Animal-to-Animal Variability in Neuromodulation and Circuit Function

ALBERT W. HAMOOD AND EVE MARDER

*Volen Center and Biology Department, Brandeis University,
Brandeis University, Waltham, Massachusetts 02454*

Correspondence: marder@brandeis.edu

Each animal alive in the world is different from all other individuals, while sharing most attributes of form and function with others of the same species. Still other attributes are shared within a phylum, and still others are common to most eukaryotic organisms. All animals have mechanisms that modulate the strength of their synapses or alter the intrinsic excitability of component neurons. What animal-to-animal variability in behavior arises from differences in neuronal structure, ion channel expression, or connectivity, and what variability arises from neuromodulation of brain states? Conversely, can robust behavior be maintained despite variability in circuit components by the action of neuromodulatory inputs? These are fundamental issues relevant to all nervous systems that have been illuminated by many years of study of the small, rhythmic motor circuits found in the crustacean stomatogastric nervous system.

In the early days of circuit study, the crustacean stomatogastric nervous system was considered a “simple system” (Maynard 1972; Fentress 1976) because the single stomatogastric ganglion (STG) found in each animal has only 27 to 30 neurons and generates stereotyped and rhythmic motor patterns. The STG quickly became a preferred preparation for the study of the mechanisms underlying the generation of rhythmic movements (Mulloney and Selverston 1974a,b; Selverston and Mulloney 1974; Hartline and Maynard 1975; Selverston et al. 1976; Hartline 1979; Hartline and Gassie 1979; Miller and Selverston 1982a,b) because when removed from the animal and placed in physiological saline, it continues to generate fictive motor patterns that resemble closely those that are seen in vivo (Fig. 1).

The pioneering work on the STG and on other “simple systems” preceded much of what we know today about the richness of ion channel diversity and neuromodulator function. Consequently, the initial goals of those seeking to understand the central pattern generating circuits that drove rhythmic movements were to (1) establish the wiring diagram, or connectivity among the neurons of the circuit, and (2) determine if a given neuron was part of the central pattern generating circuit or was merely being driven by the central pattern generating circuit. These goals were subsequently modified when it became clear that central pattern generating networks are richly modulated by tens of amines and neuropeptides (Marder 2012). Moreover, synaptic strength and intrinsic membrane properties also depend strongly on the recent history of neuronal activity (Turrigiano et al. 1996; Manor et al. 1997, 2003; Goaillard et al. 2010). Thus, the challenge is to explain how the rich dynamics of a circuit arise from its cellular mechanisms. This requires exploring the full ranges of circuit outputs that are produced by normal,

healthy individuals (Bucher et al. 2005; Goaillard et al. 2009; Hamood et al. 2015). It also requires understanding how neuromodulatory inputs can alter circuit performance without disrupting appropriate physiological actions (Marder 2012).

THE RANGE OF NORMAL PYLORIC RHYTHMS

The crustacean stomatogastric nervous system (Fig. 1A) consists of four ganglia: the single STG, the midline esophageal ganglion (OG), and the paired commissural ganglia (CoGs). The STG produces two major motor patterns: the fast triphasic pyloric rhythm (Fig. 1) and the slower gastric mill rhythm. Sensory neuron activation organizes activity in sets of descending neuromodulatory inputs that reside in the CoGs and OG, which in turn influence both the pyloric and gastric mill rhythms (Harris-Warrick and Marder 1991; Nusbaum and Beenhakker 2002; Beenhakker and Nusbaum 2004; Blitz et al. 2004; Marder and Bucher 2007; Blitz and Nusbaum 2011).

In vivo recordings of the pyloric rhythm from a variety of species and temperatures show periods of ~2.5 sec in fasting animals and periods closer to 1 sec after feeding (Rezer and Moulins 1983; Clemens et al. 1998, 1999; Soofi et al. 2014). An important feature of the pyloric rhythm in vivo is that it is always present, except just at molting (Clemens et al. 1999).

The preponderance of work on the STG has been done with in vitro preparations in which fictive motor patterns are recorded from the nervous system after it has been dissected off the surface of the stomach (Fig. 1A). When the anterior modulatory inputs are left intact, the pyloric rhythm is invariably active, with characteristic pyloric

