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An overview of silicon-based neural probes: from technological evolution to biomedical applications



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Highlights:

- Reviews the evolution from passive silicon probes to active CMOS architectures for scalable recording.
- Summarizes multimodal silicon-based probes integrating optogenetics, microfluidics, and electrochemical sensing.
- Cross-species applications of silicon-based probes from rodent and NHP circuit discovery to human clinical recording.
- Discusses system-level bottlenecks and future paths of silicon-based neural probes.

Abstract: Silicon-based neural probes are essential tools in modern extracellular electrophysiology, enabling the recording and manipulation of neural circuits with high spatial and temporal resolution. This review systematically summarizes the technological evolution, functional classifications, and biomedical applications of silicon-based neural probes. We first categorize these devices into passive architectures and active complementary metal-oxide-semiconductor (CMOS) integrated platforms based on their electronic integration. Passive probes focus on channel scaling, impedance reduction, and mechanical biocompatibility, whereas active probes overcome physical wiring limits through on-chip signal amplification, multiplexing, and digitization. We then highlight recent advances in multimodal interfaces that integrate optical waveguides, microfluidic channels, and chemical sensors to transform conventional probes into active closed-loop systems. Furthermore, we examine their translational utility across animal models from rodents to non-human primates, as well as their clinical application in human intraoperative neurophysiology. Finally, we discuss key engineering challenges, including long-term stability of chronic implantation, the integration of flexible structures with active CMOS chips, and localized thermal management, while outlining future directions toward intelligent neural interfaces for decoding complex large-scale network and advancing fundamental neuroscientific discovery.

Keywords: silicon-based neural probes; neuropixels; CMOS integration; multimodal probes; cross-species recording



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1. Introduction

Neuroscience has become a pivotal domain of scientific inquiry. On the fundamental spectrum, deciphering neural circuits is essential for understanding human cognition and consciousness, offering biological paradigms for advanced artificial intelligence architectures. On the clinical spectrum, precise neurophysiological mapping remains a prerequisite for formulating targeted interventions against severe neurological and psychiatric disorders, such as Alzheimer's disease, epilepsy, and major depressive disorder. To achieve these fundamental and clinical objectives, recording neuronal activity with high spatial and temporal resolution is a critical prerequisite [1–4].

Early recognition of bioelectricity by Galvani and du Bois-Reymond established the theoretical basis for electrophysiology, which eventually diverged into non-invasive macro-scale modalities like the electroencephalogram and invasive cellular-scale techniques [5,6]. The invention of the tungsten microelectrode by Hubel in 1957 marked a turning point for single-unit sampling in awake animals [7]. Fabricated as a sharpened, insulated wire, the tungsten microelectrodes possess a high mechanical modulus capable of penetrating the tough dura mater but are constrained by their one-dimensional architecture, prohibiting the concurrent monitoring of large neural ensembles [2,8]. Consequently, achieving simultaneous large-scale recording of neuronal activity with high spatiotemporal resolution remains a major technical challenge.

To resolve this limitation, silicon-based probes offer a transformative solution by leveraging semiconductor micromachining to pattern dense microelectrode arrays along micron-scale shanks through precise photolithography and etching. This methodology originated with the single-channel silicon probe developed by Wise and Angell in 1970, seeding the application of semiconductor micro-nanofabrication in neuroscience (Figure 1a) [9]. Building upon planar fabrication, the multi-site Michigan probe emerged in the 1980s to enable continuous electrophysiological depth profiling along a single penetrating axis (Figure 1b) [10]. Concurrently, the three-dimensional Utah array provided an alternative spatial geometry, optimizing mechanical stability for superficial cortical mapping (Figure 1c) [11]. In the 21st century, the focus of technological evolution shifted toward high-density active probes. In 2017, the first-generation Neuropixels probe was introduced (Figure 1d) [12,13]. By integrating nearly a thousand addressable sites alongside localized amplification and digitization circuitry, such high-density active architectures effectively eliminate external wiring limits and enable simultaneous recordings from hundreds of single neurons across multiple brain regions in awake animals [14,15].

The rising demand for long-term recording has highlighted the critical importance of probe biocompatibility, driving growing interest in flexible neural electrodes which are designed to better match the mechanical properties of brain tissue, either through soft materials such as low-modulus polymers [16–19], elastomers [20] and hydrogels [21], or through specialized structural designs including mesh, serpentine, and ultrathin configurations [22–25]. Despite this trend, silicon-based probes still retain some advantages that flexible materials have yet to replace. The primary benefit lies in its native compatibility with complementary metal-oxide-semiconductor (CMOS) fabrication processes, which allows the monolithic integration of recording sites with complex integrated electronics, achieving a level of functional density that remains challenging for flexible substrates. Beyond electronic density, the mature commercial semiconductor infrastructure ensures high scalability, reproducibility, and cost-effectiveness for mass production. Structurally, the mechanical rigidity of silicon offers sufficient stiffness for direct

penetration of the dura mater and cortical tissue without requiring additional insertion guides, which is advantageous for acute recordings and reaching deep brain structures with minimal trajectory deviation. Thus, while flexible materials excel in tissue compliance, the combined advantages of CMOS compatibility, scalable manufacturing, and structural robustness ensure that silicon probes remain vital for neural interfacing.

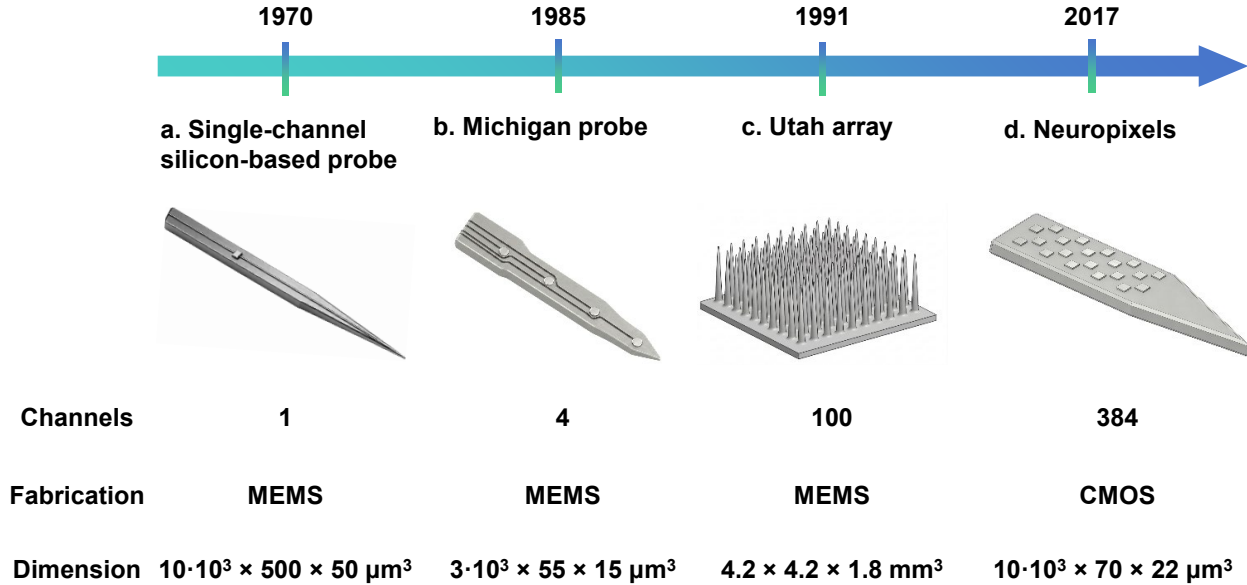


Figure 1. Timeline of the key milestones in the development of silicon-based neural probes. (a) Single-channel silicon-based probe [9]; (b) Michigan probe [10]; (c) Utah array [11]; (d) Neuropixels [12].

