REVIEW | Central Pattern Generators

Use of the Aplysia feeding network to study repetition priming of an episodic behavior

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Cropper EC, Jing J, Perkins MH, Weiss KR. Use of the Aplysia feeding network to study repetition priming of an episodic behavior. J Neurophysiol 118: 1861–1870, 2017. First published July 5, 2017; doi:10.1152/jn.00373.2017.—Many central pattern generator (CPG)-mediated behaviors are episodic, meaning that they are not continuously ongoing; instead, there are pauses between bouts of activity. This raises an interesting possibility, that the neural networks that mediate these behaviors are not operating under “steady-state” conditions; i.e., there could be dynamic changes in motor activity as it stops and starts. Research in the feeding system of the mollusk Aplysia californica has demonstrated that this can be the case. After a pause, initial food grasping responses are relatively weak. With repetition, however, responses strengthen. In this review we describe experiments that have characterized cellular/molecular mechanisms that produce these changes in motor activity. In particular, we focus on cumulative effects of modulatory neuropeptides. Furthermore, we relate Aplysia research to work in other systems and species, and develop a hypothesis that postulates that changes in response magnitude are a reflection of an efficient feeding strategy.

invertebrate; neuromodulation; neuropeptides; feeding microstructure

SOME CENTRAL PATTERN GENERATORS (CPGs) are active all the time. This is particularly likely to be true when it is essential that the mediated behavior be continuously ongoing. For example, this is the case for the heartbeat in the leech (Calabrese et al. 2016; Kristan et al. 2005; Lamb and Calabrese 2011). Other CPG-mediated behaviors are episodic, meaning that bouts of rhythmic activity are separated by periods of quiescence. Most studies of the neural basis of episodic behavior have focused on the decision-making process that turns the CPG on or off (e.g., Getting and Dekin 1985; Kristan et al. 2003). Because CPGs that mediate episodic behaviors are not active all the time, they do not necessarily operate under “steady-state” conditions. A less commonly investigated question is whether the process of starting and stopping has inherent consequences of its own. One experimentally advantageous system where this issue has been addressed is the feeding system of the mollusk Aplysia (Dacks et al. 2012; Friedman and Weiss 2010; Friedman et al. 2015; Proekt et al. 2004, 2007). In this review we describe this research and its relevance to work in other systems.

Feeding in Aplysia

To begin, we provide a brief overview of feeding behavior in Aplysia and the network that mediates it. These sections are not meant to be comprehensive because their primary purpose is simply to provide sufficient background information for subsequent sections of the text. The following is a list of more extensive reviews of the feeding network (Cropper et al. 2004; Elliott and Susswein 2002; Jing et al. 2017). Feeding in Aplysia is similar to behaviors in many species in that it can be divided into appetitive (anticipatory) and consummatory phases (Craig 1917, 1918; Kupfermann 1974a, 1974b). Appetitive behaviors include locomotion and head movements (Bablanian et al. 1987; Nagahama et al. 1993, 1994; Teyke et al. 1990). Consummatory behaviors include “bites,” “bite-swallows,” and “swallows” (Kupfermann 1974b). The research described in this review focuses on consummatory behaviors.

To ingest food, Aplysia (and a number of other mollusks) utilize a toothed chitinous structure, known as the radula (Elliott and Susswein 2002; Howells 1942; Wentzell et al. 2009). The radula can move forward or backward in the buccal cavity; i.e., it can protract or retract. Additionally, in Aplysia the radula has a longitudinal fold in its center that acts as a hinge and allows its two halves to open and close (Howells...
Feeding in Aplysia is Mediated by a Multifunctional CPG

Organized oscillatory activity of the feeding circuitry in Aplysia can be triggered in the absence of the periphery, indicating the involvement of a CPG (Church and Lloyd 1994; Morton and Chiel 1993a, 1993b). In this regard, Aplysia is similar to other species. Thus consummatory feeding movements are known to be CPG mediated in mammals (Doty et al. 1967; Lund 2011; Wiesenfeld et al. 1977) and in other mollusks and invertebrates (Benjamin 2012; Benjamin and Rose 1979; Brierley et al. 1997; Elliott and Benjamin 1985; Elliott and Susswein 2002; Kemenes et al. 2001; Marder and Calabrese 1996; Schoofs et al. 2010; Staras et al. 1998).

