Challenges motivate innovations and give rise to opportunities (figure 6). Indeed, there have been many advances in recent years toward overcoming these challenges, many of which opened new ways to image the brain.

To address limitations in imaging technology, researchers have developed hardware to increase speed, sensitivity, and spatiotemporal resolution. For example, new fMRI techniques using ultrahigh fields can now readily reach submillimeter resolution to resolve cortical layers close to the spatial scale of fundamental neuronal ensembles [121], while diffusion MRI with ultrastrong gradient coils can resolve cortical columns that can help identify earliest signs of

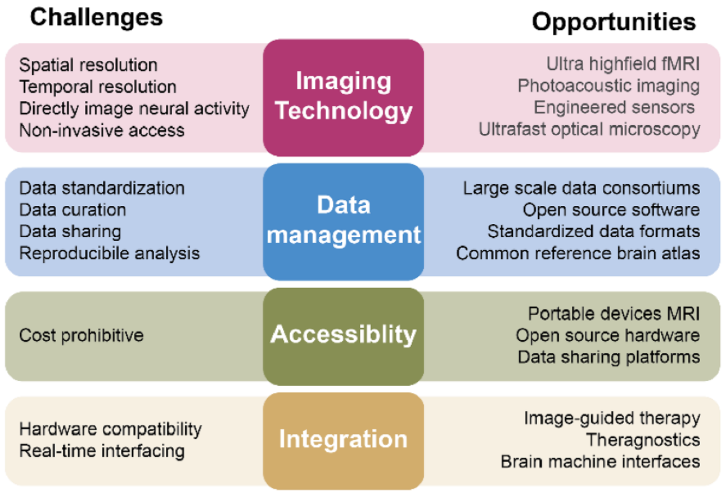

Figure 6. Current challenges and opportunities in neural imaging target imaging technology, data management, accessibility of neural imaging, and integration with other technologies.

neurodegeneration [122]. Recent advances in photoacoustic imaging in humans have shown great promise in indirectly mapping neural activity (e.g. through hemodynamics) at both high spatial and temporal resolution, if accurate modeling of the human skull can be obtained [123]. Continued effort is being made toward direct imaging of neuronal activation in humans [124], with most advances in pre-clinical imaging where advanced genetically encoded sensors [125–128] paired with ultrafast optical imaging [129] are providing unprecedented access to neural activity. However, the highly scattering nature of the brain remains a technical challenge for light-based neuroimaging where advances such as adaptive optics [130] have shown promise for improved imaging depth. Future innovations are aimed at the ultimate goal of imaging the human brain at single neuron resolution. While we are unlikely to achieve this in the next 10 years, it remains as the grand challenge of the field.

Advances in image acquisition go hand in hand with the improved data management to enable standardization for both data sharing and reproducibility of research outcomes. The advent of large neuroimaging consortia such as the Human Connectome Project, ABCD, UK Biobank, and the Allen Brain Observatory, has demonstrated the feasibility and tremendous value of large neuroimaging data acquisition, harmonization, analysis, inference, and sharing [131–134]. Containerized environments for reproducible Neuroimagedata analysis [135] have ushered in a new era of open science to promote repeatable and accessible scientific inquiry. In parallel, preclinical imaging has promoted data standardization through the development of standardized data formats [136], modular architectures for neurophysiology data [137, 138], common reference brain atlases [134, 139], and open source software packages for image analysis [140–143], which has enabled large scale data platforms through the Allen Brain Institute and the International Brain Laboratory. Importantly, along with the rise of AI, advanced analysis algorithms that take advantage of big data to improve signal extraction, pattern recognition, and clinical diagnosis are rapidly emerging.

In the recent past, most significant effort has been invested in advancing neuroimaging methods for faster, bigger, and better performance leaving many under-served regions and populations without sufficient access to modern neuroimaging technologies. For example, the number of MRI machines per million people in the US and developed world are about 20–50, while in Africa this number is less than 1. To address this glaring gap, recent effort has also been invested in portable and satellite-based wireless imaging devices (even MRIs, [144]), which can serve many under-served regions with insufficient reliability in regular electricity and internet connectivity. In light-based preclinical imaging, open hardware (e.g. [145–148]) has emerged as a leading candidate to enable broad adoption of advanced neuroimaging techniques.

Finally, the role of neuromaging has been evolving from that of a diagnostic tool toward an active contributor to therapeutic approaches. For example, neuroimaging has been playing an increasingly important role in closed-loop theragnostic approaches, or image-guided therapy, through integration with other neuroengineering disciplines such as closed-loop BMIs to acquire and analyze neuronal activation data in real time, and guide neuromodulation or other external device (e.g. robotics) to improve treatment planning, implementation, rehabilitation, and monitoring [149]. In many ways, neuroimaging is the cornerstone technology that provides data for developing neural models, for training AI and machine learning algorithms, for providing feedback to BMIs, and for seemly limitless future applications. This integration may be one of the most exciting new opportunities for neuroimaging in the near future with applications in preclinical imaging leading the field in technology integration.

Concluding remarks

The field of neural imaging is evolving rapidly toward the ultimate goal of visualizing fundamental neuronal units and their activities across the brain in real time. With improved precision and portability, the future of neural imaging holds immense promise as it can be employed to provide a precise map to guide neuromodulation or to provide feedback to external devices such as through closed-loop brain-machine interfaces. These innovations have the potential to transform both diagnosis and treatment of brain disorders. As such, the future is bright (pun intended).

7. Technology for augmented rehabilitation

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Status

The use of technology to enhance therapy and treatment for neurological and musculoskeletal disabilities has been common practice for a long time. Artificial limbs and body parts have been documented in times Before the Common Era with electric technologies for artificial limbs employed for over 100 years [150]. Electrical therapies have a history that goes back at least hundreds of years, with some reports as old as 2000 years [151]. It has been ∼50 years since robotic devices have first been tried as training assistants for rehabilitation [152] and virtual and augmented reality devices experiments for rehabilitation soon followed [153]. We use the term augmented rehabilitation here to refer to all of these types of technologies. In the past, some researchers have used the term augmented rehabilitation to apply more strictly to augmented reality and/or virtual reality rehabilitation [154], but language like technology evolves over time. The wide range of technologies that have emerged in the last few decades for rehabilitation require a more inclusive accounting to map a plan for future developments.

Over the last thirty years, robotics and computer science technologies have rapidly increased their impact on rehabilitation. Best practices in rehabilitation have often relied on personal experiences of clinicians due to the difficulty in recording therapeutic interactions and tracking patient progress in recovery. In addition, the high variability in injuries and recovery across patients contribute to the difficulty in performing randomized clinical trials. With the advent of new rehabilitation technologies that could quantitatively measure improvements as well as enhance therapies, the field has become more evidence-based in the approach to adopting new technologies. Many innovations have not yet reached widespread clinical use, but the adoption of rigorous assessment approaches has been widespread, in part due to the new technologies available.

The most recent technological innovations for rehabilitation include both hardware and software. Robotics has brought new actuators and sensors that helped standardize therapies and quantify patient progress. Computer processor power and speed gains have enabled new sensing and control approaches. Subsequent advances in artificial intelligence and control theory have provided adaptive human interfaces. Some of the technologies have focused on replacing (e.g. active prostheses) [155, 156] or restoring (e.g. exoskeletons) [157] lost human function as assistive devices. Other technologies have focused on enhancing the therapy process to allow humans to recover their own sensory and motor capabilities with practice (e.g. robotic gait trainers) [158]. Most recently, neuroelectric medicine has been aided by minimally invasive delivery mechanisms that allow them to more effectively alter nervous system activity [159]. TMS and direct current stimulation can alter cortical excitability non-invasively both in the short and long term, yielding considerable opportunities for new treatment strategies [160]. Peripheral nerve stimulation and spinal stimulation have also shown promise as pathways to enhance neural plasticity during therapy [161]. Augmented and virtual reality hardware and software have been advanced through the years, but evidence for their efficacy in neurological rehabilitation above and beyond a similar amount of standard therapy has been sporadic and mixed [162, 163].

Translation of the technological advances to clinical practice is coming slowly. Innovative devices require time-intensive pilot studies and clinical trials. For example, we have many robotic devices that can manipulate physical interaction forces and many electrical devices that can stimulate motor and sensory neurons to alter adaptation and learning during rehabilitation. However, we do not fully understand how to optimize device parameters to yield the best outcomes. As a result, there are many clinical research studies that show negligible to moderate effects. Some researchers have even started to combine multiple technologies simultaneously in the hope of improving clinical outcomes, with the result of increasing the permutations of parameter optimization considerably. This complicated process in rehabilitation engineering design and development is confounded by a lack of basic science knowledge on principles of neural plasticity. As a result, augmented rehabilitation technology has yet to achieve its full promise to clinical practice.