This review systematically summarizes the technological evolution, functional classifications, and translational achievements of silicon-based neural probes. We first categorize these devices based on the integration of active electronics. Passive probes rely on metallized interconnects and passive recording sites, whereas active probes incorporate CMOS circuitry for on-chip signal amplification, multiplexing, and digitization. Beyond electronic classification, we highlight recent advances in multimodal interfaces that integrate optical, microfluidic, and chemical modalities. Furthermore, we examine their translational applications across diverse animal models and clinical settings. Finally, we discuss key engineering challenges and outline future directions toward intelligent, closed-loop neural interfaces in decoding large-scale network dynamics.

2. Passive silicon probe architectures

Initial silicon-based neural probes were exclusively passive devices consisted of customized microelectromechanical systems (MEMS). Passive silicon probes integrate no active electronics on the implantable shank, incorporating only microelectrodes and their associated routing pathways defined by planar microscale manufacturing including photolithography, thin-film deposition and etching [26,27]. By leveraging the geometric determinism inherent to automated MEMS fabrication, passive probes successfully reconciled the competing demands of structural scaling and cellular precision, achieving unprecedented uniformity and spatial resolution [28,29]. As network neuroscience advances, the need to capture synchronous circuit dynamics drives the demand for high-density, high-fidelity, and

chronically stable neural interfaces. Consequently, contemporary research on passive probes focuses primarily on maximizing spatial channel density, optimizing electrochemical signal fidelity, and ensuring long-term biocompatibility for chronic recording [2,3,8,30,31].

To enable large-scale neural recording, researchers have continuously increased the number and density of electrode sites on silicon-based probes. In passive architectures, every site demands an independent conductive path, thus total channel count is limited by linewidth, trace spacing and the permissible physical footprint of the silicon substrate. The original Michigan probe accommodates fewer than 10 metal sites on a 50 μm wide shank with an 8 μm linewidth and a 10 μm spacing [10]. Advances in MEMS fabrication enabled the gradual reduction of trace dimensions and a concomitant increase in recording capacity. The implementation of electron-beam lithography enabled the scaling of gold interconnects to 290 nm widths, facilitating the integration of 64 independent sites alongside a narrow silicon shank [32]. Additionally, the probe incorporates an on-shank multiplexing chip to reduce external connections to six functional wires, mitigating the cabling bottleneck. This miniaturization trajectory culminated in 128-channel single-shank capacities utilizing commercial 130 nm CMOS foundry processes and a four-layer aluminum metallization network [33]. The probe reduces trace widths to 200 nm and employs porous titanium nitride (TiN) microelectrodes to maintain low interfacial impedance. Despite the capability of modern CMOS technologies to pattern even smaller features, the recording density on a purely passive shank is approaching physical saturation. Aggressively scaling down interconnect dimensions further is no longer viable, as it severely amplifies thermal noise and exacerbates inter-channel capacitive crosstalk.

To circumvent the density constraints of single-shank layouts, architectural design has transitioned toward multi-dimensional spatial expansion. Two-dimensional (2D) multi-shank planar probes were introduced in the 1980s, limited to a few shanks separated by several hundred micrometers [29,34]. Advances in microfabrication have enabled the miniaturization of shank dimensions and lateral spacing, allowing greater shank integration within a constrained volume. Nowadays a cellular-scale multi-shank probe can integrate up to 32 parallel shanks, each narrowed to a 10 μm width with a 66 μm compact pitch, yielding 256 recording channels within a highly localized footprint (Figure 2a) [35]. To capture volumetric circuit dynamics, this topological expansion is required to be extended into the third dimension [36,37]. By assembling planar components into three-dimensional matrices, researchers have successfully distributed 1,024 independent recording sites across a 0.6 mm³ anatomical volume (Figure 2b) [38]. Configurations employing 16 closely spaced shanks, each hosting 64 sites, establish continuous high-density depth profiling, providing the necessary lateral and axial coverage for interrogating distributed neural networks.

Miniaturizing spatial arrays inevitably incurs an elevated electrochemical impedance at the tissue interface and inter-channel crosstalk, thereby threatening signal fidelity [39,40]. Counteracting these degradations requires targeted surface engineering and structural shielding. Nanostructured metallic coatings, such as porous platinum black, and conductive polymers are routinely deposited onto electrode sites to significantly lower the impedance [41]. Simultaneously, parasitic capacitance is disrupted by embedding localized ground lines and tailored dielectric encapsulation directly within the probe architecture [38,42]. For instance, combining platinum black modifications with strategically positioned, variable-diameter grounding contacts successfully depressed the motion artifact baseline to 4 μV , achieving a 15-fold enhancement in signal-to-noise ratio (SNR) during free movement [43]. Beyond

passive surface optimizations, intermediate hybrid strategies address signal fidelity by physically integrating active CMOS signal-processing chips with passive MEMS probes via high-density wire bonding and surface-mount assembly (Figure 2c) [44]. This hybrid configuration delivers localized amplification, filtering, and digitization, yielding substantial noise immunity and a compact form factor while remaining more cost-effective than fully monolithic active architectures.

Apart from channel count and signal amplitude, long-term recording stability remains arguably the most fundamental limitation of silicon-based probes. The stark elastic modulus disparity between the silicon substrate and the soft cortical parenchyma translates physiological micromotion into continuous interfacial shear stress. This mechanical trauma sustains a chronic foreign-body cascade, culminating in glial encapsulation that electrically isolates the recording sites, progressively degrades signal quality, and can ultimately lead to device failure [45,46]. Establishing reliable chronic interfaces thus requires structural and material interventions to buffer this mechanical incompatibility [47–49]. Incorporating locally flexible regions within a hybrid silicon-parylene framework provides a promising structural paradigm (Figure 2d) [48]. This architecture provides sufficient axial rigidity for surgical insertion while mechanically decoupling lateral shear forces to suppress localized neuroinflammation and glial scarring. Optimization of electrode site and insulation materials offers another approach to extend the chronic stability of silicon-based neural probes. At the electrochemical boundary, coating sites with materials like TiN, iridium oxide (IrO_x), or poly(3,4-ethylenedioxythiophene) (PEDOT) minimizes impedance without necessitating larger geometric areas [12,50,51]. The application of biocompatible composite and drug layers coatings onto the electrodes such as Pt/PEDOT:PSS/dipeptide or PEDOT/carbon nanotube (CNT)/Dexamethasone can significantly mitigate tissue rejection responses [52,53]. Encapsulation strategies employing laminated composite layers of SiC or SiO_2 and SiN stacks have been widely implemented to provide a barrier against the corrosive biological environment [54,55]. However, current coating strategies still face critical technical bottlenecks that limit their long-term *in vivo* performance. Poor interfacial adhesion between organic conductive layers and inorganic substrates often results in coating delamination caused by chronic micromotion at the tissue interface [56]. Furthermore, the gradual depletion of embedded anti-inflammatory agents and the structural degradation of polymer networks over extended periods lead to a progressive loss of therapeutic efficacy [52]. To overcome these limitations, future optimization should focus on enhancement of mechanical stability and engineering responsive coating systems capable of sustained immunomodulation for true long-term biocompatibility.