The Aplysia feeding CPG is like a number of other CPGs in that it is primarily, but not exclusively, composed of interneurons (Dembrow et al. 2003; Hurwitz et al. 1994, 1997; Hurwitz and Susswein 1996; Jing et al. 2004, 2011; Jing and Weiss 2001, 2002; Kabotyanski et al. 1998; Plummer and Kirk 1990; Sasaki et al. 2009, 2013, 2007; Susswein and Byrne 1988). Furthermore, it has a modular organization (Jing et al. 2004; Jing and Weiss 2001, 2002). Modules are often defined as groups of neurons that create distinct, coordinated body movements (Briggman and Kristan 2008). Importantly, in Aplysia, one set of neurons controls radula protraction/retraction movements, and a second set controls radula opening/closing movements (Jing and Weiss 2002).

The feeding network is multifunctional in that it can generate more than one type of motor program (e.g., ingestive and egestive; Cropper et al. 2004). Although multifunctionality has been most clearly demonstrated in studies of motor systems (e.g., Getting 1989; Kristan et al. 1988; Marder and Calabrese 1996), more recently it has become apparent that it is more universal. For example, reconfiguration of frontoparietal and frontotemporal networks has been observed during working memory tasks in humans (Braun et al. 2015).

Feeding in Aplysia is Episodic

Although CPGs that mediate certain ingestive behaviors can be continuously active (e.g., Selverston et al. 1976), most CPGs that control food intake have pauses between periods of activity. In some species the term “microstructure” has been used to describe the patterning of ingestive responses (Fig. 2) (Bowdan 1988; Davis and Smith 1992; Itskov et al. 2014; Ma et al. 2016; Mendez et al. 2016; Stellar and Shrager 1985). For example, when Drosophila feed, what are known as “sips” are organized into “bursts” (Itskov et al. 2014). There are multiple bursts per feeding session, and interburst intervals are significantly longer than intervals between sips. In Aplysia, investigators have not explicitly used the term microstructure but have described bouts of feeding responses (Susswein et al. 1983, 1984).

Repetition Priming in Feeding Behavior

A number of factors can determine or influence feeding microstructure. Namely, there is often an effect of the motivational state of the animal, i.e., how hungry it is (Davis et al. 1999; Itskov et al. 2014; Yapici et al. 2016). Second, characteristics of the ingested food can be important (Davis and Smith 1992; Itskov et al. 2014; Ma et al. 2016; Stellar and Shrager 1985). In a number of situations, changes in microstructure reflect a change in the total number of feeding responses, which produces an overall change in food intake. For example, the rate of food consumption generally decreases as animals satiate (Davis et al. 1999, 2001; Itskov et al. 2014; Yapici et al. 2016). In other situations, changes in microstructure reflect a change in the total number of feeding responses, which produces an overall change in food intake. Interburst intervals are significantly longer than interresponse intervals.

Fig. 2. Schematic representation of the microstructure of an episodic behavior such as feeding. Each tick represents an individual response (e.g., in the context of feeding a bite or a sip). Responses are grouped into bouts. Interbout intervals are significantly longer than interresponse intervals.
Microstructure is often characterized with the use of techniques that determine whether or not a response occurred. These data are used to compute response frequency (Davis and Smith 1992; Itskov et al. 2014; Wong et al. 2009). In *Aplysia*, investigators have also quantified changes in response magnitude (Cullins et al. 2015; Susswein et al. 1976; Weiss et al. 1986; Ye et al. 2006). Experiments utilizing these techniques have addressed the question of whether or not the efficacy of behavior is impacted by how it is patterned. That this is an interesting issue is suggested by the fact that variables that have the same general effect on overall response number do not necessarily have identical effects on feeding microstructure. For example, sham feeding in rats can increase the number of licks by increasing the number of clusters (without increasing cluster size). In contrast, within a certain range, increases in sucrose concentration increase cluster size (Davis and Smith 1992). This suggests that particular patterns of activity may be appropriate under different conditions. An interesting question without an obvious answer is, why would this be the case?

