A Computational Study of Operant and Classical Conditioning in a Central Pattern Generator Neural Circuit

Drew C. Thompson, Irving Z. Basanez, Douglas A. Baxter and John H. Byrne
Department of Neurobiology and Anatomy, The University of Texas-Houston Medical School

Abstract:

The present study constructed a Hodgkin-Huxley based computational model of the *Aplysia californica* feeding central pattern generator (CPG). The present study used a former model (Cataldo 2006 et. al) as a framework and expanded the model, in part, by extracting additional circuit parameters (i.e. cell capacitance, membrane potential, voltage dependent conductance, synaptic conductance, etc.) from previously published studies. The expanded model reproduced patterns consistent with electrophysiological recordings from the buccal ganlgia during a buccal motor pattern (BMP). Operant and classical conditioning have been shown to increase the number of ingestion BMPs expressed by intact animals and reduced samples of the buccal ganglia. A number of cellular correlates of conditioning have been identified within the buccal and cerebral ganglia. Incorporating these changes into the expanded model resulted in patterns more similar to ingestion BMPs. However, simulations suggest that previously identified correlates of operant and classical conditioning failed to fully reproduce empirical observations. To bridge the gap between the known cellular changes and behavior modifications, a set of additional cellular and synaptic alterations to the circuit were applied, which resulted in ingestive BMPs.

Introduction:

Central pattern generators (CPG) are neural networks that produce rhythmic neural activity responsible for a wide variety of behaviors including eating, walking, swimming, and scratching. The anatomical underpinnings of only a few CPGs are currently understood. The behavior and physiology of CPGs on the network and cellular levels alters in response to conditioning and learning, but the connection between cellular changes and behavioral modification is not well established.

The CPG responsible for the feeding behavior of the mollusk *Aplyisa californica* lends itself to computational modeling because of its relative simplicity and the plethora of information available from studies detailing its key cells and connections. The CPG of interest for the current study is located within the Aplysia buccal ganlgia and generates buccal motor patterns (BMP), motor neuron activity that drives feeding behavior in Aplysia. This CPG has the ability to create ingestion BMPs, for biting and swallowing, and rejection BMPs, for expelling inedible material from the animal. The activity of the radula, a tongue like organ that grasps food, determines the nature of a given BMP. Three basic radular functions (protraction, retraction, and closure) are the building blocks of ingestion and rejection feeding behaviors. Both behaviors begin with radular protraction and end with radular retraction. During ingestion, the radula protracts in the open position and closes during retraction to pull food into the esophagus. During rejection, the radula closes while protracting, grasping inedible

food lodged in the esophagus, and opens at the beginning of retraction to expel the object from the mouth (Figure 1).

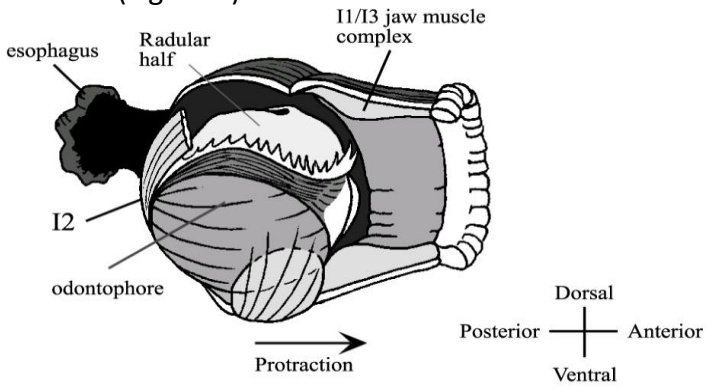

Figure 1: A schematic picture of the buccal mass, the structure responsible for biting, swallowing, and rejection behavior in Aplysia (Managan 2005).

The neural circuit responsible for this behavior is located in the buccal and cerebral ganglia. Sensory cells within the cerebral ganglia receive input from tissue surrounding the mouth and in turn excite command –like cerebral buccal interneurons (CBI). CBI activity triggers the CPG responsible for feeding behavior located within the buccal ganglia (Figure 2).

Roles of several CBI and buccal ganlgia neurons, represented by an uppercase B followed by a number for identification, have been investigated with respect to the feeding behavior of Aplysia. Recordings from intact animals, reduced preparations, and isolated neurons have elucidated the properties of these cells over years of research, and the behavior of these cells has been shown to be nearly identical from animal to animal. Activity in some of the cells has been found to correlate strongly to specific components of feeding, i.e. radular retraction, protraction, or closure, and have been assigned functional roles. For instance, B63 activity can initiate a BMP by mediating radular protraction, and B64 activity signals the end of protraction and the beginning of retraction.

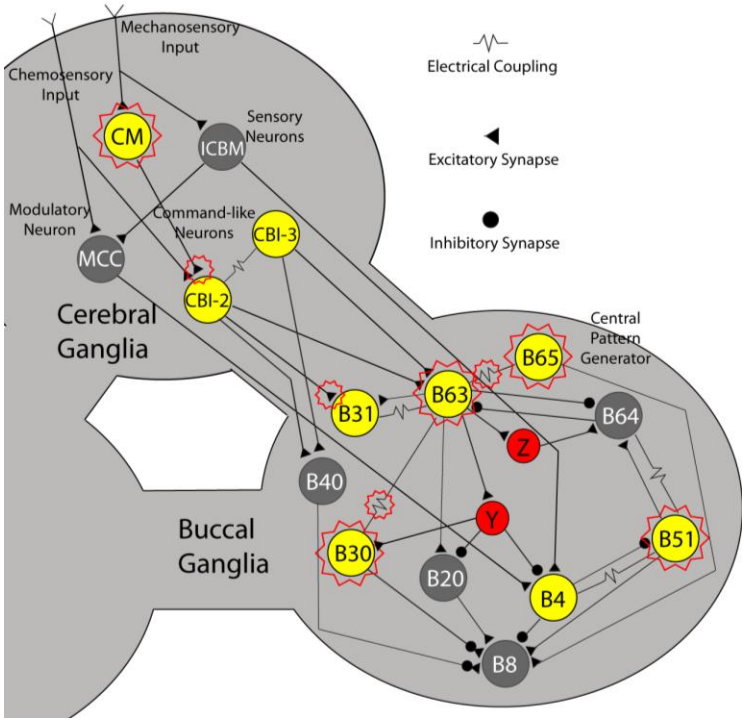

Figure 2: Cerebral mechanoafferents (CM) and Interganlgiaic cerebral buccal mechanoafferents (ICBM) receive input from the lips and elicite activity in the buccal ganlgia. Cells highlighted with yellow have been investigated after associative learning and areas circled in red have been identified as neural correlates of operant or classical conditioning. This figure represents only a fraction of the cells involved in the generation of the pattern. The two cells in red represent aspects of the CPG that are not yet accounted for empirically but are thought to be necessary, if not yet discovered, components of the circuit.

