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The function of brain lateralisation in *Drosophila* decision-making

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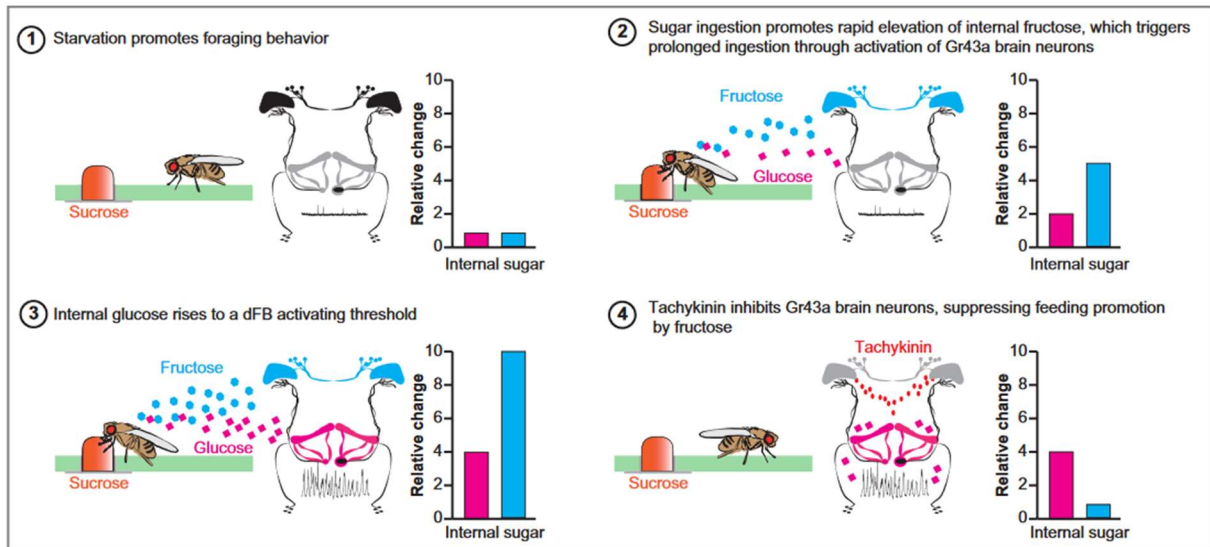
Introduction:

While studies on asymmetry were already performed in the 19th century, they disappeared for a time due to the belief the feature was unique to humans. The subject reemerged during the 1970s, and since then it has become accepted that lateralisation is a feature that appears throughout the animal kingdom. Lateralisation defines the difference between the right and left hemisphere of the brain, or a difference in the controlling of behaviour (Güntürkün et al., 2020). Individual lateralisation means most members of a species have brain regions that are larger and or more active on either one of the two sides. Directional or populational level of lateralisation means that most individuals have a dominant brain area on one side. Lateralisation has to appear systematically in most members of a species to be differentiable from individual differences in brain architecture and firing patterns (Rogers, 2021). Two underlying principles could explain how laterality could arise. A system could have been developed in a lateralised way during the lifecycle of the animal in which case the neural computations could only be carried out in a lateralised way. Waddington's epigenetic landscape represents symmetry as a ball rolling down the hill in a canal, that, when arriving at a bifurcation point, will either roll right or left. An effect at this point could either consistently guide the ball in one direction (populational lateralisation), lateralising to one side or randomly choose a side (individual lateralisation), which would also chose to which side is it lateralised (McManus, 2022). If an animal starts to habitually use its limb or sensory organ on one side for certain tasks a compound effect may take place where the continued training with those organs would result in more effective task execution and the resulting positive feedback would further encourage the lateralised usage making the system increasingly lateralised. (Güntürkün et al., 2020). Altogether the behavioural effects of a lateralised brain have been widely theorised to increase cognitive performance by reducing redundancy in the nervous system and increasing available neuronal processing power, as such, it can also play an important role in decision making (Wu et al., 2022), (Rogers, 2021), (Güntürkün et al., 2020).

Choosing what to eat, when to eat and how much can greatly impact the reproductive fitness of the animal but requires a multi-level integration of external and internal information to make the most appropriate choice according to the situation. For example, the fruit fly *Drosophila melanogaster* often forages on decomposing food where it needs to balance acquiring essential nutrition with avoiding toxins (Sareen et al., 2021), it may also need to account for its reproductive state (Bowman & Tatar, 2019), the saliency of competing (visual) cues (Zhang et al., 2007) and several other internal and external factors. Perhaps one of the most important of an animal's internal state is hunger. As an animal becomes hungrier, it will be in its best interest to consume as much food as possible since it can't be certain of its next meal. The central complex is responsible for the integration of many such inputs, and is also computing navigation and has access to motor neurons (Hulse et al., 2021) (Wolff & Rubin, 2018) (Pool & Scott, 2014), which makes it ideal for directing food choice too.

Indeed, it has also been described in relation to food choice under the motivational state of hunger. Musso and his colleagues described a circuit located in the central complex that is responsible for mediating food intake when the fly is hungry. The circuit consist of 3 parts, gr43a brain neurons sense a rise in the glucose content of the fruit fly's haemolymph, this serves as a signal that the animal has started eating, their activity promotes continuous feeding behaviour. vΔA_a neurons located in layers 8 and 9 of the fan-shaped body, project to the asymmetric bodies (AB) and sense the circulating glucose levels in the haemolymph. Their oscillations are mediated by starvation; lower glucose levels weaken vΔA_a neuron oscillations. The vΔA_a neurons are secreting Tachykinin, which binds to and inhibits gr43a brain neurons. While the fly is sated, the vΔA_a neurons are active, and thus the circuit functions as an "emergency system" that creates a strong preference for food high in fructose

content when the fly is hungry and needs to eat the most. It is unclear whether the same mechanism is also responsible for continuous control of feeding, as the fructose preference



1. Figure: Model for how fructose serves as a cue for promoting sugar ingestion and how rising glucose levels signal satiety through vΔA_a neurons, which then inhibit sensitivity to fructose and terminate feeding. (Musso et al., 2021)

only appears after about 8 hours of starvation. The 3rd member of the circuit is the SA^{uni} neuron, which provides continuous glutamatergic input to vΔA_a neurons by connecting to them in the asymmetric bodies allowing them to fire when enough glucose is present. Altogether, the circuit is responsible for creating a fructose preference in hungry flies (Musso et al., 2021).

