Built to Last: Functional and structural mechanisms in the moth olfactory network mitigate effects of neural injury

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Abstract

Most organisms are exposed to neural damage throughout their lives, which can reduce their ability to carry out core behavioral tasks. Their neural circuits need to maintain functionality despite injury, which often requires that key readout signals from the system be preserved. In this work, we explore whether and how certain structural and functional network motifs act as injury mitigation mechanisms by protecting these readouts. Specifically, we examine how (i) Hebbian learning, (ii) high levels of noise, and (iii) presence of parallel inhibitory and excitatory connections contribute to robustness of the olfactory system in the Manduca sexta moth.

We simulate injuries on a detailed computational model of the moth olfactory network in which structures-under-test are parametrically varied. Neuronal impairments are modeled as focal axonal swellings, an axonal pathology observed across all severities of traumatic brain injuries and present in other leading brain disorders. Axonal swellings effectively compromise spike train propagation along the axon and consequently reduce the effective neural firing rate delivered to downstream neurons.

All three of the network motifs examined significantly mitigate the effects of injury on readout neurons, either by reducing injury’s impact on readout neuron responses or by restoring these responses to pre-injury levels through reinforcement learning. These motifs may thus be partially explained by their value as adaptive mechanisms to minimize the functional effects of neural injury. More generally, these experiments suggest that robustness to injury is a vital design principle to consider when analyzing biological neural systems. Indeed, it is possible that some neural structures and mechanisms, including the ability to learn, are best understood as evolutionary solutions to the challenge of maintaining system function despite injury.

Author Summary

Neuronal injuries and degeneration are commonplace across species and organisms, compromising cognitive function and neurosensory integration. Despite abrupt or gradual neuron impairment, neuronal circuits and networks must maintain functionality of key outputs in order to provide robust performance. Focal Axonal Swellings (FAS) are a ubiquitous form of neuronal pathology known to compromise spike trains following traumatic brain injuries as well as a number of leading neurological diseases such as Alzheimer’s, Parkinson’s, and Multiple Sclerosis. All such disorders have an enormous societal impact as patients may experience cognitive impairments that impede their routine activities. Injured neurons may distort, confuse or block the information encoded in spike trains. We utilize a detailed model of the olfactory circuitry of the Manduca sexta moth as a platform to examine network features that may help protect cognitive function and neurosensory integration from the effects of this collective signal distortion due to injury.
Table 1. Common acronyms used throughout this manuscript

| Acronym | Definition                          |
|---------|------------------------------------|
| AL      | Antennal Lobe                      |
| EN      | Extrinsic (readout) Neuron         |
| FAS     | Focal Axonal Swelling              |
| FR      | Firing Rate                        |
| MB      | Mushroom Body                      |
| MON     | Moth Olfactory Network             |
| PN      | Projection Neuron                  |
| QN      | Inhibitory Projection Neuron       |
| RN      | Receptor Neuron                    |
| SNR     | Signal-to-Noise Ratio              |
| SSNR    | Signal-to-Spontaneous Noise Ratio  |

Introduction

Injuries are inevitable for most organisms, yet maintaining a satisfactory level of functionality can be decisive for their survival. The progressive wear of a honeybee’s wings, for example, challenges the insect to sustain its load lift or face less nourishing foraging trips [1,2]. Functional robustness is desirable for neural systems as well. While computer devices operate in a regime of near-zero tolerance for physical damage, the middle-aged human brain undergoes significant neuronal losses on a daily basis [3]. Robustness to injury is often overlooked when analyzing the purpose and function of neural structures while the transmission of maximum information, high signal-to-noise ratio, and low energy consumption are often primarily considered [4]. Analyzing neural information processing in the context of these principles is certainly important, but arguably incomplete. The goal of this work is to examine whether certain neural mechanisms and architectural structures can be understood as adaptive, built-in systems for robustness to brain injury, aging, and/or other disorders.

The Manduca sexta moth provides an ideal model organism to investigate certain injury mitigation mechanisms, as its olfactory system exhibits (i) Hebbian plasticity, (ii) high noise levels, and (iii) inhibitory feed-forward channels running parallel to excitatory channels. This network also contains well-defined readout neurons, which are downstream outputs that deliver key actionable encodings to the rest of its body [5,6]. See Figure 1 for a system schematic. All such features are captured by our computational model, which incorporated known biophysical parameters and was calibrated to in vivo firing rate dynamic data recorded during learning tasks [7]. To explore the injury-mitigation properties of neural architectures, we ran several in silico injury simulations on this model and close variants. We focused on how the readout neurons, i.e. the key deliverables of the neural system, were affected by injuries and injury-mitigation mechanisms: From a functional viewpoint, internal damage is unimportant as long as key outputs of the system are preserved.

The consequences of damage to individual neuronal dynamics are modeled following the axonal injury studies of Maia and Kutz [21-23]. Focal Axonal Swelling (FAS) is a key pathological signature across all severities of traumatic brain injuries [24-33]. As reviewed in [20], the development of FAS following brain damage is studied both in vivo [34-37] and in vitro experiments [38-43], and is tracked whenever possible in human patients [24-44,49]. FAS are implicated in other leading brain disorders such as Alzheimer’s Disease [50-53], Parkinson’s Disease [54-56], Multiple Sclerosis [57-59] and others (see the background section in [20] and references therein). Fig 1C exemplifies how FAS distorts the propagation of spike trains along the axon, effectively blocking or filtering signals encoded to downstream neurons. Recent computational studies that consider the effects of FAS injury in neural networks are providing new insight to decision-making deficits [20], learning impairments [60,61], memory deterioration [62], and motor-function decline [63].

In our simulations, we varied the parameters of each network feature-under-test, applied FAS-type injuries to different subnetworks of the system (simulating the outcome of a traumatic brain injury or concussion) and assessed the overall effects on the readout neuron outputs. Our experiments led to four main findings concerning injury-mitigation structures in the moth olfactory system:

1. The learning mechanism, based on octopamine and Hebbian growth, can restore downstream neural responses after upstream neurons are injured, though it does not repair the actual injury.
2. The presence of inhibitory neurons parallel to excitatory neurons connecting the subnetworks can mitigate the effects of injury through a “canceling out” effect.
3. A broad noise envelope on neural firing rates (FRs) enables a key subset of downstream neural responses to continue to exceed action-triggering thresholds, despite upstream injury.
Figure 1. Overview of the Moth Olfactory Network (MON) and axonal injury mechanisms. A, B: The MON is organized as a feedforward cascade of four distinct subnetworks and a reward mechanism [8, 9]. Receptor Neurons (RNs) in the Antennae detect relevant odors in the environment and transmit specific signals to the Antennal Lobe (AL) [10, 11], which acts as a pre-amp, providing gain control and sharpening odor codes [12]. The AL neurons project odor codes forward to the Mushroom Body (MB) [13] by means of noisy [14] excitatory Projection Neurons (PNs), and to a smaller number of parallel inhibitory neurons (here called QNs). The Kenyon Cells in the MB fire sparsely and encode odor signatures as memories [15, 16]. (wiring to one of two MB calyces is shown). Finally, Extrinsic Neurons (ENs) are viewed as readout units that interpret the MB codes, delivering actionable output to the rest of the body [5, 6]. In response to reward (sugar at the proboscis), a large neuron sprays octopamine over the AL and MB. This neuromodulator induces stronger responses in AL neurons, and strengthens the plastic synaptic connections (AL→MB and MB→ENs) [11, 17]. Learning fails in the absence of octopamine [18, 19].

C: Focal Axonal Swellings (FAS) are ubiquitous across all severities of traumatic brain injuries and present in other leading brain disorders. They can cause some or all neural spikes in the train to die off in transit, reducing the overall firing rate arriving at the downstream target neuron. Adding FAS effects to the MON are the basis of our damage/injury protocols. Panel C is adapted from [20]. See the Materials and Methods section for more details.

4. Simple ablation injuries to an upstream region produce distinct downstream effects from those of more biologically-plausible types of injury. That is, ablation may be a poor proxy for FAS injury.

It is, of course, expected that post-injury plasticity should improve the overall network performance. Our computational approach allows us to quantify this effect beyond a qualitative level by estimating the limits of recovery as a function of injury level and injury location. We can systematically increment the injury level (randomizing targeted neurons), and systematically adjust structural features-under-test such as the noise level in the AL. Additionally, we run enough simulations to control for each variable and also estimate inter-trial variability.

Results

Throughout this work, we target two distinct regions with our injury protocols: (i) the Antennae and (ii) the channel between the Antennal Lobe (AL) and the Mushroom Body (MB). Their specific locations are shown in Fig 2.

