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Evaluation of electrochemical methods for tonic dopamine detection *in vivo*

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A B S T R A C T

Dysfunction in dopaminergic neuronal systems underlie a number of neurologic and psychiatric disorders such as Parkinson's disease, drug addiction, and schizophrenia. Dopamine systems communicate via two mechanisms, a fast "phasic" release (sub-second to second) that is related to salient stimuli and a slower "tonic" release (minutes to hours) that regulates receptor tone. Alterations in tonic levels are thought to be more critically important in enabling normal motor, cognitive, and motivational functions, and dysregulation in tonic dopamine levels are associated with neuropsychiatric disorders. Therefore, development of neurochemical recording techniques that enable rapid, selective, and quantitative measurements of changes in tonic extracellular levels are essential in determining the role of dopamine in both normal and disease states. Here, we review state-of-the-art advanced analytical techniques for *in vivo* detection of tonic levels, with special focus on electrochemical techniques for detection in humans.

1. Introduction

The typical human brain has been estimated to have over 100 trillion synapses. Each of these synapses has a unique chemical composition further complicated by intricate regulation of neurotransmitter release and clearance kinetics, as well as connectivity with other brain regions. Understanding neurotransmitter signaling dynamics provides insights into healthy and diseased brain activity and network regulation. For example, normal functioning of dopaminergic systems underlie learning, incentive-motivation, and reward processing [1–7]. However, dysregulation of dopamine neurotransmission is found in many disease states, most notably in neurological and psychiatric disorders such as Parkinson's disease, drug addiction, schizophrenia, Tourette's syndrome, and indirectly in mediating anhedonia in depression [8,9]. Given that the population of patients affected by these diseases is substantial, understanding dopamine signaling dynamics is requisite for probing and treating these diseases. In this review we describe various techniques used for *in vivo* tonic dopamine detection. We also evaluate their usefulness in both clinical and pre-clinical investigations. Finally, we discuss the applicability of electrochemical techniques for enhancing understanding of neurochemical changes that may arise in response to deep brain stimulation (DBS) therapy in the treatment of these diseases characterized by dopaminergic dysfunction.

Dopamine release in the brain occurs on two timescales, termed phasic and tonic [8,10–12]. Phasic dopamine neurotransmission occurs as a result of burst-firing of neurons that release dopamine rapidly into the synaptic cleft in relatively high concentrations [12,13]. Relatively slower tonic release is caused by pace-maker-like firing of neurons that leads to an extrasynaptic tonic level dopamine [8,12,14–16]. Overall dopaminergic tone has been thought to consist primarily of extrasynaptic escape of intrasynaptic dopamine

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molecules [8,17]. This spillover, or volume transmission, produces and enhances tonic dopamine levels that affect transporter function and synaptic plasticity [15,18,19].

Changes in tonic dopamine levels are postulated to have important functional roles in incentive-motivation and underlie behavioral flexibility [14]. For example, increases in tonic dopamine levels in the striatum and nucleus accumbens have been shown to be positively correlated with movement and motivation, respectively [20–23]. Studies have also shown that elevations in tonic dopamine levels directly relate to long-term average reward response rates [21,24]. In contrast, decreases in the tonic firing of dopaminergic neurons have been observed where expected rewards have been omitted (i.e., reward prediction error) or where aversive stimuli have been applied [3,25–28]. Omission of expected rewards, and decreased tonic dopamine levels in the striatum and nucleus accumbens, are thought to facilitate behavioral flexibility and learning of new response strategies by affecting cortico-striatal processing [29,30]. Further research has found that this may be mediated through reductions or pauses in tonic dopamine stimulation of high-affinity D2 receptors [31], which exhibit effects on prefrontal cortical inputs [32]. As such, techniques that can measure variations in tonic dopamine levels *in vivo* with high resolution will certainly help to clarify the functional role of dopaminergic tone and are indeed important for studying disease pathology in pre-clinical and clinical investigations.

Techniques developed to effectively quantify basal dopamine extracellular levels in the brain can be divided into three technological *in vivo* methodologies: (1) microdialysis, (2) imaging, and (3) electrochemical techniques. Microdialysis has been classically used for measurements of tonic levels of neurochemicals due to its ability to collect and selectively measure concentrations of a number of chemical species in the extracellular space [33]. However, its applicability in humans is limited by reliance upon external analysis techniques which are not made in real-time or easily translatable to ambulatory subjects. Furthermore, microdialysis probes are relatively large and as a result have been shown to cause inflammatory damage which may affect accurate sampling [34]. More recent advances in tonic dopamine detection have centered on imaging and voltammetric techniques. While the established clinical use and the non-invasive nature of functional MRI (fMRI) and positron emission tomography (PET) imaging are major advantages, they are currently unable to directly probe tonic dopamine levels, have poor spatial resolution (>1 mm), and are considerably less cost-effective than electrochemical techniques [35,36]. Therefore, substantial efforts have been made to develop new electrochemical methods for tonic dopamine detection due to their accessibility and enhanced spatial and temporal resolution.

Presently, electrochemical techniques for tonic dopamine concentration measurements encompass amperometry, fast-scan cyclic voltammetry (FSCV), and recently developed complex voltammetric waveform techniques. While amperometric techniques have indeed been shown to measure, albeit through simulations, tonic dopamine levels [37], their lack of chemical specificity and limited measurement lifetime have prompted a shift in focus towards modified FSCV and complex waveform techniques. Notable modifications to FSCV for tonic dopamine measurement include: kinetic uptake and diffusion modeling, waveforms that rely on charge balancing, and modified waveforms with stripping and adsorption parameters. These techniques have been successfully applied *in vivo* to terminal fields of rodent models and demonstrated consistency within ~100 nM extracellular concentrations of dopamine between studies [38–40]. In addition to modified FSCV techniques, a number of complex voltammetric waveform techniques have been conceived [41–43]. One notable technique uses multiple cyclic square waves with dynamic background subtraction and current modeling (termed multiple-cyclic square wave voltammetry or M-CSWV) to achieve objective and reproducible measurements of tonic levels [42,44]. The success of these various electrochemical methods, including their high spatial, temporal, and chemical resolution, provides great promise for the study of neurophysiology and the treatment of disease in humans. We foresee that the continued development of these techniques will change the way we understand and treat neurologic disease [45,46].

2. Techniques for neurochemical activity monitoring

2.1. Microdialysis

Microdialysis is a technique used to sample chemicals from the extracellular fluid [47]. A microdialysis probe consists of an inner lumen and an outer lumen with a semi-permeable membrane that allows for diffusion of molecules from the external environment into the probe. Perfusion fluid is pumped into the inner lumen, and the resultant dialysate is collected (Fig. 1). The dialysate is then purified for the analyte of interest and quantified with external analysis [47]. Microdialysis has several advantages for quantification of tonic dopamine levels, most important of which is the ability to analyze the dialysate with a variety of techniques that provide high chemical specificity (e.g., high-performance liquid chromatography followed by electrochemical detection, fluorescence, or mass spectrometry) [33,47–51]. In addition, these techniques can detect and distinguish dopamine at low nanomolar concentrations [52–54]. One particular variation of microdialysis that has been especially important for determination of tonic dopamine concentrations is termed no-net-flux calibration. This technique differs from conventional microdialysis by adding known concentrations of the neurotransmitter of interest to the perfusate. By doing so, this method accounts for neurotransmitter clearance kinetics which can confound measurements, and thus provides a means of estimating extracellular concentrations adjacent to the dialysis membrane surface [55]. Studies that have examined tonic dopamine concentration using no-net-flux calibration have found normal striatal levels to be in the 2.5–15 nM range [56–59]. In addition to its use in examining normal and disease brain physiology, microdialysis can also be applied to investigate therapeutic mechanisms. For example, a study in a rodent Parkinson's disease model showed striatal tonic dopamine levels increased in response to subthalamic nucleus deep brain stimulation [60].

While microdialysis has been used to measure tonic extracellular dopamine concentrations *in vivo*, it has limitations for human translation. The diameter and typical length of the microdialysis probe's sampling membrane (>200 μm and 1–2 mm, respectively) is larger than the diameter of typical neuronal cells and terminals (~10–50 μm and 0.1–1 μm, respectively) and thus, inherently causes significant tissue damage [34,61]. This damage can perturb normal neuronal function and extracellular concentration estimates may be inaccurate [34,62–64]. Thus, while microdialysis has been thought to measure absolute concentrations of neurochemicals in extracellular fluid, computer modeling has shown tissue damage affects neuronal terminal dynamics and can obstruct normal extracellular volume transmission, ultimately obfuscating concentration estimates [65]. In addition, while < 4 min sampling rates have been achieved for catecholamines [53,66–71], more commonly, 10 min sampling rates are necessary at flow rates of 0.1–3.0 μL/min. This rate allows for enough analyte to cross the membrane into the dialysate to be collected for analysis. Due to this, the interpretation of microdialysis has caused some controversy because of tissue damage from the probe [34,72] and disruption in release and reuptake mechanisms affecting

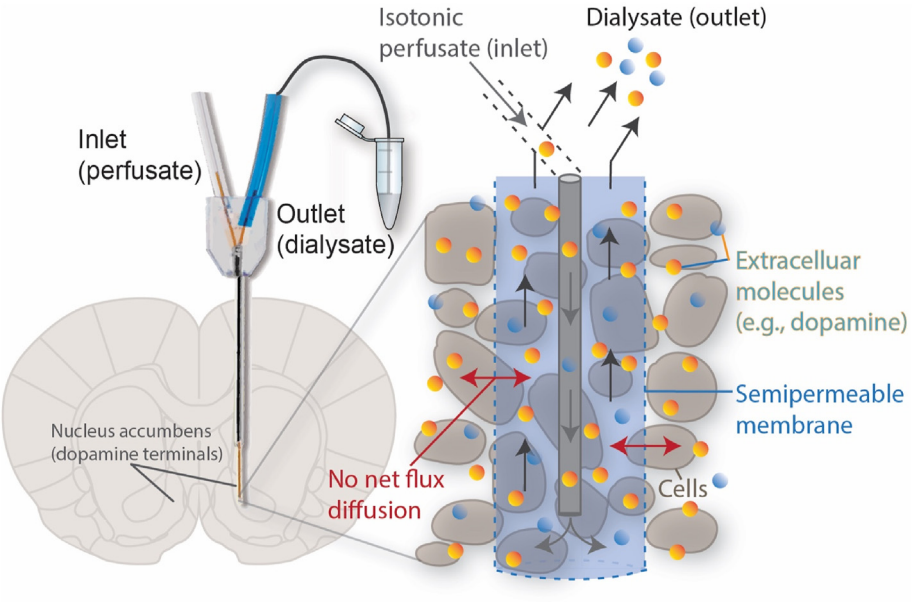

Fig. 1. No-net-flux microdialysis to determine the extracellular concentrations of analytes in the brain. A microdialysis probe is inserted into the brain region of interest and perfused with a known concentration of analyte. When no net flux through the semipermeable membrane is established, the known perfusate concentration is equal to the extracellular concentration. Dialysate flows through the outlet and is collected for external analysis.

neurotransmitter concentrations within the extracellular space [47,65,73]. In addition, microdialysis perfusion, dialysate collection, and detection instrumentation is not presently amenable to chronic human studies and therefore its use is limited to pre-clinical and intra-operative investigations [74,75]. Advances in microfabrication, sampling methods, and modulation of the immune response around the probe have all expanded microdialysis applications and may one day permit chronic human studies [68–70]. Furthermore, future advances may eventually enable temporal resolution capable of recording individual efflux events with high spatial resolution, which would expand the phenomena accessible for study with microdialysis [71].

