Vision and Goals Despite advances in performance of deep learning (DL) artificial neural networks (ANNs) on difficult control problems, most algorithms use abstract neurons and rely on massive amounts of data/energy. Neurobiological learning mechanisms differ from methods used to train ANNs. The brain only utilizes a small fraction of the energy of ANNs, and yet generates widely generalizable intelligence[1]. Bridging performance between these two types of systems is a major challenge that requires a paradigm shift in understanding how neural systems learn and adapt[2,3]. Efforts to meet this challenge are stymied by lack of detailed models grounded in brain imaging and electrophysiological data collected in well-defined behavioral conditions. We recently developed models of the sensorimotor cortex and trained them to play individual games including Pong and CartPole[4–6]. However, those models included representations from only a minimal set of local sensory and motor microcircuits, despite experimental evidence for wider representations of sensorimotor information across the brain. The brain's resting-state activity forms an efficient *global* information-processing backbone on top of which all other *local* task-specific computations take place[7,8]. Furthermore, those models lacked tuning to physiological neural data recorded during game-play. Therefore, leveraging brain-wide functional imaging and invasive recordings obtained during rest and behavior to tune computer models at multiple scales will be critical in advancing the field.

Our goal is to simultaneously record several datasets from humans and nonhuman primates (NHP) during resting-state and sensorimotor behaviors while subjects play games, and use the data to construct and optimize a whole-brain mean-field model of the brain interfaced with local thalamocortical microcircuits. The datasets will consist of fMRI and EEG signals, intracranial EEG (iEEG) signals, and laminar profiles of field potential signals obtained from NHP. The full set of multiscale dynamics will be implemented in models that integrate whole-brain dynamics based on human/NHP recordings and microcircuit dynamics based on NHP recordings. Models will incorporate dynamics during sensorimotor learning as well as skilled behavior, to enable generalized brain-wide distributed learning. Interfacing neocortical microcircuit models of biophysically-detailed spiking neurons into the whole-brain model, will offer an unparalleled look into the brain's multiscale interactions. We will train the integrated model to perform sensorimotor behaviors during game-play using biologically inspired learning algorithms that operate at whole-brain, cortical circuit, and single neuron levels through the following **Specific Aims (SA):**

SA1. Construct a whole-brain population-level model constrained by primate fMRI/EEG data. Each node in the whole-brain model will consist of a neural mass model with excitatory and inhibitory populations. We will base model structural connectivity on primate MRI and diffusion tensor imaging (DTI) data, and tune model connection weights to replicate functional connectivity patterns observed in the data. Spatially sparse EEG data will provide additional control to cross-validate temporal dynamics of models at corresponding nodes.

SA2. Construct detailed biophysical microcircuit models and integrate them with brain level models. Microcircuit models will consist of sensory and motor areas responsible for integrating information from simulated game environments and using the information to produce motor decisions. In each case, striatal inputs for reward modulation, and cerebellar inputs for fine-tuning motor actions will be identified and studied based on their known target layers[9–11]; they will be modeled by modulating activity in these layers. Microcircuit models will produce EEG/iEEG, and local field potential (LFP) signals directly comparable to and constrained by invasively recorded primate electrophysiology data, including laminar LFP and iEEG. Whole-brain models' population firing rates will drive synaptic activation in the microcircuits using non-homogeneous Poisson processes. In turn, neuronal firing rates from the microcircuit models will directly drive activity in the neural mass models.

SA3. Train the models to perform behaviors using biologically inspired learning rules. Our spike timing-dependent reinforcement learning and evolutionary algorithms span multiple temporal and spatial scales, ideal for training our models to perform behaviors in dynamic environments. We will first independently train microcircuit models, and then embed them within the whole-brain model, to enable microcircuits to use global brain dynamics and representations. We will assess performance of each type of model. Finally, we will compare model performance/efficiency against commonly used deep learning algorithms. We will perform the comparisons after learning single and multiple tasks, to assess both efficiency and generalizability.

