Cascades and convergence: dynamic signal flow in a synapse-level brain network

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(Dated: July 30, 2025)

Connectomes—maps of synaptic connectivity—constrain how signals flow through the nervous system, shaping the transmission of sensory information to downstream targets involved in perception, decision-making, and action. Here, we use a simple, network-based spreading model to simulate sensory signal propagation across the adult Drosophila connectome. This approach allows us to trace modality-specific cascades, quantify their overlap, and identify convergence zones—neurons activated by multiple sensory pathways. Extending the classical spreading model, we introduce cooperative and competitive dynamics to simulate multisensory integration scenarios. Finally, we classify neurons based on their dynamical response profiles across all simulations, yielding a data-driven taxonomy grounded in both structure and dynamics. Our results highlight how abstract models can reveal organizing principles of neural computation and generate hypotheses for future experimental validation.

INTRODUCTION

Connectomes are wiring maps that describe the connectivity of neural elements—cells, populations, areas—to one another [1–6]. These physical connections support signaling and communication across neural systems [7–10], enabling the transformation of sensory inputs into adaptive behavioral responses [11–14]. Identifying the pathways that govern this information flow is a central aim of systems and behavioral neuroscience [15, 16].

Network neuroscience provides a framework for representing and analyzing brain networks using tools from graph theory [17–20]. Here, neural elements are encoded as nodes and their pairwise connections as edges in a directed, weighted graph. Such models can support both structural analyses and simulations of network-constrained dynamics [21–24]. One class of models, spreading dynamics, imagines that activation initiated in a small set of seed nodes propagates stepwise across synaptic connections, resulting in activation cascades that spread through the network [25–27]. These simplified models offer analytical tractability and insight into how network architecture shapes large-scale dynamics. They also provide an idealized description of sensory processing—tracking how input from peripheral sensory neurons flows through the brain to drive downstream activity [28, 29].

Recent advances in large-scale electron microscopy have yielded nanoscale connectomes of entire nervous systems [30–34]. The largest and most complete to date is that of the adult female fruit fly, *Drosophila melanogaster*, comprising roughly 138,000 neurons and 54 million synapses [35]. In addition to its scale, the connectome features detailed cell-type annotations and modular subdivisions [36–38], enabling integrative analyses that link structure, function, and lineage.

In *Drosophila*, sensory systems are initially segregated by modality, but their signals converge onto shared higher-order structures such as the lateral horn, mushroom body, and central complex [39–41]. These regions are thought to support associative learning, multisensory integration, and behavioral decision-making. Behavioral and physiological studies have shown that flies integrate information across sensory channels [42], though the circuit-level mechanisms remain poorly understood.

Using anatomical annotations of the fly connectome, it is now possible to identify sensory neurons and track how activity initiated in specific modalities spreads through the brain. In this study, we use and extend a recently developed spreading model [43] to explore how signals propagate from distinct sensory systems. We examine three scenarios: (1) *unimodal cascades*, in which single modalities are seeded independently; (2) *cooperative cascades*, in which paired modalities jointly influence activation timing; and (3) *competitive cascades*, where pairs of modalities vie for influence over shared downstream targets. We show that individual sensory cascades follow distinct trajectories but converge in central structures, particularly the central complex. We identify the neurons and connections that facilitate early, rapid activation, and analyze which neurons lie at the interface between competing signals. Finally, we use cascade-based summary statistics to group neurons by their roles in signal propagation.

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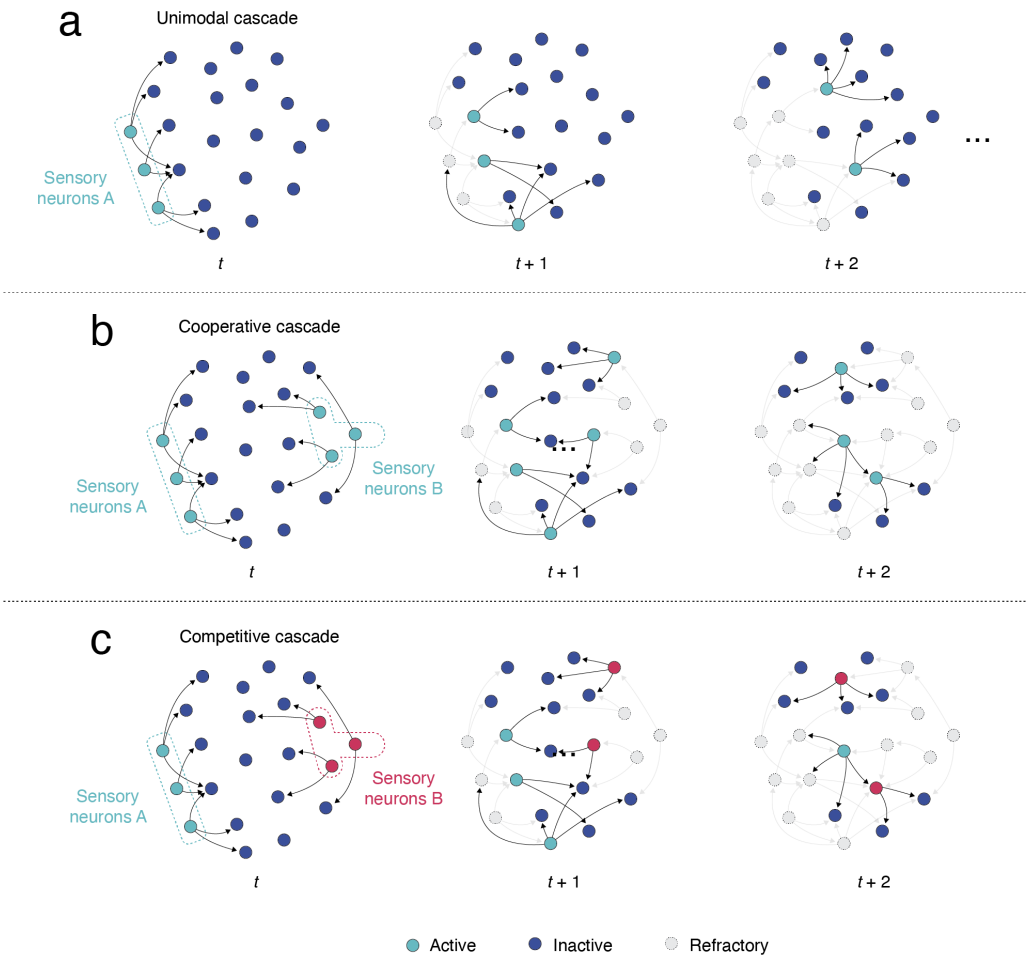

Figure 1. **Schematic illustration of cascade model.** Neurons can take on three states; active, inactive, or refractory. Inactive neurons are activated probabilistically by their pre-synaptic partners. Once a neuron has been activated, it enters a refractory period, wherein it cannot be activated at any subsequent time point. We consider three variations of this model. (a) Unimodal sensory cascades: wherein the initial population of active neurons (the seed population) are all of the same sensory modality. The model proceeds until either all neurons have been activated or there exists a time point wherein no neurons are currently active. (b) Cooperative sensory cascades: we consider two populations of sensory neurons, each of which represents a different sensory modality. Nonetheless, in their active states, these neurons carry identical information (the same state value), and therefore generally improve (reduce) activation times such that neuron i will tend to be activated earlier in the cooperative condition than in the unimodal condition. (c) Competitive sensory cascades: we, again, consider two populations of sensory neurons, but force them to carry different information and therefore "compete" for territory.

RESULTS

Here we analyzed the connectome of a single adult female *Drosophila melanogaster* (publicly available through `https://codex.flywire.ai/`; all analyses were carried out on the v783 connectome) [35]. The connectome comprised $N = 138,639$ neurons, $M = 15,091,983$ edges, $M_w = 54,492,922$ synapses.

Neuronal wiring of sensory systems

Synaptic connectivity between neurons enables the propagation of signals—including sensory information—throughout the nervous system. The configuration of these connections—the connectome's topology—thus plays a central role in shaping information flow [44]. To investigate how network structure contributes to sensory integration, we first examine the wiring among $N_{sensory} = 16,349$ annotated sensory

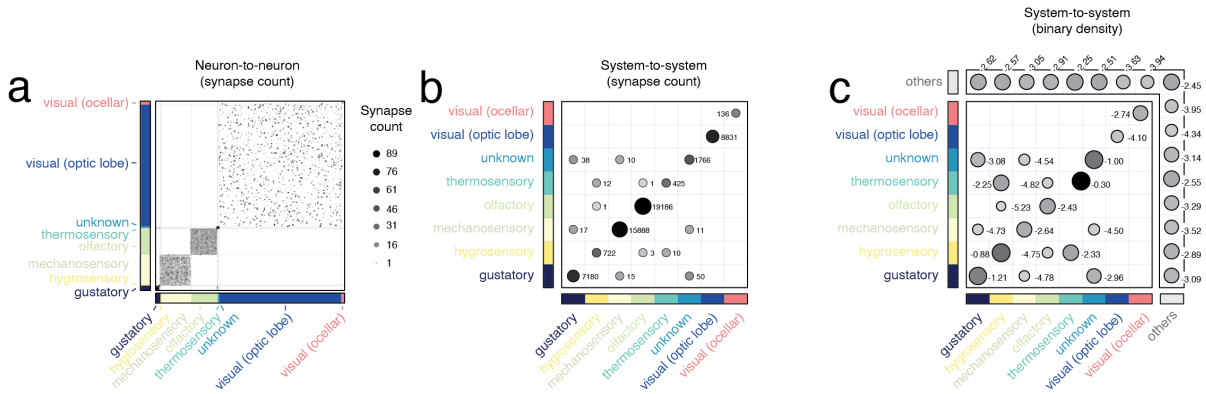

Figure 2. **Synaptic connectivity within and between primary sensory neurons.** (a) Complete sub-network of sensory-to-sensory connections. Gray lines delineate systems (modalities) from one another. (b) Synapse count between pairs of systems. (c) Binary density of connections between pairs of systems (and remaining neurons, labeled "others"). Note that in c the color and labels are on a logarithmic scale.

neurons. These neurons span several distinct modalities: gustation, hygrosensation, mechanosensation, olfaction, thermosensation, vision (both optic lobe and ocellar), and a category labeled "unknown."

We extracted the 16349 × 16349 subgraph comprising all synaptic connections between sensory neurons (Fig. 2a). This subgraph was notably sparse, with a binary connection density of $d_{sensory} = 1.3 \times 10^{-4}$—approximately six times lower than the full connectome's density ($d_{connectome} = 7.8 \times 10^{-4}$). Moreover, it was significantly sparser than randomly sampled subgraphs of the same size ($p < 10^{-3}$; 1000 random samples).

The sensory subgraph also exhibited strong modularity. Of the 54,302 synapses, 54,134 (99.7%) connected neurons within the same modality (Fig. 2b). This high degree of within-modality wiring highlights a parallel, segregated architecture with minimal direct cross-talk between modalities.

Taken together, these results indicate that direct sensory-sensory interactions are both rare and strongly modality-specific. This organization suggests that multimodal integration likely occurs through polysynaptic pathways that recruit non-sensory populations.

To explore this possibility, we used a stochastic cascade model to simulate how activation might spread from sensory neurons across the full connectome. This abstract model is broadly applicable to networked systems [45], and provides a tractable framework for studying the spatiotemporal dynamics of signal propagation.

In the model, each neuron can be in one of three states: active, inactive, or refractory. At time $t = 0$, a small set of N_{seed} "seed" neurons is initialized as active—all others begin inactive. These seeds can be thought of as neurons activated directly by a sensory stimulus. At each subsequent time step, active neurons attempt to activate each of their postsynaptic partners with probability $p_{transmission}$. Simultaneously, they enter a refractory state and cannot be reactivated. The cascade continues until no neurons remain active. See Fig. S1 for example cascades and for details on the influence of model parameters.

