

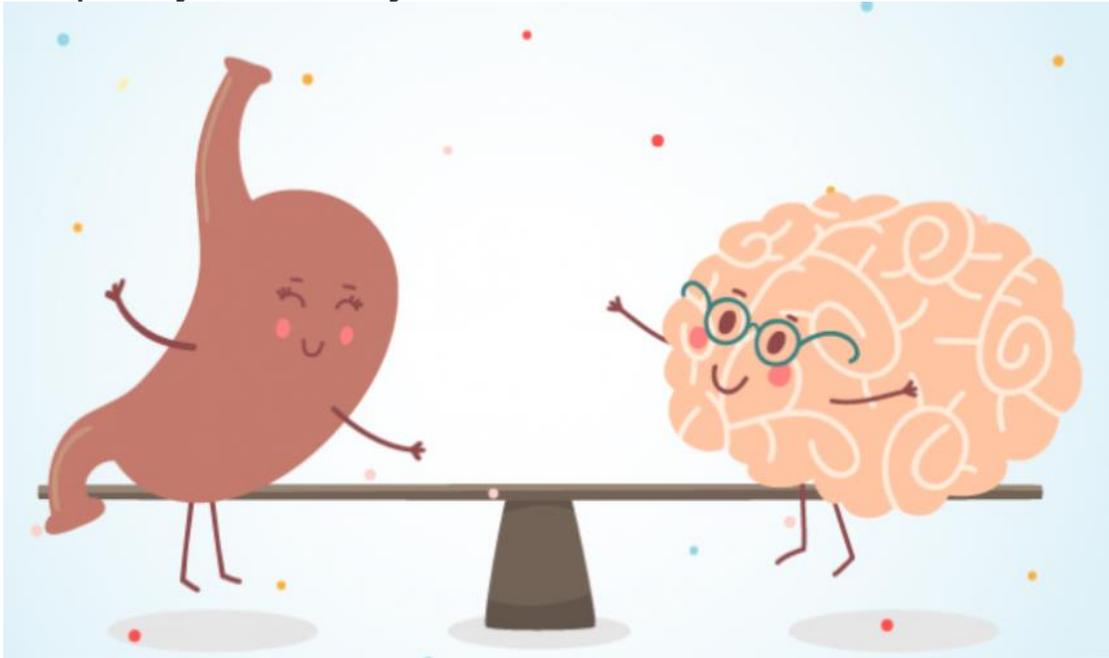
Irene Miguel-Aliaga

The sex of organs



More to the gut than digestion: the brain-gut axis

- Bidirectional **communication between our nervous system and gastrointestinal tract** controls food intake, adiposity, immunity



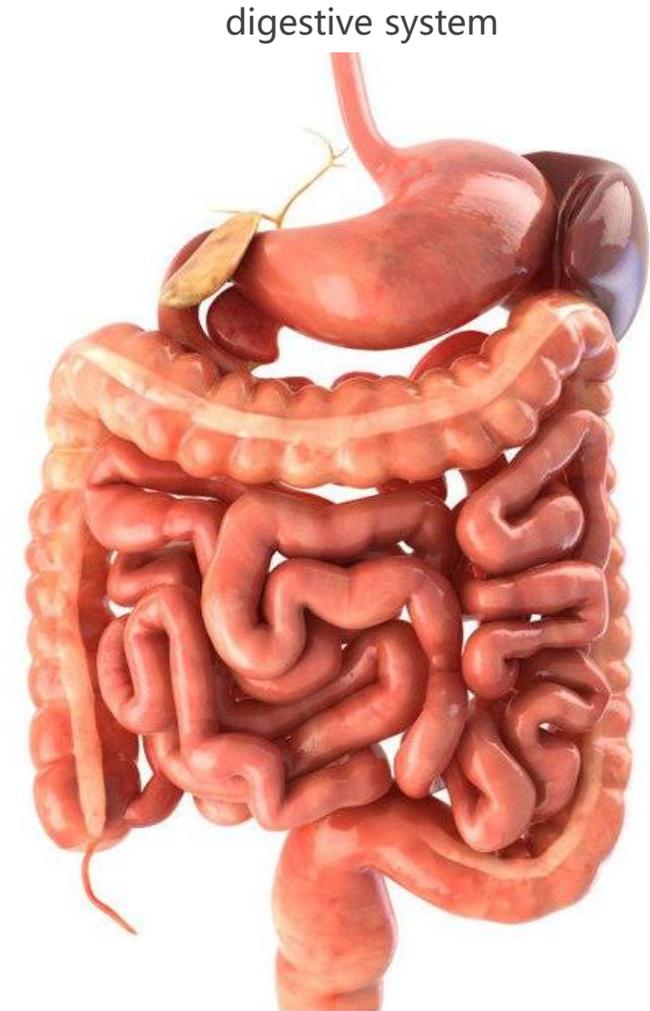
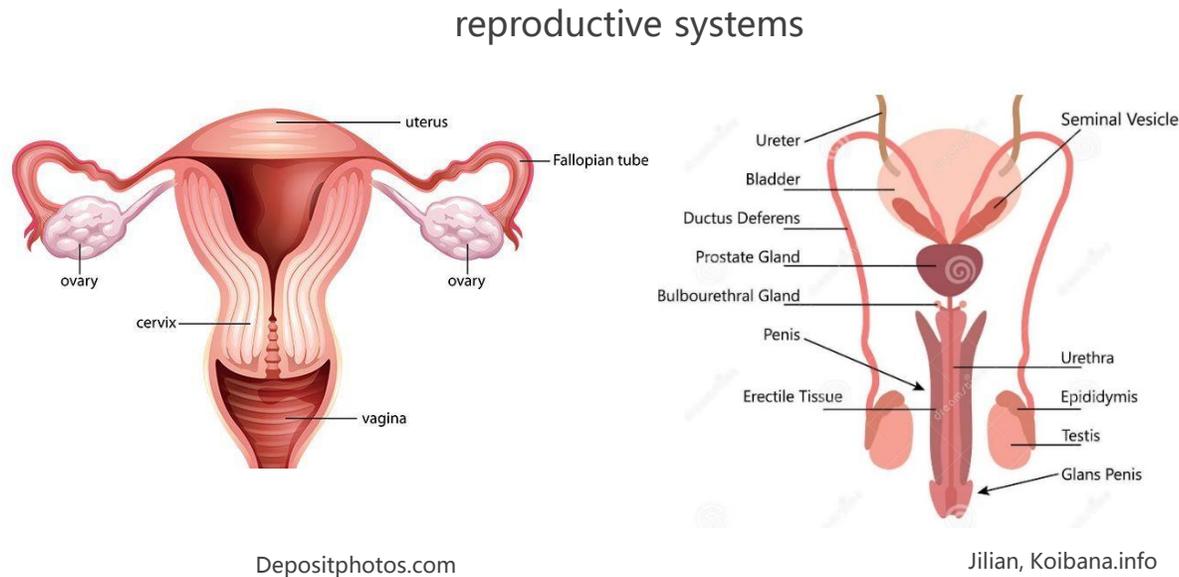
Broth of Life