(i) The antennae comprise the outermost region of the olfactory system and are arguably the most exposed to external environmental shocks. Damage in this location should affect primarily the Receptor Neuron (RN) subpopulation. We note that ~500 RNs for a given odor volatile are spread throughout the antennae, ensuring that
Damage to Antennae affects the Receptor Neurons (RNs) (red stars) and reduce the overall input to the Antennal Lobe (AL). Damage to the AL→MB channel (orange stars) will weaken the signals passed by both excitatory projection neurons (PNs) and inhibitory projection neurons (QNs).

localized damage to an antenna does not disproportionately impact a single class of volatile receptor.

(ii) The AL→MB channel is an internal region and is one of the core centers for signal transfer in the network. Damage in this location should affect both excitatory projection neurons (PNs) and inhibitory projection neurons (QNs) that link the AL to the MB.

The Moth Olfactory Network (MON) contains some plastic synaptic connections, and it can learn: In response to reward (sugar at the proboscis), a large neuron sprays octopamine over the AL and MB. This strengthens the plastic synaptic connection in the AL→MB and MB→Readout channels in a Hebbian-like way, enabling readout neurons (extrinsic neurons, ENs) to deliver actionable encodings to the rest of the body. Typical EN responses before injury, after injury, and after subsequent training, are shown in Fig.3.

![Figure 2. Location of injuries in experiments.](image)

Estimating the limits of plasticity-induced recovery from injury

The goal of this set of experiments was to examine how far the learning mechanism can compensate for neural injury. In the first experiment, RNs in the Antennae→AL channel were injured (Fig.2A). In the second experiment, PNs in the AL→MB channel were targeted (Fig.2B). AL noise was set to naturalistic levels (calibrated per *in vivo* data [7]) and FAS injury levels ranged from 0% to 60%. The MON was subsequently retrained with 5, 10, or 15 odor puffs.
The average EN response was recorded, as a key measure of the actionable output of the system. A typical timecourse is shown in Fig.3. In each experiment, over 60 moths were generated from template and tested at each injury level. Training restored some of the lost EN response in both experiments, though the MON was much more robust to RN (antennae) damage than to PN damage. Complete restoration was achieved (on average) for injury levels below 25% for RN damage and below 8% for PN damage. At these injury values, injury reduced EN odor responses to approximately 70% of the naive baseline, and training restored them to baseline. See the plots in Fig.4. We note that at low injury levels, the system was able to boost EN output by about 140% to 150%, a value constrained by the model’s saturation parameter for the synaptic connection weights. At high levels of injury to PNs, however, the learning mechanism’s ability to recover EN performance decreased. (see green curves in Fig.4).

Figure 4. Learning as injury compensation mechanism. Red/orange: Post-injury EN odor response, normalized by naive, healthy odor response. Blue: Post-training EN response, normalized by naive, healthy odor response. Green: Relative increase from post-injury response due to training. $\mu \pm \sigma$. A: Injury to RNs: Trained EN responses (blue) fully regained their pre-injury levels (black line) from injured levels (red) if injury was on average $\leq 25\%$. The ability of training to recover lost ground was fairly steady vs injury level (green). B: Injury to PNs was more traumatic: Post-injury EN response (orange) was lower, and trained responses (blue) fully regained pre-injury levels if injury was on average $\leq 8\%$. Also, the ability of training to recover lost ground decreased as injury level increased (green). Each datapoint shows the mean and std dev, over $\geq 60$ moths. A moth’s EN response was defined as its mean response to 15 odor exposures.

Parallel inhibitory neurons and a protective canceling out effect

Each glomerulus in the AL has $\approx 5$ excitatory PNs that project forward to the MB. In addition, the moth has a smaller number of inhibitory neurons (here called QNs) that also feed forward to the MB. At first glance this could appear to be a wasteful design. The goal of this set of experiments was to test whether the presence of QNs parallel to PNs might mitigate the effect of injuries applied to this region (orange stars in Fig.2). We varied the QN:PN ratio (0, 2, 4, 5, and 7 QNs per glomerulus, with 5 PNs per glomerulus fixed) while injuring the AL→MB channel. We found out that high numbers of QNs correlated strongly with reduced effects on EN outputs from upstream injury.

Moths with high QN counts had stronger post-injury EN odor responses, and post-injury training sessions allowed them to fully recover from much higher levels of injury than moths with few or no QNs ($\approx 8\%$ injury for QNs = 0, $\approx 15\%$ injury when QNs = 4, and $\approx 30\%$ injury when QNs = 7). High QN counts had another, unexpected advantage regarding the signal-to-noise ratio,

\[
SNR = \frac{\mu(F)}{\sigma(F)},
\]

where $F$ is the set of discrete EN firing rate responses to a series of odor puffs. Naive SNR values (ie pre-injury, pre-training) were similar for all QN counts (Fig.5D). While post-injury SNR always dropped proportionally to the severity of the injury, high QN counts substantially reduced losses to SNR, suggesting that raw EN firing rates were better preserved (Fig.5E).
Figure 5. **Effects of parallel inhibitory channels.** A: Post-injury EN odor responses normalized by naive healthy odor responses, vs injury level. Each curve corresponds to a number of QNs per 5 PNs, from 0 to 7. Higher QN:PN ratios resulted in much lower impact on EN responses for a given level of injury. B: Post-training EN odor responses normalized by naive healthy odor responses, vs injury level. Each curve corresponds to a number of QNs per 5 PNs, from 0 to 7. Higher QN:PN ratios resulted in stronger recovery. C: Ratio of post-training to post-injury EN odor responses vs injury level. Recovery rate dropped off at injury levels $\geq 20\%$ for $\#QN = 0$, but higher numbers of QNs reduced this drop-off, i.e. ensured better recovery. D: Ratio of naive healthy EN odor responses to spontaneous EN noise (SSNR). This measure of signal clarity was much lower in moths with high QN counts. E: Raw Signal-to-Noise Ratio (SNR) of naive healthy EN responses was fairly uniform across $\#QNs$. F: Post-injury SNR normalized by pre-injury SNR. High QN counts gave strong protection against injury-induced degradation of SNR.
However, high QNs counts also carried a downside. They had a much lower EN signal-to-spontaneous noise ratio,

\[ SSNR = \frac{\mu(F)}{\mu(s)}, \]  

where \( F \) is defined as above and \( s \) is the spontaneous EN firing rate. The SSNR measures the clarity of the signal with respect to background noise, and their values for different QN counts are shown in Fig.5F. Many templates with high QN counts were rejected due to untenably high naive spontaneous noise.

Our results demonstrate that the presence of parallel inhibitory neurons help protect the signal from injury (at the cost of decreased SSNR). We hypothesize that QNs achieve this by a canceling out mechanism: When inhibitory QNs are injured, the overall transmitted signal increases, offsetting the decreases caused by injury to excitatory PNs.

**AL noise preserves the highest EN responses**

The AL is a noisy network. We ask whether this neural noise has injury-mitigation benefits. Suppose that odor-related behavior is triggered when the EN responses exceed a certain threshold, and that because the moth gets multiple exposures to a given odor plume, a triggering response (i.e. above threshold) is not required for every exposure. In this case, it suffices for the system to protect only the strongest EN responses from injury-induced attenuation in order to maintain its behavioral response. The goal of this set of experiments was to examine whether higher AL noise might preferentially protect the top-scoring tranche of EN responses. We therefore tested (a) whether larger noise envelopes on neural firing rates in the AL give stronger injury resistance, and (b) whether the top-scoring tranche of EN responses receive relatively more protection from AL noise levels.

The AL noise level is controlled by a single parameter in our computational model. We adjusted neural noise in the AL to different multiplicative factors of the “natural” AL noise level (i.e. the level matching our in vivo data). Factors were 0, 0.33, 0.67, 1.0, and 1.33, where 1.0 is the natural level. Various severities of FAS injury were applied to RNs in the Antennae→AL channel (Fig.2A). Over 60 moths were generated from template for each \{AL noise, injury level\} datapoint. We defined the normalized top-scoring EN output as:

\[ \frac{\mu(F) + \sigma(F)}{\mu(F_h) + \sigma(F_h)}, \]  

where \( \mu \) and \( \sigma \) correspond to the mean and standard deviation, \( F \) is the set of discrete responses after injury, and \( F_h \) is the set of naive healthy responses. This measure gives a sense of how injury and AL noise affect the highest-firing tranche of a moth’s EN odor responses relative to this tranche’s healthy behavior.

Higher AL noise reduced the attenuation of top-scoring EN responses caused by a given level of injury (Fig.6A), and increased the post-training recovery possible (Fig.6B). Full recovery occurred for injury \( \leq 20\% \) when AL noise = 0, and \( \leq 28\% \) when AL noise was greater than natural level.

However, high AL noise levels had a significant downside, namely, lower SNR (signal to noise ratio) and SSNR (signal to spontaneous noise ratio) values, as seen in Fig.6C-E. This suggests that the MON must make a trade-off between robustness to injury and signal quality.