Many gaps remain in the understanding of the Aplysia feeding CPG. Although cells have been implicated in a variety of roles within the circuit, a clear explanation of how these cells function collectively remains elusive. For instance, B63 and B64 fire during protraction and retraction respectively, but the switch from B63 to B64 activity has not yet been fully explained or accounted for experimentally. The most recent explanation, and the one incorporated in this study, is the existence of an unidentified Z cell, which receives excitatory input from B63 and then excites B64 (Cataldo et. al 2006). Computer modeling provides the clear advantage of having a means of observing the function of individual neurons during an activity. This study seeks to consolidate the expanse of data taken from the cells of the cerebral and buccal ganglia in order to elucidate the overarching generation of behavior. Using a prior ten cell model, a 16 cell model was constructed. The model simulated rejection-like BMPs and was shown to be robust.

Operant and classical conditioning can increase the expression of BMPs and increase the likelihood of those patterns being ingestive (Baxter and Byrne 2006). This has been observed in both intact animals and reduced preparations (Moazzachiodi et. al 2003, Lorenzetti et. al 2006). The explanation for this observed alteration of behavior lies, in part, within the circuitry of the CPG responsible for the behavior. Cellular recordings from animals after training revealed several changes in individual cells in the cerebral and buccal ganglia resulting from conditioning. A full explanation of how these changes relate to one another and whether or not they are sufficient to account for observed behavioral modifications does not exist. The current study applied these cellular changes to a simulation of the feeding CPG and observed the changes in network function. While an increase in the ingestive-character of the simulated patterns was observed, the known biological changes within the circuit did not generate an ingestion BMP. Hypothetical additional changes were proposed that fully switched the behavior to an ingestive pattern. These results showed that only minor changes were required to switch to an ingestion pattern and gave a new direction in which to seek for conditioning correlates.

Methods:

The equivalent electrical circuit forms the basis of the Hodgkin and Huxley neuronal model. The cell membrane is represented by an electrical circuit, complete with capacitance, resistance, and a potential difference (Figure 3). Together these parameters result in a membrane current according to the following equation:

$$I_m = C_M \frac{dV_m}{dt} + g_{Na}(V_m, t)(V_m - E_{Na}) + g_K(V_m, t)(V_m - E_K) + g_l(V_m - E_l)$$

where $I_m$is membrane current and V_m is membrane potential. The voltage dependent conductances varied from

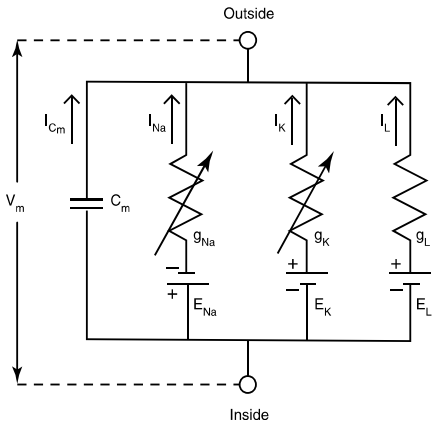

Figure 3: Membrane diagram. Illustrated are the basic conductances of the membrane, Na, K, and leak. The slanted arrows indicate voltage dependence.

ion to ion but were structured according to the following equation:

$$g(V_m, t) = y(V_m, t)\bar{g}$$

where y is one or more gating variables that vary between zero and one and $\bar{g}$ is the maximum conductance of that ion. Individual gating variables, also represented with y, were modeled by the following equation.

$$\frac{dy}{dt} = \frac{y_\infty(V_m) - y}{\tau_y(V_m)}$$

Each cell was fit with equations for $y_\infty(V_m)$ and $\tau_y(V_m)$ that best suited empirical data (Figure 4). Apart from the conductances shown above, many of the cells exhibit additional conductances, which were incorporated into the model accordingly.

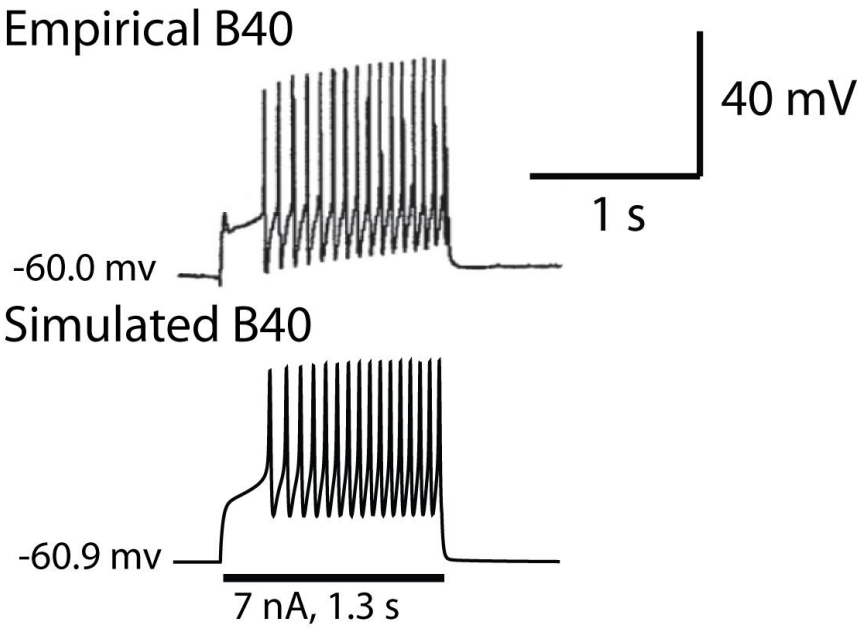

Figure 4: Construction of B40 model. The model of B40 in the simulation was matched to an average of empirical information from a number of papers. The top figure is an empirical recording taken from Jing Weiss 2003 and the bottom figure is a simulation run on SNNAP where B40 was stimulated with a 7 nA current for 1.3 seconds. The empirical recording and simulation exhibited a similar delay in spiking and produced nearly the same number of spikes, 15 for the top panel and 16 for the bottom panel. Other cells in the circuit were matched using a similar process.