Edge contributions to cascades

The cascade model allows us to track how activity spreads not only across neurons, but also across individual synapses. This feature enables the identification of dynamic sensory pathways—sequences of synaptic contacts—that support the propagation of activation from sensory neurons into the broader brain. We can then ask: which types of neurons participate in these cascades? Do these pathways align with structural features of the connectome? And are the most active synapses associated with classical hub neurons?

To address these questions, we focused on a condition where $N_{seed} = 16$ sensory neurons were randomly drawn across all modalities and activated with $p_{transmission} = 0.01$. At each time step, we measured three quantities: the total number of active synapses, the number of unique synapses used, and their ratio (unique/total). A high ratio would indicate consistent usage of the same synapses across simulations; a low ratio would suggest variable, diverse pathways.

Early in the cascade, we observed a pronounced "bottlenecking" effect—specific synapses were repeatedly and consistently used to relay activity from the sensory

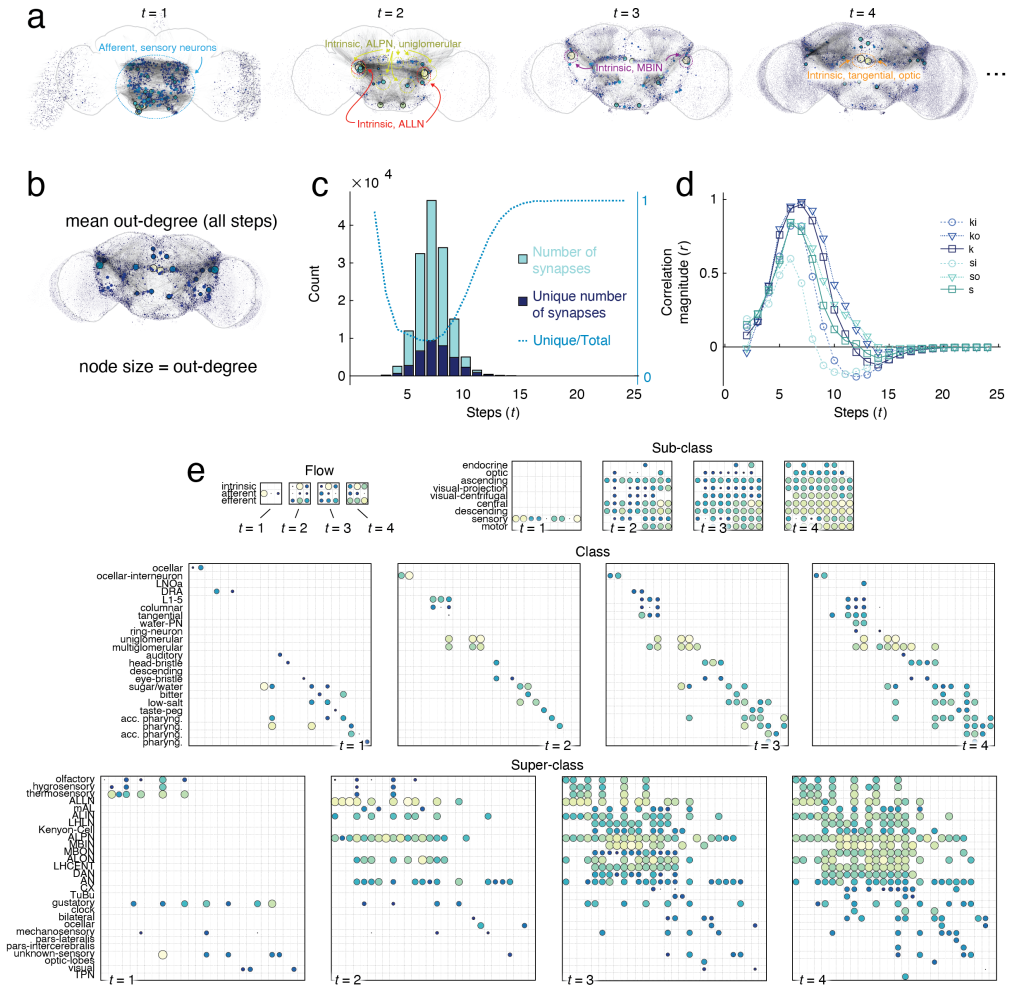

Figure 3. **Edge sequencing.** (*a*) Top 1000 edges (by usage) over first four time steps. (*b*) We constructed a weighted connectivity matrix by averaging edge usage across all time points, where at each time point an edge is present if it activates a postsynaptic neuron. We then calculate the out-degree of each node to highlight influential spreaders. (*c*) Across 1000 simulations, we count the total number of active synapses at each time point along with the unique number of active synapses. If the same synapses were active across all runs, then these numbers would coincide; however, due to the stochasticity of the cascade model and variation in the set of seeded neurons, different synapses appear at different time points. (*d*) Correlation of the instantaneous out-degree with basic structural properties of the network. (*e*) Active synapses (edges) grouped by annotation data. Circumference and color circle are proportional to the logarithm of their usage (count).

seeds into the rest of the brain (Fig. 3c). This consistency declined at later stages, as the cascade diversified into multiple alternative routes (Fig. 3c). These findings suggest that a small set of high-traffic synapses mediates the initial wave of integration, while later dynamics engage a broader array of pathways.

To examine whether synapse usage could be predicted from static network features, we computed the out-degree of each neuron based on edge usage and compared this to their degree and strength in the underlying connectome. Early in the cascade, correlations between dynamic and structural centrality were weak (maximum $r = 0.15$), indicating that highly connected neurons in the static network did not dominate the initial spread (Fig. 3d). However, as activity progressed beyond $t = 6$, correlations rose sharply, exceeding $r > 0.9$ by $t = 7$, consistent with a transition toward greater reliance on structural hubs for sustaining propagation.

To better understand the cellular and anatomical substrates of these dynamics, we aggregated the $138{,}639 \times 138{,}639$ edge usage matrix at each time point by hierarchical annotation categories—"Flow", "Super-

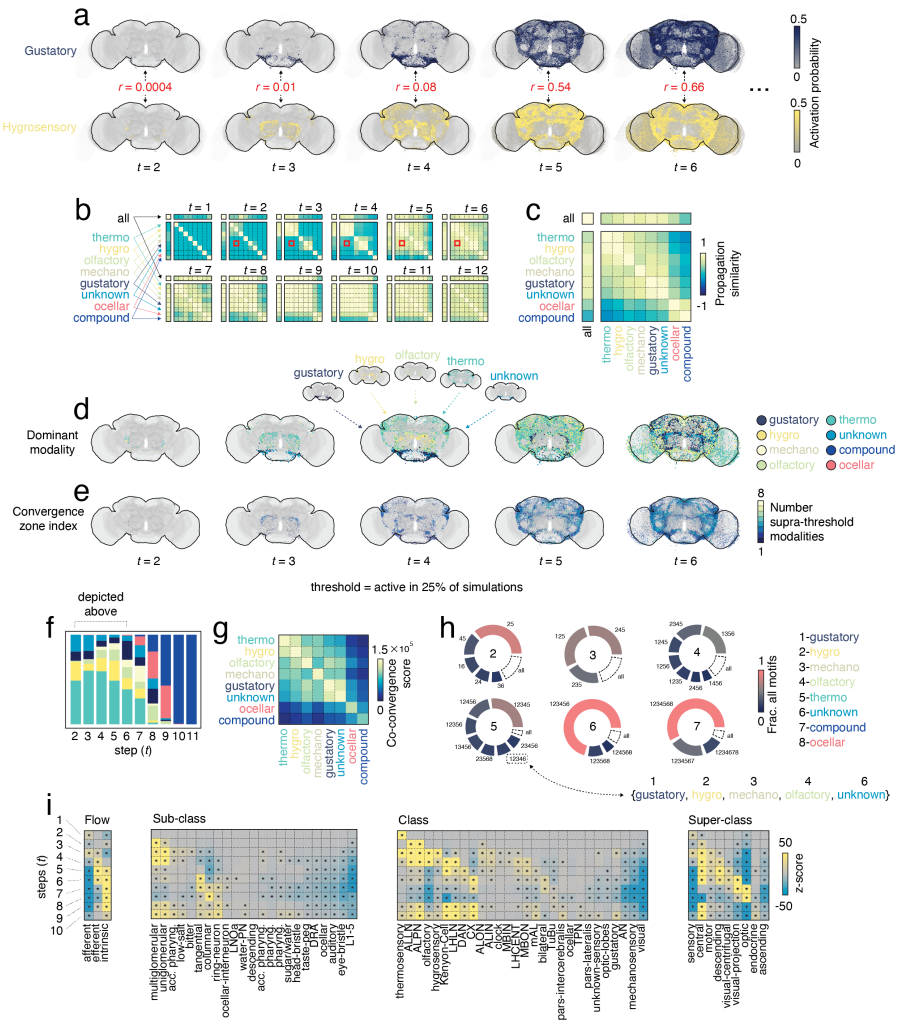

Figure 4. **Modal specificity and similarity of cascades.** Here, we consider cascades in which neurons associated with different sensory modalities are treated as seeds. From these seeds we simulate cascades and compare the spatiotemporal trajectories between sensory modalities. (a) Schematic for comparing cascades. For two sensory modalities (gustation and hygrosensation, in this case) we calculated the similarity between spatial maps at each time step as a correlation. (b) We extended this comparison to all pairs of sensory modalities as well as the "all" category (pan-sensory cascade), wherein sensory neurons from all modalities are treated as seeds, and show the similarity between all pairs at each time step, from $t = 1$ to $t = 12$. (c) We also concatenated the activation probability maps across time steps for a given sensory modality and computed the similarity between these omnibus maps, yielding a single time-invariant similarity score for pairs of sensory modalities. (d) We calculated dominance maps, where each neuron is assigned the label of the sensory modality corresponding to the greatest activation probability at a given time step. (e) We also calculated a "convergence index" for neurons as the number of sensory modalities with activation probability exceeding some threshold (here, 25%) at a given time step. (f) Composition of dominant modality as a function of time. (g) Pairwise co-convergence between pairs of sensory modalities. That is, how often did two sensory modalities simultaneously exceed the activation probability threshold together. (h) Frequency of overlap motifs, ranging from size 2 to size 7. (i) Enrichment statistics for convergence zone index across annotations as a function of time.

class", "Class", and "Sub-class" (see **Materials and Methods**). Early cascade stages primarily involved synapses between afferent and intrinsic neurons, many of which were sensory (Fig. 3e, top panels). At intermediate time steps, uni- and multiglomerular projection neurons became prominent, including reciprocal interactions among these cell types and with tangential neurons—suggesting the involvement of antennal lobe circuits and early olfactory integration (Fig. 3e, middle).

From $t = 2$ onward, activation increasingly in-

volved downstream targets such as the mushroom body—particularly Kenyon cells—and neurons of the central complex. These populations serve as known convergence zones for multi-modal integration in *Drosophila* [46–48], and they relayed activity to neurons in the optic lobes at later stages (Fig. 3e, bottom). These dynamics suggest a structured flow from afferent sensory neurons through intermediate integration zones toward broader, distributed activation of the brain.

Overlapping and distinct spatiotemporal profiles of unimodal sensory cascades

In the previous section, we examined cascade dynamics following simultaneous activation of neurons from *all* sensory systems. Here, we restrict seeding to individual modalities, allowing us to isolate features that are shared across, or unique to, specific sensory systems.

