Computational Modeling:
A Tool for New Psychiatric Medication Development

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Computational models are being used in a variety of medical applications, including drug discovery research, where genomic and proteomic software tools facilitate modeling complex intracellular pathways. Increasing understanding of brain functioning due to advances in basic neuroscience techniques and imaging modalities has led to the emergence of computational modeling as an important tool for studying brain mechanisms and circuits. Recent advances in the areas of cellular neurophysiology and synaptic plasticity permit the development of biophysically realistic models that more closely approximate learning, both

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at the network and membrane levels. Such models have the potential to enhance a psychiatrist's understanding of brain circuits with applicability to a range of phenomena from the mechanism of action of drugs to the neural basis of mental illness. An example case is provided in the fear circuit to illustrate the ability of a model to provide insights into possible sites for the storage of auditory fear and extinction memories. Since disruption of the fear circuit is thought to underlie the pathology of posttraumatic stress disorder (PTSD) and other anxiety disorders, such a model could potentially provide ideas and approaches for the development of new medications.

INTRODUCTION

The human brain is a dynamic system made up of about 100 billion neurons connected in complex circuits and synapses, humming with continuous electrical and chemical activity. It is divided into different areas including the evolutionary older parts of the central nervous system and the newer parts, such as the cortex. Most of the normal and pathological changes in brain processes can be attributed to changes in transmission and excitability of neurons in specific circuits connecting these areas. Treatment modalities, such as psychiatric medications, lead to changes in the excitability of neurons either through the direct action of neurotransmitters on membrane channels or through indirect action via receptors triggering a cascade of intracellular reactions. Such reactions typically modulate release of neurotransmitters by the presynaptic neuron or modulate the excitability of the postsynaptic neuron, and ultimately control the target symptoms (see Figure 1).[1]

Rapid advances in basic neuroscience techniques, including single cell recordings and microdialysis, continue to add to our understanding of brain function at intracellular and cellular (membrane) levels. Structural neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), have, at the same time, made possible high-resolution visualization at the network/systems level of brain regions in patients. Functional imaging techniques provide more detailed understanding of brain function with real-time images using techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon-emission computed tomography (SPECT). Major advances such as these, both in basic neuroscience and in neuroimaging techniques, continue to enhance our understanding of the neural basis of mental illness and of treatment modalities. In most cases, however, findings are limited to specific mechanisms/processes/cells, and fail to generalize to higher brain circuits and regions.

MODELING

A computational model combines different types of information related to a system using mathematical equations and then describes the system's response to prescribed inputs. In neuroscience, there are typically two types of models: phenomenological models using connectionist (eg, artificial neural network) and statistical schemes, and biophysical models, which attempt to model the underlying biological mechanisms directly. Biophysical models are typically either at the intracellular level (eg, of gene interactions, pathways),[2] cellular level (eg, of cell firing patterns, effect of blockers/drugs on channel conductances), network/systems level (eg, of interconnected neurons in the fear circuit, which is the case study reported in this paper), or may include several of these levels. The most powerful approach is to combine the cellular and network levels to model regional interactions with biological realism.

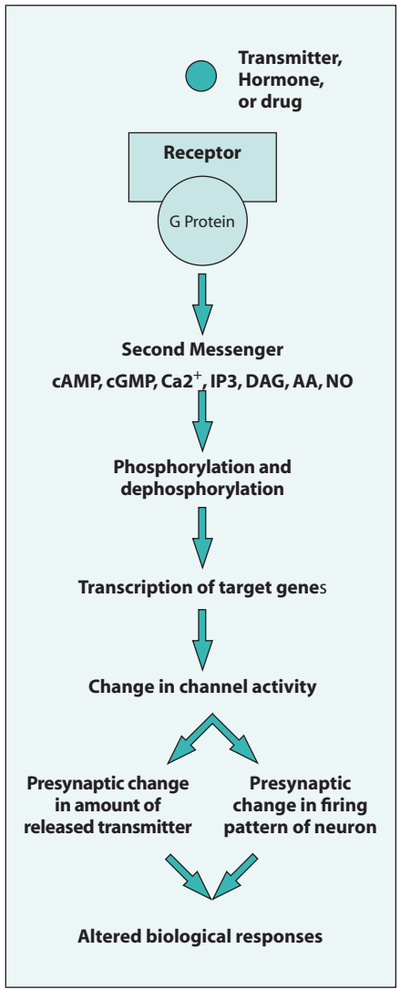

Figure 1. Major pathways for the modulation of synaptic transmission. (Adapted from 1).