What role the SA^{uni} neurons play beyond permitting the vΔA_a neurons to fire however was left unclear. 28-48 hours after pupa formation, the SA^{uni} neurons undergo a remodelling phase after which ~95% of the flies become unilateral, only having the right side of the asymmetric bodies innervated, while 5% of the flies remain bilateral, having both sides of their asymmetric bodies innervated (Lapraz et al., 2023).

The SA^{uni} neuron's laterality has been implicated to shape other processes as well. Bilaterality impairs the long-term memory of the fruit fly but still leaves its short-term memory intact (Pascual et al., 2004). The asymmetry of the SA^{uni} neurons' innervation could be an important component to their function, in regards to feeding as well, the asymmetry in the vΔA_a neuron oscillation could likely be influenced by it, though one would need electrophysiological recordings to confirm such a theory (Musso et al., 2021). As a first step to answer this question, in our research we examined whether changing the innervation patterns of the SA^{uni} neurons would impair the fructose preference described by Musso and his colleagues.

Objective:

Hypothesis: AB lateralisation is important for sugar preference. Starved flies with bilaterally innervated asymmetric bodies would have their sugar preference abolished in Wnt4 and unc5 mutants, and wild type Canton-S flies. Starved flies with unilaterally innervated AB-s will show a fructose preference.

Materials and Methods

Flies and antibodies used during tissue preparation: Flies were starved for 45 hours or appetized for 6 hours on a 1% Agar solution. At the time of testing, all flies were 5-9 days old mated females following previous research (Musso et al., 2021).

Control experiment: Canton-S flies were raised and kept at room temperature, then starved for either 6 or 45 hours. All flies were 5-9 days old at the time of the experiment. Experiments were performed at 25°C within an incubator.

Primary Antibodies	Secondary Antibodies
anti-Fas2 (M) 1:10	anti-M(H) 488 1:500
anti-Ncad (Rat) 1:10	anti-Rat 647 1:500

Unconditional Wnt4 RNAi knockdown experiments: Flies were raised at 18°C and kept at room temperature for 5-9 days before the day of the experiment. Experiments were performed at 25°C within an incubator.

Experimental group: ;Wnt4EMS23; x Canton S

Control group: Canton-S raised at 18°C

Primary Antibodies	Secondary Antibodies
anti-Fas2 (M) 1:10	anti-M(H) 488 1:500
anti-Ncad (Rat) 1:10	anti-Rat 647 1:500

Unconditional Unc5 RNAi knockdown: Flies were raised and kept and tested (in an incubator) at 25°C.

Experimental group parents:

Virgin females: ;R72A10-lexA, lexAop-mCD8::GFP/CyO; R72A10-Gal4/TM6B, Hu,
e

Males: UAS-unc-5RNAi

F1-Genotype: ;R72A10-lexA, lexAop-mCD8::GFP/+; R72A10-Gal4/UAS-unc-5RNAi

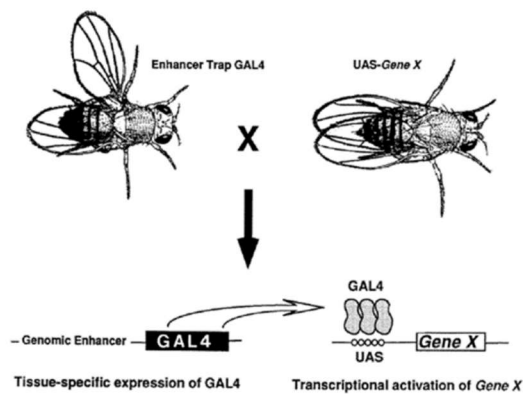
Control group parents:

Virgin females: Canton-S

Males: UAS-unc-5RNAi

Primary Antibodies	Secondary Antibodies
anti-GFP (Rb) 1:1000	anti-Rb 488 1:500
anti-Fas2 (M) 1:10	anti-M(H) 568 1:300
anti-Ncad (Rat) 1:10	anti-Rat 647 1:500

Gal4 system: The system allows for targeted gene expression that will result in selective

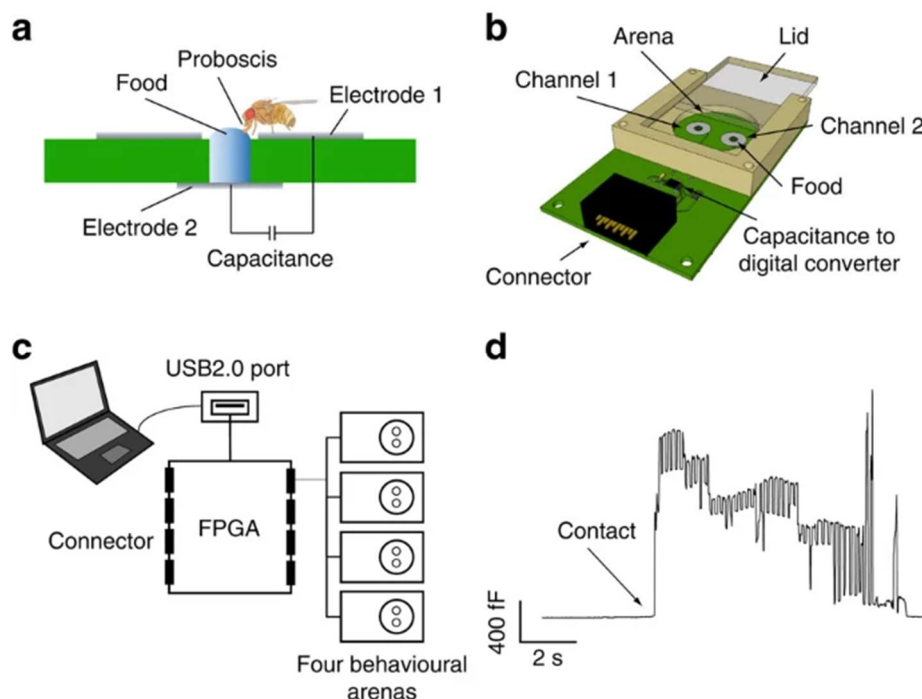


2. Figure: Schematic of the Gal4 system. Tissue-specific expression of Gal4 will activate transcription for gene X.

activation of any cloned gene in tissue and cell specific patterns. Gal4 is an activator derived from yeast and can activate transcription only from Gal4 binding site promoters. The binding site promoter is called the Upstream Activation Sequence (UAS), and if a target gene is behind it, it will drive its expression, making it a highly versatile and precise tool as only in cells where both the Gal4 and the UAS is expressed, could (or should) an effect be observed. Furthermore, the system can be “stored” separately in two transgenic lines and activated by crossing them. The system can be restricted to work in specific cells or tissues in embryos, larvae and adults by choosing enhancers (Brand & Perrimon, 1993).