Synaptic connections were modeled according to the following equation.

$$I_{cs} = g_{cs}(t)(V_m - E)$$

The time dependent conductance of the synapse, g_cs(t), is modeled by the following equation.

$$g_{cs}(t) = \bar{g}_{cs} \times At$$

The variable At represents the time dependent-activation of the synapse and can be represented by a number of methods. The one most representative of each synapse was implemented in the model (Figure 5).

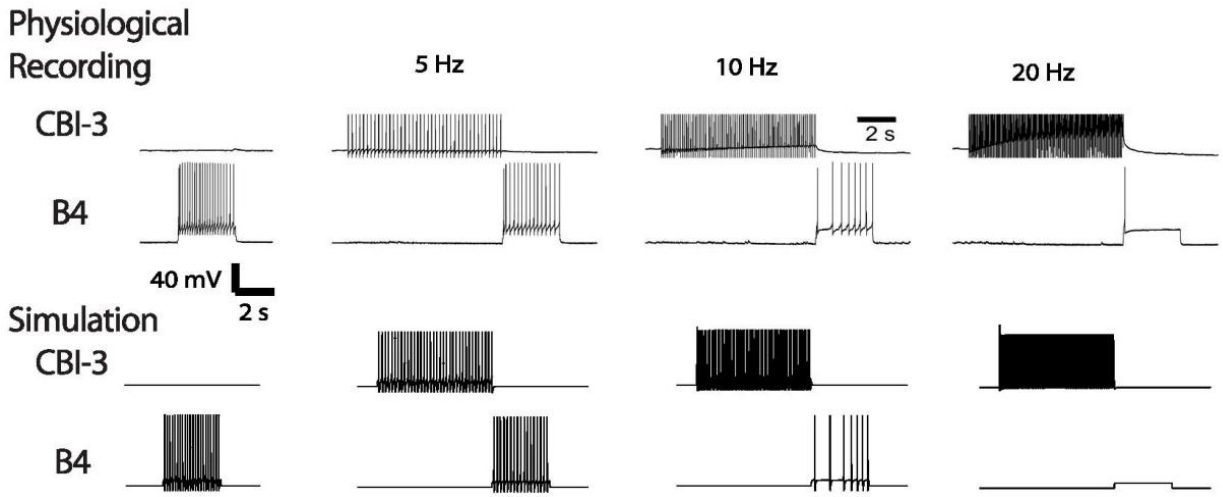

Figure 5: CBI-3 to B4 connection. B4 spiked 22 times without CBI-3 activity. B4 activity reduced to 16 spikes, 7 spikes, and 1 spike when CBI-3 fired at 5 Hz, 10 Hz, and 20 Hz, respectively (Jing et. al 2003). In the model B4 went from 22 spikes to 17 spikes, 7 spikes, and 0 spikes with the same levels of CBI-3 activity.

All simulations were run on version 8 of SNNAP (Simulator for Neural Networks and Action Potentials) using a Windows XP operating system and a computer with a Pentium 4 processor (Baxter et. al 2006).

Three CBI cells, 13 buccal ganglia cells, and two hypothetical cells comprised the final circuit. (Figure 6).

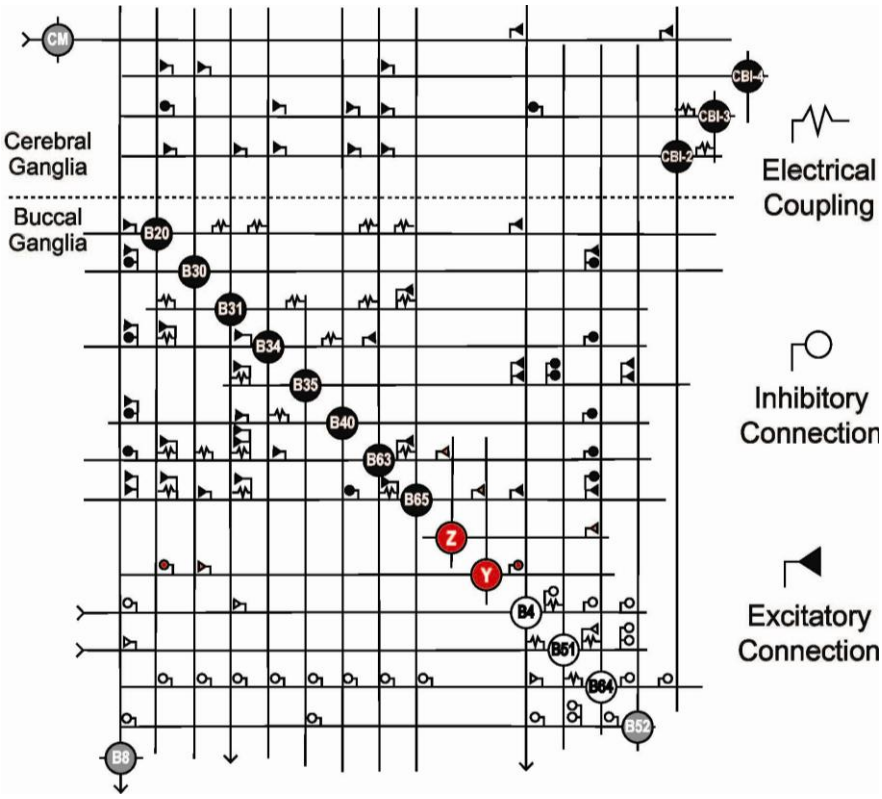

Figure 6: Circuit Diagram. Cells in black are active during protraction, cells in white are active during retraction, and cells in gray are active during both protraction and retraction.