Computational modeling is a tool that has been effectively used to integrate information related to different aspects of a problem, and to provide testable predictions in a variety of disciplines. For instance, computational modeling is currently an indispensable part of the design of airplanes, (eg, Boeing 777). For an airplane, such a model would integrate the complex mathematical equations describing different types of dynamics, such as the air flow, vibrations, and response

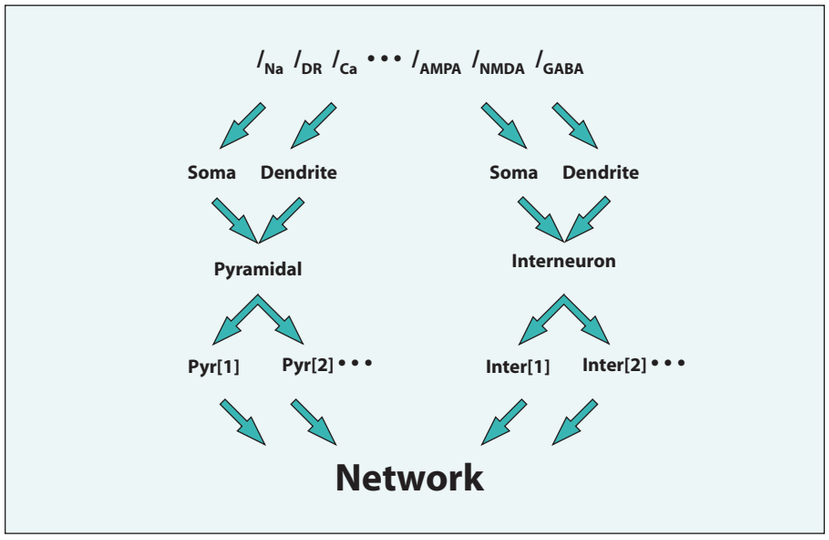

Figure 2. Elements in GENESIS are organized in a tree structure.[7] The symbol "I" represents current (eg, Na is the sodium current). The network comprises cells (pyramidal and interneurons here), which in turn consist of soma and dendrites populated with the various current channels. The software developers aim to provide these as "Lego blocks" facilitating the process of model development.

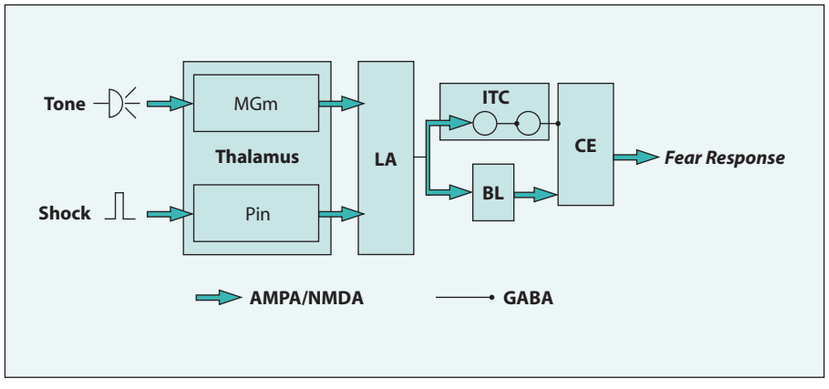

Figure 3. Auditory fear conditioning. The tone information is delivered to LA via the medial division of medial genicular body (MGm), and the shock information is delivered to LA via posterior intralaminar nucleus (PIN). The tone input to LA is potentiated when tone and shock are paired. Output from the LA projects to the central nucleus (CE) through inter-calated cells (ITC) or BL neurons, eliciting a fear response.