In addition, we found that this protection did not apply to all EN responses: The tranche of top-scoring EN responses received more injury-mitigation benefit from higher AL noise levels than did average EN responses. That is, the extra robustness to injury conferred by higher noise levels was greater for the top tranche of responses than for all responses. This difference in protective effect is shown in Fig.7.
Figure 6. Effects of AL noise: Given RN injury, AL noise protects downstream neurons from loss (A, B), but exacts a cost in terms of signal-to-spontaneous noise ratio (SSNR, C and D) and signal-to-noise ratio (SNR, E). A: Post-injury EN responses of the top 15% tranche (ie the strongest odor responses), normalized by their pre-injury response, vs injury level. Higher AL noise reduced attenuation due to injury, at any level of injury. Each curve corresponds to a level of AL noise, from 0 to 1.33 where 1 = “natural” level. Pre-injury response = black line. B: Post-injury EN responses of the top 15% tranche, normalized by their pre-injury response, vs injury level. Higher AL noise allowed training to give full recovery of these top EN responses from larger injuries, ≈28% injury given maximum noise vs ≈20% injury given no AL noise. C: Naive healthy ratio of EN SSNR was much lower at high AL noise levels. D: Post-injury SSNR, normalized by pre-injury ratios, vs injury level. Injury lowered SSNR far more in moths with high AL noise. E: Naive healthy SNR by AL noise level. SNR was much lower in moths with high AL noise.
Figure 7. Protective effects of AL noise on strongest vs average EN responses. Given RN injury, increased AL noise had a greater protective effect on the top 15% tranche of EN odor responses than on more average odor responses, both post-injury and post-training. Each curve corresponds to a noise level. A wider spread of curves indicates greater injury mitigation from higher noise. A, B: Top 15% of EN responses, normalized to their pre-injury responses, post-injury (red, grey) and post-training (blue, grey). The spread of curves indicates the relative benefit of higher noise. (These are the same subplots as in Fig. 6 A, B.) C, D: All responses, normalized by their pre-injury responses, post-injury (red, grey) and post-training (blue, grey). High noise gave less injury mitigation benefit to more average EN responses.

Ablation is a poor proxy for biological injury

Neuronal pathologies are often modeled in a binary way, i.e. by treating a neuron and/or its connections as either fully functional or fully impaired. But recent FAS studies show that most injured neurons maintain some residual firing rate activity. On large, homogeneous populations of neurons where outputs are pooled and statistical approximations can be applied, one could expect an approximate equivalence in ablation and FAS, modulo a conversion factor. In this case, we estimate that ablation alone is roughly 1.75x more harmful than FAS injury (i.e. n% ablation ≈ 1.75n% FAS; see calculations in the Materials and Methods section).

However, where neuron numbers are smaller and neural outputs are not pooled, so that individual neurons have relatively unique effects on the system, it is not clear that ablation effects can be reliably mapped to effects of more biologically-plausible neural injuries (e.g. FAS). In the moth AL-MB, damage to RNs (i.e. to the antennae) represents the large homogeneous case, assuming a pool of about 500 RNs per glomeruli, and RNs dispersed uniformly over the antennae so that damage is also dispersed uniformly. In contrast, damage to PNs more closely resembles the small-scale case, since there are only 60 glomeruli.
Since ablation injuries are widely studied in theoretical and experimental settings, we ran experiments to test whether the effects of ablation had a consistent 1.75x relationship to FAS injury at these two locations, i.e. the RN channel (red stars in Fig.2) and the PN channel (orange stars in Fig.2). All parameters were generated from our calibrated moth template, with AL noise at natural levels and number of QNs = 0 (QNs = 2 per glomerulus gave similar results). Half the moths were injured by ablation and half were injured by FAS, with injury levels from 0 to 60%, in order to compare the relative empirical effects on EN outputs. In each experiment, over 60 moths were generated for each injury (type, level, location) datapoint.

The relative effects of the two injury types varied drastically depending on the site of injury. For RN channel damage, ablation effects were roughly in line with that predicted by theory for large populations, i.e. 1.75x FAS damage. This makes sense given the assumptions on number and distribution of RNs stated above.

In contrast, ablation injury to the PN channel was roughly 50% less harmful relative to FAS injury than predicted by theory. This is perhaps because FAS affects more neurons overall than a nominally-equivalent ablation, resulting in more widespread distortion of the signal. In the case of PN channels, the widespread, lower distortion induced by FAS was evidently more harmful than the concentrated, higher distortion induced by ablation.

Percent losses to EN response in all cases are given in Fig.8 (RNs: A, PNs: B). We remark that the discrepancy between theoretical and actual effects is not at the site of injury, but at the downstream (readout) neurons. The impact of the upstream injury is nonlinearly modulated as it moves through the cascaded system.

![Figure 8. Ablation does not map to FAS injury](image)

**A:** When RNs were injured, ablation induced loss to EN response consistent with theory for large populations with pooled outputs. **B:** When PNs were injured, ablation induced a ~50% smaller loss than expected relative to FAS injury.

**Discussion**

Our simulations indicate that the network mechanisms and motifs we tested have clear injury-mitigation properties. In this section we suggest mechanisms by which these structures might protect readout neuronal activity from upstream injury. We note that from a functional point of view, overall resilience of a cascaded system depends partly on whether upstream regions can avoid damage, but mainly on whether downstream units can still transmit key readout signals to the rest of the body despite upstream damage. Cascaded networks are ubiquitous among biological neural systems, and it is likely that the principles discussed in the moth’s olfactory network may be applicable to other settings. We also discuss the discrepancy between axonal swelling injuries vs ablation injuries. Finally, we argue that robustness to injury is a key principle of biological neural design.

**Estimating the limits of plasticity-induced recovery from injury:** Injury to the upstream regions of the network results in spike deletions and weaker encodings arriving at downstream neurons. If the damaged region
cannot activate downstream neurons with the existing synaptic connection strengths, there is a functional loss of information. However, internal plasticity mechanisms can evidently mitigate or reverse this effect.

Learning in the moth olfactory network occurs via a combination of octopamine stimulation and Hebbian growth. Octopamine stimulation temporarily boosts neural firing rates during reinforcement by sugar reward, while Hebbian updates strengthen the synaptic weight $w_{ab}$, between two neurons $a$ and $b$, proportionally to the product of their firing rates:

$$
\Delta w_{ab} \propto f_a(t)f_b(t).
$$

We propose that degraded firing rates in downstream neurons are restored via the following mechanism (see schematic in Fig.9A):

1. Octopamine temporarily increases the firing rates of injured upstream neurons.
2. The transient boosted encodings are sufficient to trigger firing in the downstream neurons with the existing synaptic connection strengths.
3. Since neurons on both sides of the plastic connections are firing, Hebbian growth strengthens their connections.
4. Firing rates from the injured upstream region return to their reduced rate once octopamine is withdrawn. However, due to the stronger synaptic connections, these encodings are now sufficient to trigger the downstream neurons. This restores the transmission of key information to the rest of the body.

We note that the original injured neurons are not themselves being repaired, since the effects of plasticity only boost downstream connections. The limit for this restorative capacity depends on the parameters of the moth template, especially the synaptic/learning saturation level. Our results quantify how learning itself acts as an effective injury compensation mechanism, sometimes restoring the system’s original performance despite injury.

**Inhibitory neurons and protective canceling out effect:** The moth olfactory network has both excitatory projection neurons and inhibitory projection neurons that feed-forward from the antennal lobe to the mushroom body. We propose a mechanism to explain how this can protect downstream neurons from the effects of upstream damage, assuming downstream dynamics depend on the summed input from upstream neurons:

$$
(w \cdot u) = w^+ \cdot u^+ - w^- \cdot u^-.
$$

Where

- $w^+$ = connection weights from excitatory neurons
- $u^+$ = FRs from upstream excitatory neurons
- $w^-$ = connection weights from inhibitory neurons
- $u^-$ = FRs from upstream inhibitory neurons.

When FAS injury is applied to the PN/QN pipeline in our neural architecture (mimicking the outcome of a physical shock), the net effect on the summed signal reaching downstream target neurons varies according to the proportion of QNs to PNs ($u^- : u^+$, assuming uniform weights $w$). When all feed-forward signals are excitatory (i.e., $u^- = 0$), injury will always lower the summed input reaching the downstream neurons. If QNs exist, however, the overall loss should be mitigated via a “canceling out” mechanism. Fig.9B shows a schematic.