Results:

The buccal ganlgia produces BMPs through stimulation of a number of different cells, including CBI-2, B63, CBI-4, B31, B30 and B65 (Susswein and Byrne 1988, Kabotyanski et. al 1998, Jing and Weiss 2003, Nargoet et. al 2009). The model elicited rejection like BMPs under stimulation of each of these cells individually (Figure 7). These patterns were characteristic of rejection-like patterns not only because B8 was active predominately during protraction, but the activity of B4, B20, B34 were also consistent with a typical rejection like pattern (Jing Weiss 2001, Kabotyanski 2000). Simultaneous stimulation of CBI-2 and CBI-3 has been shown to increase the ingestive character of BMPs because of the inhibitory effect of CBI-3 on B4 and B20 and the excitatory effect of CBI-3 on B40 (Morgan 2002, Jing Weiss 2003). Stimulating CBI-2 and CBI-3 with 2 nA currents in the model created a pattern more ingestive-like than stimulating CBI-2 alone. The simulation proved to be robust because randomly altering voltage gating, chemical synapse, and electrical coupling parameters according to a Gaussian distribution did not significantly alter the function of the circuit.

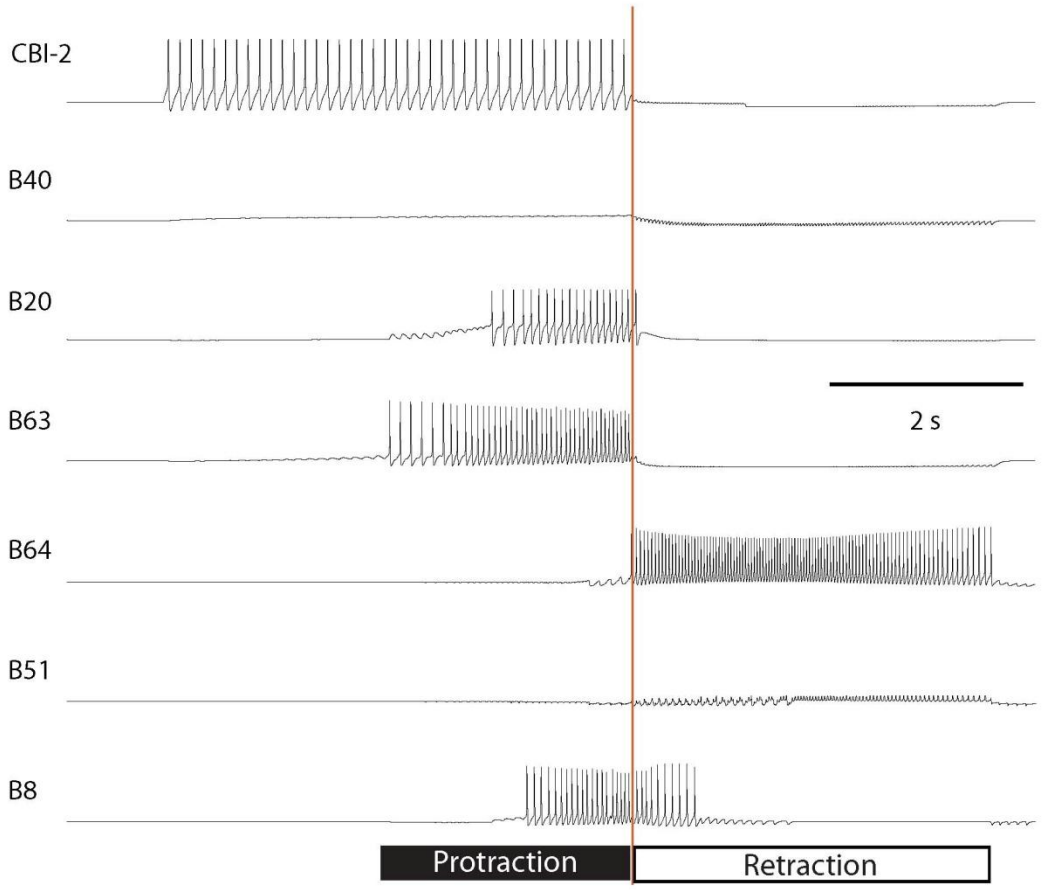

Figure 7: Rejection-Like Pattern. B63 activity indicates protraction and B64 activity indicates retraction. B8 spikes 9 times during retraction and 20 times during protraction, making the pattern more rejection-like. B20 drives B8 activity, and lack of B51 activity, in part, accounts for lack of major B8 activity during retraction.

Classical Conditioning

Classical conditioning of Aplysia using seaweed as an unconditioned stimulus (US) and touching the lip of the animal with a brush as a conditioned stimulus (CS) has been shown to increase the number of biting behaviors during the presentation of the CS alone. The cellular correlates of this behavior are an increase in the CS-evoked excitatory synaptic inputs to CBI-2, B31, and B51, an increase in CS-evoked spike activity in CBI-2, and an increase in the threshold for eliciting a plateau potential in B51 (Mozzachiodi 2003, Baxter and Byrne 2006). These changes were mimicked in the circuit by increasing the leak conductance of B51 from 0.1 µS to 0.16 µS, increasing the excitatory input to CBI-2 from 1.8 nA to 2.0 nA, and exciting B51 and B31 with 1.0 nA and 0.7 nA stimulations respectively to mimic CS excitation. A regular CBI-2 elicited pattern produced 9 spikes in B8 during retraction and 20 spikes in B8 during protraction, but, after implementing the prescribed changes from classical conditioning, B8 spiked 22 times during protraction and 43 times during retraction, which loosely qualified the pattern as ingestive (Figure 8). The behavior of the rest of the circuit, however, did not manifest all of the characteristics of an ingestion-like pattern. For example, both B30 and B40, one or both of which is required for an ingestion BMP, remained quiescent, and B20, a rejection promoter, fired at the same rate as it did before the classical conditioning modifications.

