

Do sit near the
front

Zombie Ants & Fearless Mice

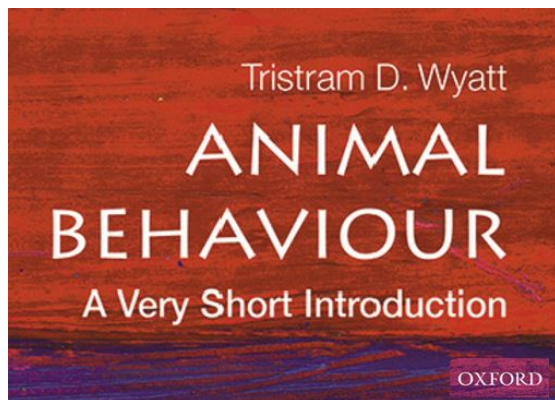
Parasites and the Brain

Tristram Wyatt

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Biosciences, University College London

Researching book on animal behaviour

- Some of most exciting stories were parasite manipulations
- Could also give some insights into how animal behaviour is controlled – taking us into the ‘black box’



Wyatt TD (2017) *Animal Behaviour: A Very Short Introduction*. OUP

Parasites in fiction

From Wikipedia, the free encyclopedia



WIKIPEDIA
The Free Encyclopedia

[Parasites](#) appear frequently in [biology-inspired fiction](#) from ancient times onwards, with a flowering in the nineteenth century.^[1] These include intentionally disgusting^[2] alien monsters in [science fiction](#)

~ 50% of world's species are parasites

including viruses, bacteria, fungi, protozoans, insects, worms (lots), crustaceans, fish, plants ...

- But ~ all species have parasites so ...
- parasites in turn have their own parasites: hyper-parasites
- even they have parasites: hyper-hyper-parasites

Charles Darwin,

in a letter to Professor Asa Gray, 22 May 1860.

‘I cannot persuade myself that a
beneficent & omnipotent God would have
designedly created the Ichneumonidæ
[parasitic wasps] with the express
intention of their [larvae] feeding within
the living bodies of caterpillars, or that a
cat should play with mice.’

Ichneumonid wasp bodyguard

Cotesia glomerata and cabbage butterfly caterpillar *Pieris brassicae*



Caterpillar is guarding against hyper-parasitic wasp which parasitizes the first wasp's cocoons



Does protection work?
yes, hyper-parasitism reduced
by 50% if caterpillar 'guarding'


Tempting wriggling morsels

1830s German polymath recognized
something strange

Worm broodsac sporocyte pulsates in light,
normally shade-loving snail climbs high onto
sunny leaf ...

Do *Leucochloridium* sporocysts manipulate the
behaviour of their snail hosts? **Yes, + active**

Wesołowska, W & Wesołowski, T (2014) *J Zoology* 292: 151-155.



Do birds peck? yes, 19C
experiments with tame birds.
No field observations

Spontaneous generation?

Complex life cycles, multiple hosts: Very hard to decipher

- Snail-sheep-snail (liver fluke, *Fasciola hepatica*) first trematode life cycle, only worked out in 1881; tho' worm itself recognized 1379)

Human-mosquito-human (malaria, Ross, 1897)

Wasp-caterpillar-wasp

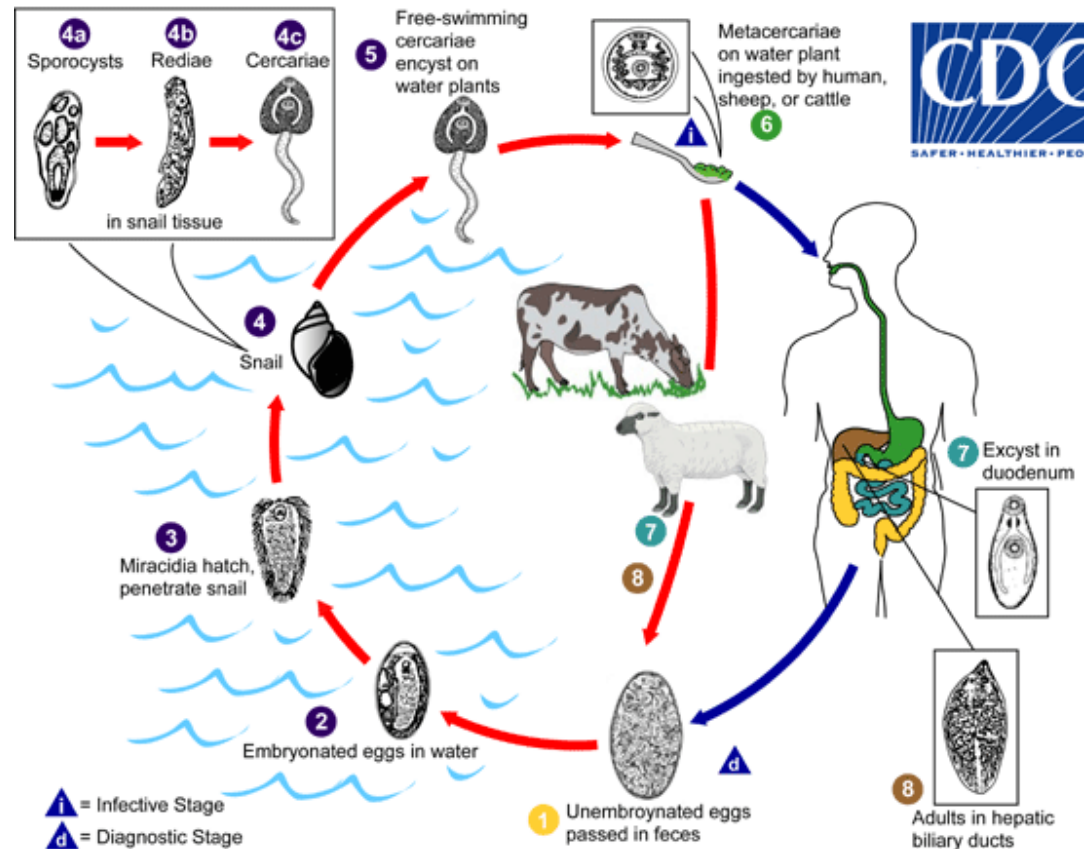
Snail-bird-snail

Snail-frog-bird-snail

Big_fish-clam-little_fish-big_fish

Ant-bird-ant

Ant-ant



**It's all about getting into the
next host**

Parasites *can* manipulate behaviour of their hosts

- ‘puppet-masters’
- ‘evolutionary neuroscientists’
- ‘evolution’s neurobiologists’
- ‘neuroparasitology’