Current and future challenges

The three biggest challenges to developing better augmented rehabilitation technology are a need for: (a) better actuators, (b) better bidirectional human-machine interfaces, and (c) optimization of delivery parameters for maximizing adaptation, learning, and plasticity (figure 7).

Most rehabilitation robotics devices have used hard actuators with relatively low power to weight ratios, but biological systems typically rely on soft actuators with very high power to weight ratios [170]. Creating flexible, lightweight actuators that can mimic the advantages of biological muscles

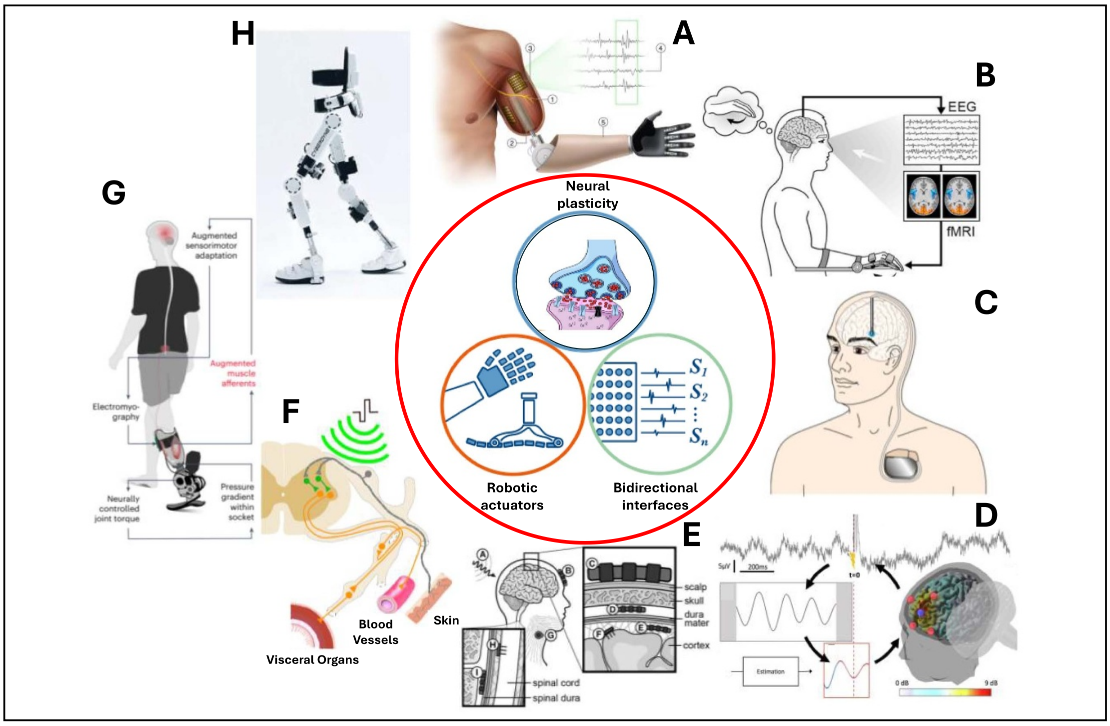

Figure 7. Technological innovations from robotics, computer science, and neuroscience have led the way for better devices for augmented rehabilitation. (A): Upper limb prosthesis with osseointegration and targeted muscle reinnervation (Reproduced from [155], with permission from Springer Nature). (B): Closed-loop brain-computer interface for therapy (Reproduced from [164]. CC BY 4.0). (C): Deep brain stimulation (Reproduced from [165], with permission from Springer Nature). (D): Closed-loop brain stimulation (Reproduced from [166]. CC BY 4.0). (E): Brain and spinal cord stimulation/recording (Reproduced from [167]. CC BY 4.0). (F): Non-invasive spinal cord stimulation (Reproduced with permission from [168]. © The Author(s) 2023. CC BY-NC-ND 4.0). (G): Lower-limb prostheses with bi-directional interfacing (Reproduced from [156]. CC BY 4.0). (H): Cyberdyne HAL exoskeleton. I: Manual dexterity test (box & block test) in extended reality, using immersive virtual reality with controllers (Reproduced from [169]. CC BY 4.0).

would substantially improve rehabilitation devices. Actuators that have a large range of motion, high mechanical power outputs, and series elasticity could allow exoskeletons and prostheses to assist more human movement tasks. In addition to the actuators themselves, there is a need for better transmission mechanisms. Mechanical interactions that keep skin compression and stress levels low while not losing large percentages of actuator energy to soft tissue compression would be a major improvement over the status quo. Sockets for prostheses are one example of mechanical interaction between the user and rehabilitation device that is uncomfortable, often causes skin damage, and can lead to obstructed blood flow [155].

Human bodies typically operate with bidirectional pathways between the nervous system and the musculoskeletal system. However, many rehabilitation engineering devices have primarily relied on unidirectional control. There is the need to use multimodal pathways to implement functional bidirectional interfaces. For example, providing haptic, position, and force feedback from a prosthetic limb to the user's nervous system would make it much easier for the user to develop an internal model of the prosthesis and adopt it into their body schema [171, 172]. Similarly, the likelihood for bidirectional interfaces to improve embodiment is important in many other wearable technologies [173, 174]. Another example is the use of closed-loop DBS approaches that sense ongoing brain activity to determine when and how much to stimulate the brain [175]. Researchers have barely touched the surface on using real-time biofeedback to shape immersive virtual and augmented reality tasks and environments [176]. Whether a biomechanical device, a neural device, or a hybrid neuromechanical device, incorporating bidirectional sensing and control has the potential to improve performance.

Another major obstacle to widespread clinical implementation of augmented rehabilitation technology has been inadequate understanding of sensorimotor adaptation, learning, and plasticity [164]. Optimization of training, stimulation, and feedback parameters is a slow process that takes considerable time after initial prototype development. The large inter-subject variability makes it difficult to systematically test parameter sensitivity in small research studies. A better fundamental understanding of how the nervous system responds to mechanical, electrical, and sensorimotor stimulation would facilitate optimization of interventions. Virtual reality in humans and non-human animals offer the opportunity to use neural imaging and biomarkers to reveal fundamental new information about neuroscience principles involved in sensorimotor adaptation, learning, and plasticity.

Advances in science and technology to meet challenges

In regards to engineering new actuators, there is more diversity in approaches than ever before [170]. For electromechanical and hydraulic actuators that are still heavy and bulky, it has become common to use cable transmissions to transmit force and power to distal limb segments. Carrying added mass at the torso or even off the body reduces the metabolic penalty compared to carrying the added mass on the limb segments. Moreover, compliant actuators that can endure high jerk values without damage have many advantages over stiff actuators that are not backdrivable. As a result, engineers have looked to develop artificial muscles using novel geometries and materials, such as hydraulic and pneumatic origami, shape memory alloys, or electroactive polymers [170, 177]. The recent advances with twisted and coiled artificial muscles, rope-like structures with fibers that compress with thermal or chemical control, hold potential for soft and flexible mechanical human-machine interfaces in the future [170].

Several new approaches to bidirectional neural interfaces have been developed in the last two decades. For example, motor nerve fibers can now be interfaced with many types of electrodes, including intrafascicular micro-electrodes. Alternatively, nerve transfer surgical techniques offer the ability to connect peripheral nerves to muscle tissue, which acts as a bioelectric amplifier of the nerve activity [155]. Nerve transfers and muscle interfacing for decoding motor intent have revolutionized prosthesis control, especially in the case of proximal amputations. Stimulating sensory nerve fibers can be done with electrical, magnetic, and even ultrasound stimulators on the skin's surface (e.g. handheld vagus nerve stimulators) [167, 172]. Electrical and ultrasound stimulators may also provide controlled stimulation to the spinal cord. Human experiments have revealed that even simple low-level non-invasive stimulation to the spinal cord can increase excitability and improve motor function after neurological injury [159, 168]. Determining the optimal timing and stimulation parameters remains to be achieved but these non-invasive stimulators hold great promise for near-term translation to the clinic. Meanwhile, DBS has become a standard for treatment of symptoms in Parkinson disease, essential tremor, and dystonia [165, 178], and may soon extend its application to other pathologies.