Food: Flies were raised and kept on standard food and fasted on a 1% Agar solution. For the sugar choice experiments Fructose or Glucose was dissolved in a 1% Agar solution at a concentration of 50mMol. The sugar solutions were heated for 1 hour before the experiment to 96°C, they were parcelled into the electrodes at 2 microlitres.

Behavioural experiment: The experiments were performed using the fly Proboscis and Activity Detector (flyPAD) device. The flyPAD device consist of 32 circular arenas with two electrodes placed in the middle of each one at equal distance from each other.



3. Figure: The flyPAD setup. a: concept of a feeding interaction, as the proboscis touches the food a circuit is created, and the capacitance measured. b: Diagram of 1 fly arena. c: Diagram of the complete system. 32 arenas can be connected at a time. d: capacitance trace of the fly interacting with the food (Itskov et al., 2014)

As the fly's proboscis touches the liquid food, a circuit is created and capacitance is measured. The capacitance measurements closely correlate to the amount of food consumed and allow for real-time monitoring of feeding behaviour (Itskov et al., 2014).

Since the capacitance data allows for the exact recording of each sip the fly takes, sugar preference (preference index or PI) can be calculated as follows: $\text{substrate1 sips} - \text{substrate2 sips} / \text{substrate1 sips} + \text{substrate2 sips}$. The rhythmic motor programme of feeding is described by sip durations and inter sip intervals (Itskov et al., 2014). The results of the PI were considered significant if flies took significantly more sips from either sugar.

Tissue preparation: Flies were immobilised with CO₂ and sacrificed in 96% ethanol. Their brains were extracted in Phosphate Buffer (PB) under a light microscope and handled individually. They were fixed in Paraformaldehyde (PFA) for 20 minutes to preserve them in a lifelike state, then washed in Phosphate buffer with Triton (PBT) for 1 hour, during which I changed the solution on them once, this step was done to increase membrane permeability and remove residual PFA. Then non-specific binding sites were blocked using Goat serum dissolved in PBT at 10%, and the brains were left with primary antibodies to incubate over two nights. The brains were then washed with PBT for one hour (I changed the liquid on them once) and left with secondary antibodies to incubate over two nights. Finally, the PBT washing step was repeated and brains were mounted on glass slides in drops of Vector shield. Any time I changed the liquid on the brains, I did it under a light microscope. Brain positions during mounting were checked with a fluorescent microscope.

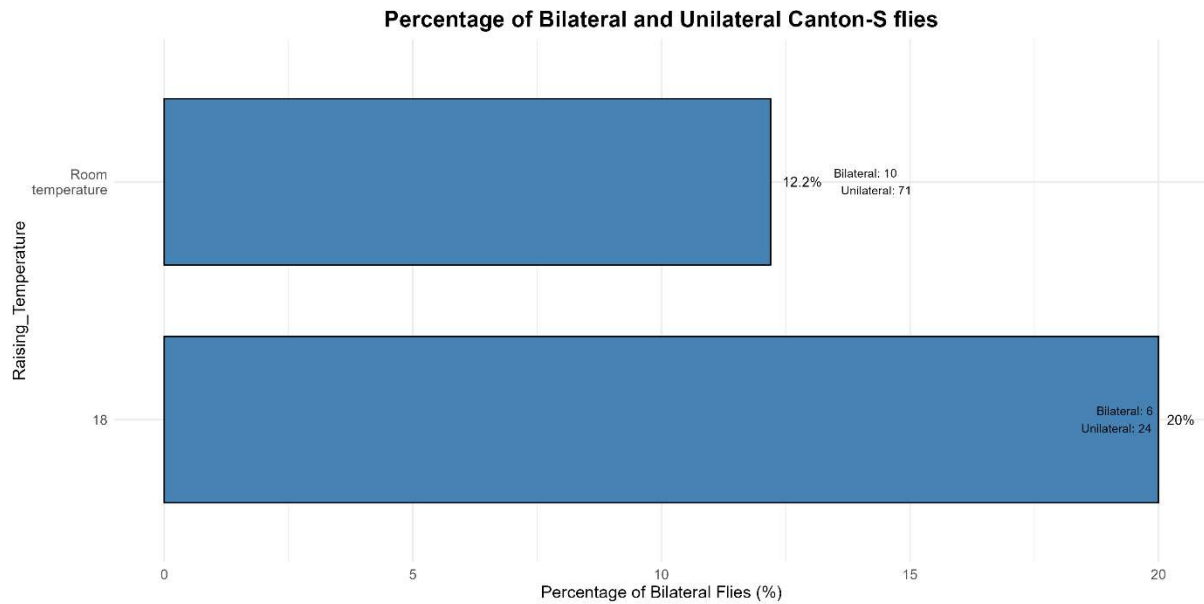
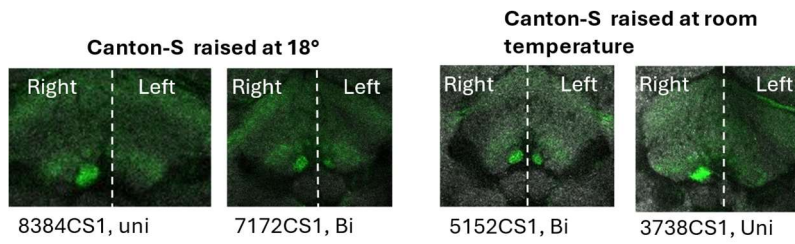
Image acquisition and processing: Images were taken with the TCS SP5 Leica confocal microscope at 20X magnification. The S08036 Immersion liquid was used. Argon and HeNe 633 lasers were used at 25% strength, image format was set to 512X512, speed was set to 400Hz. Z step-size was 1,5, images were taken between frames. The images were analysed using the ImageJ software.

Behavioural data was matched with brain laterality and analysed with R studio: due to the non-normal distribution of the data the Wilcoxon test was performed to compare the results for statistical significance, and the rank-biserial correlation was used to measure effect size.

