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Computational Modeling of Neurotransmitter Release Evoked by Electrical Stimulation: Nonlinear Approaches to Predicting Stimulation-Evoked Dopamine Release

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Abstract

Neurochemical changes evoked by electrical stimulation of the nervous system have been linked to both therapeutic and undesired effects of neuromodulation therapies used to treat obsessive-compulsive disorder, depression, epilepsy, Parkinson's disease, stroke, hypertension, tinnitus, and many other indications. In fact, interest in better understanding the role of neurochemical signaling in neuromodulation therapies has been a focus of recent government- and industry-sponsored programs whose ultimate goal is to usher in an era of personalized medicine by creating neuromodulation therapies that respond to real-time changes in patient status. A key element to achieving these precision therapeutic interventions is the development of mathematical modeling approaches capable of describing the nonlinear transfer function between neuromodulation parameters and evoked neurochemical changes. Here, we propose two computational modeling frameworks, based on artificial neural networks (ANNs) and Volterra kernels, that can characterize

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The authors of this manuscript would like to encourage other researchers attempting to replicate or take advantage of these approaches to contact us, James Trevathan (trevathan.james@mayo.edu) or J. Luis Lujan, Ph.D. (lujan.luis@mayo.edu), for specific support in the form of code or answers to questions.

the input/output transfer functions of stimulation-evoked neurochemical release. We evaluate the ability of these modeling frameworks to characterize subject-specific neurochemical kinetics by accurately describing stimulation-evoked dopamine release across rodent ($R^2 = 0.83$ Volterra kernel, $R^2 = 0.86$ ANN), swine ($R^2 = 0.90$ Volterra kernel, $R^2 = 0.93$ ANN), and non-human primate ($R^2 = 0.98$ Volterra kernel, $R^2 = 0.96$ ANN) models of brain stimulation. Ultimately, these models will not only improve understanding of neurochemical signaling in healthy and diseased brains but also facilitate the development of neuromodulation strategies capable of controlling neurochemical release via closed-loop strategies.

Graphical Abstract

Keywords

Fast scan cyclic voltammetry; deep brain stimulation; dopamine; artificial neural network; Volterra kernels; machine learning; neurochemical sensing

INTRODUCTION

Neurochemical signaling has been implicated in both therapeutic and undesired effects of neuromodulation therapies for a myriad of clinical indications. In fact, interest in better understanding the role of neurochemical signaling in neuromodulation therapies with regard to the intended therapeutic effects and unwanted side effects has been a focus of recent government and industry efforts, including the National Institutes of Health (NIH) Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative and Stimulating Peripheral Activity to Relieve Conditions (SPARC) Common Fund Program, the Defense Advanced Research Projects Agency (DARPA) Electrical Prescriptions (ElectRx) and Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) Programs, and the GlaxoSmithKline Bioelectric Medicines Initiative. The fundamental goal of these programs is to bring forth an era of personalized neuromodulation therapies that are capable of detecting and responding to real-time changes in patient status. Achieving this goal requires characterization of the nonlinear relationships between the applied neuromodulation parameters and the evoked distal effects, such as changes in electrophysiologic activity and neurochemical signaling.

In general, the study of changes in neurochemical signaling evoked by electrical stimulation has been limited by the measurement and analysis techniques available. For example, noninvasive indirect measurement techniques such as positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) have poor spatial and temporal resolution,^{1,2} while invasive direct measurement techniques like dialysis alter the fundamental dynamics

of local neurochemical release.³ Given the growing interest in and need for precision neuromodulation therapies, it is important to note that there is evidence suggesting that these low spatial or temporal resolution neurochemical sampling techniques may mischaracterize highly focal and nonhomogeneously evoked neurochemical release.^{4,5}

Numerous studies have built upon existing low resolution neurochemical sampling techniques by taking advantage of lesion-based and pharmacological interventions to demonstrate that (1) electrical stimulation can elicit proximal and distal neurochemical changes and (2) changes in neurochemical signaling are related to symptom reduction or induction of side effect.^{6–8} Unfortunately, these approaches result in a binary measurement system with only “yes” or “no” resolution and provide very little information on the extent of neurochemical fluctuations associated with specific changes in the underlying physiology. Thus, measurement of neurochemical signaling with high spatial and temporal resolution is paramount to both elucidate the fundamental biological mechanisms of action underlying neuromodulation interventions and enable precision neurochemical control strategies (e.g., via closed-loop).

Fast-scan cyclic voltammetry (FSCV) is a neurochemical sensing technique capable of subsecond and sub-millimeter resolution.^{9,10} In contrast to dialysis techniques, FSCV creates minimal tissue disruption and can record neurochemical activity for up to several months.¹¹ Combined, these characteristics make FSCV an excellent technique for informing the development of mathematical models and potentially as a feedback signal for neuromodulation therapies. In fact, FSCV data have already been utilized to develop mathematical models describing the relationship between synaptic neurochemical release and phasic changes in extracellular dopamine concentration.^{12–14} However, current mathematical modeling techniques aimed at characterizing the relationship between electrical stimulation parameters and the corresponding evoked changes in neurochemical signaling are limited. In fact, to our knowledge, no nonlinear modeling techniques have been presented in the literature.¹⁵

It is well-known that activation of nervous tissue near the stimulating electrode is subject to a number of variable factors such as distance from the electrode to the nervous tissue, orientation of the nerve/neuron with respect to the electrode, degree of myelination, tissue conductivity, and several others.^{16–18} Similarly, the ability to measure neurochemical release will depend upon several patient-specific factors such as diffusion properties, reuptake rates, stimulation and measurement targets, and disease processes.^{5,19,20} Consequently, a model of the input/output relationship between electrical stimulation parameters and evoked neurochemical changes must be able to incorporate these unknown and inherently nonlinear variables on a subject-by-subject basis. Additionally, model complexity must allow for real-time analysis, architectural flexibility, and cross-platform portability in order to facilitate the development and implementation of closed-loop control strategies and embedding in implantable neuromodulation devices.