3. Imaging

3.1. PET and fMRI

Positron emission tomography (PET) is a technique whereby molecular radiotracers, structurally similar to drugs that bind endogenous targets, are used to indirectly measure neurotransmission. Radioactive analogs first bind to endogenous receptors; subsequent displacement of the radiotracer by the endogenous analyte causes a measurable change in radioactivity that is dependent on the concentration of the endogenous analyte [35,76]. A number of radiotracers for dopamine receptors have been developed, both receptor agonists and antagonists [76]. These have enabled indirect measurement of tonic dopamine dynamics in disease states, during behavioral tests, and in response to pharmacological agents and electrical stimulation [77,78]. One newly reported technique utilized the radioligand [^{11}C]raclopride to visualize sub-second dopamine dynamics [79]. These variations in the [^{11}C]raclopride signal were used to extrapolate low frequency extracellular dopamine fluctuations and the results were validated against FSCV *in vivo* [80].

In addition to PET imaging, functional MRI (fMRI) has been used as a non-invasive way to measure regional metabolic activity and indirectly yield information about dopaminergic neurotransmission [81]. fMRI takes advantage of the magnetic properties of hydrogen to visualize tissues and fluids of interest. This can be applied to visualize blood flow in the brain. When hemoglobin, a ferrous component of blood that transports oxygen, is oxygenated, it is diamagnetic and opposes the applied magnetic field. When it is de-oxygenated, it is paramagnetic, and aligns with the magnetic field. Therefore, the oxygenation level of blood determines image contrast, and this is known as the blood oxygen level-dependent (BOLD) signal [82]. BOLD signals have been shown to correlate with blood flow and thus, metabolic rate. Therefore, brain areas experiencing high metabolic rates have greater BOLD signals [82]. Brain regions known for dopamine transmission (e.g., the nucleus accumbens), can be assessed with fMRI and dopamine content indirectly quantified [81]. The resolution of fMRI with BOLD contrast is typically 4 mm, which is sufficient for differentiation between dopaminergic centers in the human brain and the surrounding structures. With perturbations, for example pharmacologic drug modulators, indirect estimations of dopamine concentrations have been extrapolated [36,83,84]. Additionally, changes in regional metabolic activity can be measured when patients are undergoing behavioral tasks, taking pharmacologic agents, or receiving electrical stimulation [36]. However, it is important to note that fMRI techniques may only suggest changes in neurotransmitter concentrations due to changes in blood flow; a fundamental limitation of fMRI is the inability to definitively report changes in dopamine concentration. This limitation precludes the use of fMRI for clinical and pre-clinical studies that are aimed at determining specific chemical changes that arise in various disease states. PET and fMRI presently remain unable to provide precise and direct measurements of tonic dopamine levels, limiting their use for detailed physiological studies. In addition, the current resolution is limited to the supra-millimeter range. Furthermore, the resources and costs for imaging make this technique inaccessible [85]. Efforts are underway to address these shortcomings, including the development of fMRI coupled in real-time with PET imaging to provide an integrated approach to *in vivo* dopamine visualization [86–88].

Research has been conducted to develop molecular probes to better quantify dopamine levels with MRI, and two have the

potential to measure tonic dopamine levels. First, is the development of a dopamine-sensitive probe derived from the bacterial cytochrome P450 BM3 [89]. This probe has a dopamine-specific ligand pocket embedded with a paramagnetic iron atom that decreases in MRI signal intensity with dopamine binding. *In vivo* experimentation successfully measured dopamine over other interferents with both pharmacological and electrical stimulation [89–91]. Despite the promise of this technique, it currently suffers from a number of technical and practical limitations: 1) it has a micromolar limit of detection, far greater than what has been demonstrated extrasynaptically, 2) it can only measure a relative percent change in dopamine concentration, 3) it has not been demonstrated to cross the blood-brain-barrier and thus requires direct infusion, and 4) the resolution is limited to the voxel size. The second recent and promising molecular imaging technique uses the paramagnetic pigment neuromelanin [92]. Neuromelanin is a product of L-Dopa and dopamine metabolism known to accumulate in the substantia nigra, giving it its characteristic dark color [93]. Binding of iron to neuromelanin forms a paramagnetic complex capable of MRI detection. *In vivo* application demonstrated the use of neuromelanin as an indirect correlate of dopamine concentration and values derived from this technique were successfully validated against post-mortem histology, fMRI, and PET imaging. The limitations of this technique are similar to those outlined for the dopamine-sensitive probe, which are limitations general to all molecular MRI probes. Additionally, as noted by the authors, lack of complete signal specificity and signal interferents from tissue properties can confound neuromelanin measurement, reducing the usefulness of this technique.

3.2. Biochemical and genetically encoded optical dopamine sensors

Genetically encoded sensors are presently restricted for use in pre-clinical studies, however recent advances that have the potential to achieve tonic dopamine detection in pre-clinical models warrant discussion in this review. Most genetically encoded sensors are designed to take advantage of endogenous recognition elements (e.g., a dopamine receptor, DR). This allows for sensor tunability with large linear dynamic ranges and high selectivity. Rapidly advancing capabilities in genetic manipulation of pre-clinical animal models has led to the creation of several genetically encoded dopamine sensors. A recent prominent advance was the development of dLight1 by Patriarchi and colleagues [94,95]. The dLight platform relies on the engineering of a fluorescent indicator protein fused with the dopamine receptor. When endogenous dopamine binds to the receptor-indicator, a conformational change increases fluorescence. This elegant design can be applied to several subtypes of dopamine receptors, which have K_d values that range from 4 nM to 1.6 μM. While this ratiometric technique allows for measurement of relative changes in dopamine concentration, the initial report only investigated phasic changes in dopaminergic signaling. Patriarchi et al. comment on the potential use of dLight1.4 (the D4R sensor, K_d 4 nM) for measurement of dopaminergic tone. This technology is still in early developmental stages and whether its broad applicability stretches into the realm of pre-clinical tonic dopamine detection remains to be determined.

The Genetically Encoded GPCR-Activation-Based-Dopamine$_{(DA)}$ ($GRAB_{DA}$) sensor also uses a DR-GFP chimera protein to detect dopamine using ratiometric fluorescence [96]. It was shown to monitor dopamine release in flies, fish, and mice performing complex behaviors. Two variants of the sensor demonstrated affinity to dopamine with EC_{50} values of 10 and 130 nM with temporal resolution of seconds. Additionally, the $GRAB_{DA}$ sensor platform made tonic dopamine measurements in freely moving mice over the course of several minutes in response to pharmacological manipulations and optogenetic stimulation of dopamine releasing cell bodies. The $GRAB_{DA}$ platform may be the most promising genetically encoded sensor for pre-clinical tonic dopamine detection.

Another genetically encoded sensor, DRD2-*i*Tango2, which uses cells that express the *i*Tango platform, allows for identification of dopamine releasing cells *in vivo* [97]. Cells with the *i*Tango platform express higher levels of a blue light-induced reporter gene when in the presence of dopamine. The second generation *i*Tango2 demonstrated enhanced temporal resolution (5 min) when compared to its predecessor and was successfully employed in behaving animals to identify neurons sensitive to dopamine in reward-based learning [97,98]. The use of *i*Tango2 for tonic dopamine detection appears challenging at present.

Cell-based Neurotransmitter Fluorescent Engineered Reporters (CNiFERs), while not genetically encoded, are injectable cell-based calcium sensors that have been used to indirectly quantify dopamine release *in vivo* with temporal resolution of seconds [99]. Upon binding of endogenous dopamine to the dopamine D2 receptor expressed on the CNiFER cell, downstream calcium release results in a fluorescence resonance energy transfer (FRET) change that is proportional to the extracellular dopamine concentration. Unfortunately, among other limitations, this technique requires implantation of the cell-based CNiFERs into the brain region of interest, which is technically challenging and relatively damaging to the brain. Nonetheless, with the aid of *in vivo* and *in vitro* calibrations, CNiFERs have the potential for use in tonic dopamine detection in response to behavioral and pharmacological manipulations. In addition to CNiFERs, near-infrared fluorescent catecholamine sensors have been developed that are able to detect phasic changes in dopamine with low-micrometer spatial resolution and sub-second temporal resolution and represent an important advance in *in vivo* dopamine detection [100,101].

The use of genetic techniques to measure tonic dopamine *in vivo* is in its infancy. Genetically encoded sensors have relatively large dynamic ranges and enhanced selectivity, due to their basis in endogenous recognition elements. Unfortunately, they often suffer from low signal-to-noise ratios, which complicates their usefulness *in vivo*. Additionally, they often require site-specific injections of fluorescent dyes, or other elements necessary for analyte detection [102]. Finally, reliance on fluorescent and luminescent probes limits the continuous use of these sensors to the sub-hour temporal regime due to sensor photobleaching. Overall, the use of biochemical and genetically encoded sensors for tonic dopamine detection shows promise but further development is necessary to elucidate their usefulness *in vivo* before human translation can be considered.

4. Electrochemistry

4.1. Early attempts

4.1.1. Constant potential amperometry

In constant potential amperometry, an electrode is held at a specific DC potential to oxidize or reduce chemical species of interest [103]. Using Faraday's Law, $Q = nmF$ (where Q = charge passed, n = numbers of electrons, m = the moles of substance oxidized, and F = Faraday's constant) and integration of the current generated to determine charge, the moles of the species of interest can be calculated. Its application *in vivo* has allowed direct measurement of neurotransmitter release in a variety of disease models and behavioral studies [104,105]. The benefit of this technique is that the sub-millisecond temporal resolution is limited only by the data acquisition rate and the mass transport rate of the analyte. In addition, the small diameter size of the electrode (<10 μm) causes

minimal tissue damage and allows for single-cell recording. Studies have demonstrated this technique is highly sensitive and can achieve attomole to zeptomole quantification of neurotransmitter exocytosis from single neurons [106,107]. Venton et al. applied this technique with simulated tonic firing (asynchronous electrical stimulation) and model-derived dopamine release kinetics to monitor tonic dopamine concentrations [37]. This model determined tonic dopamine concentrations to be ~30 nM with pulled glass capillary carbon-fiber microelectrodes (CFMEs).

