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Current Opinion in Electrochemistry

Review Article

Advancements in real-time electrochemical sensing of brain neurochemicals

Ajay Pradhan and Ann-Sofie Cans

Neurochemical signaling can be investigated across multiple spatial scales, ranging from quantal exocytotic neurotransmitter release at single synapses to extracellular fluctuations in neurochemical concentrations across intact brain circuits associated with physiology and behavior. Electrochemical techniques are particularly suited for monitoring these processes because they combine high temporal resolution and chemical sensitivity with miniaturized electrodes enabling spatially resolved measurements from single cells to freely behaving animals with minimum tissue damage. This review highlights recent advances in carbon fiber microelectrodes, alternative electrode materials, nanostructured interfaces, surface modification strategies and electrochemical methodologies that improve analytical performance. It also examines novel molecular-recognition and biosensing strategies including aptamers, molecularly imprinted polymers, enzyme-based biosensors, liquid-liquid junction microelectrodes, photoelectrochemical sensors and synthetic receptor-based platforms that extend detection also to non-electroactive neurotransmitters. Particular focus is placed on simultaneous multianalyte detection and complementary methodologies enabling to better understand how neurotransmitter dynamics relate to brain function and dysfunction.

Addresses
Department of Chemistry and Chemical Engineering, Chalmers University of Technology, Kemigården 4, Gothenburg, 412 96, Sweden

Corresponding author: Cans, Ann- Sofie (cans@chalmers.se)

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Introduction

Real-time monitoring of neurochemical dynamics is essential for understanding mechanisms that regulate brain function and dysfunction. The human brain comprises approximately 86 billion neurons and a comparable number of glial cells, both of which contribute to tightly regulated neurochemical signaling. At chemical synapses, action potentials trigger synaptic vesicle exocytosis and rapid neurotransmitter release from presynaptic terminals. These molecules diffuse across the synaptic cleft and activate receptors of neighboring cells, thereby mediating intercellular communication. More than 100 neurotransmitters and neuromodulators have been identified, ranging from classical small-molecule neurotransmitters to neuropeptides. Together, they form complex, interconnected signaling networks whose coordinated spatiotemporal interplay shapes neuronal circuits and supports brain functions such as learning, memory, cognition and behavior. Understanding the molecular interaction within such networks requires technologies capable of tracking multiple neurochemical signals with high spatiotemporal resolution.

Electrochemical techniques offer unique quantitative, real-time measurements of neurotransmission with high temporal resolution and chemical sensitivity and are compatible with miniaturized electrodes. These capabilities support investigations across spatiotemporal scales spanning from individual sub-millisecond quantal exocytosis events at single cells to sub-second fluctuations in extracellular neurochemical concentrations within intact brain circuits of freely behaving animals. Advances in electrochemical sensing are driven not only by the need to improve analytical performance of individual neurotransmitter measurements but also by growing interest in simultaneously monitoring multiple neurochemicals to better understand how their coordinated interplay regulates brain function. This review highlights recent developments in electrode design, molecular recognition strategies, multianalyte detection and multiplexing platforms for investigating neurochemical signaling across spatial and temporal scales.

Recent advances in electrochemical neurotransmitter detection: from established carbon fiber microelectrodes to emerging sensor technologies

Since their first implementation by the group of Ralph Adams in the 1970s [1], carbon fiber microelectrodes

(CFMEs) have remained the gold standard for real-time electrochemical detection of neurotransmitter release. Their small footprint (5−7 μm diameter) combined with high sensitivity and rapid electron transfer kinetics enable the detection of electroactive neurotransmitters like dopamine and serotonin with minimal tissue damage [2]. The versatility of CFMEs has supported measurements across different biological scales. At single cells, high-speed amperometric recordings sampled up to 100 kHz can resolve individual vesicle release events and sub-millisecond features associated with fusion pore regulated exocytosis [3,4]. In brain tissue, CFMEs coupled with fast-scan cyclic voltammetry (FSCV) provide sub-second monitoring and chemical discrimination based on characteristic oxidation and reduction peaks in cyclic voltammograms, making them particularly suitable for measuring extracellular neurotransmitter dynamics *in vivo* of freely behaving animals. However, CFMEs face limitations associated with biological and chemical fouling, reduced temporal resolution due to adsorption kinetics, and limited selectivity between analytes with similar redox properties (Reviewed in Refs. [2,5]). Considerable efforts have therefore been directed towards modifying CFME surfaces and geometries to improve their analytical performance.

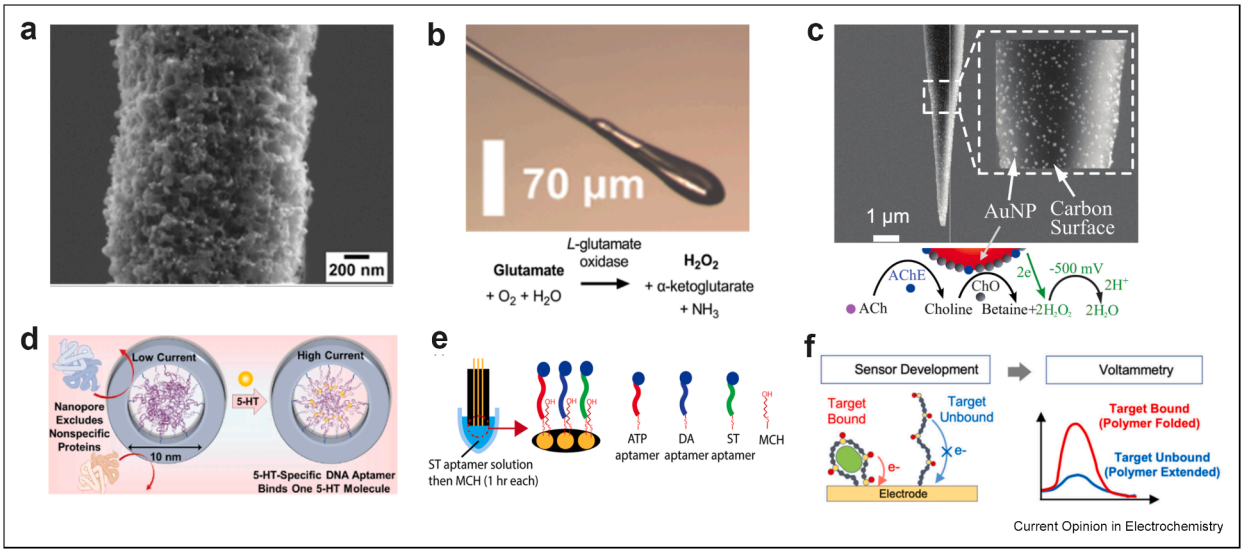
Chemical, electrochemical, and thermal treatments can enhance CFME sensitivity by altering its surface chemistry and introducing nanoscale structures. For example, positioning a CFME near the heating filament of a conventional glass capillary puller enables time- and temperature-controlled heat etching, producing nanotip electrodes with tip diameters of approximately 150 nm and roughened surfaces comprising carbon nanodots and nanocavities [6] (Figure 1a). Together with the increased abundance of oxygen-containing functional groups, these structural changes enhance electrochemical sensitivity. Such porous structures are attractive because analyte confinement within the pores amplify electrochemical signals [2]. Controlled electrochemical etching using a potassium hydroxide droplet has been similarly used to tailor carbon fiber geometry and size, enabling the fabrication of short ultralow-noise electrodes with tunable needle- and cone-shaped profiles [7,8]. Compared with earlier nanotip electrodes with exposed length of 50−100 μm, electrodes with exposed carbon lengths of ∼10 μm provide lower-noise amperometric recordings [9]. Their nanotip dimensions and minimal electroactive surface area facilitate positioning the sensor close to the individual synapses, thereby enabling localized measurements of single-vesicle exocytosis in single-cell studies. Electrode geometry has also been shown to directly influence neurotransmitter detection performance [10,11]. Reducing the electroactive surface area generally lowers recording noise and improves spatial resolution, while larger surfaces can increase signal intensity by sampling greater tissue volumes. For *in vivo* measurements in awake animals, sensor dimensions need to be controlled to confine measurements to brain region of interest. Minimizing the implanted sensor dimensions is also important because larger probes can cause tissue damage and inflammatory responses, particularly during long-term implantation. As sensor size and geometry also affect neurotransmitter diffusion and mass transport, electrode design must be matched to both the spatial scale and biological setting of the measurement.