Belle et al (2017) *Cell*, www.transparent-human-embryo.com

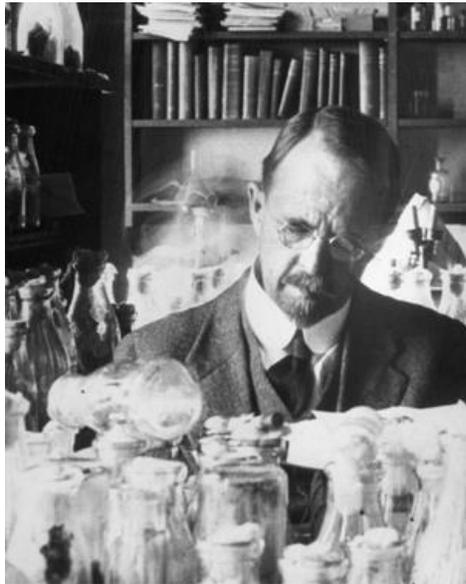
- **Gut nerve cells** and **hormone-secreting gut cells** as mediators of this important
- **communication**
- **But all intestines are the same... are they?**

Sex differences in our digestive system?



- Historically not considered... but most gastrointestinal diseases are sex-biased, as are many aspects of our physiology

> 100 years of *Drosophila* research, 6 Nobel prizes



Thomas Hunt Morgan, 1910



A fly room, >100 years later

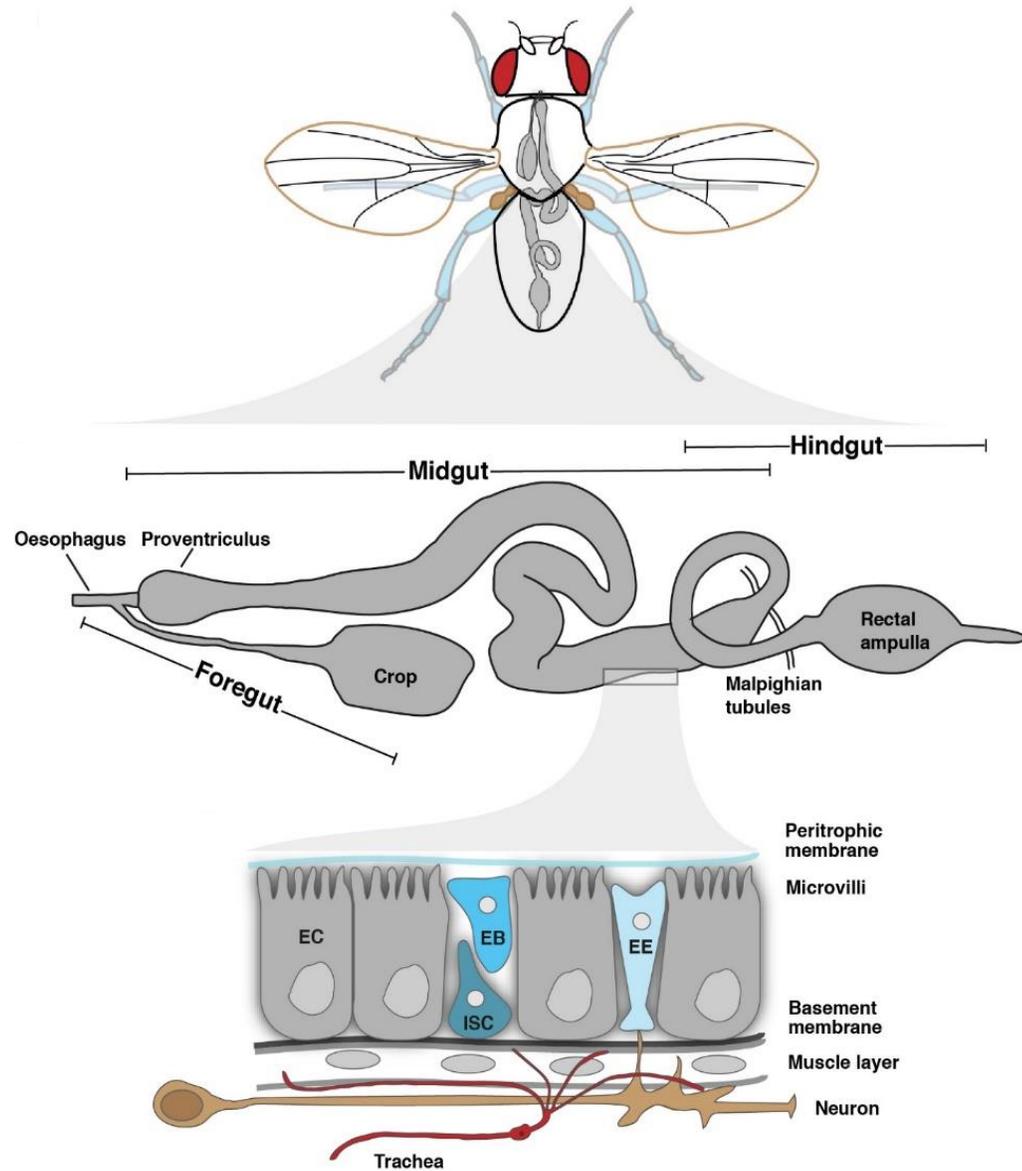
Why flies?

- Genetic similarities: 60-75% genes “shared” between flies and humans
- Inexpensive, short generation time
- Ability to turn genes/nerve cells on/off with temporal/spatial control, many genes at a time

Powerful discovery tool: immunity, neurobiology, developmental biology...

and the **brain-gut axis**?

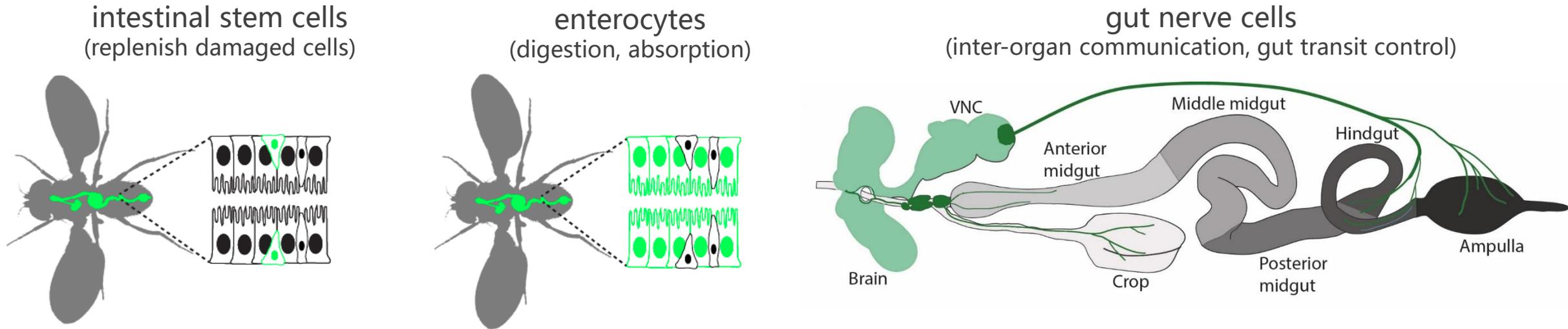
The fly intestine: equally fascinating, genetically tractable



- Flies have **brains and guts**
- Flies make complex **food choices**, get **fat** and **diabetic**