But questions

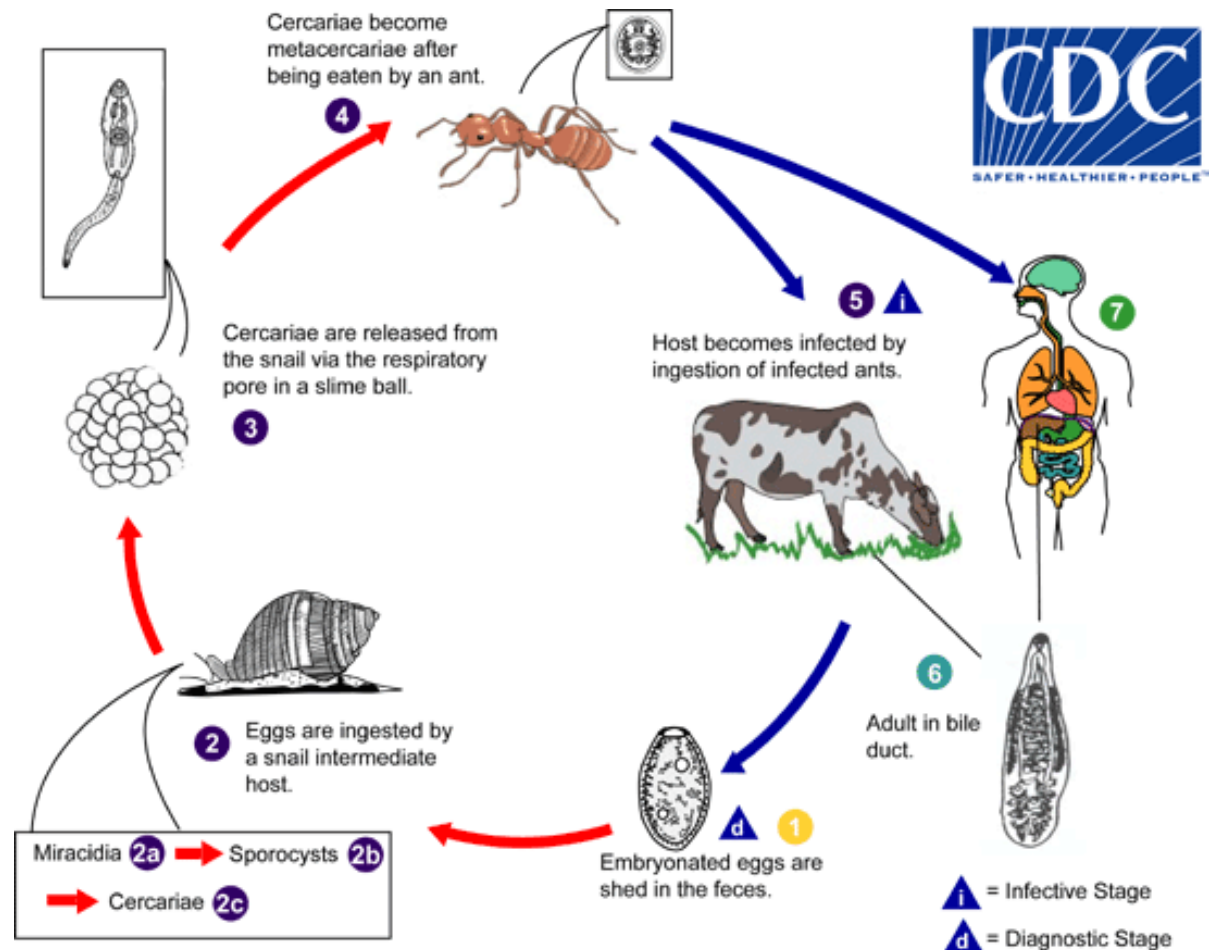
- Does it *really* increase transmission?
- *How* does it work? Mechanisms?

trematode worm *Dicrocoelium dendriticum*, the lanceolate fluke.

Fluke rests on
brain of ant

Evening, ant leaves
colony, climbs up
grass, bites stem at
top.

If not eaten by cow
by next morning,
climbs down and
rejoins colony,
repeat!



Cherry red ant 'berries'

(extended phenotype of parasitic nematode)
behaviour, structure & appearance



Uninfected turtle ant



Infected with nematode

(Photos: Stephen Yanoviak)

Hughes et al (2008) Extended phenotype: Nematodes turn ants into bird-dispersed fruits. *Current Biology* 18: R294-R295.

Next stage needed in water:

Diving, drowning crickets and ants



Parasite takes control of behaviour
remotely from its position in body cavity
– not near brain

Zombie ants - fungus

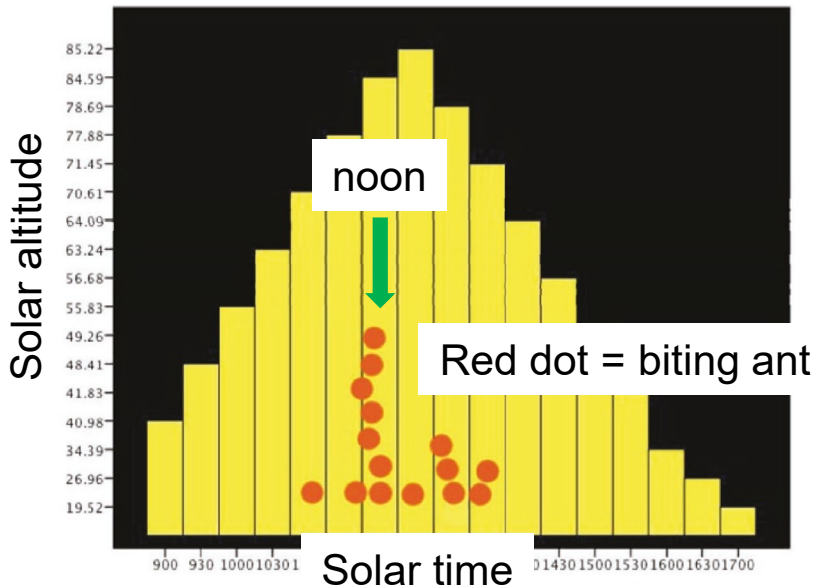
- Fungus: *Ophiocordyceps unilateralis*
- Carpenter ants *Camponotus* spp
- Noted in 1859 by Alfred Russel Wallace

'While the manipulated individual may look like an ant, it represents a fungal genome expressing fungal behavior through the body of an ant'

David Hughes (Penn State Uni)

Zombies at high noon

- ‘Normal ants’, high in canopy, late morning leave colony, turn into zombies, random walk,
- staggering like horror film ‘mummies’, repeated convulsions that make them fall down,
- ~25 cm from ground, walk to leaf, underside,
- at noon, face north-west, bite mid-rib, death-grip



Hughes et al (2011) Behavioral mechanisms and morphological symptoms of zombie ants dying from fungal infection. *BMC Ecology* 11: 13.