Decades of engineering refinement have established passive silicon architectures as highly reliable, commercially viable platforms for localized, moderate-density electrophysiology. Their mature fabrication processes and straightforward designs continue to provide cost-effective options for targeted brain research. Nevertheless, the evolutionary development of passive devices is bounded by fundamental scaling limits and conflicting physical requirements. Expanding total channel capacity strictly mandates increasing the substrate footprint, aggravating tissue damage. Conversely, aggressively scaling down geometric features to preserve tissue integrity sharply amplifies thermal noise and capacitive crosstalk [3,4,40,57]. To meet the growing demands of neuroscience and achieve large-scale recordings with higher spatiotemporal resolution, silicon-based probes must evolve beyond passive configurations.

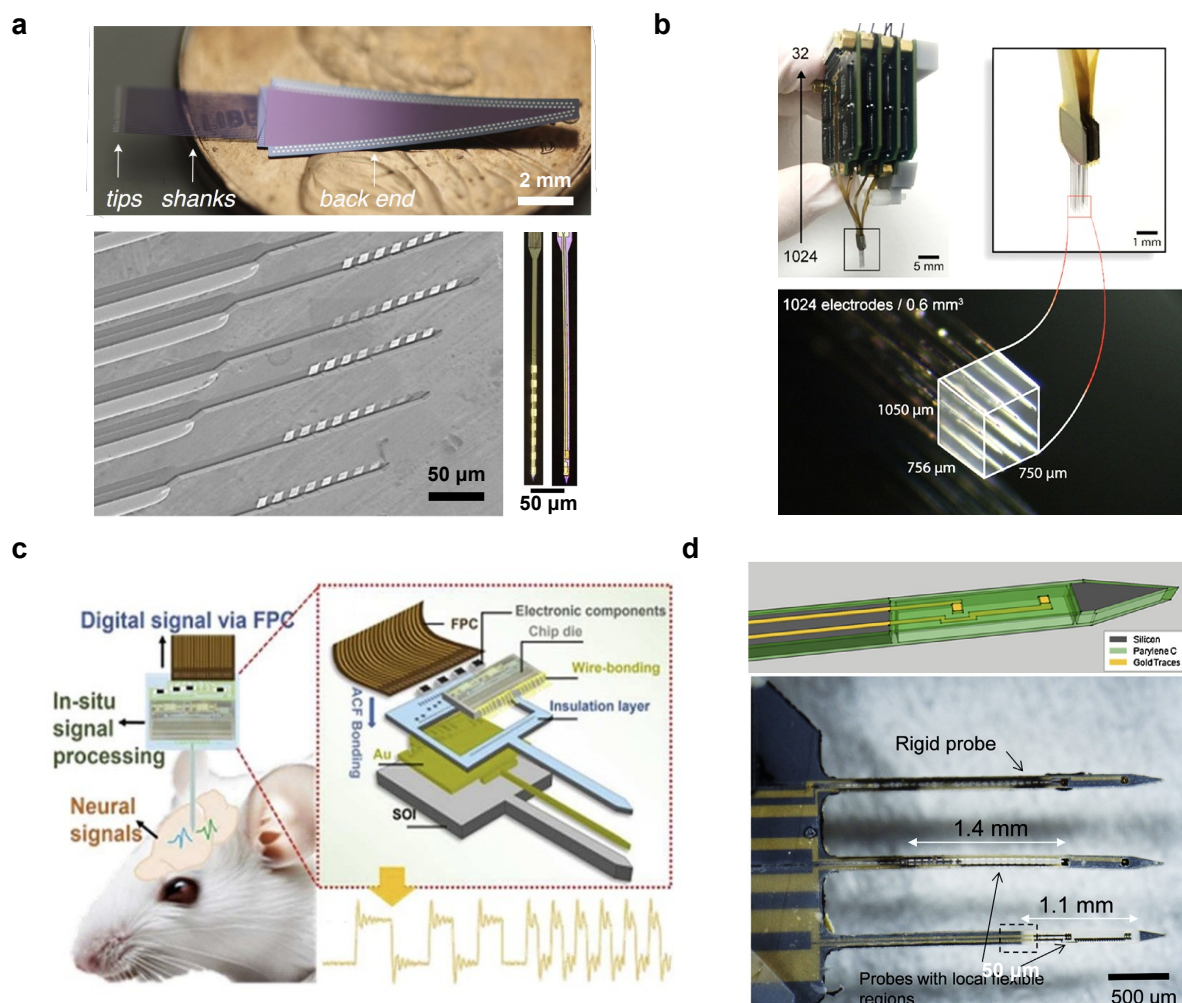


Figure 2. Passive silicon-based neural probes. **(a)** A multi-shank silicon-based probe integrated with 32 parallel silicon shanks for high-density localized neurophysiology [35]. Reproduced with permission. Copyright 2020, American Physiological Society; **(b)** A 3D silicon-based probe matrix designed for volumetric mapping of deep neural structures [38]. Reproduced with permission. Copyright 2016, American Chemical Society; **(c)** An integrated MEMS-CMOS electrode based on high-density wire-bonding techniques and surface-mount technology [44]. Reproduced with permission. Copyright 2025, IEEE; **(d)** A hybrid silicon-parylene neural probe incorporating locally flexible regions to buffer tissue-electrode micromotion [48]. Reproduced with permission. Copyright 2014, Elsevier.

3. Active CMOS-integrated probes

To resolve the fundamental physical constraints of passive architectures, active silicon-based neural probes integrate CMOS components directly within the implantable silicon substrate. By incorporating on-shank microelectronics, such as preamplification circuits and routing matrices, active interfaces execute signal conditioning and multiplexing immediately at the tissue-electrode boundary. This localized processing severs the traditional dependency between total channel capacity and the physical dimensions of the interconnect traces. Despite the practical constraint of high fabrication costs that can restrict widespread routine adoption, mature industrial CMOS fabrication supplies sub-micron resolution

and yield consistency. Consequently, active probes transcend the limitations of traditional physical wiring, establishing a scalable platform for high-density brain mapping [58–60].

