Figures and figure supplements

Generalization of learned responses in the mormyrid electrosensory lobe

Conor Dempsey et al
Figure 1. Canceling the effects of the EOD under natural conditions requires generalization. (A) Schematic of ELL circuit elements responsible for cancellation of self-generated electrosensory responses. Granule cell corollary discharge responses form a temporal basis (blue trace at left) that is shaped by an anti-Hebbian spike-timing dependent synaptic plasticity rule into a negative image of the predictable sensory response to an EOD (blue trace at right). Signals related to the EOD (orange traces, left and right), along with behaviorally relevant stimuli that the system is meant to detect (not shown), are conveyed by afferent fibers (orange) originating from electroreceptors on the skin. Question mark indicates the process of sensory cancellation being studied. (B) A sequence of inter-EOD intervals recorded in a freely swimming mormyrid fish, adapted with permission from Toerring and Moller (1984). Note the wide range of discharge rates and abrupt transition from lower, irregular rates to a high regular rate (arrow). Such transitions highlight the need for negative images to generalize across different EOD rate regimes.

DOI: https://doi.org/10.7554/eLife.44032.002
Figure 2. Sensory cancellation in ELL output cells generalizes from low to high EOD rates. (A) Top, pre-learning response of an ELL output cell to a sequence of mimics triggered by EOD commands at 10 Hz. Shaded box indicates the learning condition. Empty dashed box indicates that no learning was performed at 60 Hz in this series of experiments. Red ticks show the times of EOD commands and black ticks show the times of EOD mimics. Bottom, response of the same cell after learning at 10 Hz. Dashed line is the response of the cell to the EOD mimic presented independent of the command after learning. Note, the response to the mimic is largely cancelled at both 10 and 60 Hz even though learning occurred only at 10 Hz. Responses were also probed at 40 Hz in this cell with similar results (not shown). Scale bar is 1 s. (B) Top, pre-learning responses of an ELL output cell to paired EOD command and mimic sequences at 10 and 60 Hz. Shaded boxes indicate that learning took place at both 10 Hz and 60 Hz. Bottom, the response of the same cell after learning. Learning was also conducted at 40 Hz in this cell with similar results (not shown). (C) Degree of cancellation at each rate for learning only at 10 Hz, expressed as the ratio of the power of the residual response after learning to the power of the pre-learning response (n = 17, median residual power ratios are 0.34, 0.48, 0.63 at 10, 40, and 60 Hz respectively). (D) Degree of cancellation at each rate when learning and testing were at the same frequencies of 10, 40, and 60 Hz, expressed as in C (n = 12, median residual power ratios are 0.36, 0.49, 0.61 at 10, 40, and 60 Hz respectively).

DOI: https://doi.org/10.7554/eLife.44032.003
Figure 2—figure supplement 1. ELL neurons form negative images that generalize across EOD rates. (A) Top, responses of an ELL output cell at 10, 40, and 60 Hz, after pairing only at 10 Hz. Blue shows the response to the mimic alone, black shows the response to the command alone after pairing. Responses in the latter period are due to corollary discharge inputs and resemble an approximate negative image of the response to the mimic across rates, despite pairing being conducted only at 10 Hz. Periods of high firing evoked by the command alone (red arrows) correspond to periods of low firing induced by the EOD mimic. Bottom, responses of the same cell after pairing with an opposite-polarity mimic at 10 Hz. Purple shows the response to the mimic alone, black shows the response to the command alone. Note that the corollary discharge response has completely changed (compare black trace in top panel), generalizing appropriately, despite pairing with the new stimulus only at 10 Hz. (B) Similar to (A) but for a different cell, this time paired at all rates.

DOI: https://doi.org/10.7554/eLife.44032.004
Figure 3. Regularization of synaptic plasticity improves but does not fully account for generalization. (A) Top, pre-learning response of a model ELL neuron to paired EOD command and mimic sequences delivered at 10 Hz. Shaded box indicates the learning condition. Red ticks show the times of EOD commands and black ticks show the times of EOD mimics. Bottom, response of the model cell after learning. The response to the mimic is largely cancelled at 10 Hz but is dramatically over-cancelled at 60 Hz. (B) Top, pre-learning response of a model ELL neuron to paired EOD command and mimic sequences at 10 and 60 Hz. Shaded boxes indicate the learning conditions. Bottom, response after learning. The response is largely cancelled at both 10 and 60 Hz. (C) Degree of cancellation at 10 Hz and 60 Hz for model and real cells across rates when training occurred at both rates. (D) Degree of cancellation at 10 Hz for real cells and model cells, with full and minimal regularization, when learning was only at 10 Hz. (E) Degree of cancellation at 60 Hz for real and model cells, with full and minimal regularization, when learning was only at 10 Hz.