Artificial neural networks (ANNs) and time-series approaches utilizing Volterra kernels are two common methods with varying computational complexity capable of modeling the input/output transfer functions in physiological systems with inherently nonlinear dynamics

and several unknown parameters.^{21,22} Here, we evaluate the suitability of both ANN and Volterra kernels for modeling the input/output transfer functions between stimulation parameters and evoked changes in striatal dopaminergic signaling in rodent, swine, and nonhuman primate (NHP) models of electrical stimulation. In particular, Volterra kernels are able to characterize neurochemical dynamics of varying order (i.e., short-term and long-term effects of previous stimuli) and thus are uniquely suited for describing the dependence of neurochemical responses on previous stimuli sequences. Additionally, training of Volterra kernels is flexible, making it easily applicable to other neurotransmitters, anatomical targets (i.e., stimulation and neurochemical sensing locations), and animal models with little or no modification.²³ In contrast the ANNs are uniquely suited for learning input/output relationships described by compartmental models of neurochemical release.^{12,24} This simplifies model training and improves model performance by decreasing the number of output parameters modeled by the network. Although using compartmental models of striatal dopamine release as a feature extraction method for the ANN modeling approach offers benefits, it also prevents the model from being extended to situations where the neurochemical release is less well understood and modeling techniques are not well established. Development of these mathematical characterization approaches will enable the development of a neurochemical patch-clamp system capable of studying neurochemical signaling evoked by neurostimulation therapies. In turn, this characterization will lead to the development of novel techniques for controlling changes in neurochemistry via modulation of electrical stimulation of nervous tissue.

RESULTS AND DISCUSSION

In these experiments, the focus was to develop mathematical modeling frameworks that can be used to characterize neurochemical signaling for multiple neurochemical analytes across different animal models, regardless of stimulation location, electrode/tissue geometry, and stimulation parameters. To this end, both the ANN and Volterra kernel models were selected as general, flexible models that could easily be extended to meet the requirements of a particular neurochemical stimulation and recording paradigm. These models were trained on neurochemical data collected using FSCV and evoked by electrical stimulation in rodent, swine, and NHP animal models (Figure 1).

Modulation and Neurochemical Recording of Stimulation-Evoked Dopamine Responses

Dopaminergic signaling from the SNc/VTA, as well as dopaminergic axons in the MFB, have been shown to play important roles in both motivation and reward and have been implicated in depression and Parkinson's disease.^{25–27} Our preliminary data showed maximal striatal dopamine release occurring at 60 Hz or greater for the rodent model,⁵ 130 Hz for the swine model,²⁸ and 120–130 Hz in the NHP model, which is an agreement with previously reported data.⁴ Thus, we chose to stimulate rodents, swine, and NHP models using 90, 130, and 130 Hz frequencies, respectively. Stimulation of the MFB or SNc/VTA in 12 anesthetized rats (MFB), four anesthetized swine (SNc/VTA), and one anesthetized NHP (SNc/VTA) led to nonlinear increases in striatal dopamine release as a function of stimulation amplitude (Figure 2A,C,E). Similarly, these stimulation-evoked extracellular dopamine levels increased nonlinearly as a function of stimulation pulse width (Figure

2B,D,F). Therefore, it is possible to modulate striatal dopamine by modulating the stimulus intensity (e.g., pulsewidth and amplitude) applied to the SNc/VTa and MFB.

Parametric Characterization and Prediction of Stimulation-Evoked Neurochemical Release

Stimulation-evoked dopamine release was modeled using parametric models of neurochemical kinetics (eqs 1–3, Figure 3A). These parametric mathematical models, trained on experimental *in vivo* neurochemical responses, accurately described the forward relationships between stimulus duration, amplitude, and pulse-width, and the corresponding stimulation-evoked extracellular dopamine responses for a wide range of stimulation parameters (Table 1). Specifically, the compartmental model describing the kinetics of dopamine release (eqs 1–3) fit each experimental stimulation-evoked dopamine response with low nMSE in all three animal models (Figure 3D, Table 2). In order to decrease the number of free parameters needed to describe each stimulation-evoked dopamine response, model parameters were separated into subject-specific (Q , T_1 , T_2 , and reuptake parameters) and response-specific ($[DA]_{p1}$ and $[DA]_{p2}$) parameters. Subject-specific parameters described the rates of reuptake and transfer between model compartments. Response-specific parameters described individual components of release that result from the specific stimulation parameters applied. This approach allowed each stimulation-evoked dopamine release to be described by just two parameters, while only minimally decreasing the nMSE of the fit (Figure 3F,G, Table 2). When the compartmental model was applied to the recorded stimulation responses, both $[DA]_{p1}$ and $[DA]_{p2}$ increased nonlinearly with increases in amplitude (Figure 4A,C) and pulse width (Figure 4B,D). This is consistent with the expectation that stimulation-evoked dopamine increases as a function of stimulation amplitude and pulse width.

The multicompartmental model for dopamine kinetics described here builds upon a restricted diffusion model recently proposed by Walters and colleagues,^{12,24} which relies on a single component of dopamine release equivalent to $[DA]_{p1}$.¹² When applied to our stimulation-evoked dopamine release data, the Walters et al. model was capable of fitting individual dopamine release responses (results not shown). However, the Walters model was unable to accurately characterize the initial dopamine kinetics and peak concentration in response to varying stimulation parameters, when subject-specific parameters were used (Figure 3E). In our multicompartment model, the maximum $[DA]_{p1}$ value that can be evoked remained constant over the duration of each experimental session, while the maximum evocable value of $[DA]_{p2}$ decreased exponentially (Figure 4F). Previous studies of dopamine release in the dorsal striatum suggest that there are multiple spatial domains exhibiting fast and slow dopamine release kinetics.^{5,20,29} Specifically, these studies suggest that there is a slow background domain with small pockets of fast release interspersed throughout the dorsal striatum.²⁹ As such, fast scan cyclic voltammetry recordings may receive contributions from both fast and slow dopamine domains based on the specific anatomical location of the recording electrode. Thus, $[DA]_{p1}$ may describe the magnitude of dopamine release from slow domains around the recording electrode, while $[DA]_{p2}$ may describe the magnitude from fast domains around the recording electrode. However, additional research incorporating pharmacological interventions that differentially manipulate fast and slow domains is required to validate the physiological significance of these model parameters.²⁹

Predictive models trained on the subject-specific parameters of the compartmental model accurately characterized the relationship between stimulation parameters and evoked dopaminergic responses (Figure 2) for all stimulation-evoked neurochemical responses and for all stimuli. These predictors were based on ANNs due to their ability to learn the input/output transfer functions without *a priori* knowledge of the nonlinear system dynamics and their excellent generalization capabilities.^{30,31} Using this approach, the 30 s of neurochemical responses that followed the onset of each stimulation event were modeled. The trained ANN models resulted in successful prediction of the kinetic changes in dopamine responses evoked by novel stimulation parameters (i.e., not used during training) across all three animal models ($R^2 = 0.86$ for rodent, $R^2 = 0.93$ for swine, $R^2 = 0.96$ for NHP) (Figure 5, Table 3). The subject-specific model parameters remained constant during each experiment, while response-specific parameters were identified for each evoked response in a given experiment. This resulted in reduced ANN complexity and training time, as well as improved system performance as determined by low MSE values. A sensitivity analysis on the fitting performance revealed that the optimal predictive performance (i.e., lowest fitting MSE) for the rodent data was obtained when 9 ± 7 hidden neurons were used to train the model. For the swine and NHP data, optimal performance was observed when 14 ± 6 and 8 hidden neurons, respectively, were used.