In addition to modifying their intrinsic surface properties and geometry, CFMEs can be further functionalized with materials such as gold or platinum nanoparticles, polymers, carbon nanotubes (CNTs), and graphene oxide [5]. Depending on the material properties, these modifications can increase the electroactive surface area, accelerate electron transfer, enhance chemical selectivity, or reduce surface fouling. CFMEs modified with single-atom Fe nanozyme catalyst with antioxidant properties have also been explored and shown to reduce inflammatory responses upon *in vivo* implantation [12]. In addition to electrode design and functionalization, selecting the appropriate electrochemical technique is equally critical for maximizing the detection limit and for enabling detection at speeds comparable to biological time scales of interest. Although techniques like differential pulse and square wave voltammetry offer high sensitivity and analyte identification, they are generally too slow to capture rapid exocytotic neurotransmitter release dynamics at single cells. At single cells, high-speed amperometry provides microsecond temporal resolution that can resolve individual vesicular release events and sub-millisecond features of fusion-pore dynamics, although it lacks chemical identification. In contrast, *in vivo* studies generally monitor sub-second fluctuations in extracellular neurotransmitter concentrations reflecting the collective activity of neuronal populations. FSCV is well-suited for such measurements in awake animals as it combines sub-second temporal resolution with chemical identification. However, these recordings are typically limited to several minutes due to sensor drift, particularly with surface-modified electrodes. Matching carbon fiber sensor design with the appropriate electrochemical method is therefore essential for investigating neurotransmission from single-vesicle exocytosis to population dynamics *in vivo*.

Exploration of alternative carbon-based electrode materials

In parallel with CFME modifications, alternative carbon-based electrode materials have been explored for neurotransmitter detection, particularly for *in vivo*

Figure 1



(a) Scanning electron microscopy (SEM) image of a heat-etched carbon fiber microelectrode (CFME) exhibiting a defect-rich nanostructured surface. Adapted from the study by Gupta et al. (Ref. [6]) with permission. **(b)** Bright-field micrograph of a CFME modified with chitosan and glutamate oxidase for dual detection of dopamine and glutamate, where dopamine is detected by direct oxidation and glutamate through enzymatic production of hydrogen peroxide (H_2O_2). Adapted from the study by Kimble et al. (Ref. [32]) with permission. **(c)** SEM image of a gold nanoparticle (AuNP) modified carbon fiber nanotip electrode functionalized with the enzymes acetylcholinesterase (AChE) and choline oxidase (ChO) for acetylcholine detection at single synapses. Adapted from the study by Wang et al. (Ref. [9]) with permission. **(d)** Schematic showing the working principle of an aptamer-modified nanopipette biosensor for serotonin detection. Serotonin binding induces a conformational change in the aptamer layer that increases ion permeability and the measured current, while the 10 nm pipette opening prevents the entry of interferents. Adapted from the study by Nakatsuka et al. (Ref. [20]) with permission. **(e)** Schematic of an aptamer-modified microelectrode array for multianalyte detection of dopamine, serotonin, and ATP. Aptamer for ATP was first deposited onto three electrodes, followed by removal at two of the electrodes via electrochemical treatment. Aptamers for dopamine and serotonin were then deposited sequentially using the same addition and removal process, generating a three-electrode aptamer microarray with distinct molecular recognition surfaces. Adapted from the study by Sen and Lazenby (Ref. [25]) with permission. **(f)** Schematic of the sensing mechanism of a linear-chain stimuli-responsive polymer in its target-free and target-bound states. In the absence of the target neurotransmitter, the polymer in the unbound state inhibits electron transfer between the polymer-attached redox probe and the electrode surface. Neurotransmitter binding alters the polymer conformation and facilitates electron transfer, which increases the voltammetric current. Adapted from the study by Ahmadian-Alam et al. (Ref. [28]) with permission.

applications [5]. Flexible carbon nanotube (CNT) yarns represent an attractive alternative to conventional CFMEs because their graphitic edge plane defect sites and extensive sp2-hybridization offer both fast electron transfer and antifouling properties [5,13]. Graphene oxide fibers have also shown favorable performance for serotonin detection, including improved fouling resistance compared to CFMEs [14]. Another recently reported innovative design involves pyrolyzed Parylene-N coatings on metal wires to generate defect-rich carbon electrodes showing excellent performance for detection of dopamine, adenosine and serotonin *in vivo* while resisting chemical fouling [15,16]. Other emerging electrode platforms include boron-doped diamond electrodes [17], 3D-printed carbon electrodes [18], and carbon-coated nanopipettes [19]. Despite these advances, the broader adoption of emerging electrode materials will depend not only on analytical performance but also on fabrication accessibility, reproducibility and cost. Some of these modern sensors described here require advanced nanofabrication facilities including expensive chemical vapor deposition equipment, that are accessible to relatively few research laboratories. In contrast, carbon fibers are commercially available and can be readily fabricated and modified using standard laboratory equipment. This practical advantage is particularly important for *in vivo* applications, where the ease of sensor fabrication and modification is also equally important. Accessible approaches such as simple heat-induced surface modification may therefore help CFMEs remain widely used alongside emerging carbon-based sensor technologies [6].