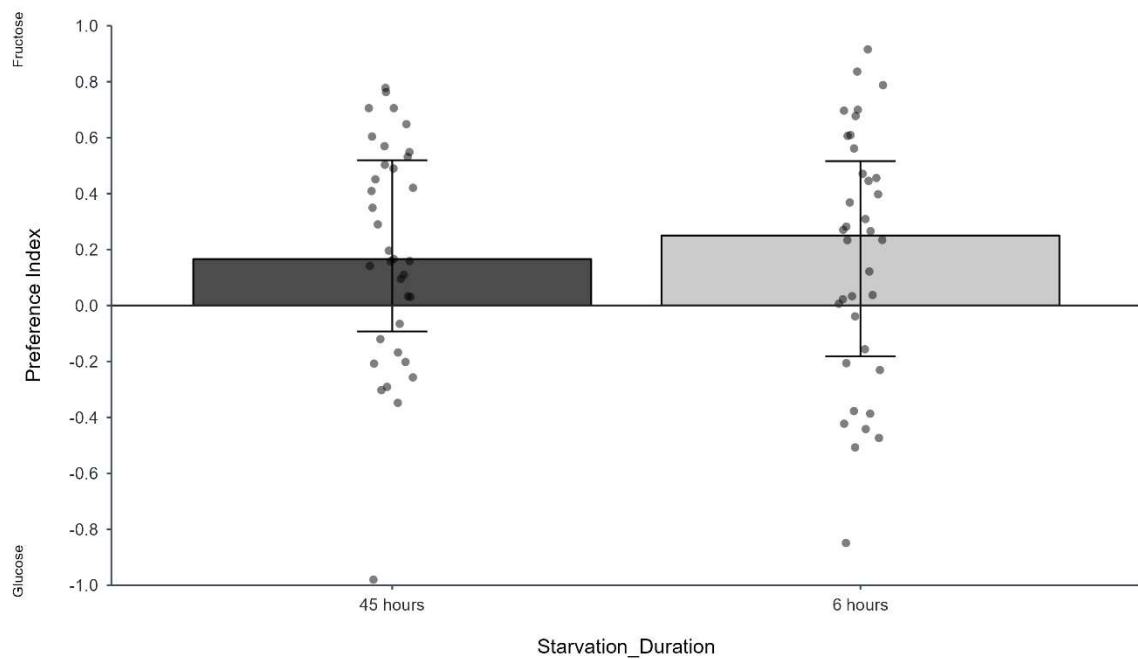
Results:

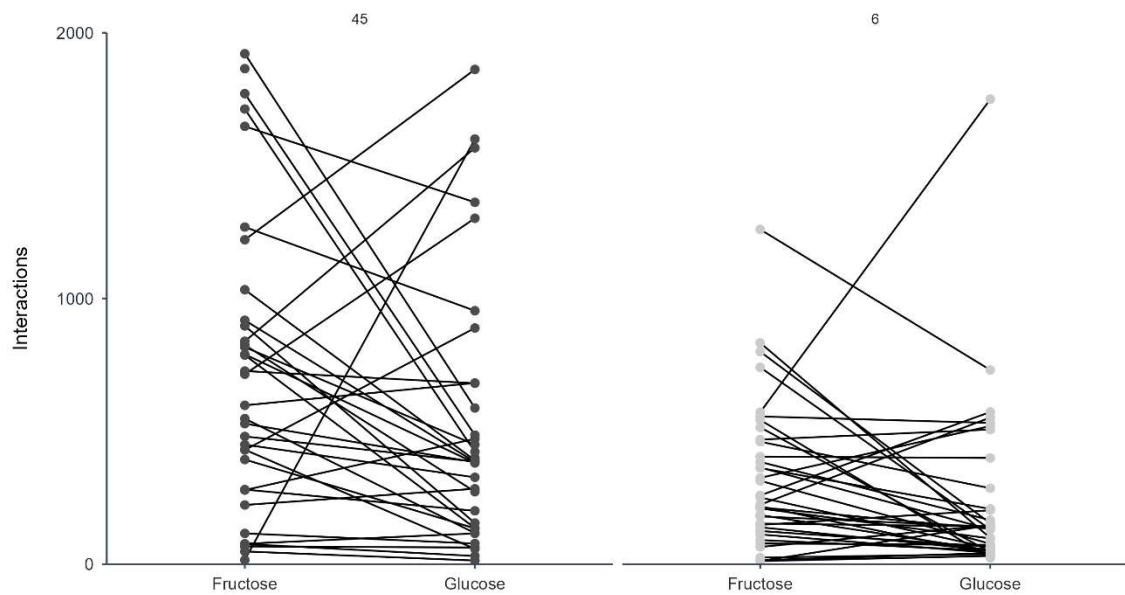
1: The Fructose preference control experiments:

Musso and his colleagues described a significant fructose preference appearing after 8 hours of starvation, to this end, we compared flies starved for 6 hours and flies starved for 45 hours on room temperature to serve as controls. We considered the preference index test results significant if the difference between the sips the flies took from fructose and glucose was significant. We found that there was a significant fructose preference for both the flies starved for 6 hours (p-value = 0.02136, effect size = -0.3836058) and the ones starved for 45 hours (p-value = 0.04946, effect size = -0.3320821). The difference between their preference indices wasn't statistically significant (p-value = 0.8059, effect size = 0.4898279). The rate of bilateral flies were as expected with Canton-S raised at 18° having higher rates (20%) than the ones raised at room temperature (12.2%).



4. Figure: Representative images of Canton-S flies raised at 18° and room temperature and the overall rate of bilateral-to-unilateral flies.