Time-Series Characterization and Prediction of Stimulation-Evoked Neurochemical Release

The Stone–Weierstrass theorem suggests that time series based on Volterra series can approximate a nonlinear system to any desired precision as long as the polynomial order is sufficiently large.³² Based on this theorem, Volterra kernels are capable of modeling the nonlinear dynamics between stimuli and the corresponding evoked dopamine responses as a function of time. Herein, time-series analysis with Volterra kernels successfully described the stimulation-evoked dopamine responses with high coefficients of determination ($R^2 = 0.83$ for rodent, $R^2 = 0.90$ for swine, $R^2 = 0.98$ for NHP) under a wide range of stimulation parameters and across all three animal models (Figure 6, Table 4).

The Volterra predictor of stimulation-evoked dopamine release presented here is based on a sequence of stimuli, rather than on the parameters from one individual stimulus. This is crucial for understanding the dependence of dopamine release on previous stimuli and stimuli sequences. The trade-off was the exponential growth of the unknown model parameters, which could lead to overfitting of the data. The use of second and third order Volterra kernels greatly reduced the dopamine response prediction error (Table 5). However, third-order kernels resulted in overfitting of the test data. For the test data, the second-order kernel offered the best predictive performance (nMSE = 5.7). The number of model parameters also grew exponentially as a function of kernel order, resulting in $1 + L$ unknown parameters for the first order model, $1 + L + LK$ for the second-order model, and $1 + L + LK + LKK$ for the third-order model (eq 8). Ridge regression showed the lowest nMSE when a second-order kernel with $K = 10$ basis functions and a regularization value $\lambda = 0.13$ were used (eq 10). An unbiased estimate of the model parameters required a large amount of input/output data. Unfortunately, the experimental data collected for each subject was limited to approximately 2000 stimuli within a period of 5 h. With a time resolution of 100

ms and a history dependence of 180 to 300 s, the number of free model parameters with a second order approximation corresponded to more than one million. Therefore, it is paramount to carefully select specific kernels and kernel order in order to fit the problem at hand while minimizing the number of parameters required.

Appropriate basis functions were identified using principal component analysis and Ridge regression regularization. This prevented excessive growth of the free parameters and allowed characterization of the kinetics of dopamine release for single and paired stimuli, while reducing the probability of overfitting the training data. The basis functions of the first and second order kernels were chosen using the first 4 ± 3 principal components of the experimental data (i.e., FSCV signals measured) and the first 10 principal components of exponential decay functions (eq 11), which resulted in a balance between improved fit performance and reduced computational cost. The use of these 10 basis functions reduced model complexity for the second and higher order kernels without compromising model performance. In this model, the first order kernel and the first dimension of the second order kernel represent the kinetics of dopamine release (Figure 7). The kernels identified for all three animal models showed a decaying exponential behavior.

The predictive ability of the second-order Volterra model evaluated on the 30 s of data following each stimulus onset, as well as the complete time-series (including time between stimuli), is shown in Figures 6 and 8, respectively. Considerable variation in performance was observed across data sets (Table 4). Despite the ability to predict the responses to trains of stimuli, the nMSE for prediction of the complete time series was greater than the error calculated from predicting the 30 s of data immediately following each stimulation event. The Volterra model showed the largest errors when predicting swine responses (Table 4) because the measured FSCV background currents defining the baseline for all measurements showed significant shifts during the course of an experiment (Figure 9B). In contrast, the Volterra model exhibited the lowest error when predicting the NHP data due to a particularly stable baseline for this data set.

Changes in baseline, also known as background current, can be the result of faradaic currents caused by unrelated neurochemical events such as changes in ion concentration, release of other electroactive neurochemicals, pH changes, biofouling, and dissolution of the recording electrode.^{10,33–35} These fluctuations in the measured current cannot be described by the relationship between stimulation parameters and evoked responses and, therefore, negatively affected model performance. To improve characterization of the phasic dopaminergic signals, baseline was subtracted from the experimental data by applying a detrending algorithm prior to model training. However, rapid baseline fluctuations negatively affected the measurement of phasic responses to stimuli, which decreased model performance and increased prediction errors (Figure 9B). Prediction errors were further increased by the presence of stimulus artifacts in the FSCV recordings (Figure 9A). Interleaving stimulation with the FSCV waveform minimized the effect of stimulus artifacts.³⁶

Comparison of Parametric and Time-Series Approaches for Prediction of Stimulation-Evoked Neurochemical Release

Volterra kernels were able to predict neurochemical release evoked by stimulation by taking into account previous stimulation-evoked responses. The ability of Volterra kernels to characterize and describe the dependence of neurochemical responses on previous stimuli sequences offers a significant advantage for designing algorithms for optimal characterization and ultimately control of dopamine release. Additionally, the flexibility of the Volterra kernel approach makes it applicable to other neurotransmitters, anatomical targets for stimulation and neurochemical sensing, and animal models with little or no modification. However, Volterra kernels were sensitive to noise and baseline shifts and did not adapt to changing environmental factors in real time. In contrast, models based on ANNs were less sensitive to noise and baseline shifts and could easily be adapted by adjusting the ANN weights based on novel data in real-time. Additionally, the parametric approach used for extracting ANN features greatly reduced the number of parameters required to characterize stimulation-evoked experimental data, thereby reducing computational complexity and making the development of an embedded implantable control system a real possibility. On the other hand, the compartmental model used to describe striatal dopamine release may require adjustments in order to model other neurochemicals or brain regions or even to reflect changes in release, diffusion, and reuptake mechanisms during disease progression. The ANN approach is not dependent on the history of previous stimulation. In contrast, Volterra series approaches relies on historical data. Therefore, the ANN greatly benefits from randomly selected data sets as a way to learn the relationship between inputs and outputs without learning the effects of hysteresis. Conversely, the Volterra series approach inherently requires contiguously selected data. In order to take full advantage of both modeling techniques and allow the best comparison of the two models, different test data from the same experiments were used to test each modeling technique. However, a comparison of performance on the same test data was completed by retraining the ANN model using the training and test data as used for the Volterra kernel approach (Table 6). Although this provides a direct comparison of the two modeling approaches on the same test data set, the training of the ANN model is suboptimal due to the potential of biasing the network with sequential training and test data. The general frameworks described herein were applied to measurements of neurochemical signaling but could also be applicable to the analysis of electrophysiological activity.^{23,37–41} Overall, both ANN and Volterra kernel-based approaches successfully modeled the nonlinear and time-variant relationships between stimulation parameters and evoked dopamine release responses for all three animal models. Thus, it is likely that optimal characterization of stimulation-evoked dopamine responses may require a combination of parametric and time-series approaches and that optimal architecture configuration will depend on the desired application.