Model development will build on open-source tools including the NEURON simulator[12,1312] and NetPyNE platform for multiscale brain circuit modeling[14]. For model simplification and enhanced efficiency, we will use BINDSnet[15] to simulate neuronal circuits on graphics processing units (GPUs). We will use the open-source The Virtual Brain (TVB) platform for whole-brain population-level modeling[16]. We recently

developed a co-simulation interface between NetPyNE and TVB, that bridges molecular, cellular, circuit and whole-brain network scales. Our end product will offer new open-source tools to the community that bridge noninvasive brain imaging data with detailed multiscale models of the brain and biological learning.

Approach and Methodology: We will integrate noninvasive brain imaging and invasively recorded electrophysiology data measured at multiple spatial/temporal scales with a novel brain model that encompass brain-wide and local microcircuit dynamics, combined with neurobiologically inspired learning algorithms. Our unique multiscale brain datasets will be obtained during resting state[17] and sensorimotor behavior. We will apply a suite of biological learning rules to train our model to perform the same behaviors as subjects. Our research goals are organized according to the above **SAs**.

SA1: Construct a whole-brain population-level model constrained by primate fMRI/EEG data. Each node of this model will consist of a neural mass model, with excitatory and inhibitory populations connectivity constrained using primate functional MRI and Diffusion Tensor Imaging (DTI) data. We will use a set of optimization algorithms, including evolutionary strategy (EVOL) algorithms to optimize the models to replicate functional connectivity patterns observed in the data[18]. This whole-brain model will serve as a *reservoir,* containing high-dimensional representations that can be harnessed for behavior[19].

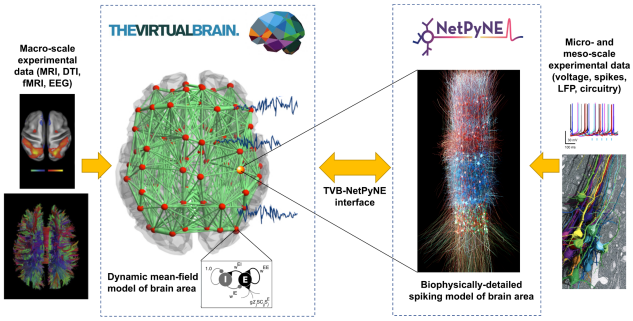

Figure 1: *Whole-brain multiscale model with interconnected nodes/regions modeled using population mean-field or biophysically detailed models. Biophysically detailed cortical models include dynamics at cellular and circuit scales, and will interact bidirectionally with the whole-brain dynamics simulated through a network of population mean-field models.*

Preliminary data: We have a unique dataset of simultaneously recorded primate fMRI and EEG signals obtained during resting state movie-watching experiments. This data was recently obtained from 20 participants across two sessions. The recordings utilize MRI-compatible electrodes, demonstrating feasibility of this simultaneous data collection method. We are writing a data descriptor manuscript, to release the data.

SA1.1: Perform primate fMRI/EEG experiments to assess dynamics at multiple spatial/temporal resolutions simultaneously. We will acquire data from 30 humans, and 2 NHP participants over the first 2 years of the project. We will first conduct the fMRI/EEG experiments during resting state, to provide a baseline for comparison with dynamics during sensorimotor behaviors. Resting state sessions will take ~30 minutes each. After, we will record from the same subjects performing a sensorimotor integration task. For the tasks, we will use Pong and CartPole video games on screen. Subjects will use a button box (2 buttons) and/or joystick from the fMRI system to control the game. At the end of the session we will acquire high angular resolution DTI data and structural MPRAGE scans.[20]