Since the inception of silicon-based neural probes, researchers have actively explored the integration of active CMOS components. Initial demonstrations of on-chip signal processing circuitry emerged with early Michigan architectures [61]. By combining preamplifiers, an analog multiplexer, and self-testing circuitry at the probe base, this device records from 10 sites through merely three external lines, substantially mitigating packaging complexity and transmission noise. Subsequently, researchers iteratively optimized active silicon neural probes leveraging CMOS technology, surpassing the previous limits of several dozen channels to achieve much higher channel counts [59]. A structural milestone in this trajectory is the NeuroSeeker probe, engineered via a 130 nm CMOS process to support 1356 TiN electrodes (Figure 3a) [51]. Utilizing a time-division multiplexing (TDM) architecture, NeuroSeeker routes every group of eight electrodes into a single transmission line on the base chip, enabling synchronous recording of all channels. This synchronized architecture allows the simultaneous acquisition of over a thousand distributed neurons during a single insertion.

In 2017, the Neuropixels probe family was developed, which has become a widely used neural recording system in modern electrophysiology [12]. The foundational Neuropixels 1.0 iteration utilizes a silicon-on-insulator (SOI) CMOS process to pattern 966 TiN electrodes along a 10 mm length, $70 \times 22 \mu\text{m}^2$ cross-section shank (Figure 3b). A programmable switch matrix is embedded directly along the shank beneath the 966 electrodes to flexibly select 384 active recording sites. The external probe base houses dual-band filtering and amplification stages to separate action potentials (AP) from local field potentials (LFP), alongside 10-bit analog-to-digital converters (ADCs) and digital control modules, outputting a digital data stream from the selected channels. This architecture enables high-throughput recording on a slender probe, allowing the simultaneous capture of hundreds of individual neurons in freely behaving rodents. Subsequent iterations aggressively scaled this topological framework. the Neuropixels 2.0 dramatically compressed the base dimensions while expanding a four-shank configuration to accommodate 5120 total electrodes and 384 readable channels (Figure 3b) [62]. Pushing spatial resolution further, Neuropixels Ultra reduces recording sites to $5 \times 5 \mu\text{m}^2$ with a $6 \mu\text{m}$ pitch (Figure 3c) [63]. This compression clusters 6,144 electrodes across a 4.6 mm span, to intentionally oversample individual action potentials across adjacent sites. In 2025, the Neuropixels 1.0 NHP was introduced to accommodate large animal models by elongating the length to distribute 4416 recording sites (Figure 3d) [14]. This variant enables deep, brain-wide electrophysiological recordings at single-neuron resolution in large animals like macaques. In 2026, Neuropixels Opto was engineered for simultaneous high-density electrical recording and targeted optogenetic stimulation [64]. Through these iterations, the Neuropixels family has evolved toward miniaturization, higher density, and versatile applicability, forming a comprehensive high-throughput neural interface ecosystem.

Beyond the switching-matrix multiplexing paradigm represented by Neuropixels, there exist other technological approaches for high-throughput active silicon-based neural probes [51,65,66]. The multi-shank active SiNAPS probe distributes 1024 independent channels across eight shanks, assigning a dedicated amplification and low-pass filtering microcircuit directly beneath every recording site (Figure 3e) [66]. Leveraging the modularity of CMOS-based active pixel sensor technology, this probe integrates independent active recording channels distributed across eight parallel shanks, achieving continuous, low-noise recordings at 20 kHz per channel from all 1,024 sites simultaneously.

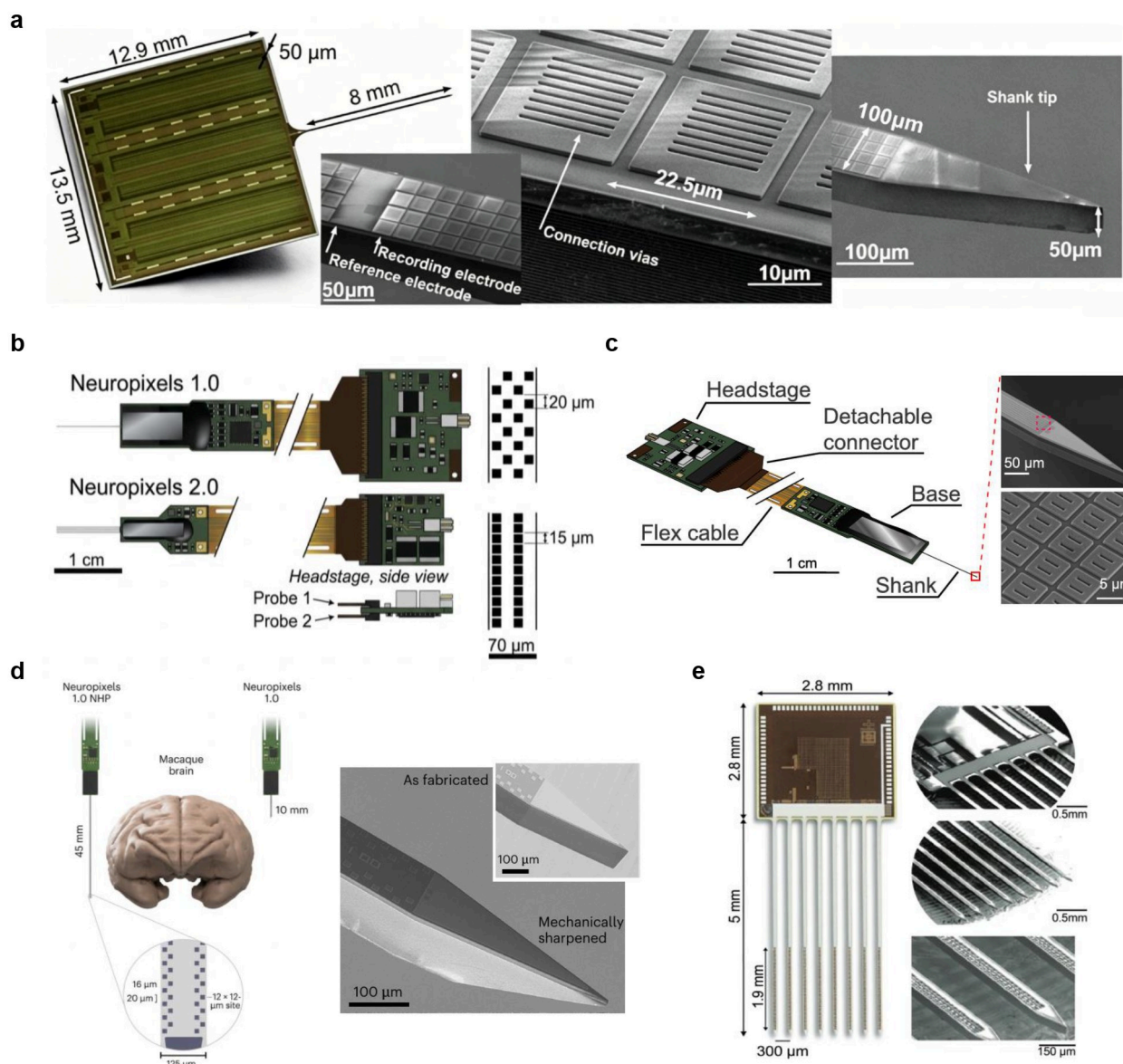


Figure 3. Active CMOS-integrated probes. **(a)** NeuroSeeker probe integrating 1356 dense electrode sites with on-shank multiplexing switches [51]. Reproduced with permission. Copyright 2017, MDPI; **(b)** Neuropixels 1.0 and 2.0 which feature integrate CMOS instrumentation circuitry providing hundreds of configurable, digitized recording channels [62]. Reproduced with permission. Copyright 2021, AAAS; **(c)** Neuropixels Ultra probe scaling down the inter-electrode pitch to enhance microscopic spatial resolution [63]. Reproduced with permission. Copyright 2025, Elsevier; **(d)** Neuropixels NHP probe extending the shank length up to 45 mm for deep-brain recording in non-human primates [14]. Reproduced with permission. Copyright 2025, Springer Nature; **(e)** SiNAPS probe with multi-shank 1024 channels for large multi-regional topographical electrophysiological mapping [66]. Reproduced with permission. Copyright 2025, Wiley-VCH.