Experiments in *Aplysia* have studied the effect of patterning on the magnitude of radula opening and closing (i.e., food grasping behaviors) (Susswein et al. 1976; Weiss et al. 1986; Zhurov et al. 2005). This work has demonstrated that when intact animals begin to feed, the initial bite is relatively weak and ineffective. With successive responses, however, there are progressive increases in bite strength. Similar changes have been noted when ingestive responses have been monitored in semi-intact preparations (Zhurov et al. 2005). This indicates that there are changes in the efficacy of feeding in *Aplysia* as it stops and starts. Feeding responses are initially weak but are enhanced by repetition.

The progressive changes in feeding responses observed in *Aplysia* have been referred to as repetition priming (Cropper et al. 2014; Dacks et al. 2012; Friedman and Weiss 2010; Friedman et al. 2015; Proekt et al. 2004). Repetition priming is a tractable form of implicit memory that has been extensively documented in other species, including humans (Fowler et al. 1985; Kristjánsson and Campana 2010; Tresp et al. 1995; Yashar et al. 2013). In some of these situations the priming is not necessarily mediated by changes in motor or premotor pathways. In other cases, however, it clearly is (Tresp et al. 1995; Yashar et al. 2013). Thus repetition priming is ubiquitous and is becoming increasingly popular as a phenomenon that can be used to study implicit memory. Nevertheless, outside of the *Aplysia* research, there have been few efforts to characterize its underlying cellular/molecular mechanisms in a tractable model system.

**How Is Repetition Priming in the Feeding Network Mediated at the Cellular/Molecular Level?**

Episodic behavior is not unusual. In fact, it is probably more common than continuous activity. Consequently, mechanisms that induce dynamic changes in feeding in *Aplysia* potentially operate in a number of other systems. Experiments that have studied plasticity in feeding have taken advantage of the fact that motor activity can be induced in experimentally advantageous, “reduced” preparations. For example, feeding in molluscs can be triggered in preparations in which the periphery remains attached (e.g., in whole feeding head preparations) or in more reduced semi-intact preparations (Evans and Crop- 1998; Jing and Weiss 2005; Kabotyan et al. 2000; McClellan 1982; McManus et al. 2012; Weiss et al. 1986; Willows 1980). Additionally, feeding motor programs can be triggered in the isolated nervous system (Church and Lloyd 1994; Morgan et al. 2002; Rosen et al. 1991; Sánchez and Kirk 2001). Thus motor activity can be triggered in preparations that can be used to characterize cellular/molecular mechanisms responsible for dynamic changes in motor output.

In *Aplysia* (and many other model systems), motor activity is initiated in reduced preparations by stimulating neurons that provide input to the behavior-mediating CPG. These neurons can be sensory (Beenhakker et al. 2004; Beenhakker and Nusbaum 2004; Blitt et al. 2004; Combes et al. 1999), command (Frost and Katz 1996; Kupfermann and Weiss 1978), or command-like neurons (Church and Lloyd 1994; Kemenes et al. 2001; Rosen et al. 1991; Sánchez and Kirk 2001). In *Aplysia*, ingestive activity is most commonly triggered by stimulating a command-like cell, cerebral buccal interneuron 2 (CBI-2; Fig. 3) (Church and Lloyd 1994; Morgan et al. 2002; Rosen et al. 1991; Sánchez and Kirk 2001). CBI-2 is activated by food contact, and with steady-state stimulation it triggers biting-like movements in semi-intact preparations (Jing and Weiss 2005; Rosen et al. 1991). Egestive activity is most commonly triggered by stimulating the esophageal nerve (EN; Fig. 3) (Dacks and Weiss 2013; Friedman et al. 2009, 2015; Proekt et al. 2004, 2007; Siniscalchi et al. 2016; Zhurov et al. 2005). The EN contains the processes of sensory neurons that innervate the esophagus (Kulsansky et al. 1987). In intact