CONCLUSIONS

In this paper, we present two novel mathematical frameworks for characterizing *in vivo* neurochemical dynamics evoked by electrical stimulation. This mathematical characterization was achieved by mapping the forward relationship between stimulation amplitude and pulse width, and the instantaneous changes in extracellular dopamine

concentration evoked by electrical stimulation in rodent, swine, and non-human primate brains. The frameworks presented herein include mathematical models that enable novel preclinical studies where control of neurochemical responses can be used to study the specific roles of dopamine, adenosine, serotonin, and other important neurotransmitters during normal physiologic and pathologic brain function. Although striatal dopaminergic signaling in a healthy brain was the focus of the experiments presented herein, both mathematical models, based on ANNs and Volterra kernels, can be extended to other neurochemical transmitters, sensing and stimulation paradigms, anatomical targets, and different neurologic disorders.

In addition to characterizing neurochemical responses, both modeling frameworks accurately predicted stimulation-evoked dopamine release in response to novel stimuli not used experimentally (Figures 5 and 6), which is paramount for enabling precise control of extracellular neurotransmitter concentration. In this way, these mathematical models will facilitate novel studies into the role of extracellular dopamine and other neurotransmitters in neurologic health and disease, as well as leading to the development of precision therapeutic interventions.

METHODS

Animal Subjects

Stimulation-evoked dopaminergic responses were studied in 12 female Sprague-Dawley rats weighing 250–350 g, four male young adult pigs age 8–12 months weighing 25–35 kg, and one male non-human primate rhesus macaque three years of age. Rodents were kept in social housing, while swine and the NHP remained in individual areas. All animals were kept on a 12-h light/dark cycle at a constant temperature (21 °C) and humidity (45%) and were fed once daily, with *ad libitum* access to water. All animal studies were performed *in vivo* with approval from the Mayo Clinic Institutional Animal Care and Use Committee (IACUC) and following National Institutes of Health (NIH) guidelines for animal research.

Surgical Procedure

Rodents were sedated prior to surgery with intraperitoneal urethane (1.5 g/kg in a 0.26 g/mL). Swine were sedated with intramuscular Telazol (6 mg/kg) and xylazine (2 mg/kg), which was followed by intubation and inhalation anesthesia,⁴² and the NHP was sedated with intramuscular ketamine (10 mg/kg) and xylazine (0.5 mg/kg), followed by intubation and inhalation anesthesia. Anesthesia was maintained for both swine and NHP studies using 1.5–3% isoflurane during electrode implantation and 1.5–2% isoflurane during the rest of the experiment. Analgesia was maintained with intramuscular buprenorphine for both rodents and pigs (0.06 mg/kg rodents, 0.03 mg/kg in swine) and intramuscular buprenorphine slow release (SR) for NHP (0.06 mg/kg). For swine and NHP, SpO₂ (100), heart rate (70–110 bpm for swine and 100–130 bpm for NHP), blood pressure (110/80 mmHg for swine and 98 ± 17/54 ± 13 mmHg for NHP), and core body temperature (36–38 °C) were continuously monitored to ensure proper anesthesia depth and to determine overall animal welfare. Additionally, vecuronium (3 mg intravenous bolus, followed by a 17

mg/h intravenous drip) was administered to swine during neurochemical recording to prevent motion artifacts induced by electrical stimulation.

During the surgical procedure, anesthetized swine and NHP were secured in a custom-made stereotactic frame.^{28,43} Rodents were placed in a Kopf stereotactic system (David Kopf Instruments, Tujunga, CA). A scalp incision (1.5–2.0 cm for rodents, 5–7 cm for swine and NHP) was made to expose the skull, and three trephine burr holes (approximately 3 and 7 mm in diameter for rodent and large animals, respectively) were drilled to allow implantation of the stimulating, neurochemical sensing, and reference electrodes (Figure 1A,B).

Stereotactic Targeting and Electrode Implantation

To implant the electrodes in rodents, the stereotactic coordinates of the medial forebrain bundle (MFB) and striatum with respect to bregma were obtained according to a rat brain atlas.⁴⁴ A dual manipulator stereotactic system (David Kopf Instruments, Tujunga, CA) was used to insert a bipolar stimulating electrode (stainless steel, 250 μ m diameter, 20 mm long polyimide-coated shaft, PlasticsOne, Roanoke, VA) into the rodent MFB. The same stereotactic system was used to implant a custom-made carbon fiber microelectrode (CFM) into the rat striatum for neurochemical sensing via fast-scan cyclic voltammetry. The stimulating and FSCV electrode coordinates are given in Table 7. A silver/silver-chloride FSCV reference electrode was implanted into the contralateral hemisphere.

For both the swine and NHP models, preoperative 3T MRI was used to identify the location of the striatal and ventro tegmental area/substantia nigra pars compacta (VTA/SNc) targets. The stereotactic targets and electrode trajectories were defined using the COMPASS stereotactic targeting platform (COMPASS International Innovations, Rochester, MN) and anatomical brain atlases (Figure 1A,B).^{45–47} A six-contact stimulating electrode (0.625 mm in diameter and 0.5 mm height, separated by 0.5 mm) (NuMed, Hopkinton, NY) was implanted into the VTA/SNc region. Electrode insertion was individually controlled for the stimulating and FSCV electrodes using a computer-driven microdrive (Alpha Omega Co., Alpharetta, GA). The lead of the stimulating electrode was secured to the skull using bone screws and retaining plate. In contrast, the FSCV electrode was held at its target location via the stereotactic head frame.