To systematically evaluate the engineering specifications across active CMOS-integrated platforms, Table 1 provides a quantitative comparison of NeuroSeeker, Neuropixels 1.0, Neuropixels 2.0, and SiNAPS. Despite their advanced acute performance, all platforms face chronic signal degradation

originating from both physical and biological failure modes. Physically, gradual insulation failure from fluid ingress and structural probe fracture compromise electrical integrity, which elevates channel-to-channel noise variation. Biologically, persistent mechanical mismatch exacerbates glial encapsulation, which isolates the recording sites and progressively attenuates the signal. To mitigate these failure modes and extend functional longevity, various platforms have implemented specific structural and algorithmic optimizations, resulting in distinct stable chronic recording windows. For NeuroSeeker, high-quality neural signal acquisition can be maintained for at least 15 days post-implantation [67], and incorporating floating implant architectures and flexible interconnects can extend this stable recording window to 65 days by buffering mechanical mismatch for similar probes with wider physical profiles [68]. Neuropixels series have achieved chronic recording windows of up to 364 days through specially designed chronic implantation assistance systems combined with motion-correction algorithms [69]. For SiNAPS, chronic recording windows of 180 days have been achieved through optimized electrode-pixel circuit dimensions that reduce its cross-sectional shank area [70]. Despite inherent mechanical and biological failure modes, active silicon-based probes have demonstrated modest long-term recording stability through the implementation of specialized mechanical designs and algorithmic optimizations.

Table 1. Comparison of different active CMOS-integrated probes.

Parameter	NeuroSeeker [51]	Neuropixels 1.0 [12]	Neuropixels 2.0 [62]	SiNAPS [66]
Electrodes/channels	1356/1356	966/384	5120/384	1024/1024
Electrode area (μm^2)	400	144	144	196
Electrode pitch (μm)	22.5	20	15	30
Shank ($\text{L} \cdot \text{W} \cdot \text{T}$) (μm^3)	$8 \cdot 10^3 \times 100 \times 50$	$10 \cdot 10^3 \times 70 \times 22$	$10 \cdot 10^3 \times 70 \times 24$	$5 \cdot 10^3 \times 88 \times 50$
Base ($\text{L} \cdot \text{W}$) (mm^2)	12.9×13.5	9×5	8.67×2.2	2.8×2.8
AP noise (μV_{rms})	12.4	6.36	7.44	6.67
LFP noise (μV_{rms})	50.2	10.3	7.65	16.45
Power/Ch (μW)	45	49.06	95.1	6
Long-term stability	≥ 15 days [67]	364 days [69]	364 days [69]	180 days [70]

By monolithically integrating CMOS circuitry onto the probe, active silicon-based neural probes overcome the physical bottlenecks in channel count, SNR, and system complexity that have constrained passive architectures. Active probes achieve parallel recording across thousands of channels while leveraging on-chip preamplification, bandpass filtering, and digitization to convert analog neural signals into high-fidelity digital streams at the source, providing the indispensable technological foundation for decoding brain-wide neural populations at single-cell resolution.

4. Multimodal sensing and modulation

As the capability for electrophysiological recording continues to mature, neuroscience research is progressively shifting from single-modal monitoring toward multimodal interaction. Deconstructing complex brain networks increasingly requires concurrent optogenetic manipulation, localized pharmacological delivery, or neurotransmitter tracking alongside electrical recording [71–74]. Accommodating these diverse experimental requirements drives the architectural expansion of purely electronic platforms into heterogeneous functional interfaces. While flexible polymer platforms can also incorporate optical waveguides or fluidic channels, maintains distinct engineering superiority

derived from its established microfabrication infrastructure. Crucially, silicon enables sub-micron lithographic precision and high integration density, allowing low-loss photonic waveguides such as Si_3N_4 , non-deformable microfluidic channels, and specialized chemical sensing sites to be monolithically integrated with active CMOS control circuits on a single compact shank. Furthermore, the high dimensional stability of silicon guarantees exact spatial alignment and depth-matching among stimulation, delivery and recording sites, which prevents the structural collapse of microchannels or optical displacement caused by substrate flexing during tissue insertion. Driven by superior integration density, device performance, and manufacturing maturity, silicon establishes itself as a uniquely capable platform for multimodal neural interfacing.

To manipulate specific neuronal populations with high spatiotemporal precision, optogenetics has emerged as a powerful tool due to its cell-type specificity and millisecond-scale resolution [75]. While earlier studies combined external optical fibers or Micro-LED with neural recording probes, the physical separation between stimulation and recording sites limits the ability to target the exact same neuronal population [76,77]. Consequently, directly integrating optogenetic functionalities onto silicon shanks for co-localized, depth-matched stimulation and recording has become a key technical focus [71,73,78]. Silicon nitride (Si_3N_4) serves as an optimal waveguide material for this integration, providing broadband visible transparency, favorable refractive index contrast to minimize scattering, and seamless compatibility with semiconductor foundries [64,72,79–81]. Utilizing this material, reconfigurable nanophotonic architectures have been engineered to route external illumination through integrated gratings, delivering sub-millisecond stimulation that is precisely synchronized with localized electrophysiology [79]. This targeted delivery paradigm is further exemplified by the Neuropixels Opto platform, which embeds discrete blue and red emitters alongside Si_3N_4 waveguides to support dual-wavelength modulation across 960 electrical sensing sites (Figure 4a) [64]. Beyond optogenetic stimulation, silicon-based neural probes can be further integrated with fluorescence detection capabilities. A multimodal multi-shank fluorescence neural probe incorporate optical LEDs, fibers, photodiodes and electrodes (Figure 4b) [82]. With optical fibers and LEDs delivering excitation for both optogenetic stimulation and fluorescence imaging, and photodiodes and electrode arrays capturing fluorescence and electrical signals in parallel, this multimodal probe achieves simultaneous fluorescence and electrophysiological recording for cell-type-specific neural interfacing. However, combining optical stimulation with electrophysiological recording will introduce significant noise. During optogenetic modulation, incident photons striking the silicon substrate generate excess charge carriers through the photoelectric effect which produces photoelectric artifacts. To mitigate these artifacts, specially designed total internal reflection layers or opaque metal layers can be incorporated to isolate the optical pathways [83]. Additionally, the photovoltaic effect can be suppressed by using heavily doped silicon substrates to reduce carrier lifetime, while metallization and grounding of lightly doped silicon substrates have also been shown to effectively lower polarization potential, thereby further minimizing optical noise interference [84].