of the control surfaces, and then predict their effect on responses, such as ride quality. Computational models have now become indispensable for the airplane designer because they enable rapid and inexpensive evaluation of a variety of "what if" scenarios, including the effect of design changes. It is argued that increased understanding of the functional organization of the brain requires integration of similar mathematical/statistical equations from molecular, cellular, and network level studies, something that can be facilitated by computational models.[3] For instance, recent technical advances have resulted in a rapid accumulation of information on intracellular signaling pathways and relationships to long-term neuronal changes.[4] Computational techniques and tools are being developed to model such mechanisms with increasing accuracy and are found to be essential to generate an understanding of the underlying functions in such cases.[3,5] Indeed, drug discovery and development teams now include computational techniques as an important tool in their repertoire. The term "computational neuropharmacology" has recently been proposed for the application of computational modeling to drug development, drug discovery, and the modeling of the mechanisms of action of psychiatric drugs.[6]

SOFTWARE

Software exists currently to model systems in neuroscience at typically only one of the levels, which are the molecular, cellular, or network/systems level. One reason for modeling is the large difference in both temporal and spatial complexities between the levels.[2]

Once the mathematical equations/model for the neuron or network is developed, the values of the biophysical parameters in the model have to be determined systematically. In addition to research articles, sources for such information include databases such as CellPropDB, NeuronDB and ModelDB (http://neuron.duke.edu/). After collecting information pertaining to biophysical parameters, one can make use of public domain software packages available for modeling neurons and networks.

Computational modeling platforms at the cellular and network levels range from general purpose software such as Matlab (http://www.mathworks.com/), which directly models the mathematical equations, to special purpose public domain ones such as GEneral NEural SImulation System (GENESIS)[7] and Neuron,[8] which are being designed for biologists and require minimal understanding of the underlying mathematics. Figure 2 shows the hierarchical structure used for modeling in GENESIS. The packages can perform simulations of models ranging from single neurons to complex networks representing brain circuits. For example, Leblois et al[9]

used a systems level Neuron model to explain the pathology in the basal ganglia circuit with Parkinson's disease.

CASE STUDY: MODELING ACQUISITION AND EXTINCTION OF FEAR

PTSD is a condition that involves exposure to trauma followed by symptoms of avoidance, re-experiencing, and hypervigilance. Studies indicate that patients with PTSD demonstrate delayed extinction learning as compared with controls.[10,11] Disruption of the fear circuit, which includes thalamus, amygdala, prefrontal cortex, and the locus coeruleus, is thought to underlie the pathology of PTSD and other anxiety disorders.[12] Although much of the neural data originated in rodent studies, recent brain imaging studies in humans show that homologous areas of ventral medial prefrontal cortex (mPFC) show both morphological and functional abnormalities, suggesting that extinction circuits are compromised in PTSD.[13] A computational model of the fear circuit would enable the integration of such findings and provide insights into the pathology of PTSD and also provide ideas for potential treatments.[14]

The amygdaloid complex is an important component of the fear circuit. It is located within the medial temporal lobe and is critical in the acquisition and expression of learned fear.[15,16] The amygdala is subdivided into different parts including the lateral nucleus (LA), the basal nucleus (BL), and the central nucleus (CE).[17] Lateral nucleus of the amygdala is the sensory-receptive region and is particularly important in mediating fear conditioning.[18] In auditory fear conditioning, the tone (conditioned stimulus, CS) and foot-shock (unconditioned stimulus, US) inputs are paired in experiments. The impulses from thalamus and cortex converge in LA,