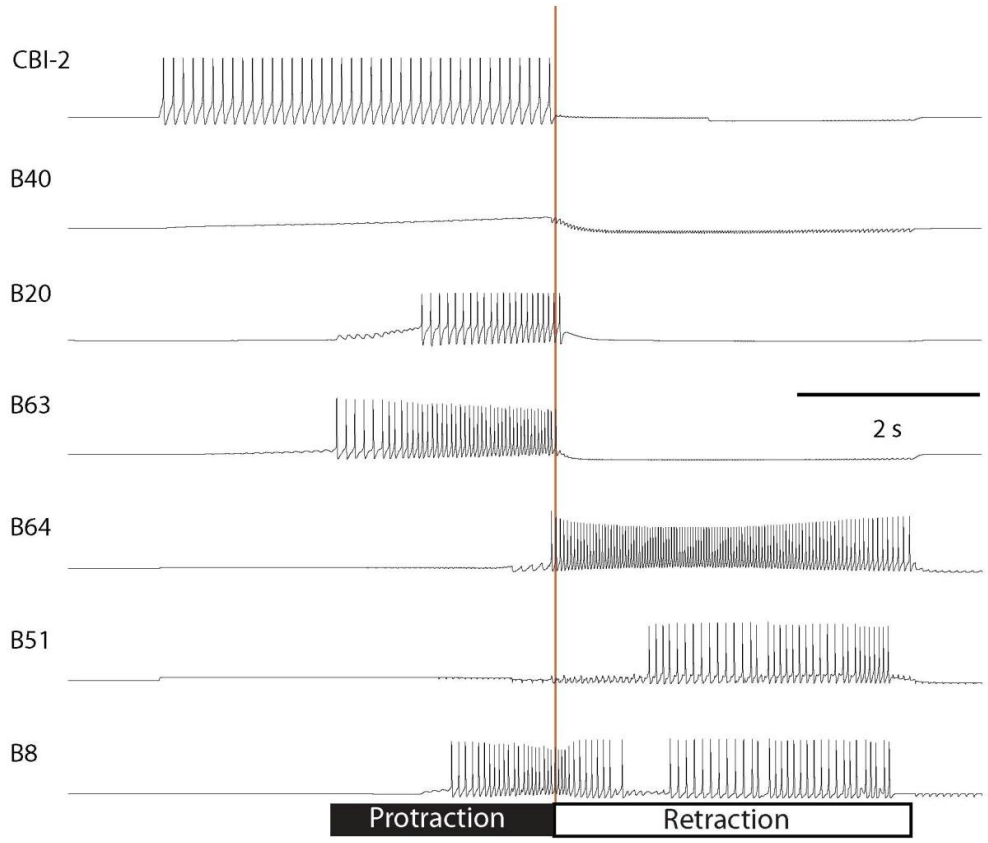

Figure 8: Simulation of Classical Conditioning. Increased CBI-2 activity from the CS caused the pattern to initiate sooner. B8 spikes much more during retraction compared to Figure 6 due to CS evoked excitation of B51, but B8 remains active during protraction. The excitation of B8 during protraction and the gap in B8 excitation during retraction both indicate that additional cellular changes are required for this pattern to be classified as ingestive. Modifications of B40 and B20 activity were implicated as the probable cause of the discrepancy.

To fully account for the change in behavior more modulation to the circuit was necessary. These changes should be plausible and reproduce an ingestion-like pattern by inhibiting B8 activity during protraction and enhancing it during retraction. The best explanation found to solve this problem was to increase the electrical coupling between CBI-2 and CBI-3 and increase the leak conductance of B20 (Figure 9). Both of these changes are reasonable because they are based on changes observed in other cells in the buccal ganlgia as a result of conditioning (Nargeot 2009, Mozzachiodi 2003).

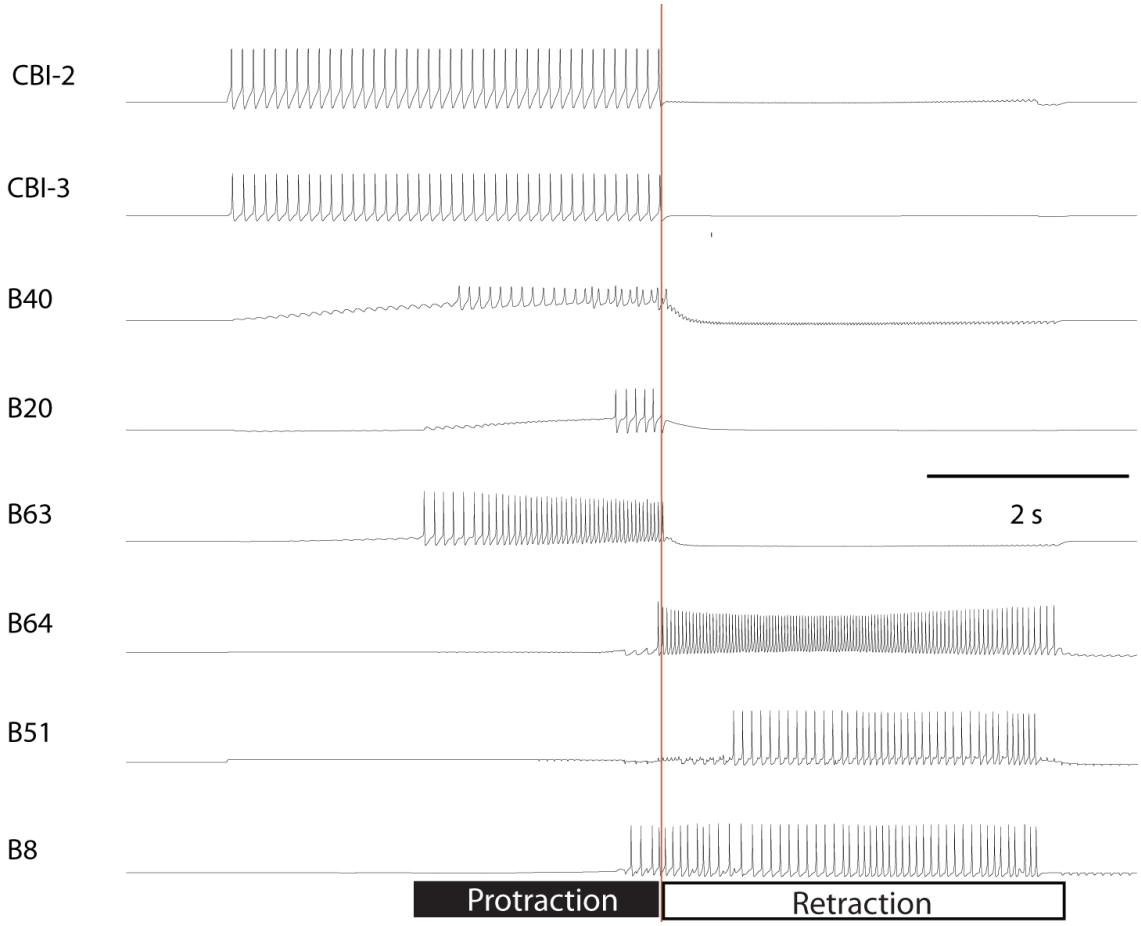

Figure 9: Proposed Classical Conditioning Paradigm. Increasing the coupling constant between CBI-2 and CBI-3 from 2% to 12% and increasing the leak conductance of B20 from 0.1 µS to 0.16 µS resulted the pattern shown in Figure 9. CBI-3 activity excited B40, which closed the gap in B8 activity, and inhibited B8 during protraction. Increasing B20 leakage conductance reduced its firing rate and kept it from exciting B8 during protraction. The result was an ingestion BMP.

