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Neuromodulation as a mechanism for the induction of repetition priming

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Abstract

It is becoming apparent that the activity of many neural networks is shaped by effects of endogenous neuromodulators. Modulators exert second messenger-mediated actions that persist. We consider how this may impact network function and its potential role in the induction of repetition priming (increased performance when behavior is repeated). When effects of modulators persist and modulatory substances are repeatedly released, their effects will accumulate (summate) and become more pronounced. If this enhances the ability of a network to generate a particular output, performance will improve. We review data that support this model, and consider its implications for task switching. This model predicts that priming of one type of network activity will negatively impact the rapid transition to an incompatible type.

Introduction

Many neural networks are subject to modulation, which is essential for normal functioning. Recently there have been a number of comprehensive reviews that have addressed the question: Why is this modulatory input important? A consensus that has emerged is that it is essential for functional flexibility because it overcomes the inherent limitations of a hard-wired network [1–5]. How this can be achieved has been extensively reviewed at both cellular and molecular levels.

This review focuses on an important topic that has been less extensively discussed. Namely, we consider potential consequences of the persistence that is characteristic of

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neuromodulation. More specifically, we focus on persistence that lasts on the order of seconds and minutes. Further, we consider a particularly interesting situation—one in which modulator release is coupled to network activity, e.g., endogenous modulators are phasically released every time a cycle of activity is generated. This includes, but is not limited to the situation where modulators are intrinsic to the central pattern generator (CPG) itself. If modulatory actions persist, this is likely to lead to a situation where effects of modulators summate and cumulative effects become larger as activity progresses (Fig. 1B). We suggest that this type of mechanism is ideally suited for the induction of a well-known phenomenon—repetition priming (Fig. 1A). Repetition priming is defined as a progressive improvement in performance when behavior is repeated. Thus *a very effective means of inducing an activity-dependent, progressive improvement in behavior is via cumulative effects of endogenously released modulatory substances.*

That this occurs under physiologically relevant conditions is suggested by work in an experimentally advantageous model system—the feeding system of the mollusc *Aplysia*. Below we briefly review some of this work. Subsequently, we discuss similarities between the *Aplysia* feeding system and other systems.

The *Aplysia* feeding system

The *Aplysia* feeding network is multifunctional and generates both ingestive and egestive behaviors [6]. During ingestion the radula, the food-grasping organ, is open as it protracts (i.e., moves forward) and is closed as it retracts (i.e., moves backward). This pulls food into the buccal cavity. During egestion the radula is closed as it protracts and open as it retracts. This pushes food out. Repetition priming has been demonstrated at the behavioral level, e.g., progressive increases in the magnitude of biting responses are observed as animals begin to repetitively feed [7].

Repetition priming in *Aplysia* has also been extensively studied *in vitro*. These experiments take advantage of the fact that feeding motor programs can be triggered using inputs that drive ingestive or egestive responses. An ingestive input is a command-like projection neuron, CBI-2 [8]. CBI-2 receives excitatory input from sensory neurons activated when food contacts the lips [8]. Egestive activity is triggered by stimulating a branch of the esophageal nerve (EN) (e.g., [9, 10]. The EN contains processes of sensory neurons innervating the gut [11, 12].

Interestingly, when a single cycle of a motor program is triggered in a quiescent preparation, evoked activity is neither ingestive nor egestive (Fig. 2A) [9]. Instead motor programs are poorly defined and are referred to as having ‘intermediate’ characteristics. This is the case both when activity is triggered by stimulating CBI-2, and when activity is triggered by stimulating the EN. In this situation, the network is in a default state [13]**.

When an input is repeatedly activated so that multiple cycles of motor programs are induced, however, program definition occurs (Fig. 2A) [13**–18]**. With repeated stimulation of CBI-2, activity becomes progressively more ingestive. With repeated stimulation of the EN, activity becomes progressively more egestive. Progressive changes in motor neuron activity that are observed under these conditions are sufficient to produce significant changes in

feeding movements. For example, when CBI-2 is repeatedly stimulated there are progressive increases in the firing frequency of the radula opener motor neuron B48 that persist after CBI-2 stimulation ceases (Fig. 2B). Changes in motor neuron activity are sufficient to alter the magnitude of radula opening movements [17].

To determine how these persistent changes are mediated, experiments have focused on modulatory substances that are released by input activation. CBI-2 contains acetylcholine, which can exert muscarinic effects on the feeding circuitry [13, 19] and two modulatory neuropeptides CP-2 and FCAP [20–23]. EN afferents contain and release several neuropeptides including *Aplysia* Neuropeptide Y (aNPY) [24], the Small Cardioactive Peptides (SCPs) [25], and the FRFamide peptides [26].