Figure 1. (A) Schematic diagram of the stomatogastric nervous system (STNS), as pinned out for electrophysiological recordings. The motor neurons of the pyloric rhythm reside in the stomatogastric ganglion (STG, center), whereas modulatory inputs arrive from anterior ganglia including the paired CoGs and the OG. Activity in the pyloric rhythm may be monitored extracellularly by recording from the lateral ventricular nerve (lvn). (B–D) Example lvn recordings from three preparations of the STNS, showing spontaneous pyloric rhythms. Although frequencies vary, approximate phase relationships between the pyloric (PY), pyloric dilator (PD), and lateral pyloric (LP) neurons are maintained. (E) Histogram shows the distribution of pyloric frequencies for intact preparations of the STNS ($N = 123$). (F) Pyloric phase relationships are approximately maintained across frequency for the pyloric rhythm of the same $N = 123$ intact preparations. Phase is quantified relative to PD on. Lines represent fits by linear regression. (E,F, Adapted from Hamood et al. 2015.)

rhythm frequencies in the 1-Hz range. Raw traces from three different preparations are shown in Figure 1B–D, with activity in the PD, LP, and PY neurons indicated. Although these preparations exhibit rhythms of different frequencies, their phase relationships (relative timing) are maintained. Figure 1E shows pooled data from 123 preparations showing the range of pyloric rhythm frequencies generated under these standard control conditions (Hamood et al. 2015). Note that there is an approximately threefold range in frequencies, but over this range of frequencies, the phases are frequency-invariant (Fig 1F). This robust phase maintenance ensures that the associated muscles at the output of the circuit are activated in a

sequential manner, with their relative timing, and thus appropriate behavior, preserved.

The mechanisms that underlie the maintenance of phase over this range of frequencies have intrigued investigators, because membrane and synaptic currents have characteristic time constants, which would tend to create fixed delays, not constant phase (Hooper 1998; Manor et al. 2003; Hooper et al. 2009; Tang et al. 2010), and it is thought that phase maintenance requires the interaction of multiple synaptic and intrinsic conductances (Manor et al. 2003; Tang et al. 2010).

PYLORIC RHYTHMS IN THE ABSENCE OF NEUROMODULATION

When the descending neuromodulatory inputs are removed, the pyloric rhythm slows down or sometimes stops (Fig. 2; Russell 1979; Miller and Selverston

Figure 2. (A) Schematic diagram of the STNS including location of nerve transection known as decentralization. This perturbation severs modulatory inputs to the STG. (B–D) Example lvn recordings from the same three preparations as in Figure 1, 30 min following decentralization. (E) Histogram shows the distribution of pyloric frequencies for preparations of the STNS decentralized for 30 min ($N = 115$). (F) Pyloric phase relationships for the same $N = 115$ decentralized preparations show a stronger correlation with pyloric frequency than for those left intact. Phase is quantified relative to PD on. Lines represent fits by linear regression. (E,F, Adapted from Hamood et al. 2015.)

1982a,b; Moulins and Cournil 1982; Hamood et al. 2015). Although it has long been known that these modulatory inputs provide an excitatory drive to the network required for output in the normal frequency range, recently it has been shown that other features of the pyloric rhythm are also affected (Hamood et al. 2015). As the rhythm becomes less frequent, phase relationships between pyloric neurons advance beyond the range seen in intact controls (Fig. 2F). These phase relationships become highly correlated with pyloric frequency, compared with the weak or nonexistent correlations measured from intact preparations (Bucher et al. 2005). Additionally, the output of the pyloric rhythm becomes much more variable, reminiscent of the increased variability in the low-frequency rhythms seen in development (Richards et al. 1999; Richards and Marder 2000). Across animals, this increase in variability can be measured by the coefficient of variation (CV), which increases for all examined properties of the pyloric rhythm, including frequency, phase relationships, and the number of spikes per burst of pyloric cells (Fig. 3A). An increase in variability can also be seen within preparations, as the average cycle-to-cycle variability in the pyloric rhythm is also increased following loss of modulatory inputs (Fig. 3B,C). These changes occur rapidly within 15–30 min following decentralization, and persist as preparations are maintained in culture for up to weeks (Hamood et al. 2015).

Figure 3. (A) Across-animal variability in many features of the pyloric rhythm increases following decentralization, as measured by the CV. (B) Histogram shows the average cycle-to-cycle variability in pyloric frequency, as a percentage, for $N = 123$ intact preparations of the STNS. Bar on the far right indicates all preparations with a $>20\%$ average pyloric cycle variability. (C) Histogram shows the average cycle-to-cycle variability in pyloric frequency, as a percentage, for $N = 115$ preparations of the STNS 30 min following decentralization. Bar on the far right indicates all preparations with a $>20\%$ average pyloric cycle variability. (B,C, Adapted from Hamood et al. 2015.)