Molecular recognition and biosensing strategies for neurotransmitter detection

Nucleic acid aptamers are versatile molecular recognition elements for neurotransmitter sensing because of their high affinity and selectivity. Aptamer-based sensors have been developed for small molecule neurotransmitters [20–22], neuropeptides [23], and multianalyte detection of several neurochemicals [24,25]. Despite challenges with aptamer stability and biofouling, recent advances have enabled real-time *ex vivo* and *in vivo* neurotransmitter measurements.

Examples include aptamer-functionalized field effect transistors [21], graphene microtransistors [26], and differential sensing systems based on paired nanopipettes approximately 10 nm in diameter, with one serving as reference for subtracting signals arising from non-specific interactions [27]. Molecularly imprinted polymers (MIPs) have similarly emerged as synthetic recognition elements and may overcome some of the stability limitations of aptamers. MIPs are templated polymers containing binding cavities designed to recognize specific analytes with high affinity and selectivity. Recent developments have extended these platforms to multianalyte detection [28,29]. Both aptamer- and MIP-based biosensors can target electroactive and non-electroactive neurotransmitters. Nevertheless, enzyme-based biosensors remain the most commonly used strategy for monitoring non-electroactive neurotransmitters like glutamate [30] and acetylcholine [31]. Enzymatic biosensors commonly use oxidases that, through the enzymatic reaction, convert the target analyte while generating hydrogen peroxide (H_2O_2). Subsequent oxidation or reduction of H_2O_2 at the electrode surface, produces a current proportional to the analyte concentration. Enzymatic detection can also be combined with direct electrochemical detection to enable dual-analyte sensing. For example, CFMEs modified with glutamate oxidase-containing chitosan hydrogel have been used for simultaneous, sub-second detection of dopamine and glutamate in brain slices [32] (Figure 1b). Extending enzymatic biosensing to single-cell amperometry requires a response sufficiently rapid to resolve fusion pore regulated exocytotic release from individual synaptic vesicles. This has been achieved by reducing the enzyme coating at the electrode surface to a molecular monolayer, thereby minimizing the diffusion distance of enzymatically generated H_2O_2 to the electrode surface and enabling sub-millisecond detection [30]. Enzymatic glutamate sensing has since been extended to several additional applications [32–36]. Similarly, ultrafast monitoring of acetylcholine exocytosis at individual synaptic release sites have been demonstrated, together with intracellular quantification of vesicular acetylcholine content [9,31,37] (Figure 1c).

Alternative strategies have also been developed for detecting non-electroactive neurotransmitters. Micro- and nano-scale interfaces between two immiscible electrolyte solutions (ITIES) have been developed and used by the Shen group for acetylcholine detection, including recent *in vivo* measurements [38]. Rather than relying on electron transfer, these sensors detect potential-driven ion transfer from the aqueous medium into an organic phase contained within the sensor probe. The composition of the organic phase can be optimized to favor transfer of particular analytes, thereby improving sensor selectivity. To date, however, neurotransmitter applications of this approach has so far focused primarily on acetylcholine. Further, the reported experiments were only performed acutely, leaving long-term stability unexplored, and sensor fouling was observed even during short-term implantation [38]. The use of toxic organic chemicals, which can leak if the glass pipette encasing the solution is damaged in living animals after implantation, may also raise biocompatibility concerns.

Gu et al. reported a photoelectrochemical biosensing strategy based on isolated zinc atoms supported on a TiO_2 substrate [39]. The rationally designed zinc-TiO_2 structure selectively interacts with the molecular moieties present on the norepinephrine molecule via molecular docking, enabling sensitive norepinephrine detection *in vivo* with selectivity over structurally similar neurotransmitters [39]. Interestingly, its reported response time of 60 ms is sufficiently fast for monitoring neurochemical dynamics *in vivo*. Finally, engineered glutamate receptor proteins immobilized on electrode surfaces provide a non-enzymatic sensing mechanism analogous to the molecular recognition used in fluorescent glutamate probes [40]. Glutamate binding induces a structural change in the receptor that disrupts the electron transfer between ferrocene molecules conjugated at the gold-coated sensor and the underlying gold surface [40]. The sensor exhibited a response time of 30–40 ms, which is sufficient for sub-second recordings of basal neurotransmitter dynamics but is significantly slower than enzymatic glutamate biosensors with monolayer enzyme coating with sub-millisecond response [30], in addition to having a significantly more complex sensor functionalization pipeline [40].

Recent progress in electrochemical multi-neurotransmitter detection

Understanding neurochemical interactions in the brain requires tools capable of monitoring multiple neurochemicals simultaneously. Several emerging strategies enable multi-neurotransmitter detection at a single electrochemical sensor, ensuring that signals are collected from the same spatial location and avoiding the separation inherent to measurements using multiple probes (Table 1). In carbon-based sensors, polymer coatings can shift neurotransmitter oxidation peak potentials and facilitate dual-analyte detection [41]. Overlapping FSCV signals can also be deconvoluted with machine learning pipelines [42,43].

Multianalyte measurements can further be achieved by combining direct electrochemical detection with enzymatic biosensing. Enzyme-based sensors commonly detect H_2O_2 through oxidation at higher positive potentials or reduction at negative potentials, allowing this reporter signal to be distinguished from the redox signals of redox-active neurotransmitters like dopamine. Accordingly, the Sombers group demonstrated

Table 1

Summary of recent works demonstrating simultaneous detection of release of several neurochemicals with a single sensor.