All gut cells “know their sex”, but through different mechanisms

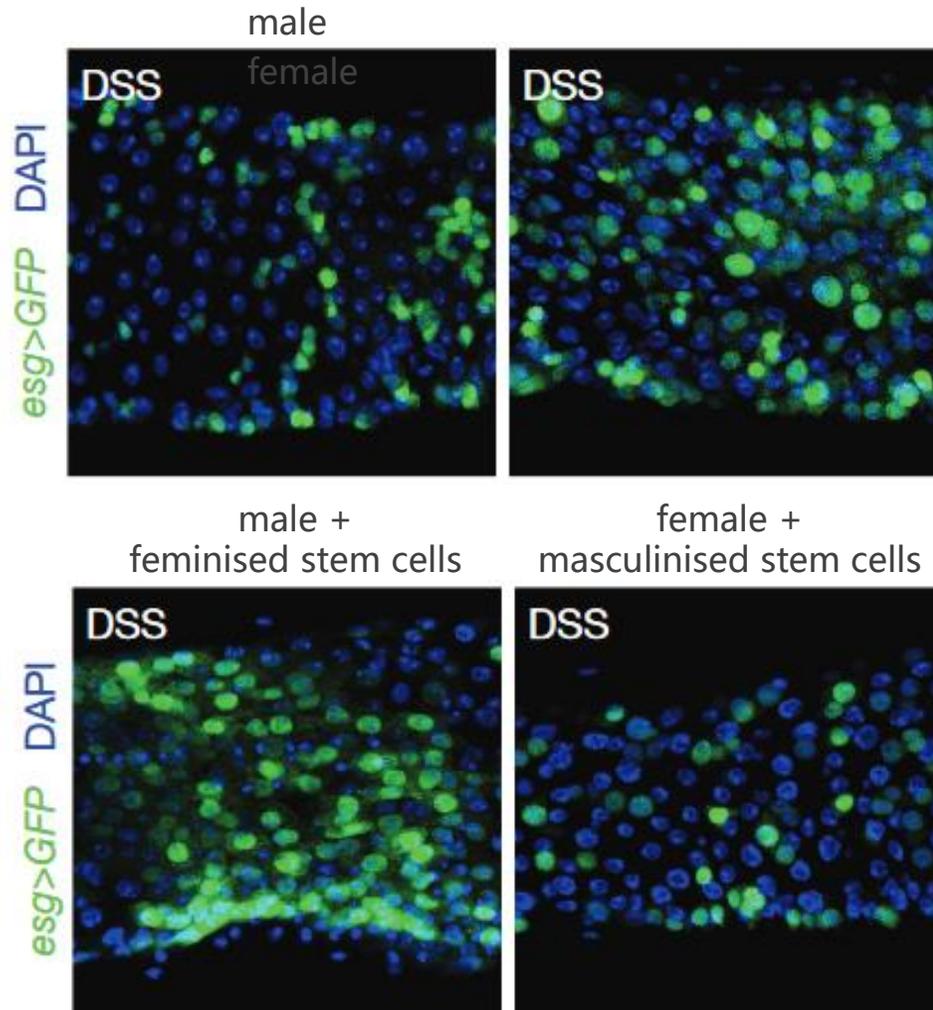


- Three **different ways to specify “sexual fate” within the same organ**: one for each cell type, some intrinsic (sex chromosomes), some extrinsic (sex hormones). Sexual fate is **actively maintained** and therefore reversible
- Each mechanism controls **different sexually dimorphic features** of cell/organ biology
- Collectively, they seem to adjust organ-level properties to optimise female or male reproduction: **the sex of the gut sustains reproduction**