![Fig. 3. Organization of the feeding circuitry in *Aplysia*. Ingestive motor activity is triggered when food activates sensory neurons that excite cerebral buccal interneurons (CBIIs) such as CBI-2. CBI-2 is a cholinergic neuron that contains feeding circuit-activating peptide (FCAP) and cerebral peptide-2 (CP-2) (Koh et al. 2003; Morgan et al. 2000; Sweedler et al. 2002). CBI-2 activates the feeding central pattern generator (CPG), and with repeated stimulation an ingestive motor program is induced. Egestive motor activity is triggered when afferents with processes in the esophageal nerve (EN) are activated, e.g., by the presence of an inedible object. EN afferents also activate the feeding CPG and contain the modulatory peptides SCP (small cardioactive peptides), apNPY (*Aplysia* neuropeptide Y1), FMRFamide, and the RFamide peptides (Jing et al. 2007; Vilein et al. 2010; Wu et al. 2010). With repeated stimulation of the EN, egestive motor programs are triggered.](http://jn.physiology.org/10.1152/jn.00373.2017)
animals, rejection responses are triggered when an object that cannot be ingested makes esophageal contact (Kupfermann 1974b). Electrical stimulation of the EN in semi-intact preparations produces rejection movements (Chiel et al. 1986).

With repeated induction, the “articulation” of feeding motor programs improves. Because the efficacy of feeding behavior in *Aplysia* is influenced by its microstructure, it would be expected that episodic induction would impact feeding motor programs. A number of studies have demonstrated that this is the case. For example, when CBI-2 is stimulated, the first cycle of the evoked motor program is not well “articulated” (Fig. 4A) (Dacks et al. 2012; Friedman and Weiss 2010; Proekt et al. 2004, 2007). Activity in radula protraction motor neurons precedes activity in radula retraction motor neurons (as it should). However, radula closer motor neurons fire at a low frequency during both radula protraction and retraction. During protraction, radula opener motor neurons fire with the radula closer neurons at comparable (low) frequencies. Activity is referred to as being poorly articulated because it is not clearly patterned in what is likely to be a functional sense.

These data presumably provide at least a partial explanation for the observation that feeding responses triggered after a period of inactivity are relatively weak (Susswein et al. 1976; Weiss et al. 1986; Zhurov et al. 2005). In general, the amplitude of a muscle contraction in the feeding system is heavily influenced by motor neuron firing frequency (Cohen et al. 1978; Friedman et al. 2009). Consequently, low-frequency activity generally produces a weak contraction. Furthermore, in this context, the coactivation of antagonistic motor neurons is presumably counterproductive.

Motor programs change, however, if they are repeatedly induced and the intercycle interval is relatively short (i.e., tens of seconds instead of minutes). For example, the firing frequency of radula closer motor neurons progressively increases during radula retraction (Fig. 4A) (Dacks et al. 2012; Proekt et al. 2004, 2007), and the firing frequency of radula opener motor neurons progressively increases during protraction (Friedman and Weiss 2010; Friedman et al. 2009). Experiments conducted in semi-intact preparations have demonstrated that these increases in firing frequency are sufficient to alter radula movements. Thus frequencies observed after repetition priming are sufficient to significantly open and close the radula (Friedman et al. 2009). In contrast, frequencies observed during initial cycles of motor activity are not (Friedman et al. 2009).

With repeated stimulation of the “egestive” input to the CPG, the EN, “opposite” changes in motor activity are observed. Motor programs become egestive, in part due to progressive increases in the firing frequency of radula closing motor neurons during protraction (instead of retraction) (Fig. 4B) (Dacks et al. 2012; Proekt et al. 2004, 2007). Additionally, motor neurons that produce radula opening are recruited during radula retraction (instead of protraction) (Friedman et al. 2009, 2015).

To summarize, these data indicate that episodic induction impacts feeding motor programs. After a period of network inactivity, the initial motor program triggered is not well articulated. Antagonistic motor neurons that open and close the radula are coactive. Furthermore, these motor neurons fire at relatively low frequencies. With repeated induction, however, cycles of motor activity progressively change. Motor neurons fire at higher frequencies, and phase relationships of antagonistic motor neurons become more clearly defined.