A major disadvantage of constant potential amperometry for tonic measurements is its chemical non-selectivity. As the electrode is held at a constant potential, any electroactive analyte that oxidizes or reduces at that potential will be detected. The low chemical specificity of this technique complicates measurements in heterogeneous solutions, such as the brain. As such, it is necessary to verify amperometric signals through administration of selective drug modulators (e.g., GBR12909 reuptake inhibitor for dopamine) or by electrical stimulation of known neuronal populations that elicit release of the neurotransmitter of interest [37]. Despite these controls, it remains difficult to resolve the true change in a select species if multiple analytes constitute the signal. Thus, this technique has limited potential for future application due to poor specificity when compared to other electrochemical techniques.

4.1.2. Chronoamperometry

Chronoamperometry is a modified amperometric technique that employs potential step waveforms to increase analyte resolution [108]. Double potential step chronoamperometry, which includes an anodic and cathodic step, is commonly used to access both oxidative and reductive properties of the analyte. The current recorded during the anodic step is proportional to the neurochemical concentration, and typically measured at a fixed time in the step (usually at the end of the step to minimize non-faradaic interference) [109,110]. The ratio of the oxidation and reduction currents is used to identify the species (e.g., dopamine: 0.55 V oxidation potential, −0.2 V reduction potential vs. Ag/AgCl) allowing for better chemical identification than with constant potential amperometry. Indeed, this technique has been successfully used to measure neurotransmitter fluctuations [111–114]. Tonic dopamine quantification was achieved by Blaha et al. who conducted measurements in the striatum over 3 weeks in rats chronically implanted with stearate-modified graphic paste recording electrodes [115]. They determined the tonic dopamine concentration to be ~85 nM and were among the first studies to demonstrate that microdialysis underestimated tonic concentrations [116]. While this technique is an improvement over constant potential amperometry for the measurement of dopamine, pharmacologic drugs that perturb dopamine concentrations are still necessary to validate measurements. Furthermore, this technique, without some form of electrode surface modification [117], is unable to delineate biologic amines from their metabolites, a capability of other voltammetric techniques (discussed henceforth). These limitations have led to its decline in use and thus chronoamperometry has limited applicability for tonic dopamine recording in animals and in humans.

4.1.3. Differential normal pulse voltammetry

In 1982, differential normal pulse voltammetry [118] was designed to combine the advantages of differential pulse voltammetry and normal pulse voltammetry [119] to measure mammalian extracellular DA concentrations. The differential pulse waveform consists of sequential pulses with increasing amplitudes, within which, there is a double potential step and equivalent return to a constant baseline potential. The current is measured immediately before the application of a pulse and at the end of the pulse. The current difference is plotted as a function of the applied potential resulting in a differential pulse voltammogram [120]. By sampling the current just before the potential is changed, the effect of the capacitive charging current can be decreased leaving the faradaic signal for analysis. Background capacitive currents are constant and thus can be subtracted out of each sampled current signal, leaving the faradaic signal for analysis. Differential pulse voltammetry can be used with myriad voltammetric waveforms as described in Osteryoung et al. [121]. Further development of this technique by Gonon et al. achieved measurements of tonic dopamine levels [122]. Use of this technique with CFMEs measured extracellular tonic dopamine concentrations to be 15–25 nM in the rat striatum and 23–40 nM in the nucleus accumbens [122,123]. Like chronoamperometry, this technique is limited by its inability to discriminate against known electroactive interferents, such as 3,4-dihydroxyphenylacetic acid (DOPAC), a principle metabolite of dopamine. In addition, it is unable to account for background drift in the capacitive current over time, which limits its use for chronic recording. Therefore, it too has limited applicability for tonic dopamine recording in the laboratory and in humans.

4.2. Modified FSCV techniques

Fast-scan cyclic voltammetry (FSCV) is a well-established electrochemical technique used to measure relative (i.e., phasic) changes in electroactive neurotransmitters [124]. Standard FSCV uses a triangular waveform applied to a recording electrode. The potential is quickly swept anodically then cathodically causing oxidation and reduction currents. For the measurement of dopamine, the potential window for these electrochemical reactions is typically −0.4 V–1.3 V and the triangle waveform is repeated every 100 ms (10 Hz) with a typical sweep rate of 400 V/s [125]. Due to the speed of the potential sweep, a large capacitive background current is generated, together with much smaller faradaic currents superimposed on the capacitive current at the electrode. To remove the background current from the signal to permit accurate measurement of the faradaic current for dopamine quantification, background subtraction is performed [126]. Traditional background subtraction precludes accurately determining tonic dopamine concentrations. One reason for this is the background current is only stable for approximately 2 min before it begins to drift in magnitude, which complicates the subtraction [125]. In addition, oxidation at the electrode surface by application of the FSCV waveform results in progressive etching of the carbon fiber, resulting in current changes and further complications [127,128]. Thus, only phasic changes in concentration over a relatively brief period of time (1–2 min) following the single initial background subtraction can be quantified using FSCV. New voltammetric techniques (*vide infra*) are being developed to overcome these limitations and allow for tonic dopamine measurements.

A unique modification of FSCV to measure tonic dopamine concentrations using additional background subtraction steps was proposed by Borland and Michael [17]. They used FSCV (waveform: 0.0 V to 1.0 to −0.5 V–0.0 V at a scan rate of 300 V/s and a frequency of 2.5 Hz) and a modified background subtraction to examine dopamine release in response to intra-striatal infusions of a glutamate receptor antagonist, kynurenate. To validate the chemical species, they averaged voltammograms collected over 200 s intervals and subtracted them from a baseline interval. They then compared the resultant voltammogram with an experimental dopamine voltammogram. Using this method, they were able to measure a decrease in dopamine of 2.6 ± 0.2 μM (mean ± SEM, n = 19 rats) after kynurenate infusion. However, selectivity for dopamine over metabolites such as DOPAC, a known electroactive interferent, was not addressed. Additionally, the use of background

subtraction over a relatively long time period (200 s) is concerning given background currents are known to shift after approximately 120 s [125].

Charge-balancing multiple waveform fast-scan cyclic voltammetry (CBM-FSCV) builds on previous FSCV-modified waveforms for tonic neurotransmitter measurements [39]. This technique utilizes a charge-balanced waveform and two novel parameterizations to address capacitive charging current issues. The first parameter is a charge balancing waveform with a 0 V holding potential to reduce the background current variance between multiple pulses in a series. The second is a dual subtraction method whereby an initial subtraction is made in each pulse within the waveform train, and a second subtraction is made from a single reference point before dopamine is detected. This technique demonstrated sensitivity for dopamine of 85.4 ± 14.3 nA/μM and a limit of detection of 5.8 ± 0.9 nM for CFMEs *in vitro*. This level of detection is sufficient for measuring meaningful ranges of dopamine *in vivo* [129]. In addition, this technique achieved selectivity over the major electroactive interferents, DOPAC and ascorbic acid. Furthermore, *in vivo* studies demonstrated stable tonic recordings for 2 h with a temporal resolution of 0.1 Hz and the ability to measure both increases and decreases in dopamine when levels were experimentally modified with drug manipulation. However, this technique is limited by the ability to measure only prolonged changes in tonic dopamine levels, and not absolute levels. New techniques capable of absolute tonic measurements have limited the application of CBM-FSCV.

4.3. Modified voltammetric techniques for tonic dopamine measurements

To indirectly assess tonic dopamine levels, Chen and Budygin modified the dopamine kinetic equation first described by the Wightman group that implies a zero basal concentration [73,129]. They adjusted this model to consider theoretical uptake and experimental clearance rates of dopamine after electrical stimulation of dopaminergic neurons. This analysis was applied as a post-processing step and therefore is able to extract tonic concentration estimates using conventional FSCV waveforms. Application *in vivo* determined dopamine concentration values to be between 95 and 220 nM, significantly higher than classical concentration estimates determined by no-net-flux microdialysis, but in line with prior electrochemical analysis experiments and our own work [38,42,115,129,130]. This method is limited by the inability to measure absolute values. In addition, it is based on the assumption of normal uptake and clearance rates, which may be altered with stimulation, in disease states, or with pharmacological agents [131]. However, the advantage of this technique is its ability to estimate changes in tonic levels with FSCV data, which may be useful in both pre-clinical research and in human translation when both phasic and tonic data are desired.

Fast-scan controlled-adsorption voltammetry (FSCAV, Fig. 2) uses the principles of stripping voltammetry to determine tonic dopamine concentrations in real-time [38,132]. First, to minimize adsorption, a triangular waveform (−0.4 V−1.3 V, scan rate of 1200 V/s) is applied at 100 Hz to a CFME. Then, a constant holding potential is applied (−0.4 V) for 10 s, allowing dopamine to adsorb to the CFME surface until equilibrium is reached. Then, the same triangular waveform is re-applied, and the recorded dopamine measurement is representative of the equilibrium-state (or tonic) dopamine concentration. *In vitro* studies with Nafion-coated CFMEs demonstrated FSCAV was sensitive up to 3.4 ± 0.8 nM of dopamine [132]. Importantly, these studies showed selectivity over the interferents DOPAC, ascorbic acid, and pH changes. *In vivo* studies where FSCAV was applied in the mouse nucleus accumbens core determined tonic dopamine concentrations to be 90 ± 9 nM (mean ± SEM, n = 20 animals) [38]. In addition, stable measurements were achieved over 90 min and pharmacological drug manipulations (AMPT, GBR-12909, and pargyline, synthesis inhibitor, reuptake blocker, and monoamine oxidase inhibitor, respectively) validated the ability of the technique to detect both increases and decreases in tonic dopamine concentrations. Therefore, the sensitivity, selectivity and ability to resolve absolute dopamine concentrations make it ideal for continued pre-clinical research and ultimately human translation.

Convolution-based non-faradaic current removal has been developed for use with FSCV to allow tonic dopamine detection with high temporal resolution [40] and does not require significant waveform modification [133]. The major innovations include a new mode of background subtraction and an altered holding potential. In this method developed by the Wightman group, a pre-scan small-amplitude pulse is performed to elucidate non-capacitance ionic interferents of the faradaic oxidative current of dopamine. The derivative of the current response from the pulse is convolved with the waveform to generate a background prediction that is digitally subtracted out. In addition, it was found that a 0 V holding potential resulted in a more complete background subtraction by removing quinone-like species. The authors demonstrated the success of this technique and selectivity over interferents (ascorbic acid, DOPAC) both *in vitro* and *in vivo* (41 nM dopamine, n = 3 rats). Furthermore, they were able to achieve sampling rates of 1 Hz, improved over other new techniques such as FSCAV. However, this technique suffers from a lower sensitivity and poorer chemical resolution, likely due to adsorption kinetics at relatively high sampling rates. It remains to be determined if further reductions in the scan frequency resolve this confound. Nevertheless, this technique is advantageous if applications require high sampling rate over sensitivity.

Square wave voltammetry is the superposition of a traditional square wave on a staircase waveform [121]. This waveform combines the advantages of both cyclic voltammetry and pulse techniques. As multiple square wave potential changes are contained within each staircase waveform (Fig. 3A), a wealth of electrochemical information can be obtained [134]. Due to the complex design of the waveform, square wave voltammetry typically has a relatively slower scan rate in comparison to FSCV, and its application for phasic neurochemical measurement has historically been limited. However, this technique has recently gained attention for applications where temporal resolution can be traded for chemical resolution, as is the case for measuring tonic dopamine levels [135].