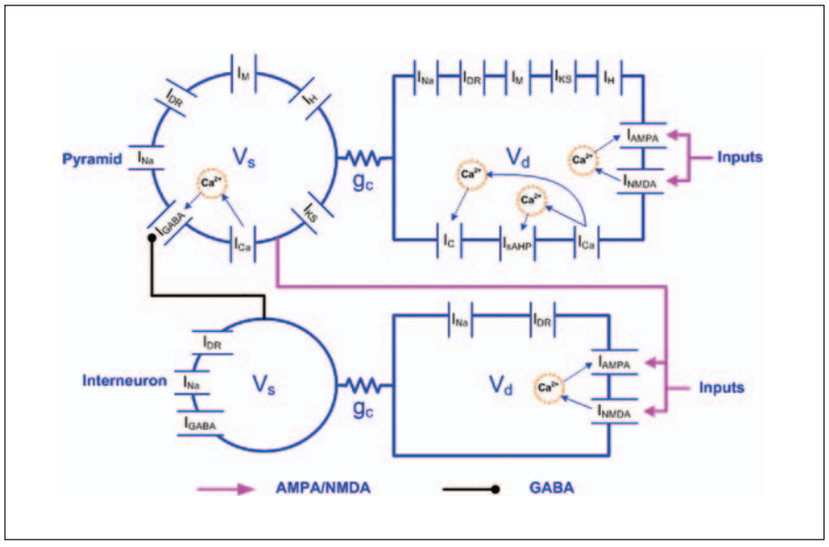

Figure 4. Two-cell model of pyramidal cell and interneuron with ionic and synaptic channels. Each cell model has soma (spherical) and dendrite (cylindrical) compartments with each having the specific current channels shown. The Ca^{2+} pools involved in the learning algorithm implemented are also depicted. Both cells receive afferent inputs (tone and shock) via AMPA/NMDA synapses. In addition, the interneuron receives excitatory input from the pyramidal cell and provides feed-forward/feedback inhibition to the pyramidal cell.

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which then project to the central nucleus via intercalated (ITC) cells, and then to the brain stem and hypothalamic sites, eliciting the fear response (see Figure 3, page 298).[19] Following conditioning, repeated presentation of tone without shock leads to an extinction of the fear response.[20,21] Although the neural mechanisms of fear extinction are not well understood, it is now generally accepted that extinction does not erase the CS-US association but instead forms a new memory that inhibits the original fear conditioned response.[22,23] The lateral nucleus of the amygdala has been proposed as a site of inhibition in extinction.[24] In addition, recent studies have identified the mPFC as an important part of the neural circuit for fear extinction.[13,25] Since deficits in extinction learning are thought to underlie PTSD,[26,27] a model that could integrate these findings would be an important tool for studying such circuits.

We initiated model development of the overall fear circuit using a bottom-up approach and biophysical realism, starting with the core unit, the LA, as a first step. Our future goal is to use the overall model to determine potential sites in the fear circuit for the storage of fear and extinction memories in PTSD and to elucidate the underlying mechanisms. We illustrate below the potential of a computational model to provide insights into fear acquisition and extinction mechanisms, using a simple, two-cell model.

Single-cell Characteristics

There are two main types of neurons within the LA and the BL: pyramidal-like glutamatergic projection