Deep Brain Stimulation for Characterization of Dopaminergic Response

Subsequent to stereotactic targeting and electrode implantation, the target region (MFB for rats and SNc/VTA for swine and NHP) was stimulated using a comprehensive range of stimulation parameters (Table 1). Simultaneously, the magnitudes and temporal patterns of dopamine release evoked by stimulation were measured. The minimum and maximum stimulation amplitudes leading to threshold and saturation dopamine responses when the pulse width was held constant at 0.2 ms were identified. Then, pulse width values were identified that lead to threshold and saturation dopamine responses when amplitude was held at the previously identified maximum value. Each combination of stimulation parameters was presented in random order to identify system dynamics while eliminating the effects of

hysteresis. Each stimulation event was followed by a dopamine stabilization period of 3–5 min.

Neurochemical Recording of Stimulation-Evoked Dopamine Responses

Stimulation-evoked dopamine responses were measured within the ipsilateral striatum using FSCV.^{10,48–50} A triangular FSCV waveform was created by ramping the microelectrode potential at 400 V/s from a resting value of -0.4 V to a maximum of 1.5 V, before ramping the potential back to the resting value (Figure 1E). This waveform was repeated at 10 Hz with the CFM held at the resting potential between scans. The magnitude of the dopamine oxidation current, typically detected at $+0.6$ V on the triangular FSCV waveform (Figure 1C,D), was measured and converted to dopamine concentration using postoperative *in vitro* calibration of each CFM.⁵¹ Calibration was performed by placing each CFM in a flowing stream of Tris buffer solution to which multiple 5 s boluses of a sodium chloride dopamine solution (i.e., 0.1 μ M, 0.5 μ M, 1.0 μ M) were injected via an electronic loop injector (FIALab Instruments, Seattle, WA) at 6 mL/min. FSCV was performed to identify the relationships between injected dopamine concentrations and the corresponding oxidation currents measured by the CFM.

Parametric Characterization and Prediction of Stimulation-Evoked Neurochemical Release

In vivo stimulation-evoked striatal dopamine responses measured by FSCV were characterized using parametric models of release and reuptake (Figure 3A) based on biological kinetics and compartmental models.^{12,13,24} This mathematical model consisted of three coupled differential equations that describe the concentration of stimulation-evoked dopamine, [DA], across three compartments C_1 , C_2 , and C_3 ([DA] _{C_1} , [DA] _{C_2} , and [DA] _{C_3} , respectively). Compartment C_3 represents the dopamine concentration at the FSCV electrode, and all three compartments are abstract mathematical constructs used to model dopamine release and transfer processes and are not associated with any anatomical structures (Figure 3A). In this model, dopamine released into compartment C_1 ([DA] _{C_1}) is described by eq 1 and occurs during stimulation at a rate proportional to the stimulation frequency (f) and a concentration increase of [DA]_{p1} per pulse of stimulation. Dopamine transfer from C_1 to C_3 is described by a rate constant T_1 . Dopamine concentration in compartment 2 ([DA] _{C_2}) is described using similar processes of release and transfer as those used for compartment C_1 (eq 1) plus an additional exponential decay at a rate Q . Dopamine transfer from compartment C_2 to compartment C_3 is defined by rate T_2 .

The parameter [DA]_{p1} describes a component of dopamine release that remains constant during stimulation (eq 1). Similarly, the parameter [DA]_{p2} describes an exponentially decreasing component found in dopamine release (eq 2). The dopamine concentration measured by FSCV is represented by [DA] _{C_3} , which depends on dopamine reuptake and transfer from C_1 and C_2 . A volume correction for compartment C_3 is defined by V_{C3} and was set as 10^6 μ m³ as described in previous literature.^{12,24}

Equation 3a describes the dopamine concentration measured by FSCV in the NHP subject. Here, dopamine reuptake was modeled as a continuous process that obeys Michaelis-Menten kinetics.¹⁴ In contrast, eq 3b describes the dopamine concentration measured by FSCV in

the rodent and swine subjects. In this case, dopamine reuptake was modeled as a first order kinetic process with a rate R . This approximates Michaelis-Menten kinetics when $[DA]_{C3} \ll$

K_m with $R = \frac{V_{max}}{K_m}$, where V_{max} defines the maximum reuptake rate and K_m represents the substrate concentration at which the reaction rate is half of V_{max} . Changes in extracellular dopamine concentration ($[DA]_{C3}$) evoked during stimulation were determined by solving the following system of differential equations:

$$\frac{d[DA]_{C1}}{dt} = f[DA]_{p1} - T_1[DA]_{C1} \quad (1)$$

$$\frac{d[DA]_{C2}}{dt} = f[DA]_{p2}e^{-Qt} - T_2[DA]_{C2} \quad (2)$$

$$\frac{d[DA]_{C3}}{dt} = \frac{T_1[DA]_{C1} + T_2[DA]_{C2}}{V_{C3}} - \frac{V_{max}}{K_m/[DA]_{C3} + 1} \quad (3a)$$

$$\frac{d[DA]_{C3}}{dt} = \frac{T_1[DA]_{C1} + T_2[DA]_{C2}}{V_{C3}} - R[DA]_{C3} \quad (3b)$$

At the end of stimulation, the stimuli-dependent release described in eqs 1 and 2 disappears, and the equations become

$$\frac{d[DA]_{C1}}{dt} = -T_1[DA]_{C1} \quad (4)$$

$$\frac{d[DA]_{C2}}{dt} = -T_2[DA]_{C2} \quad (5)$$

while eq 3 remains unchanged. Additionally, the measured dopamine signal depends on the temporal response of dopamine measurement via FSCV, which is primarily affected by adsorption/deadsorption of dopamine at the electrode interface and needs to be accounted for by using impulse response function. In particular, the kinetics of adsorption/deadsorption of dopamine and dopamine- o -quinone are described in eq 6^{52,53}

where DA_{soln} and DOQ_{soln} correspond to dopamine and dopamine-*o*-quinone dissolved in solution, DA_{ads} and DOQ_{ads} correspond to dopamine and dopamine-*o*-quinone adsorbed at the carbon fiber microelectrode, k_1 and k_2 describe the adsorption rate constants, and k_{-1} and k_{-2} describe the desorption rate constants. $F_a(m)$ represents the impulse response function for measurement of dopamine at the CFM (Figure 3C) and is given by⁵³