Repetition priming is an example of a dynamic change in motor activity. It has been suggested that it is important to view multifunctional networks as continuous dynamical systems (Briggman and Kristan 2008). Thus, not only are multifunctional networks capable of generating more than one discrete

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**Fig. 4.** Repetition priming in the feeding circuit. Plotted is the firing frequency of a radula closer motor neuron during radula protraction (x-axis) and radula retraction (y-axis). Dashed lines mark clusters of ingestive and egestive activity. Cycles of activity were evoked with an intercycle interval of 30 s by using either CBI-2 to induce ingestive repetition priming (A) or the EN to induce egestive repetition priming (B). Insets are typical intracellular recordings from a radula closer motor neuron (RC; top trace) and extracellular recordings from the I2 nerve (bottom trace). Activity in the I2 nerve marks the protraction phase of the motor program. Note that in both A and B, the first cycle that was triggered was poorly articulated. The radula closer motor neuron fired at a relatively low frequency (cycle 1) in both A and B. With repeated input activation, however, program definition occurred. For example, with repeated stimulation of CBI-2, motor activity became clearly ingestive (e.g., the firing frequency of the radula closer motor neuron increased during retraction; A). With repeated stimulation of the EN, motor programs became egestive (e.g., the firing frequency of the radula closer motor neuron increased during protraction; B). [Data are replotted from Friedman et al. (2009) and Friedman and Weiss (2010).]
state, but they transition between states in a manner that has certain dynamics that can be described. Studies of repetition priming in the feeding network beautifully illustrate the importance of characterizing transition dynamics. For example, it has been demonstrated that with repetition priming, one type of motor program can slowly evolve into another; i.e., eggestive activity is slowly converted to ingestive (Proekt et al. 2004). As is described in more detail below, this finding has informed mechanistic experiments that that have sought to determine how repetition priming is mediated at the cellular/molecular level.

Modulatory neuropeptides reconfigure motor activity: chemical coding in the feeding network. A specific question that has been addressed is, why are feeding motor programs reconfigured when they are repeatedly induced with a relatively short intercycle interval? Interestingly, it has been noted that this does happen when motor activity is triggered using CBI-2 and the EN, but does not happen if motor activity is repeatedly triggered from within the CPG itself, e.g., by stimulating a protraction interneuron (Siniscalchi et al. 2016). Inputs to the feeding CPG, i.e., CBI-2 and the EN, contain modulatory neuropeptides (Fig. 3). For example, CBI-2, which is cholinergic (Hurwitz et al. 2003), also contains feeding circuit-activating peptide (FCAP) (Koh et al. 2003; Sweedler et al. 2002) and cerebral peptide 2 (CP-2) (Fig. 3) (Morgan et al. 2000). Occlusion (and other) experiments have indicated that both peptides play an important role in determining phase and timing relationships of motor neurons during ingestive motor programs (Friedman and Weiss 2010; Koh et al. 2003; Koh and Weiss 2005, 2007; Morgan et al. 2000).

Stimulation of the EN releases a number of modulatory neuropeptides, including small cardioactive peptide (SCP) (Wu et al. 2010) and Aplysia neuropeptide Y (apNPY) (Fig. 3) (Jing et al. 2007). In addition, neural processes in the EN contain FMRFamide and the FRFamide peptides (Vilim et al. 2010). FMRFamide and the FRFamide peptides act together to promote eggestive activity (Friedman et al. 2015; Vilim et al. 2010).

In summary, data indicate that modulatory peptides released when CPG inputs are repeatedly activated play an essential role in configuring motor activity as repetition priming occurs. One set of peptides makes activity ingestive; a second set makes activity eggestive. These results are consistent with the idea that a form of “chemical coding” is used in the selection of feeding motor programs.

A further question that has been addressed in the context of radula opening is, do ingestive and eggestive peptides act via different second messenger systems? Radula opening motor neurons are behavior specific. Thus, when motor programs become ingestive, the motor neuron B48 is recruited during the protraction phase of the motor program (Friedman et al. 2009). In contrast, a second motor neuron, B44, is recruited during the retraction phase when programs become eggestive (Friedman et al. 2009). In both cases, recruitment results from a peptide-mediated increase in motor neuron excitability. During ingestion, the excitability of B48 is increased by FCAP/CP2 released from CBI-2 (Friedman and Weiss 2010; Perkins et al. 2013; Perkins and Weiss 2012). During eggestion, the excitability of B48 is decreased (Perkins et al. 2013; Perkins and Weiss 2012), and the excitability of B44 is increased by SCP released from afferents with processes in the EN (Friedman and Weiss 2010; Wu et al. 2010). Effects of FCAP/CP2 are cAMP mediated, whereas effects of SCP are PKC mediated (Friedman and Weiss 2010; Friedman et al. 2015; Perkins et al. 2013; 2015). These data therefore suggest that chemical coding in the feeding system is observed intracellularly (as well as intercellularly).