To illustrate modality-specific dynamics, we compare cascades seeded from gustatory and hygrosensory neurons by visualizing their activation probability maps from $t = 2$ to $t = 6$ (Fig. 4a). Early-stage activity patterns are largely uncorrelated, consistent with non-overlapping sensory pathways. However, over time, cascades converge, with activation maps becoming increasingly similar.

This convergence is a general feature of unimodal cascades. At early time points, each modality follows a distinct trajectory, but progressively merges into larger, more overlapping clusters (Fig. 4b). For instance, thermosensory, hygrosensory, and olfactory cascades form a cluster beginning at $t = 2$ that persists until around $t = 5$, echoing known anatomical and functional coupling between these systems [49]. Gustatory and "unknown" modalities form a smaller cluster at $t = 3$, later joined by mechanosensory inputs at $t = 4$. In contrast, ocellar and compound visual cascades remain distinct from all other modalities through at least $t = 6$, forming their own cluster around $t = 7$ and maintaining separation until $t = 12$.

To quantify overall relationships between modalities, we computed an "omnibus" similarity matrix. For each cascade, we concatenated activation probability vectors from $t = 1$ to $t = 12$ and calculated pairwise correlations between modalities (Fig. 4c). These relationships recapitulate known connectivity patterns—modalities with similar anatomical wiring also produce more similar cascade profiles (Fig. S2).

We further analyzed the progression of cascade overlap using two complementary statistics. First, for each neuron i, we identified the dominant sensory modality at each time step—i.e., the modality with the highest activation probability (Fig. 4d). Second, we calculated a "convergence zone index," defined as the number of unimodal cascades exceeding a 25% activation threshold for a given neuron and time step (Fig. 4e).

Notably, dominant modalities shift over time. From $t = 2$ to $t = 6$, thermosensory cascades dominate large fractions of the network, peaking at $t = 4$ and then declining as other modalities—especially hygrosensory, olfactory, gustatory, and mechanosensory—gain influence. Visual cascades, by contrast, remain inactive until around $t = 7$, by which time other modalities are already declining.

We summarized convergence patterns by computing a co-convergence matrix. For each pair of modalities, we identified neurons with supra-threshold activation for both modalities at the same time step and tallied across time and space (Fig. 4g). As expected, the co-convergence matrix mirrors the cascade similarity matrix: visual cascades rarely co-activate with others, while thermosensory + hygrosensory and gustatory + unknown modalities frequently do. Mechanosensory and olfactory cascades exhibit less consistent clustering, suggesting more selective or delayed engagement with broader network dynamics.

To characterize multi-modal convergence more finely, we tabulated the most frequent combinations of 2 to 7 modalities co-activating a neuron. These groups consistently include thermosensory, hygrosensory, gustatory, olfactory, and mechanosensory inputs (Fig. 4h). Visual modalities appear only in the final stages, and no neurons were activated by all eight modalities under these parameters.

Finally, we performed a time-resolved enrichment analysis on convergence zone scores. At each time t, we computed mean convergence for each annotation category, standardized against a null distribution obtained by permuting labels (Fig. 4i). As expected, early convergence is enriched among afferent, thermosensory, and sensory neurons (step $t = 1$). At $t = 2$, enrichment shifts to antennal lobe and glomerular neurons, consistent with their role in propagating activity. At later stages, convergence is enriched in intrinsic and efferent neurons (steps $t = 3-5$), tangential and columnar neurons (steps $t = 6-7$), and specific populations such as Kenyon cells, lateral horn, and central complex neurons.

Together, these results suggest that sensory cascades initially activate distinct and largely non-overlapping subnetworks, before converging on common populations of intrinsic neurons. Visual modalities remain the most distinct, engaging late and following unique trajectories through the network. These patterns reflect and reinforce known principles of modularity and sensory integration in the *Drosophila* brain.

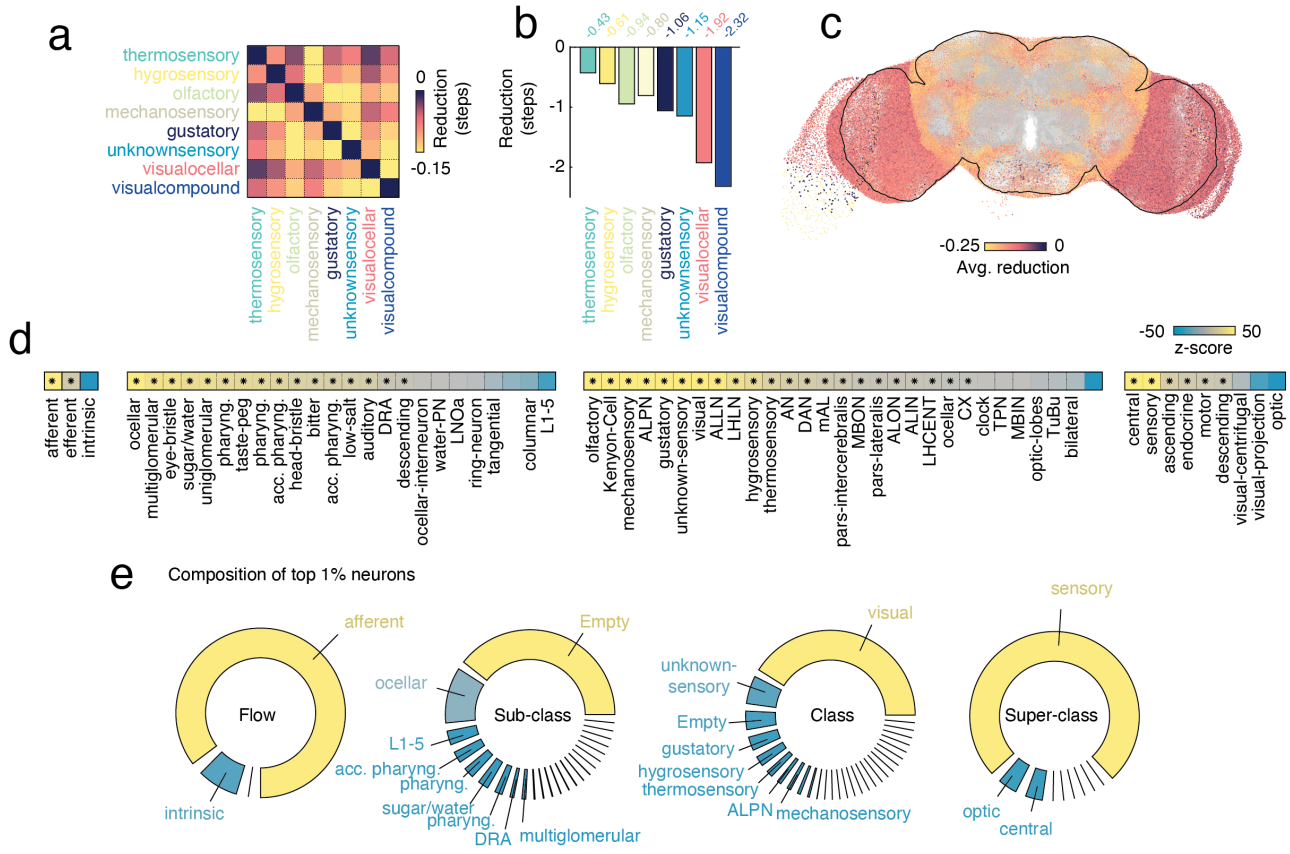

Figure 5. **Cooperative cascade statistics.** Here, we consider cascades in which neurons associated with different sensory modalities are treated as seeds. In contrast with the competitive cascade model, where postsynaptic neurons are activated by one sensory modality or the other, neurons here can be activated by *either* sensory modality. In principle, then, the cooperative cascade leads to reductions in activation time for "synergistic" sensory modalities. That is, pairs that target distinct neuronal populations or sufficiently enhance the probability of activating a single neuronal population. (*a*) Average reduction in activation time for all pairs of sensory modalities. Note that the colormap is inverted, so that the greatest reductions are depicted in bright colors. (*b*) We also compared unimodal cascade activation times against the scenario where *all* neurons in all sensory modalities are seeded. Here, we show the mean reduction in activation time for such a scenario. (*c*) The same information at single-cell resolution and in anatomical space. (*d*) Enrichment statistics for speed-ups. (*e*) The distribution of speed-ups was heavy-tailed. Here, we highlight the tail of this distribution (the top 1% of neurons by average reduction in activation time), showing their composition across annotation categories.

Cooperative sensory cascades

At the end of the previous section, we defined a measure—the convergence zone—to relate the spatiotemporal trajectories of multiple sensory cascades. However, this measure was based on non-interacting cascades. A more realistic extension of the model allows cascades to interact—either cooperatively or competitively. Here, we examine a cooperative model in which the seed list includes neurons from two sensory modalities—e.g., both hygrosensory and thermosensory neurons. Postsynaptic neurons can be activated by either pathway, which can lead to earlier activation. Conceptually, this reflects polysensory integration, where multimodal sensory events (e.g., a change in temperature and visual input) occur simultaneously, boosting signal propagation through the nervous system. This type of early multisensory convergence has been observed *in vivo* in the *Drosophila* brain, particularly in thermosensory and olfactory circuits [49], and is consistent with integration within higher-order centers like the mushroom body and lateral horn [39, 40].

To characterize this phenomenon, we simulated cooperative cascades in which seed neurons were drawn from pairs of sensory modalities. After 1000 simulations per pair, we computed each neuron's mean activation time