SA1.2: Construct whole-brain level model. Using the data collected in **SA1.1**, we will construct and optimize our whole-brain level models, by integrating fMRI and EEG data[21]. In our whole-brain models some nodes/regions will be population mean-field models, and others will be detailed neuronal network models (**Figs. 1,2**). The TVB-NetPyNE co-simulation tool will generate input/output signals from each type of model, linking interactions across cellular, circuit, and whole-brain scales. This will provide a unique method to investigate interactions between fMRI-based whole-brain functional activity and circuit/cellular components. Each whole-brain model will use structural/functional connectivity data obtained from one participant, optimizing connection weights so the model's functional connectivity matches patterns from the subject[18]. Next, we will optimize model functional connectivity during sensorimotor tasks to match subject data, by providing inputs representing game sensory stimuli. **Expected outcomes:** After optimization, our models will replicate functional connectivity patterns from the fMRI/EEG data that support efficient learning and behavior through high dimensional representations, similar to those used in reservoir computing[19]. **Pitfalls:** Optimization may not yield sufficiently realistic functional connectivity on large scale models. If this occurs, we can reduce the large-scale model to a few key areas, increasing chances of finding good solutions.

SA2: Construct detailed biophysical microcircuit models and integrate them with brain level models. We will develop biophysically detailed microcircuit models of sensory and motor cortices constrained by invasively recorded primate data during rest and task performance. Microcircuit models will produce EEG/iEEG, and laminar LFP signals directly comparable to and constrained by the invasively

recorded primate electrophysiology data. For cerebellar and Basal Ganglia circuits we will use open-source, detailed models previously developed[22–24]. We will embed these models within the whole-brain level field model, providing interactions between the different-scale brain areas.

Preliminary data: We use data from electrophysiology and circuit mapping experiments to develop detailed microcircuit models of the sensory, motor, and auditory system [25–27], as shown in **Figs. 1,2**. In this aim, we will first perform experiments to obtain new LFP,iEEG data, and use that data to optimize novel neocortical circuit models. Finally, we will integrate the neocortical microcircuit models, and cerebellar and striatal circuit models previously developed, with the whole-brain level field models developed in **SA1**.

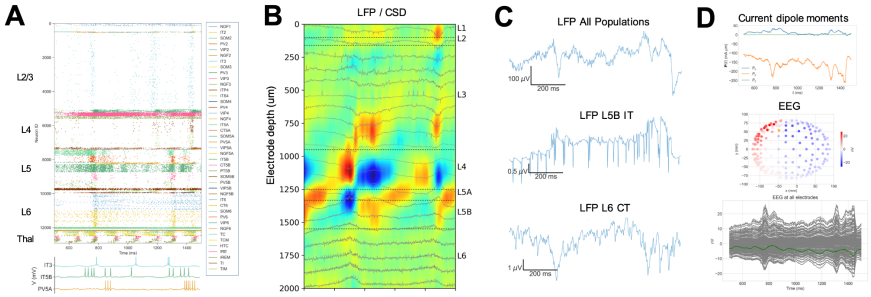

***Figure 2**: Detailed neocortical microcircuit model simulates recordings at multiple scales. **A)** Spiking raster plot and example neuron voltage traces. **B)** Laminar local field potential (LFP) overlaid over current source density analysis. **C)** Contribution of different populations to LFP. **D)** Current dipole moments and EEG at different electrodes.*

SA2.1: Perform primate LFP and human iEEG experiments to acquire invasively recorded signals at rest and during game-play. Laminar LFP records signals from all cortical layers, allowing dissecting the dynamics and contributions of each cortical layer to sensorimotor integration function from a single brain region. In contrast, iEEG signals cover a wider spatial extent, useful for optimizing multiple local microcircuits in the model. We will primarily aim to collect the data from motor areas associated with finger/hand movements during game play, sensorimotor integration (lateral intraparietal cortex), and motion-sensitive visual areas (MT), but will also collect data from the frontal eye fields. All of these regions are covered with iEEG electrodes in patients at Northwell with sufficient frequency to reach the proposed number of recordings, and are similarly accessible in NHP.