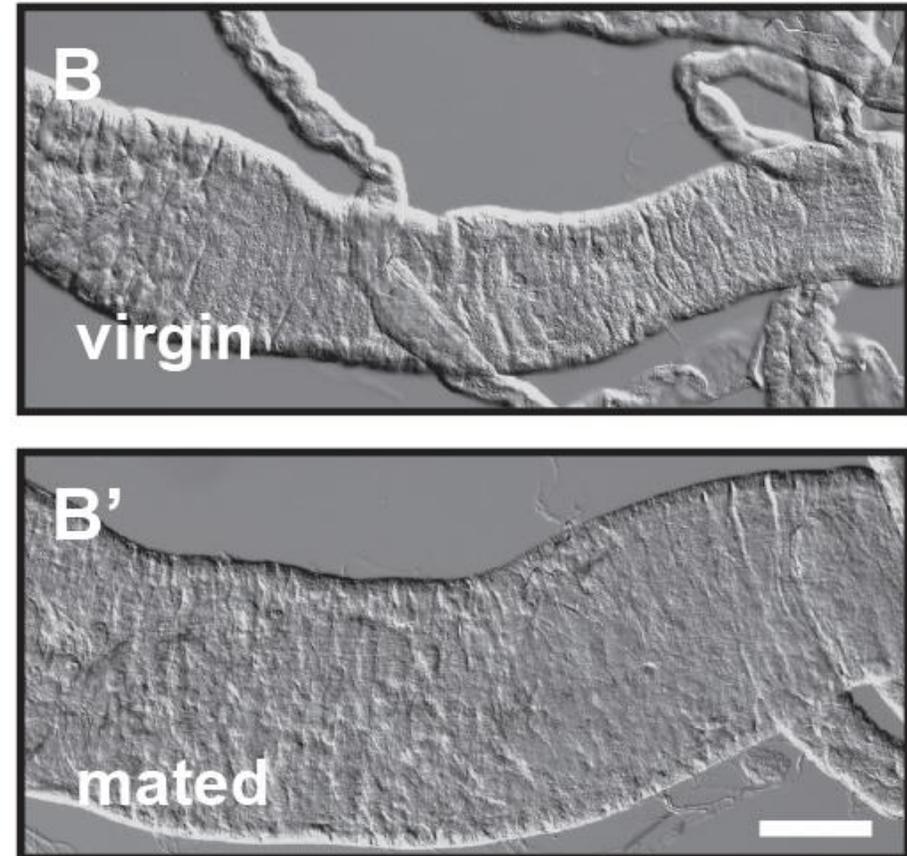
1. The sex of intestinal stem cells

Female stem cells divide more often

- Stem cell sex is **cell-intrinsic** and **adult-reversible**

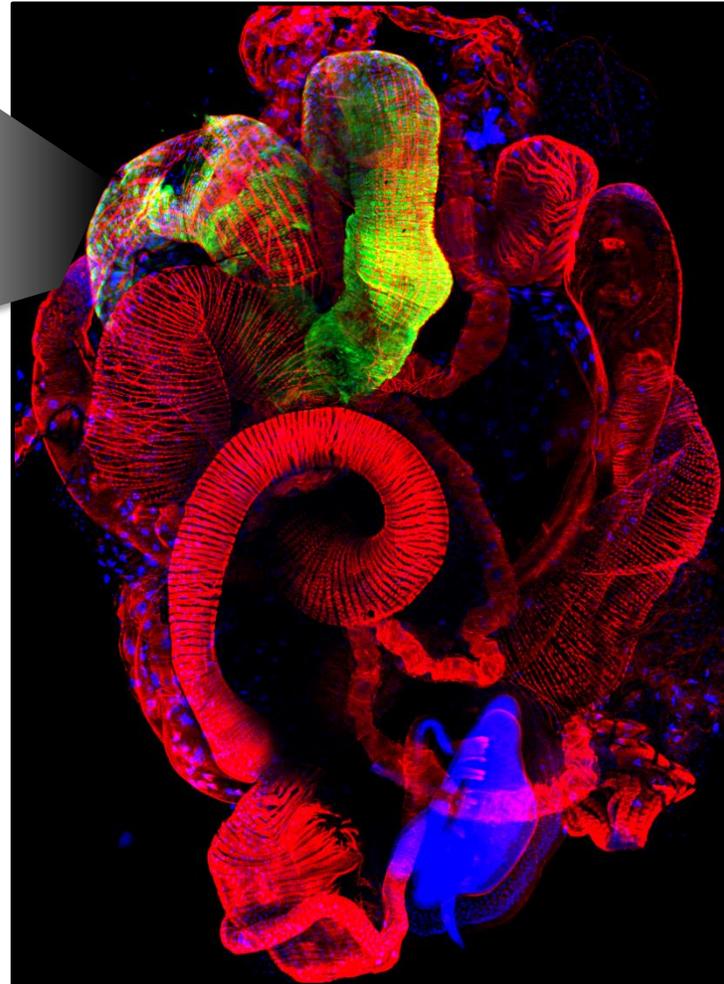
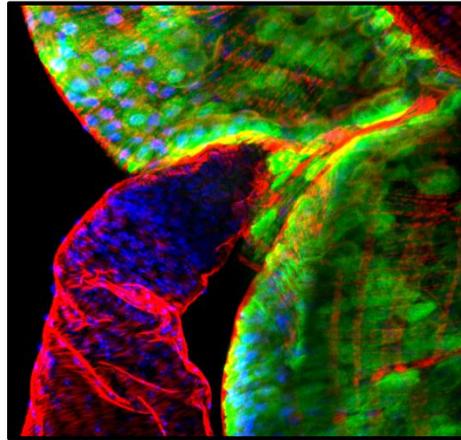


- Female identity required for the maternal gut to **grow during reproduction, sustaining fecundity**