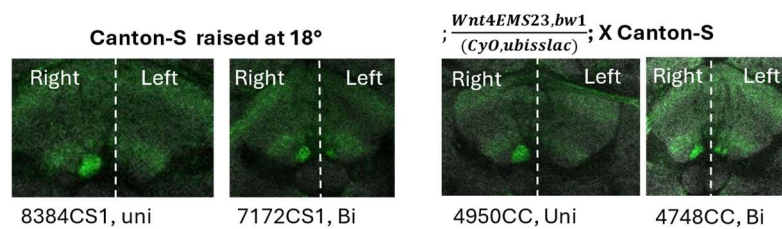


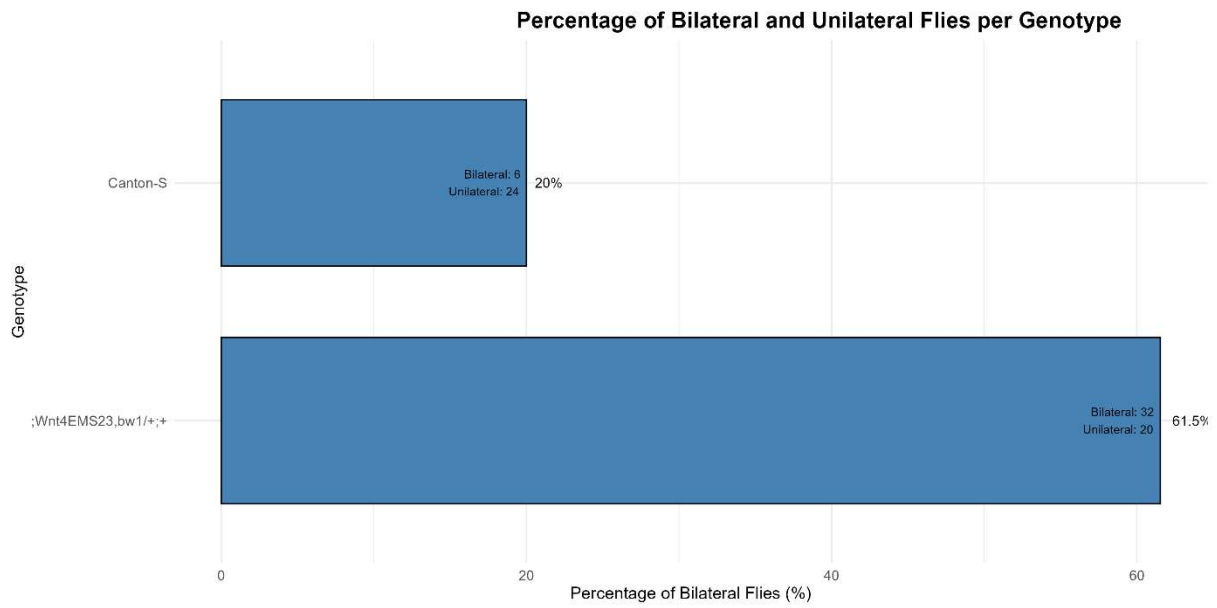


5. Figure: Comparing preference indices for Canton-S flies starved for 6 and 45 hours and comparison of the number of sips each groups took from Fructose and Glucose.

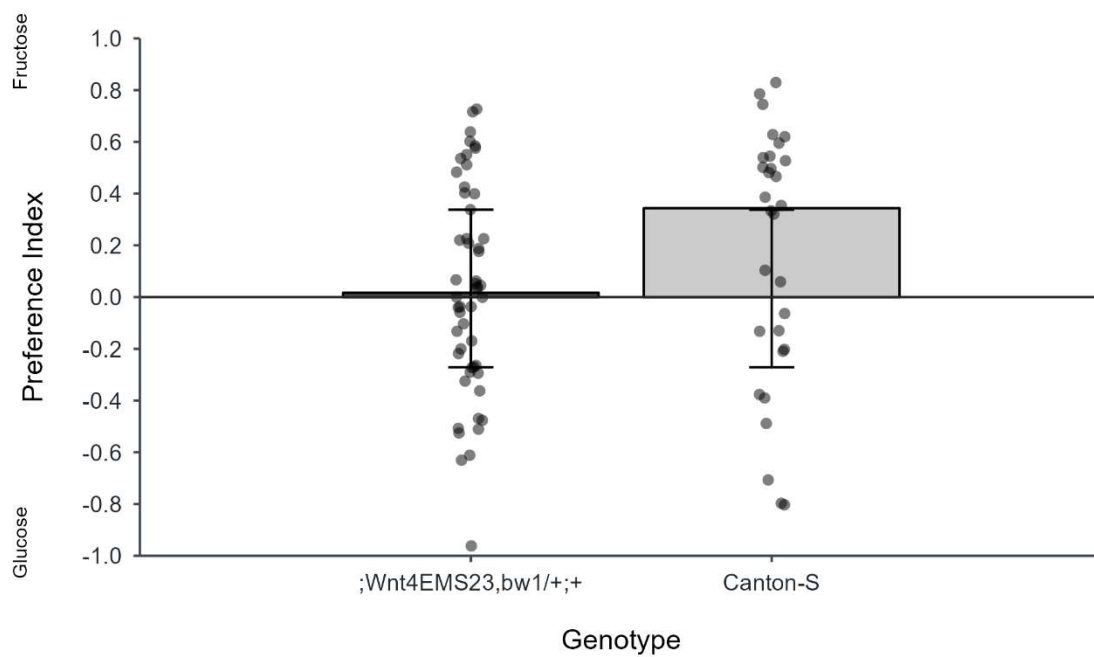
3: The $Wnt4^{EMS23}$ mutant experiments:

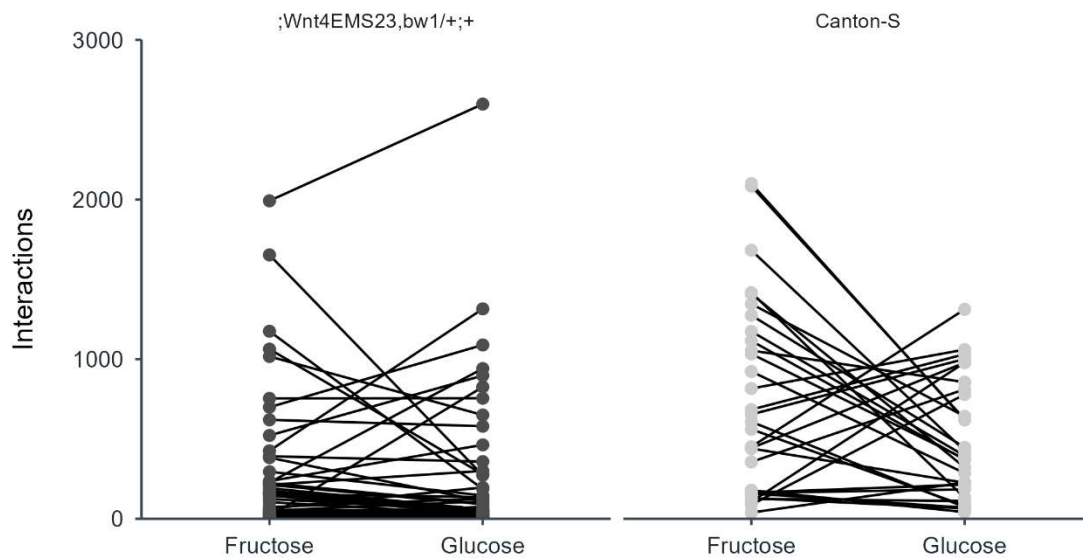
The $Wnt4^{EMS23}$ mutation was expected to increase the bilaterality rate of the flies to $\sim 60\%$, and indeed it did (61.5%). All flies were raised at 18° to achieve this effect. However, we found no significant difference between the preference indices of the $Wnt4$ group and the Canton-S group (p-value = 0.1344, effect size = 0.6332648). The difference between the number of Fructose and glucose sips also wasn't statistically significant between these groups ($Wnt4$ group: p-value = 0.5834, effect size: -0.0478955, Canton-S group: p-value = 0.06267, effect size: -0.3913978).