Authors	NTs	Methods	Sensor modification	RT dual detection of NT release?	Biological sample
Qi et al. [47]	DA, adenosine	FSCV	Carbon coated-gold MEA electrodes	Yes	DA detected in NAc of living rats
Han et al. [48]	DA, 5-HT	CV	CNT and Nafion-modified CFMEs	No	Detection of injected DA, 5-HT in living crayfish
Huang et al. [45]	DA, 5-HT	DPV	MOF–MOF composite-modified carbon paper	No	Spiked serum, and DA detection in PC12 cells
Goyal et al. [42]	DA, NE, 5-HT	Multiple cyclic SWV	CFMEs	Yes	NAc of living rats
Park & Venton [43]	DA, octopamine	FSCV	CFMEs	No	DA and octopamine injected into *D. melanogaster* brain
Berger et al. [44]	DA, Met-Enkephalin	FSCV	CFME	Yes	Rat striatal brain slices
Kimble et al. [32]	DA, glutamate	FSCV	Chitosan and enzyme-modified CFMEs	Yes	Rat striatal brain slices
Chu et al. [33]	Glutamate, GABA	Amperometry	Enzyme/Pt-black-modified microarray	Yes	Anesthetized rat brain

Abbreviations used in Table.
5-HT: serotonin, CFMEs: carbon fiber microelectrodes, CNT: carbon nanotubes, CV: cyclic voltammetry, DA: dopamine, DPV: differential pulse voltammetry, FSCV: fast scan cyclic voltammetry, MEA: multi-electrode array, MIP: molecularly imprinted polymer, MOF: metal–organic framework, NAc: nucleus accumbens, NE: norepinephrine, NT: neurotransmitters, Pt: platinum, RT: real-time, SWV: square wave voltammetry.

simultaneous real-time detection of directly oxidized dopamine and enzymatically generated glutamate signals in striatal brain slices using a single FSCV waveform [32]. Direct dual detection of dopamine and neuropeptides has also been achieved using specialized sawhorse FSCV waveforms [44]. Simultaneous enzymatic detection of two non-electroactive neurotransmitters presents a greater challenge. Dual glutamate and gamma-aminobutyric acid (GABA) detection has recently been demonstrated albeit requiring sentinel electrodes [33]. Enzymatic GABA sensing is complicated and requires alpha-ketoglutarate as a co-substrate. However, alpha-ketoglutarate generated during glutamate oxidase-catalyzed conversion of glutamate is sufficient for effective GABA sensing. This coupled enzymatic pathway provides a potential basis for simultaneous *in vivo* sensing of both neurotransmitters [33].

Other promising multianalyte platforms include aptamer-based sensors [25], molecularly imprinted polymers (MIPs) [28,29] and metal−organic frameworks (MOF)- modified electrodes [45]. Although their suitability for *in vivo* applications remains to be established, these approaches are expanding the capabilities of electrochemical neurotransmitter sensing. While single-sensor multianalyte sensing using aptamers has been demonstrated for cytokines [46], microelectrode arrays are generally preferred for multi-neurotransmitter sensing (Figure 1e). The number of molecular targets that can be distinguished at a single sensor is limited by the availability of redox probes with sufficiently separated peak potentials. Additionally, signal dilution occurs with a decreased proportion of aptamer detection probes per analyte [25]. Synthetic recognition polymers have also enabled multi-neurotransmitter detection, but conventional cross-linked MIPs require incubation times of approximately 20 min, making them unsuitable for monitoring neurotransmitter dynamics *in vivo* [29]. Stimuli-responsive polymers have significantly accelerated binding kinetics of approximately 1 min, but their selectivity and cross-reactivity in complex neurochemical matrices remain insufficiently characterized [28] (Figure 1f). Further, improvements in response time and molecular discrimination will therefore be required before these materials can be applied to real-time multianalyte measurements.

Multiplexing electrochemical detection with complementary techniques *in vivo*

Miniaturized electrochemical sensors can be integrated with complementary methods to provide multimodal *in vivo* measurements (Table 2). For example, FSCV-based dopamine detection has been successfully combined with functional resonance imaging (fMRI) [49] and fluorescent glutamate sensing [50]. Driscoll and colleagues recently demonstrated a multimodal platform incorporating CNTyarn electrodes for FSCV-based dopamine sensing and electrophysiological recordings, together with a polymer-fiber waveguide for optogenetics [13] (Figure 2c). The platform also supports

Table 2

Summary of key recent works showcasing multiplexed electrochemical detection with other methods.

Authors	NTs	Methods	RT detection of NT release?	Biological sample
Shnitko et al. [49]	DA	FSCV, fMRI	Yes	NAc of anesthetized rat brain
Shrestha et al. [50]	DA, glutamate	FSCV for DA, fluorescent glutamate probe	Yes	Caudate putamen of mouse brain slices
Driscoll et al. [13]	DA	FSCV, electrophysiology, fiber photometry, fMRI, behavior	Yes	NAc of awake behaving mice
Fan et al. [54]	DA	Amperometry, local field potentials	Yes	Striatum of awake behaving mice
Qi et al. [47]	DA	FSCV, electrophysiology	Yes	NAc of living rats
Wang et al. [51]	DA	Amperometry, local field potentials, behavioral	Yes	Caudate putamen of awake mice
Xie et al. [52]	Glutamate	Amperometry, action potentials, local field potential	Yes	Cortex and hippocampus of living rats
Hasegawa et al. [34]	Glutamate	Amperometry, field potential	Yes	Mouse hippocampal brain slices

Abbreviations used in Table.
DA: dopamine, FSCV: fast scan cyclic voltammetry, fMRI: functional magnetic resonance imaging, NAc: nucleus accumbens, NTs: neurotransmitters, RT: real-time.