Recently, Oh et al. developed a novel methodology using square wave voltammetry which exploits adsorption equilibrium at the CFME surface to measure basal concentrations of dopamine *in vivo* with high selectivity, sensitivity, and a 10 s (0.1 Hz) temporal resolution. Multiple cyclic square wave voltammetry (M-CSWV, Fig. 3) uses cyclic square wave voltammetric waveforms in conjunction with a delayed holding potential period to control dopamine adsorption to the CFME surface [42]. Dynamic background subtraction [39] and capacitive current modeling were used to eliminate large capacitive background currents, allowing basal dopamine concentrations to be measured. M-CSWV demonstrated high sensitivity (limit of detection of ~0.17 nM) and selectivity against potential electroactive interferents, including ascorbic acid, DOPAC, and pH changes. M-CSWV in preliminary *in vivo* studies was successfully used to measure tonic dopamine levels in rat striatum at 120 ± 18 nM (n = 7 rats). As is the case for many emerging electrochemical measurement techniques [38,42,116], this concentration is considerably higher than values obtained with no-net-flux microdialysis. In addition, pharmacological drug manipulations, which include nomifensine, pargyline, and AMPT,

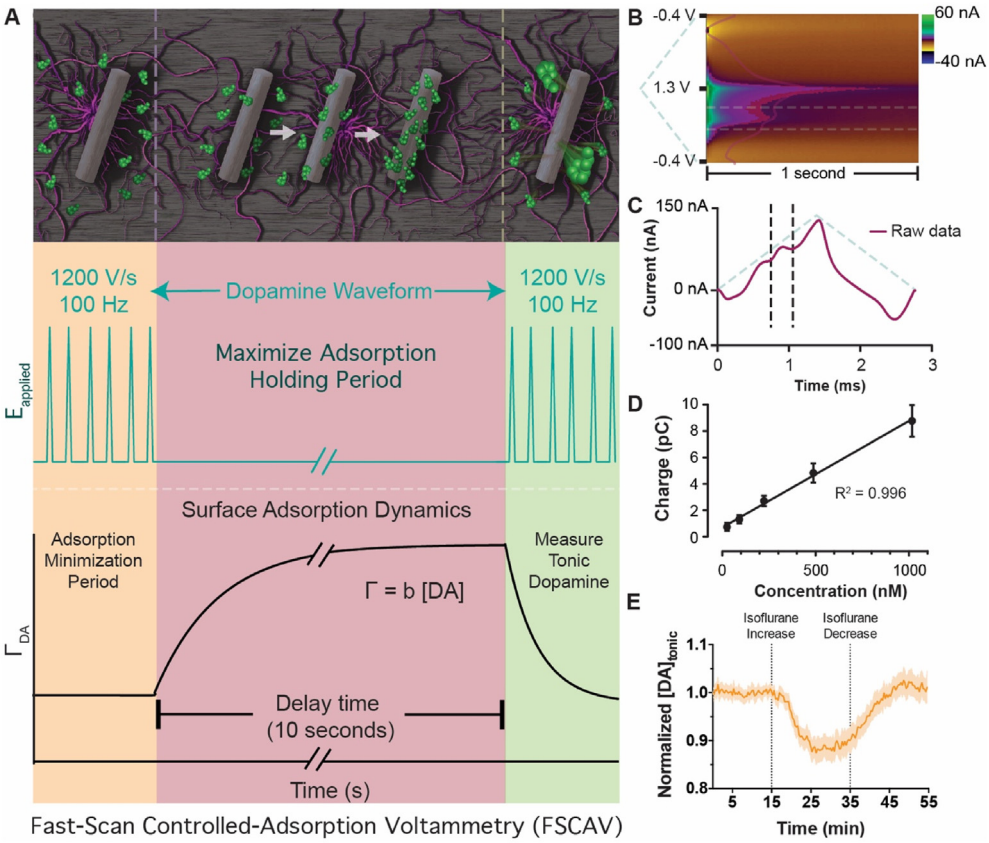

Fig. 2. Fast-scan controlled-adsorption voltammetry. (A, Left) Adsorption of dopamine at the electrode surface is minimized during the application of the 100 Hz triangle waveform. (A, middle) The electrode is held at a negative potential for 10 s, during which time dopamine maximally adsorbs to the electrode surface and an adsorption equilibrium is reached. (A, right) The 100 Hz triangle waveform is re-applied, and information rich measurement is made that represents the equilibrium dopamine concentration (i.e., the tonic level). (B) Pseudo-color representation of recorded current and superimposed integration limits (horizontal dashed lines) typically used for dopamine quantification. (C) Current taken from the 12th scan after the holding period is used for tonic dopamine quantification. Superimposed integration limits and applied waveform are shown in dashed lines. (D) Calibration of electrodes in dopamine solutions demonstrates a linear dynamic range over several orders of magnitude. Adapted from Ref. [38] with permission from the Royal Society of Chemistry. (E) Example of tonic dopamine detection data in response to changing levels of the anesthetic isoflurane.

validated M-CSWV's selectivity to dopamine and the ability to measure both increases and decreases in tonic levels [42,44]. Like FSCAV, M-CSWV shows considerable promise for continued pre-clinical investigation and ultimately human translation.

Another technique, recently reported by Taylor et al., utilized square wave voltammetry (SWV) for tonic dopamine recording (Fig. 4) [43]. Similar to M-CSWV, this technique has dynamic background subtraction and filtering to remove capacitive charging currents and noise. This technique was demonstrated *in vitro* to selectively record dopamine against electroactive interferents ascorbic acid, DOPAC, and uric acid. Additionally, *in vivo* studies performed with both CFMEs and gold microelectrode arrays (MEA) coated with poly (3,4-ethylenedioxythiophene (PEDOT)/carbon nanotube (CNT) [136] successfully measured tonic dopamine in the striatum (~82 nM). Using MEAs (see Section 4 below), they were able to simultaneously measure changes in tonic dopamine at multiple electrode sites simultaneously, the first demonstration of its kind. This adds considerable dimensionality for *in vivo* recording, and could provide a greater depth of understanding where proximal but distinct regions have different dopaminergic activity, such as the nucleus accumbens core and shell [137]. Additional studies of SWV and electrode design will need to examine biofouling and the capability for chronic monitoring. Nevertheless, this SWV technique and integration with MEA design are opportune for future development, and demonstrate that multichannel tonic recordings are on the horizon.

A summary of techniques described in section 3 can be found in Table 1.

5. Electrodes for tonic measurement

A comprehensive review of electrodes for tonic dopamine detection is outside of the scope of this review. However, we will briefly describe select prominent electrodes and surface modifications used for dopamine detection. For more detail on electrodes used for *in vivo* dopamine measurement please see Puthongkham & Venton [138] or Sajid et al. [139].

5.1. Carbon-fiber microelectrodes

CFMEs have been the backbone of voltammetry since their introduction in the 1970s [140]. They are recognized for their small size, adsorptive properties, stable charging currents, and moderate resistance to biofouling [141]. These CFMEs are commonly 50–200 μm in length with a diameter of <10 μm. The size permits greater spatial resolution and less tissue damage [142]. These properties make them very attractive for monitoring neurotransmission over long periods of time (hours – months) [143]. Commonly, AS-4 carbon fibers are used for dopamine detection, which have a polyacrylonitrile (PAN)-based structure. While these bare pyrolytic carbon electrodes have demonstrated robustness in their ability to detect neurotransmitters, a number of surface

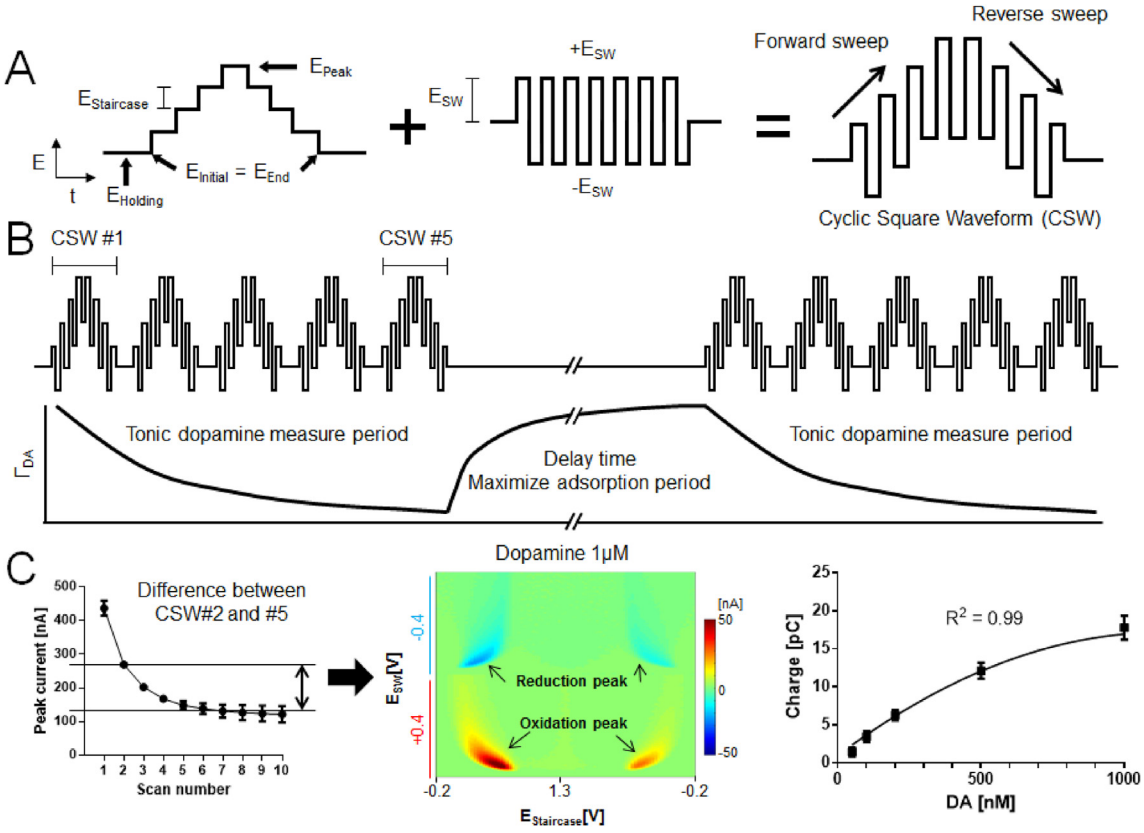

Fig. 3. Multiple cyclic square wave voltammetry permits tonic dopamine quantification. (A) Schematic design of the cyclic square waveform. (B) Multiple cyclic square wave (CSW) applied repeatedly and dopamine adsorption time profile utilized to determine basal dopamine concentrations. (C) Peak current of dopamine (1 μM) at each CSW (left), pseudo-color plot of difference between CSW #2 and #5 (middle), M-CSWV signal correlates with tonic dopamine concentration (right; n = 4 electrodes). Adapted from Ref. [42] with permission from Elsevier.