The injury resistance provided by high QN counts come at a cost of higher spontaneous EN noise relative to odor response. Presumably, biological networks have QN counts which optimally balance the benefits of injury mitigation on one hand versus the need for high signal-noise-ratio, as well as other concerns such as the energy cost to the organism. If the QN counts are low (eg QN:PN $\leq 20\%$, as in the moth), this injury mitigation benefit is likely less important relative to other architectural or functional constraints. We note that learning and plasticity are not pre-requisites for this mechanism.
Figure 9. Injury mitigation hypotheses: In a cascaded network, various architectures can mitigate the effects of injury to upstream neurons by protecting or restoring functionality of downstream units. **A:** Learning itself can compensate for injury: Octopamine temporarily stimulates the damaged neuron, allowing Hebbian growth to strengthen downstream synaptic connections. Though the injured neuron’s signal is not restored, the downstream neurons receive an amplified input, cancelling out the injury. **B:** Parallel inhibitory channels can reduce the effect of generalized injury by spreading damage among excitatory and inhibitory signals, so that losses cancel out in terms of inputs to downstream neurons. **C:** Wide noise envelopes on upstream neuron outputs can protect the strongest stimulus responses from injury-induced attenuation $\delta$, to the degree that their std dev $\sigma > \delta$. This allows the injured neuron’s strongest responses to still exceed their activation threshold (green line) for downstream neurons, protecting downstream functionality. **D:** Two simple examples of non-linearities that can result in qualitative change in the relative effects of ablation and FAS injury: In an AND gate, ablation can have a worse effect than FAS downstream, depending on the gate’s input threshold $T$. In an OR gate, ablation can be harmless, while FAS can have a worse effect downstream, depending on $T$.

**Upstream noise protects downstream behavior:** Suppose that the behavioral response is preserved after injury if at least a subset of stimuli elicit downstream responses that exceed action-triggering thresholds. In this case, a large noise envelope on upstream neurons may help protect the network’s functionality.

Assume the firing rate of an upstream neuron $FR$ responds to stimuli following a Gaussian distribution $N(\mu, \sigma)$, and that it needs to exceed a threshold $T$ to activate downstream neurons. If the neural damage reduces this $FR$ in average by $\delta$, a large noise envelope (large $\sigma$) will ensure that some post-injury responses still exceed threshold, i.e., that $\mu - \delta + \sigma \geq T$. This idea is sketched in Fig.9C for two FRs characterized by $N(\mu, \sigma_1)$ and $N(\mu, \sigma_2)$ with $\sigma_1 > \sigma_2$.

Our experiments indicate that AL noise does enable the highest EN responses to exceed threshold after injury, even as the average EN response drops. However, increased upstream noise impacts the effectiveness of the system elsewhere, for example, by reducing signal-to-noise ratio. Noise levels in biological networks (such as in the antennal lobe) may represent an evolved/optimal trade-off between injury mitigation effects and negative side-effects such as reduced SNR. We note that the sparsity of the MB acts as a powerful noise filter [7]. Plasticity is not a pre-requisite to this mechanism.

**Ablation is a poor proxy to biological injury:** Neuronal pathologies are often modeled in a binary way, i.e. by treating a neuron and/or its connections as either fully functional or fully impaired. Our results indicate, however, that in some situations ablations are a poor proxy for more naturalistic FAS-types of injuries regarding effects measured downstream from the injury site.
When the neuron population to be injured is large, and has pooled outputs to the next layers (in our model, the antennae/RNs), ablation maps to FAS injury in a predictable manner due to averaging effects over the population (see calculations in Methods). However, when the neuron population is small (in our model, the PNs) the effects of ablation vs FAS are not predictable. Ablation of PNs had much lower impact than large-population theory would predict.

The key point is that ablation effects are inconsistent relative to FAS effects, calling into question the value of ablation as a proxy for naturalist neural injuries. Because we measured injury effects downstream from the regions injured, there is a complex interplay between the injuries and network nonlinearities, making the outcome somewhat unpredictable. Simple examples of the effects of non-linearities (AND and OR gates) are shown in Fig.9D.

Limitations: Our computational model assumed only one readout neuron and one broadly-activating odor. A more realistic assessment of injury and mitigation might involve several readout neurons to allow for disparate effects on various readouts, and might use more narrowly-activating odors. Our choice of the PN/QN channel as a target for injury may not have been realistic, although it enabled us to investigate deficits caused by innermost hubs. Our study certainly did not exhaust all potentially interesting combinations of structures-under-test and injuries.

Conclusion

We have investigated the moth olfactory network with the goal of understanding how its basic architectural components serve to make sensory processing robust to injury. Since most organisms are exposed to neuronal damage throughout their lives, it is important to understand how such neuronal circuits are structured to maintain functionality despite impairments. In this work, we showed explicitly how certain structural and functional network motifs act as injury mitigation mechanisms. Specifically, we examined how (i) Hebbian learning, (ii) high levels of noise, and (iii) presence of both inhibitory and excitatory connections, can support overall robustness to injury in the olfactory system in the *Manduca sexta* moth.

Our findings indicate that, in addition to accurate sensory processing, biological neural networks such as those found in the moth olfactory system have robustness to injury as a central design principle. Our findings also suggest an additional hypothesis: Plasticity coupled with neuromodulatory stimulation, now central to learning, may have originally evolved as a repair mechanism for neural systems to offset injury and maintain function, and was only later ported to the task of developing responses to new information. If this is the case, then the gift of learning is due originally to the exigencies of brain damage.

Our results also show that these architectures can in fact cause worse performance by some other performance metrics, eg SNR. Thus, trying to explain them from the point-of-view of, for example, information theory risks running against the fact that the architectures are actually suboptimal according to that particular lens. This suggests that a more comprehensive and nuanced framing of the neural signal processing task, like that shown here, can serve to more accurately understand the robustness of neurosensory processing. That is, a neural architecture can be understood only if its injury mitigation function, and the trade-offs between this and other desired functions, are considered. Indeed, it is possible that some neural structures and mechanisms, including the ability to learn, are best understood as evolutionary solutions to the challenge of maintaining function despite injury.

Materials and Methods

In this section, we first detail the computational model *MothNet* used in all experiments. We then describe focal axonal swelling (FAS), a characteristic form of neuronal injury utilized as a model of damage, and how it was applied to the network. Lastly, we provide details about the experimental setup involved in our key findings.
**MothNet architecture**

We use close variants of the model of the moth olfactory network (*MothNet*) developed in [7], modifying the architecture features as needed for each experiment. *MothNet* uses integrate-and-fire dynamics for neural firing rates [64], evolved as stochastic differential equations [65], and Hebbian plasticity for synaptic weight updates [66]. A typical learning simulation (without injury), showing neural firing rates throughout the system, is given in Fig.10. Full governing equations and parameters are given below. All code was written in Matlab and will be found at: https://github.com/charlesDelahunt/BuiltToLast

For these experiments, the relevant architectural structures of the MON were:

**Antennae**: Network structures in which chemical receptors detect odor and send signals to the Antennal Lobe via receptor neurons (RNs). There are approximately 30k RNs (assumed here to be ≈ 500 per glomerulus) that *MothNet* combines into one averaged RN per glomerulus. All injury protocols applied to RNs account for this many-to-one abstraction.

**Antennal Lobe (AL)**: The AL acts as a pre-amp, converting weak electrical signals into an output signal strong enough to tolerate noise and allow further processing. It also modulates the odor’s encoding via intra-AL lateral inhibition. The AL structure contains approximately 60 neural units (glomeruli) which process odors and send excitatory signals (via projection neurons PNs, ≈ 5 per glomerulus) and inhibitory signals (via QNs) downstream to the mushroom body. In the version of *MothNet* used here, QNs were innervated in one glomerulus, rather than in several (as in the actual MON), and were parametrized as inhibitory analogs to PNs. This enabled our experiments concerning QN:PN ratios. The ratio of QNs to PNs varied from 0 to 1.4 according to experiment.

**Mushroom Body (MB)**: The MB is a high-dimensional (~ 4000 neurons), sparsely-firing structure that encodes odor signatures and memories, and contains plastic synaptic connections. Sparsity in the MB is enforced by either the Lateral Horn [67], or global self-inhibition by the MB (*drosophila* [68], *locust* [69]). Odor responses feed-forward from the AL to the MB, and from the MB to the Readout Neurons.

**Readout Neurons (ENs)**: Odor codes in the Mushroom Body (MB) feed-forward to Readout Neurons (Extrinsic Neurons, ENs), which are assumed to act as decision-making neurons. Strong EN responses trigger actionable messages (such as “fly upwind”). When assessing effects of injury, we focus on the ENs, since these represent the final, actionable output of the system. *MothNet* posits one EN, whose output firing rate serves to measure the functional effects of upstream injury.

**Moth template parameters**

In each experiment, 60+ moths (per data point) were randomly generated from the *MothNet* template defining the architecture, which included biologically-plausible choices for numbers of neurons, synaptic connection weights, and how odor is projected onto the glomeruli of the AL. The templates were realistic in the senses of having (i) PN firing rate behavior matching *in vivo* data from live moths and (ii) architecture parameters that match what is known from the literature [7]. Some templates were moved to the boundaries of, or out of, a known realistic regime by varying key parameters-under-test when required by the experiment.