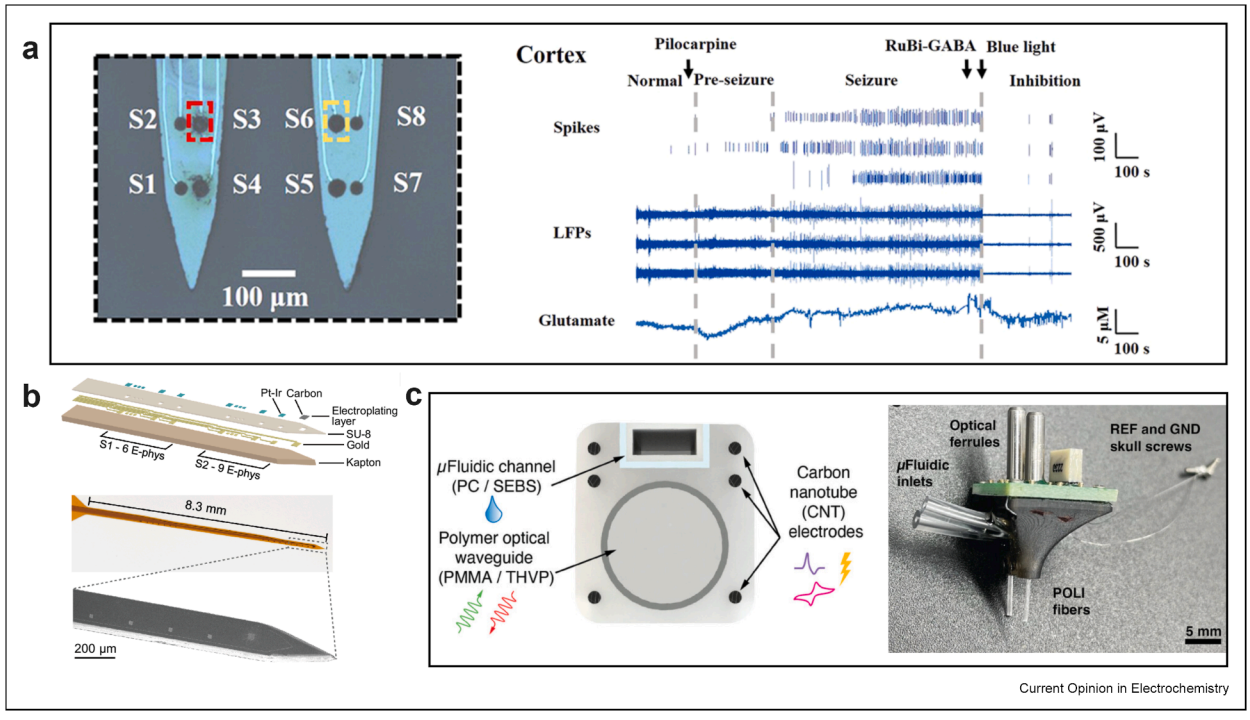
fiber photometry recordings of calcium activity and is compatible with fMRI and behavioral experiments, although FSCV was evaluated separately from these other methods [13]. Other platforms have combined electrochemical neurotransmitter sensing with electrophysiology [47,51] (Figure 2b), including a smaller number of them integrating glutamate sensing [34,52] (Figure 2a). By correlating chemical signaling with electrical activity, these approaches can provide a more comprehensive understanding of neuronal circuit function. Electrochemical neurotransmitter measurement is also possible in a plate-reader format for two-dimensional cell cultures [53], although their integration with electrophysiological recordings in neuronal cultures remains unexplored. Although such strategies are extremely valuable in neuroscience research, their complex design, specialized fabrication requirements and limited commercial availability, currently restrict widespread adoption of this technology. With efforts focused on reproducible manufacturing, standardized interfaces and compatibility with commonly available instrumentation, these multimodal electrochemical technologies could become more accessible to the broader neuroscience community.

Conclusions and future outlook

Real-time electrochemical neurotransmitter sensing offers a powerful means of investigating neurochemical signaling across wide spatial and temporal scales. Advances in controlling electrode dimensions, geometry, surface structure and recognition chemistry have broadened the range of detectable neurochemicals while improving sensitivity, spatial resolution and compatibility with complex biological environments. These capabilities allow sensors to be adapted to specific biological questions, from resolving single-vesicle exocytosis at individual cells to monitoring extracellular neurotransmitter dynamics within intact neural circuits *in vivo*. The evolution of CFME-based sensing demonstrates this progress, from its introduction for detection of electroactive neurotransmitters such as dopamine, to now having its surface miniaturized, structurally modified, and functionalized with catalytic materials and molecular recognition elements to support increasingly diverse applications.

The field is now progressing toward simultaneous multianalyte measurements and integration with electrophysiological and optical-based approaches, providing

Figure 2



(a) Micrograph of a multimodal sensor integrating enzymatic glutamate sensing with electrophysiological recordings. The sensor simultaneously resolved action potentials, local field potentials, and glutamate levels. Adapted from the study by Xie et al. (Ref. [52]) with permission. **(b)** Schematic and images of a Kapton-based sensor for simultaneous *in vivo* dopamine sensing at the carbon-coated gold surface and electrophysiological recordings at the platinum-iridium surface. Adapted from the study by Qi et al. (Ref. [47]) with permission. **(c)** Schematic and an image of a fMRI-compatible multimodal sensing device integrating drug delivery, optical stimulation and sensing through a polymer optical waveguide, and six CNT yarn electrodes for electrical stimulation, electrophysiological recordings and dopamine sensing using FSCV. Adapted from the study by Driscoll et al. (Ref. [13]) with permission.

complementary information on the intricacies of neuronal communication and mechanisms of brain diseases. Aptamers, MIPs, enzymatic recognition, tailored FSCV waveforms, and computational signal deconvolution are expanding the chemical information obtainable from individual sensors and arrays. However, such ambitious undertaking comes with important challenges such as analyte cross-talks, overlapping electrochemical signatures, biofouling, signal drift, sensor-to-sensor variability and limited long-term stability. Wider adoption will also require reproducible fabrication, standardized validation, compatibility with common instrumentation and commercial availability.

Most real-time neurochemical measurements have primarily been performed in animal models, which cannot fully reproduce the specific human neurophysiology. Studies in human-relevant systems remain largely limited to stem cell-derived neuronal cultures [55] and surgically extracted brain tissue from patients with epilepsy [36]. Advanced three-dimensional cultures, organoids, and other human-derived models could therefore help bridge between animal studies and clinical translation. In the longer term, integration with clinically implanted devices such as deep-brain stimulation electrodes, may enable neurochemical monitoring in patients. Achieving this goal will require substantial advances in biocompatibility, selectivity, recording stability, and safety. Importantly, regulatory approval must be addressed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Wightman RM, Strope E, Plotsky PM, Adams RN: **Monitoring of transmitter metabolites by voltammetry in cerebrospinal fluid following neural pathway stimulation**. *Nature* 1976, **262**: 145–146, https://doi.org/10.1038/262145a0.

2. * Ostertag BJ, Ross AE: **Editors' choice—review—the future of carbon-based neurochemical sensing: a critical perspective**. *ECS Sens Plus* 2023, **2**, 043601, https://doi.org/10.1149/2754-2726/ad15a2.
A comprehensive review of sensing neurotransmitters with carbon-based sensors, including limitations and future outlook.

3. Mosharov EV, Sulzer D: **Analysis of exocytotic events recorded by amperometry**. *Nat Methods* 2005, **2**:651–658, https://doi.org/10.1038/nmeth782.

4. Leszczyszyn DJ, Jankowski JA, Viveros OH, Diliberto EJ, Near JA, Wightman RM: **Nicotinic receptor-mediated catecholamine secretion from individual chromaffin cells. Chemical evidence for exocytosis**. *J Biol Chem* 1990, **265**: 14736–14737, https://doi.org/10.1016/S0021-9258(18)77173-1.

