Connectome-scale chemical lateralization predicts asymmetric memory computation in the adult Drosophila mushroom body

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SCIENTIFIC QUESTION

Why do the two mushroom bodies show different serotonin-sensor responses?

Bilateral anatomy provides a constraint; sensor calibration and circuit history affect inference.

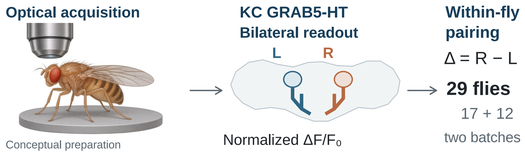
OBSERVATION + CONSTRAINT

Right-biased sensor sensitivity contrasts with left-biased DPM anatomical contacts.

Circuit origin remains unresolved. Calibration and timing-matched perturbations provide discriminating tests.

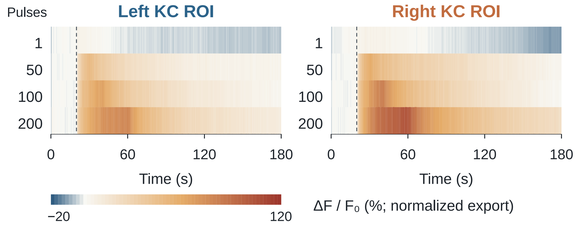
01 PAIRED SENSOR EVIDENCE

A Bilateral DPM stimulation and paired KC readout



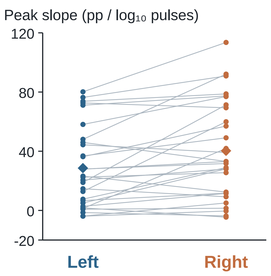
5 Hz; 1 / 50 / 100 / 200 pulses; mecamylamine background.
29 paired flies in two batches (17 / 12); paired L/R measurements at every dose.

B Dose–time response atlas



Means of 29 paired flies; all 300 time samples are retained.
Dashed line: inferred onset (20 s). Pulse count and train duration covary.

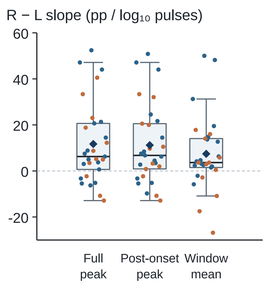
C Right-biased sensitivity



R − L = +11.71

95% CI [5.71, 18.11]; 22 / 29 positive
Batch-stratified fly bootstrap
Paired sign-flip P = 0.00070

D Endpoint sensitivity

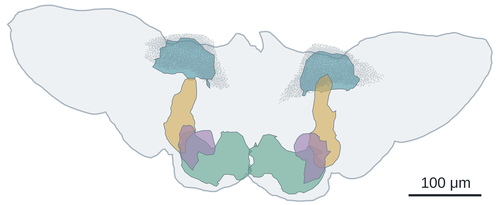


Means: 11.71 / 11.21 / 7.43

Same 29 flies across endpoints.
Box: IQR; line: median; ◆ mean.
Raw dots show both acquisition batches.

02 ANATOMICAL CONSTRAINTS

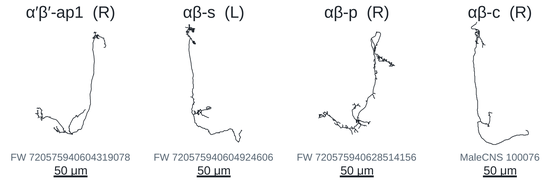
E Reference brain and the complete KC cohort



FlyWire v783 · native XZ projection · all 5,177 KC somata

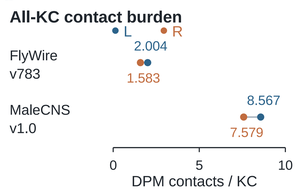
Reference brain	Left KC	Right KC	Total
FlyWire v783	2,580	2,597	5,177
MaleCNS v1.0	2,019	2,045	4,064

F Real KC morphologies at a common physical scale



Native XZ; four illustrative cells. Cross-specimen homology is not inferred.

G DPM contact burden is left-biased



All KCs, including zero-input cells.
1 specimen/dataset; separate sensor cohort.

α′β′ mixing proxy M

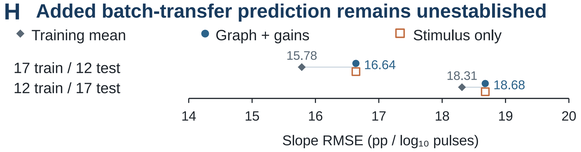
Rows: ROI; columns: DPM

FlyWire	L	R
L	1.0395	0.0007
R	0.0007	0.9590

MaleCNS	L	R
L	1.1902	0.0013
R	0.0333	0.7752

Shared mean row-sum scaling.
Concentration transfer is uncalibrated.

H Added batch-transfer prediction remains unestablished



FlyWire; training-only fits. Graph and stimulus-only estimates nearly overlap.
Paired loss intervals include zero; added value remains unestablished.

03 FROZEN SIMULATION → TESTABLE PREDICTIONS

I One signed graph, two explicit readouts

FlyWire: 138,486 nodes / 15,089,754 nonzero weights
MaleCNS: 160,433 nodes / 24,580,903 nonzero weights

$$W_{ij} = \frac{C_{ij} s_j}{\max(T_i, 1)}$$

$$\varphi_k = \max\{0, \tanh(0.8\, W r_k + 0.05 + u_k)\}$$

$$r_{k+1} = m \odot [(1-\alpha) r_k + \alpha \varphi_k]$$

α = Δt / τ = 0.25; Δt = 5 ms; τ = 20 ms

C: contact count; s: source sign; T: full target input total.
Target rows / source columns; mask m acts on the whole update.