Death-grip by infected ant



Perfect humid location for development of fruiting body – snow of fungal spores onto ant trail below. Death grip holds ant there



Photo: David P. Hughes



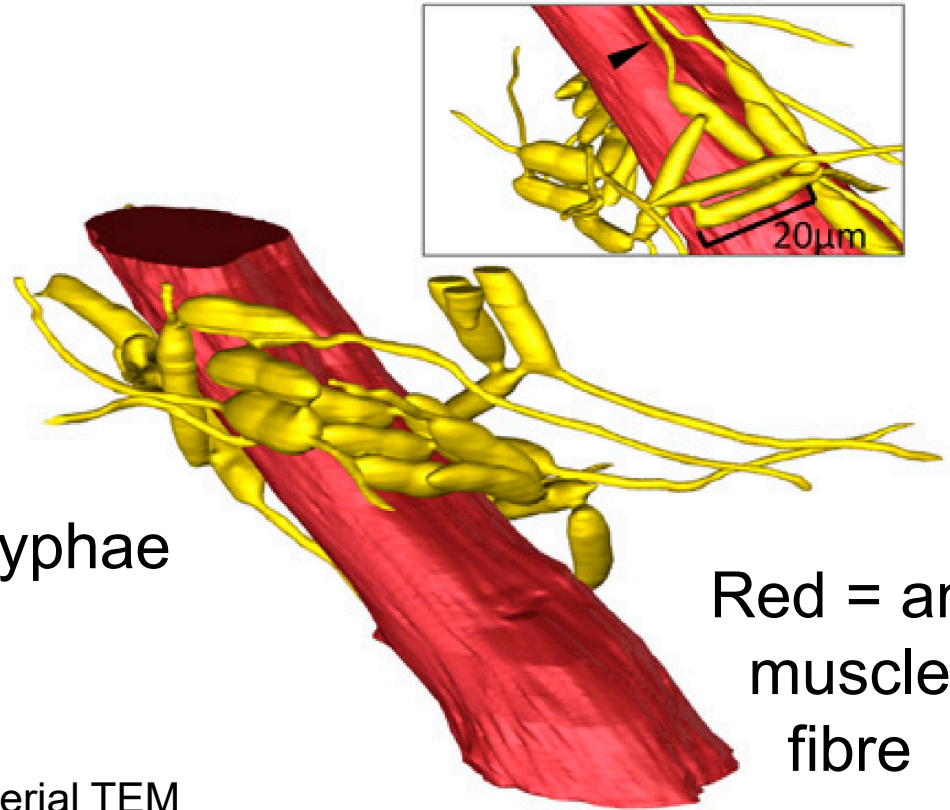
But – fungus fills body, into muscles, ~none in brain

Half weight of ant is fungus, wrapped around and through its muscle fibres.

yellow = fungal hyphae

Red = ant muscle fibre

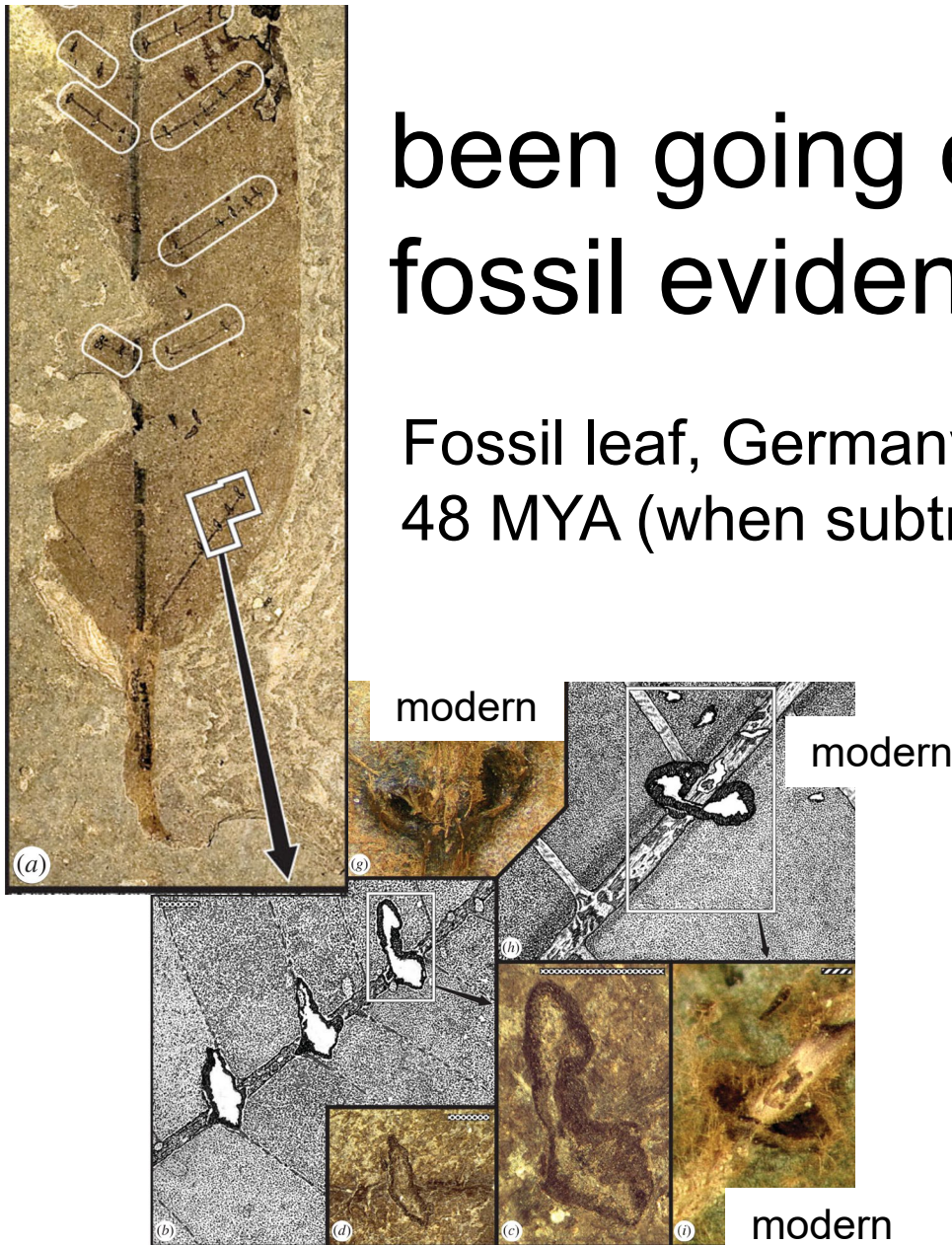
3D reconstruction from serial TEM



Fredericksen, et al (2017) Three-dimensional visualization and a deep-learning model reveal complex fungal parasite networks in behaviorally manipulated ants. *PNAS* 114: 12590-12595.

been going on a long time: fossil evidence of death-grips

Fossil leaf, Germany,
48 MYA (when subtropical)



Hughes et al (2011) Ancient death-grip leaf scars reveal ant-fungal parasitism. *Biological Letters* 7: 67-70.