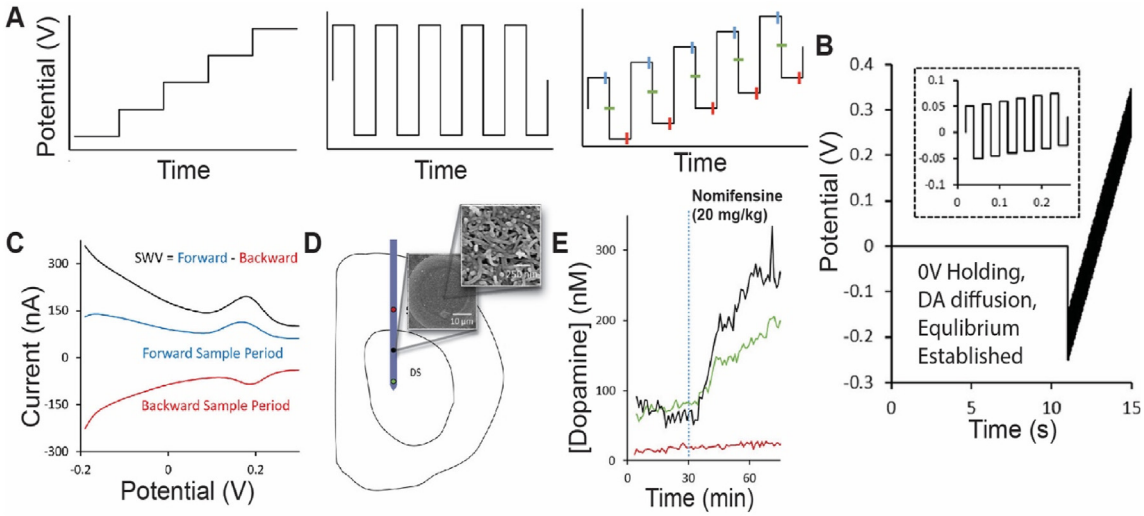

Fig. 4. PEDOT/CNT-functionalized carbon-fiber microelectrode measurements of tonic dopamine via SWV. (A) The waveform consists of the superposition of a staircase wave and a square wave. Forward current is measured at the end of each anodic holding period, and backward current is measured at the end of each cathodic holding period. (B) An initial 0 V hold followed by a series of anodic and cathodic step and holds (zoom shown in the inset) that transverse the defined potential window is applied. (C) Representative SWV measurement of a 1 μM standard solution of dopamine reveals the SWV current (black) response to be the difference of the forward (blue) and reverse (red) current responses. (D) Schematic of microelectrode array placement in the dorsal striatum (DS) of the rat. Multiple recording sites indicated by red, black, and green circles. SEM image of CNT functionalization on electrode surface. (E) Electrodes located within the DS (green and black) showed clear, nomifensine-dependent DA detection. Adapted with permission from Ref. [43]. Copyright 2019 American Chemical Society.

Table 1
Electrochemical techniques for tonic dopamine measurement.

Technique	Temporal resolution	Limit of detection (nM)	Reported $[DA]_{tonic}$	Hardware & software	Ref.
Chronoamperometry	1 min	19 ± 6	86 ± 6 nM, rat striatum	E-chempro	[115]
FSCAV	20 s	3.7 ± 0.5	90 ± 9 nM, mouse NAc	NI DAQ, LabVIEW	[38]
CBM-FSCV	10 s	5.8 ± 0.9	>73 ± 5 nM,[a] rat striatum	NI DAQ, LabVIEW, Matlab	[39]
Convolution-based current removal	1 s	<40[a]	41 ± 13 nM, rat NAc	NI DAQ, LabVIEW	[133]
M-CSWV	10 s	0.17 ± 0.03	120 ± 18 nM, rat striatum	NI DAQ, WINCS, LabVIEW	[42]
SWV	15 s	2.03 ± 0.09	82 ± 6 nM, rat striatum	N/A[a], Matlab	[43]

[a] not reported in original manuscript.

modifications (e.g., PEDOT and Nafion) have been employed that improve sensitivity and selectivity [43,144–158].

5.2. Diamond electrodes

Long-term application of FSCV waveforms has been found to cause CFMEs to erode and decline in sensitivity to dopamine [128,159]. This decline impedes their use for chronic *in vivo* monitoring, and the superior material properties of diamond electrodes (hardness, biofouling resistance) have led to their investigation as a potential solution [160,161]. Most recent advances in the field by Puthongkham et al. developed nano-diamond coated CFMEs [41]. They reported a limit of detection of 3 nM and 50% less biofouling compared to uncoated CFMEs, which is in line with previous studies by Bennet et al. and Rusinek et al. [161,162]. Despite this finding, diamond electrodes have generally suffered from lower sensitivity than CFMEs, and thus have not gained much traction in pre-clinical studies. In addition, they have yet to be tested with tonic recording techniques. Further research in material design and integration with tonic recording techniques are ultimately needed to resolve their future potential. Nonetheless, diamond electrodes are an attractive solution to electrode longevity for eventual in-human recordings.

5.3. Electrode arrays

Microelectrode arrays (MEA) permit multiplexing and increase the total amount of tissue sampled, which allows spatially resolved measurements of dopamine and other neurochemicals across brain microenvironments. This is notable as structures like the striatum have gradients of interneuron densities that may contribute to altering levels of dopamine release [163]. Carbon has been used in MEAs due to its excellent electrochemical properties and compatibility with FSCV [164–168]. In addition to carbon fibers and carbon nanotubes, conductive metals and diamond have been used for array detection of dopamine [169–172]. Recently, Taylor et al. developed a PEDOT/CNT-coated gold vertically-stacked MEA with 200 μm spacing capable of tonic dopamine detection simultaneously across multiple electrode contacts [43].

5.4. Challenges in longevity and safety

A major limitation of tonic neurochemical recording techniques is microelectrode lifetime, where signal quality has been found to degrade over time. The longest reported *in vivo* recording at a CFME thus far has been four months [143]. For clinical applications, most notably in closed-loop DBS, tonic recordings may well need to occur for the remaining lifespan of the patient (i.e., years). Efforts are being made in microelectrode composition to increase implantable electrode lifetime [161]. For example, diamond-based electrodes erode 90% slower and composite coatings with PEDOT/Nafion and Nafion/CNT have demonstrated decreased biofouling *in vivo* [43,147,161]. In addition to biofouling, safety and therapeutic benefit will need to be thoroughly addressed before long-term human use is considered. While the risks of permanently implanted recording electrodes are likely similar to those of implanted DBS electrodes and shunts (e.g., infection, hemorrhage, and cognitive decline [173]), differences in instrumentation architecture, material composition, and implantation location necessitate extensive independent study.

6. Conclusion: future perspectives for electrochemical tonic dopamine detection

Tonic neurotransmitter recording techniques hold considerable importance for understanding neural mechanisms and pathophysiology. Diseases such as Parkinson's disease, Tourette syndrome, drug addiction, and schizophrenia are all characterized by dopaminergic dysfunction. To treat these conditions more effectively, it is vital to develop techniques that enhance understanding of dopaminergic function, particularly in disease models. To this end, microdialysis has been used substantially and successfully in pre-clinical research [174] and new efforts are being made to address issues of temporal resolution [68,175,176]. However, microdialysis collection and detection techniques currently prohibit chronic human studies [12]. In addition, the size of the dialysis probe limits the spatial resolution of study [34,61,62,177].

While microdialysis has proven useful, its present limitations encourage the further development of *in vivo* electrochemical techniques. The development of tonic *in vivo* recording techniques, such as FSCAV and M-CSWV, have for the first time allowed investigation of tonic dopamine dynamics at relatively high temporal resolution in real-time with micrometer resolution. We anticipate these techniques will gain widespread use in neurophysiological study, especially with the incorporation of multichannel arrays. Efforts are being made in our laboratories and others to develop instrumentation and software for widespread dissemination and use in animal, and eventually, human studies. Once achieved, these techniques will allow for myriad uses in probing nervous system physiology that was previously unachievable.

6.1. Human application

Measurement of tonic dopamine concentrations in humans with voltammetry is on the horizon [178]. Already, phasic dopamine, adenosine, and serotonin have been successfully recorded intraoperatively by two groups [45,161,179,180]. The same surgical procedures and electrode designs used in these human studies can be readily applied for tonic measurements, increasing the speed of translation. In contrast to microdialysis, PET, or fMRI, for example, voltammetric signals can be wirelessly sent to portable computers [181–184] permitting chronic clinical investigations in ambulatory subjects. We foresee two potential uses for *in vivo* human application, investigation of disease mechanisms and closed-loop deep brain stimulation (DBS) therapy.

An exciting foreseeable in-human application is for intra-operative investigation of dysfunctional neurophysiology. In Parkinson's disease, for example, degradation of nigrostriatal dopaminergic neurons is thought to perturb striatal tonic dopamine levels [185,186]. Investigation of disease physiology has been hampered by the difficulty in creating animal models that adequately represent the human condition. Furthermore, animal models do not capture individual variation in disease characteristics, are phenotypically and genetically homogenous, and live in highly controlled environments. Therefore, the optimal setting for monitoring dopamine in these diseases lies in humans. While implantation of recording electrodes for academic objectives is fraught with ethical complication (see next section), there exists opportunity for investigation during surgical implantation of deep brain stimulation electrodes in human subjects undergoing Phase-II epilepsy monitoring and other brain neurosurgical interventions. Surgical trajectories often include the striatum, where dopaminergic dysfunction is thought to exist in many of the aforementioned diseases [187]. Therefore, intra-operative tonic recordings can be achieved in humans without added risk of patient harm, and provide unparalleled insight into disease pathophysiology. This strategy has already been employed by Kishida et al. and Agnesi et al. to measure phasic dopamine fluctuations in the human striatum with CFMEs [45,188]. With the insight gained from these studies, we foresee future experimentation in chronic tonic recording paradigms where patients are fitted with implanted state-of-the-art recording technology. To this end, new miniature recording devices are being developed that would allow for recording outside of the operating room [184,189]. For the first time, tonic neurotransmitter fluctuations can be correlated with disease symptomatology, drug therapy, and stimulation. These will inevitably power new therapeutic strategies.

One promising therapeutic strategy is to probe the effects and mechanism(s) of DBS therapy in order to develop smart systems that provide real-time control of disease symptomatology [190]. Current DBS systems are static and require manual parameter optimization (e.g., frequency, voltage, pulse width) via open-loop systems to maximize therapeutic value and minimize stimulation side effects [175]. These systems can take months, and even years in some cases, of manual adjustments before optimal control is achieved, all while patients receive sub-optimal therapy. These settings are then typically left static while efficacy diminishes either due to disease progression or DBS electrode biofouling, with limited and time-consuming adjustments made by a neurologist [175]. A smart system with biochemical feedback control could remedy this issue and improve therapy. Indeed, the development of closed-loop DBS systems are underway, and successful development of FDA-approved systems based on electrophysiologic feedback have ensued (e.g., Neuropace, Medtronic Percept) [191,192]. Thus, in a similar fashion, tonic dopamine levels, including other electroactive neurotransmitters such as serotonin, may be used as an additional and direct biomarker for closed-loop DBS systems. Efforts are underway to understand if lab-drawn conclusions on dopaminergic dysfunction can be used as a biomarker for stimulation modulation [184,193,194].