NEURAL READOUT

2 frozen input vectors → **Original W** → **DNa02**
Seeds 3002 / 3009 → **KC × DPM clamps** → **Right − left rate**

200 / 1000 ms drive; 1200 ms integration; no movement calibration.
Input-vector identities are not recovered in the compact archive.

SENSOR READOUT

Bilateral DPM pulses → ΔrDPM → slow kernel → M → ROI gains

$$\hat{y}(t) = G M[h * \Delta r_{DPM}](t)$$

Fitted kernel: 40 s

5 Hz, 10 ms model pulses; selected case: inhibitory DPM→KC, KC→DPM removed.
The fitted sensor kernel is separate from the 20 ms neural time constant.

J The same perturbation under two circuit histories

α′β′ KCs	DPM on	DPM off
KC on	Intact Y00	DPM off Y01
KC off	KC off Y10	Both off Y11

Pre-equilibrated
Own condition fixed point

Acute at input onset
Common intact fixed point
t = 0

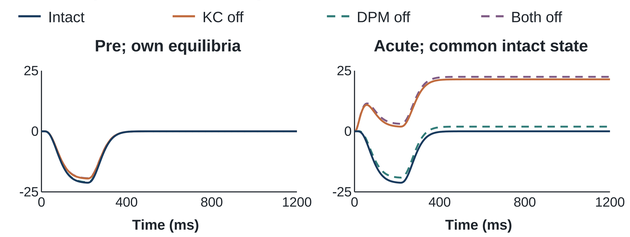
α′β′ KCs: 917 (FW) / 695 (MC); 2 DPMs.
Whole-cell masks; original denominators remain fixed.

$$E_{on} = Y_{10} - Y_{00} \qquad E_{off} = Y_{11} - Y_{01}$$

$$I = E_{off} - E_{on}$$ KC × DPM interaction

2 brains × 2 inputs × 4 states × 2 histories × 2 durations
= 64 numerical integrations; these are not biological replicates.

K Clamps alter DNa02 trajectories



DNa02 R − L from actual pre-state (×10⁻⁶ model rate)

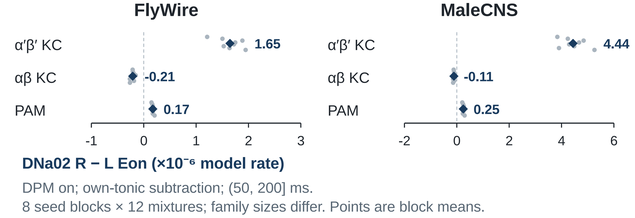
FlyWire; seed 3002; 200 ms drive. Same y limits and all 241 samples.
Each curve is a numerical condition, not an observed animal trajectory.

L A common reference resolves the apparent amplification

KC effect Eon on DNa02 R − L (×10⁻⁶ model rate)

Same absolute reference: −6.06% (FW) / −2.35% (MC).
Large evoked differences mainly reflect baseline subtraction.

M Largest tested family effect: α′β′ KC



DNa02 R − L Eon (×10⁻⁶ model rate)

DPM on; own-tonic subtraction; (50, 200] ms.
8 seed blocks × 12 mixtures; family sizes differ. Points are block means.

N KC effects persist after whole-DPM clamping

Eoff / Eon = 0.959 (FW) / 0.978 (MC)
Pre, absolute; 2 inputs; descriptive ratios, not a mediation estimate.

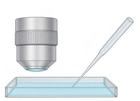
O Conclusions and discriminating wet validation

PROPOSED VALIDATION · NO NEW VALIDATION DATA

01 Sensor sensitivity is right-biased

Observed: paired slope difference +11.71 pp / log₁₀ pulses; 22 / 29 flies positive.

PROPOSED WET TEST



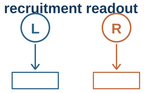
Independent L/R sensor calibration
Constrain local 5-HT exposure and background.
Compare calibrated R − L with the original gap.

A gap explained by calibrated transfer supports a measurement contribution.

02 Anatomy does not identify the cause

Constraint: all-KC DPM contacts are left-biased in both reference brains.

PROPOSED WET TEST



Simultaneous recruitment and sensor readout
Vary pulse count and duration independently.
Verify perturbation efficacy in each preparation.

Test whether the gap follows recruitment or remains after bilateral recruitment is matched.

03 Model KC effects persist without DPM

Prediction: absolute KC effects retain 95.9% / 97.8% after whole-DPM clamping.

PROPOSED WET TEST



Timing-matched KC × DPM neural recording
Measure bilateral DNa02: absolute and evoked.
Add 5-HT-specific controls and movement readout.

An opposite-sign neural effect challenges the frozen prediction; behavior requires its own validation.

Sources: normalized sensor exports and BioFly v31 / frozen v30 simulation archive; FlyWire v783; MaleCNS v1.0. Methods, numerical values, limitations and asset provenance are included in the editable package.

Support: FDU IDH2338002/001 · Contact: rbzhang@fudan.edu.cn · Generated fly / assay artwork is conceptual; anatomy and data plots are source-derived. · Washington, DC · Walter E. Washington Convention Center, Halls A–C