5. Subedi V, Kumar SM, Weese-Myers ME, Ross AE: **Innovating carbon-based electrodes for direct neurochemical detection along the brain-immune axis**. *Curr Opin Electrochem* 2025, **51**, 101678, https://doi.org/10.1016/j.coelec.2025.101678.

6. * Gupta P, Pradhan A, Gupta VK, Karlsson-Fernberg H, Wang Y, Hanrieder J, Zetterberg H, Cans A-S: **Temperature and time-controlled etching of carbon fiber nanotip electrodes: creating nanocavity- and nanodot-modified surfaces for enhanced neurotransmitter detection**. *Carbon* 2025, **243**, 120612, https://doi.org/10.1016/j.carbon.2025.120612.
This work shows that time- and temperature-controlled heat etching using the heating filament of a glass capillary puller produces short (8–10 μm) highly nanostructured carbon fiber nanotip electrodes for sensitive detection of electroactive neurotransmitters.

7. Wang Y, Gupta P, Pradhan A, Trouillon R, Hanrieder J, Zetterberg H, Cans A-S: **Electrochemical droplet sculpturing of short carbon fiber nanotip electrodes for neurotransmitter detection**. *ACS Electrochem* 2025, **1**:1698–1709, https://doi.org/10.1021/acselectrochem.5c00135.

8. Chang Y, Zhang D, Liu Z, Wang L, Guo G, Wang X: **Concentration gradient-controlled electrochemical etching: a universal strategy for nanoelectrodes with tunable geometries**. *Small Methods* 2026, **10**, e70723, https://doi.org/10.1002/smtd.70723.

9. Wang Y, Pradhan A, Gupta P, Hanrieder J, Zetterberg H, Cans A-S: **Nanotip acetylcholine biosensor reveals cholinergic differentiated SH-SY5Y cells release partial vesicle content during exocytosis**. *Bioelectrochemistry* 2026, 109260, https://doi.org/10.1016/j.bioelechem.2026.109260.

10. Wang Y, Pradhan A: **Geometry-dependent redistribution of exocytotic spike-shape populations revealed by ultrafast disk and nanotip acetylcholine biosensors**. *ChemRxiv* 2026, **2026**, https://doi.org/10.26434/chemrxiv.15005964/v1.

11. Kwon H, Cho H-U, Sim J, Boo K-J, Kang Y, Hwang S, Kwak Y, Jang J, Kim KM, Jeon SJ, Shin CY, Bennet KE, Oh Y, Shin H, Lee KH, Jang DP: **Improved longevity and *in vivo* performance of neurotransmitter detection using 30 μm cone-shaped carbon fiber microelectrode**. *Front Bioeng Biotechnol* 2025, **13**, 1579380, https://doi.org/10.3389/fbioe.2025.1579380.

12. Gao X, Wei H, Ma W, Wu W, Ji W, Mao J, Yu P, Mao L: **Inflammation-free electrochemical *in vivo* sensing of dopamine with atomic-level engineered antioxidative single-atom catalyst**. *Nat Commun* 2024, **15**:7915, https://doi.org/10.1038/s41467-024-52279-5.

13. ** Driscoll N, Antonini M-J, Cannon TM, Maretich P, Olaitan G, Van VDP, Nagao K, Sahasrabudhe A, Paniagua EV, Frey EJ, Kim YJ, Hunt S, Hummel M, Mupparaju S, Jasanoff A, Venton BJ, Anikeeva P: **Multifunctional neural probes enable bidirectional electrical, optical, and chemical recording and stimulation in vivo**. *Adv Mater* 2025, **37**, 2408154, https://doi.org/10.1002/adma.202408154.
This work developed an fMRI-compatible, multi-modal sensing platform for simultaneous *in vivo* recordings of dopamine release with FSCV, electrical stimulation and electrophysiology recording, along with optical waveguide for optogenetics.

14. Jarosova R, Ostertag BJ, Ross AE: **Graphene oxide fiber microelectrodes with controlled sheet alignment for sensitive neurotransmitter detection**. *Nanoscale* 2023, **15**: 15249–15258, https://doi.org/10.1039/d3nr02879h.

15. Zhao H, Markow O, Olaitan G, Donarski ED, Lester KC, Lavrik NV, Venton BJ: **Pyrolyzed Parylene-N for *in vivo* electrochemical detection of neurotransmitters**. *ACS Electrochem* 2025, **1**:730–740, https://doi.org/10.1021/acselectrochem.4c00180.

16. Eyimegwu F, Zhao H, Shrestha K, Surendran D, Lavrik NV, Vmy earsenton BJ: **Pyrolyzed parylene electrodes for detection of tryptophan, tyrosine, and gonadotropin-releasing hormone**. *ACS Meas Sci Au* 2026, **6**:214–223, https://doi.org/10.1021/acsmeasuresciau.5c00165.

17. Lytvynenko A, Baluchová S, Zima J, Krůšek J, Schwarzová-Pecková K: **Biofouling and performance of boron-doped diamond electrodes for detection of dopamine and serotonin in neuron cultivation media**. *Bioelectrochemistry* 2024, **158**, 108713, https://doi.org/10.1016/j.bioelechem.2024.108713.

18. Shao Z, Zhao H, Dunham KE, Cao Q, Lavrik NV, Venton BJ: **3D-Printed carbon nanoneedle electrodes for dopamine detection in drosophila**. *Angew Chem Int Ed Engl* 2024, **63**, e202405634, https://doi.org/10.1002/anie.202405634.

19. Yang C, Hu K, Wang D, Zubi Y, Lee ST, Puthongkham P, Mirkin MV, Venton BJ: **Cavity carbon-nanopipette electrodes for dopamine detection**. *Anal Chem* 2019, **91**:4618–4624, https://doi.org/10.1021/acs.analchem.8b05885.

20. Nakatsuka N, Heard KJ, Faillétaz A, Momotenko D, Vörös J, Gage FH, Vadodaria KC: **Sensing serotonin secreted from human serotonergic neurons using aptamer-modified nanopipettes**. *Mol Psychiatr* 2021, **26**:2753–2763, https://doi.org/10.1038/s41380-021-01066-5.

21. Zhao C, Cheung KM, Huang I-W, Yang H, Nakatsuka N, Liu W, Cao Y, Man T, Weiss PS, Monbouquette HG, Andrews AM: **Implantable aptamer–field-effect transistor neuroprobes for *in vivo* neurotransmitter monitoring**. *Sci Adv* 2021, **7**, eabj7422, https://doi.org/10.1126/sciadv.abj7422.