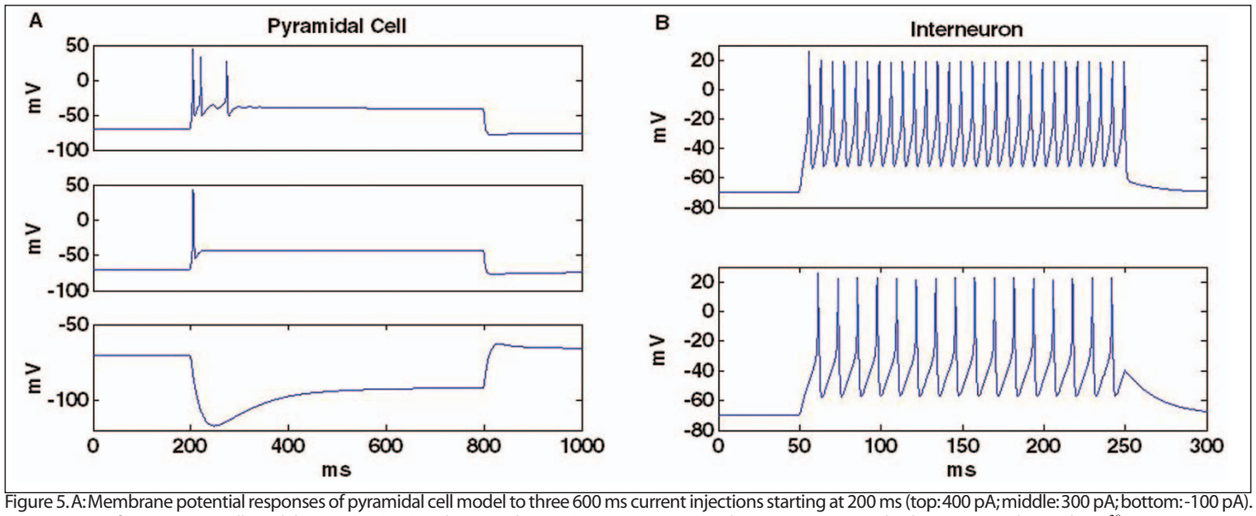

Figure 5. A: Membrane potential responses of pyramidal cell model to three 600 ms current injections starting at 200 ms (top: 400 pA; middle: 300 pA; bottom: -100 pA). B: Responses of interneuron cell model to 400 pA (top) and 200 pA (bottom) current injections. These estimates matched experimental recordings.[28]

neurons and local circuit GABAergic interneurons.[17] Principal neurons in the LA exhibit a range of firing properties in response to prolonged current injection;[28] accordingly two types of pyramidal cells were modeled, type A with strong frequency adaptation, and type B with medium frequency adaptation. The interneuron was modeled as a basket-type, fast-spiking, spiny cell with each compartment containing a fast Na_+ current and a delayed rectifier K_+ current with different kinetics from those of pyramidal cells to reproduce the much shorter spike duration.[29] Similar to pyramidal cells, interneurons can also receive excitatory glutamatergic inputs from the thalamus and/or the cortex and inhibitory inputs from other local interneurons. For each cell, the excitatory alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and the N-methyl-D-aspartate (NMDA) channels were placed in the dendrite compartment, and the inhibitory $GABA_A$ channels were placed on the soma. Figure 4 (see page 299) provides details of the pyramidal cell and interneuron models with the various ionic and synaptic channels.

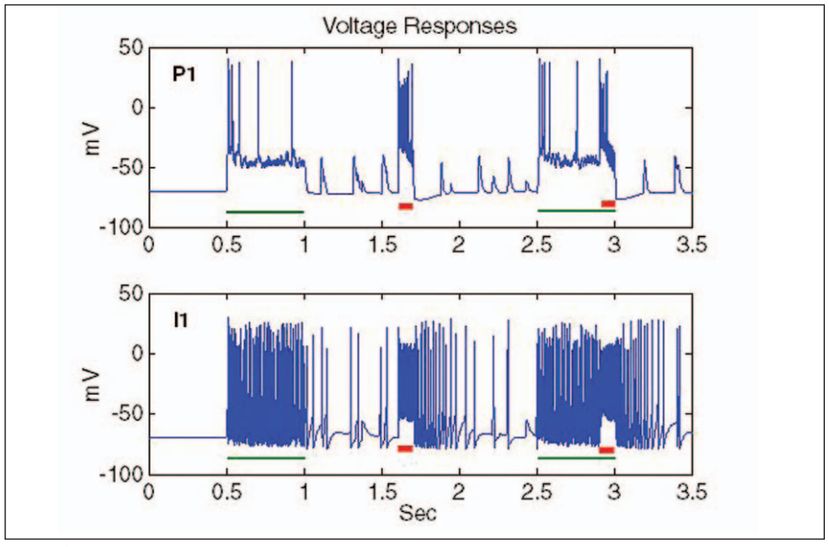

Figure 6a. Membrane potential responses for pyramidal cell (top panel) and interneuron (lower panel) to a segment of the training trial. In the segment, the input consists of a series of two tones (green bars) and two shocks (red bars), with the second tone paired with the second shock.