1. The number of QNs per glomerulus varied from 0 to 7, in order to test the injury-mitigating effect of inhibitory QNs in parallel with PNs in the feed-forward AL → MB channel. PNs were fixed at 5 per glomerulus, as in live moths. In live moths, each QN is innervated by several glomeruli. In these experiments, each QN was innervated by one glomerulus, like PNs, to provide symmetry to the PN-QN structure and to make QN:PN ratios meaningful. Live moths may have QN:PN ratio of (very) roughly ≈ 0.2 (ie relatively few QNs), insofar as a ratio can be estimated. Actual values are not known.

2. The level of Gaussian noise affecting all AL neurons varied from 0 to 1.33, where 1.0 represents natural levels (i.e. fitted to *in vivo* data). The purpose of this noise range was to test for any injury-mitigating values for the AL structure.
3. For experiments examining effects of learning and of AL noise, we set the number of QNs per glomerulus to zero. Setting the number of QNs equal to 2 (equivalently, QN:PN ratio = 0.4) gave similar results. These QN values remain close to that of realistic models.

The extremes of the parameter regimes described above deviated significantly from calibrated models, and sometimes created moths with unacceptably noisy, dysfunctional EN responses to odor. Thus, we discarded moths with naive EN odor response-to-spontaneous FR (SSNR) outside an envelope defined by $\frac{\mu(F)}{\mu(s)} < 12$. These comprised about 12% of moths generated, with the percentage depending on the varied parameters: Templates with high numbers of QNs and/or very high AL noise had more rejected moths; templates with few QNs and normal/low AL noise had few rejected moths. Extra moths were generated as needed to match numbers across all experiments.

**Focal Axonal Swellings (FAS)**

FAS is a neural injury associated with traumatic brain injury (TBI), typically caused by physical shock. Examples in current events include blast injuries from recent wars, as well as impact injuries in contact sports. FAS presents as swollen neural axons (the signal delivery pipelines) with dramatic diameter changes, causing signals from the upstream source to be diminished or lost entirely before reaching downstream target neurons [70]. This degradation can be expressed as reduced FRs from upstream neurons, characterized in a computational model by [20], which found that signals traveling down an injured axon are attenuated to greater or lesser degree according to the amount of swelling and the firing rate of the signal. While ablation is a ready and oft-used means to model neural injury, it imposes a binary “all-or-nothing” effect which is not present in FAS injuries. In these experiments we model neural injury according to [20], hereafter “FAS type” or “FAS”.

**Location of injured regions**

Two sites were targeted independently for FAS injury (RNs or PNs/QNs), with the choice determined by the experiment. See Fig 2.

**RNs:** We posited the Antennae $\rightarrow$ AL channel, i.e. the RNs, as a likely site for FAS injury due to their exposure to external impacts. Fig 2 (red stars) shows this injury location. There are about 30k RNs, which we divide as 500 RNs responding to each of 60 atomic volatiles. These volatile-focused groups send their inputs to a single glomerulus in the AL, where their inputs are averaged to reduce noise. The receptors for a given glomerulus are distributed across the antennae. Thus, we expect injury to an antenna to affect each glomerulus’ RN input roughly equally, and to affect a roughly equal percentage of each glomerulus’ 500 inputs.

**PNs/QNs:** There is a channel that carries PN (and QN) axons from AL$\rightarrow$MB. We modeled damage to this channel by injuring both PNs and QNs with equal probability. Fig 2 (orange stars) shows this injury location. We assumed that the degree of sparsity enforced on the MB (either by the Lateral Horn, or by global self-inhibition by the MB) remained stable over modulations of input signal from the AL.

**Injury methods**

FAS due to physical trauma does not affect all neurons in a targeted brain region equally, nor does it operate in an “all or nothing” way [71]. We used an injury regime derived in [20], which calculates the fractions of injured neurons falling into each of four injury types: FR unaffected (transmission); FR cut by half (reflection), FR destroyed (ablation), or FR filtered according to

$$f_{injured}(s) = F(f_{healthy}(s)),$$

where $f_*$ = firing rate, $s$ is a stimulus, and $F$ is a lowpass filter. FAS injury fractions were as follows: 15% transmission, 35% reflection, 35% ablation, and 15% low-pass filtering. Neurons in the target group were randomly selected for injury according to the percentage specified in the particular experiment (0 to 60%). Each injured neuron in the target group was then randomly assigned one of the damage types.
Applying this injury regime to populations of PNs and QNs in the model is straightforward, since these neurons are modeled one-to-one (i.e., one neuron in the model represents one actual neuron). Injury to RNs was handled differently because in MothNet each RN (inputting to one glomerulus in the AL) stands for \( \approx 500 \) RNs in the live moth. Injury of RNs worked as follows:

1. The FAS injury level was converted into a theoretically equivalent ablation injury level \( n \), where \( 100n = \% \) ablation.
2. Each RN’s FR was multiplied by \( (1 - n) \) (i.e. attenuation), since the glomerulus had fewer inputs.
3. The RN noise parameter was multiplied by \( \frac{1}{\sqrt{1-n}} \), since the glomerulus was averaging fewer inputs, giving less noise reduction from averaging.
4. 15% of FAS injury was low-pass filtering, which depends on the injured neuron’s firing rate. This part of the FAS injury to RNs varied according as the RN firing rate varied. So the actual \( n(t) \) affecting a given RN fluctuated slightly with odor inputs.

**Simulation protocols**

Each experiment consisted of many moths, all generated from the same template with only the parameters-under-test varied. Over 20 moths (trials) were run for each parameter combination (e.g., “4 QNs, 50% injury, and 10 training odor puffs”), giving over 60 moths for each key parameter pair (e.g., “4 QNs, 50% injury”) with training on 5, 10, or 15 odor puffs. A single trial consisted of first injuring and then training a single moth, in five stages:

1. Pre-injury baseline: Odor was applied without octopamine (15 odor puffs, each 0.2 mSec) to assess naive EN odor response.
2. Injury was applied.
3. Post-injury odor: Odor was applied without octopamine (15 odor puffs) to assess the effects of injury on EN odor response.
4. Training: Odor plus octopamine were applied (5, 10, or 15 odor puffs), with Hebbian plasticity “turned on”, to train the system.
5. Post-Training odor: Odor was applied without octopamine (15 odor puffs) to assess post-training EN odor response.

Firing rate \( f(t) \) from a single EN was recorded, to track the actionable effect of injury and training on the system. A timecourse of EN firing rates, from a typical experiment, is shown in Fig.3.

**Additional simulation details**

**Learning compensates for injury:** Moth templates were biologically plausible, in the sense that their AL behavior matched in vivo data, and they demonstrated learning behavior. Moths in this experiment had 0 QNs, i.e. no feed-forward inhibitory signals from AL→MB (2 QNs per glomerulus gave very similar results). In two separate experiments, either the RN channel (Antennae→AL) or the PN/QN channel (AL→MB) was injured with FAS (0% to 60%).

**Parallel inhibitory neurons protect EN responses:** Moths were generated from biologically plausible template but with \( \{0, 2, 4, 5, \text{ or } 7\} \) QNs per 5 PNs. The corresponding QN:PN ratios are \( \{0, 0.4, 0.8, 1.0, \text{ or } 1.4\} \). AL noise was set to a natural level (matching in vivo data). The PN/QN channel was injured with FAS (0% to 60%). PNs and QNs were treated equally in terms of injury.

**AL noise preserves the highest EN responses:** Moths templates had AL noise level from 0 to 1.33, where 1.0 corresponds to natural AL noise. Moths in this experiment had only excitatory PNs (i.e. \( \#\text{QNs} = 0 \)). Moth templates with 2 QNs per glomerulus gave similar results. The RN channel was injured with FAS from 0% to 60%. 

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Figure 10. Overview of AL-MB. Left: System schematic. Green lines show excitatory connections, red lines show inhibitory connections. Lateral horn inhibition of the MB is global on the MB. Light blue ovals show plastic connections into and out of the MB.