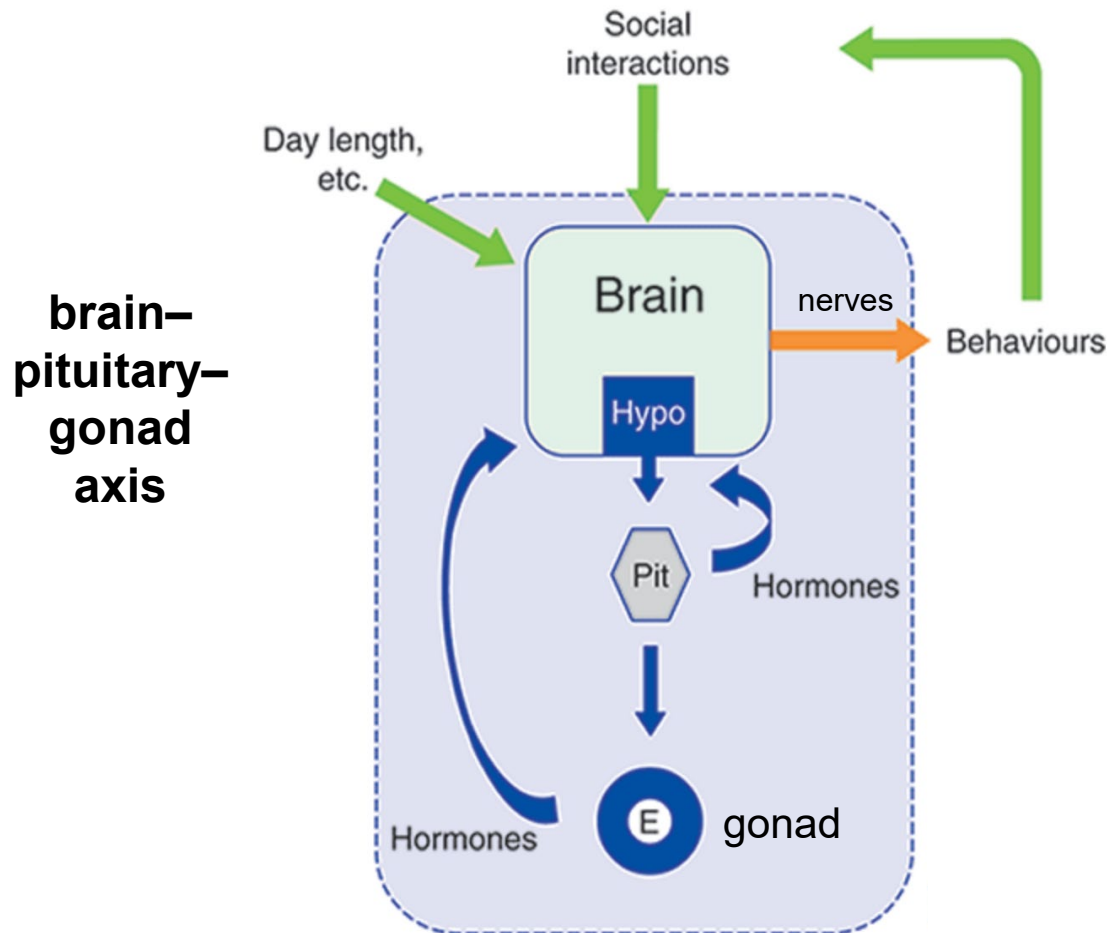
Hyperparasite – another fungus



Photo: David P. Hughes

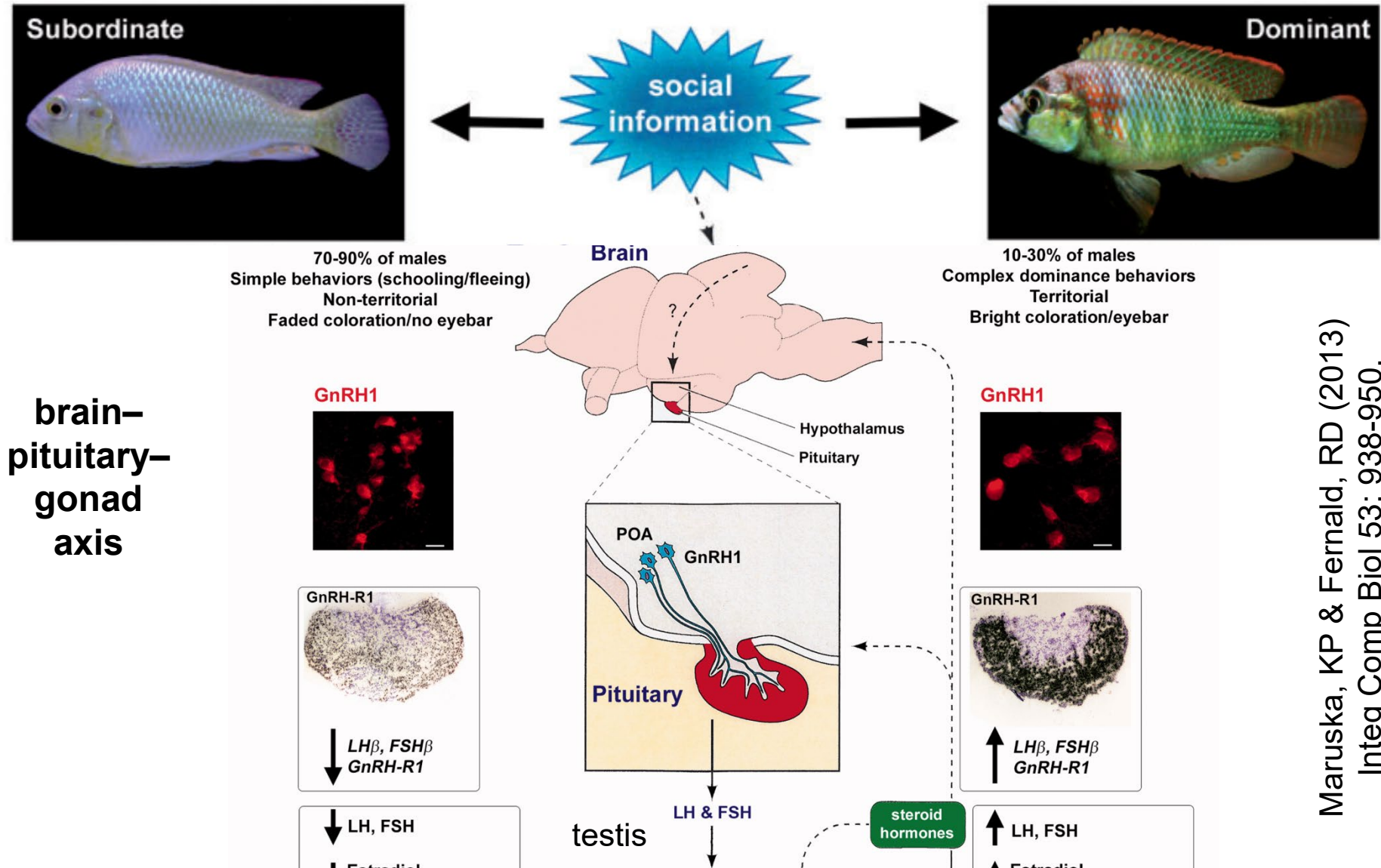
Mechanisms of mind control by parasites – ‘look, no hands’