Using GENESIS to Model a Single Cell

Single cell models were developed[30] for the pyramidal cell and the interneuron (see Figure 4, page 299) using the GENESIS software package. The modeling process involves several steps where different "Lego blocks" are defined, such as the soma or cell body of the neuron, the dendrite, the axons, and the membrane channels (see Figure 2, page 298). The software provides a virtual environment, making most of the mathematical details transparent to the user. The model parameters are then iteratively adjusted, within biophysical bounds, to match certain baseline characteristics. The membrane potential responses to different levels of current of the pyramidal cell and interneuron models (see Figure 5) showed characteristics consistent with experimental observations, for both depolarizing and hyperpolarizing current cases.[28]

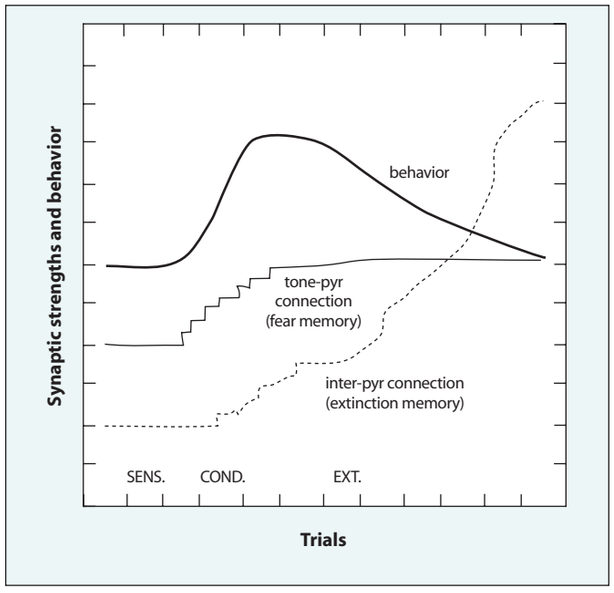

Figure 6b. Schematic showing the connections between synaptic strengthening/weakening and behavior. The training protocol had four phases: SENS — unpaired tone/shock; COND — paired tone/shock; a gap with no tone or shock; and EXT — tone alone.

Synaptic Connections are Sites of Plasticity

Learning of conditioned fear leads to changes in synaptic strength in the neural circuitry in LA. Three different excitatory glutamatergic LA synapses that are capable of strengthening (long term potentiation, LTP) or weakening (long term depression, LTD) with training[31,32] are:

1. Thalamic/cortical auditory tone synapses to pyramidal cells or interneurons;
2. Synapses between the pyramidal cells themselves;
3. Pyramidal cell to interneuron synapses.

In addition, LTP can be induced in GABAergic inhibitory synapses from interneurons to pyramidal cells.[33] After modeling single cells, a network model consisting of multiple cells, synaptic connections, and inputs, can be developed using GENESIS. We illustrate such a development using the two-cell model schematic in Figure 4 (see page 299). In the model, both the pyramidal cell and the interneuron received direct afferent tone/shock inputs via synaptic connections. The pyramidal cell was inhibited by the interneuron via a GABAergic synapse. The pyramidal cell, on the other hand, excited the interneuron via excitatory AMPA/NMDA synapses. Both the cells received random background inputs that represent afferent connections from other brain areas, such as prefrontal cortex and hippocampus. The frequency and strength of the random inputs was adjusted to obtain pyramidal cell spontaneous firing rates of less than 1 Hz.[34]

Model Training and Predictions

We implemented LTP/LTD in these synapses[30] using an NMDA-based learning rule, and then "trained" the model with the fear conditioning protocol used in experiments.[35] After training, the model was probed to determine the synaptic sites for the storage of fear and extinction memories.