A basic, mechanistic understanding of the neurophysiological structures and processes targeted by augmented rehabilitation technologies is lacking. This knowledge gap is slowly being filled by adopting results of neurophysiological studies in the design of rehabilitation systems. Long-term potentiation (LTP)/long-term depression (LTD) in neural circuits are key elements for learning and training. A particularly relevant form of LTP/LTD plasticity in the context of motor learning is that achieved using associative interventions, where pairs of stimuli are delivered to converging inputs onto a neuron in (temporal or spatial) association, altering the synaptic efficacy. An example of these approaches is Paired Associative Stimulation, extensively tested in humans, which has been translated into methods for neuromodulation in rehabilitation systems. For example, brain interfacing is being incorporated into rehabilitation robotics to establish an associative link between motor commands (decoded by the brain interface) and sensory feedback (provided by the rehabilitation robot via limb movements). Moreover, closed-loop brain stimulation has systematically assessed the efficacy of the stimulation in relation to brain oscillations [166]. Another methodological approach for tracking neural plasticity in human experiments is mobile brain imaging with high-density EEG or functional near-infrared spectroscopy [179]. These imaging modalities can provide relatively fast feedback about changes in brain dynamics with rehabilitation interventions without waiting weeks or months for behavioral outcomes. ECoG and other invasive brain recording modalities can provide information from an even greater range of brain structures with improved spatial resolution [180], but the requirement for surgery is a drawback.

Concluding remarks

Augmented rehabilitation technologies, such as virtual and augmented reality, exoskeletons, prostheses, and gait trainers, have had relatively slow clinical translation over the last few decades. This delay is evident when compared to other neurotechnologies, such as cochlear implants and visual prostheses. The slow implementation has been primarily due to challenges in small sample size studies, widely varying experimental paradigms, lack of bidirectional interfaces, and inadequate understanding of neural plasticity mechanisms at the systems level. Rehabilitation technology clinical trials are difficult, laborious, and expensive. Important steps have been made to improve the technologies, and the future will likely see accelerated widespread adoption. Continued advances in miniaturized electronics, high computational capacity, soft actuators, biomimetic materials, machine learning & artificial intelligence, and human in the loop controllers will continue to push augmented rehabilitation technology to a much larger number of patients.

Acknowledgements

Supported by the Leo Claire & Robert Adenbaum Foundation (DPF) and by the European Research Council (ERC) (DF).

8. Neuromaterials

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Status

Therapeutic and diagnostic interventions that have been enabled through neural interfaces rely heavily on the development of safe and effective materials. From hermetically constructed packages for protecting electronics, to the active electrodes which communicate with living tissues, it is critical that the materials are not only functional but well tolerated by the body across patient lifetimes. While early devices focused on critical restoration of neural functions, such as pacing of excitable cells, recent decades have sought to improve the longevity and integration of devices with the body.

Electronics within the body must be adequately protected and approaches for hermeticity have been a topic of significant research. However, these components can be implanted in areas of the body that are more tolerant of fibrotic encapsulation. Conversely, the interconnects and electrode arrays that reside within the target tissue must be carefully tailored to ensure that mechanical and chemical properties are biocompatible and stable across chronic implantation. To this end an intense research effort has focused on improving the conductive elements of neurotechnology predominantly through the exploration of new materials and manufacturing processes.

Historically both recording and stimulating implanted electrodes have been fabricated from metals, such as platinum (Pt) and platinum alloys, due their stability within a biological environment (figure 8). However, it is known that metals have significant mechanical mismatch with soft tissues and limited safe charge injection due to poor efficiency of the transduction of electrons within metals to ions within the body [181–183]. To improve the charge injection capacity of electrodes, metal oxide and other semi-metal materials have been exploited as coatings [184, 185]. These materials can address some of the electrochemical limitations but do little to ameliorate the mechanical mismatch between hard devices and soft tissues. In contrast, polymer and other organic based approaches have been demonstrated to facilitate not only an ability to improve the operational bandwidth of an electrode by widening the electrochemical safety window but also enable tailoring of the mechanical and biological properties, providing more stable performance under both recording and stimulation conditions [107]. Inherently conductive polymers and carbon technologies, such as graphene, have shown promise at enabling mechanically tailored and bioactive solutions to neural interfacing [186, 187]. The most advanced approaches in this area include living or biohybrid devices, which seek to utilize not only synthetic organic electroactive materials but also living components such as cells, to create synaptic interfaces and integrated neural networks between devices and endogenous neural tissues [187].

Current and future challenges

While functional bench-top performance of polymeric electrodes has been shown to be comparable across a wide range of material chemistries there is some difficulty in comparing the biological performance of these materials. Direct comparisons between different material chemistries is made more difficult due to the variation in device formats, characterization protocols, and *in vivo* testing methodologies. A more general evaluation of material 'biocompatibility' is complicated by the tissue specific interplay which includes both the materials surface and device mechanics, where the latter depends on both the materials and form factor. As such, a standard for comparison and an understanding of the level of improvement enabled by new materials is a critical need for informed design and comparative assessment. In the specific case of electrodes, steps have been made toward common metrics for performance. The most important aspect is to enable low impedance from a small surface area and to safely inject charge [191]. The increased amount of charge that can be delivered within the electrochemical limits of organic neuromaterials supports their utility and translation [181, 191, 192].

While many new materials have been proposed and characterized, there is a much smaller number of neuromaterials that have been translated to industry and implemented in the clinic, despite the potential these novel materials have in solving key challenges facing the field of neural engineering. Major hurdles to the application of these next generation neuromaterials are evidence of long-term efficacy and the burden of regulation to understand the potential degradation products of materials that are arguably more complex than traditional metals [193]. For biohybrid devices that are combinatorial, being both the highest risk in medical device regulations (active implantable medical devices) and with living components such as stem cells, there is no unifying global regulation [194]. As such, the translation of neuromaterials involves not only meeting the existing regulations but also defining and safely navigating an undefined area of device regulation.

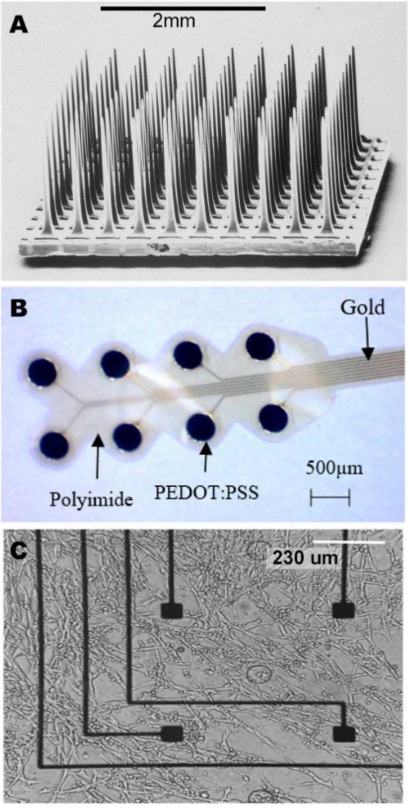

Figure 8. (A) A conventional electrode array, the Utah Intracortical Electrode Array with 100 electrodes made from silicon shanks metallized with platinum. Reprinted from [188], Copyright (1998), with permission from Elsevier. (B) Organic electrode array based on gold tracks in flexible polyimide substrate. The electrodes are electrochemically coated with PEDOT:PSS. Reproduced from [189]. CC BY 4.0. (C) Human iPSC-derived myocytes cultured on an electrode array based on PEDOT:PSS coated gold electrodes in a parylene C substrate. Once implanted on a nerve the culture myocytes form neuromuscular junctions with the native tissue. Reproduced from [190]. CC BY 4.0.

However, there is a need for change, with neural electrode advancement being stymied by the lack of translation. While the development of miniaturized and low noise electronics has driven the maturity of the neurotechnology field, the size and number of electrodes that are being implanted in patients has not changed substantially [195]. Electrode arrays with tens and occasionally hundreds of electrodes are implanted clinically, but within the literature devices with thousands of electrodes are designed and validated. These devices are routinely used in research, such as neurophysiology studies, but with few exceptions have not advanced to clinical application. While many applications do not require electrode numbers in the hundreds to thousands, some applications such as bionic eye devices benefit greatly from increased channel counts. There remains an unrealized potential for improved clinical recording and stimulation, enabling personalized and dynamic treatment of neurological conditions.