Behaviour is not just nerves



Hormones switch
genes on and off
(epigenetic effects)

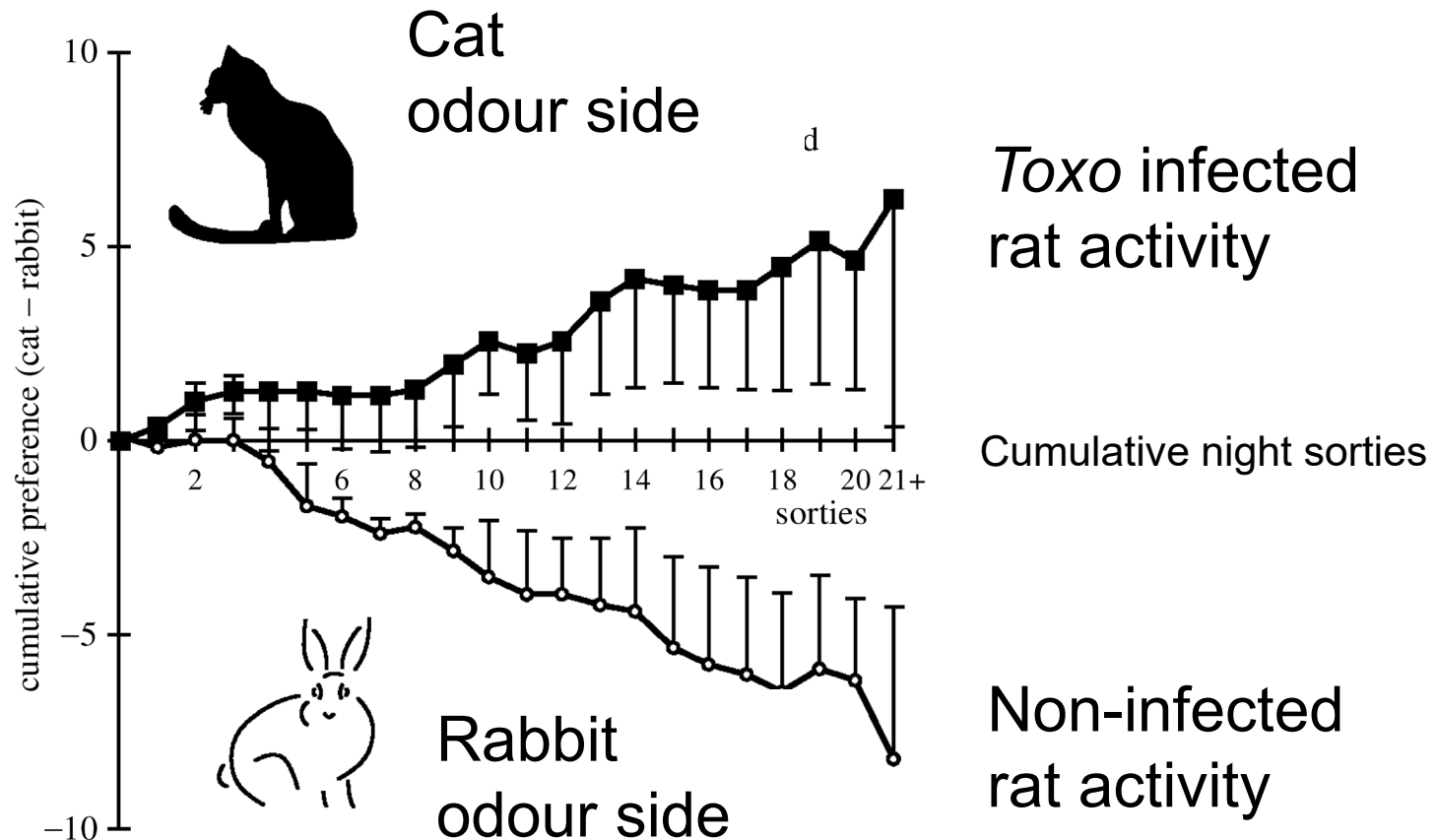
Social status – wide hormonal and epigenetic change: cichlid fish males



Parasites can manipulate all
these hormonal circuits

Fearless mice (and rats)

Berdoy, Manuel, Webster, Joanne & Macdonald, David W (2000) Fatal attraction in rats infected with *Toxoplasma gondii*. *Proc RS B* 267: 1591-1594.



Toxoplasmosis



Photo: Wendy Ingram/Adrienne Greene

Some infected mice and rats show 'fatal attraction'

Kochanowsky & Koshy (2018) *Toxoplasma gondii*. *Current Biology* 28: R770-R771.