6. Figure: Representative images of Canton-S and *Wnt4^{EMS23}* flies raised at 18°, and the overall rate of bilateral-to-unilateral flies.



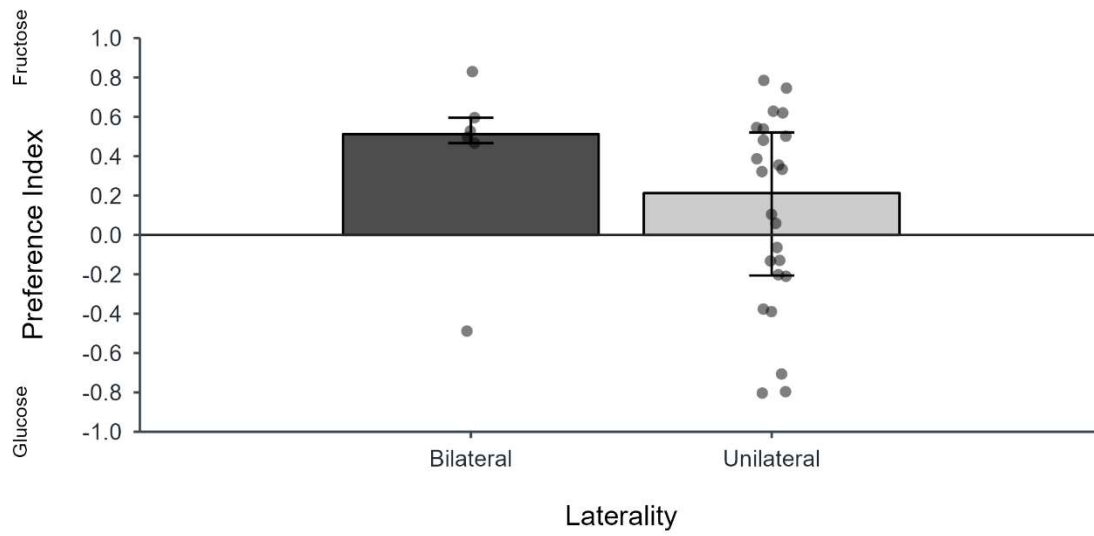


7. Figure: Comparing preference indices for Canton-S and $Wnt4^{EMS2}$ flies starved for 45 hours and raised at 18° and comparison of the number of sips each group took from Fructose and Glucose.

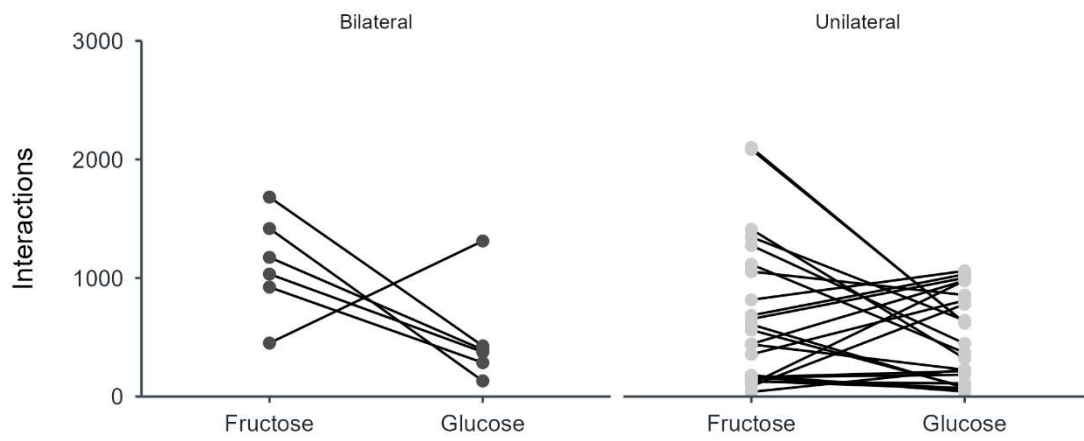
During the experiments flies were dissected individually, this allowed us to match each individual datapoint and their corresponding brains. However, during this further examination of the results, no significant differences could be detected. Contrary to expectations, a trend could be observed where bilateral flies showed a greater preference for fructose then unilateral flies.

Preference Index comparisons between Groups:	p-value (Wilcoxon test)	effect size (Rank biserial correlation)
Wnt4 unilateral vs Wnt4 bilateral	0.3973	0.6015965
Canton-S unilateral vs Canton-S bilateral	0.1914	0.6121212
Wnt4 unilateral vs Canton-S unilateral	0.2659	0.5784946
Wnt4 bilateral vs Canton-S bilateral	0.06852	0.6167341
Comparison of the number of sips within groups:	p-value (Wilcoxon test)	effect size (Rank biserial correlation)
Wnt4 unilateral	0.6813	-0.09183423
Wnt4 bilateral	0.2899	-0.1871034
Canton-S unilateral	0.2776	-0.2216431
Canton-S bilateral	0.2188	-0.5020877