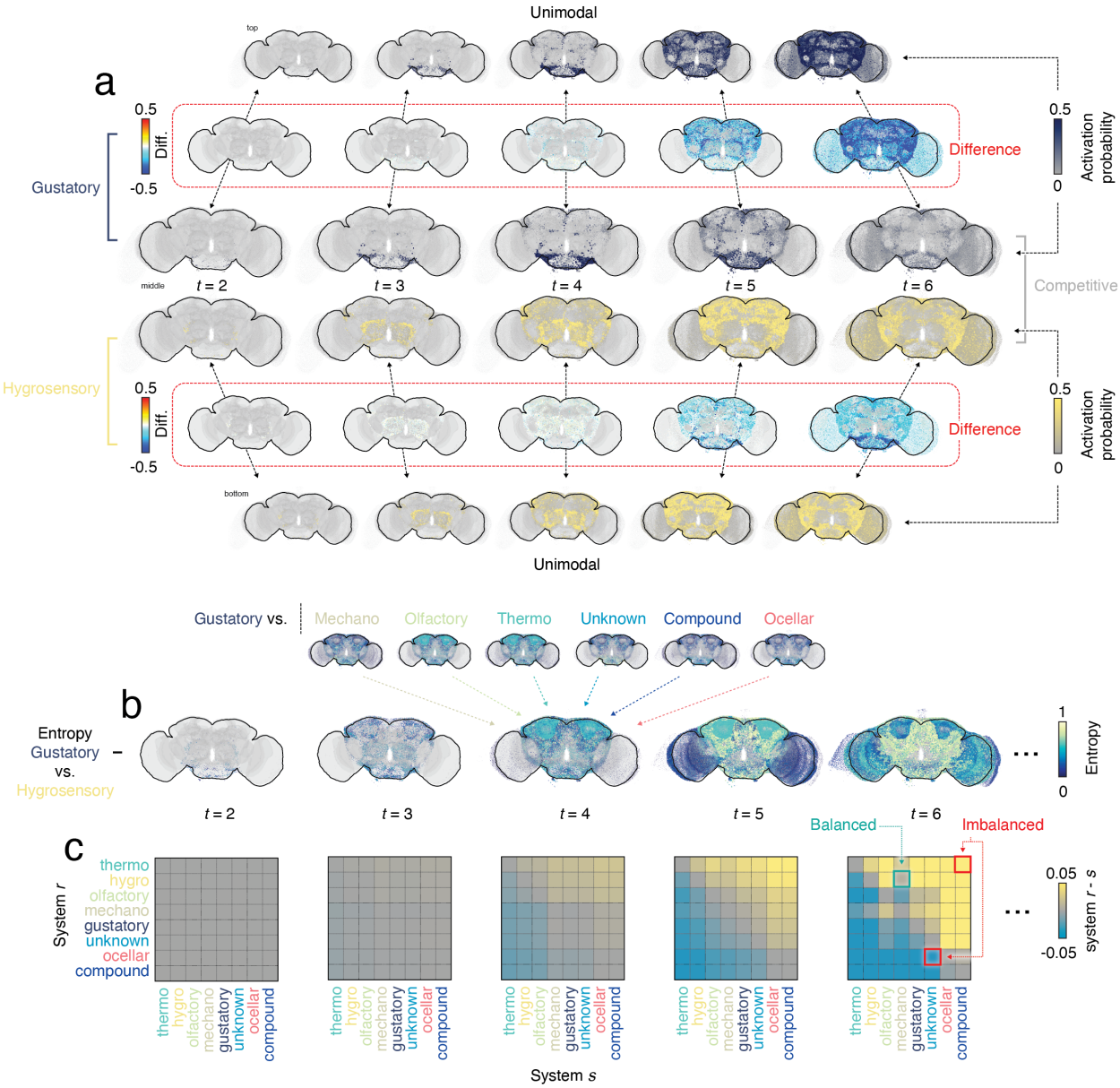

Figure 6. **Competitive cascade statistics.** (a) Comparison between unimodal gustatory and hygrosensory cascades (top and bottom) with competitive cascade (middle). (b) Entropy map for the gustatory and hygrosensory competitive cascade. High entropy neurons have "diverse" neighborhoods, i.e. their neighbors are activated by both gustatory and hygrosensory neurons. The inset with smaller brain maps depicts entropy maps of other competitive cascades involving the gustatory sensory modality at $t = 4$. (c) For every pair of neurons and at each time step, we calculated the relative dominance of one sensory modality over the other. That is, when we consider all active neurons, is one sensory modality over-expressed? Here, we plot this balance as a difference in proportion for all pairs of systems from time steps $t = 2$ to $t = 6$.

and compared it to the same neuron's activation time in unimodal simulations. This yielded a measure of relative speed-up—i.e., the reduction in activation time due to cooperation.

We found that, in general, cooperative stimulation resulted in modest speed-ups. Across all system pairs, the average activation time reduction was -0.11 ± 0.05 steps. Pairs that yielded the greatest reductions included gustatory+unknown (-0.18), olfactory+unknown (-0.18), compound+ocellar visual systems (-0.18), and gustatory+olfactory (-0.17) (Fig. 5a).

To explore a more extreme case of cooperation, we simulated pan-sensory cascades where all eight sensory modalities were simultaneously seeded. This condition led to significantly faster propagation: compared to unimodal cascades originating in compound or ocellar visual systems, the pan-modality cascade reduced activation time by nearly 2 steps (Fig. 5b). For completeness, we visualized the reduction in activation time for each neuron in anatomical space (averaged over all eight unimodal conditions; Fig. 5c).

We also used annotation-based enrichment analyses to examine the neurons most affected by multisensory cooperation (Fig. 5d). Because activation time reductions were heavy-tailed—a small number of neurons showed large effects—we focused on the top 1% of neurons (ranked by activation time reduction). Fig. 5e summarizes the raw annotation counts for this subset, highlighting that cooperation disproportionately benefits certain neuron classes.

Together, these results suggest that visual cascades, which follow distinctive trajectories compared to other modalities, benefit most from multisensory stimulation. Nevertheless, the modest mean reductions indicate that even unimodal cascades can leverage connectome architecture to propagate efficiently through the brain.

Competitive sensory cascades

An alternative scenario for exploring interacting cascades is the so-called competitive cascade, wherein the signal propagated from two sensory modalities retains modal specificity. That is, neurons activated by either of these two modalities inherit the "label" of their respective sensory activator, maintaining the distinct identity of each signal. As with the cooperative cascade, the competitive cascade model can be interpreted in terms of multisensory stimulation. However, unlike the cooperative case, where multiple sensory modalities amplify a signal, in the competitive scenario, the more "salient" of the two modalities can dominate, effectively muting responses from the other modality. This dynamic may resemble behavioral scenarios in which conflicting sensory cues must be resolved by suppressing one modality to favor another [40, 49]. In this section, we report results under this competitive scenario.

As an illustrative example, we show distinctions between unimodal and competitive cascades originating in gustatory and hygrosensory neurons. In Fig. 6a (top+bottom), we show probabilistic activation maps corresponding to unimodal gustatory and hygrosensory cascades—i.e., without any competitive interaction. However, when we allow the cascades to evolve simultaneously and compete for territory, we find distinct spatiotemporal trajectories (Fig. 6a, middle). We highlight these distinctions by calculating the difference in activation probability (competitive minus unimodal).

One of the useful statistics that arises from competitive cascades is the so-called "neighborhood entropy"—a summary measure of how balanced a neuron's neighbors are in terms of their assigned labels. A neuron whose neighbors all have only one label will have low entropy, whereas if the labels are distributed uniformly, the entropy is high. In Fig. 6b, we depict neighborhood entropy in anatomical space for the gustatory versus hygrosensory competitive cascade. Neurons with high entropy—indicated by bright colors—sit at the boundaries of competing cascades. Thus, entropy serves as a complementary metric for identifying locations where multiple signals converge onto shared targets, potentially supporting multisensory integration.

We estimated the "winning" sensory modality at each time step by calculating the imbalance in the number of neurons assigned to each label. In Fig. 6c, we show the balance metric as a function of time step. Each entry in this matrix corresponds to the difference in territory occupied by sensory system r versus s. For example, at $t = 6$, two cascade pairs show strong imbalances (red). In one case, thermosensory neurons outcompete compound visual neurons; in another, unknown sensory neurons dominate ocellar inputs. We also show a more balanced case (hygrosensory *vs.* mechanosensory), where territorial differences are minimal at $t = 6$.

This competitive cascade model helps us better understand how multisensory signals might resolve within a weighted and directed connectome. For instance, we can use neighborhood entropy to track the formation of "fronts" or boundaries between competing sensory signals. Neurons with high entropy are structurally poised for integration—they receive input from, or project to, neurons with differing sensory identities. Because the *Drosophila* connectome is directed, we defined three forms of entropy: based on presynaptic partners, postsynaptic partners, and their union. In a pan-sensory competitive cascade model, where all sensory systems were seeded equally, these three measures were highly correlated (mean pairwise similarity across time points $r = 0.81 \pm 0.21$). Nonetheless, subtle differences were evident, likely due to the strong—but not perfect—correlation between in- and out-degree ($r = 0.82$) [39].

We further found that a neuron's degree was strongly predictive of its time-averaged entropy ($r = 0.91$; Fig. 7b). In general, high entropy neurons tended to be structural hubs, consistent with their broad connections across sensory domains. This was true for both binary and weighted degrees (Fig. 7c). However, a neuron's role in sensory integration is not static: entropy varied across time. Mean entropy increased rapidly to a peak at step 5 before decreasing (Fig. 7d). Entropy maps showed low similarity across time—maps from early and late steps were even anti-correlated (Fig. 7e), suggesting

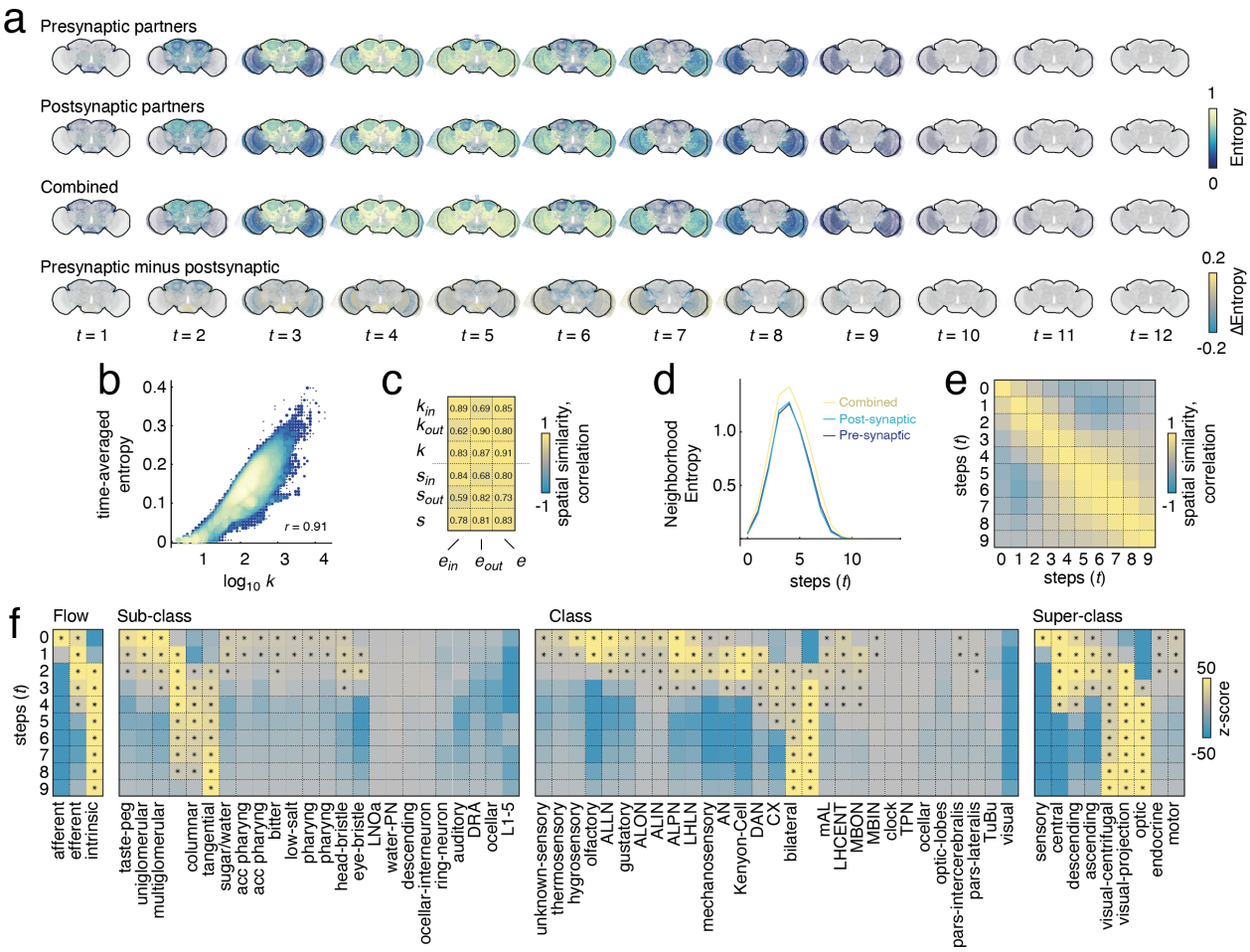

Figure 7. **Additional competitive cascade statistics.** The entropy patterns vary depending upon how one defines a neuron's "neighborhood". For instance, one can define a neighborhood based on a neuron's pre- or post-synaptic neighbors or the combined neighborhood. Here, we compare these three definitions in panel *a*. We also related entropy to conventional network statistics. (*b*) Scatterplot of time-averaged entropy against the logarithm of nodes' total degrees. (*c*) Correlation of entropy with various other network statistics: in/out/total degree and strength. (*d*) Mean whole-brain entropy of different neighborhood definitions as a function of step. (*e*) Similarity of whole-brain combined-neighborhood entropy patterns between time steps $t = 0$ to $t = 9$. (*f*) Enrichment statistics for whole-brain combined-neighborhood entropy.

a complex temporal dynamic shaped by cascade propagation and network topology.