22. Zhu F, Liu Y, Sun Z, Ni J, Jiang Y: **Aptamer-based galvanic potentiometric sensor for real-time monitoring of serotonin signaling under psychosocial stress**. *Angew Chem Int Ed* 2025, **64**, e202501701, https://doi.org/10.1002/anie.202501701.

23. López L, Martínez LM, Caicedo JR, Fernández-Vega L, Cunci L: **Measurement of neuropeptide Y in aptamer-modified planar electrodes**. *Electrochim Acta* 2024, **488**, 144243, https://doi.org/10.1016/j.electacta.2024.144243.

24. Hu Z, Zhu R, Figueroa-Miranda G, Feng L, Offenhäusser A, Mayer D: **Potential-pulse-assisted co-immobilization of multiple aptamers on microelectrode arrays for multiplexed neurotransmitter detection**. *Biosens Bioelectron* 2025, **290**, 117992, https://doi.org/10.1016/j.bios.2025.117992.

25. * Sen D, Lazenby RA: **Selective Aptamer Modification of Au Surfaces in a Microelectrode Sensor Array for Simultaneous Detection of Multiple Analytes**. *Anal Chem* 2023, **95**: 6828–6835, https://doi.org/10.1021/acs.analchem.2c05335.
This work introduces an aptamer microarray for simultaneous sensing of the neurotransmitters dopamine, serotonin, and ATP.

26. Wu G, Zhang N, Matarasso A, Heck I, Li H, Lu W, Phaup JG, Schneider M, Wu Y, Weng Z, Sun H, Gao Z, Zhang X, Sandberg SG, Parvin D, Seaholm E, Islam SK, Wang X, Phillips PEM, Castro DC, Ding S, Li D-P, Bruchas MR, Zhang Y: **Implantable aptamer-graphene microtransistors for real-time monitoring of neurochemical release *in vivo***. *Nano Lett* 2022, **22**:3668–3677, https://doi.org/10.1021/acs.nanolett.2c00289.

27. Stuber A, Cavaccini A, Manole A, Burdina A, Massoud Y, Patriarchi T, Karayannis T, Nakatsuka N: **Interfacing aptamer-modified nanopipettes with neuronal media and Ex vivo brain tissue**. *ACS Meas Sci Au* 2023, **4**:92–103, https://doi.org/10.1021/acsmeasuresciau.3c00047.

28. Ahmadian-Alam L, Andrade A, Song E: **Electrochemical detection of glutamate and histamine using redox-labeled stimuli-responsive polymer as a synthetic target receptor**. *ACS Appl Polym Mater* 2024, **6**:5630–5641, https://doi.org/10.1021/acsapm.4c00121.

29. Wang Y, Guo M, Li Y, Chen Y, Wei H, Mo X, Chai G, Du Y, Hu F: **Development of a dual-template molecularly imprinted electrochemical sensor for the simultaneous detection of depression markers 5-HT and Glu**. *Microchim Acta* 2024, **191**: 528, https://doi.org/10.1007/s00604-024-06558-z.

30. Wang Y, Mishra D, Bergman J, Keighron JD, Skibicka KP, Cans A-S: **Ultrafast glutamate biosensor recordings in brain slices reveal complex single exocytosis transients**. *ACS Chem Neurosci* 2019, **10**:1744–1752, https://doi.org/10.1021/acschemneuro.8b00624.

31. * Wang Y, Pradhan A, Gupta P, Hanrieder J, Zetterberg H, Cans A-S: **Analyzing fusion pore dynamics and counting the number of acetylcholine molecules released by exocytosis**. *J Am Chem Soc* 2024, **146**:25902–25906, https://doi.org/10.1021/jacs.4c08450.
First publication showing electrochemical detection of fusion pore regulated quantal acetylcholine release from 2D neuronal cultures with ultrafast enzymatic biosensors.

32. * Kimble LC, Twiddy JS, Berger JM, Forderhase AG, McCarty GS, Meitzen J, Sombers LA: **Simultaneous, real-time detection of glutamate and dopamine in rat striatum using fast-scan cyclic voltammetry**. *ACS Sens* 2023, **8**:4091–4100, https://doi.org/10.1021/acssensors.3c01267.
This publication demonstrates dual sensing of dopamine and glutamate in brain slices using FSCV and electrochemically pretreated carbon fiber with enzyme entrapped within a chitosan hydrogel.

33. Chu SS, Nguyen HA, Lin D, Bhatti M, Jones-Tinsley CE, Do AH, Frostig RD, Nenadic Z, Xu X, Lim MM, Cao H: **Development of highly sensitive, flexible dual L-glutamate and GABA microsensors for *in vivo* brain sensing**. *Biosens Bioelectron* 2023, **222**, 114941, https://doi.org/10.1016/j.bios.2022.114941.

34. Hasegawa A, Matsuda N, Suzuki I: **Development of a microelectrode array system for simultaneous measurement of field potential and glutamate release in brain slices**. *Biosens Bioelectron* 2025, **287**, 117696, https://doi.org/10.1016/j.bios.2025.117696.

35. Zhang F-L, Gao R-X, Tian S-Y, Yang X-K, Qi Y-T, Wang L-J, Zhang X-W, Huang W-H: **Nanosensor detection of synaptic glutamate release and its enhancement in long-term potentiation**. *Small Methods* 2025, **9**, e00783, https://doi.org/10.1002/smtd.202500783.

36. Zhao S, Li C, Zheng Y, Wang F, Wang Y, Ma K, Li Y, Zhang L, Zhang X, Gao J, Yao Y, Chen P, Sun J, Shen X: **Pathological glutamate release profiles in the epileptogenic zones of patients revealed by a novel ultra-fast glutamate sensor**. *Biosens Bioelectron* 2026, **296**, 118332, https://doi.org/10.1016/j.bios.2025.118332.

37. Zhu W, Zhang Y, Yu H, Wang D, Zhang X, Du X, Wu S, Li B, Zhang Y, Xin H, Guo X, Liu Y: **A novel acetylcholine nanosensor for single vesicle storage and sub-quantal exocytosis in living neurons and organoids**. *Angewandte Chem* 2026, e20854, https://doi.org/10.1002/ange.202520854.

38. * Xu P, Shen M: **Liquid/liquid junction microelectrodes for monitoring cholinergic transmitter in live mice brain *in vivo***. *Biosens Bioelectron* 2025, **278**, 117315, https://doi.org/10.1016/j.bios.2025.117315.
This work showcases microITIES electrodes that selectively detect acetylcholine through ion transfer across a liquid–liquid interface, enabling *in vivo* sensing of acetylcholine in the living mouse brain.