Toxoplasma lifecycle

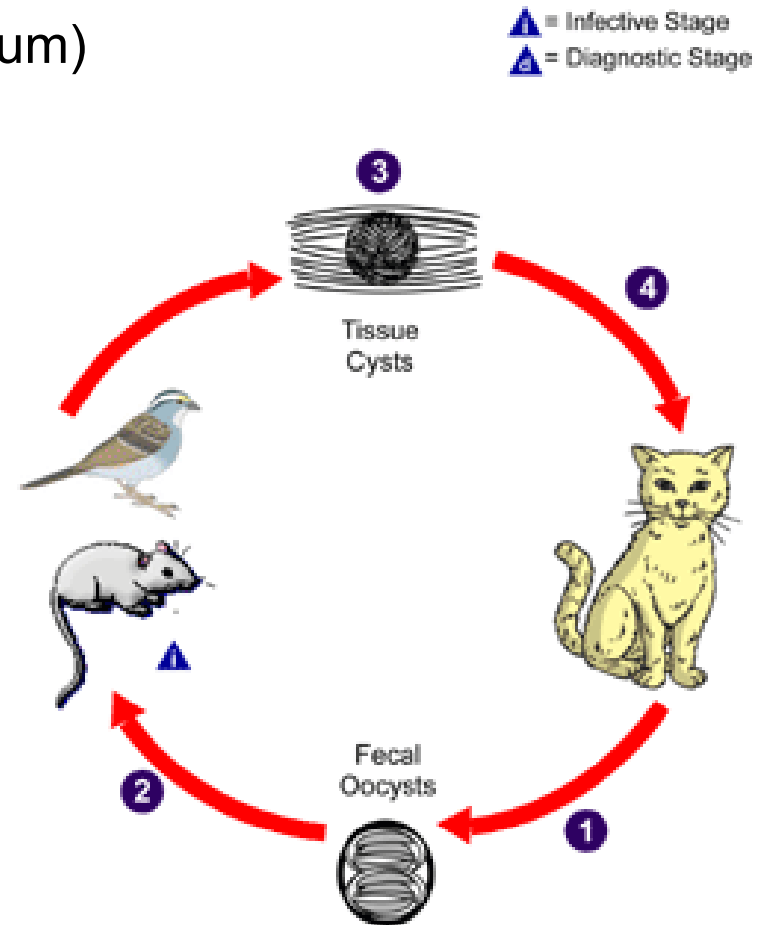
Obligate intracellular protozoan parasite
(same family as malaria and Cryptosporidium)

Sexually reproduces in cat's gut

Removes fear response to cat odour
(but other predator odours still give fear)

Sexually transmitted in rats, makes
male rats more attractive to females

Cysts in brain – especially in nerves



Vyas, A (2015) Mechanisms of host behavioral change in
Toxoplasma gondii rodent association. *PLoS Pathog* 11:
Kochanowsky & Koshy (2018) *Toxoplasma gondii*.
Current Biology 28: R770-R771.

www.cdc.gov/parasites/toxoplasmosis/biology.html

Toxoplasma's effects?

Mechanisms for no cat fear?

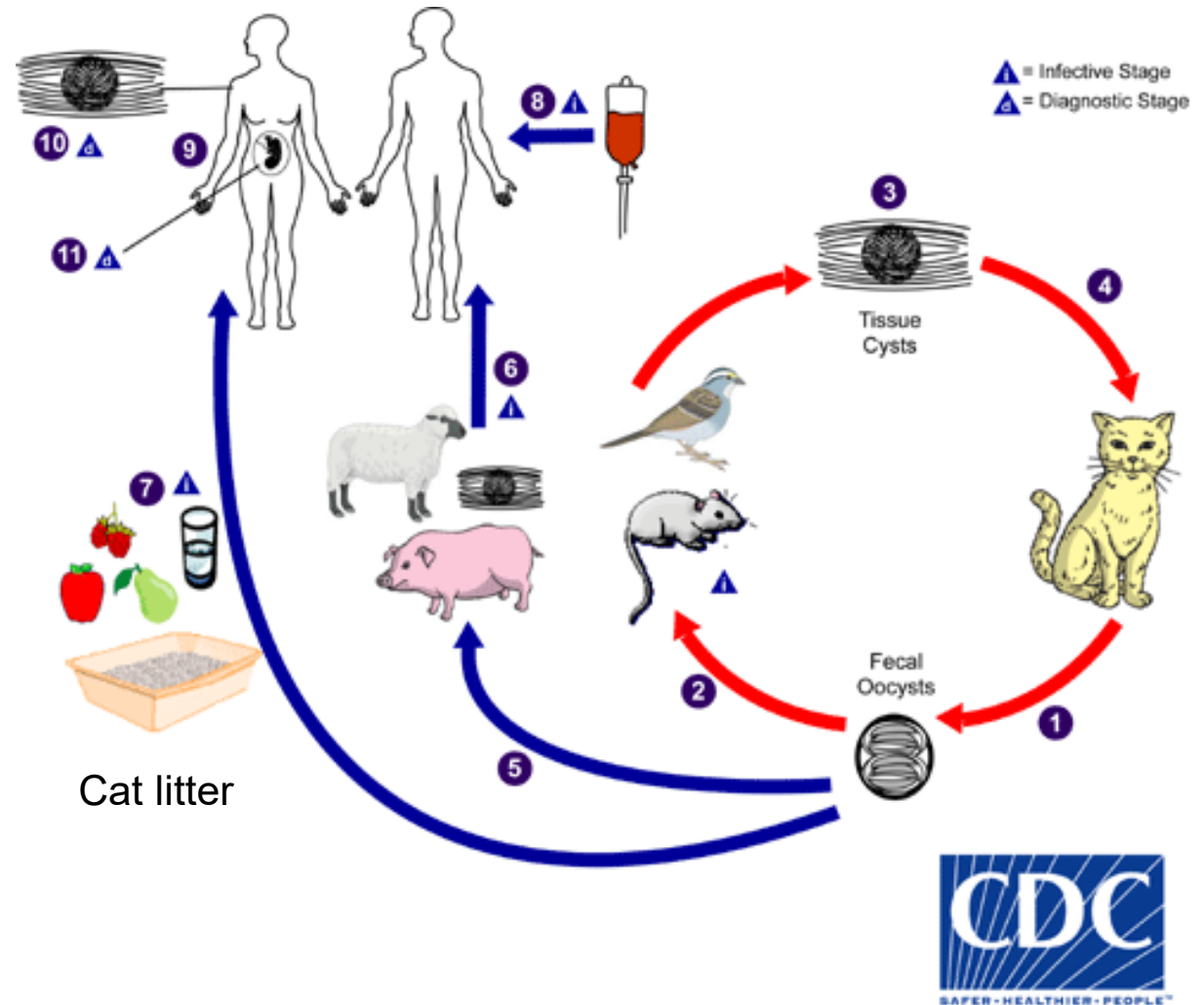
- **Cysts in specific regions of brain**
(local manipulation/damage of neurons?)
- **Disruption of dopamine signalling in brain**
- **Hormonal upheavals and concomitant epigenetic changes**

Vyas, A (2015) Mechanisms of host behavioral change in *Toxoplasma gondii* rodent association. *PLoS Pathog* 11: e1004935.

Open verdict on mechanism

Toxoplasma lifecycle in humans

Human latent infection
~15 - 90%
depending on
country &
population



Does *Toxo* affect human behaviour?

E.g.

- Flegr, et al (2009) Increased incidence of traffic accidents in *Toxoplasma*-infected military drivers and protective effect RhD molecule revealed by a large-scale prospective cohort study. *BMC Infect Dis* 9: 72.
- Flegr, J (2013) How and why *Toxoplasma* makes us crazy. *Trends in Parasitology* 29: 156-163.
- Johnson et al (2018) Risky business: linking *T gondii* infection and entrepreneurship behaviours across individuals and countries. *Proc RS B* 285.