SA 2.2 Develop and optimize sensory and motor microcircuit models. Microcircuit models include multicompartment conductance-based neuron models with multiple ion channels and synapse types. Neuron densities, distribution, morphology and biophysics, and connectivity at long-range, local and dendritic scales, are constrained by experimental data. We use the NEURON simulator and NetPyNE multiscale modeling tool[14], facilitating development, parallel simulation, optimization, and analysis of our circuit models. We fit models using evolutionary/genetic algorithms and Bayesian optimization[26,28,29]; simulate EEG/iEEG using LFPy 2.0[30]; and fMRI BOLD-like signals using a new neurovascular coupling model, more accurate than the classic Balloon model[31,32]. We will use laminar LFP and iEEG data recorded from **SA2.1** to optimize circuit models to replicate oscillatory[33] and population-specific multi-unit firing patterns during rest and behavior. Optimization parameters include synaptic weight gains between populations of excitatory and inhibitory neurons, and background synaptic inputs.

SA2.3 Embed microcircuit models within large-scale brain models. Field/firing-rate models will bidirectionally interface with neocortical microcircuit models. To enable field→microcircuit interactions, we will periodically sample firing rates from field models to generate non-homogeneous Poisson spike trains of inputs to microcircuit synapses[34]. In the other direction, we will sample microcircuit spiking activity to drive modeled fields. We will interface sensory/motor circuits with the whole-brain population models, based on structural connectivity from primate experiments. We will vary the interface weights, to ensure the optimized functional connectivity is maintained after bidirectional embedding. For reducing models, we will use BindsNET[15]. BindsNET supports efficient use of GPUs, significantly improving computational performance on machine learning (ML) tasks. **Expected outcomes:** Integration between models of different levels will offer unprecedented views into interactions between whole-brain and microcircuit activity during behavior. Software tools developed will benefit the research community.

Pitfalls: Embedding microcircuit models into whole-brain models requires software interfaces allowing seamless communication. Our TVB-NetPyNE co-simulation interface demonstrates this is possible, and suggests a similar interface between TVB and BindsNET (both Python-based) is feasible.

SA3: Train the models to perform behaviors using biologically inspired learning rules. In the final stage of this work, we will train our models to play games using spike-timing-dependent reinforcement learning (STDP-RL), inspired by the dopaminergic reward system, and evolutionary algorithms (EVOL).

Preliminary data: We used STDP-RL and EVOL to train neocortical visual/motor and sensory/motor networks to perform behaviors in dynamic environments [4,6,28,35], such as in the Pong and Cartpole games [36] as shown in **Fig. 3**. Our algorithms were *data-sparse*, effective even when only providing infrequent temporal rewards. While each learning algorithm was effective on its own, multi-timescale training through iterations of STDP-RL followed by EVOL (EVOL+STDP-RL) produced the most robust performance, and most efficient use of data. Here, we will use similar learning strategies.

SA3.1: Train isolated microcircuit models to perform sensorimotor tasks. We first train isolated sensorimotor models directly interfaced with games providing a stream of sensory information. Prior to training, we run hyperparameter optimization of network architectures. Next, we will train models using an interleaved EVOL+STDP-RL algorithm. After training, we quantify model performance with learned synaptic weights fixed, to ensure further learning does not influence performance measures.