Figure 6a (see page 300) shows the membrane potential responses of a pyramidal cell and interneuron for a segment of the training cycle. This segment consisted of two tones (500 ms each) and two shocks (100 ms each) with the second shock present in the last 100 ms of the second tone. Both tone and shock excited the cells, with shock input having a stronger effect. Embedded in a more complex system, this unit of two cells illustrates how conditioning and extinction can be learned. Due to Hebbian strengthening between tone inputs and shock inputs, the tone input to the pyramidal cell strengthens during conditioning and is maintained throughout extinction. In the interneuron, on the other hand, tone inputs strengthen during extinction phase, due to Hebbian pairing between different sets of tone inputs. This causes inhibition of pyramidal excitation and reduction in fear behavior. Consistent with behavioral findings, the fear memory is not lost during extinction but is suppressed by LTP like potentiation of the interneuron. This is illustrated schematically in Figure 6b (see page 302).

Overall Fear Circuit Model

The authors are currently extending the model to include other regions including the ITC, CE, pre-frontal cortex and hippocampus, which could also have sites for LTP/LTD in fear acquisition and extinction. Once completed, such an overall model would be useful for studying disruptions associated with the fear circuit, leading to PTSD and anxiety disorders. For instance, studies have shown that in humans with PTSD there is a delay in acquisition of extinction as compared with controls.[36] With the model, one can modify parameters to predict changes in the fear circuit that could be correlated with a delay in acquisition of extinction. These parameters would then point to the changes in the circuit in PTSD and provide insights into the pathology of the illness. The model would also shed light on therapeutic approaches, such as cognitive restructuring, which could provide a new emotional significance to a negative cognition and reducing physiological arousal.[37]

A computational model can combine different types of information related to a system using mathematical equations, and then describes the system's response to prescribed inputs.

Potential Application to Drug Development

Another application of such a model would be in the development of psychiatric medications for PTSD. The computational model predicted that three types of glutamatergic synapses (including NMDA synapses) and one type of GABAergic synapse could be involved in storing fear and extinction memories. These predictions seem to be consistent with recent experimental findings, two of which are:

1. A partial NMDA agonist D-cycloserine, which has been shown to facilitate extinction of fear conditioning in rats.[38] D-Cycloserine was also effective in treating social anxiety disorder and acrophobia in combination with psychotherapy.[39,40] The mechanism of action of D-Cycloserine and other drugs acting on the glutamatergic system can now be modeled at the receptor and at the cellular level in the specific LA neurons indicated by the model; and

2. NMDA receptors in the amygdala activate an intracellular signaling cascade leading to new protein synthesis.[41-43] One such synthesized protein, gephyrin, clusters GABA receptors near the synapse, thereby increasing their inhibitory effect. The level of gephyrin goes down during fear conditioning and then increases to baseline values with extinction learning.[44] The return to baseline level of gephyrin is associated with an increase in the surface expression of $GABA_A$ receptors, corresponding to more inhibitory neurotransmission in the amygdala.[45]

Drugs that impact these mechanisms would have potential for the treatment of PTSD and anxiety disorders. Finally, the cannabinoid receptor CB1 has been shown to modulate GABAergic neurons in the amygdala and facilitate

extinction.[44] A similar strategy could be used in humans. This is consistent with the model prediction that the inhibitory synapse from the interneuron to the pyramidal cell could be a site for the storage of extinction memory.

CONCLUSION

Computational models can predict how a complex system evolves with experience. A new class of models incorporates biophysical realism with known synaptic connectivity, to more effectively model the learning brain. Such models integrate the intracellular and cellular levels of neuroscience with the network/systems level to provide a coherent picture of the higher level functions in health and disease (eg, behavior, symptom). A case study of auditory fear conditioning was used to illustrate the ability of a computational model to provide insights into the neural causes of disruptions in the fear circuit thought to underlie symptoms of PTSD and anxiety disorders. Such insights have the potential to aid in drug discovery research, by allowing scientists to test predictions about the cellular and behavioral effects of new drugs.

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