Verdict: not proven. Effects small, inconsistent

But does *Toxo really* adaptively manipulate rodent hosts?

Worth et al (2013) Adaptive host manipulation by *Toxoplasma gondii*: fact or fiction? *Trends in Parasitology* 29: 150-155.

- Inconsistencies in experimental results,
- no evidence that it does increase predation,
- no evidence that sexual stage is essential

Mechanisms of mind control by parasites – ‘look, no hands’

- Psychoneuroimmunological [cytokines]
- neuropharmacological [use drugs]
- genomic- and proteomic-based [epigenetic: activate/shutdown or add/delete genes]

Understanding neural circuits

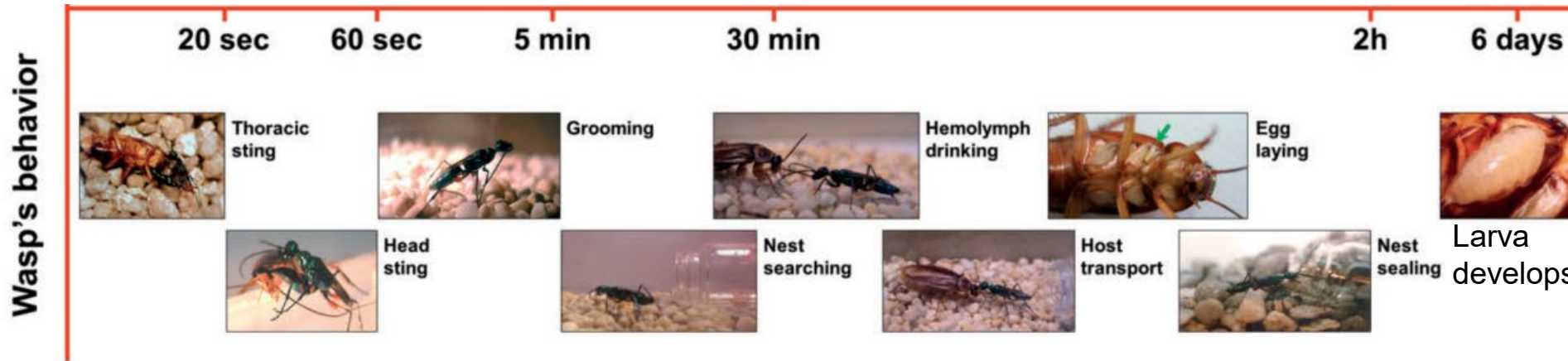
- **Parasitoid insects can take over nervous system**
- **Inject neurotoxins to precise locations**

The wasp always stings twice

Jewel wasp and American cockroach



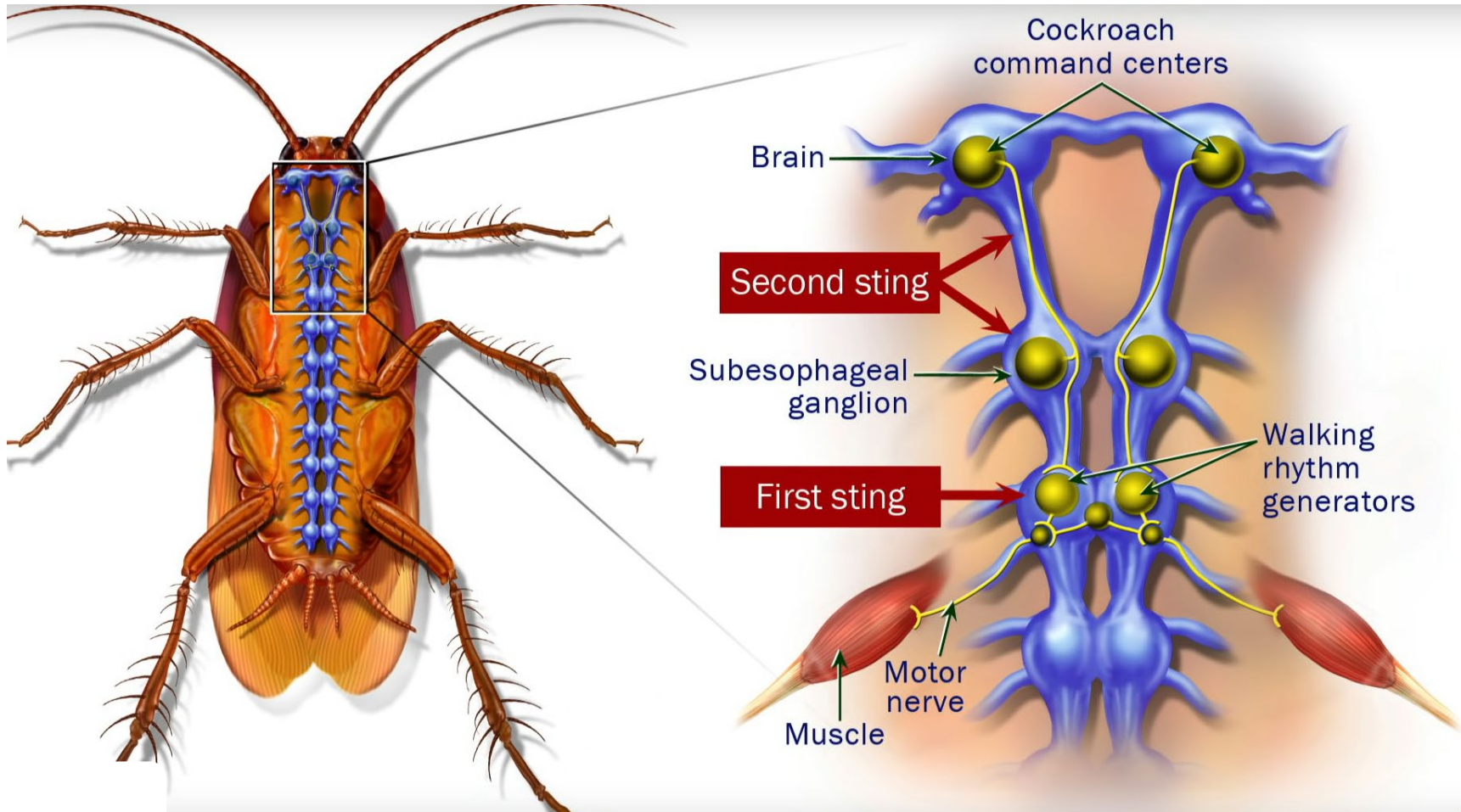
Photo: Fred Libersat



Libersat & Gal (2014) Wasp voodoo rituals, venom-cocktails, and the zombification of cockroach hosts. *Integ Comp Biol* 54: 129-142.