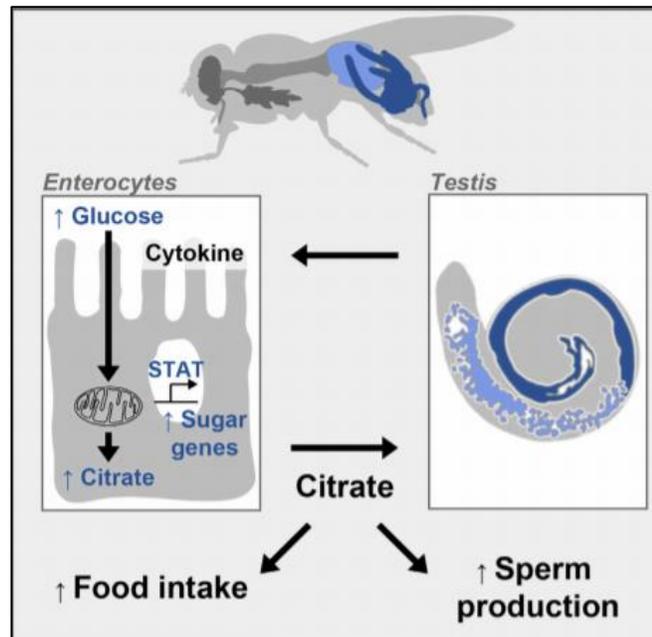


2. The sex of enterocytes

Testes “masculinise” the gut to get the metabolites they need

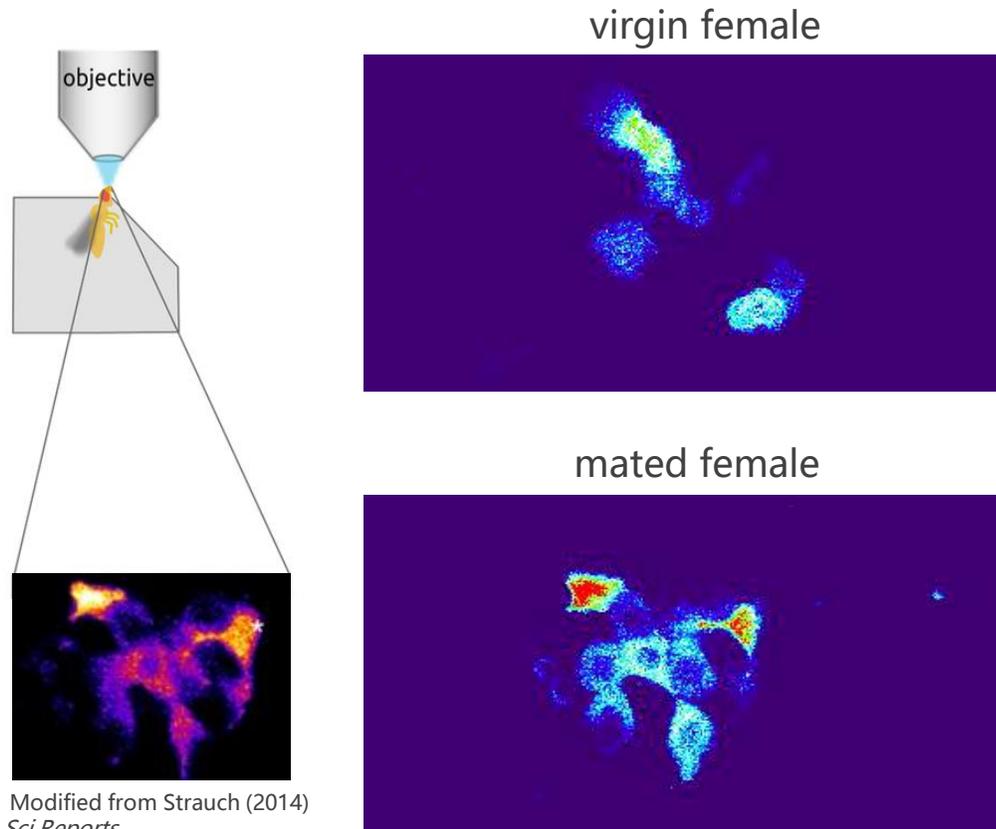


- In males, **testes “talk to” adjacent gut region** and changes gut handling of carbohydrates
- **“Masculinised” enterocytes secrete a metabolite (citrate)**, which is taken up by male gonad and **used for spermatogenesis**