To tie effects of modulators to repetition priming, analytical experiments have been performed at key sites in the feeding circuitry. This work has focused on motor neurons that open and close the radula since the phasing of this activity is altered when there are changes in the ingestive vs. egestive nature of feeding motor programs [27]. For simplicity this review will focus on one locus where effects of modulators are particularly well characterized—changes in the activity of a motor neuron that produces radula opening (B48).

As motor programs become ingestive, there are progressive increases in B48's firing frequency that result from progressive increases in its excitability [17, 18]**. Excitability increases in B48 persist and outlast periods of CBI-2 stimulation [17]. They are observed when FCAP and CP-2, the two peptides present in CBI-2, are exogenously applied, and importantly, peptide application occludes effects of repetitive CBI-2 stimulation [18]**. Effects of FCAP/CP-2/CBI-2 on B48 excitability are cAMP mediated [18]**. For example, they are mimicked by application of the cAMP analog 8-Br-cAMP, which also produces increases in B48's firing frequency during motor programs. Further, peptide effects are enhanced and prolonged in the presence of the phosphodiesterase inhibitor IBMX. Finally, Rp-cAMP blocks both peptide and CBI-2 induced increases in excitability.

To summarize, ingestive and egestive inputs to the feeding circuitry contain modulators that exert second messenger mediated effects that persist after input activation ceases. With repetitive input activation effects of modulators become cumulative and there are progressive alterations in motor neuron activity. This leads to progressive enhancements in feeding movements, i.e., repetition priming.

Endogenous modulation in other systems

In the *Aplysia* feeding system endogenous modulators are present in projection neurons and sensory neurons that trigger activity. This type of arrangement has been described. The best-characterized example is the crustacean stomatogastric ganglion (STG) (see Fig. 2 in [1] for a recent diagram that summarizes characterized modulatory input to the STG). Persistent effects of stimulation of STG projection neurons, or neurons that excite projection neurons have been noted (with differing time constants) [28, 29]. Differences in timing have also been noted in the *Aplysia* feeding system (e.g., effects of ingestive repetition priming often last longer than effects of egestive priming) [14]. In the feeding system these differences are likely to reflect, at least in part, differences in the second messenger systems utilized.

Interestingly not all of the modulatory input to the STG arises in this manner. Some modulatory input is referred to as ‘tonic’ and consists of substances that are released into the hemolymph. Tonic STG modulators appear to be important for maintaining basal circuit function [30–32]**. For example, dopaminergic tone regulates the conductance of a transient potassium current (I_A) via a mechanism that is dependent on translation [32]**. Not all effects of dopamine on the STG are however tonic, i.e., there are also ‘phasic’ effects. Interestingly, tonic effects of dopamine differ from (actually oppose) phasic effects. For example, tonic dopamine produces an increase in the I_A $G_{\max}$ whereas phasic dopamine produces depolarizing shifts in the voltage dependence of I_A . *Thus the stomatogastric nervous system is a well-characterized system in which phasic modulatory actions can be contrasted with a second type of modulation (tonic).*

In some systems modulators are intrinsic to the CPG itself. This clearly results in a situation where modulator release is closely tied to network activity. One of the first systems where this was described is the circuitry that mediates escape swimming in *Tritonia* [33–39]. Here serotonin is present in a CPG element, an identified neuron known as 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 [40, 41] and persist long enough so that they are likely to carry over from cycle to cycle [42].

An advantage of the invertebrate networks discussed above is that they are well characterized, e.g., individual neurons are re-identifiable and consequently are functionally characterized. It is therefore (relatively) simple to determine whether or not they are a part of the actual CPG. In the vertebrate networks these distinctions are not always as clear. Nevertheless it is apparent that vertebrate networks are heavily modulated by endogenous neural input. For example, the Pre-Botzinger (PreBotC) respiratory network receives aminergic and peptidergic input that is essential for maintaining normal activity (for review see [43]). When hypoxia alters its ability to respond to norepinephrine, activity becomes irregular [44]*.

It has long been apparent that the vertebrate locomotor CPG receives ‘extrinsic’ modulatory input from the brainstem [45]. Additionally, however it is becoming increasingly apparent that it is regulated by modulators that are intrinsic to the spinal cord. For example, ACh released from spinal VO_c neurons binds to m2 receptors on motor neurons to increase motor neuron excitability and make motor neurons more responsive to input. VO_c activity is tightly phase-locked to motor neuron activity during fictive locomotion [46]. Effects of nitric oxide (NO) on locomotor activity have also been demonstrated in the tadpole [47], lamprey [48, 49] and more recently in the mouse [50]. In the mouse and lamprey, nitric oxide effects are cGMP mediated [48, 50]. In the mouse persistent effects of relatively low NO concentrations induce long-lasting enhancements of the amplitude of locomotor network output [50].