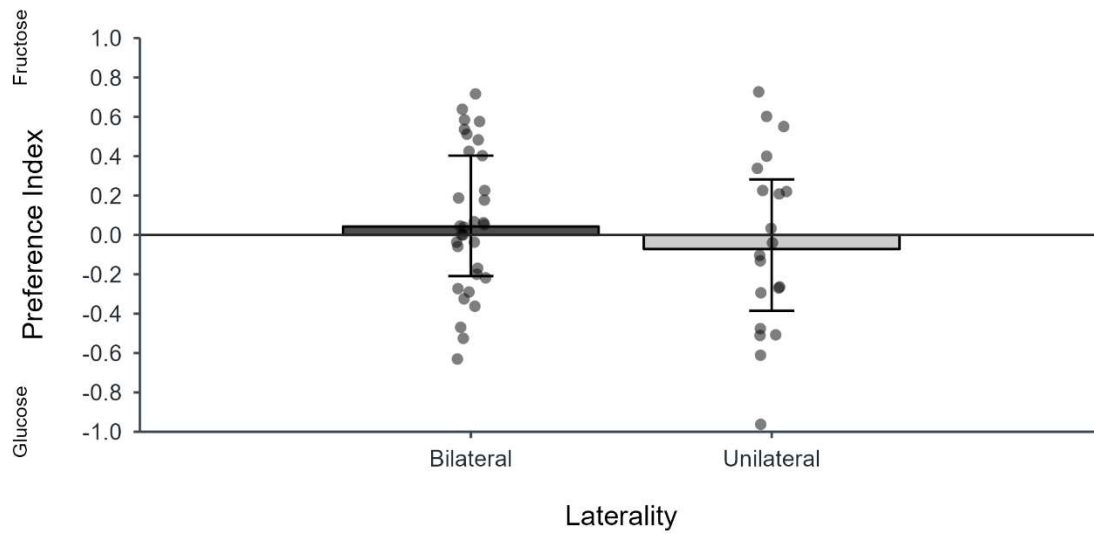
Canton-S



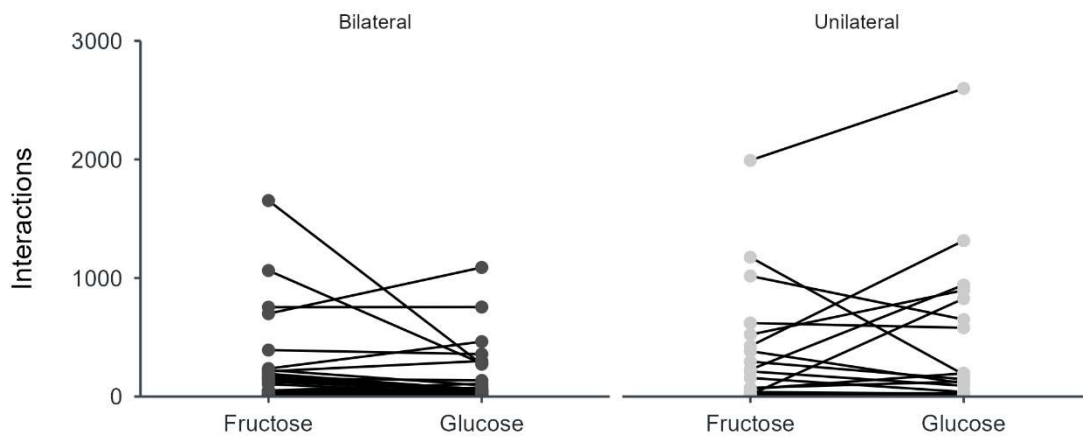
Canton-S



;Wnt4EMS23,bw1/+;+



;Wnt4EMS23,bw1/+;+

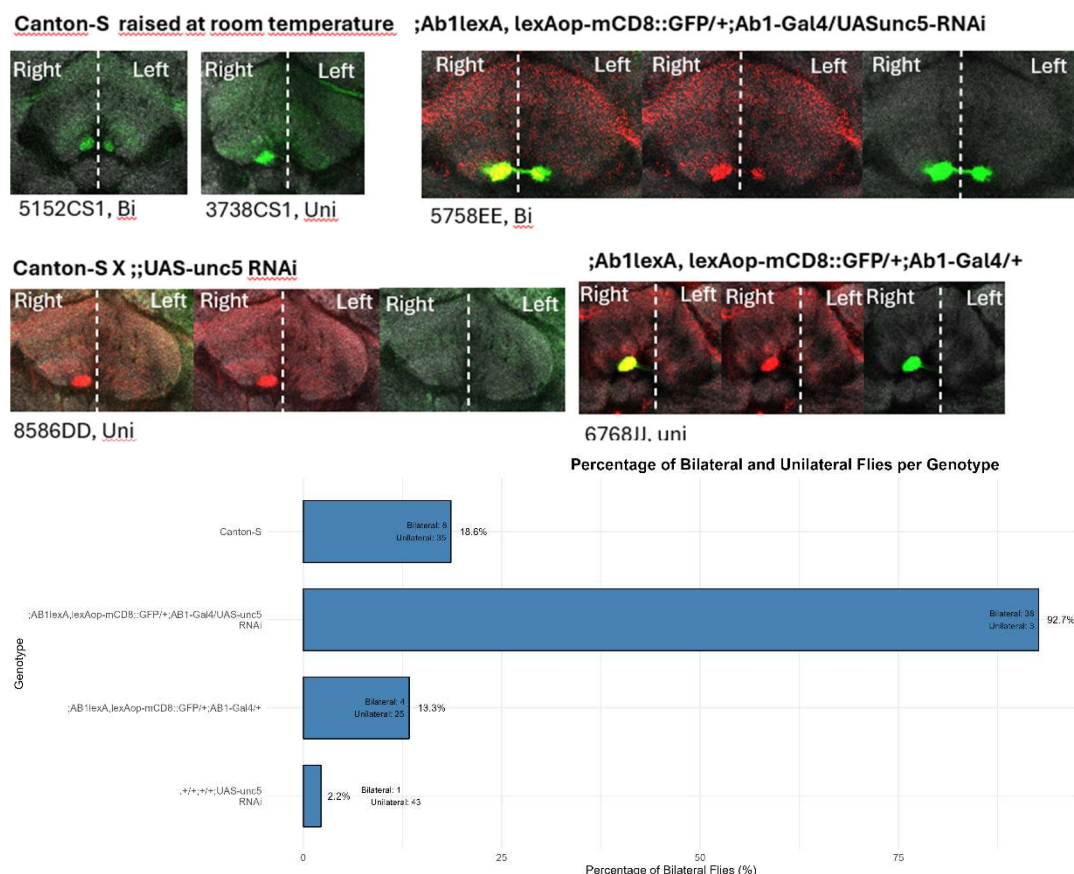


8. Figure: Comparing preference indices for bilateral and unilateral Canton-S and *Wnt4^{EMS2}* flies starved for 45 hours and raised at 18° and comparison of the number of sips each group took from Fructose and Glucose.

4: The *unc5* experiments:

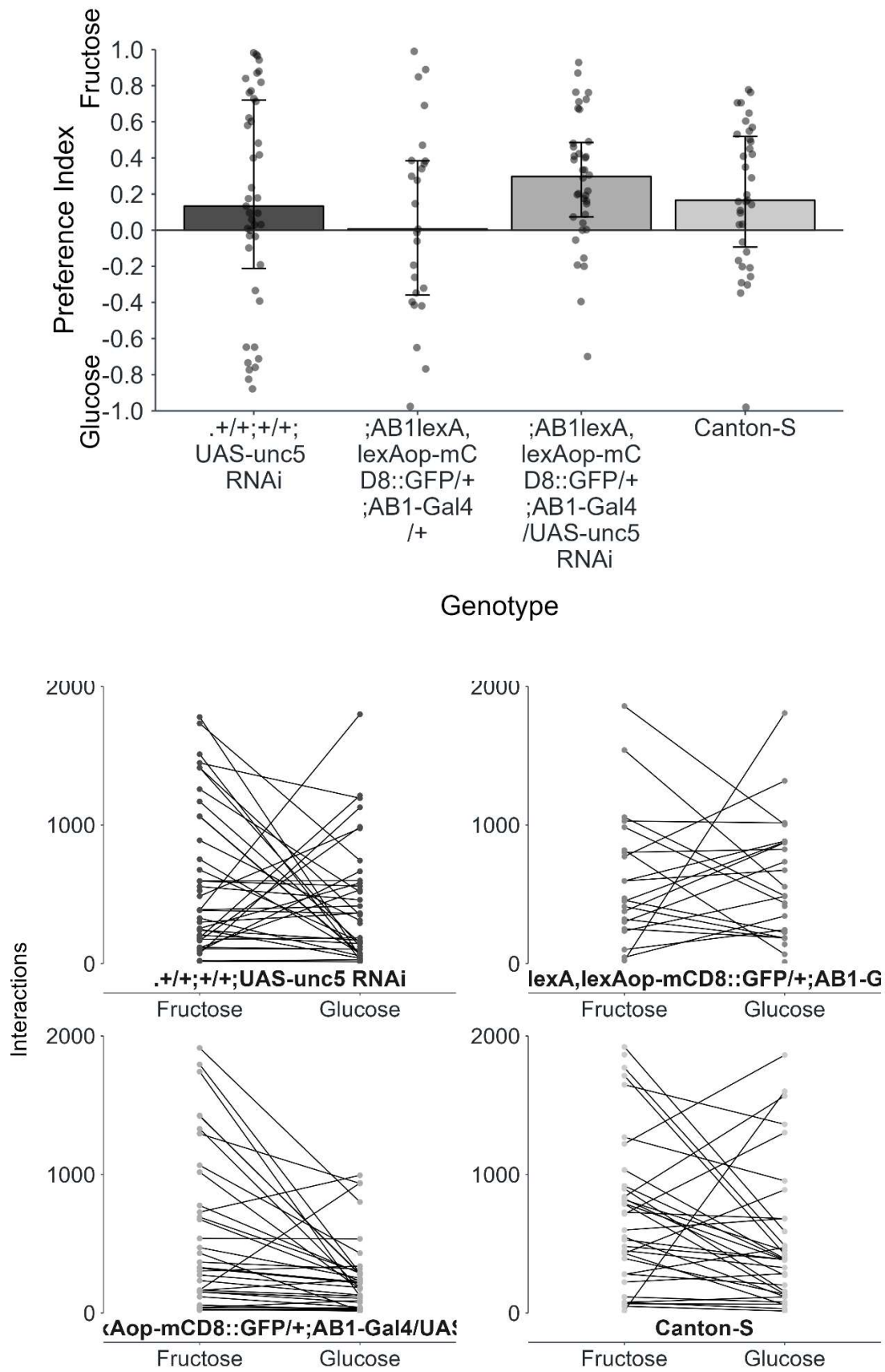
Knockdown of *unc5* RNAi increased the bilaterality rate to 92.7%, due to the low number of unilateral flies in this group, the bilateral flies' PI-s were compared to values from unilateral flies with different genetic backgrounds. The differences between the PI-s of the different

groups weren't statistically significant, within the different groups, the Canton-S and unc5 RNAI knockdown flies showed a preference for fructose, while the control groups for the two parts of the Gal4 system didn't.



9. Figure: Representative images of Canton-S flies raised at room temperature, and of unc5RNAi knockdown, UAS and Gal4 control group flies. The unc5 group and UAS control were raised at 25°, the Gal4 control group was raised at room temperature.

Preference Index comparisons between Groups:	p-value (Wilcoxon test)	effect size (Rank biserial correlation)
UAS control vs unc5RNAi knockdown	0.5047	-0.223163
Gal4 control vs unc5RNAi knockdown	0.05696	-0.5309648
Canton-S vs unc5RNAi knockdown	0.4107	-0.2185732
Comparison of the number of sips within groups:	p-value (Wilcoxon test)	effect size (Rank biserial correlation)
UAS control	0.06467	- 0.3455922
Gal4 control	0.5424	- 0.4448
unc5 RNAi knockdown	7.727e-05	- 0.1759003
Canton-S	0.04946	- 0.3183673



10. Figure: Comparison of Preference indices and number of sips taken by each group.

Discussion:

After 6 hours of starvation, the Canton-S flies already showed a fructose preference:

Musso and his colleagues didn't work with wild-type flies during their experiments (Musso et al., 2021), and the fructose preference didn't show even after 45 hours of starvation for some of the control groups of the Gal4-UAS systems. These results confirm the theory that fructose serves as a cue for the flies that they started eating, in a wild-type genetic background this preference could also appear sooner than in mutant flies as Canton-S flies' genetic functions haven't been disturbed.

A trend could be observed, where bilateral flies showed a greater preference for Fructose than unilateral flies:

While the differences between the PI-s weren't statistically significant in the Wnt4^{EMS23} experiments, and the flies didn't show a fructose preference, trends could still be observed. The bilateral Canton-S flies raised at 18° displayed a greater tendency to choose fructose over glucose than the unilateral ones. The Wnt4^{EMS23} mutant flies when bilateral displayed a small glucose preference, while unilateral ones displayed a small fructose preference. The Wnt4^{EMS23} mutation is active in all cells of the fly's body, and as such could have contributed to the lower tendencies the flies displayed in their sugar preferences. Nevertheless, the bilateral flies in the unc5RNAi knockdown group also displayed a sugar preference, and, although not significant, this preference was greater than the sugar preference of the Canton-S flies raised at room temperature. The trends displayed in the results contradict the hypothesis that the bilaterality would impair the sugar preference of the flies. This effect could perhaps be explained by the connection between the SA^{Uni} and the vΔA_a neurons. Since the vΔA_a neurons release Tachykinin when they sense the rising glucose levels in the haemolymph and inhibit feeding, and the SA^{Uni} neurons provide them with an excitatory glutamatergic input (Musso et al., 2021), the bilaterality could impair the connection between the two, and thus the feeding inhibiting effect of the vΔA_a neurons could be impaired. This would explain why bilateral flies showed a trend towards a fructose preference, as without the inhibiting effect of the Tachykinin, the Gr43a brain neurons could be active more and compel the fly to choose fructose over glucose. While more data could still be collected to improve the statistical significance of the findings, other follow-up research could focus on the relationship between the vΔA_a and SA^{Uni} neurons, to see if the innervation patterns of the SA^{Uni} neurons would affect the activity of the vΔA_a neurons.

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ChatGPT 4 and 4o were used to help write the code for R studio that created the plots and it helped with the data analysis.

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