39. * Gu S, Xu D, Huang J, Zhou X, Liu Y, Zhang Z: **Photoelectrochemical biosensor with single atom sites for norepinephrine sensing and brain region synergy in epilepsy**. *Nat Commun* 2025, **16**:4765, https://doi.org/10.1038/s41467-025-60148-y.
This work developed a Zn single-atom modified TiO_2 photoelectrochemical biosensor with selective molecular docking sites for norepinephrine enabling its photoelectrochemical detection *in vivo*.

40. ** Liu J, Liu Y, Yin D, Tian Y: **Electrochemical sensor toolkit for simultaneous glutamate detection at edge of cleft and perisoma**. *Cell Chem Biol* 2025, **32**:885–898.e11, https://doi.org/10.1016/j.chembiol.2025.05.002.
This publication introduced a novel non-enzymatic electrochemical glutamate sensor strategy combining glutamate-binding proteins with ferrocene reporters for rapid, spatially resolved glutamate monitoring.

41. Weber IC, Zosso Y, Patino DU, Rijns L, Düsselberg ALM, Bao Z: **Tuning selectivity of electrochemical sensors with polymer coatings**. *Adv Mater* 2026, e74000, https://doi.org/10.1002/adma.74000.

42. Goyal A, Yuen J, Sinicrope S, Winter B, Randall L, Rusheen AE, Blaha CD, Bennet KE, Lee KH, Shin H, Oh Y: **Resolution of tonic concentrations of highly similar neurotransmitters using voltammetry and deep learning**. *Mol Psychiatr* 2024, **29**: 3076–3085, https://doi.org/10.1038/s41380-024-02537-1.

43. Park C, Venton BJ: **Machine learning for separating dopamine and octopamine electrochemical signals in drosophila**. *Anal Chem* 2026, **98**:249–257, https://doi.org/10.1021/acs.analchem.5c04155.

44. Berger JM, Todorov J, Turner KM, McCarty GS, Romanova EV, Sweedler JV, Sombers LA: **Unveiling dopamine and met-enkephalin dynamics: Simultaneous Co-Detection in rat striatum**. *Anal Chem* 2025, **97**:25032–25046, https://doi.org/10.1021/acs.analchem.5c03599.

45. Huang Z, Lu H, Dong H, Chen Z, Lu R, Zhao Y, Du Y, Liu Y, Wu Y, Xu M, Bi Y, Zhou Y: **Fe3O4/Ni nanoparticles anchored nitrogen-doped porous carbon derived from core-shell MOF for simultaneous electrochemical detection of dopamine and 5-hydroxytryptamine**. *Talanta* 2025, **286**, 127522, https://doi.org/10.1016/j.talanta.2025.127522.

46. Liu Y, Liu Y, Matharu Z, Rahimian A, Revzin A: **Detecting multiple cell-secreted cytokines from the same aptamer-functionalized electrode**. *Biosens Bioelectron* 2015, **64**:43–50, https://doi.org/10.1016/j.bios.2014.08.034.

47. Qi Y, Jang D, Ryu J, Bai T, Shin Y, Gu W, Iyer A, Li G, Ma H, Liou J, van der Meer M, Qiang Y, Fang H: **Stabilized carbon coating on microelectrodes for scalable and interoperable neurotransmitter sensing**. *Nat Commun* 2025, **16**:3300, https://doi.org/10.1038/s41467-025-58388-z.

48. Han J, Ho T, Stine JM, Overton SN, Herberholz J, Ghodssi R: **Simultaneous dopamine and serotonin monitoring in freely moving crayfish using a wireless electrochemical sensing system**. *ACS Sens* 2024, **9**:2346–2355, https://doi.org/10.1021/acssensors.3c02304.

49. Shnitko TA, Walton LR, Peng T-YR, Lee S-H, Chao T-HH, Verber MD, Wightman RM, Shih Y-YI: **Measurement of electrochemical brain activity with fast-scan cyclic voltammetry during functional magnetic resonance imaging**. *Nat Protoc* 2026, **21**:1682–1704, https://doi.org/10.1038/s41596-025-01250-9.

50. Shrestha K, Chang Y, Zhang Y, Venton BJ: **Multiplexing FSCV and iGluSnFR3 sensors reveals adenosine transiently inhibits stimulated dopamine and glutamate release**. *J Neurochem* 2025, **169**, e70147, https://doi.org/10.1111/jnc.70147.

51. Wang X, Xu M, Yang H, Jiang W, Jiang J, Zou D, Zhu Z, Tao C, Ni S, Zhou Z, Sun L, Li M, Nie Y, Zhao Y, He F, Tao TH, Wei X: **Ultraflexible neural electrodes enabled synchronized long-term dopamine detection and wideband chronic recording deep in brain**. *ACS Nano* 2024, **18**:34272–34287, https://doi.org/10.1021/acsnano.4c12429.

52. ** Xie J, Dai Y, Xing Y, Wang Y, Yang G, He E, Xu Z, Fan P, Mo F, Wu Y, Song Y, Cai X: **PtNPs/rGO-GluOx/mPD directionally electroplated dual-mode microelectrode arrays for detecting the synergistic relationship between the cortex and hippocampus of epileptic rats**. *ACS Sens* 2023, **8**:1810–1818, https://doi.org/10.1021/acssensors.3c00140.
This publication showcased multiplexed simultaneous glutamate sensing and electrophysiological recording, including action potential spikes and local field potential in living animals.

53. González Brito R, Montenegro P, Méndez A, Carabelli V, Tomagra G, Shabgahi RE, Pasquarelli A, Borges R: **Multielectrode arrays as a means to study exocytosis in human platelets**. *Biosensors (Basel)* 2023, **13**:86, https://doi.org/10.3390/bios13010086.

54. Fan P, Wang Y, Dai Y, Jing L, Liang W, Lu B, Yang G, Song Y, Wu Y, Cai X: **Flexible microelectrode array probe for simultaneous detection of neural discharge and dopamine in striatum of mice aversion system**. *Sensor Actuator B Chem* 2023, **390**, 133990, https://doi.org/10.1016/j.snb.2023.133990.

55. Bohl B, Prieto P, Andriuskevicius T, Hashemi P: *Measuring real-time neurotransmitter dynamics from human-derived serotonergic systems towards translating voltammetry from animal to human models*. 2025, https://doi.org/10.2139/ssrn.5390878.