An important theme that is emerging from work on both vertebrate and invertebrate networks is that small molecule transmitters can themselves exert modulatory effects via metabotropic glutamate receptors (e.g., [43, 51]), GABA_B receptors [43, 52]**, and

muscarinic ACh receptors [19, 46, 53]. These effects can be quite complex (e.g., see [52]** for a recently described situation where effects of GABA are exerted over three timescales). Some of these situations constitute clear cases of intrinsic modulation. *Thus, the view that is emerging is that endogenous, often intrinsic modulation may be more of a rule than an exception.*

Repetition priming is observed in many contexts

The phenomenon repetition priming is of considerable general interest since it is a tractable form of implicit memory. Consequently, it has been extensively studied in psychology experiments using human subjects. For example, an early use of the term was to describe effects of pre-exposing subjects to words with a common ‘morphology’ [54]. Related research has also demonstrated priming in situations where recognition of faces or objects is impacted by repeated presentation (for review see [55]). In some of these tasks there is a motor as well as sensory component. For example, one recent study (of the priming of Pop-out) specifically demonstrated a role of the motor response [56]*. In these experiments subjects searched for a color singleton target and either responded to its shape (go trial) or passively watched the display (no go). Repetition effects were larger after go trials.

Other studies have demonstrated repetition priming using sound stimuli (e.g., [57]) and in experiments that studied effects of anoxia on respiratory activity [58]. More recently priming has even been demonstrated during cognitive tasks (i.e., mathematical problem solving) [59]. In summary, repetition priming is observed in a number of contexts and is becoming increasingly popular as a tool for the study of implicit memory. Nevertheless, its underlying cellular/molecular mechanisms are currently not well understood. This is likely to change as tractable model systems are characterized where it can be studied.

General implications of these findings for future work

The suggested model, in which repetition priming is mediated via persistent effects of endogenous modulators, has interesting implications for task switching. Namely it predicts that a ‘cost’ may be observed if one behavior ceases and another begins shortly thereafter. This has in fact been demonstrated in ‘input switching’ experiments in the *Aplysia* feeding network (Fig. 2C) [14, 16, 17]. For example, if an egestive state is induced by repeated EN stimulation and a cycle of activity is then induced by stimulating CBI-2, this cycle will be egestive rather than intermediate (or ingestive). Task-switch costs are observed in other species (e.g., humans), and can significantly impact performance [60, 61]. In future work it will be of interest to determine how they arise on a cellular/molecular level, and whether endogenous modulators play a role in systems other than the *Aplysia* feeding network. Further, it will be of interest to determine whether repetition priming and task-switch costs commonly go hand in hand.

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Highlights

- Many networks are persistently modulated by endogenous input
- Modulator release is often ‘phasic’ and closely tied to network activity
- Effects of modulators can become cumulative with repeated network activity
- Cumulative effects of neuromodulation can lead to repetition priming

Figure 1.

Schematic representation of the suggested role of endogenous modulation in the induction of repetition priming. (A) Repetition priming is induced when stimuli are applied with a short interstimulus interval (ISI) (red-orange panel). Repetition priming is manifested as progressive improvements in performance, which can be measured in a number of ways (e.g., as progressive decreases in latency (or increases in speed), as progressive increases in accuracy, or as progressive increases in response amplitude (magnitude)). Note that effects of repetition priming persist (right of red-orange panel). This is apparent when the ISI is lengthened, i.e., returned to the control value. (B) Our model postulates that priming can result from effects of modulators, which summate and become progressively larger with network activation with a short ISI (red-orange panel). Effects of repetition priming persist because it takes time for cumulative effects of modulators to dissipate (right of red panel).

Figure 2.

(A) *Light blue*, Repetition priming in the feeding network of *Aplysia*. When ingestive (CBI-2) or egestive (EN) inputs are stimulated in a rested preparation the first cycle of induced activity is poorly defined, i.e., it has intermediate characteristics. It is only with repetitive input activation that motor programs become either ingestive or egestive. *Pink*, With infrequent input activation programs lose their ingestive or egestive character. (B) Persistence of repetition priming, manifested as an increase in firing frequency of the radula opener motor neuron B48. *Left of dashed line*, Cycles of activity induced by stimulating CBI-2 with a relatively short ISI. This induces repetition priming (here manifested as a progressive increase (build-up) in the firing frequency of the 'ingestive' motor neuron B48). *Right of dashed line*, Cycles of activity induced by stimulating CBI-2 with a relatively long ISI, following repetition priming. Note that effects of repetition priming persist, i.e., it takes time for the B48 firing frequency to return to control levels. (C) Task-switch costs are observed in the *Aplysia* feeding network. For example, when a cycle of activity is induced by stimulating the ingestive input CBI-2 following a period of egestive activity, the cycle is egestive (dark blue).