Advances in science and technology to meet challenges

There is a trade-off to be considered for advanced devices that not only communicate with the neural system but also integrate and promote regenerative environments. The addition of biological components such as cells and biomolecules that can modify the environment of the target cells, also inherently bear a greater risk to patient safety and challenge to regulation, clinical testing, and sterilization. As such, the future of neuromaterials and biohybrid technologies should mitigate patient risks while enabling technologies that can not only communicate with the neural tissue but address the underlying disease or injury pathology using novel approaches including regenerative strategies and biomimetic stimulation strategies.

Synthetic biology provides options for cellular-like components that can be tuned to dynamically respond to their environment. These vesicles can release trophic factors, deliver gene transfects, or contain organelles that are both responsive to, and effectively immunoprotected from, the host environment [196]. By removing or synthetically constructing the biological component, the risk of immune reactions is mitigated, but significant development is required to ensure stability and temporal efficacy of these constructs.

Surgical approaches can be used to provide alternative tissue engineered constructs without requiring cells sourced from outside of the host. Regenerative peripheral nerve interfaces are surgical constructs that use spared patient muscle or dermal tissues. These surgical constructs could be used in combination with organic electronics to create high resolution interfaces for control of prosthetics and sensory feedback [197]. By reusing tissues that are deemed non-critical to the patient quality of life, this approach may be more easily translated than other biohybrid neuromaterials. This example of effective repurposing of tissues for patient benefit may find utility in other neural interfacing applications.

New materials also have an important role to fill to allow combining neurotechnological interventions with other modalities, e.g. the combination with MRI. While metals typically generate imaging artifacts, and conversely MR signals generate large recording artifacts overshadowing neural signal data, organic and carbon materials can be fully MR compatible [198]. Additionally, conducting neuromaterials can allow *in situ* degradable neurotechnology. In some clinical use cases there is only temporary need for monitoring or stimulation, and the threshold for clinical use may be reduced if this functionality can be provided without the need to perform explant surgery [199]. While a plethora of degradable insulators already exist, the major remaining hurdle is still the lack of conducting materials with sufficiently low resistivity that disintegrate into constituents that are harmless and bioresorbable. Several pathways exist in composites of both conducting polymers and metals to explore degradability.

Concluding remarks

For many decades Pt has been the main conductor used clinically in electrodes and connections, with well-known limitations to high resolution connections with the nervous system. However, with increasing options spanning metal oxides, carbon, and polymeric conductors, there are many more emergent solutions that will provide increased functionality, improved patient outcomes, and completely new opportunities. The development of and adherence to protocols for comparing neuromaterials and embedding of studies which align closely with the international standards for device safety and efficacy, is critical to seeing neuromaterials make impact within the clinic. This parallels the need for identifying optimal design criteria for specific clinical applications and mapping the translational pathway to ensure that there is also significant stakeholder engagement supporting the design and clinical implementation of devices based on advanced material systems. Blurring the divide between tissue engineering and bioelectronics has been a critical step across recent years. However, further merging may provide opportunities to enable more personalized and bespoke solutions without the risk of poor biological responses to foreign components (such as allogenic biologics). This is particularly important for stimulation applications and recording in confined areas where smaller electrodes are necessary to achieve greater spatial resolution.

Acknowledgements

[Please include any acknowledgements and funding information as appropriate.]

Data availability statement

This is a review and commentary, and, as such, there are no data to make available.

Author contributions

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Conceptualization (equal), Methodology (equal), Project administration (equal), Writing – original draft (equal), Writing – review & editing (equal)

References

[1] Kennedy P R and Bakay R A 1998 Restoration of neural output from a paralyzed patient by a direct brain connection *Neuroreport* **9** 1707–11

[2] Chapin J K, Moxon K A, Markowitz R S and Nicolelis M A 1999 Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex *Nat. Neurosci.* **2** 664–70

[3] Taylor D M, Tillery S I H and Schwartz A B 2002 Direct cortical control of 3D neuroprosthetic devices *Science* **296** 1829–32

[4] Serruya M D, Hatsopoulos N G, Paninski L, Fellows M R and Donoghue J P 2002 Instant neural control of a movement signal *Nature* **416** 141–2

[5] Pandarinath C, Nuyujukian P, Blabe C H, Sorice B L, Saab J, Willett F R, Hochberg L R, Shenoy K V and Henderson J M 2017 High performance communication by people with paralysis using an intracortical brain-computer interface *elife* **6** e18554

[6] Collinger J L, Wodlinger B, Downey J E, Wang W, Tyler-Kabara E C, Weber D J, McMorland A J, Velliste M, Boninger M L and Schwartz A B 2013 High-performance neuroprosthetic control by an individual with tetraplegia *Lancet* **381** 557–64

[7] Hochberg L R *et al* 2012 Reach and grasp by people with tetraplegia using a neurally controlled robotic arm *Nature* **485** 372–5

[8] Willsey M S, Shah N P, Avansino D T, Hahn N V, Jamiolkowski R M, Kamdar F B, Hochberg L R, Willett F R and Henderson J M 2024 A real-time, high-performance brain-computer interface for finger decoding and quadcopter control *bioRxiv and accepted at Nature Medicine* pp 2024–02

[9] Bouton C E *et al* 2016 Restoring cortical control of functional movement in a human with quadriplegia *Nature* **533** 247–50

[10] Ajiboye A B *et al* 2017 Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration *Lancet* **389** 1821–30

[11] Willett F R *et al* 2023 A high-performance speech neuroprosthesis *Nature* **620** 1031–6

[12] Card N S *et al* 2024 An accurate and rapidly calibrating speech neuroprosthesis *New Engl. J. Med.* **391** 609–18

[13] Vansteensel M J *et al* 2024 Longevity of a brain–computer interface for amyotrophic lateral sclerosis *New Engl. J. Med.* **391** 619–26

[14] Metzger S L *et al* 2023 A high-performance neuroprosthesis for speech decoding and avatar control *Nature* **620** 1037–46

[15] Normann R A, Maynard E M, Rousche P J and Warren D J 1999 A neural interface for a cortical vision prosthesis *Vis. Res.* **39** 2577–87

[16] Anumanchipalli G K, Chartier J and Chang E F 2019 Speech synthesis from neural decoding of spoken sentences *Nature* **568** 493–8

[17] Barrese J C, Rao N, Paroo K, Triebwasser C, Vargas-irwin C, Franquemont L and Donoghue J P 2013 Failure mode analysis of silicon-based intracortical microelectrode arrays in non-human primates *J. Neural Eng.* **10** 066014

[18] Patel P R *et al* 2023 Utah array characterization and histological analysis of a multi-year implant in non-human primate motor and sensory cortices *J. Neural Eng.* **20** 014001

[19] Chestek C A *et al* 2011 Long-term stability of neural prosthetic control signals from silicon cortical arrays in rhesus macaque motor cortex *J. Neural Eng.* **8** 045005

[20] Rubin D B *et al* 2023 Interim safety profile from the feasibility study of the BrainGate neural interface system *Neurology* **100** e1177–e92

[21] Wu W, Shaikhouni A, Donoghue J R and Black M J 2004 Closed-loop neural control of cursor motion using a Kalman filter *26th Annual Int. Conf. IEEE Engineering in Medicine and Biology Society* vol 2 (IEEE) pp 4126–9

[22] Sussillo D, Nuyujukian P, Fan J M, Kao J C, Stavisky S D, Ryu S and Shenoy K 2012 A recurrent neural network for closed-loop intracortical brain–machine interface decoders *J. Neural Eng.* **9** 026027 Bonizzato M, Hottin R G, Côté S L, Massai E, Choinière L, Macar U and Dancause N 2023 Autonomous optimization of neuroprosthetic stimulation parameters that drive the motor cortex and spinal cord outputs in rats and monkeys *Cell Rep. Med.***4**

[23] Costello J, Temmar H, Cubillos L, Mender M, Wallace D, Willsey M, Patil P and Chestek C 2023 Balancing memorization and generalization in RNNs for high performance brain-machine *Int. Advances in Neural Information Processing Systems* vol **36** pp 7462–74

[24] Willsey M S, Shah N P, Avansino D T, Hahn N V, Jamiolkowski R M, Kamdar F B, Hochberg L R, Willett F R and Henderson J M 2025 A high-performance brain–computer interface for finger decoding and quadcopter game control in an individual with paralysis *Nat. Med.* **31** 96–104

[25] Ganguly K and Carmena J M 2009 Emergence of a stable cortical map for neuroprosthetic control *PLoS Biol.* **7** e1000153

[26] Hennig J A *et al* 2021 Learning is shaped by abrupt changes in neural engagement *Nat. Neurosci.* **24** 727–36