Finally, we examined whether neighborhood entropy was enriched within specific cell types and brain regions. As in previous analyses of activation time and convergence zones, we found distinct temporal trajectories by annotation. Afferent sensory neurons peaked in entropy early (steps 1–2), followed by efferent and intrinsic neuron types—including columnar neurons, Kenyon cells, central complex neurons, ascending/descending neurons, and visual centrifugal neurons (Fig. 7f). These trajectories reinforce earlier observations that central brain neurons serve as hubs for signal convergence [39, 40], with their entropy dynamics reflecting their role in integrating competing signals over time.

These observations suggest that intrinsic neurons in the central brain are key loci of sensory integration. Positioned at the boundaries of competing cascades and exhibiting high neighborhood entropy, these neurons are structurally and functionally poised to arbitrate between conflicting or convergent sensory inputs. Although high-degree neurons tend to show high entropy, the temporal dynamics of the competitive model underscore that a neuron's role as integrator depends on timing and network context, not just connectivity.

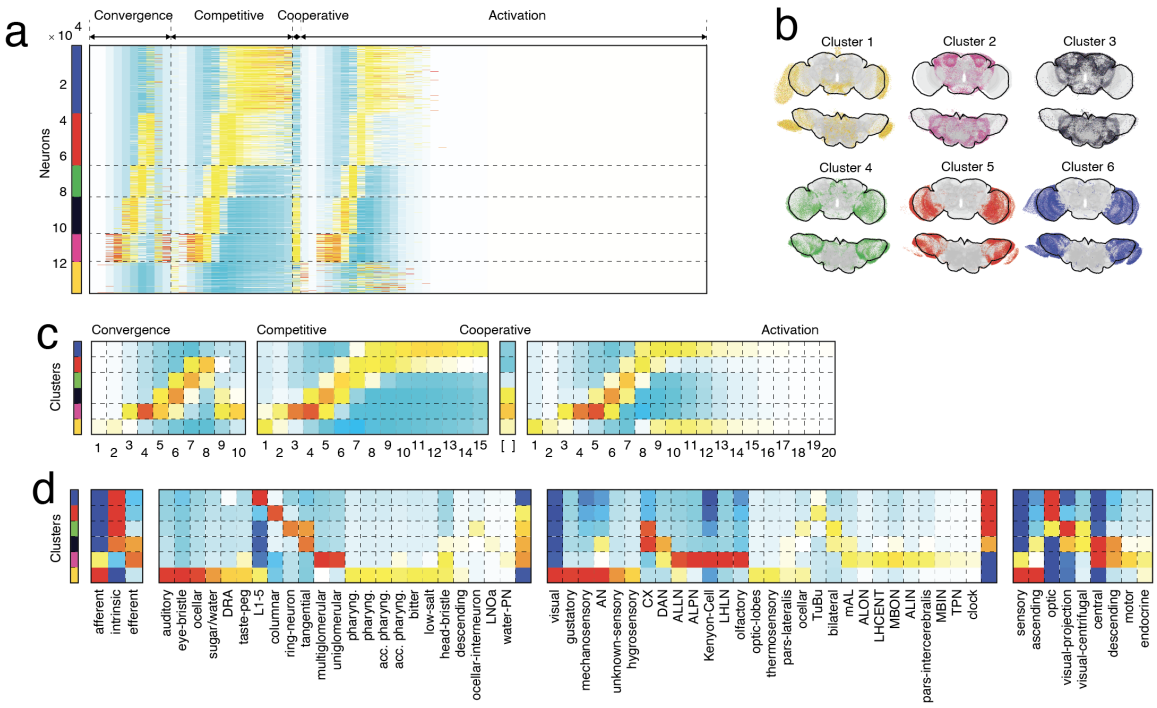

Figure 8. **Clustering neurons based on their cascade properties.** (*a*) Neurons ordered by cluster assignment. Columns correspond to z-scored cascade metrics. (*b*) Cluster labels depicted in anatomical space. (*c*) Cluster centroids. (*d*) Enrichment of cluster labels across annotations.

Data-driven clustering of neurons based on cascade properties

We previously introduced a set of summary statistics derived from the spatiotemporal evolution of sensory cascades. These included activation time, convergence, competitiveness (entropy), and cooperative speed-up. We used enrichment analyses to relate these features to neurobiological annotations. Here, instead of aligning with known labels, we clustered neurons based solely on cascade-derived features to identify data-driven functional groupings.

To do so, we aggregated the aforementioned statistics—convergence, entropy (from competitive cascades), reduction in activation time (from cooperative cascades), and activation timing—into an $N \times N_{\text{features}}$ matrix. We standardized (z-scored) each feature and applied k-means clustering using a correlation-based distance metric (Fig. 8a). We varied k from 1 to 50, performed 100 random restarts per k, and selected $k = 6$ based on the "elbow" of the within-cluster sum of squared errors curve (Fig. 8b). Spatial projections of these six clusters are shown in Fig. 8b.

Each cluster was associated with a distinct centroid—an archetypal profile across cascade features (Fig. 8c). Cluster 1 (yellow), for example, exhibited the earliest activation times and early-onset entropy. This cluster was enriched for afferent, sensory, and ascending neurons, consistent with its role as a cascade initiator. Cluster 2 (pink) followed temporally, with peaks in convergence, entropy, and activation between steps $t = 3$ and $t = 6$. It was enriched for efferent neurons, multiglomerular/monoglomerular projection neurons, and central complex interneurons, including Kenyon cells.

Clusters 3 through 6 exhibited progressively later activation profiles and distinct enrichment patterns. All were composed largely of intrinsic neurons and converged on visual projection and centrifugal neurons in the optic lobes.

These findings suggest that sensory spreading dynamics constrained by the connectome can be used to derive functionally meaningful, temporally ordered groupings of neurons. These groups reflect similarity in cascade participation and their respective roles in competition, cooperation, and convergence across the network.

Additional analyses

We conducted several supplementary analyses to assess the robustness and generality of our results. First, we verified that our findings were not sensitive to weak synaptic connections: thresholding the connectome to retain only synapses with at least five connections had minimal effect on results. Summary statistics remained highly correlated with those from the unthresholded network (Spearman correlations: $\rho_{\text{act}} = 0.80$, $\rho_{\text{coop}} = 0.56$, $\rho_{\text{comp}} = 0.82$; all estimated with $p_{\text{transmission}} = 0.01$ and $N_{\text{seed}} = 16$).

Second, we showed that activation timing could not be predicted solely from shortest path length—a static graph measure derived from connectivity alone (Fig. S3; see also [50]). Third, we examined how cascades unfolded across neurotransmitter classes, revealing transmitter-specific activation time distributions (Fig. S4).

Fourth, we compared sensory-driven cascades to cascades seeded from random non-sensory neurons. These exhibited systematically different spatiotemporal profiles, underscoring the distinctive topological embedding of sensory neurons (Fig. S5).

Fifth, we analyzed community structure in the connectome using a nested stochastic block model [51, 52]. Cascade-derived statistics were highly enriched within and segregated between communities (Fig. S6, Fig. S7). These findings support the idea that communities serve as mesoscale substrates for sensory integration and signal flow (see also [53–55]).

As a complementary continuous approach, we performed a principal components analysis on cascade features. The resulting components captured brain-wide gradients of variation and reflected global organizational motifs in cascade dynamics (Fig. S8).

DISCUSSION

The *Drosophila* connectome contains approximately 140,000 neurons and over 15 million synaptic connections, forming a sparse yet structured network with profound implications for information flow and processing. As we showed, sensory neurons from different modalities are highly segregated, with minimal direct synaptic links, suggesting architecture tailored for specialized, parallel sensory processing.

Yet many brain functions require integration across signals—such as decision-making [56], navigation, or motor planning—and depend on multi-step polysynaptic pathways not obvious from first-order connectivity. One way to explore these circuits is through dynamic simulations constrained by the connectome, rather than relying solely on anatomical graphs [57, 58].

In this work, we employed a spreading, cascade-style model that abstracts away full biophysical detail in favor of analytic clarity. While mechanistic models (e.g., integrate-and-fire) offer realism, our approach foregrounds interpretability, enabling us to trace cascade evolution directly under network constraints. Related spreading models have informed human brain dynamics [27], as well as larval *Drosophila* modeling [43].

Our results show that sensory cascades—initially modality-specific—rapidly converge onto overlapping sets of secondary nodes, many located in the central complex and involving descending and motor neurons. This proximity between sensors and effectors is consistent with behavioral observations and suggests streamlined sensorimotor pathways.

Of course, the simplicity of our model introduces limitations. Cascades always reach an inactive equilibrium, which is biologically unrealistic, yet this property enables clear ranking of neurons by mean activation time—a metric tightly controlled by user-defined seed size and transmission probability, and directly tied to connectivity.

Comparatively, computational studies using whole-brain leaky integrate-and-fire models (e.g. [59]) demonstrate excellent alignment with experimental data for gustatory and grooming circuits. Those bottom-up models focus on detailed circuit dynamics and specific behaviors, while our top-down network approach accommodates broad hypotheses about sensorimotor flow from minimal assumptions.

We offer testable predictions around multisensory integration—specifically that thermo- and hygrosensory pathways co-activate overlapping neuronal groups, as identified by our convergence index. These hypotheses can be evaluated experimentally using paired or combinatorial multisensory stimulation paradigms.

Another important insight comes from the passive nature of our model: activation flows without external control signals, emerging solely from structural connectivity. This emphasizes the role of network architecture in shaping dynamic propagation—even without directed regulation.

Looking forward, combining structure with experimental data—e.g. matching stimulus-evoked recordings to connectomic projection maps—offers promising opportunities for linking wiring to function more directly. Similar approaches in human macroscale network neuroscience have already yielded predictive insight about functional connectivity [60, 61].

Our model could be further enhanced by including synaptic polarity, inhibitory/excitatory distinctions, and transmitter-specific dynamics. For instance, connectome-informed weight estimates often disagree with simply assuming synapse count corresponds to weight [62]. Likewise, expanding the model to include ventral nerve cord circuits and motor neuron pathways

would better approximate the full sensorimotor axis.

One caveat remains: the current *Drosophila* connectome is incomplete—roughly half of all synapses are unassigned [35]. That said, our sensitivity analysis using a thresholded connectome (only edges with ≥ 5 synapses) produced similar activation ordering, with generally slower timescales. This suggests increased density from filling missing synapses would mostly compress timescales, preserving relative ranking among neurons.

More broadly, our work bridges nanoscale connectomics with system-level network neuroscience. While most network theory has focused on meso- and macroscale graphs revealing small-world structure, rich clubs, modularity, and cost-efficiency, we demonstrate that the same tools and principles apply—and even reveal new patterns—at the synapse-level resolution. Unlike previous work in larger brains, our cascades uncover functional trajectories and temporal motifs that arise purely from synaptic architecture.

Taken together, this suggests that synapse-scale connectomes may shape—and be shaped by—the same organizational principles operating in larger neural networks, while also supporting their own novel dynamic motifs specific to sensorimotor processing in small, tractable nervous systems.