6.2. Ethical considerations

The ethical implications of neurochemical monitoring must be taken into consideration for human translation. Dopamine plays a fundamental role in shaping one's personality, as evidenced by its role in reward and incentive-motivation. This is also apparent when one considers how dopamine receptor antagonists are the backbone of antipsychotic treatment. Therefore, recording and modulating dopamine must be examined with the best interests of the patient in mind (benevolence) [195]. Furthermore, in recording neurochemicals, we face issues of privacy. Information storage and access safeguards are crucial elements that must be addressed in counsel with the patient (justice). When considering modulating (e.g., stimulating) neurochemistry, we must ensure a patient's autonomy is not compromised. Moreover, the idea of self-estrangement, or even creation of a new self, is evidently a problem [196]. In summary, we must be cautious of our proposals, careful and deliberative with our decisions, and engaged with the goals and wishes of the patient.

Declaration of competing interest

The authors declare no competing financial interest.

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References

[1] W.X. Pan, R. Schmidt, J.R. Wickens, B.I. Hyland, J. Neurosci. 25 (2005) 6235.
[2] R.A. Wise, Drug Alcohol Depend. 51 (1998) 13.
[3] P.N. Tobler, C.D. Fiorillo, W. Schultz, Science 307 (2005) 1642.
[4] K.C. Berridge, T.E. Robinson, Brain Res Brain Res Rev 28 (1998) 309.
[5] T.M. Jay, Prog. Neurobiol. 69 (2003) 375.
[6] B.W. Balleine, M.R. Delgado, O. Hikosaka, J. Neurosci. 27 (2007) 8161.
[7] J. LeDoux, Neuron 73 (2012) 653.
[8] A.A. Grace, Nat. Rev. Neurosci. 17 (2016) 524.
[9] S.E. Hyman, R.C. Malenka, Nat. Rev. Neurosci. 2 (2001) 695.
[10] A.A. Grace, Addiction 95 (Suppl 2) (2000) S119.
[11] J.K. Dreyer, K.F. Herrik, R.W. Berg, J.D. Hounsgaard, J. Neurosci. 30 (2010) 14273.
[12] A.A. Grace, B.S. Bunney, J. Neurosci. 4 (1984) 2877.
[13] J.Y. Cohen, S. Haesler, L. Vong, B.B. Lowell, N. Uchida, Nature 482 (2012) 85.
[14] Y. Goto, S. Otani, A.A. Grace, Neuropharmacology 53 (2007) 583.
[15] K.A. Keefe, M.J. Zigmond, E.D. Abercrombie, J. Neural Transm. Gen. Sect. 91 (1993) 223.
[16] A.A. Grace, B.S. Bunney, Brain Res. 333 (1985) 271.
[17] L.M. Borland, A.C. Michael, J. Neurochem. 91 (2004) 220.
[18] A.A. Grace, Neuroscience 41 (1991) 1.
[19] S.B. Floresco, A.R. West, B. Ash, H. Moore, A.A. Grace, Nat. Neurosci. 6 (2003) 968.
[20] C.R. Freed, B.K. Yamamoto, Science 229 (1985) 62.
[21] A.A. Hamid, J.R. Pettibone, O.S. Mabrouk, V.L. Hetrick, R. Schmidt, C.M. Vander Weele, R.T. Kennedy, B.J. Aragona, J.D. Berke, Nat. Neurosci. 19 (2016) 117.
[22] M.W. Howe, P.L. Tierney, S.G. Sandberg, P.E. Phillips, A.M. Graybiel, Nature 500 (2013) 575.
[23] P.E. Phillips, G.D. Stuber, M.L. Heien, R.M. Wightman, R.M. Carelli, Nature 422 (2003) 614.
[24] Y. Niv, N.D. Daw, D. Joel, P. Dayan, Psychopharmacology (Berl) 191 (2007) 507.
[25] A.A. Grace, B.S. Bunney, Eur. J. Pharmacol. 59 (1979) 211.
[26] M.A. Ungless, P.J. Magill, J.P. Bolam, Science 303 (2004) 2040.
[27] M.A. Pezze, C.A. Heidbreder, J. Feldon, C.A. Murphy, Neuroscience 108 (2001) 91.
[28] P.A. Dombrowski, T.V. Maia, S.L. Boschen, M. Bortolanza, E. Wendler, R.K. Schwarting, M.L. Brandao, P. Winn, C.D. Blaha, C. Da Cunha, Behav. Brain Res. 241 (2013) 112.
[29] W.H. Meck, A.M. Benson, Brain Cognit. 48 (2002) 195.
[30] Y. Goto, A.A. Grace, Nat. Neurosci. 8 (2005) 805.
[31] C. Yapo, A.G. Nair, L. Clement, L.R. Castro, J. Hellgren Kotaleski, P. Vincent, J. Physiol. 595 (2017) 7451.
[32] Y. Matsuda, A. Marzo, S. Otani, J. Neurosci. 26 (2006) 4803.
[33] V.I. Chefer, A.C. Thompson, A. Zapata, T.S. Shippenberg, Curr Protoc Neurosci Chapter 7 (2009). Unit7 1.
[34] K.L. Clapp-Lilly, R.C. Roberts, L.K. Duffy, K.P. Irons, Y. Hu, K.L. Drew, J. Neurosci. Methods 90 (1999) 129.
[35] J.J. Vaquero, P. Kinahan, Annu. Rev. Biomed. Eng. 17 (2015) 385.