Operant Conditioning

Operant conditioning of feeding behavior in Aplysia produces more spontaneous biting in animals (Baxter and Byrne 2006). Spontaneous BMPs occur independent of the cerebral ganlgia and the associated cerebral buccal interneurons (CBI) during fictive training of just the buccal ganlgia (Nargeot et. al 1997). For this reason, the simulation was stimulated via B63

rather than CBI-2. In response to B63 stimulation and in the absence of any conditioning modifications the, circuit produced a predominately rejection-like pattern (Figure 10).

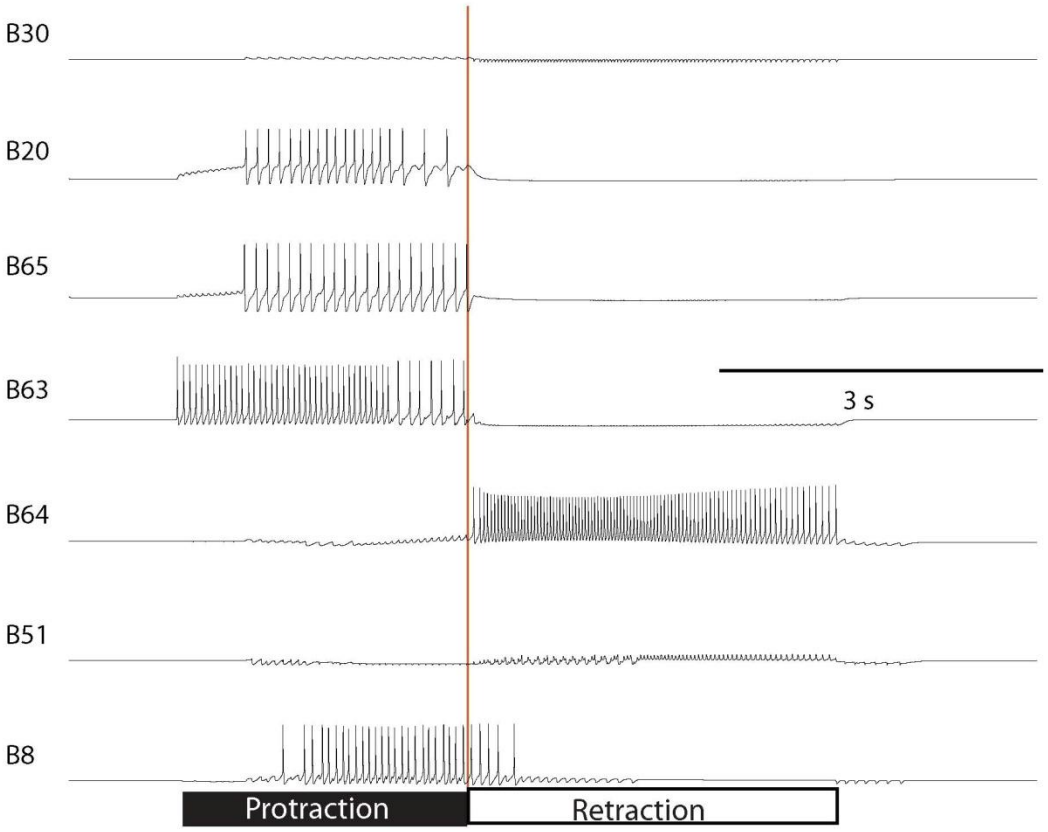

Figure 10: B63 elicited rejection BMP. B8 spiked 25 times during protraction and 5 times during retraction, making it a rejection-like pattern. With no B30 or B51 activity there is no means of stimulating B8 during retraction. During this simulation B63 was given a 3 nA current for 3 seconds.

The modifications of the circuit observed after operant conditioning include: increased coupling of B63, B30, and B65; decreased threshold of B63, B65, and B30; and increased input resistance and decreased threshold of B51. Implementing these changes into the circuit produced a pattern slightly closer to ingestion (Figure 11).