DOI: https://doi.org/10.7554/eLife.44032.005
Figure 3—figure supplement 1. Modeling the responses of late mossy fibers across EOD command rates. (A) Schematic of the spiking response of a late mossy fiber evoked by an isolated EOD command. The response consists of a delay followed by a period of spikes, as shown. (B) Schematic of the modeled response of the same mossy fiber to a sequence of two EOD commands. The pattern of delay and spiking is copied after each EOD command, but the delay following each EOD command erases any spikes caused by the previous command that fall within the delay period following the current command, as shown.

DOI: https://doi.org/10.7554/eLife.44032.006
**Figure 4.** Command rate-dependence of granule cells and their mossy fiber inputs. (A) Membrane potential of a granule cell in response to a 60 Hz sequence of 25 EOD commands, with stimulus artifacts removed. Red ticks show the times of EOD commands. (B) The response to a single command at 10 Hz along with the time at which a subsequent command would occur at a rate of 60 Hz (red arrow). Bottom trace is the electromotoneuron volley recorded near the electric organ. Same cell as in (A). (C) Distribution of median percentage increase in maximum membrane voltage from 10 Hz to 60 Hz command rates across \( n = 28 \) model granule cells. Dashed line shows the experimental value of 0.006 (\( p=0.03 \)). (D) Distribution of median slope of membrane voltage in response to a 60 Hz sequence for model granule cells, dashed line shows value from the data, \(-0.43 \text{ mV/s (} p<0.002 \text{).} \) (E) Initial portion of the response of the granule cell shown in panel (A). Black lines are data with stimulus artifacts removed, blue dashed line shows a fit using a model granule cell with input spike times inferred from the recorded membrane voltage. (F) Example traces from an early mossy fiber recorded extracellularly in the granular layer. Responses to 25 commands in a 10 Hz (top), 40 Hz (middle), or 60 Hz (bottom) sequence are overlaid. Note the ‘dropping’ of spikes in the burst at high rates. Bottom trace is the electromotoneuron volley recorded near the electric organ. (G) Average number of spikes fired per EOD command by early mossy fibers (gray, \( n = 9 \)). Symbols show the mean \( \pm \text{S.D.} \) (H) Average firing rate across all inferred tonic mossy fiber inputs to granule cells across EOD command frequencies (mean \( \pm \text{SEM, } n = 19 \)).

DOI: https://doi.org/10.7554/eLife.44032.007
Figure 4—figure supplement 1. Example recorded granule cells receiving early input. Membrane voltage of two granule cells receiving early mossy fiber input (i-ii) in response to a 60 Hz sequence of EOD commands, with stimulus artifacts removed. An action potential at ~300 ms in (i) is truncated. Red ticks show the times of EOD commands. Black lines are data. Blue lines show model fits. Expanded traces reveal a decrement over time in the number of inflections (bumps) on the depolarizing responses for successive commands at high rates, indicative of early mossy fiber input spikes dropping out. Arrow indicates a rare case in which a microstimulation pulse failed to evoke a command.

DOI: https://doi.org/10.7554/eLife.44032.008
Figure 4—figure supplement 2. Granule cells in the original model fire nonlinearly and this nonlinearity is greater for cells with slower inputs. (A) Example model granule cells showing the response to EOD sequences at three different rates (10, 40, 60 Hz), colored lines. Grey lines show the predicted response if each cell were linear. (B) EPSPs for the model cells in (A), showing that there is significant variability in real and model granule cell EPSP time constants and that cells with longer EPSP time constants fire more nonlinearly due to greater temporal summation.

DOI: https://doi.org/10.7554/eLife.44032.009
Figure 4—figure supplement 3. Tonic mossy fibers decrease their firing rate at high EOD command rates. In all panels, vertical red lines show EOD command times. (A) Example membrane voltage (four trials overlaid) of a putative unipolar brush cell exhibiting command rate-dependent inhibition of tonic firing in response to command sequences from 10 to 60 Hz. (B) Example membrane voltage of a granule cell receiving tonic mossy fiber input (black lines show times of inferred input spikes) in response to EOD command sequences from 10 to 60 Hz.

DOI: https://doi.org/10.7554/eLife.44032.010
Figure 4—figure supplement 4. Pause mossy fibers cease firing at high command rates. (i-iii) Show the firing rate of three example pause mossy fibers in response to a single EOD command (left), a 10 Hz sequence of 25 EOD commands (center), and a 60 Hz sequence of 25 EOD commands (right). Pause mossy fibers show tonic firing with a pause in response to a single EOD command, and at higher EOD command rates cease firing altogether (n = 6).