Right: Neuron outputs for each network (typical simulation) with time axes aligned. Timecourses are aligned with their regions in the schematic. The AL timecourse shows all responses within $\pm 2.5$ std dev of mean spontaneous rate as medium blue. Responses outside this envelope are yellow-red (excited) or dark blue (inhibited). MB responses are shown as binary (active/silent). Timecourse events are as follows: 1. A period of no stimulus. All regions are silent. 2. Two odor stimuli are delivered, 3 puffs each. AL, MB, and ENs display odor-specific responses. 3. A period of control octopamine, i.e. without odor or Hebbian training. AL response is varied, MB and EN are silent. 4. The system is trained (octopamine injected) on the first odor. All regions respond strongly. 5. A period of no stimulus. All regions are silent, as in (1). 6. The stimuli are re-applied. The AL returns to its pre-trained activity since it is not plastic. In contrast, the MB and EN are now more responsive to the trained odor, while response to the untrained odor is unchanged. Green dotted line in the EN represents a hypothetical "action" threshold. The moth has learned to respond to the trained odor.
Effects of ablation vs FAS injury: To compare effects of ablation vs FAS injury, we ran parallel experiments using ablation and FAS. Injury levels were set between 0% to 60%, using either FAS type or ablation. FAS injury fractions were 15% transmission, 35% reflection, 35% ablation, and 15% low-pass filtering (~0.7x – 0.9x in most cases). Assuming averaging over a large population in injured neurons, the theoretical conversion rate from FAS type to ablation is as follows:

100 units FAS \approx (15 \times 1) + (35 \times 0.5) + (35 \times 0) + (15 \times 0.7) \approx 43 \text{ units of survival},

\Rightarrow 57 \text{ units of ablation}, which gives a conversion rate \approx 1.75.

Thus, a 20% ablation nominally converts to 35% FAS injury.

Plasticity: Our model assumes a Hebbian mechanism for growth in synaptic connection weights \[17,66\]. The synaptic weight \( w_{ab} \) between two neurons \( a \) and \( b \) increases proportionally to the product of their firing rates (“fire together, wire together”): \( \Delta w_{ab}(t) \propto f_a(t)f_b(t) \).

Thus, synaptic plasticity is defined by:

\[
\Delta w_{ab}(t) = \gamma f_a(t)f_b(t), \quad \text{where} \quad \gamma \text{ is a growth parameter.} \quad (7)
\]

There are two layers of plastic synaptic weights, pre- and post-MB: AL→MB \((M^{P,K}, M^{Q,K})\), and MB→ENs \((M^{K,E})\).

Learning rate parameters of MothNet were calibrated to match experimental effects of octopamine on PN firing rates and known moth learning speed (e.g., 4 - 8 trials to induce behavior modification) \[72\]. The version of MothNet we used did not decay unused synaptic weights. Training does not alter octopamine delivery strength matrices \((M^{O,*})\); that is, the neuromodulator channels are not plastic (unlike, for example, the case in \[73\]).

Odor and octopamine injections: Odors and octopamine are modeled as hamming windows. The smooth leading and trailing edges ensures low stiffness of the dynamic ODEs, and allows a 10 mSec timestep to give accurate evolution of the SDEs in simulations.

Training: Training on an odor consists of simultaneously applying puffs of the odor, injecting octopamine, and “switching on” Hebbian growth. Training with 5 to 10 odor puffs typically produces behavior change in live moths.

Governing equations and numerical schemes

The following equations govern the time-stepped simulations of the MON system \[7\].

\[
\begin{align*}
\tau_r \cdot \dot{u}^R &= f_R(u^R, u^K, u^S, M^{L,R}, M^{S,R}, M^{O,R}, o(t)) + dW^R \\
\tau_r \cdot \dot{u}^P &= f_P(u^P, u^K, u^L, M^{L,P}, M^{R,P}, M^{O,P}, o(t)) + dW^P \\
\tau_Q \cdot \dot{u}^Q &= f_Q(u^R, u^K, u^L, M^{L,Q}, M^{R,Q}, M^{O,Q}, o(t)) + dW^Q \\
\tau_L \cdot \dot{u}^L &= f_L(u^P, u^K, M^{L,L}, M^{R,L}, M^{O,L}, o(t)) + dW^L \\
\tau_K \cdot \dot{u}^K &= f_K(u^P, u^K, u^D, M^{P,K}, M^{O,K}) + dW^K \\
\tau_E \cdot \dot{u}^E &= f_E(u^K, u^S, M^{K,E}) + (8) \\
\end{align*}
\]

where

\[
\begin{align*}
f_R &= -u^R + \text{sigmoid}\left[-(I - \gamma \cdot o(t) \cdot M^{O,R})M^{L,R}u^L + (I + o(t) \cdot M^{O,R})M^{S,R}u^S\right] \\
f_P &= -u^K + \text{sigmoid}\left[-(I - \gamma \cdot o(t) \cdot M^{O,P})M^{L,P}u^L + (I + o(t) \cdot M^{O,P})M^{R,P}u^R\right] \\
f_Q &= -u^K + \text{sigmoid}\left[-(I - \gamma \cdot o(t) \cdot M^{O,Q})M^{L,Q}u^L + (I + o(t) \cdot M^{O,Q})M^{R,Q}u^R\right] \\
f_L &= -u^L + \text{sigmoid}\left[-(I - \gamma \cdot o(t) \cdot M^{O,L})M^{L,L}u^L + (I + o(t) \cdot M^{O,L})M^{R,L}u^R\right] \\
f_K &= -u^K + \text{sigmoid}\left[-(u^D + M^{O,K}u^K) + M^{P,K}u^K\right] \\
f_E &= -u^K + M^{K,E}u^K \\
\end{align*}
\]
### Table 2. List of model parameters and variables.

| Symbol | Type     | Size/Value | Description and Remarks                                                                 |
|--------|----------|------------|-----------------------------------------------------------------------------------------|
| R      | superscript |            | Refers to the receptor neurons subpopulation.                                            |
| P      | superscript |            | Refers to the excitatory projection neurons subpopulation.                               |
| Q      | superscript |            | Refers to the inhibitory projection neurons subpopulation.                               |
| L      | superscript |            | Refers to the lateral neurons subpopulation.                                             |
| K      | superscript |            | Refers to the Kenyon cells subpopulation.                                                |
| E      | superscript |            | Refers to the readout extrinsic neurons subpopulation.                                  |
| O      | superscript |            | Refers to the octopamine neurotransmitter.                                               |
| nG     | scalar    | 60         | Number of glomeruli in the antennal lobe.                                               |
| nS     | scalar    | 2-4        | Number of different stimuli (odors).                                                     |
| nQ     | scalar    |            | Number of inhibitory projection neurons.                                                |
| nK     | scalar    | 2000       | Number of Kenyon cells.                                                                 |
| nE     | scalar    | 1          | Number of extrinsic neurons.                                                            |
| u_R    | vector    | nG × 1     | FRs of the receptor neurons subpopulation.                                              |
| u_P    | vector    | nG × 1     | FRs of the excitatory projection neurons subpopulation.                                 |
| u_Q    | vector    | nQ × 1     | FRs of the inhibitory projection neurons subpopulation.                                 |
| u_K    | vector    | nK × 1     | FRs of the Kenyon cells subpopulation. Sparse.                                           |
| u_E    | vector    | nE × 1     | FRs of the extrinsic neurons subpopulation.                                             |
| u_D    | vector    |            |                                                                                         |
| M_{R,R} | matrix    | nG × nS    | Stimulus → u_R connections.                                                             |
| M_{O,R} | matrix    | nG × nG    | Octopamine → u_R connections. Diagonal matrix.                                          |
| M_{O,L} | matrix    | nG × nG    | Octopamine → u_L connections. Diagonal matrix.                                          |
| M_{R,L} | matrix    | nG × nG    | Connection weights u_R → u_L.                                                           |
| M_{R,P} | matrix    | nG × nG    | Connection weights u_R → u_P.                                                           |
| M_{R,Q} | matrix    | nQ × nG    | Connection weights u_R → u_Q.                                                            |
| M_{P,K} | matrix    | nK × nG    | Connection weights u_P → u_K.                                                            |
| M_{Q,K} | matrix    | nK × nQ    | Connection weights u_Q → u_K.                                                            |
| M_{L,R} | matrix    | nG × nG    | Connection weights u_L → u_R.                                                            |
| M_{L,P} | matrix    | nG × nG    | Connection weights u_L → u_P.                                                            |
| M_{L,Q} | matrix    | nQ × nG    | Connection weights u_L → u_Q.                                                            |
| M_{L,L} | matrix    | nQ × nG    | Connection weights u_L → u_L.                                                            |
| M_{K,E} | matrix    | nE × nK    | Connection weights u_K → u_E.                                                            |
| o(t)   | function  | 0 or 1     | Flags when octopamine is active (typically during training).                            |
| γ      | scalar    | 0.5        | Scaling factor for octopamine's effects on inhibition.                                  |
| τ_R    | scalar    |            |                                                                                         |
| τ_P    | scalar    |            |                                                                                         |
| τ_Q    | scalar    |            |                                                                                         |
| τ_L    | scalar    |            |                                                                                         |
| τ_K    | scalar    |            |                                                                                         |
| τ_E    | scalar    |            |                                                                                         |

* Each glomerulus receives one RN and one octopamine input, and initiates one PN and one LN.