[36] T.J. Bruinsma, V.V. Sarma, Y. Oh, D.P. Jang, S.Y. Chang, G.A. Worrell, V.J. Lowe, H.J. Jo, H.K. Min, Front. Neurosci. 12 (2018) 238.
[37] B.J. Venton, H. Zhang, P.A. Garris, P.E. Phillips, D. Sulzer, R.M. Wightman, J. Neurochem. 87 (2003) 1284.
[38] C.W. Atcherley, K.M. Wood, K.L. Parent, P. Hashemi, M.L. Heien, Chem Commun (Camb) 51 (2015) 2235.
[39] Y. Oh, C. Park, D.H. Kim, H. Shin, Y.M. Kang, M. DeWaele, J. Lee, H.K. Min, C.D. Blaha, K.E. Bennet, I.Y. Kim, K.H. Lee, D.P. Jang, Anal. Chem. 88 (2016) 10962.
[40] J.A. Johnson, N.T. Rodeberg, R.M. Wightman, Anal. Chem. 90 (2018) 7181.
[41] P. Puthongkham, B.J. Venton, ACS Sens. 4 (2019) 2403.
[42] Y. Oh, M.L. Heien, C. Park, Y.M. Kang, J. Kim, S.L. Boschen, H. Shin, H.U. Cho, C.D. Blaha, K.E. Bennet, H.K. Lee, S.J. Jung, I.Y. Kim, K.H. Lee, D.P. Jang, Biosens. Bioelectron. 121 (2018) 174.
[43] I.M. Taylor, N.A. Patel, N.C. Freedman, E. Castagnola, X.T. Cui, Anal. Chem. 91 (2019) 12917.
[44] A.S. Barath, A.E. Rusheen, J.M. Rojas Cabrera, J.B. Price, R.L. Owen, H. Shin, D.P. Jang, C.D. Blaha, K.H. Lee, Y. Oh, Front. Neurosci. 14 (2020).
[45] K.T. Kishida, I. Saez, T. Lohrenz, M.R. Witcher, A.W. Laxton, S.B. Tatter, J.P. White, T.L. Ellis, P.E. Phillips, P.R. Montague, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 200.
[46] A. Kasasbeh, K. Lee, A. Bieber, K. Bennet, S.Y. Chang, Stereotact. Funct. Neurosurg. 91 (2013) 141.
[47] C.J. Watson, B.J. Venton, R.T. Kennedy, Anal. Chem. 78 (2006) 1391.
[48] T. Yoshitake, S. Yoshitake, K. Fujino, H. Nohta, M. Yamaguchi, J. Kehr, J. Neurosci. Methods 140 (2004) 163.
[49] A. Santos-Fandila, A. Zafra-Gomez, A. Barranco, A. Navalon, R. Rueda, M. Ramirez, Talanta 114 (2013) 79.
[50] C. Ji, W. Li, X.D. Ren, A.F. El-Kattan, R. Kozak, S. Fountain, C. Lepsy, Anal. Chem. 80 (2008) 9195.
[51] S. Greco, W. Danysz, A. Zivkovic, R. Gross, H. Stark, Anal. Chim. Acta 771 (2013) 65.
[52] C.A. Heidbreder, L. Lacroix, A.R. Atkins, A.J. Organ, S. Murray, A. West, A.J. Shah, J. Neurosci. Methods 112 (2001) 135.
[53] H. Gu, E.L. Varner, S.R. Groskreutz, A.C. Michael, S.G. Weber, Anal. Chem. 87 (2015) 6088.
[54] T. Yoshitake, J. Kehr, K. Todoroki, H. Nohta, M. Yamaguchi, Biomed. Chromatogr. 20 (2006) 267.
[55] J.B. Justice Jr., J. Neurosci. Methods 48 (1993) 263.
[56] A. Tang, P.M. Bungay, R.A. Gonzales, J. Neurosci. Methods 126 (2003) 1.
[57] R. Martin-Fardon, F. Sandillon, J. Thibault, A. Privat, J. Vignon, J. Neurosci. Methods 72 (1997) 123.
[58] N.H. Chen, Y.J. Lai, W.H. Pan, Neurosci. Lett. 225 (1997) 197.
[59] L.H. Parsons, J.B. Justice Jr., J. Neurochem. 58 (1992) 212.
[60] N. Bruet, F. Windels, A. Bertrand, C. Feuerstein, A. Poupard, M. Savasta, J. Neuropathol. Exp. Neurol. 60 (2001) 15.
[61] D.H. Szarowski, M.D. Andersen, S. Retterer, A.J. Spence, M. Isaacson, H.G. Craighead, J.N. Turner, W. Shain, Brain Res. 983 (2003) 23.
[62] H. Benveniste, N.H. Diemer, Acta Neuropathol. 74 (1987) 234.
[63] G. Di Chiara, E. Carboni, M. Morelli, A. Cozzolino, G.L. Tanda, A. Pinna, G. Russi, S. Consolo, Neuroscience 55 (1993) 451.
[64] C.D. Blaha, A. Coury, A.G. Phillips, Neuroscience 75 (1996) 543.
[65] H. Yang, J.L. Peters, C. Allen, S.S. Chern, R.D. Coalson, A.C. Michael, Anal. Chem. 72 (2000) 2042.
[66] K.T. Ngo, E.L. Varner, A.C. Michael, S.G. Weber, ACS Chem. Neurosci. 8 (2017) 329.
[67] H. Yang, A.B. Thompson, B.J. McIntosh, S.C. Altieri, A.M. Andrews, ACS Chem. Neurosci. 4 (2013) 790.
[68] A.M. Young, J. Neurosci. Methods 138 (2004) 57.
[69] J. Cheng, M.G. Feenstra, Learn. Mem. 13 (2006) 168.
[70] M. Shou, C.R. Ferrario, K.N. Schultz, T.E. Robinson, R.T. Kennedy, Anal. Chem. 78 (2006) 6717.
[71] R.T. Kennedy, Curr. Opin. Chem. Biol. 17 (2013) 860.
[72] K.C. Chen, J. Neurochem. 92 (2005) 46.
[73] K.C. Chen, E.A. Budygin, J. Neurosci. Methods 164 (2007) 27.
[74] R. Kanthan, A. Shuaib, R. Griebel, H. Miyashita, Stroke 26 (1995) 870.
[75] T. Suominen, P. Uutela, R.A. Ketola, J. Bergquist, L. Hillered, M. Finel, H. Zhang, A. Laakso, R. Kostiainen, PloS One 8 (2013), e68007.
[76] P.H. Elsinga, K. Hatano, K. Ishiwata, Curr. Med. Chem. 13 (2006) 2139.
[77] S. Pappata, S. Dehaene, J.B. Poline, M.C. Gregoire, A. Jobert, J. Delforge, V. Frouin, M. Bottlaender, F. Dolle, L. Di Giamberardino, A. Syrota, Neuroimage 16 (2002) 1015.
[78] M.J. Koepp, R.N. Gunn, A.D. Lawrence, V.J. Cunningham, A. Dagher, T. Jones, D.J. Brooks, C.J. Bench, P.M. Grasby, Nature 393 (1998) 266.
[79] V.A. Ramchandani, J. Umhau, F.J. Pavon, V. Ruiz-Velasco, W. Margas, H. Sun, R. Damadzic, R. Eskay, M. Schoor, A. Thorsell, M.L. Schwandt, W.H. Sommer, D.T. George, L.H. Parsons, P. Herscovitch, D. Hommer, M. Heilig, Mol. Psychiatr. 16 (2011) 809.
[80] R.N. Lippert, A.L. Cremer, S. Edwin Thanarajah, C. Korn, T. Jahans-Price, L.M. Burgeno, M. Tittgemeyer, J.C. Bruning, M.E. Walton, H. Backes, Nat. Commun. 10 (2019) 336.
[81] B. Knutson, G.W. Fong, S.M. Bennett, C.M. Adams, D. Hommer, Neuroimage 18 (2003) 263.
[82] N.K. Logothetis, J. Neurosci. 23 (2003) 3963.
[83] B.G. Jenkins, Neuroimage 62 (2012) 1072.
[84] J. Ren, H. Xu, J.K. Choi, B.G. Jenkins, Y.I. Chen, Synapse 63 (2009) 764.
[85] A.K. Buck, K. Herrmann, T. Stargardt, T. Dechow, B.J. Krause, J. Schreyogg, J. Nucl. Med. Technol. 38 (2010) 6.
[86] C.Y. Sander, J.M. Hooker, C. Catana, M.D. Normandin, N.M. Alpert, G.M. Knudsen, W. Vanduffel, B.R. Rosen, J.B. Mandeville, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 11169.
[87] C.Y. Sander, S. Hesse, Q. J. Nucl. Med. Mol. Imaging 61 (2017) 414.
[88] R.D. Badgaiyan, Prog. Brain Res. 211 (2014) 165.
[89] M.G. Shapiro, G.G. Westmeyer, P.A. Romero, J.O. Szablowski, B. Kuster, A. Shah, C.R. Otey, R. Langer, F.H. Arnold, A. Jasanoff, Nat. Biotechnol. 28 (2010) 264.
[90] T. Lee, L.X. Cai, V.S. Lelyveld, A. Hai, A. Jasanoff, Science 344 (2014) 533.
[91] N. Li, A. Jasanoff, Nature 580 (2020) 239.
[92] C.M. Cassidy, F.A. Zucca, R.R. Girgis, S.C. Baker, J.J. Weinstein, M.E. Sharp, C. Bellei, A. Valmadre, N. Vanegas, L.S. Kegeles, G. Brucato, U. Jung Kang, D. Sulzer, L. Zecca, A. Abi-Dargham, G. Horga, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 5108.
[93] L. Zecca, D. Tampellini, M. Gerlach, P. Riederer, R.G. Fariello, D. Sulzer, Mol. Pathol. 54 (2001) 414.
[94] T. Patriarchi, J.R. Cho, K. Merten, M.W. Howe, A. Marley, W.H. Xiong, R.W. Folk, G.J. Broussard, R. Liang, M.J. Jang, H. Zhong, D. Dombeck, M. von Zastrow, A. Nimmerjahn, V. Gradinaru, J.T. Williams, L. Tian, Science 360 (2018).
[95] C.V. Cosme, G.K. Palissery, T.N. Lerner, Trends Neurosci. 41 (2018) 566.
[96] F. Sun, J. Zeng, M. Jing, J. Zhou, J. Feng, S.F. Owen, Y. Luo, F. Li, H. Wang, T. Yamaguchi, Z. Yong, Y. Gao, W. Peng, L. Wang, S. Zhang, J. Du, D. Lin, M. Xu, A.C. Kreitzer, G. Cui, Y. Li, Cell 174 (2018) 481.
[97] D. Lee, M. Creed, K. Jung, T. Stefanelli, D.J. Wendler, W.C. Oh, N.L. Mignocchi, C. Luscher, H.B. Kwon, Nat. Methods 14 (2017) 495.
[98] G. Barnea, W. Strapps, G. Herrada, Y. Berman, J. Ong, B. Kloss, R. Axel, K.J. Lee, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 64.
[99] A. Muller, V. Joseph, P.A. Slesinger, D. Kleinfeld, Nat. Methods 11 (2014) 1245.
[100] A.G. Beyene, I.R. McFarlane, R.L. Pinals, M.P. Landry, ACS Chem. Neurosci. 8 (2017) 2275.
[101] A.G. Beyene, K. Delevich, J.T. Del Bonis-O'Donnell, D.J. Piekarski, W.C. Lin, A.W. Thomas, S.J. Yang, P. Kosillo, D. Yang, G.S. Prounis, L. Wilbrecht, M.P. Landry, Sci Adv 5 (2019), eaaw3108.
[102] H. Wang, M. Jing, Y. Li, Curr. Opin. Neurobiol. 50 (2018) 171.
[103] R.N. Adams, Anal. Chem. 48 (1976) 1126A.
[104] E.N. Pothos, Behav. Brain Res. 130 (2002) 203.
[105] M. Borisovska, A.L. Bensen, G. Chong, G.L. Westbrook, J. Neurosci. 33 (2013) 1790.
[106] S.E. Hochstetler, M. Puopolo, S. Gustincich, E. Raviola, R.M. Wightman, Anal. Chem. 72 (2000) 489.
[107] E.H. Jaffe, A. Marty, A. Schulte, R.H. Chow, J. Neurosci. 18 (1998) 3548.
[108] A.C. Michael, L.M. Borland, Electrochemical Methods for Neuroscience, CRC Press/Taylor & Francis, Boca Raton, 2007.
[109] R.N. Adams, Prog. Neurobiol. 35 (1990) 297.
[110] C.D. Blaha, R.F. Lane, Brain Res. Bull. 10 (1983) 861.
[111] G.A. Gerhardt, A.F. Hoffman, J. Neurosci. Methods 109 (2001) 13.
[112] A.F. Hoffman, G.A. Gerhardt, J. Neurochem. 70 (1998) 179.
[113] A.D. Miller, G.L. Forster, J.S. Yeomans, C.D. Blaha, Neuroscience 136 (2005) 531.
[114] E.L. Unger, D.J. Eve, X.A. Perez, D.K. Reichenbach, Y. Xu, M.K. Lee, A.M. Andrews, Neurobiol. Dis. 21 (2006) 431.
[115] C.D. Blaha, Pharmacol. Biochem. Behav. 55 (1996) 351.
[116] C.D. Blaha, A.G. Phillips, Behav. Pharmacol. 7 (1996) 675.
[117] C.D. Blaha, M.E. Jung, J. Electroanal. Chem. Interfacial Electrochem. 310 (1991) 317.
[118] S. Borman, Anal. Chem. 54 (1982) A698.
[119] A.G. Ewing, M.A. Dayton, R.M. Wightman, Anal. Chem. 53 (1981) 1842.
[120] K.F. Drake, R.P. Van Duyne, J. Electroanal. Chem. Interfacial Electrochem. 89 (1978) 231.
[121] J. Osteryoung, R. Osteryoung, Anal. Chem. 57 (1985) 101.
[122] F.G. Gonon, F. Navarre, M.J. Buda, Anal. Chem. 56 (1984) 573.
[123] M.M. Marcus, J.M. Mathe, G.G. Nomikos, T.H. Svensson, Neuropharmacology 40 (2001) 482.
[124] M.L. Heien, M.A. Johnson, R.M. Wightman, Anal. Chem. 76 (2004) 5697.
[125] M.L. Heien, A.S. Khan, J.L. Ariansen, J.F. Cheer, P.E. Phillips, K.M. Wassum, R.M. Wightman, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 10023.
[126] J.O. Howell, W.G. Kuhr, R.E. Ensman, R.M. Wightman, J. Electroanal. Chem. Interfacial Electrochem. 209 (1986) 77.
[127] J.G. Roberts, B.P. Moody, G.S. McCarty, L.A. Sombers, Langmuir 26 (2010) 9116.
[128] R.B. Keithley, P. Takmakov, E.S. Bucher, A.M. Belle, C.A. Owesson-White, J. Park, R.M. Wightman, Anal. Chem. 83 (2011) 3563.
[129] C.A. Owesson-White, M.F. Roitman, L.A. Sombers, A.M. Belle, R.B. Keithley, J.L. Peele, R.M. Carelli, R.M. Wightman, J. Neurochem. 121 (2012) 252.
[130] K.T. Kawagoe, P.A. Garris, D.J. Wiedemann, R.M. Wightman, Neuroscience 51 (1992) 55.
[131] R.A. Vaughan, J.D. Foster, Trends Pharmacol. Sci. 34 (2013) 489.
[132] C.W. Atcherley, N.D. Laude, K.L. Parent, M.L. Heien, Langmuir 29 (2013) 14885.
[133] J.A. Johnson, C.N. Hobbs, R.M. Wightman, Anal. Chem. 89 (2017) 6166.