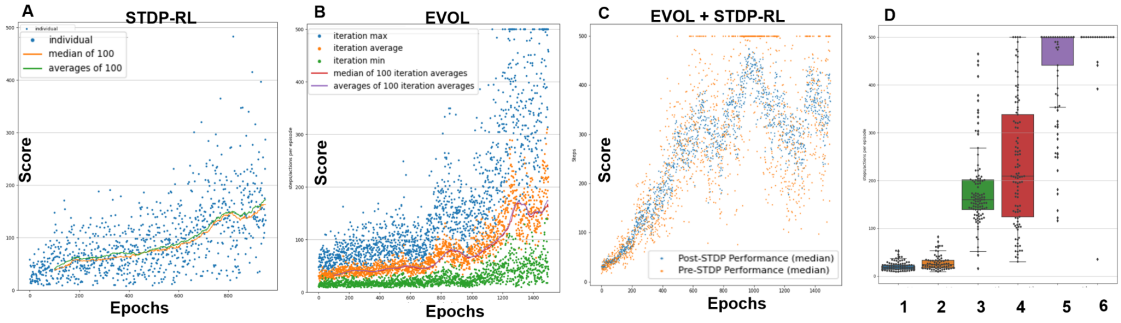

Figure 3: *Model performance after training with:* ***A)*** *STDP-RL,* ***B)*** *EVOL,* ***C)*** *EVOL+STDP-RL,* ***D)*** *Comparison. Y-axis shows model performance in CartPole (higher values are better; comparison to Random choice and before-training shows substantial improvement from learning). X-axis is the number of episodes in the training.* ***A)*** *blue dots are individual episode performance, orange is median of 100 episodes, green shows average of 100 episodes.* ***B)*** *blue dots are iteration maximum score, orange is the score average of one episode and green dot is the min score of one episode. Red is the median score of moving average of 100 episodes and purple is average of the moving average of 100 episodes.* ***C)*** *blue is the median score after SDTP and orange is the median score before STDP.* ***D)*** *performance comparison between (1) random network, (2) network before training, (3) network that trained only with STDP-RL, (4) network that trained using EVOL only, and (5) and (6) performance of two networks that were trained with STDP-RL+EVOL with two population sizes (5 and 10).*

SA3.2 Train integrated microcircuit models embedded in the whole-brain model. In addition to direct sensory information, local microcircuits will receive environmental context and higher order representations from other nodes of the whole-brain, enabling more efficient training. Each step will be performed once per subject-specific whole-brain model. We will quantify performance as a function of training duration. We will train the integrated model, with and without reward-based hebbian plasticity in the interface between the whole-brain model and the microcircuits[37]. We hypothesize that plasticity at this interface will allow microcircuit models to utilize brain-wide information more effectively. This brain-wide information is analogous to high dimensional representations used in reservoir computing [19].

SA3.3 Learning using implicitly represented sensory information in reservoirs across whole-brain We will use the reduced population-based models optimized to match functional connectivity during sensorimotor behavior from key brain areas (primary sensory, motor; see **SA1.2** Pitfalls). These areas will serve as *reservoirs*, implicitly encoding sensory information for training microcircuits. As a result, the microcircuit may not require direct sensory information. To train the microcircuit model, we will use the same learning techniques (STDP-RL, EVOL), and simplified training of weights at the interface between the reservoir and the motor circuit. We expect these techniques will enable our models to predict the next move of individual patients using high-dimensional representations from the reservoir.

SA3.4 Assess performance from final subject-specific integrated models to determine whether brain structural/functional connectivity plays a role in efficient learning and performance, and determine variability of subject-specific model dynamics/behavior. We will compare model performance (training duration, efficacy) against simplified circuit models built in BindsNET, and deep RL algorithms.

Expected outcomes: Bidirectional integration between whole-brain and microcircuit models will enable efficient use of brain-wide associations for learning. During each subaim, we will determine whether model additions improve performance and reduce required training duration.

Pitfalls: There is a risk that reservoir models with implicit sensory representations (**SA3.3**) may not capture precise sensory information to use with STDP-RL to train the microcircuit optimally. Determining model efficiency and computational cost amongst different classes of models will therefore require careful calculation of the cost of individual model components and training protocols.