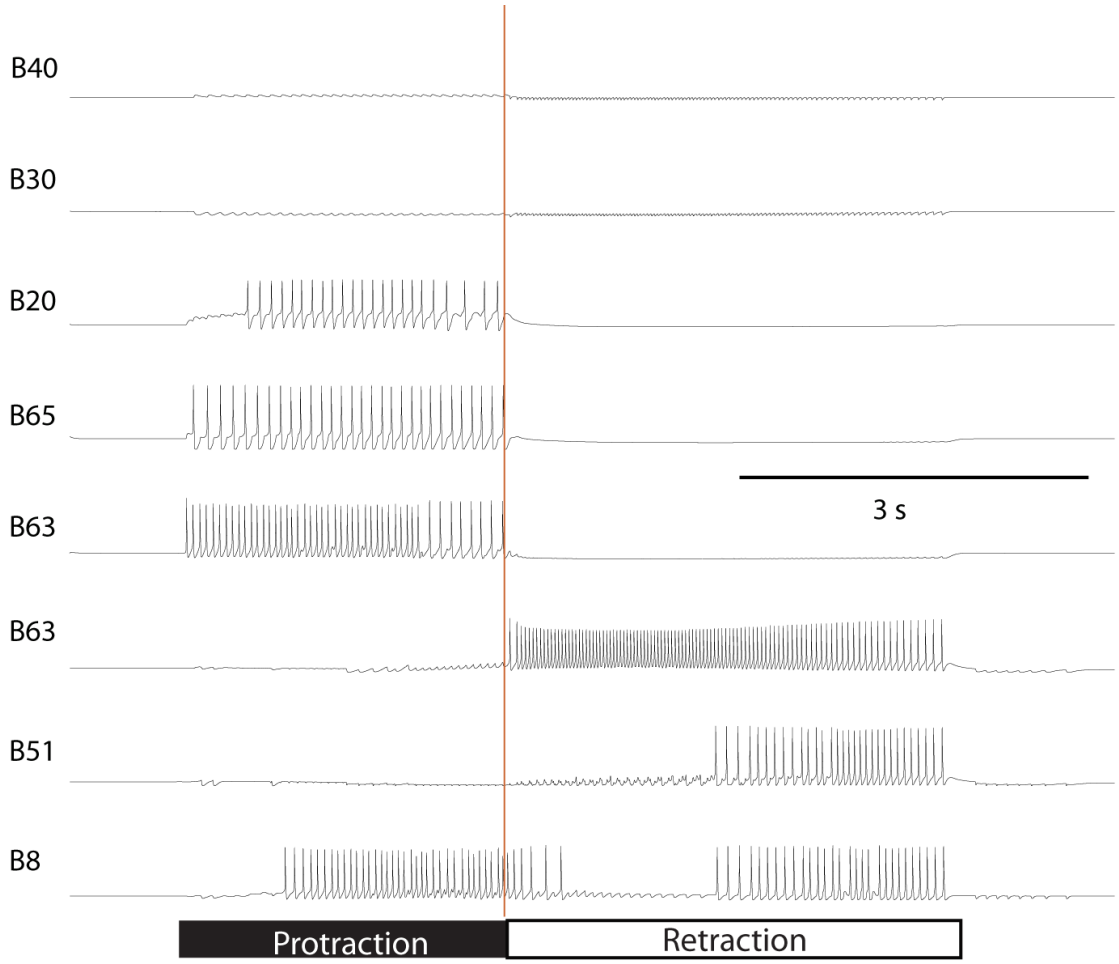

Figure 11: Operant Conditioning Simulation. The burst thresholds of B30, B63, and B65 were reduced by 33.6%, 37.1%, and 28.7% respectively. The electrical coupling constants between B63 and B65 and between B63 and B30 were increased from 3.5% to 6% and 6% to 8.5% respectively. B51 input resistance was increased by 40%, and B51 burst threshold was decreased by 31%. These changes increased the ingestive character of the BMP but failed to produce a fully ingestive pattern. Similar to Figure 7, B8 needs to be inhibited during protraction and the gap in B8 activity during protraction needs to be closed in order for the program to be classified as ingestive.

B8 activity lasted well into retraction, but neither B40 or B30, both or either of which are necessary for an ingestion-like BMP, spiked during protraction and B20 and B4 activity, which excite B8 during protraction and inhibit B8 during retraction respectively, did not decrease as a result of the cellular changes. The range of plasticity of the current buccal ganlgia model could not encompass the necessary modulations to switch the behavior to ingestion. The only cells in the buccal ganlgia that inhibit B20 and B4 (B64 and B52) are not active at the appropriate times to elicit an ingestion behavior. The pathway to excite B40/B30 required unfeasible alterations, also suggesting that the current model falls short. Without the proper connections, changing synaptic strengths and cell excitability could not make the pattern more ingestive. To solve this problem an additional hypothetical cell was added that received excitation form B63, excited B30, and inhibited B20 and B4. The addition of this cell, known as the Y cell, resulted in an ingestion-like BMP (Figure 12).