$$F_a(m) = e^{-(m+1)(k_{-1}\tau + k_{-2}t_2)} \quad (7)$$

where m is the FSCV scan number, τ is the time during the FSCV scan over which dopamine is adsorbed, and T_s is the time over which dopamine is being oxidized. The parameters τ and T_s were determined from the FSCV repetition and scan rates, respectively (Figure 1E). The desorption rate constants k_{-1} and k_{-2} were determined *in vitro* by averaging the least-squares fits of three CFMs to three 0.5 μM bolus injections of dopamine delivered over 2 s each. Taking into account the temporal response of dopamine measurement via FSCV, the measured dopamine oxidation current was calculated by convolving the response measured at the CFM ($F_a(m)$) with the extracellular dopamine concentration ($[\text{DA}]_{\text{C3}}$)

$$y(t) = F_a(m)[\text{DA}]_{\text{C3}}(t) \quad (8)$$

where $y(t)$ describes the dopamine oxidation current measured with FSCV at the CFM.

The model parameters describing the stimulation-evoked dopamine responses for each subject were identified by performing a nonlinear least-squares fit of the kinetic model to a series of intrasubject experimental responses (i.e., global fit). Herein, kinetic model parameter values obtained using a global fit are referred to as subject-specific values, while parameter values that differ across individual responses are referred to as response-specific values. Global parameter fit was repeated using 20 different initial conditions to prevent getting caught in local minima. Initial parameters were selected according to previous experience and values reported in the literature.^{12,24} Subject-specific values for T_2 and Q were calculated by performing a second global fit using the previously calculated values for T_1 and reuptake (R or V_{max} and K_m), while the response-specific values, $[\text{DA}]_{\text{p1}}$ and $[\text{DA}]_{\text{p2}}$, were calculated by fitting each individual dopamine response using the subject-specific parameters for T_1 , T_2 , Q , and reuptake.

Following mathematical parametrization, the nonlinear and time-varying relationships between stimulation-evoked dopamine kinetics and stimulation parameters were characterized for each experimental data set using a multilayer feed-forward artificial neural network (ANN) in order to predict stimulation-evoked responses for novel stimuli not used

for model training. This ANN model, or system model, was implemented using Matlab (The Mathworks, Natick, MA) via a double layer feed forward ANN with sigmoidal and linear transfer functions in the hidden and output layers, respectively. The system model consisted of three inputs (pulse amplitude, pulse width, and time since the beginning of stimulation), H hidden neurons, and two outputs (changes in dopamine concentration $[DA]_{p1}$ and $[DA]_{p2}$). The network weights and biases were initialized using random values prior to training the system model using the Levenberg-Marquardt backpropagation algorithm. A sensitivity analysis was performed for each experimental data set to optimize the number of neurons in the hidden layer from 5 to 20 hidden neurons. Additionally, ten ANNs were trained using random initial weights and biases, and the ANN with the lowest validation mean square error was selected.

Time-Series Characterization and Prediction of Stimulation-Evoked Neurochemical Release

In addition to the parametric characterization and prediction described in the previous section, a time series approach based on Volterra kernels was used to characterize the dopaminergic responses evoked by electrical stimulation, $y(t)$:

$$y(t) = h_0 + \sum_{t_1} h_1(t_1)x(t-t_1) + \sum_{t_1} \sum_{t_2} h_2(t_1, t_2)x(t-t_1)x(t-t_2) + \sum_{t_1} \sum_{t_2} \sum_{t_3} h_3(t_1, t_2, t_3)x(t-t_1)x(t-t_2)x(t-t_3) + \dots \quad (9)$$

where $x(t)$ describes electrical stimuli at time t and h_i describes the Volterra kernels of order i that approximate the kinetics of dopamine release. The Volterra kernels were approximated using a weighted sum of finite length basis functions

$$h_1(t_1) = \sum_{l=1}^L b_l B_l(t_1) \quad (10a)$$

$$h_2(t_1, t_2) = M(t_1)N(t_2) \quad (10b)$$

$$M(t_1) = \sum_{l=1}^L k_l B_l(t_1) \quad (10c)$$

$$N(t_2) = \sum_{k=1}^K c_k C_k(t_2) \quad (10d)$$

$$h_3(t_1, t_2, t_3) = M(t_1)N_1(t_2)N_2(t_3) \quad (10e)$$

$$M(t_1) = \sum_{l=1}^L p_l B_l(t_1) \quad (10f)$$

$$N_1(t_2) = \sum_{k=1}^K f_k C_k(t_2) \quad (10g)$$

$$N_2(t_3) = \sum_{k=1}^K g_k C_k(t_3) \quad (10h)$$

where B_l is the l th basis of the h_1 kernel defined by the first L principal components selected from normalized dopamine release data, b_l represents the unknown parameters in the first-order Volterra model h_1 , M describes the dopamine release evoked by the current stimulus, N describes the combined effect of previous stimuli on the current stimulation-evoked dopamine response for the second and higher order Volterra models, K represents the number of principal components selected for the previous stimuli, $T_1 - T_2$ and $T_2 - T_3$ describe the time between the current and previous stimuli, and C_k is the k th basis function and determines the dependence of dopamine release on previous stimuli separated by time t_d . C_k is defined by a principal component expansion of decaying exponentials of the form

$$\{e^{-\alpha t_d}, t_d e^{-\alpha t_d}, t_d^2 e^{-\alpha t_d}, t_d^3 e^{-\alpha t_d}, \dots\} \alpha \in \{\varepsilon, \alpha_{\max}\} \quad (11)$$