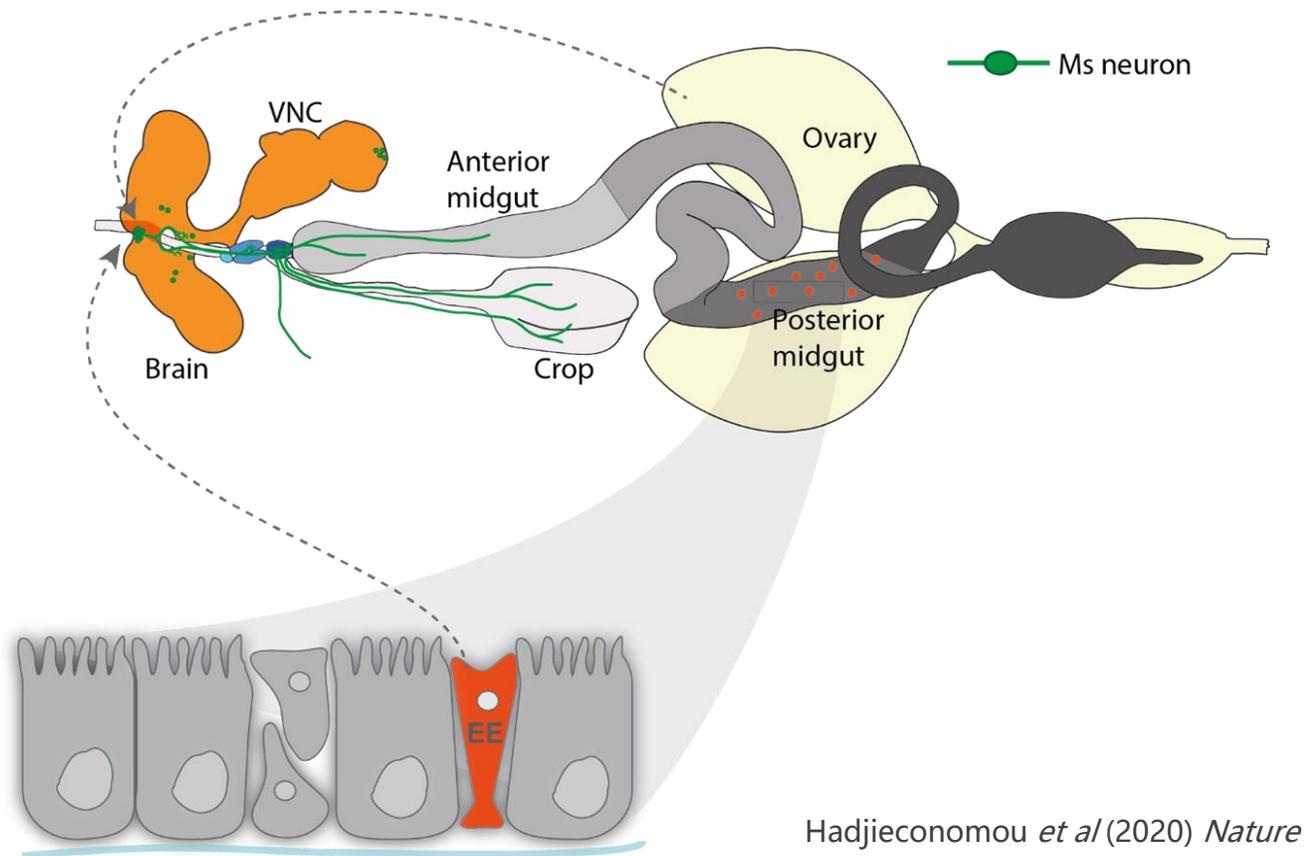


3. The sex (and reproductive status) of enteric neurons

- In females gut neurons become **more active** during reproduction
- They do so in response to reproductive changes in **circulating hormones**



Modified from Strauch (2014)
Sci Reports



Hadjieconomou *et al* (2020) *Nature*

- The neurons' activity change **mediates the maternal increase in food intake** during reproduction

Just good for flies?