[27] Gilja V *et al* 2012 A high-performance neural prosthesis enabled by control algorithm design *Nat. Neurosci.* **15** 1752–7

[28] Wang Y, Wang F, Xu K, Zhang Q, Zhang S and Zheng X 2014 Neural control of a tracking task via attention-gated reinforcement learning for brain-machine interfaces *IEEE Trans. Neural Syst. Rehabil. Eng.* **23** 458–67

[29] Gallego J A, Perich M G, Chowdhury R H, Solla S A and Miller L E 2020 Long-term stability of cortical population dynamics underlying consistent behavior *Nat. Neurosci.* **23** 260–70

[30] Tillery S H, Taylor D M and Schwartz A B 2003 Training in cortical control of neuroprosthetic devices improves signal extraction from small neuronal ensembles *Rev. Neurosci.* **14** 107–20

[31] Gage G J, Ludwig K A, Otto K J, Ionides E L and Kipke D R 2005 Naive coadaptive cortical control *J. Neural Eng.* **2** 52

[32] Jarosiewicz B, Chase S M, Fraser G W, Velliste M, Kass R E and Schwartz A B 2008 Functional network reorganization during learning in a brain-computer interface paradigm *Proc. Natl Acad. Sci.* **105** 19486–91

[33] Tan J, Zhang X, Wu S, Song Z, Chen S, Huang Y and Wang Y 2023 Audio-induced medial prefrontal cortical dynamics enhances coadaptive learning in brain–machine interfaces *J. Neural Eng.* **20** 056035

[34] Flesher S N, Downey J E, Weiss J M, Hughes C L, Herrera A J, Tyler-Kabara E C, Boninger M L, Collinger J L and Gaunt R A 2021 A brain-computer interface that evokes tactile sensations improves robotic arm control *Science* **372** 831–36

[35] Ho J C *et al* 2024 Potentiation of cortico-spinal output via targeted electrical stimulation of the motor thalamus *Nat. Commun.* **15** 8461

[36] Saleh M S *et al* 2022 CMU Array: a 3D nanoprinted, fully customizable high-density microelectrode array platform *Sci. Adv.* **8** eabj4853

[37] Zhou T, Hong G, Fu T M, Yang X, Schuhmann T G, Viveros R D and Lieber C M 2017 Syringe-injectable mesh electronics integrate seamlessly with minimal chronic immune response in the brain *Proc. Natl Acad. Sci.* **114** 5894–9

[38] Kozai T D Y, Langhals N B, Patel P R, Deng X, Zhang H, Smith K L, Lahann J, Kotov N A and Kipke D R 2012 Ultrasmall implantable composite microelectrodes with bioactive surfaces for chronic neural interfaces *Nat. Mater.* **11** 1065–73

[39] Seo D, Neely R M, Shen K, Singhal U, Alon E, Rabaey J M, Carmena J M and Maharbiz M M 2016 Wireless recording in the peripheral nervous system with ultrasonic neural dust *Neuron* **91** 529–39

[40] Lee J, Leung V, Lee A H, Huang J, Asbeck P, Mercier P P, Shellhammer S, Larson L, Laiwalla F and Nurmikko A 2021 Neural recording and stimulation using wireless networks of microimplants *Nat. Electron.* **4** 604–14

[41] Figee M, Riva-posse P, Choi K S, Bederson L, Mayberg H S and Kopell B H 2022 Deep brain stimulation for depression *Neurotherapeutics* **19** 1229–45

[42] Gratwicke J *et al* 2018 Bilateral deep brain stimulation of the nucleus basalis of Meynert for Parkinson disease dementia: a randomized clinical trial *JAMA Neurol.* **75** 169–78

[43] Donoghue T, Cao R, Han C Z, Holman C M, Brandmeir N J, Wang S and Jacobs J 2023 Single neurons in the human medial temporal lobe flexibly shift representations across spatial and memory tasks *Hippocampus* **33** 600–15

[44] Quiroga R Q, Reddy L, Kreiman G, Koch C and Fried I 2005 Invariant visual representation by single neurons in the human brain *Nature* **435** 1102–7

[45] Eisenkolb V M, Held L M, Utzschmid A, Lin X X, Krieg S M, Meyer B, Gempt J and Jacob S N 2023 Human acute microelectrode array recordings with broad cortical access, single-unit resolution, and parallel behavioral monitoring *Cell Rep.* **42** 112467

[46] Kawasaki H, Adolphs R, Kaufman O, Damasio H, Damasio A R, Granner M, Bakken H, Hori T and Howard M A 2001 Single-neuron responses to emotional visual stimuli recorded in human ventral prefrontal cortex *Nat. Neurosci.* **4** 15–16

[47] Hodgkin A L and Huxley A F 1952 A quantitative description of membrane current and its application to conduction and excitation in nerve *J. Physiol.* **117** 500–44

[48] McCulloch W S and Pitts W 1943 A logical calculus of the ideas immanent in nervous activity *Bull. Math. Biophys.* **5** 115–33

[49] Tesler F, Linne M-L and Destexhe A 2023 Modeling the relationship between neuronal activity and the BOLD signal: contributions from astrocyte calcium dynamics *Sci. Rep.* **13** 6451

[50] Buzsáki G, Anastassiou C A and Koch C 2012 The origin of extracellular fields and currents-EEG, ECoG, LFP and spikes *Nat. Rev. Neurosci.* **13** 407–20

[51] Bal T and Destexhe A (eds) 2009 *Dynamic-Clamp: From Principles to Applications* (Springer) (https://doi.org/10.1007/978-0-387-89279-5)

[52] McIntyre C C, Grill W M, Sherman D L and Thakor N V 2004 Cellular effects of deep brain stimulation: model-based analysis of activation and inhibition *J. Neurophysiol.* **91** 1457–69

[53] Aberra A S, Wang B, Grill W M and Peterchev A V 2020 Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons *Brain Stimul.* **13** 175–89

[54] Hussain M A, Grill W M and Pelot N A 2024 Highly efficient modeling and optimization of neural fiber responses to electrical stimulation *Nat. Commun.* **15** 7597

[55] Wongsarnpigoon A and Grill W M 2010 Energy-efficient waveform shapes for neural stimulation revealed with a genetic algorithm *J. Neural Eng.* **7** 046009

[56] Dubreuil A, Valente A, Beiran M, Mastrogiuseppe F and Ostojic S 2022 The role of population structure in computations through neural dynamics *Nat. Neurosci.* **25** 783–94