A principal component analysis (PCA) of the stimulation-evoked dopamine response was performed for the first order kernel to determine the number of optimal principal components (i.e., principal components whose eigenvalues were greater than 1% of the largest eigenvalue), and thus the number of basis functions, L . The length of these basis functions for the first-order kernel was defined as the minimum time between adjacent stimuli. In contrast, the length of the basis for the second and higher order kernels was set to 100 s. A sample data set from each animal model was analyzed to determine the appropriate Volterra kernel order that did not result in overfitting. The unknown coefficients of the basis functions, W , were estimated using least-squares optimization via Ridge regression⁵⁴ as follows:

$$Y_{n \times 1} = A_{n \times p} W_{p \times 1} \quad (12)$$

$$\hat{\mathbf{W}} = (\mathbf{A}^T \mathbf{A} + \lambda \mathbf{I})^{-1} \mathbf{A}^T \mathbf{Y} \quad (13)$$

where $\mathbf{Y}$ is the measured stimulation-evoked dopamine, $\mathbf{A}$ is defined by the linear convolution of the input stimuli and the model basis functions, n represents the length of the time series, p defines the number of unknown parameters (basis weights, $b_k, k, c_k, \dots$ plus a bias term, h_0), λ is the ridge regularization parameter; and $\mathbf{I}$ represents the identity matrix. When λ is zero, eq 13 becomes the solution of the least-squares optimization. Prior to fitting the stimulation-evoked responses using Volterra kernels, experimental data were detrended using a moving average filter with a 400 s time window, which allowed retention of phasic responses throughout the time series. Once the free parameters $\mathbf{W}$ were estimated from the detrended FSCV data, eq 12 predicted dopamine responses evoked by novel stimuli.

Training and Evaluation of the Dopaminergic Response Predictors

Both Volterra and ANN predictor models were trained and tested on experimental stimulation-evoked dopamine responses recorded using FSCV data from rodent, swine, and NHP models of electrical stimulation. The experimental data from each subject was divided into smaller subsets encompassing 70%, 15%, and 15% of the data for training, validation, and testing, respectively. For the Volterra kernel model, the first 70% of the measured FSCV data was used for training and the subsequent 15% of the data was used to evaluate model performance. The remaining 15% of the data were ignored to allow a direct comparison of the performance between the parametric and time-series approaches on the same amount of data. Hyperparameters of the Volterra kernel model (e.g., the number of basis functions, type of regression (lasso vs ridge), and regularization parameters) were optimized to improve model performance on the validation data (one data set from each species). The optimal Volterra kernel order was selected based on an F-test and considering computational cost necessary to lower validation error. This analysis was performed on a restricted data set due to the computational time involved.

For the parametric ANN model, the data for each category (i.e., training, validation, and test) was selected at random. Validation data was used to prevent overfitting and estimate generalization error, while test data was used only for evaluating model performance. Network complexity was controlled by early stopping once the smallest prediction error with respect to the validation data set was obtained.⁵⁵ As an additional way to compare the ANN and Volterra kernel approaches, both were evaluated on the same sequentially acquired test data.

Model performance was evaluated for each model using their respective test data sets. For the Volterra kernel model, the predictive performance was analyzed for the entire testing data set as well as for a shorter response period of 30 s following each stimulus to allow for direct comparison with the parametric model. Finally, the performance of both parametric and time-series predictors was determined by calculating the mean squared error (MSE) between the dopamine responses predicted by the model in response to novel stimuli, and

the corresponding responses measured experimentally *in vivo*—normalized by the product of the mean of experimental and predicted responses (nMSE).

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Figure 1.

Representative experimental setup as conducted in the swine model of electrical stimulation. (A) A stimulating electrode was implanted in the substantia nigra pars compacta (SNc)/ventro tegmental area (VTA). (B) A carbon fiber microelectrode (CFM) was implanted in the anterior caudate. Electrode position shown is from coregistration of the preoperative targeting MRI with a 3D pig atlas (ref 47). (C) A representative cyclic voltammogram for dopamine obtained using fast scan cyclic voltammetry (FSCV). The voltammogram shows a dopamine oxidation peak at 0.6 V as well as a dopamine reduction peak at -0.2 V. (D)

Pseudocolor representation of a FSCV recording showing dopamine release in response to a stimulus (4.75 V, 0.6 ms, 130 Hz, 260 pulses). (E) Triangular FSCV waveform repeated at 10 Hz that was used for recording extracellular changes in dopamine concentration evoked by deep brain stimulation.

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Figure 2.

Peak stimulation-evoked dopamine release response as a function of stimulation amplitude (A, C, E) and pulse width (B, D, F) in the rat, swine, and non-human primate (NHP) model of electrical stimulation, respectively. Experimentally recorded peak values are shown by single dots with color corresponding to amplitude or pulse width of the applied stimulation. To show stimulus amplitude and pulse width related trends in the data correspondingly colored smoothing splines were fit using data in Matlab (The Mathworks, Natick, MA).

NHP data (E, F) at other pulse widths and amplitudes contain a limited number of data points and are not shown for clarity.

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Figure 3.

Mathematical model of dopamine release evoked by electrical stimulation. (A) Compartment model used to describe the kinetics of dopamine (DA) release; C1, C2, and C3 are compartments 1, 2, and 3, respectively; f is the frequency of stimulation; $[DA]_{p1}$ and $[DA]_{p2}$ are DA concentration increases that occur in C1 and C2 with each pulse of stimulation; Q is the rate of attenuation of release into C2 with time; T_1 and T_2 are transfer rates between compartments; reuptake is a process that follows either linear or Michaelis-Menten kinetics depending on the animal model. (B) Impulse response function used to describe dopamine

concentration [DA] at a carbon fiber microelectrode. (C) Dopamine concentration in C1 and C2 ([DA]C1 and [DA]C2) in response to a stimulus of (4 V, 0.5 ms, 130 Hz, 390 pulses) intensity in a swine model of electrical stimulation. (D) Fits of the kinetic model data to stimulation-evoked dopamine responses measured using fast scan cyclic voltammetry (FSCV) in rodent, swine, and non-human primate models of electrical stimulation. (E) Dopamine responses modeled using the kinetic model described by Walters et al.^{12,24} to five stimulation-evoked dopamine release responses measured over 2 h from a single subject. These modeled responses relied on subject-specific transfer and reuptake parameters. (F) Fit of our kinetic model to the same dopamine release responses using subject-specific parameters for R , T_1 , T_2 , and reuptake. (G) Fit of our kinetic model to the same responses using a combination of subject-specific and response-specific parameters for each stimulation-evoked response.

Figure 4.