* Octopamine decreases the response to inhibition less than it increases the response to excitation.
Discretization: We use the standard Euler-Maruyama (EM) forward-step method for SDEs.  

- Euler (noise-free): $x_{n+1} = x_n + \Delta t f(x_n)$  
- Euler-Maruyama: $x_{n+1} = x_n + \Delta t f(x_n) + \epsilon \text{ randn}(0,1)\sqrt{\Delta t}$, where $\epsilon$ controls the noise intensity.

Convergence: The timestep $\Delta t$ was chosen such that noise-free EM evolution gives the same timecourses as Runge-Kutta (4th order), via Matlab’s ode45 function. $\Delta t = 10$ mSec suffices to match EM evolution to RK in noise-free moths. Values of $\Delta t \leq 20$ mSec gives equivalent simulations in moths with AL noise calibrated to match in vivo data. Values of $\Delta t \geq 40$ mSec show differences in evolution outcomes given AL noise.

References

1. Higginson AD, Barnard CJ, Tofilski A, Medina L, Ratnieks F. Experimental Wing Damage Affects Foraging Effort and Foraging Distance in Honeybees Apis mellifera. Psyche. 2011;Available from: http://dx.doi.org/10.1155/2011/419793.

2. Roberts JC, Cartar RV. Shape of wing wear fails to affect load lifting in common eastern bumble bees (Bombus impatiens) with experimental wing wear. Canadian Journal of Zoology. 2015;93(7):531–537. Available from: https://doi.org/10.1139/cjz-2014-0317.

3. Pouget A, Narain C. A Conversation with Alexandre Pouget. Cold Spring Harb Symp Quant Biol 2014. 2014;79:285–287.

4. Ganguli S, Sompolinsky H. Compressed Sensing, Sparsity, and Dimensionality in Neuronal Information Processing and Data Analysis. Annual Review of Neuroscience. 2012;35(1):485–508. PMID: 22483042. Available from: https://doi.org/10.1146/annurev-neuro-062111-150410.

5. Campbell R, Honegger K, Qin H, Li W, Demir E, Turner G. Imaging a Population Code for Odor Identity in the Drosophila Mushroom Body. Journal of Neuroscience. 2013;33(25):10568–81.

6. Hige T, Aso Y, Rubin GM, Turner GC. Plasticity-driven individualization of olfactory coding in mushroom body output neurons. Nature. 2015 Sep;526:258 EP –. Available from: http://dx.doi.org/10.1038/nature15396.

7. Delahunt CB, Riffell JA, Kutz JN. Biological Mechanisms for Learning: A Computational Model of Olfactory Learning in the Manduca sexta Moth, with Applications to Neural Nets. arXiv. 2018;Available from: https://arxiv.org/abs/1802.02678.

8. Martin JP, Beyerlein A, Dacks AM, Reisenman CE, Riffell JA, Lei H, et al. The neurobiology of insect olfaction: Sensory processing in a comparative context. Progress in Neurobiology. 2011;95(3):427 – 447. Available from: http://www.sciencedirect.com/science/article/pii/S0301008211001742.

9. Kvello P, Løfaldli B, Rybak J, Menzel R, Mustaparta H. Digital, three-dimensional average shaped atlas of the heliothis virescens brain with integrated gustatory and olfactory neurons. Frontiers in Systems Neuroscience. 2009;3:14. Available from: https://www.frontiersin.org/article/10.3389/neuro.06.014.2009.

10. Wilson RI. Neural and behavioral mechanisms of olfactory perception. Current Opinion in Neurobiology. 2008;18(4):408 – 412. Sensory systems. Available from: http://www.sciencedirect.com/science/article/pii/S0959438808000883.

11. Masse NY, Turner GC, Jefferis GSXE. Olfactory Information Processing in Drosophila. Current Biology. 2009;19(16):R700 – R713. Available from: http://www.sciencedirect.com/science/article/pii/S0960982209013013.
12. Bhandawat V, Olsen SR, Gouwens NW, Schlief ML, Wilson RI. Sensory processing in the Drosophila antennal lobe increases reliability and separability of ensemble odor representations. Nature Neuroscience. 2007;10:1474–1482.

13. Campbell RAA, Turner GC. The mushroom body. Current Biology. 2010;20(1):R11 – R12. Available from: http://www.sciencedirect.com/science/article/pii/S096098220901851X

14. Galizia CG. Olfactory coding in the insect brain: data and conjectures. European Journal of Neuroscience. 2014;39(11):1784–1795. Available from: http://dx.doi.org/10.1111/ejn.12558

15. Perisse E, Burke C, Huetteroth W, Waddell S. Shocking Revelations and Saccharin Sweetness in the Study of Drosophila Olfactory Memory. Curr Biol. 2013 Sep;23(17):R752–R763. S0960-9822(13)00921-4[PII], 24028959[pmid]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3770896/

16. Honegger KS, Campbell RAA, Turner GC. Cellular-Resolution Population Imaging Reveals Robust Sparse Coding in the Drosophila Mushroom Body. Journal of Neuroscience. 2011;31(33):11772–11785. Available from: http://www.jneurosci.org/content/31/33/11772

17. Cassenaer S, Laurent G. Hebbian STDP in mushroom bodies facilitates the synchronous flow of olfactory information in locusts. Nature. 2007 Jun;448:709 EP –. Available from: http://dx.doi.org/10.1038/nature05973

18. Hammer M, Menzel R. Learning and memory in the honeybee. Journal of Neuroscience. 1995;15(3):1617–1630. Available from: http://www.jneurosci.org/content/15/3/1617

19. Hammer M, Menzel R. Multiple Sites of Associative Odor Learning as Revealed by Local Brain Microinjections of Octopamine in Honeybees. Learn Mem. 1998 May;5(1):146–156. 10454379[pmid]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC311245/

20. Maia PD, Kutz JN. Reaction time impairments in decision-making networks as a diagnostic marker for traumatic brain injuries and neurological diseases. Journal of Computational Neuroscience. 2017;42:323–347.

21. Maia PD, Kutz JN. Identifying critical regions for spike propagation in axon segments. Journal of Computational Neuroscience. 2014;36(2):141–155.

22. Maia PD, Kutz JN. Compromised axonal functionality after neurodegeneration, concussion and/or traumatic brain injury. Journal of Computational Neuroscience. 2014;27:317–332.

23. Maia PD, Hemphill MA, Zehnder B, Zhang C, Parker KK, Kutz JN. Diagnostic tools for evaluating the impact of Focal Axonal Swellings arising in neurodegenerative diseases and/or traumatic brain injury. Journal of Neuroscience Methods. 2015;253:233–243.

24. Adams JH, Jennett B, Murray LS, Teasdale GM, Gemmarelli TA, Graham DI. Neuropathological findings in disabled survivors of a head injury. Journal of Neurotrauma. 2011;28:701–709.

25. Edlow BL, Copen WA, Izzy S, van der Kouwe A, Glenn MB, Greenberg SM, et al. Longitudinal diffusion tensor imaging detects recovery of fractional anisotropy within traumatic axonal injury lesions. Neurocritical Care. 2016;24(3):342–352.

26. Hanell A, Greer JE, McGinn MJ, Povlishock JT. Traumatic brain injury? Induced axonal phenotypes react differently to treatment. Acta Neuropathologica. 2015;129:317–332.

27. Hay J, Johnson VE, Smith DH, Stewart W. Chronic traumatic encephalopathy: the neuropathological legacy of traumatic brain injury. Annual Review of Pathology: Mechanisms of Disease. 2016;11:21–45.

28. Henninger N, Bouley J, Sıkoglu EM, An J, Moore CM, King JA, et al. Attenuated traumatic axonal injury and improved functional outcome after traumatic brain injury in mice lacking Sarm1. BRAIN. 2016;p. 1–12.
29. Hill CS, Coleman MP, Menon DK. Traumatic axonal injury: mechanisms and translational opportunities. Trends in Neuroscience. 2016;39(5):311–324.

30. Hemphill MA, Dauth S, Yu CJ, Dabiri BE, Parker KK. Traumatic Brain Injury and the Neuronal Microenvironment: A Potential Role for Neuropathological Mechanotransduction. Neuron. 2015;86(6):1177–1192.

31. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. Experimental Neurology. 2013;246:35–43.

32. Reeves TM, Smith TL, Williamson JC, Phillips LL. Unmyelinated axons show selective rostrocaudal pathology in the corpus callosum after traumatic brain injury. Journal of Neuropathology & Experimental Neurology. 2012;71(3):198–210.

33. Skandsen T, Kvistad KA, Solheim O, Strand IH, Folvik M, Vik A. Prevalence and impact of diffuse axonal injury in patients with moderate and severe head injury: a cohort study of early magnetic resonance imaging findings and 1-year outcome. Journal of Neurosurgery. 2010;113(3):556–563.