The “chemical coding” notion dates back to at least the 1960s (Grossman 1960; Heller et al. 1980; Kupfermann 1967, 1970; Truman 1978). In a number of characterized circumstances, the behavior (or motor program) is specified by a hormone or blood borne substance. Effects of these blood borne substances are often studied in experiments in which they are bath applied and network alterations are determined under steady-state conditions. Ingestive and eggestive modulators in the Aplysia feeding system are obviously different. They are released as neurotransmitters from neurons that provide input to a network activated in an episodic manner. Consequently, motor activity changes progressively. Work in the feeding system therefore indicates that behavioral selection does not always occur in an all-or-none manner. Instead, it can occur in a progressive manner.

Multifunctionality in the feeding network. Research in other systems has established that the ability of a network to be multifunctional results from the fact that its anatomical connectivity is not necessarily the same as its functional connectivity (Briggman and Kristan 2008; Getting 1989; Marder 2012). Functional connectivity depends on factors that can vary, i.e., synaptic strength and neuronal excitability. Both types of network parameters are altered when the feeding network is reconfigured to generate either ingestive or eggestive activity (for specifics, see Dacks et al. 2012; Dacks and Weiss 2013; Friedman and Weiss 2010; Friedman et al. 2009, 2015; Proekt et al. 2004, 2007).

Neuromodulation as a general mechanism for repetition priming. Why do changes in feeding motor programs occur gradually? Currently, there is no definitive answer to this question, but it has been suggested that it is a consequence of the persistence of neuromodulation (Cropper et al. 2014). Presumably, effects of modulators released during one cycle of a motor program last for tens of seconds, so are still present if the next cycle of activity is triggered with a relatively short delay. Consequently, modulatory effects summate and become cumulatively larger (Fig. 5) (Cropper et al. 2014). This type of model presumably explains why repetition priming is not observed in the feeding network when interresponse intervals are relatively long (i.e., minutes as opposed to seconds).

All nervous systems appear to be subject to neuromodulation (Marder 2012). This makes it possible that neuromodulation serves as a mechanism for repetition priming in other systems. Furthermore, in the Aplysia feeding system, priming is observed because modulators are present within the feeding network itself. Consequently, they are classified as “intrinsic” (Cropper et al. 1987). This type of arrangement has been described in other systems. For example, it is observed in the circuitry that mediates escape swimming in Tritonia (Katz 1998; Katz and Frost 1995a, 1995b; Sakurai et al. 2006, 2007; Sakurai and Katz 2003, 2009). Here, serotonin is present in a CPG element, the dorsal swim interneuron (DSI). This cell exerts effects on a second interneuron, C2, which is also crucial for the behavior. Effects of 5-HT are in part mediated via interaction with metabotropic receptors (Clemens and Katz.
Repetition Priming Requires Repeated Activation of CPG Inputs So That Cycles of Motor Activity Are Triggered with a Relatively Short Intercycle Interval

As discussed above, data suggest that effects of modulators released during a single cycle of an Aplysia feeding motor program persist for seconds but not minutes (Friedman and Weiss 2010; Friedman et al. 2009, 2015; Proekt et al. 2004, 2007). However, effects of repetition priming clearly last longer (e.g., more than 10 min for ingestive priming; Friedman et al. 2009; Proekt et al. 2004). The difference is likely to be a consequence of the fact that it takes time for cumulative effects of modulators to dissipate. This is likely to be a consequence of the fact that it takes time for cumulative effects of modulators to dissipate. Because the summated signal is considerably larger than the modulatory signal generated by a single cycle of a motor program, it takes longer to dissipate.

Possible Physiological Consequences of Repetition Priming

Repetition priming requires repeated activation of CPG inputs so that cycles of motor activity are triggered with a relatively short intercycle interval (Cropper et al. 2014; Dacks et al. 2012; Friedman and Weiss 2010; Friedman et al. 2015). At present there are no data that directly indicate when this occurs in the intact animal. It is, however, most likely that it happens in the maintained presence of a stimulus (such as food). In this situation, there is likely to be maintained afferent activation, which will trigger repeated motor activity either directly (in the case of EN afferents) or indirectly (in the case of the sensory neurons that activate CBI-2). Furthermore, when food is continuously present, there are likely to be changes within the feeding CPG itself. Thus food presentation results in a form of operant conditioning that is manifested as changes in membrane and synaptic properties of pattern-initiating neurons (Brembs et al. 2004; Lorenzetti et al. 2006; Mozzachiodi et al. 2008; Nargeot et al. 2007, 2009; Sieling et al. 2014). These changes tend to make feeding movements more frequent and regular (which will obviously tend to promote repetition priming).