Genetic and anatomical sex differences in mouse and human guts



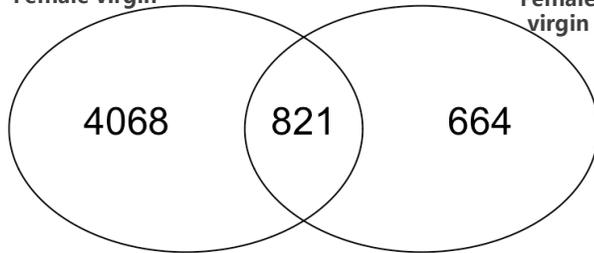
Differential gene expression:
sex and reproductive state



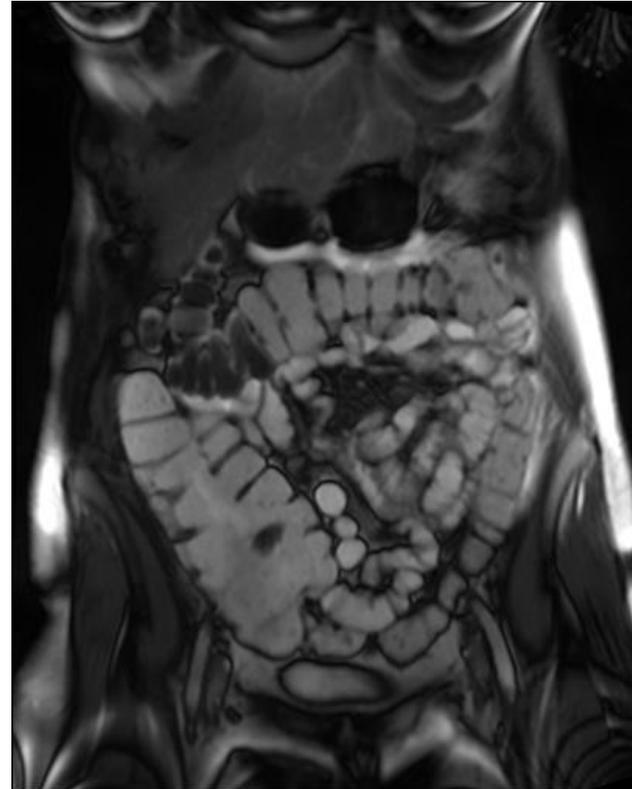
Exploring sex differences in anatomy and function in health and
gastrointestinal disease

Female lactating
vs
Female virgin

Male virgin
vs
Female virgin



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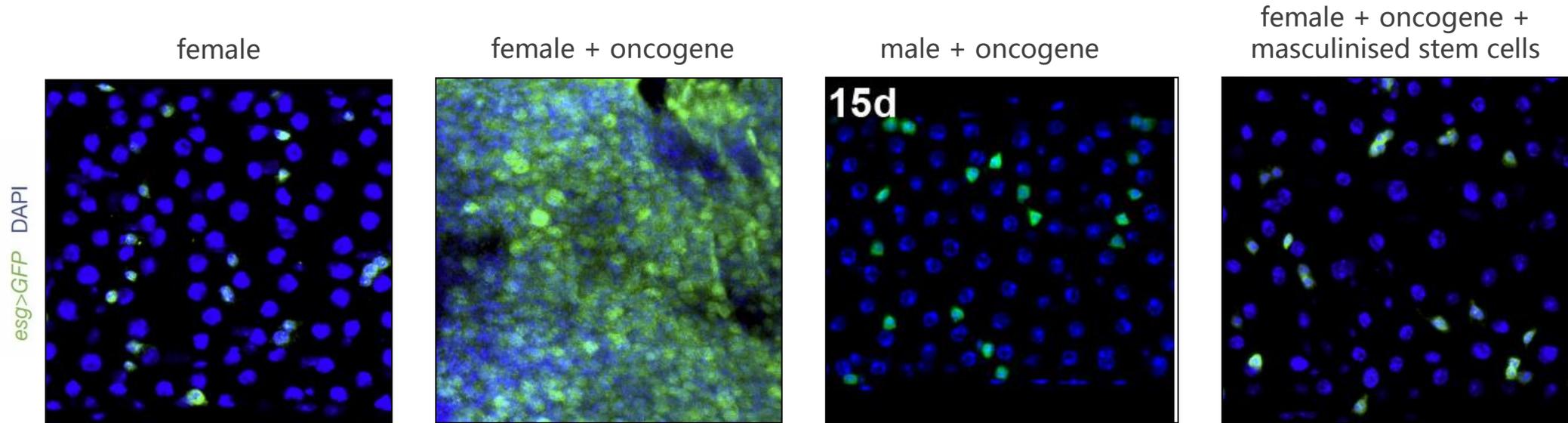
The bigger picture: trade-offs

- A “**better**” gut?