[57] Insanally M N, Albanna B F, Toth J, DePasquale B, Fadaei S S, Gupta T, Lombardi O, Kuchibhotla K, Rajan K and Froemke R C 2024 Contributions of cortical neuron firing patterns, synaptic connectivity, and plasticity to task performance *Nat. Commun.* **15** 6023
[58] Rajan K, Harvey C D and Tank D W 2016 Recurrent network models of sequence generation and memory *Neuron* **90** 128–42
[59] Wang E Y *et al* 2025 Foundation model of neural activity predicts response to new stimulus types *Nature* **640** 470–7
[60] Vyas S, Golub M D, Sussillo D and Shenoy K V 2020 Computation through neural population dynamics *Annu. Rev. Neurosci.* **43** 249–75
[61] Indiveri G *et al* 2011 Neuromorphic silicon neuron circuits *Front. Neurosci.* **5** 73
[62] Buzsáki G and Draguhn A 2004 Neuronal oscillations in cortical networks *Science* **304** 1926–9
[63] Uhlhaas P J and Singer W 2010 Abnormal neural oscillations and synchrony in schizophrenia *Nat. Rev. Neurosci.* **11** 100–13
[64] Markram H *et al* 2015 Reconstruction and simulation of neocortical microcircuitry *Cell* **163** 456–92
[65] Billeh Y N *et al* 2020 Systematic integration of structural and functional data into multi-scale models of mouse primary visual cortex *Neuron* **106** 388–403.e18
[66] Goldman J S, Tort-Colet N, Di Volo M, Susin E, Bouté J, Dali M, Carlu M, Nghiem T-A, Górski T and Destexhe A 2019 Bridging single neuron dynamics to global brain states *Front. Syst. Neurosci.* **13** 75
[67] Amunts K *et al* 2022 Linking brain structure, activity, and cognitive function through computation *eneuro* **9** eneuro.0316–21.2022
[68] Turner N L *et al* 2022 Reconstruction of neocortex: organelles, compartments, cells, circuits, and activity *Cell* **185** 1082–1100.e24
[69] Shapson-coe A *et al* 2024 A petavoxel fragment of human cerebral cortex reconstructed at nanoscale resolution *Science* **384** eadk4858
[70] Ecker J R, Geschwind D H, Kriegstein A R, Ngai J, Osten P, Polioudakis D, Regev A, Sestan N, Wickersham I R and Zeng H 2017 The BRAIN initiative cell census consortium: lessons learned toward generating a comprehensive brain cell atlas *Neuron* **96** 542–57
[71] Beniaguev D, Segev I and London M 2021 Single cortical neurons as deep artificial neural networks *Neuron* **109** 2727–2739.e3
[72] Aberra A S, Lopez A, Grill W M and Peterchev A V 2023 Rapid estimation of cortical neuron activation thresholds by transcranial magnetic stimulation using convolutional neural networks *Neuroimage* **275** 120184
[73] Montagni E, Resta F, Tort-Colet N, Scaglione A, Mazzamuto G, Destexhe A, Pavone F S and Allegra Mascaro A L 2024 Mapping brain state-dependent sensory responses across the mouse cortex *iScience* **27** 109692
[74] Sacha M, Tesler F, Cofre R and Destexhe A 2025 A computational approach to evaluate how molecular mechanisms impact large-scale brain activity *Nat. Comput. Sci.* **5** 405–17
[75] Glaser J I, Benjamin A S, Chowdhury R H, Perich M G, Miller L E and Kording K P 2020 Machine learning for neural decoding *eneuro* **7** eneuro.0506–19.2020
[76] St-yves G, Allen E J, Wu Y, Kay K and Naselaris T 2023 Brain-optimized deep neural network models of human visual areas learn non-hierarchical representations *Nat. Commun.* **14** 3329
[77] Craik A, He Y and Contreras-vidal J L 2019 Deep learning for electroencephalogram (EEG) classification tasks: a review *J. Neural Eng.* **16** 031001
[78] Lawhern V J, Solon A J, Waytowich N R, Gordon S M, Hung C P and Lance B J 2018 EEGNet: a compact convolutional neural network for EEG-based brain–computer interfaces *J. Neural Eng.* **15** 056013
[79] Liu W, Qiu J L, Zheng W L and Lu B L 2022 Comparing recognition performance and robustness of multimodal deep learning models for multimodal emotion recognition *IEEE Trans. Cogn. Dev. Syst.* **14** 715–29
[80] Jiang W-B, Wang Y, Lu B-L and Li D 2025 NeuroLM: a universal multi-task foundation model for bridging the gap between language and EEG signals *Proc. Int. Conf. on Learning Representation* (https://doi.org/10.48550/arXiv.2409.00101)
[81] Chan Z S, Lu B-L and Wu W 2025 Representation learning and foundation models for EEG analyses: current trends, fundamental insights and future directions *IEEE Signal Process. Mag.* **42** 36–57
[82] OpenAI Introducing OpenAI O1-preview (available at: https://openai.com/index/introducing-openai-o1-preview/) (Accessed 2024)
[83] Liu A *et al* 2024 Deepseek-v3 technical report (arXiv:2412.19437)
[84] Zhang D, Yuan Z, Chen J, Chen K and Yang Y 2024 Brant-X: a unified physiological signal alignment framework *Proc. 30th ACM SIGKDD Conf. on Knowledge Discovery and Data Mining* pp 4155–66
[85] Jiang W-B, Zhao L and Lu B-L 2024 Large brain model for learning generic representations with tremendous EEG data in BCI *Proc. Int. Conf. on Learning Representation* (available at: https://iclr.cc/virtual/2024/poster/18658)
[86] Kiessner A-K, Schirrmeister R T, Gemein L A W, Boedecker J and Ball T 2023 An extended clinical EEG dataset with 15,300 automatically labelled recordings for pathology decoding *NeuroimageClin.* **39** 103482
[87] Abedi A, Colella T J F, Pakosh M and Khan S S 2024 Artificial intelligence-driven virtual rehabilitation for people living in the community: a scoping review *npj Digit. Med.* **7** 25
[88] Wu D, Lu B L, Hu B and Zeng Z 2023 Affective brain–computer interfaces (aBCIs): a tutorial *Proc. IEEE* **111** 1314–32
[89] Vaswani A *et al* 2017 Attention is all you need *Advances in Neural Information Processing Systems*
[90] Ienca M *et al* 2022 Towards a governance framework for brain data *Neuroethics* **15** 20
[91] Rajpura P, Cecotti H and Meena Y K 2024 Explainable artificial intelligence approaches for brain-computer interfaces: a review and design space *J. Neural Eng.* **21** 041003
[92] Sorrell E, Rule M E and Leary T 2021 Brain–machine interfaces: closed-loop control in an adaptive system *Annu. Rev. Control Robot. Auton. Syst.* **4** 167–89
[93] Han C, Cheung V C and Chan R H 2025 Aging amplifies sex differences in low alpha and low beta EEG oscillations *Neuroimage* **312** 121231
[94] Liu W, Zheng W-L, Li Z, Wu S-Y, Gan L and Lu B-L 2022 Identifying similarities and differences in emotion recognition with EEG and eye movements among Chinese, German, and French People *J. Neural Eng.* **19** 026012
[95] Guo D *et al* 2025 Deepseek-r1 incentivizes reasoning in LLMs through reinforcement learning *Nature* **645** 633–8
[96] Achiam J *et al* 2023 Gpt-4 technical report (arXiv:2303.08774)
[97] Yang A *et al* 2025 Qwen3 technical report (arXiv:2505.09388)
[98] Wang G, Liu W, He Y, Xu C, Ma L and Li H 2024 EEGPT: pretrained transformer for universal and reliable representation of eeg signals *Advances in Neural Information Processing Systems* vol 37 pp 39249–80
[99] Feng F, Hou L, She Q, Chan R H M and Kwok J T 2024 Power law in deep neural networks: sparse network generation and continual learning with preferential attachment *IEEE Trans. Neural Netw. Learn. Syst.* **35** 8999–9013
[100] Feng F, Liu Q, Peng Z, Zhang R and Chan R H M 2023 Community channel-net: efficient channel-wise interactions via community graph topology *Pattern Recognit.* **141** 109536