MATERIALS AND METHODS

Drosophila connectome dataset

All connectome data, including synaptic connectivity, three-dimensional coordinates, neuropil volumes, and annotations were obtained from `https://codex.flywire.ai/`. These derivatives represent the output of a process beginning with nanometer-resolution electron microscopy images of an adult female *Drosophila* [63]. The FlyWire project allowed citizen scientists to trace neurons [64] to reconstruct the connectome. Combined with automated approaches [65, 66], the end result was a complete map of synaptic connections among approximately 139,000 neurons.

Neurons in *Drosophila* are polyadic, thus the same pair of neurons can synapse onto one another at multiple distinct sites. The `https://codex.flywire.ai/` are shared in two versions: one in which pairs of neurons were connected if they were linked by, at minimum, five synapses and another in which even a single synapse was considered evidence that two neurons were connected (unthresholded). In the main text, we analyze the unthresholded connectome, but note that results are consistent with those obtained using the thresholded version.

Annotation data were obtained from at the same time as the connectome data. Annotations were grouped into four distinct categories [37]. The first two annotations are "dense," in the sense that every neuron is assigned a label.

1. "Flow": afferent, efferent, intrinsic.
2. "Super-class": sensory (periphery to brain), motor (brain to periphery), endocrine (brain to corpora allata/cardiaca), ascending (ventral nerve cord (VNC) to brain), descending (brain to VNC), visual projection (optic lobes to central brain), visual centrifugal (central brain to optic lobes), or intrinsic to the optic lobes or the central brain

The other two categories are not dense–i.e. not all neurons are assigned a label. The "Class" and "Subclass" annotations are nested hierarchically within the the parent "Super-class" and describe cell groups reported in the extant literature, e.g. neurons in the optic lobe [67].

Cascade model

Here we explore an abstract cascade model. In this model, each neuron exists in one of three states: active, inactive, or refractory. In our simulations, we set select sets of neurons to be active at time $t = 0$. These initially activated neurons are referred to as "seeds" and are selected from among sensory neurons alone. The seeds are intended to represent sensory stimuli.

In this model, neurons that are active at time t probabilistically activate their post-synaptic partners at $t+1$. Suppose neuron i makes a single synapse onto neuron j. Given that i is active at t, the probability that neuron i activates j at $t+1$ is given by the transmission probability parameter, $p_{transmission}$. Conversely, the probability that i does *not* activate j is simply $q = 1 - p_{transmission}$.

Oftentimes, neuron i makes multiple synapses onto j. We treat these as independent trials; only one successful trial is sufficient to activate neuron j. What is the probability that at least one event is successful? In the space of possible outcomes, there is exactly one outcome in which none of the synapses successfully activate j. Its probability is given by: $q^{\#synapses} = (1 - p_{transmission})^{\#synapses}$. All other possibly outcomes include at least one successful transmission event. Hence, the probability that j is activated by neuron i at time $t+1$ is given by: $1 - q^{\#synapses}$.

Activation probability

The cascade model is stochastic. In principle, each run can yield a different sequence of neuronal activa-

tions. For every experiment, we summarize across 1000 independent runs by estimating the probability a given neuron was active at time t (see Fig. S1 for example maps). We denote the activation probability of neuron i at time t as $P_i(t)$. In the main text we describe several statistics calculated directly from the probabilistic activation curves.

Dominance maps

We use the cascade model to simulate sensory cascades by allowing a fixed number of sensory neurons with specific modalities to be active at time $t = 0$. In total, we consider eight sensory modalities as determined by hierarchical annotations of sensory neurons: thermosensation, hygrosensation, olfaction, mechanosensation, gustation, vision (ocellar and compound), and an unknown sensory class (no clear assignment). For estimate modality-specific activation probability curves for each neuron. Given that sensory neurons associated with modality m were seeded at time $t = 0$, we denote the probability that neuron i is active at time t as: $P_i^m(t)$. From these estimates, can calculate the "dominant" modality for each neuron at any given timepoint as the m that maximizes $P_i^m(t)$.

Convergence index

The dominance index represents a "winner take all" measure, ascribing dominance to a single sensory modality. In reality, there could be multiple near-maximal modalities, all with similar activation probabilities. To account for this possibility, we defined the convergence index. Specifically, we define a threshold, τ, and calculate: $C_i(t) = \sum_m [P_i^m(t) \geq \tau]$. That is, we count the number of sensory modalities for which the activation probability of node i at time t is at least τ.

Cooperative cascades

We explored several variations of the cascade model. The first variant focused on "unimodal" cascades, wherein the seed neurons were selected from among a single sensory modality. However, we also considered a second "cooperative" variant, in which pairs of sensory systems were seeded (doubling the total number of seed neurons). We then calculated the reduction in the mean activation time (speed-up) as a result of the dual-seed approach as: $A_{rs} - \min(A_r, A_s)$, where A_{rs} is the activation time of a given neuron under the cooperative, dual-seed model A_r and A_s are the activation times of the same neuron under the unimodal model where modalities r and s were seeded independently.

Competitive cascades

We also considered a "competitive" variant of the cascade model. In this case, we imagine two distinct sensory signals ("blue" and "red") spreading throughout the connectome carrying distinct information. Post-synaptic neurons activated by a majority blue/red pre-synaptic neurons will be blue/red at the following timestep. In the rare event of a tie–i.e. equal number of red and blue activating neurons–the post-synaptic neuron becomes blue/red at the following timestep with equal probability.

Neighborhood entropy

Under the competitive model, we can calculate an entropy measure that describes whether a node is positioned in the network so that its neighbors are mostly homogeneous in terms of their redness/blueness or whether their neighbors are diverse. To do this, we identify each neuron's connected neighbors and, for at time t, those the proportion of those that are active and are blue/red. We then rescale these values so that their total sums to 1, and calculate an entropy, $H_i(t) = -p_{blue} log_2(p_{blue}) + -p_{red} log_2(p_{red})$. Intuitively, when this entropy is close to 1, it implies that the distribution of blue/red neighbors is approximately equal. However, values close to zero imply that one of the two colors is more dominant.

An important consideration is how one defines "neighborhood" in this context. In the main text, we consider three possibilities: a neuron's pre-synaptic partners, its post-synaptic partners, and the union of those two sets.

Note that in all of the above calculations, we disregard inactive or quiescent neurons. That is, only active neurons contribute to the entropy scores.

Community detection

Many studies have shown that biological neural networks at varying spatial scales can be meaningfully partitioned into clusters or communities [5, 52, 68–75]. In general, community structure is unknown ahead of time and must be estimated or inferred algorithmically. The procedure is referred to as community detection [76], and there exist many approaches for doing so [77–82], each of which makes specific assumptions about what constitutes a community.

One of the oldest approaches for community detection is the stochastic blockmodel [83–87]. Briefly, blockmodels imagine that every node in the network is assigned a label. The probability that any pair of nodes are connected and the weight of that connection depends only upon the communities to which they are assigned. In general, blockmodels estimate community labels and connection probability/weight distributions so as to maximize the likelihood that the model generated the observed network.

Recently, there has been renewed interest in the application of blockmodels to brain network data [20, 74, 88–95]. Here, we leverage a nested and weighted variant of the classical blockmodel to partition the *Drosophila* connectome into hierarchical communities [51]. Using this model, we obtained an estimate of the consensus hierarchical partition using a Markov Chain Monte Carlo procedure [96]. Briefly, this procedure entails allowing the Markov chain to equilibriate and sampling 10000 high-quality partitions. These partitions are aligned to one another to discover latent "modes" – partitions that share many characteristics with one another [97]. From these modes, we obtained for each neuron the community it was most likely assigned to. All analyses using communities were carried out on the resulting partition (Fig. S6 and Fig. S7).

Clustering based on cascade properties

In the main text, we derived a series of statistics for neurons based on their activation times, convergence, neighborhood entropies, and speed-ups. We can use these data to partition neurons into clusters based not on their connectivity (information derived from the connectome) but these dynamic, cascade-based properties.

To do this, we constructed a $[N \times F]$ matrix, where N is the number of nodes and $F = 27$ is the total number of features. In this case, we considered the following features derived from omnibus sensory cascades–i.e. where all sensory modalities were seeded:

1. **Activation probability**: The $[N \times 1]$ vector of each neuron's mean activation time.
2. **Convergence index**: The $[N \times 10]$ array of neurons' convergence indices over the first 10 time steps.
3. **Neighborhood entropy**: The $[N \times 15]$ array of neurons' neighborhood entropy (estimated using both pre-/post-synaptic partners).
4. **Speed up**: The $[N \times 1]$ vector of speed-ups (reductions in activation times) from single-modality unimodal cascades to the omnibus cascade.

To cluster these data, every column was standardized (z-scored). We then used k-means clustering to assign neurons to a unique cluster [98]. We selected the optimal number of clusters based on the inflection point in the summed square errors of cluster centroids relative to their constituents. Based on these analyses, we identified $k = 6$ as the optimal number of clusters.

Annotation enrichment analysis

Throughout this manuscript we describe an "enrichment" procedure for linking continuous data to categorical labels–e.g. annotations. The aim of this procedure, in more detail, was to determine if a particular variable was over-expressed (enriched) within a given annotation category. To do this, we calculated the variable of interest's mean value within all neurons associated with a specific annotation. We then randomly permuted the annotation labels (keeping the total number constant) and calculated the new mean. We repeated this procedure 1000 times, generated a null distribution of mean values. The enrichment score for that variable within that annotation category is the original mean expressed as a z-score with respect to the null distribution.

ACKNOWLEDGEMENTS

Data and code availability statement

All data are publicly available through `https://codex.flywire.ai/` with no restrictions. Code is available upon request.

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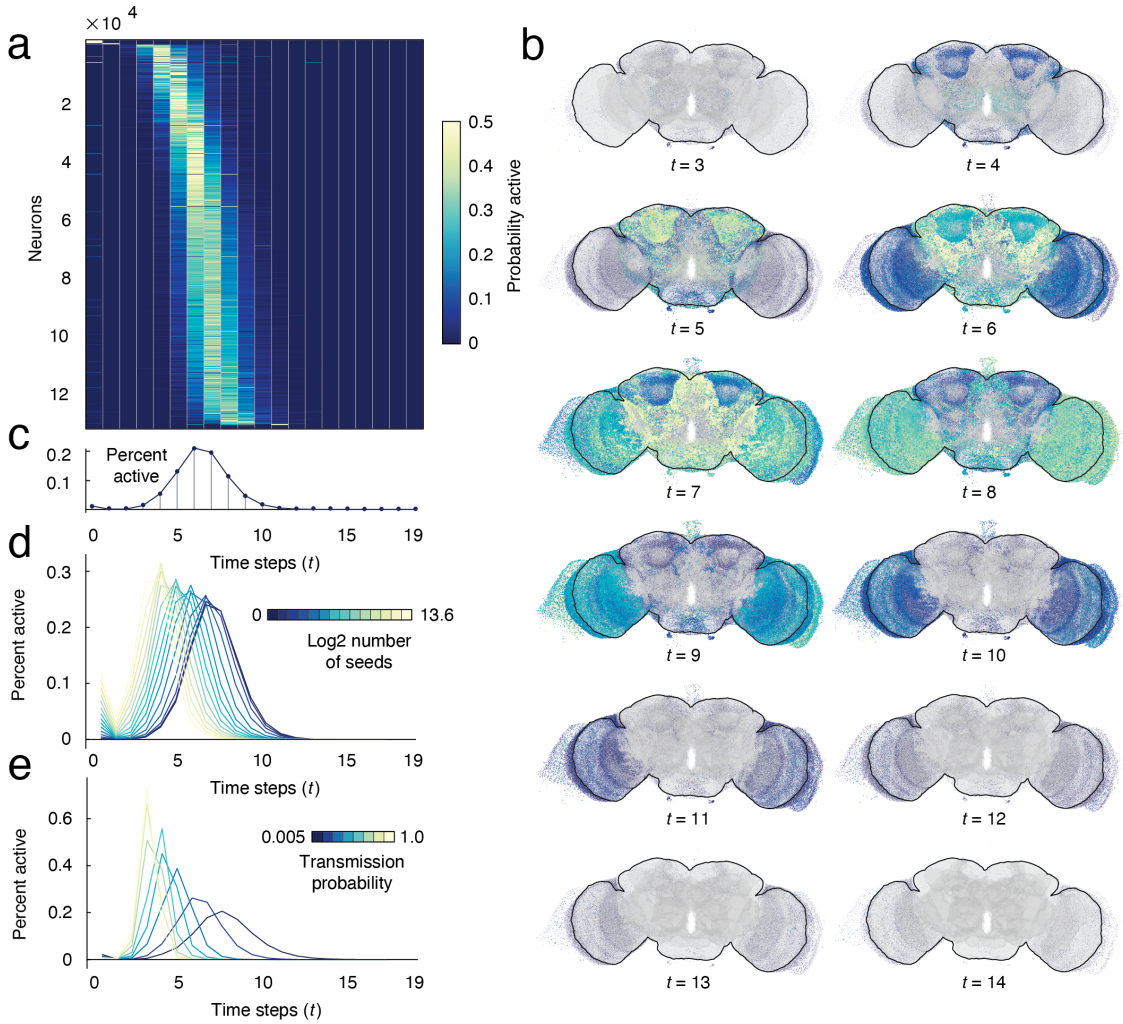