34. Browne KD, Chen XH, Meaney DF, Smith DH. Mild Traumatic Brain Injury and Diffuse Axonal Injury in Swine. Journal of Neurotrauma. 2011;28(9):1747–1755.

35. Dikranian K, Cohen R, Donald CM, Pan Y, Brakefield D, Bayly P, et al. Mild traumatic brain injury to the infant mouse causes robust white matter axonal degeneration which precedes apoptotic death of cortical and thalamic neurons. Experimental Neurology. 2008;211:551–560.

36. Maxwell WL, Povlishock JT, Graham DL. A Mechanistic Analysis of Nondisruptive Axonal Injury: A Review. Journal of Neurotrauma. 1997;17(7):419–440.

37. Wang J, Hamm RJ, Povlishock JT. Traumatic axonal injury in the optic nerve: evidence for axonal swelling, disconnection, dieback and reorganization. Journal of Neurotrauma,. 2011;28(7):1185–1198.

38. Chen YC, Smith DH, Meaney DF. In-Vitro Approaches for Studying Blast-Induced Traumatic Brain Injury. Journal of Neurotrauma. 2009;26(6):861–876.

39. Fayanz I, Tator CH. Modeling axonal injury in vitro: injury and regeneration following acute neuritic trauma. Journal of Neuroscience Methods. 2000;102:69–79.

40. Hellman AN, Vahidi B, Kim HJ, Mismar W, Steward O, Jeonde NL, et al. Examination of axonal injury and regeneration in micropatterned neuronal culture using pulsed laser microbeam dissection. Lab on a Chip. 2010;16:2083–2092.

41. Hemphill MA, Dabiri BE, Gabriele S, Kerscher L, Franck C, Goss JA, et al. A Possible Role for Integrin Signaling in Diffuse Axonal Injury. PLoS ONE. 2011;6(7):e22899.

42. Magdesian MH, Sanchez FS, Lopez M, Thostrup P, Durisic N, Belkaid W, et al. Atomic force microscopy reveals important differences in axonal resistance to injury. Biophysical Journal. 2012;103(3):405–414.

43. Morrison B, Elkin BS, Dolle JP, Yarmush ML. In vitro models of traumatic brain injury. Annual Reviews in Biomedical Engineering. 2011;13(1):91–126.

44. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. Journal of Neurotrauma. 1995;12:565–572.

45. Christman CW, Grady MS, Walker SA, Hol-Loway KL, Povlishock JT. Ultra-structural studies of diffuse axonal injury in humans. Journal of Neurotrauma. 1994;11:173–186.
46. Grady MS, Mclaughlin MR, Christman CW, Valadaka AB, Flinger CL, Povlishock JT. The use of antibodies against neurofilament subunits for the detection of diffuse axonal injury in humans. Journal of Neuropathology and Experimental Neurology. 1993;52:143–152.

47. Jorge RE, Acion L, White T, Tordesillas-Gutierrez D, Pierson R, Crespo-Facorro B, et al. White matter abnormalities in veterans with mild traumatic brain injury. American Journal of Psychiatry. 2012;169(12):1284–1291.

48. Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, et al. White matter damage and cognitive impairment after traumatic brain injury. Brain. 2010;p. 1–15.

49. Povlishock JT, Katz DI. Update of Neuropathology and Neurological Recovery After Traumatic Brain Injury. Journal of Head Trauma Rehabilitation. 2005;20(1):76–94.

50. Adalbert R, Nogradi A, Babetto E, Janeckova L, Walker SA, Kerschensteiner M, et al. Severely dystrophic axons at amyloid plaques remain continuous and connected to viable cell bodies. BRAIN. 2009;132:402–416.

51. Daianu M, Jacobs RE, Town T, Thompson PM. Axonal diameter and density estimated with 7-tesla hybrid diffusion imaging in transgenic Alzheimer rats. SPIE Proceedings. 2016;9784:1–6.

52. Krstic D, Knusel I. Deciphering the mechanism underlying late-onset Alzheimer disease. Nature Reviews Neuroscience. 2012;9(1):25–34.

53. Tsai J, Grutzendler J, Duff K, Gan WB. Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. Nature Neuroscience. 2004;7:1181–1183.

54. Tagliaferro P, Burke RE. Retrograde Axonal Degeneration in Parkinson Disease. Journal of Parkinson’s Disease. 2016;6:1–15.

55. Louis ED, Faust PL, Vonsattel JPG, Honig LS, Rajput A, Rajput A, et al. Torpedoes in Parkinson’s Disease, Alzheimer’s Disease, Essential Tremor, and Control Brains. Movement Disorders. 2009;24(11):1600–1605.

56. Galvin JE, Uryu K, Lee VM, Trojanowski JQ. Axon pathology in Parkinson’s disease and Lewy body dementia hippocampus contains α-, β-, and γ-synuclein. Proceedings of National Academy of Science. 1999;96:13450–13455.

57. Friese MA, Schattling B, Fugger L. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. Nature Reviews Neurology. 2014;10:225–238.

58. Nikic I, Merkler D, Sorbara C, Brinkoetter M, Kreutzfeld M, Bareyre F, et al. A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. Nature Medicine. 2011;17(4):495–499.

59. Trapp BD, Nave KA. Multiple Sclerosis: An Immune or Neurodegenerative Disorder? Annual Review Neuroscience. 2008;31(1):247–269.

60. Lusch B, Weholt J, Maia PD, Kutz JN. Modeling cognitive deficits following neurodegenerative diseases and traumatic brain injuries with deep convolutional neural networks. Brain and Cognition. 2018;123:154 – 164. Available from: http://www.sciencedirect.com/science/article/pii/S0278262616303827.

61. Rudy S, Maia PD, Kutz JN. Cognitive and behavioral deficits arising from neurodegeneration and traumatic brain injury: a model for the underlying role of focal axonal swellings in neuronal networks with plasticity. Journal of Systems and Integrative Neuroscience. 2016;.

62. Weber M, Maia PD, Kutz JN. Estimating Memory Deterioration Rates Following Neurodegeneration and Traumatic Brain Injuries in a Hopfield Network Model. Frontiers in Neuroscience. 2017;11.
63. Kunert JM, Maia PD, Kutz JN. Functionality and Robustness of Injured Connectomic Dynamics in C. elegans: Linking Behavioral Deficits to Neural Circuit Damage. PLOS Computational Biology. 2017 01;13(1):1–21. Available from: https://doi.org/10.1371/journal.pcbi.1005261

64. Dayan P, Abbott LF. Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems. The MIT Press; 2005.

65. Higham DJ. An Algorithmic Introduction to Numerical Simulation of Stochastic Differential Equations. SIAM Rev. 2001 Mar;43(3):525–546. Available from: http://dx.doi.org/10.1137/S0036144500378302.

66. Hebb DO. The organization of behavior : a neuropsychological theory. Wiley New York; 1949.

67. Bazhenov M, Stopfer M. Forward and Back: Motifs of Inhibition in Olfactory Processing. Neuron. 2010;67(3):357 – 358. Available from: http://www.sciencedirect.com/science/article/pii/S0896627310005842.

68. Lin AC, Bygrave AM, de Calignon A, Lee T, Miesenböck G. Sparse, decorrelated odor coding in the mushroom body enhances learned odor discrimination. Nature Neuroscience. 2014 Feb;17:559 EP –. Article. Available from: http://dx.doi.org/10.1038/nn.3660.

69. Gupta N, Stopfer M. Functional Analysis of a Higher Olfactory Center, the Lateral Horn. Journal of Neuroscience. 2012;32(24):8138–8148. Available from: http://www.jneurosci.org/content/32/24/8138.

70. Maia PD, Kutz JN. Compromised axonal functionality after neurodegeneration, concussion and/or traumatic brain injury. Journal of Computational Neuroscience. 2014 Oct;37(2):317–332. Available from: https://doi.org/10.1007/s10827-014-0504-x.

71. Wang J, Hamm RJ, Povlishock JT. Traumatic Axonal Injury in the Optic Nerve: Evidence for Axonal Swelling, Disconnection, Dieback, and Reorganization. J Neurotrauma. 2011 Jul;28(7):1185–1198. 21506725[pmid]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136743/.

72. Riffell JA, Lei H, Abrell L, Hildebrand JG. Neural Basis of a Pollinator’s Buffet: Olfactory Specialization and Learning in Manduca sexta. Science. 2012;Available from: http://science.sciencemag.org/content/early/2012/12/05/science.1225483.

73. Grant WS, Tanner J, Itti L. Biologically plausible learning in neural networks with modulatory feedback. Neural Networks. 2017;88(Supplement C):32 – 48. Available from: http://www.sciencedirect.com/science/article/pii/S0893608017300072.