[101] Muratore D G and Chichilnisky E J 2020 Artificial retina: a future cellular-resolution brain-machine interface *The Frontiers Collection* ed B Murmann and B Hoefflinger NANO-CHIPS 2030 (Springer) (https://doi.org/10.1007/978-3-030-18338-7_24)
[102] Horgan J 2005 The forgotten era of brain chips *Sci. Am.* **293** 66–73
[103] Spira M E and Hai A 2013 Multi-electrode array technologies for neuroscience and cardiology *Nat. Nanotechnol.* **8** 83–94
[104] Wise K D, Anderson D J, Hetke J F, Kipke D R and Najafi K 2004 Wireless implantable microsystems: high-density electronic interfaces to the nervous system *Proc. IEEE* **92** 76–97
[105] Harris K D, Henze D A, Csicsvari J, Hirase H and Buzsáki G 2000 Accuracy of tetrode spike separation as determined by simultaneous intracellular and extracellular measurements *J. Neurophysiol.* **84** 401–14
[106] Rincón Montes V, Gehlen J, Ingebrandt S, Mokwa W, Walter P, Müller F and Offenhäusser A 2020 Development and *in vitro* validation of flexible intraretinal probes *Sci. Rep.* **10** 1–14
[107] Aregueta-robles U A, Woolley A J, Poole-warren L A, Lovell N H and Green R A 2014 Organic electrode coatings for next-generation neural interfaces *Front. Neuroeng.* **7** 1–18
[108] Fuchsberger K, Goff A L, Gambazzi L, Toma F M, Goldoni A, Giugliano M, Stelzle M and Prato M 2011 Multiwalled carbon-nanotube-functionalized microelectrode arrays fabricated by microcontact printing: platform for studying chemical and electrical neuronal signaling *Small* **7** 524–30
[109] Najafi K, Ji J and Wise K D 1990 Scaling limitations of silicon multichannel recording probes *IEEE Trans. Biomed. Eng.* **37** 1–11
[110] Maynard E M, Nordhausen C T and Normann R A 1997 The Utah intracortical electrode array: a recording structure for potential brain-computer interfaces *Electroencephalogr. Clin. Neurophysiol.* **102** 228–39
[111] Minev I R *et al* 2015 Electronic dura mater for long-term multimodal neural interfaces *Science* **347** 159–63
[112] Fromherz P and Stett A 1995 Silicon-neuron junction: capacitive stimulation of an individual neuron on a silicon chip *Phys. Rev. Lett.* **75** 1670–4
[113] Cogan S F 2008 Neural stimulation and recording electrodes *Annu. Rev. Biomed. Eng.* **10** 275–309
[114] Jäckel D, Frey U, Fiscella M, Franke F and Hierlemann A 2012 Applicability of independent component analysis on high-density microelectrode array recordings *J. Neurophysiol.* **108** 334–48
[115] Grill W M, Norman S E and Bellamkonda R V 2009 Implanted neural interfaces: biochallenges and engineered solutions *Annu. Rev. Biomed. Eng.* **11** 1–24
[116] Palanker D V *et al* 2004 Attracting retinal cells to electrodes for high-resolution stimulation *Proc. SPIE* **5314** 306
[117] Barz F, Ruther P, Takeuchi S and Paul O 2015 Flexible silicon-polymer neural probe rigidified by dissolvable insertion vehicle for high-resolution neural recording with improved duration (https://doi.org/10.1109/MEMSYS.2015.7051036)
[118] Mirzakhalili E, Barra B, Capogrosso M and Lempka S F 2020 Biophysics of temporal interference stimulation *Cell Syst.* **11** 557–572.e5
[119] Wang M, Mi G, Shi D, Bassous N, Hickey D and Webster T J 2018 Nanotechnology and nanomaterials for improving neural interfaces *Adv. Funct. Mater.* **28** 1–28
[120] Ghaffari D H, Chang Y C, Mirzakhalili E and Weiland J D 2021 Closed-loop optimization of retinal ganglion cell responses to epiretinal stimulation: a computational study *2021 10th Int. IEEE/EMBS Conf. Neural Eng.* pp 597–600
[121] Uğurbil K 2021 Ultrahigh field and ultrahigh resolution fMRI *Curr. Opin. Biomed. Eng.* **18** 100288
[122] Overson D K, Truong T-K, Petrella J R, Madden D J, Ma Y, Johnson K G, Liu A J, O'brien R J, Whitson H E and Song A W 2025 Predicting risk of impending cognitive decline in asymptomatic individuals with early Alzheimer's disease: insights from cortical diffusion MRI *Imaging Neurosci.* **3** IMAG.a.1037
[123] Liang B, Wang S, Shen F, Liu Q H, Gong Y and Yao J 2021 Acoustic impact of the human skull on transcranial photoacoustic imaging *Biomed. Opt. Express* **12** 1512
[124] Truong T, Roberts K C, Woldorff M G and Song A W 2019 Toward direct MRI of neuro-electro-magnetic oscillations in the human brain *Magn. Reson. Med.* **81** 3462–75
[125] Hao Y A *et al* 2024 A fast and responsive voltage indicator with enhanced sensitivity for unitary synaptic events *Neuron* **112** 3680–3696.e8
[126] Liu Z *et al* 2022 Sustained deep-tissue voltage recording using a fast indicator evolved for two-photon microscopy *Cell* **185** 3408–3425.e29
[127] Yang H H and St-pierre F 2016 Genetically encoded voltage indicators: opportunities and challenges *J. Neurosci.* **36** 9977–89
[128] Sabatini B L and Tian L 2020 Imaging neurotransmitter and neuromodulator dynamics *in vivo* with genetically encoded indicators *Neuron* **108** 17–32
[129] Wu J, Ji N and Tsia K K 2021 Speed scaling in multiphoton fluorescence microscopy *Nat. Photon.* **15** 800–12
[130] Zhang Q, Hu Q, Berlage C, Kner P, Judkewitz B, Booth M and Ji N 2023 Adaptive optics for optical microscopy *Biomed. Opt. Express* **14** 1732
[131] Elam J S *et al* 2021 The human connectome project: a retrospective *Neuroimage* **244** 118543
[132] Hagler D J *et al* 2019 Image processing and analysis methods for the adolescent brain cognitive development study *Neuroimage* **202** 116091
[133] Elliott L T, Sharp K, Alfaro-almagro F, Shi S, Miller K L, Douaud G, Marchini J and Smith S M 2018 Genome-wide association studies of brain imaging phenotypes in UK Biobank *Nature* **562** 210–6
[134] Wang Q *et al* 2020 The Allen mouse brain common coordinate framework: a 3D reference atlas *Cell* **181** 936–953.e20
[135] Renton A I *et al* 2024 Neurodesk: an accessible, flexible and portable data analysis environment for reproducible neuroimaging *Nat. Methods* **21** 804–8
[136] Rübel O *et al* 2022 The Neurodata Without Borders ecosystem for neurophysiological data science *elife* **11** e78362
[137] The International Brain Laboratory *et al* 2019 Data architecture for a large-scale neuroscience collaboration *Nature* **645** 177–191
[138] The International Brain Laboratory *et al* 2023 A modular architecture for organizing, processing and sharing neurophysiology data *Nat. Methods* **20** 403–7
[139] Mansour H, Azrak R, Cook J J, Hornburg K J, Qi Y, Tian Y, Williams R W, Yeh F-C, White L E and Johnson G A 2025 The Duke Mouse Brain Atlas: MRI and light sheet microscopy stereotaxic atlas of the mouse brain *Sci. Adv.* **11** eadq8089
[140] Giovannucci A *et al* 2019 CaImAn an open source tool for scalable calcium imaging data analysis *elife* **8** e38173
[141] Pachitariu M *et al* 2016 Suite2p: beyond 10,000 neurons with standard two-photon microscopy (https://doi.org/10.1101/061507)
[142] Dong Z, Mau W, Feng Y, Pennington Z T, Chen L, Zaki Y, Rajan K, Shuman T, Aharoni D and Cai D J 2022 Minian, an open-source miniscope analysis pipeline *elife* **11** e70661
[143] Hageter J MCA: a multicellular analysis calcium imaging toolbox for ImageJ
[144] Cooley C Z *et al* 2021 A portable scanner for magnetic resonance imaging of the brain *Nat. Biomed. Eng.* **5** 229–39