Figure S1. **Unimodal cascades.** We initialize cascades by "seeding" sensory systems with a subset of active neurons. These neurons probabilistically activate their post-synaptic neighbors. (a) Activation probability for all neurons $\times$ time. In this example all sensory neurons were active at time $t = 0$. (b) Percent of neurons active at each time step. (c) Activation probability of each neuron in anatomical space. Note that here we only plot each neuron's soma and omit their arborization. The cascade model depends on two parameters: the number of seed neurons (those active at time $t = 0$) and the probability of transmission *via* a single synapse. Panels d and e illustrate how variation of these parameters impact transmission probability curves. (d) Increasing the number of seed neurons largely shifts the curve to the left. In this example transmission probability was held constant at $p_{transmission} = 0.01$. (e) Increasing transmission probability compresses and shifts and the curve.

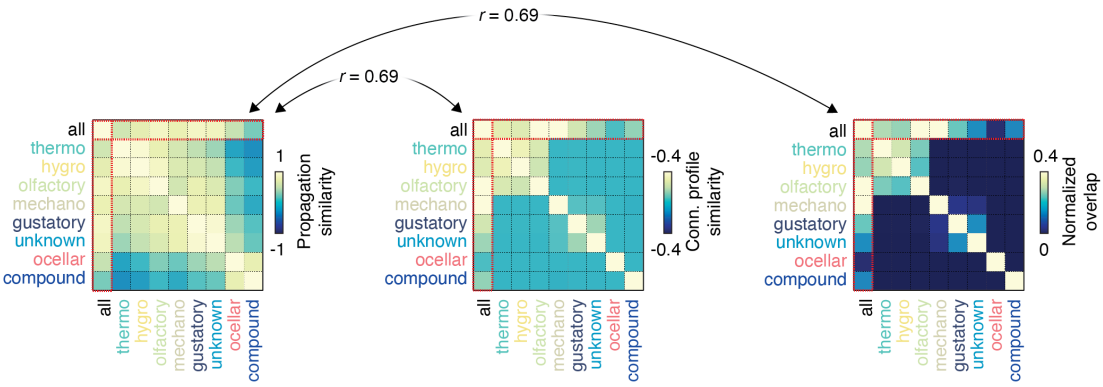

Figure S2. **Cascade similarity *versus* connectivity similarity.** Here, we show cascade similarity (from Fig. 4) alongside the similarity of connectivity profiles. Specifically, we calculated the an average connectivity profile (outgoing connections only) for all each sensory modalities combined (all) and for each sensory modality independently. The center plot shows correlations between profiles; the right plot shows normalized dot product.

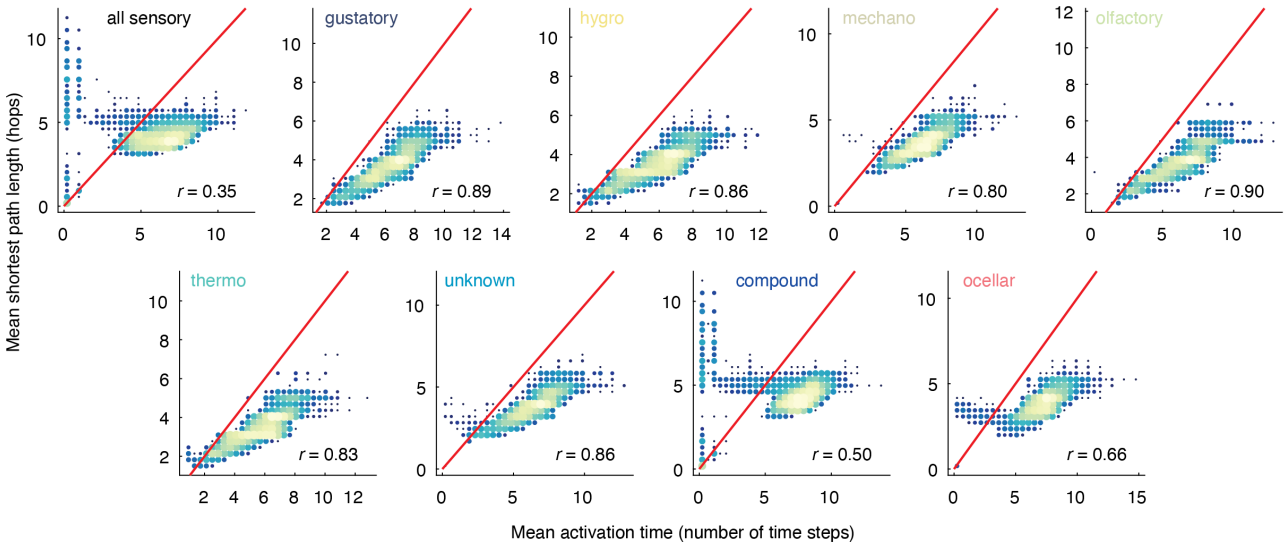

Figure S3. **Comparing shortest paths with activation times.** In the main text we reported activation times of neurons given different sensory seeds. To verify that these activation times were not strictly the consequence of shortest paths, we calculated the binary shortest path from each neuron to all other neurons in the network. For a given sensory modality, we calculated the average distance of all such sensory neurons to all other neurons in the *Drosophila* brain. We then compared those distances (measured in number of hops) with activation times. The above figures show mean activation times plotted as a function of mean shortest path for all eight sensory modalities as well as all sensory modalities combined. Note that size and color intensity of markers in each plot are proportional to the log density.

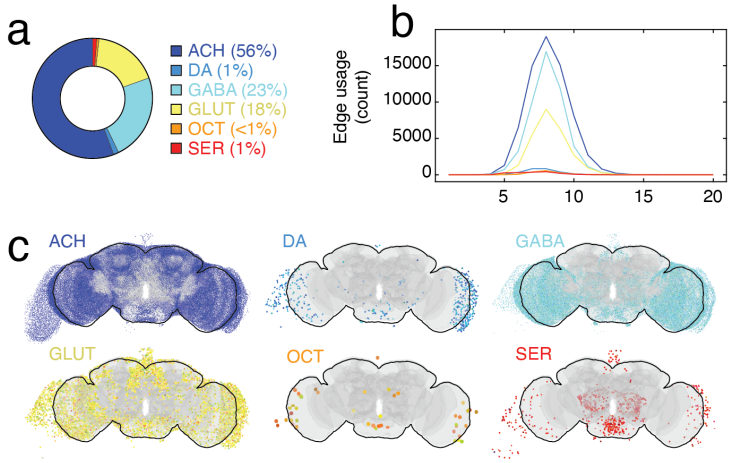

Figure S4. **Effect of synapse type on activation time.** In the main text we grouped all synapses together, making no distinction between neurotransmitter types. Here, we parse contributions made by six distinct synapse types (based on neurotransmitter). They include acetylcholine (ACH), dopamine (DA), gabaergic (GABA), glutamate (GLUT), octopamine (OCT), and seratonin (SER). (*a*) Percent of all synapses associated with each neurotransmitter. (*b*) We tracked how frequently synapses associated with different neurotransmitter types successfully activated their post-synaptic partner. In this plot, we show edge usage (number of active synapses of each type) as a function of time steps. Note that this plot was generated as the mean usage over 1000 simulations with all sensory modalities included in the seed set but with seed size fixed at 16 with transmission probability of $p_{tranmission} = 0.01$. (*c*) For each neuron, we calculated when it was first activated by by what neurotransmitter. This plot depicts, as a function of neurotransmitter, neurons likely to be activated by each of the six neurotransmitters.

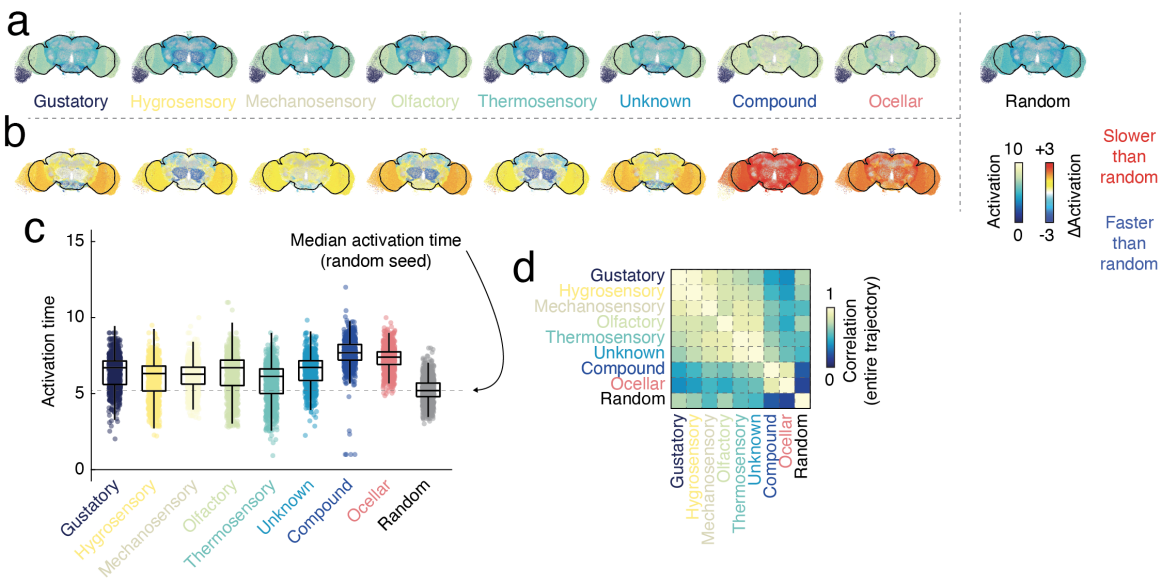

Figure S5. **Comparing random and sensory seeds.** (*a*) Mean activation time for neurons for eight sensory modalities. To the far right we show activation time for the random map. (*b*) Difference between random and sensory cascades in terms of activation time. (*c*) Boxplot of differences. (*d*) Correlation of entire (vectorized and concatenated) trajectory.