ORIGINS OF VARIABILITY

Modeling work done on the pyloric rhythm has shown that it is possible to construct pyloric-like output from circuits with variable underlying conductance parameters (Prinz et al. 2004). Even while preserving the network connectivity, large variation in ionic and synaptic conductances can be tolerated, provided that these variables are appropriately balanced. However, neuromodulation is also likely to be highly variable across animals (Spitzer et al. 2008; Williams et al. 2013). Originally motivated by theoretical studies that showed that multiple parameter solutions can produce very similar behaviors (Goldman et al. 2001; Golowasch et al. 2002; Prinz et al. 2004; Golowasch 2014), we and others measured the variability in individual cellular and synaptic parameters in the same identified neurons in many animals (Schulz et al. 2006, 2007; Khorkova and Golowasch 2007; Goaillard et al. 2009; Grashow et al. 2010; Temporal et al. 2012, 2014; Shruti et al. 2014).

Figure 4 collects data from several studies of quantitative mRNA measurements from PD neurons for many ion channels and gap junction proteins. In all cases, a significant spread of at least twofold to sixfold is observed (Schulz et al. 2007, 2008; Temporal et al. 2012, 2014; Shruti et al. 2014). Similar results from STG neurons have been shown for features such as input resistance (Grashow et al. 2010), ionic conductances (Golowasch et al. 1999; Goldman et al. 2001), coupling coefficients of electrically coupled neurons (Shruti et al. 2014), and synaptic strengths (Goaillard et al. 2009). Similar ranges of variability are seen in measurements of synaptic strength from the leech (Norris et al. 2011; Roffman et al. 2012).

Given the measured variability in individual neuronal and synaptic properties, this raises the question of how this variability is influenced by neuromodulation. Does neuromodulation contribute to neuronal variability, or does it compensate for it? Or both?

Although this answer may depend on the system studied, in the STG the increase in variability following the loss of neuromodulatory inputs suggests that these inputs may be able to compensate for underlying neuronal variability. For example, Figure 5A,B shows pyloric rhythms from two animals that, when recorded with modulatory inputs intact, produce similar output patterns. However, following decentralization (removal of the modulatory inputs) these rhythms become very different from each other (Fig. 5C,D). A straightforward interpretation of these data is that these two pyloric rhythms are produced by networks with very different parameters, including both variable ionic conductance densities and synaptic strengths, and that the descending modulation compensates for these differences. This could arise either because the effects of the descending modulatory inputs are also variable, or because of state-dependent neuromodulation (Gutierrez and Marder 2014; Marder et al. 2014).

Certainly, the extensive array of modulatory substances released on the STG from these descending inputs (Marder and Bucher 2007) grants innumerable opportunities for such variation: in the number or relative location

Figure 4. Quantitative polymerase chain reaction results showing measured mRNA copy number, in PD neurons, for many ion channels proteins including voltage-activated calcium channels, cation channels, and gap junctions. (Adapted from Schultz et al. 2006, Temporal et al. 2014, and Shruti et al. 2014.)

of their associated G-protein-coupled receptors (Rodgers et al. 2011a,b, 2013); in the concentrations and specific locations from which they are released (Blitz and Nusbaum 2011, 2012; Nusbaum and Blitz 2012); and in the relative abundance of various neuropeptides, which each also vary in the subset of pyloric neurons on which they converge (Swensen and Marder 2000, 2001; Thirumalai and Marder 2002). Thus, it is possible that when these modulatory inputs are removed from each animal, the direct impact of this removal is more or less extreme (Fig. 5).

NEUROMODULATION CAN INFLUENCE CORRELATIONS IN CONDUCTANCE EXPRESSION

Although variability in the measured features of pyloric neurons has now been repeatedly shown, this variability is not without structure. Many positive correlations have been demonstrated between the mRNA levels of various ion channels and conductances in the neurons of the STG, suggesting that they are regulated in a coordinated fashion (MacLean et al. 2003, 2005; Khorkova

Figure 5. (A,B) Example lvn recordings from two intact preparations of the STNS showing highly similar pyloric rhythms. (C,D) Following decentralization, after 30 min these same two preparations show highly divergent responses to the perturbation, with dissimilar pyloric rhythms.

Figure 6. Correlations between mRNA levels in individual PD neurons following 72 h in culture with anterior ganglia left attached (intact, *top row*) or decentralized (*bottom row*). Lines represent linear fits when significant. Several significant positive correlations between mRNA expression levels are observed in the intact population; however, these correlations are lost in preparations maintained in the absence of neuromodulatory inputs. (Adapted from Temporal et al. 2014.)

and Golowasch 2007; Schulz et al. 2007; Temporal et al. 2012, 2014), and correlations are found in neuronal models with similar properties (Hudson and Prinz 2010). Although the measured correlations may not be necessary for the electrophysiological properties of the neurons (Taylor et al. 2009), recent theoretical work shows that neuronal-specific correlations can arise from simple homeostatic tuning rules (O’Leary et al. 2013, 2014) that function at the level of transcription and translation.