DOI: https://doi.org/10.7554/eLife.44032.011
Figure 4—figure supplement 5. Golgi cells increase their firing rate with increasing EOD command rate. (A) Membrane voltage of an example Golgi cell in response to EOD command sequences from 10 to 60 Hz. Spikes are truncated. Red vertical lines show times of EOD commands. (B) Firing rates increase as a function of EOD command in Golgi cells (p<0.001, linear regression t-test, n = 3).

DOI: https://doi.org/10.7554/eLife.44032.012
Figure 5. Model granule cells with rate-dependent command inputs match recorded granule cells. (A–D) Dark versus light blue indicates model cell response with and without rate-dependent inputs matched to the data. (A) Response of a model granule cell to two EODs in a 10 Hz command sequence. Note that the cell responds very similarly at this rate with either set of inputs. (B) Response of the same model cell as in (A), but for a sequence of EOD commands at 60 Hz. Note the qualitatively distinct responses with and without input rate-dependencies at this higher rate. (C–D) Distributions of two response statistics for new and old models, dashed lines show the value found in real granule cells. (C) Median percentage increase in membrane voltage from 10 to 60 Hz (for old model p=0.03, for new model p=0.72). (D) Median membrane potential slope across a 60 Hz train of EOD commands (for old model p<0.002, for new model p=0.81).

DOI: https://doi.org/10.7554/eLife.44032.013
Figure 6. A revised ELL model accounts for generalization in ELL neurons. In all panels dashed blue traces are the sensory response to be cancelled and solid blue traces are the response to the paired EOD command plus mimic sequences. Learning occurs only at 10 Hz as indicated by grey boxes. Red ticks show the times of EOD commands and black ticks show the times of EOD mimics. (A) Top, pre-learning response of a revised model output cell with full regularization to paired EOD command and mimic sequences delivered at 10 Hz. Bottom, response of the same cell after learning. Note, the response to the mimic is largely cancelled at both 10 and 60 Hz. (B) Top, pre-learning response of a revised model output cell with minimal regularization to paired EOD command and mimic sequences delivered at 10 Hz. Bottom, response of the same cell after learning. Note, the response to the mimic is largely cancelled at 10 Hz but is now over-cancelled at 60 Hz. (C) Level of cancellation achieved at 10 Hz across different model and real ELL cells is similar (p=0.72 for minimally regularized model versus data; p=0.62 for fully-regularized model versus data, Wilcoxon signed rank test). (D) Similar to C but showing the level of cancellation achieved at 60 Hz, (p<0.001 for minimally regularized model versus data; p=0.38 for fully-regularized model versus data, Wilcoxon signed rank test). (E) Dark blue, mean spiking response of model granule cells with input rate dependencies; grey, mean response of electroreceptor afferents, both at 60 Hz EOD rate. Note the similarity in shape.

DOI: https://doi.org/10.7554/eLife.44032.014
Figure 6—figure supplement 1. Stronger regularization of synaptic plasticity restricts negative images to be proportional to the mean granule cell response and decreases variance in synaptic weights. (A) Overlap between negative image and average model granule cell activity across a 25 EOD command sequence at 60 Hz, as a function of the strength of regularization of synaptic plasticity (see Materials and methods). (B) Variance of the final set of model synaptic weights from granule cells to the model ELL neuron, after pairing, as a function of the strength of regularization of synaptic plasticity.

DOI: https://doi.org/10.7554/eLife.44032.015
Figure 6—figure supplement 2. Rate-dependence of ELL output cell responses to the EOD. (A) Firing rate of three (i.-iii.) ELL output cells to EOD mimics delivered at 10, 40, and 60 Hz. Vertical ticks above the data indicate times of electrosensory stimuli. Black lines are data and red lines are the expected response assuming the response is a linear sum of individual EOD responses (see Materials and methods). Note the decreasing response profile at high rates. (B) Rate of decay of ELL output cell firing rate across a 25 mimic sequence as a function of mimic frequency (n = 22). (C) Mean ELL output cell firing rate across a 25 mimic sequence as a function of mimic frequency (n = 22).

DOI: https://doi.org/10.7554/eLife.44032.016
Figure 6—figure supplement 3. Rate-dependence of ampullary afferent responses to the EOD. (A) Firing rate of an electroreceptor afferent to EOD mimics delivered at 10 Hz (left) and 60 Hz (right). Vertical ticks above data indicate times of electrosensory stimuli. Black lines are data and red lines are the expected response assuming the response is a linear sum of individual EOD responses (see Materials and methods). Note the decreasing response profile at high rates. (B) Rate of decay of electroreceptor afferent firing rate across a 25 mimic sequence as a function of mimic frequency (n = 12). (C) Mean electroreceptor afferent firing rate across a 25 mimic sequence as a function of mimic frequency (n = 12). (D) Example (average) impulse response of the electrosensory afferent shown in A to an isolated EOD, with both positive (green) and negative (red) lobes.
DOI: https://doi.org/10.7554/eLife.44032.017