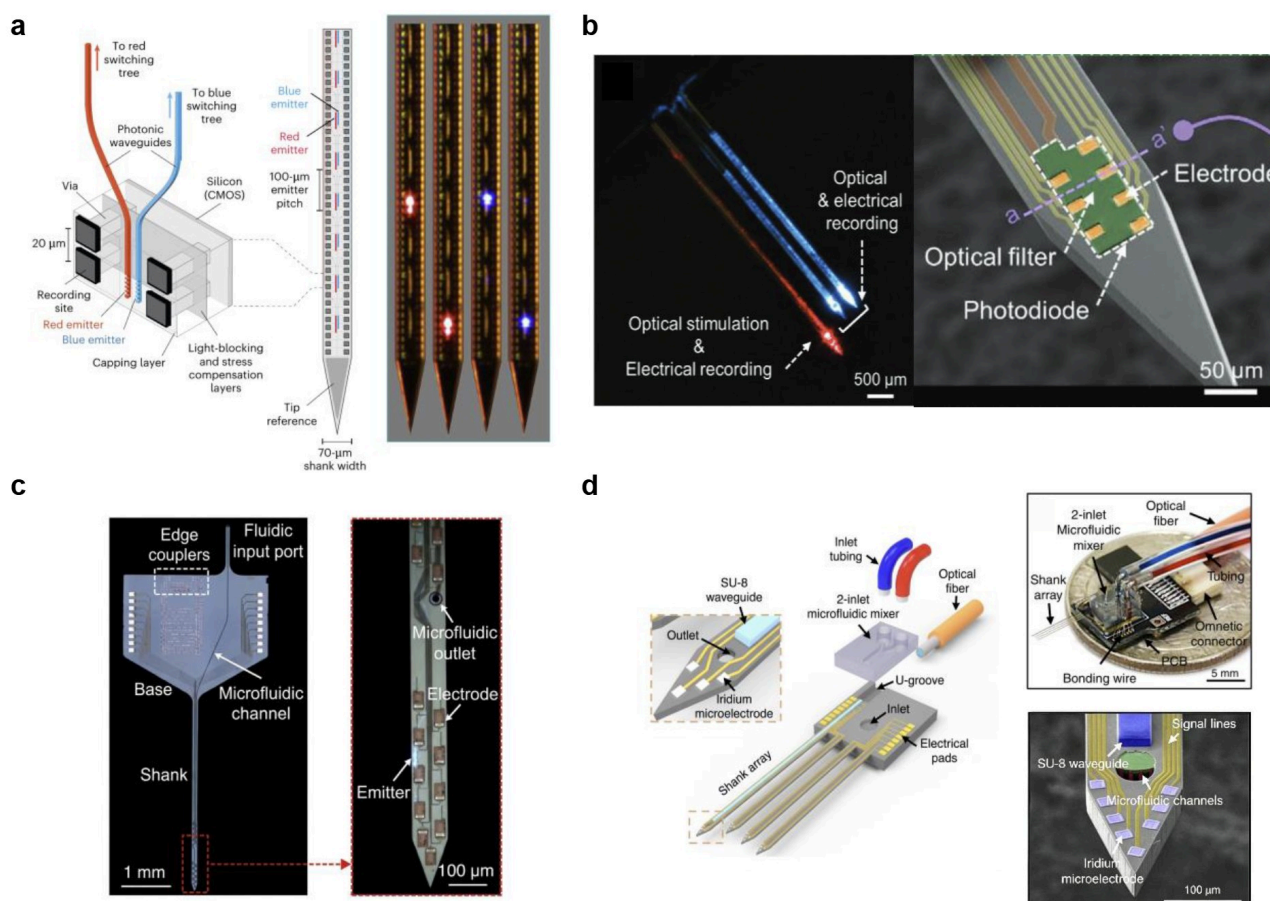


Figure 4. Multimodal sensing and modulation. **(a)** Neuropixels Opto integrated with Si_3N_4 waveguides onto the silicon shank to enable simultaneous optical modulation and electrical recording [64]. Reproduced with permission. Copyright 2026, Springer Nature; **(b)** A multimodal multi-shank neural probe integrated with photodiode and electrode-array pairs to record both fluorescence and electrical signals [82]. Reproduced with permission. Copyright 2022, Wiley-VCH; **(c)** A nanophotonic neural probe integrated with Si_3N_4 waveguides, TiN electrodes and a microfluidic channel for optical stimulation, electrophysiology, and microfluidic delivery [80]. Reproduced with permission. Copyright 2026, Springer Nature; **(d)** A multi-shank neural probe integrated with a SU-8 waveguide, microfluidic channels and microelectrode arrays for optical stimulation, drug delivery, and electrical signal recording [85]. Reproduced with permission. Copyright 2019, Springer Nature.

Parallel to optical tools, chemical modulation and monitoring serve as indispensable instruments for dissecting neural circuits and treating neurological diseases [74,80,81,85]. Microfluidic architectures patterned directly into the probe shank enable targeted fluidic interventions without necessitating auxiliary cannulas. One representative nanophotonic design features an embedded microchannel terminating adjacent to TiN microelectrodes and Si_3N_4 grating couplers, ensuring immediate physical proximity between the delivered compounds and the electro-optical sensing region (Figure 4c) [80]. Another more complex multifunctional multi-shank neural probe distributes microfluidic channels, SU-8 optical waveguides and high-density recording electrodes across parallel shanks (Figure 4d) [85]. This device incorporates a microfluidic staggered herringbone mixer with two inlets, allowing the simultaneous

delivery of two distinct chemicals or the infusion of a single chemical with dynamically adjustable concentration profiles, which enables highly localized *in vivo* pharmacological manipulation while preserving the ability to precisely stimulate and record from the same neural population. In addition to microfluidic delivery, some silicon-based probes have been paired with *in situ* chemical sensors to construct bidirectional metabolic interfaces. To monitor chemical dynamics in real-time alongside electrical and optical signals, a multifunctional neural probe integrates waveguide and specialized electrochemical sensing sites is designed [81]. By patterning Ag/AgCl reference electrodes and IrO_x electrodes directly along the silicon shank, the device achieves continuous tracking of localized pH fluctuations simultaneously with network electrical activity.

The integration of optical and chemical modalities transforms silicon-based probes into multi-dimensional interfaces capable of closed-loop neural interrogation. Modern semiconductor processing continues to broaden this functional repertoire, such as micro-scale magnetic sensors for localized field detection and thermal elements for real-time temperature monitoring [86,87]. A primary bottleneck for these advanced architectures remains the optimization of co-fabrication processes to seamlessly merge these heterogeneous materials. Ultimately, these highly integrated platforms will assist researchers in resolving the complex, multi-physical dynamics of brain circuits for both fundamental neuroscience and clinical therapeutics.