It remains largely unknown what role neuromodulation plays in the coordination of this variability, but recent experimental work suggests it might be important. In PD neurons maintained for 72 h following removal from the animal, correlations in mRNA levels seen in intact animals were lost when modulatory inputs were removed (Fig. 6; Khorkova and Golowasch 2007; Temporal et al. 2014). The mechanism by which modulatory influences might be able to produce such coordination at the molecular level is unknown.

A proof of principle that shows that variability at the level of a single neuron can be compensated by variability elsewhere comes from dynamic clamp studies in which single neurons with highly variable properties were connected by reciprocal inhibition to a simple model neuron (Grashow et al. 2010). By varying the strength of the synapses and adjusting the amount of I_H used, two-neuron circuits with similar behavior could be produced (Fig. 7). The range of the conductances needed to compensate for the variability in the individual neurons was approximately threefold, surprisingly similar to the ranges in actual measured conductances in parameters across animals (Grashow et al. 2010).

CONCLUSION

At first glance, the STG, a small circuit with well-defined connectivity (Marder and Bucher 2007), appears

simple; but extensive neuromodulation, coupled with the variability of its underlying neuronal and synaptic parameters, makes it remarkable that its function is so robust (Fig. 1). More than 30 years ago, when it was first evident that neuromodulatory influences could alter STG motor patterns (Beltz et al. 1984; Eisen and Marder 1984; Hooper and Marder 1984), the notion was that neuromodulation would provide additional behavioral flexibility to the nervous system, and this has remained an important tenet of our understanding of neuromodulation across the animal kingdom (Harris-Warrick and Johnson 2010; Harris-Warrick 2011; Bargmann 2012; Marder 2012). Nonetheless, it quickly became apparent that the activity patterns of any network at a given time are specified by the modulatory environment at that time. In behaving animals, circuits are never devoid of the influences of modulators found in circulating hormones or released from specific inputs. Consequently, as important as the connectivity of a circuit is for understanding its dynamics, it is equally important to specify the neuromodulatory condition of the network that will produce the final network configuration (Brezina 2010; Harris-Warrick 2011; Bargmann 2012; Gutierrez and Marder 2014; Marder et al. 2014).

In the STG, numerous different neuromodulatory substances can strongly activate robust pyloric rhythms (Hooper and Marder 1987; Marder et al. 1987; Nusbaum and Marder 1988; Weimann et al. 1993, 1997). This raises the possibility that the presence of multiple neuromodulatory inputs with similar but not identical physiological actions can also help ensure robustness, especially as these modulatory mechanisms can counteract some of the potentially deleterious consequences of variability in channel and receptor densities over the animal’s lifetime. Consistent with this interpretation, pyloric rhythms deprived of neuromodulatory inputs become more variable both within and across animals, lose their

Figure 7. (A) Schematic diagram of the hybrid model neuron-LP neuron circuit used in Grashow et al. (2010). ML, model Morris-Lecar neuron. LP, biological LP neuron. They are coupled by mutual inhibitory synapses via dynamic clamp. Both the I_h and synaptic conductances of the model neuron were systematically varied while connected to each of 12 different LP neurons. (B) Points show the locations in conductance space for the model neuron where each of the 12 LP-ML circuits produced a highly similar half-center oscillator. Conductances must vary across a several-fold range in the model neuron to compensate for variability across LP neurons and produce conserved circuit function. (C,D) Example traces for two LP-ML circuits, marked by shapes corresponding to their locations in B. (Adapted from Grashow et al. 2010.)

robust phase relationships, and show fewer correlations in mRNA expression levels.

Many interesting questions remain. By what mechanism are these modulatory inputs regulated? How variable are they across animals? And what role is played by the large amount of degeneracy in these modulatory systems? Additionally, it remains to be seen to what extent the role of neuromodulation with respect to neuronal variability varies depending on the system studied. In central pattern generating networks like the STG, proper behavior demands a stereotypical output pattern that is highly similar across animals, and thus neuromodulation may be tuned to reduce variability. In other systems, such as neocortex, variability in neuronal output may increase information content and thus be a desired network feature.

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Corrigendum

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Corrigendum: Animal-to-Animal Variability in Neuromodulation and Circuit Function

ALBERT W. HAMOOD AND EVE MARDER

In the original version of this article, Figure 5B was inadvertently duplicated as Figure 5D. The authors apologize for this error. The correct version of Figure 5 is printed below, and Figure 5 has been replaced in the current PDF version of the article.

Figure 5. (A,B) Example lvn recordings from two intact preparations of the STNS showing highly similar pyloric rhythms. (C,D) Following decentralization, after 30 min these same two preparations show highly divergent responses to the perturbation, with dissimilar pyloric rhythms.

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