[134] J.C. Helfrick Jr., L.A. Bottomley, Anal. Chem. 81 (2009) 9041.
[135] C. Park, Y. Oh, H. Shin, J. Kim, Y. Kang, J. Sim, H.U. Cho, H.K. Lee, S.J. Jung, C.D. Blaha, K.E. Bennet, M.L. Heien, K.H. Lee, I.Y. Kim, D.P. Jang, Anal. Chem. 90 (2018) 13348.
[136] G. Xu, L. Beibei, X.T. Cui, L. Ling, X. Luo, Sensor. Actuator. B Chem. 188 (2013) 405.
[137] G. Di Chiara, Behav. Brain Res. 137 (2002) 75.
[138] P. Puthongkham, B.J. Venton, Analyst 145 (2020) 1087–1102.
[139] M. Sajid, N. Baig, et al., Trac. Trends Anal. Chem. 111 (2019) 47–61.
[140] J.L. Ponchon, R. Cespuglio, F. Gonon, M. Jouvet, J.F. Pujol, Anal. Chem. 51 (1979) 1483.
[141] M.L. Huffman, B.J. Venton, Analyst 134 (2009) 18.
[142] J.L. Peters, L.H. Miner, A.C. Michael, S.R. Sesack, J. Neurosci. Methods 137 (2004) 9.
[143] J.J. Clark, S.G. Sandberg, M.J. Wanat, J.O. Gan, E.A. Horne, A.S. Hart, C.A. Akers, J.G. Parker, I. Willuhn, V. Martinez, S.B. Evans, N. Stella, P.E. Phillips, Nat. Methods 7 (2010) 126.
[144] M.L. Heien, P.E. Phillips, G.D. Stuber, A.T. Seipel, R.M. Wightman, Analyst 128 (2003) 1413.
[145] R.J. Rice, N.M. Pontikos, R.L. McCreery, J. Am. Chem. Soc. 112 (1990) 4617.
[146] P.M. Kovach, M.R. Deakin, R.M. Wightman, J. Phys. Chem. 90 (1986) 4612.
[147] R.F. Vreeland, C.W. Atcherley, W.S. Russell, J.Y. Xie, D. Lu, N.D. Laude, F. Porreca, M.L. Heien, Anal. Chem. 87 (2015) 2600.
[148] G. Nagy, G.A. Gerhardt, A.F. Oke, M.E. Rice, R.N. Adams, M.N. Szentirmay, C.R. Martin, Anal. Chem. (1985) 85.
[149] A. Witkowski, A. Brajter-Toth, Anal. Chem. 64 (1992) 635.
[150] K. Pihel, Q.D. Walker, R.M. Wightman, Anal. Chem. 68 (1996) 2084.
[151] C.C. Hsueh, A. Brajtertoth, A. Anal. Chem. 66 (1994) 2458.
[152] A.M. Strand, B.J. Venton, Anal. Chem. 80 (2008) 3708.
[153] C. Yang, E. Trikantzopoulos, C.B. Jacobs, B.J. Venton, Anal. Chim. Acta 965 (2017) 1.
[154] S.B. Hocevar, J. Wang, R.P. Deo, M. Musameh, B. Ogorevc, Electroanalysis 17 (2005) 417.
[155] C.B. Jacobs, T.L. Vickrey, B.J. Venton, Analyst 136 (2011) 3557.
[156] Y. Zhang, Y. Pan, S. Su, L. Zhang, S. Li, M. Shao, Electroanalysis 19 (2007) 1695.
[157] N. Xiao, B.J. Venton, Anal. Chem. 84 (2012) 7816.
[158] C.B. Jacobs, I.N. Ivanov, M.D. Nguyen, A.G. Zestos, B.J. Venton, Anal. Chem. 86 (2014) 5721.
[159] P. Takmakov, M.K. Zachek, R.B. Keithley, P.L. Walsh, C. Donley, G.S. McCarty, R.M. Wightman, Anal. Chem. 82 (2010) 2020.
[160] K. Yoshimi, Y. Naya, N. Mitani, T. Kato, M. Inoue, S. Natori, T. Takahashi, A. Weitemier, N. Nishikawa, T. McHugh, Y. Einaga, S. Kitazawa, Neurosci. Res. 71 (2011) 49.
[161] K.E. Bennet, J.R. Tomshine, H.K. Min, F.S. Manciu, M.P. Marsh, S.B. Paek, M.L. Settell, E.N. Nicolai, C.D. Blaha, A.Z. Kouzani, S.Y. Chang, K.H. Lee, Front. Hum. Neurosci. 10 (2016) 102.
[162] C.A. Rusinek, Y. Guo, R. Rechenberg, M.F. Becker, E. Purcell, M. Verber, C. McKinney, W. Li, J. Electrochem. Soc. 165 (2018) G3087.
[163] K. Nakano, T. Kayahara, T. Tsutsumi, H. Ushiro, J. Neurol. 247 (Suppl 5) (2000) V1.
[164] M.K. Zachek, P. Takmakov, B. Moody, R.M. Wightman, G.S. McCarty, Anal. Chem. 81 (2009) 6258.
[165] M.K. Zachek, J. Park, P. Takmakov, R.M. Wightman, G.S. McCarty, Analyst 135 (2010) 1556.
[166] B. Zhang, K.L. Adams, S.J. Luber, D.J. Eves, M.L. Heien, A.G. Ewing, Anal. Chem. 80 (2008) 1394.
[167] B. Zhang, M.L. Heien, M.F. Santillo, L. Mellander, A.G. Ewing, Anal. Chem. 83 (2011) 571.
[168] Y. Lin, R. Trouillon, M.I. Svensson, J.D. Keighron, A.S. Cans, A.G. Ewing, Anal. Chem. 84 (2012) 2949.
[169] I. Suzuki, M. Fukuda, K. Shirakawa, H. Jiko, M. Gotoh, Biosens. Bioelectron. 49 (2013) 270.
[170] S. Zhang, Y. Song, M. Wang, Z. Zhang, X. Fan, X. Song, P. Zhuang, F. Yue, P. Chan, X. Cai, Biosens. Bioelectron. 85 (2016) 53.
[171] S. Zhang, Y. Song, M. Wang, G. Xiao, F. Gao, Z. Li, G. Tao, P. Zhuang, F. Yue, P. Chan, X. Cai, Microsystems & Nanoengineering, 2019.
[172] G. Tomagra, F. Picollo, A. Battiato, B. Picconi, S. De Marchis, A. Pasquarelli, P. Olivero, A. Marcantoni, P. Calabresi, E. Carbone, V. Carabelli, Front. Neurosci. 13 (2019) 288.
[173] A.J. Fenoy, R.K. Simpson Jr., J. Neurosurg. 120 (2014) 132.
[174] S.M. Stahl, J.F. Pradko, B.R. Haight, J.G. Modell, C.B. Rockett, S. Learned-Coughlin, Prim. Care Companion J. Clin. Psychiatry 6 (2004) 159.
[175] C.H. Chang, A.A. Grace, Biol. Psychiatr. 76 (2014) 223.
[176] B.J. Venton, T.E. Robinson, R.T. Kennedy, S. Maren, Eur. J. Neurosci. 23 (2006) 3391.
[177] I. Westergren, B. Nyström, A. Hamberger, B.B. Johansson, J. Neurochem. 64 (1995) 229.
[178] K.H. Lee, Biomedical Engineering Letters 1 (2011) 152.
[179] R.J. Moran, K.T. Kishida, T. Lohrenz, I. Saez, A.W. Laxton, M.R. Witcher, S.B. Tatter, T.L. Ellis, P.E. Phillips, P. Dayan, P.R. Montague, Neuropsychopharmacology 43 (2018) 1425.
[180] S.-Y. Chang, I. Kim, M.P. Marsh, D.P. Jang, S.-C. Hwang, J.J. Van Gompel, S.J. Goerss, C.J. Kimble, K.E. Bennet, P.A. Garris, Wireless Fast-Scan Cyclic Voltammetry to Monitor Adenosine in Patients with Essential Tremor during Deep Brain Stimulation, Elsevier, 2012, p. 760.
[181] J.M. Bledsoe, C.J. Kimble, D.P. Covey, C.D. Blaha, F. Agnesi, P. Mohseni, S. Whitlock, D.M. Johnson, A. Horne, K.E. Bennet, K.H. Lee, P.A. Garris, J. Neurosurg. 111 (2009) 712.
[182] S.Y. Chang, T. Jay, J. Munoz, I. Kim, K.H. Lee, Analyst 137 (2012) 2158.
[183] C.J. Griessenauer, S.Y. Chang, S.J. Tye, C.J. Kimble, K.E. Bennet, P.A. Garris, K.H. Lee, J. Neurosurg. 113 (2010) 656.
[184] K.H. Lee, J.L. Lujan, J.K. Trevathan, E.K. Ross, J.J. Bartoletta, H.O. Park, S.B. Paek, E.N. Nicolai, J.H. Lee, H.K. Min, C.J. Kimble, C.D. Blaha, K.E. Bennet, Sci. Rep. 7 (2017) 46675.
[185] A.E. Lang, A.M. Lozano, N. Engl. J. Med. 339 (1998) 1130.
[186] O. Hornykiewicz, Neurology 51 (1998) S2.
[187] C.R. Gerfen, D.J. Surmeier, Annu. Rev. Neurosci. 34 (2011) 441.
[188] F. Agnesi, S.J. Tye, J.M. Bledsoe, C.J. Griessenauer, C.J. Kimble, G.C. Sieck, K.E. Bennet, P.A. Garris, C.D. Blaha, K.H. Lee, J. Neurosurg. 111 (2009) 701.
[189] B. Bozorgzadeh, D.R. Schuweiler, M.J. Bobak, P.A. Garris, P. Mohseni, IEEE Trans Biomed Circuits Syst 10 (2016) 654.
[190] J.B. Price, A.E. Rusheen, A.S. Barath, J.M. Rojas Cabrera, H. Shin, S.Y. Chang, C.J. Kimble, K.E. Bennet, C.D. Blaha, K.H. Lee, Y. Oh, Neurosurg. Focus 49 (2020) E6.
[191] M.J. Morrell, R.N.S.S.i.E.S. Group, Neurology 77 (2011) 1295.
[192] Medtronic, FDA Approves First-Of-Its-Kind Percept™ PC Neurostimulator with BrainSense™ Technology, https://newsroom.medtronic.com/news-releases/news-release-details/fda-approves-first-its-kind-percepttm-pc-neurostimulator, 2020.
[193] J.K. Trevathan, A. Yousefi, H.O. Park, J.J. Bartoletta, K.A. Ludwig, K.H. Lee, J.L. Lujan, ACS Chem. Neurosci. 8 (2017) 394.
[194] P.J. Grahn, G.W. Mallory, O.U. Khurram, B.M. Berry, J.T. Hachmann, A.J. Bieber, K.E. Bennet, H.K. Min, S.Y. Chang, K.H. Lee, J.L. Lujan, Front. Neurosci. 8 (2014) 169.
[195] M. Unterrainer, F.S. Oduncu, Med Health Care Philos 18 (2015) 475.
[196] F. Gilbert, M. Cook, T. O'Brien, J. Illes, Sci. Eng. Ethics 25 (2019) 83.