5. Cross-species and clinical applications

Silicon-based neural probes have progressively expanded their application from initial rodent models to non-human primates (NHP) and ultimately to humans, cementing their status as indispensable instruments in both neuroscience research and clinical settings [2,4,14]. Leveraging high-density, multi-channel architectures, these probes facilitate high-resolution exploration of neural circuit dynamics across species, spanning the interrogation of population mechanisms in freely behaving rodents, the tracking of cognitive-correlated neuronal activity in awake monkeys, and the acquisition of single-neuron recordings during human intraoperative procedures [88–91].

The application of silicon-based neural probes initially expanded within small mammal models, which combine the evolutionary conservation of the mammalian nervous system with high experimental tractability. Early Michigan probes contained a limited number of recording sites, monitoring the activity of only a few neurons surrounding the shank [9,10,34]. Subsequently, high-density silicon probes demonstrated high SNR in the rodent neocortex, stably capturing LFPs and APs exhibiting peak-to-peak amplitudes ranging from 0.1 to 1.1 mV [29,33]. Building on these advances, Neuropixels probes enable the concurrent acquisition of hundreds of neurons across distinct anatomical brain structures in awake head-fixed mice and facilitate long-term recordings in unrestrained rats [12]. This capability allows researchers to observe population coding dynamics on a brain-wide scale in freely moving animals, substantially advancing the understanding of network interactions underlying complex behaviors such as spatial navigation, attention, and decision-making. Beyond rodents, silicon probes have gradually extended toward higher mammalian species. For instance, integrating micro-scale giant magnetoresistive (GMR) sensors onto silicon substrates permitted the *in vivo* measurement of neuronal activity-evoked intracranial magnetic fields within the cat visual cortex [87]. Overall, silicon-based neural probes have achieved high technical maturity in non-primate mammalian applications and continue to advance toward multimodal sensing capabilities.

Non-human primates constitute an indispensable translational bridge from small mammals to clinical applications due to their high degree of structural and cognitive homology with humans. However, their larger brain volume and more robust meninges impose stringent demands on mechanical robustness, tissue penetrability and recording depth. Initial deployments of standard Neuropixels 1.0 probe in primate cortices verified basic electrophysiological compatibility, but were constrained by insufficient length to reach deep brain structures and the mechanical difficulty of penetrating the primate dura mater [89,92,93]. Overcoming these physical barriers required targeted geometric and electrochemical optimizations. Modifying single-shank architectures through substrate thickening, precision tip sharpening, and IrO_x surface treatments significantly improved dural penetration and impedance stability while preserving a minimal cross-sectional footprint [94]. The mechanical reinforcement strategy culminates in the Neuropixels 1.0 NHP, which elongates the silicon shank to 45 mm and expands the thickness to 90 μ m. Through advanced CMOS integration, it resolves the signal integrity and mechanical stress challenges inherent to ultra-long shanks, enabling continuous acute sampling spanning from superficial cortical layers to deep subcortical nuclei in a single penetration (Figure 5a) [14]. Leveraging this technological capability, researchers achieve high-throughput receptive field mapping in visual cortex, decoding of motor kinematics, isolation of face-selective neurons from, and tracking of decision-making evidence variables (Figure 5b). The scalable, cost-effective acute recording capacity of silicon-based neural probe accelerates our understanding of the neural mechanisms underlying higher-order cognitive functions in the primate brain.

The extension of silicon-based neural probes to human applications marks a dual advancement toward both fundamental mechanistic research and clinical translation. These devices enable the large-scale observation of single-neuron encoding mechanisms underlying uniquely human cognitive functions, such as language and memory, while contributing to intraoperative monitoring during neurosurgical procedures, including tumor resection and epileptic focus localization. The architectural blueprints established by early Michigan-style planar arrays formed the foundational manufacturing precedents for translating multi-channel electrophysiology into operating rooms (OR), particularly influencing the early development of targeting sensors for deep brain stimulation [29]. With advancement in MEMS fabrication and CMOS integration, a new generation of high-density silicon probes translates rapidly to clinical settings. By implementing structural reinforcement, specialized shank elongations, and sterile packaging tailored for medically compliant, researchers have overcome the engineering barriers imposed by the human operating room environment (Figure 5c) [88,95]. Leveraging these innovations, Neuropixels probes have achieved large-scale recordings within the human cortex, simultaneously extracting hundreds of single-unit spikes across cortical depths during acute intraoperative procedure (Figure 5d) [88]. This capability provides a critical experimental window during epilepsy monitoring while simultaneously resolving fundamental human neurophysiology at single-neuron resolution.