Energy Management. That feeding responses get progressively stronger when they are repeated makes sense given the fact that what is altered is a component of behavior that is important for moving food in or out of the buccal cavity (i.e., radula opening and closing). For example, in the context of ingestive activity, Aplysia presumably generate bites with weak radula opening/closing movements when they are in the vicinity of food but are not able to maintain contact with it. In contrast, when food contact is maintained, radula opening and closing are enhanced. This arrangement is likely to be energetically favorable in that food-grasping movements are only potentiated when they are actually needed (i.e., food is present so can be ingested).

"Energy management" in the context of feeding behavior has been demonstrated in other species. For example, Lymnaea generate two different types of bites: appetitive and consummatory (Crossley et al. 2016). The two types of bites differ in that swallowing motor neurons fire at a lower frequency when bites are appetitive. Consequently, they require less energy. When Lymnaea search for food, bites are appetitive (relatively low energy). Consummatory bites (high energy) are reserved for the situation where food is detected. Food-related changes
in feeding behavior are also observed in *Caenorhabditis elegans*. Namely, *C. elegans* feed on bacteria via rhythmic contractions and relaxations of the pharynx (i.e., pharyngeal pumping; Trojanowski et al. 2016). Pumping dynamics are influenced by the availability of food in the environment (Lee et al. 2017). Worms expend more energy (e.g., pump at a higher frequency) when the concentration of bacteria in the environment is high, and less energy when there is less food available (i.e., the concentration of bacteria is low).

**Role in stabilizing behavior.** Other physiological consequences of repetition priming in *Aplysia* presumably stem from the fact that it is mediated by modulatory neurotransmitters that exert persistent, second messenger-mediated effects. Interestingly, this can have an impact on the ability of the network to task switch. In the *Aplysia* feeding network this has been demonstrated in the situation where egersive repetition priming is followed by an attempt to induce an ingestive cycle of a motor program (Fig. 6). In this situation a form of task set inertia is observed (Proekt et al. 2004). Thus, immediately after egersive repetition priming, stimulation of the ingestive input to the CPG (CBI-2) triggers a cycle of a motor program that is egersive. Activity only gradually becomes ingestive as CBI-2 stimulation is maintained.

It is possible that inertia in this context is beneficial because it serves as a “stabilizer.” Thus it is likely that it would make behavior relatively resistant to disruption due to a brief, and therefore inconsequential, alteration in the external environment. In the context of feeding, it may be important to “stabilize” the egersive state because this state may be a reflection of the maintained presence of a noxious or harmful stimulus. Task-switch inertia is not unique to *Aplysia*. It has been documented in a number of species (including humans) (Bratzke et al. 2009; Heuer et al. 2004; Orban de Xivry and LeFèvre 2016). However, in higher order animals, cellular/molecular changes that impair task switching have not been described.

**Summary and Conclusion**

In this review we describe dynamic changes in motor activity that are observed during an episodic behavior—feeding in the mollusk *Aplysia*. In this experimentally advantageous system, much progress has been made in experiments that have demonstrated that episodic induction results in dynamic reconfiguration of network activity. Activity is reconfigured by intrinsic neuromodulators that exert effects that persist and summate. This is likely to be responsible, at least in part, for the progressive increases in the magnitude of feeding responses that are observed when they are repeatedly generated.

Many human behaviors, like feeding in *Aplysia*, are episodic. Furthermore, they are mediated by neural networks that contain intrinsic neuromodulators. These modulators exert persistent second messenger-mediated effects that have the potential to summate. It is, therefore, likely that a number of episodic behaviors are dynamically altered as they stop and start via mechanisms that are similar to those that mediate repetition priming in the *Aplysia* feeding network. In future work it will be important to determine whether this is indeed the case.

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