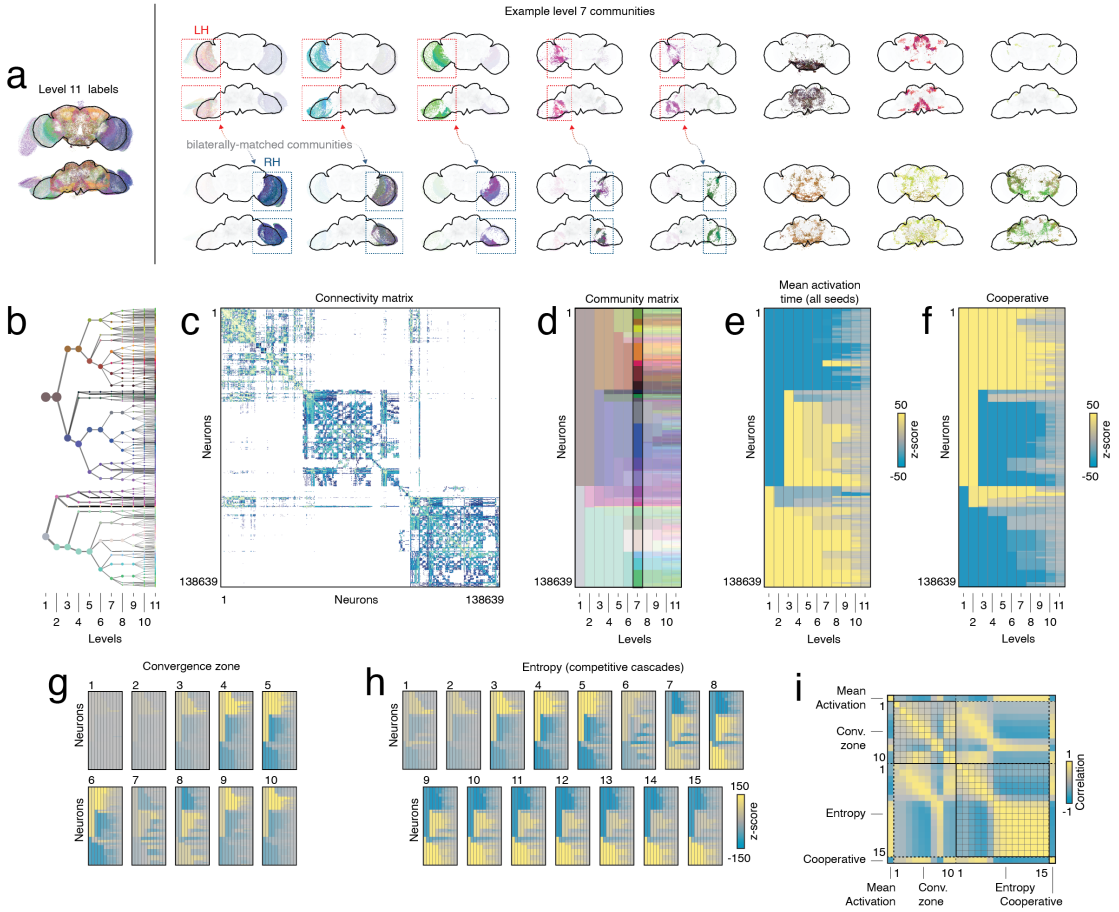

Figure S6. **Linking the modular structure of the connectome with cascade statistics.** We used a hierarchical community detection algorithm to divide neurons into nested blocks. (a) Topography of all communities with their finest (level 11) coloration. To the right, we show example communities from an intermediate scale (level 7). We highlight pairs of communities that are lateralized as well as their partners in the opposite hemisphere. (b) Community dendrogram. (c) Connectivity matrix ordered by communities. (d) An alternative visualization of community labels; each column is hierarchical level with rows ordered by communities. The colors of entries correspond to community labels. Panels e-h show enrichment scores for communities at all hierarchical levels for: (e) Mean activation time; (f) Average reduction in activation time during cooperative cascades; (g) Convergence zone as a function of time step (from $t = 1$ to $t = 10$), and (h) Entropy during competitive cascades (from $t = 1$ to $t = 15$). (i) For each measure (and each time step, for those that were temporally resolved), we retained for each community its enrichment score. We represented these scores as vectors and computed the correlation between all such vectors to yield a similarity matrix. The "hot" elements of the matrix identified enrichment patterns that were highly similar; "cooler" elements correspond to dissimilar and anti-correlated enrichment patterns.

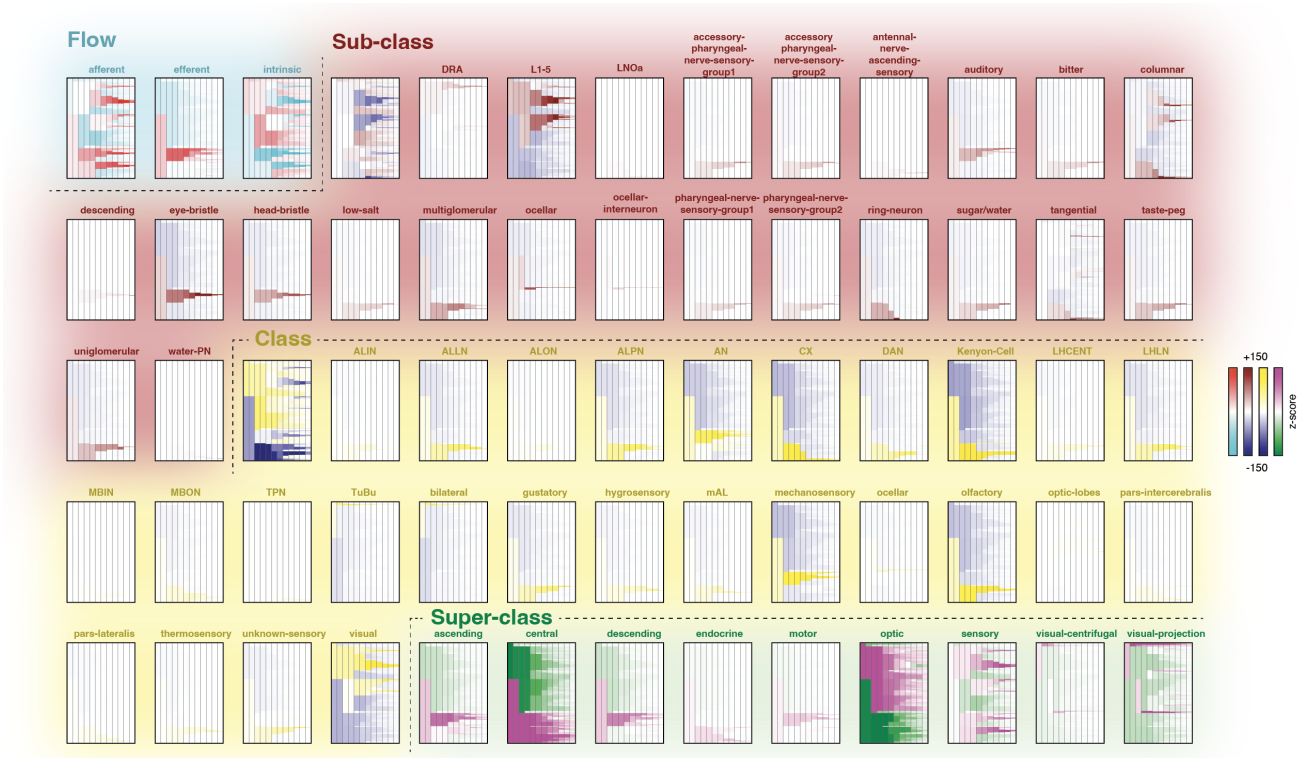

Figure S7. **Enrichment analysis of community labels within annotation data.** Each plot corresponds to a specific annotation. Each plot shows annotation enrichment across 11 hierarchical levels of communities. The colormap differs across annotations based on annotation category (Flow, sub-class, class, and super-class). Hot colors correspond to communities significantly enriched for an annotation; cooler colors correspond to communities that are avoidant with respect to a given annotation.

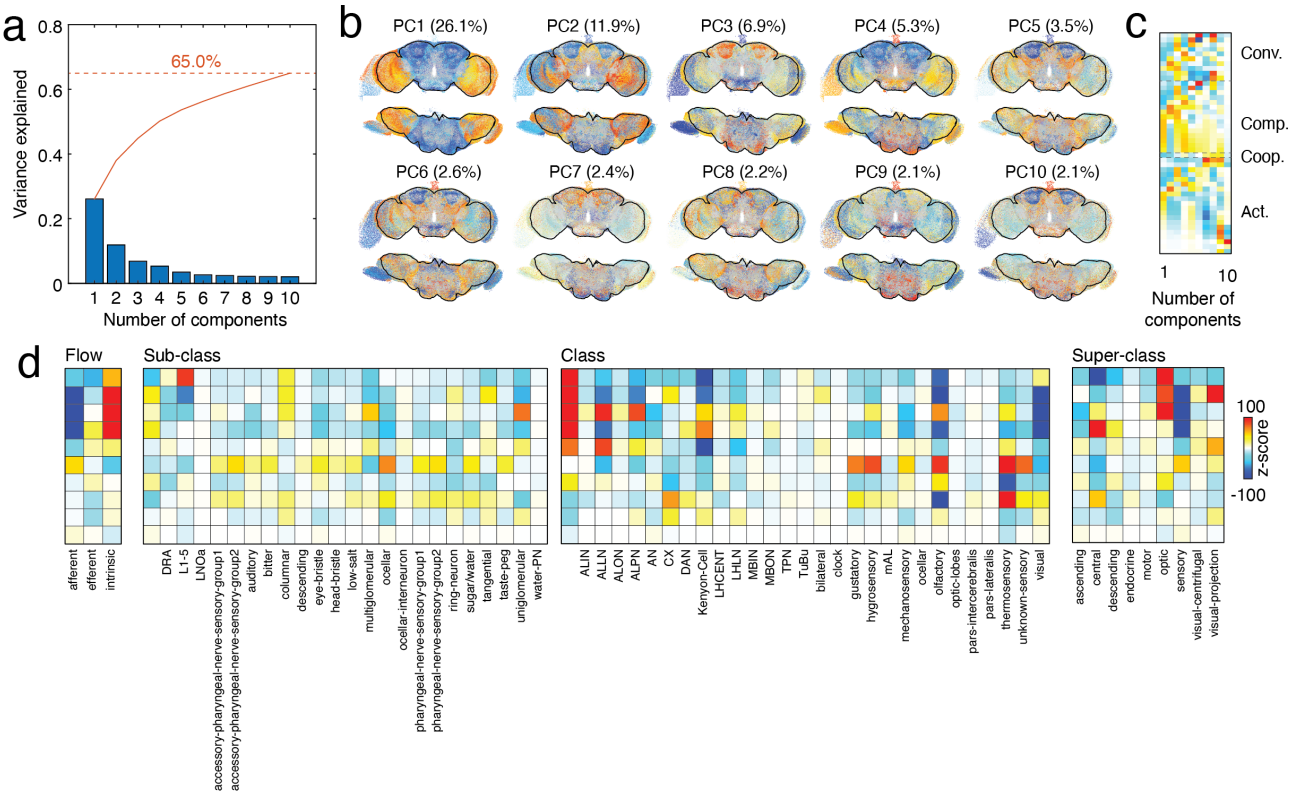

Figure S8. **Principal component analysis of cascade statistics.** In the main text, we clustered neurons to identify groups with similar cascade statistics–i.e. convergence, speed-ups, entropy, and activation times. Here, we apply PCA to the same data (after z-scoring columns). (*a*) Variance explained by each of the first 10 components (in blue). Cumulative variance explained shown in orange. (*b*) Spatial maps (components). (*c*) Coefficients. (*d*) Enrichment of spatial maps across annotations.