[145] Vladimirov N *et al* 2024 Benchtop mesoSPIM: a next-generation open-source light-sheet microscope for cleared samples *Nat. Commun.* **15** 2679
[146] Dong Z *et al* 2025 Simultaneous two-color imaging with a dual-channel miniscope in freely behaving mice *Sci. Adv.* **11** eadr6470
[147] Schottdorf M, Rich P D, Diamanti E M, Lin A, Tafazoli S, Nieh E H and Thiberge S Y 2025 TWINKLE: an open-source two-photon microscope for teaching and research *PLoS One* **20** e0318924
[148] Janelia Collaborators *Modular In Vivo Multi-photon Microscope 2.2* (available at: www.janelia.org/open-science/mimms-22-2024)
[149] Shokur S *et al* 2018 Training with brain-machine interfaces, visuo-tactile feedback and assisted locomotion improves sensorimotor, visceral, and psychological signs in chronic paraplegic patients *PLoS One* **13** e0206464
[150] Ferris D P and Schlink B R 2017 Robotic devices to enhance human movement performance *Kinesiol. Rev.* **6** 70–77
[151] Bauer W 1983 Neuroelectric medicine *J. Bioelectr.* **2** 159–80
[152] Engelhardt K G 1986 Current status and future prospects for robotic technology in health care delivery *Cent. Nervous Syst. Trauma* **3** 111–26
[153] National Research Council 1994 *Virtual Reality: Scientific and Technological Challenges* (National Academies Press) p 556
[154] Merians A S, Jack D, Boian R, Tremaine M, Burdea G C, Adamovich S V, Recce M and Poizner H 2002 Virtual reality–augmented rehabilitation for patients following stroke *Phys. Ther.* **82** 898–915
[155] Farina D, Vujaklija I, Brånemark R, Bull A M, Dietl H, Graimann B and Aszmann O C 2023 Toward higher-performance bionic limbs for wider clinical use *Nat. Biomed. Eng.* **7** 473–85
[156] Song H *et al* 2024 Continuous neural control of a bionic limb restores biomimetic gait after amputation *Nat. Med.* **30** 2010–9
[157] Siviy C, Baker L M, Quinlivan B T, Porciuncula F, Swaminathan K, Awad L N and Walsh C J 2023 Opportunities and challenges in the development of exoskeletons for locomotor assistance *Nat. Biomed. Eng.* **7** 456–72
[158] Rodríguez-fernández A, Lobo-prat J and Font-llagunes J M 2021 Systematic review on wearable lower-limb exoskeletons for gait training in neuromuscular impairments *J. Neuroeng. Rehabil.* **18** 22
[159] Davidson B, Bhattacharya A, Sarica C, Darmani G, Raies N, Chen R and Lozano A M 2024 Neuromodulation techniques—From non-invasive brain stimulation to deep brain stimulation *Neurotherapeutics* **21** e00330
[160] Rektorová I, Pupíková M, Fleury L, Brabenec L and Hummel F C 2025 Non-invasive brain stimulation: current and future applications in neurology *Nat. Rev. Neurol.* **21** 669–86
[161] Caffrey J P, Jeong W J and Del Rosario J 2026 Wearable devices for bioelectrical stimulation in rehabilitation: review of the current state *Am. J. Phys. Med. Rehabil.* in press (https://doi.org/10.1097/PHM.0000000000003035)
[162] Laver K E, Lange B, George S, Deutsch J E, Saposnik G, Chapman M and Crotty M 2025 Virtual reality for stroke rehabilitation *Cochrane Database Syst Rev.* CD008349
[163] Alashram A R, Padua E and Annino G 2022 Virtual reality for balance and mobility rehabilitation following traumatic brain injury: a systematic review of randomized controlled trials *J. Clin. Neurosci.* **105** 115–21
[164] Krucoff M O, Rahimpour S, Slutzky M W, Edgerton V R and Turner D A 2016 Enhancing nervous system recovery through neurobiologics, neural interface training, and neurorehabilitation *Front. Neurosci.* **10** 584
[165] Cagnan H, Denison T, McIntyre C and Brown P 2019 Emerging technologies for improved deep brain stimulation *Nat. Biotechnol.* **37** 1024–33
[166] Zrenner C and Ziemann U 2024 Closed-loop brain stimulation *Biol. Psychiatry* **95** 545–52
[167] Korupolu R, Miller A, Park A and Yozbatiran N 2024 Neurorehabilitation with vagus nerve stimulation: a systematic review *Front. Neurol.* **15** 1390217
[168] Moritz C *et al* 2024 Non-invasive spinal cord electrical stimulation for arm and hand function in chronic tetraplegia: a safety and efficacy trial *Nat. Med.* **30** 1276–83
[169] Everard G, Burton Q, Van de Sype V, Bibentyo T N, Auvinet E, Edwards M G, Batcho C S and Lejeune T 2024 Extended reality to assess post-stroke manual dexterity: contrasts between the classic box and block test, immersive virtual reality with controllers, with hand-tracking, and mixed-reality tests *J. Neuroeng. Rehabil.* **21** 36
[170] Hammond M, Cichella V and Lamuta C 2023 Bioinspired soft robotics: state of the art, challenges, and future directions *Curr. Robot. Rep.* **4** 65–80
[171] Losanno E, Mender M, Chestek C, Shokur S and Micera S 2023 Neurotechnologies to restore hand functions *Nat. Rev. Bioeng.* **1** 390–407
[172] Raspopovic S, Valle G and Petrini F M 2021 Sensory feedback for limb prostheses in amputees *Nat. Mater.* **20** 925–39
[173] Hybart R L and Ferris D P 2022 Embodiment for robotic lower-limb exoskeletons: a narrative review *IEEE Trans. Neural Syst. Rehabil. Eng.* **31** 657–68
[174] Pazzaglia M and Molinari M 2016 The embodiment of assistive devices—from wheelchair to exoskeleton *Phys. Life Rev.* **16** 163–75
[175] Ansó J *et al* 2022 Concurrent stimulation and sensing in bi-directional brain interfaces: a multi-site translational experience *J. Neural Eng.* **19** 026025
[176] Wen D, Liang B, Zhou Y, Chen H and Jung T P 2021 The current research of combining multi-modal brain-computer interfaces with virtual reality *IEEE J. Biomed. Health Inform.* **25** 3278–87
[177] Taghavi M, Helps T and Rossiter J 2018 Electro-ribbon actuators and electro-origami robots *Sci. Robot.* **3** eaau9795
[178] Krauss J K *et al* 2021 Technology of deep brain stimulation: current status and future directions *Nat. Rev. Neurol.* **17** 75–87
[179] Richer N, Bradford J C and Ferris D P 2024 Mobile neuroimaging: what we have learned about the neural control of human walking, with an emphasis on EEG-based research *Neurosci. Biobehav. Rev.* **162** 105718
[180] Maoz S, Suthana N and Stangl M 2023 Mobile cognition: imaging the human brain in the real world *Nat. Rev. Neurosci.* **24** 347–62
[181] Shannon R 1992 A model of safe levels for electrical stimulation *IEEE Trans. Biomed. Eng.* **39** 424–6
[182] Polikov V S, Tresco P A and Reichert W M 2005 Response of brain tissue to chronically implanted neural electrodes *J. Neurosci. Methods* **148** 1–8
[183] Chen X, Wang F, Kooijmans R, Klink P C, Boehler C, Asplund M and Roelfsema P R 2023 Chronic stability of a neuroprosthesis comprising multiple adjacent Utah arrays in monkeys *J. Neural Eng.* **20** 036039
[184] Cogan S F, Ehrlich J, Plante T D, Smirnov A, Shire D B, Gingerich M and Rizzo J F 2009 Sputtered iridium oxide films for neural stimulation electrodes vol 89B pp 353–61
[185] Meijs S, Fjorback M, Jensen C, Sørensen S, Rechendorff K and Rijkhoff N J 2015 Electrochemical properties of titanium nitride nerve stimulation electrodes: an *in vitro* and *in vivo* study *Front. Neurosci.* **9** 268
[186] Murastov G *et al* 2020 Flexible and water-stable graphene-based electrodes for long-term use in bioelectronics *Biosens. Bioelectron.* **166** 112426

[187] Boulingre M, Portillo-lara R and Green R A 2023 Biohybrid neural interfaces: improving the biological integration of neural implants *Chem. Commun.* **59** 14745–58

[188] Rousche P J and Normann R A 1998 Chronic recording capability of the Utah Intracortical Electrode Array in cat sensory cortex *J. Neurosci. Methods* **82** 1–5

[189] Pranti A S, Schander A, Bödecker A and Lang W Highly stable PEDOT: PSS coating on gold microelectrodes with improved charge injection capacity for chronic neural stimulation *Proceedings* (*25 August 2017*) vol 1 (MDPI) p 492

[190] Rochford A E *et al* 2023 Functional neurological restoration of amputated peripheral nerve using biohybrid regenerative bioelectronics *Sci. Adv.* **9** eadd8162

[191] Lewis C M, Boehler C, Liljemalm R, Fries P, Stieglitz T and Asplund M 2024 Recording quality is systematically related to electrode impedance *Adv. Healthcare Mater.* **14** 2303401

[192] Dalrymple A N *et al* 2019 Electrochemical and mechanical performance of reduced graphene oxide, conductive hydrogel, and electrodeposited Pt–Ir coated electrodes: an active *in vitro* study *J. Neural Eng.* **17** 016015

[193] Thaning E M, Asplund M L, Nyberg T A, Inganäs O W and von Holst H 2010 Stability of poly (3, 4-ethylene dioxythiophene) materials intended for implants *J. Biomed. Mater. Res. B* **93** 407–15

[194] Qiu T, Hanna E, Dabbous M, Borislav B and Toumi M 2020 Regenerative medicine regulatory policies: a systematic review and international comparison *Health Policy* **124** 701–13

[195] Thomas C A Jr, Springer P A, Loeb G E, Berwald-netter Y and Okun L M 1972 A miniature microelectrode array to monitor the bioelectric activity of cultured cells *Exp. Cell Res.* **74** 61–66

[196] Frank J A, Antonini M J and Anikeeva P 2019 Next-generation interfaces for studying neural function *Nat. Biotechnol.* **37** 1013–23

[197] Gonzalez M A, Nwokeabia C, Vaskov A K, Vu P P, Lu C W, Patil P G, Cederna P S, Chestek C A and Gates D H 2024 Electrical stimulation of regenerative peripheral nerve interfaces (RPNIs) induces referred sensations in people with upper limb loss *IEEE Trans. Neural Syst. Rehabil. Eng.* **32** 339–49

[198] Zhang Y, Le S, Li H, Ji B, Wang M H, Tao J, Liang J Q, Zhang X Y and Kang X Y 2021 MRI magnetic compatible electrical neural interface: from materials to application *Biosens. Bioelectron.* **194** 113592

[199] Lee S, Silva S M, Aguilar L M, Eom T, Moulton S E and Shim B S 2022 Biodegradable bioelectronics for biomedical applications *J. Mater. Chem. B* **10** 8575–95