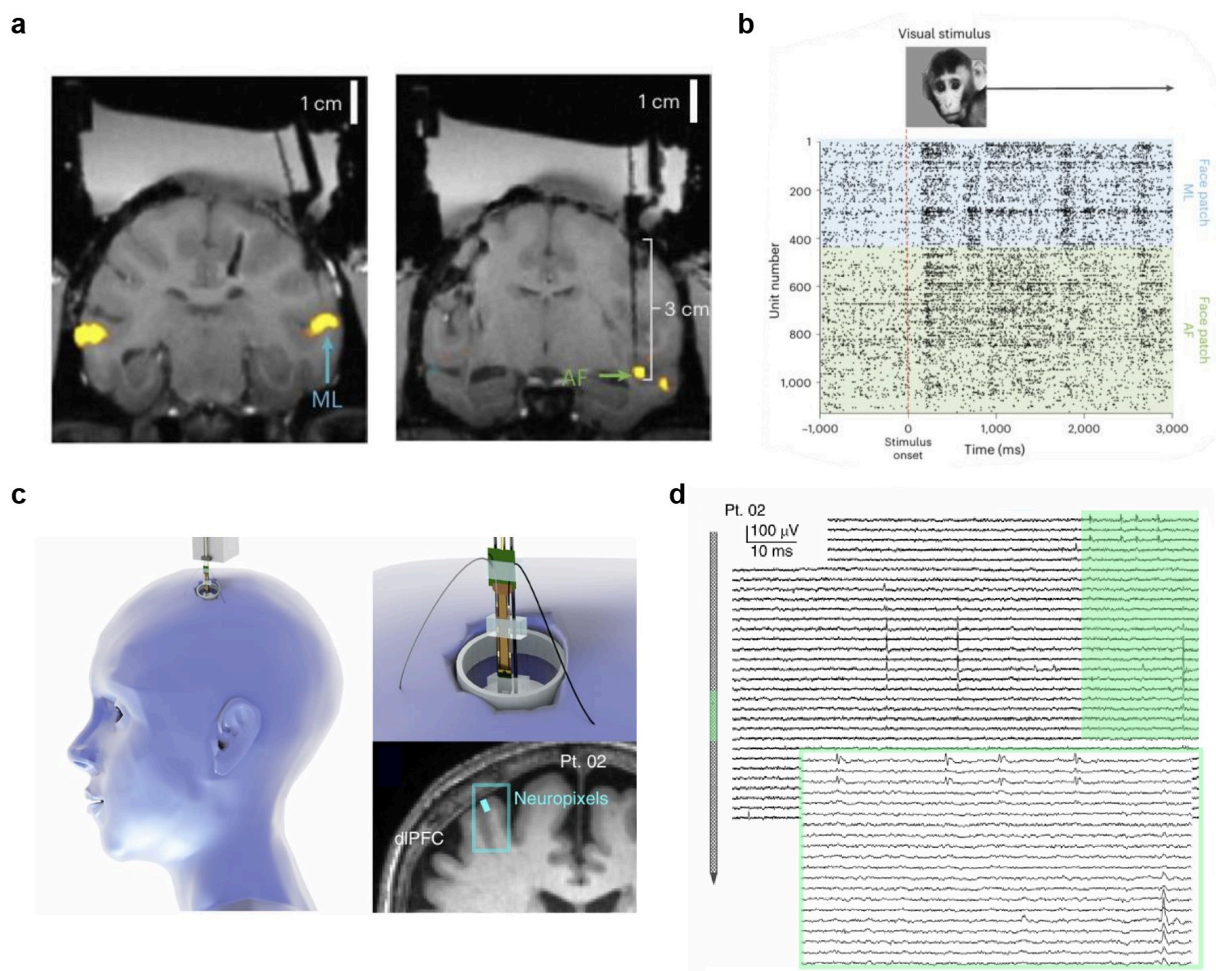


Figure 5. Cross-species and clinical applications of silicon-based neural probes. **(a)** Using Neuropixels NHP Simultaneous deep recordings from face patches in the IT cortex of monkeys [14]; **(b)** The signals recorded by Neuropixels NHP from a primate in response to visual stimuli of monkeys [14]. Reproduced with permission. Copyright 2025, Springer Nature; **(c)** Using Neuropixels to record cortical signals simultaneously in human participants during intraoperative neurosurgical procedures [88]; **(d)** Neural action potential signals recorded by Neuropixels from the human participants [88]. Reproduced with permission. Copyright 2022, Springer Nature.

Extending beyond acute intraoperative applications, silicon-based electrodes have demonstrated substantial utility in chronic long-term brain-computer interface (BCI) systems [96,97]. While Michigan-type probes provide acute spatial mapping, they are prone to mechanical buckling during meningeal penetration and displacement under chronic micromotion due to high aspect ratio and slender planar geometry, causing tissue trauma and persistent responses that limit their long-term use in large animals and humans. Conversely, the robust three-dimensional stubby architecture of the Utah array effectively overcomes these structural vulnerabilities, making it the primary platform for long-term clinical BCI systems. The Utah array has facilitated chronic intracortical BCIs for motor control, speech decoding, bidirectional somatosensory feedback and visual cortical prostheses [98–101]. For example, a patient with severe amyotrophic lateral sclerosis utilizing four Utah arrays as speech neuroprosthetics achieved independent at-home BCI operation for over 3800 hours across two years, reaching a communication rate of 56 words per minute and 92% of the sentences basic accuracy [99]. Within the

somatosensory domain, intracortical microstimulation delivered via chronically implanted arrays in the primary somatosensory cortex has restored tactile perception in participants with tetraplegia [100]. Furthermore, cortical visual prostheses relying on silicon electrode arrays have successfully induced the perception of simple shapes in blind individuals [101]. These clinical milestones validate the clinical value and translational potential of silicon-based neural probes.

6. Discussion

The evolution of silicon-based neural probes exemplifies a deep convergence of microfabrication, integrated circuits and neuroscience. Initial passive silicon probes established the foundational framework for low-invasive electrophysiology through ingenious structural mechanics, high-density site scaling, and biocompatible material functionalization. Active CMOS-integrated probes overcome the physical limitations of lead count and bandwidth, enabling population-scale single-unit recording across distributed brain networks. Building on this, multimodal probes propel neural interfaces from pure recording devices into integrated platforms for comprehensive interrogation and modulation. Leveraging these technological foundations, silicon-based probes have demonstrated remarkable cross-species versatility and clinical utility from whole-brain circuit decoding in rodents and NHPs to single-neuron intraoperative monitoring and long-term BCI application.

Despite remarkable achievements, several persistent engineering bottlenecks hinder the broader scientific and clinical adoption of silicon neural probes. During chronic implantation, the severe Young's modulus mismatch between rigid silicon substrates and soft brain tissue generates micro-motion shear stress. This mismatch triggers chronic foreign body responses (FBR) and glial scarring that degrade signal quality over time, while simultaneously increasing the risk of probe fracture [31,102,103]. Moreover, extensive glial encapsulation and interfacial metabolic reactions critically impair the sensitivity and long-term stability of multimodal sensing systems. The resulting dense cellular barrier impedes analyte diffusion and attenuates optical or electrical coupling efficiency, while localized reactive oxygen species accelerate biofouling and material degradation. To overcome these biological bottlenecks, future optimization must integrate anti-fouling surface modifications and localized anti-inflammatory release strategies. Although introducing highly flexible polymers, hydrogel interfaces, or engineered mesh structures can significantly mitigate this issue, seamlessly integrating these stress-buffering strategies with dense active CMOS architectures remains a formidable challenge [104,105]. Furthermore, as channel counts increase, power dissipation from dense active CMOS circuitry poses localized thermal risks [15,51]. Consequently, the fundamental bottleneck has shifted from merely scaling channel density to resolving system-level integration challenges, including mechanical compliance, thermal management and the long-term hermetic reliability of active chips in chronic *in vivo* environments.

Moving forward, while silicon neural interfaces show potential across various domains, their primary competitive advantage remains in short-term, high-density fundamental neuroscience. Unlike flexible interfaces, silicon-based probes uniquely leverage mature CMOS manufacturing to achieve the unparalleled electrode density, scalability, and multiplexing capabilities required for brain-wide circuit mapping. Next-generation architectures should address the massive data bottlenecks inherent in high-density multi-region recordings. Embedding edge computing and neuromorphic hardware directly onto the probe backend will enable ultra-low latency on-chip spike sorting and real-time data compression, effectively bypassing wireless data bandwidth constraints [106,107]. Furthermore, the

seamless integration of electrophysiological recording with high-density micro-LED optogenetic stimulation and ultrasensitive chemical sensors will serve as powerful tools for precise circuit interrogation and multimodal tagging in awake animal models. Driven by the advancement of low-power microelectronics and monolithic integration, intelligent silicon platforms will solidify their role as indispensable tools for decoding complex large-scale network dynamics and advancing fundamental neuroscientific discovery.

Data availability statement

All data needed to evaluate the conclusions in the paper are present in the paper.

Declaration of generative AI and AI-Assisted technologies

During the preparation of this review manuscript, the authors used AI-based tools such as DeepSeek and Gemini only for language polishing and grammar correction. After using the tools, the authors reviewed and edited the content as needed. The authors take full responsibility for the content of the manuscript and the figures.

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Authors' contribution

Conceptualization, X.S. and J.C.; investigation, J.C., W.Z. and L.C.; resources, X.S.; writing—original draft preparation, J.C.; writing—review and editing, X.S.; visualization, X.S. and J.C.; supervision, X.S.; project administration, X.S.; funding acquisition, X.S. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no competing interests.

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