Result of fitting the kinetic model to a representative data set from a swine model of electrical stimulation. (A) The concentrations of dopamine (DA) released into compartment 1 of the kinetic model ($[DA]_{p1}$), shown as a function of amplitude. (B) The concentrations of dopamine (DA) released into compartment 1 of the kinetic model ($[DA]_{p2}$), shown as a function of amplitude. (C, D) The relationships between $[DA]_{p1}$ and $[DA]_{p2}$, respectively, and pulse width. To show stimulus amplitude and pulse width related trends in the data correspondingly colored smoothing splines were fit using data in Matlab (The Mathworks,

Natick, MA). (E) The concentration $[DA]_{p1}$ for each stimulation-evoked release shown as a function of time. (F) The concentration of $[DA]_{p2}$ for each release shown as a function of time. There is a clear decrease in the maximal $[DA]_{p2}$ that can be evoked over time. This relationship is shown by fitting a declining exponential to the data filtered with a 500 s window maximum filter.

Figure 5.

Predictions of stimulation-evoked dopamine release for 30 s of data following each test stimulation using artificial neural networks coupled with the parametric model of dopamine kinetics shown in Figure 2. Measured and predicted dopamine release responses from representative rodent (A), swine (C), and non-human primate (E) subjects. Correlation between the measured and predicted dopamine release responses for all rodent (B), swine (D), and non-human primate (F) subjects. The dopamine oxidation current measured for the first 30 s following each test stimulation is shown by the black dots.

Figure 6.

Predictions of stimulation-evoked dopamine release for 30 s of data following each test stimulation using the second order Volterra kernel modeling approach. Measured and predicted dopamine release responses from representative rodent (A), swine (C), and non-human primate (E) subjects. Correlation between the measured and predicted dopamine release responses for all rodent (B), swine (D), and non-human primate (F) subjects. The dopamine oxidation current measured for the first 30 s following each test stimulation is shown by the black dots.

Figure 7. Volterra kernels trained using experimental stimulation-evoked dopamine release responses. First-order Volterra kernels created for rodent (A), swine (D), and non-human primate (G) data. Subject-specific kernels are shown using gray lines. The average kernel behavior is shown using a red line. Second order Volterra kernels created for rodent (B,C), swine (E,F), and nonhuman primate (H,I) data. For clarity, the average kernel is shown from two complementary viewing angles.

Figure 8.

Predictions of stimulation-evoked dopamine release using the second order Volterra kernel modeling approach. (A) Representative example of measured (red lines) and predicted (dotted black lines) stimulation-evoked dopamine release responses in (A) rodent, (C) swine, and (E) non-human primate models of electrical stimulation. Correlation between the measured and predicted dopamine release responses for all rodent (B), swine (D), and non-human primate (F) subjects. The dopamine oxidation current measured during the entire time-series is shown using black dots.

Figure 9.

Example of disturbance effects on the prediction (black dotted line) of experimentally measured stimulation-evoked dopamine release responses (red line) using Volterra kernels in one swine subject. (A) Model prediction is not affected despite the presence of a stimulation artifact observed in the recording. (B) Model prediction is negatively affected by fluctuations in baseline.

Table 1

Range of Stimulation Parameters Used to Evoke Dopaminergic Responses

	frequency (Hz)	pulse width (μ s)	amplitude	duration (s)
rodent	60–100	0.1–2.0	0.01–0.80 mA	1–2
swine	130	0.1–1.1	1.0–8.0 V	2–3
NHP	130	0.1–0.8	1.0–7.0 V	3

Table 2

Performance of the Kinetic Model in Fitting Stimulation-Evoked Dopaminergic Responses Recorded from All Three Animal Models^a

	nMSE	
	kinetic model (all data)	kinetic model with subject-specific parameters (all data)
rodent	0.18 (0.13)	0.33 (0.14)
swine	1.66 (0.63)	2.06 (0.79)
NHP	0.098	0.125

^aErrors reported correspond to fits obtained with and without using subject-specific reuptake and transfer rates for all responses in a data set. The normalized mean squared error (nMSE), standard deviation (STD), and correlation coefficient between experimental data and predicted responses are given for all three animal models.

Table 3

Performance of the Artificial Neural Network Predictors Evaluated on the Test Data Set (30 s Following Each Stimulus)^a

	nMSE (STD)	
	train	test
rodent	0.5 (0.2)	0.35 (0.33)
swine	3.7 (1.5)	1.8 (0.8)
NHP	0.21	0.13

^aThe normalized mean squared error (nMSE), standard deviation (STD), and correlation coefficient between experimental data and predicted responses are given for all three animal models.

Table 4Performance of the Second-Order Volterra Kernel and ANN Predictors^a

	Volterra kernels		ANN predictors
	time series	30 s post-stimulus	30 s post-stimulus
rodent	227.2 (75.6)	3.5 (1.8)	0.35 (0.33)
swine	2239.6 (109.3)	12.8 (5.8)	1.8 (0.8)
NHP	4345.3	1.5	0.13

^aPerformance is given by the normalized mean squared error and standard deviation (in parentheses) for all three animal models.

Table 5
Performance of the Volterra Kernel Models Evaluated on the Test Data Set for Different Kernel Orders^a

	<u>first-order Volterra kernel</u>		<u>second-order Volterra kernel</u>		<u>third-order Volterra kernel</u>	
	train	test	train	test	train	test
rodent	1.6 (1.3)	4.6 (6.1)	0.3 (0.2)	2.0 (3.1)	0.2 (0.1)	3.1 (3.7)
swine	133.5 (220.3)	13.1 (19.7)	12.4 (17.7)	5.7 (7.8)	2.9 (2.6)	6.0 (8.5)
NHP	2.3	1.5	0.9	1.5	0.8	1.8

^aThe normalized mean squared error (nMSE) and standard deviation (STD) between experimental data and predicted responses are given for all three animal models.

Table 6Performance of the Second-Order Volterra Kernel and ANN Predictors When Applied to the Same Test Data^a

	Volterra kernels, 30 s post-stimulus	ANN predictors, 30 s post-stimulus
rodent	3.5 (1.8)	0.97 (0.59)
swine	12.8 (5.8)	2.4 (3.7)
NHP	1.5	0.37

^aPlease note that although this provides a direct comparison of the two modeling approaches, the resulting performance of the ANN model is suboptimal due to the sequential selection of training data. Performance is given by the normalized mean squared error and standard deviation (in parentheses) for all three animal models.

Table 7Stereotactic Coordinates for Fast Scan Cyclic Voltammetry (FSCV) and Stimulating Electrodes^a

	AP (mm)	ML (mm)	DV (mm)
stimulation	−4.6	+1.2	−8.7
FSCV	+1.2	+2.0	−5.5

^aCoordinates are given in mm from bregma in the anteroposterior (AP), mediolateral (ML), and dorsoventral (DV) directions.