The female gut is more adaptable...is it always more adaptable? PROBABLY NOT
is it better than the male gut?! NO!

- **Trade-offs**

Higher stem cell proliferation renders female gut more vulnerable to tumorigenic insults



The sex of organs and why it matters



- Many (most?) features of how our organs work and decline are, at some level, different between the sexes
- Organs “know their sex” in different way (e.g. intrinsically through their own genes, but also because of the hormones they “listen” to)
- It is important to both describe and mechanistically understand these sex differences: they may be predictive of both disease susceptibility and responses to treatment

Thank you!

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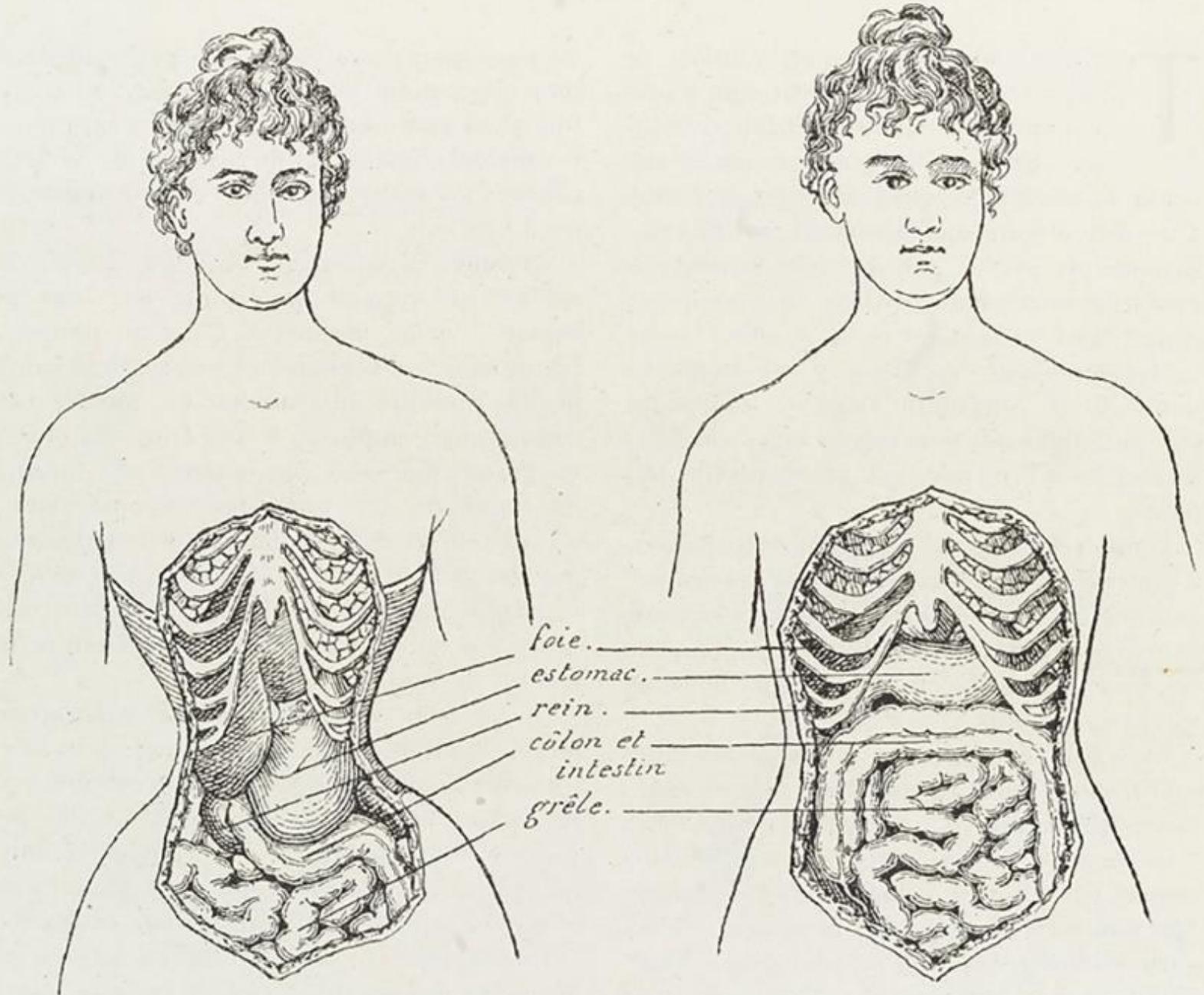


Fig. A.

Fig. B.

Les crimes du corset.