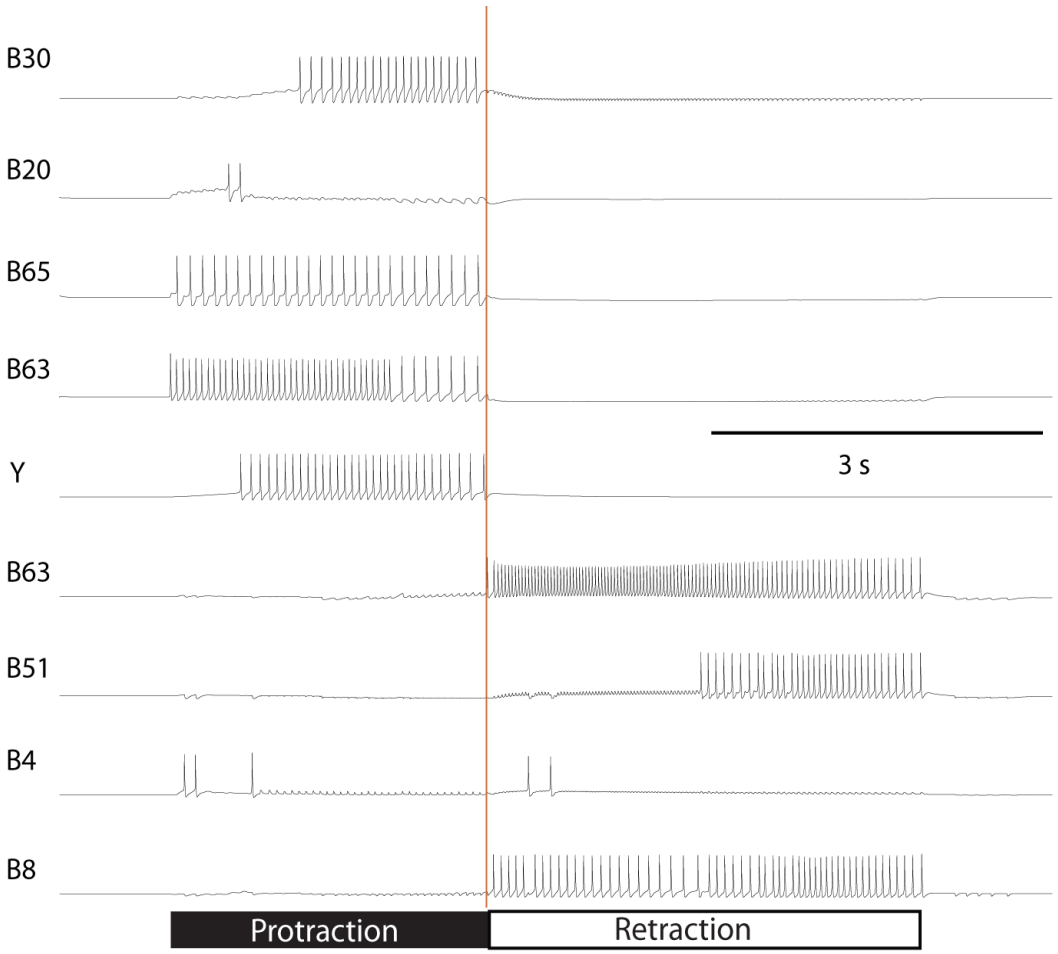

Figure 12: Proposed Operant Conditioning Paradigm. The Y cell receives excitation from B63 and in turn stimulates B30 and inhibits B20 and B4. Implementing the Y cell was necessary because there was no other way in the known circuit to inhibit B8 during protraction and excite it during retraction without the CBI cells. The Y cell acts in many of the same ways that CBI-3 does but is located within the buccal ganlgia. The Y cell is subject to operant conditioning. Before conditioning it has little effect on the overall performance of the circuit. After conditioning the input resistance of the Y cell increases from 1.0 MΩ to 2.0 MΩ, which increase its excitability and yields the simulation depicted in figure 12.

Discussion

B51:

The role of B51 was of particular interest to this study because it not only exhibited cellular changes after operant and classical conditioning, but the changes from these two types of associative learning produced opposite effects on this key cell within the circuit. B51 makes an excitatory connection with B8 and fires during retraction, meaning that its activity increases the ingestive character of motor patterns. During operant conditioning the excitability of B51 increases due to an increase in input resistance and plateau potential and a decrease in burst threshold. By changing the parameters of B51 to match the cellular correlates of operant conditioning, B51 went from not firing at all during CBI-2 and B63 elicited behaviors to firing

throughout most of retraction. B51 accounted for most of the change in B8 activity after simulated training.

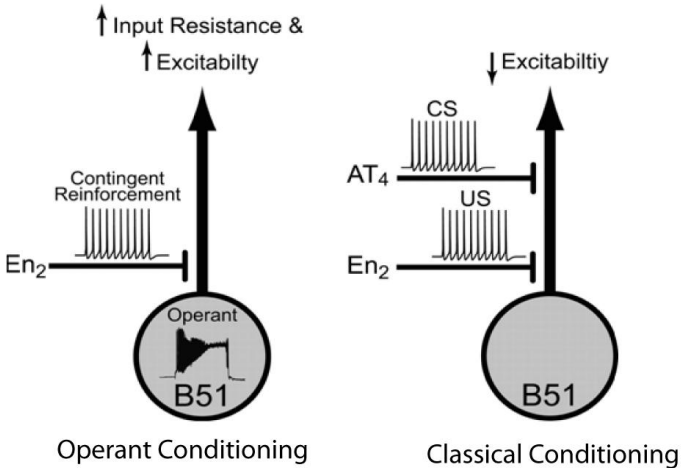

Figure 13: Schematic diagram of the different contingencies during operant vs. classical conditioning. B51 excitability increases due to operant conditioning but decreases due to classical conditioning. The excitatory input from B51 to B8 is critical for an ingestion BMP (Nargeot et. al 1999a). The model showed that the increase in CS input to B51 could reasonably overcome the decrease in B51 excitability and help account for the change in circuit behavior.

The results indicate that B51 played a similar role in classical conditioning, but, instead of becoming more excitable, it received more excitatory input. The burst threshold of B51 increases after classical conditioning. It retains its role as a driver of B8 activity, despite its reduced excitability, because of the increase in excitation from the CS. Although the burst threshold increased, B51 went from not firing at all during CBI-2-elicited behaviors to firing through most of retraction, almost identical to the behavior observed after the operant simulation. The proposed reason why the burst threshold increases as a result of classical conditioning is that without this increase the CS would excite B51 during protraction, which would excite B64, inhibit B63, and end the pattern before it began. By increasing the threshold, B51 fires at the appropriate time and increases the ingestive character of the behavior.

CBI-2 and CBI-3:

Increasing the electrical coupling of CBI-2 and CBI-3 is a plausible outcome of classical conditioning. CBI-3 has been shown to increase the ingestive character of BMPs because it inhibits B4 and B20 and excites B40 (Jing and Weiss 2003). CBI-3 receives no known excitation other than its electrical coupling with CBI-2. It is intuitive that if CBI-2 is the only means to excite CBI-3 and CBI-3 seems designed to encourage ingestion then the coupling between the two is a kind of switch capable of biasing BMPs toward ingestion. If the increase in electrical coupling is not found experimentally then it is likely that CBI-3 is activated by some other means also subject to classical conditioning.

Y cell:

While adding a second hypothetical cell to the circuit seems ad hoc, the limitations of the buccal ganlgia cells in the model left little alternative. Sufficient excitation of B30 and inhibition of B20 could not be achieved otherwise. There may be other cells, previously identified and otherwise, that could account for the role the Y cell plays in the operant conditioning simulation. The combined effect of the buccal compartment of CBI-5 and B21 is a

plausible alternative to the Y cell. The two are electrically coupled and together excite and inhibit the circuit in a way similar to the Y cell. A future model of the circuit will incorporate both of these cells and explore the extent to which they can play the part of the Y cell.

The current study provides a good starting point for experimentation and gaining a more complete understanding of the CPG of BMPs in Aplysia, but it is far from complete. It relies heavily on a handful of cells that are not always necessary to generate a BMP. For instance, the simulation could not function without B64, but experimentation shows that hyperpolarizing B64 does not stop the circuit from generating BMPs (Hurwitz and Susswein, 1996). The output of the simulation is also completely dependent upon the input. Due to the nature of the simulation, a given stimulation will yield the same pattern every time. Even when cell conductance, synaptic conductance, and electrical coupling constants are altered randomly, creating artificial noise, the circuit still produces nearly the same pattern consistently. The model is a simplification of 16 cells taken from possibly hundreds of cells ultimately responsible for generating BMPs in Aplysia. That being said, the model did strengthen our understanding of the link between cellular changes and behavioral modifications from learning. Although the known cellular changes in the buccal and CBI neurons could not fully explain the behavior modifications, only slight additional alterations were necessary to switch the circuit from producing rejection to ingestive patterns. This gave more weight to previous findings that small areas of plasticity within neural circuits sufficiently alter overall circuit function to account for learning on the network level.

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