Transformative Impact: Efficient neuromimetic learning algorithms are a foundation of future science and engineering in the country, ultimately benefiting multiple fields including healthcare. Our uniquely assembled team includes scientists from a broad range of disciplines, with the complementary expertise required to solve the overall research goal: enhancing the efficiency of machine learning algorithms by leveraging neurobiological principles. The group's expertise is distributed along three domains: theoretical/computational neuroscience (Drs. Neymotin, Dura-Bernal), machine learning (Dr. Hazan), and experimental neuroscience (Drs. Schroeder, Bickel, Franco). The theoretical neuroscientists and machine learning scientists have contributed to multiple data-driven models of hippocampal, neocortical, and thalamic circuits, and used them to understand broad principles of information processing and learning in the nervous system, implementing neurobiologically inspired learning algorithms in multiple models and ML algorithms. The experimental group has deep expertise in neurology/neurosurgery, and in designing and conducting behavioral electrophysiology experiments in awake and behaving humans and NHPs using a variety of recording modalities (fMRI/EEG/iEEG/laminar local field potentials). Dr. Schroeder pioneered the use of laminar multielectrodes in awake NHPs. The most widely used laminar electrodes in NHP studies (Plexon U, V probes) are based on a prototype developed in his lab. He and his trainees remain the foremost users of the approach, and the first to fully integrate laminar electrophysiology with cell circuit biophysical modeling in collaboration with Drs. Neymotin and Dura-Bernal. The team's synergistic views and expertise will enable breakthroughs across the different disciplines, first offering new understanding of nervous system function during sensorimotor behavior and learning, and then using the knowledge gained to design entirely new classes of efficient machine learning algorithms. The group aims to uncover the mechanistic origins of the primate brain's complex dynamics underlying perception, decision making, and behavior, a longstanding but currently unresolved goal of neuroscience. We will deliver multi-scale brain models that learn to perform behaviors similar to primates, which would also allow testing which model elements are important for efficient learning and behavior, and what alterations contribute to pathological decision-making. This could shed light on origins of neurological and psychiatric decision making disorders such as ADD/ADHD, OCD, and schizophrenia. In addition, our model construction will be designed to replicate key aspects of primate brain dynamics, including its distributed representations expressed in both the resting state and task specific behavior. These representations could pave the way to efficient machine learning algorithms with wide-ranging applications.

Broadening Participation Plan: The investigators are committed to attracting and mentoring underrepresented trainees, and ensuring the research has a wide and diverse impact. The proposed research will directly support a postdoctoral fellow and graduate student to learn computational neuroscience, a technician and postdoc (Schroeder lab) to learn electrophysiology, advanced neural data analysis and modeling from cross-training from the computational neuroscientists, and a research assistant trainee in human electrophysiology and data analysis (Bickel lab). The investigators are involved in interdisciplinary education through university and medical school courses, workshops at national and international conferences, and host undergraduate and graduate students, and postdoctoral fellows from diverse backgrounds. Their research and education efforts enhance local and broader communities. Drs. Neymotin and Dura-Bernal taught at the Latin American School for Computational Neuroscience (50% women), which takes place in Brazil, and primarily attracts students from Latin America. Dr. Neymotin taught at the Okinawa Institute of Science and Technology summer course in Computational Neuroscience (50% of the students are women). Students at both courses span undergraduate to postdoctoral levels, and participate in course research projects. Dr. Neymotin trains undergraduates through DoD sponsored summer internships (50% trainees are women). Drs. Dura-Bernal and Franco are Hispanic/Latino, from an underrepresented group in computational neuroscience, enhancing the diversity of the key researchers on our project. As part of a NY STEM program, Dr. Dura-Bernal taught neuroscience at underprivileged middle schools in Brooklyn, and supervised three Bronx high school students for the Intel Science Talent Search, two of them becoming semi-finalists. Dr. Neymotin also taught underrepresented students at SUNY Downstate early medical education courses. Both NetPyNE and BindsNET (developed by Co-PIs Dura-Bernal and Hazan) are open-source tools with a large and diverse user community of students and researchers from all over the world. Drs. Hazan, Neymotin, and Dura-Bernal support the user communities in neuroscience courses, research projects, and use of the software. All investigators will ensure the research reaches a broad community, through educational outreach, workshops, including BrainHacks (Dr. Franco previously hosted several brainhack events), and courses developed from the new software and data. All software will be made open-source, with documentation/tutorials provided on github.com and the widely used model repository, ModelDB.