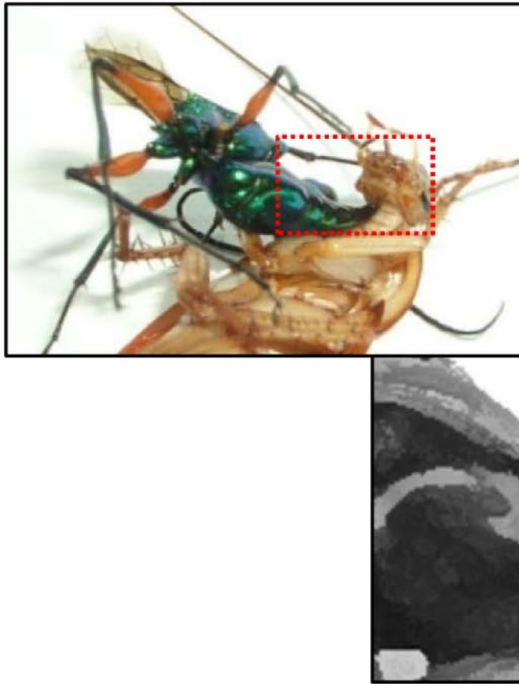
40 days,
adult
emerges

Injectons x 2

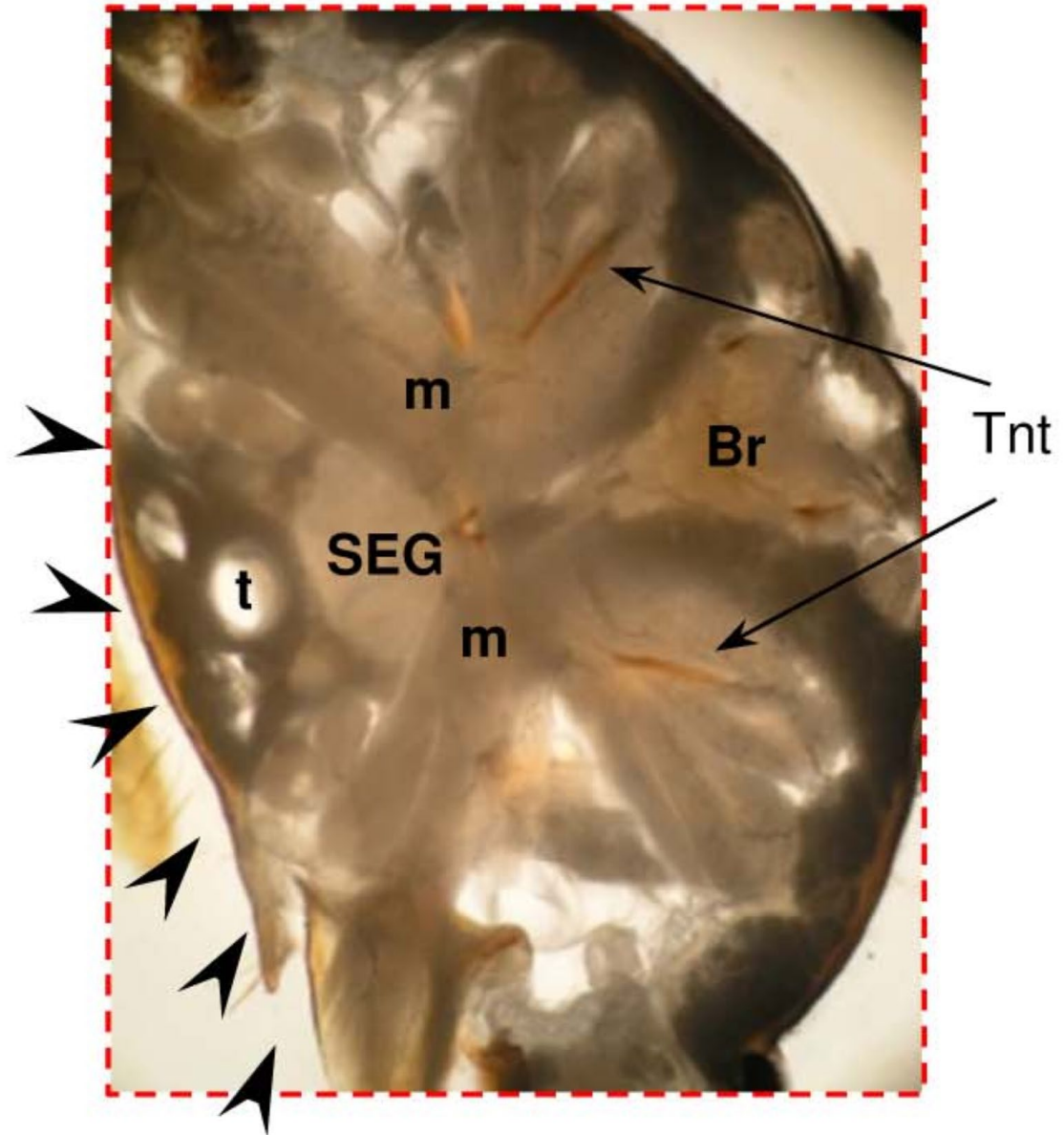


Stereotact

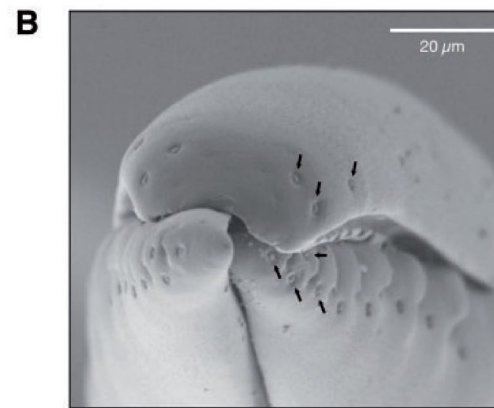
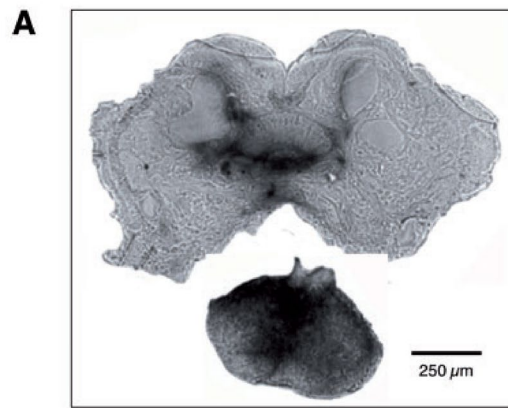
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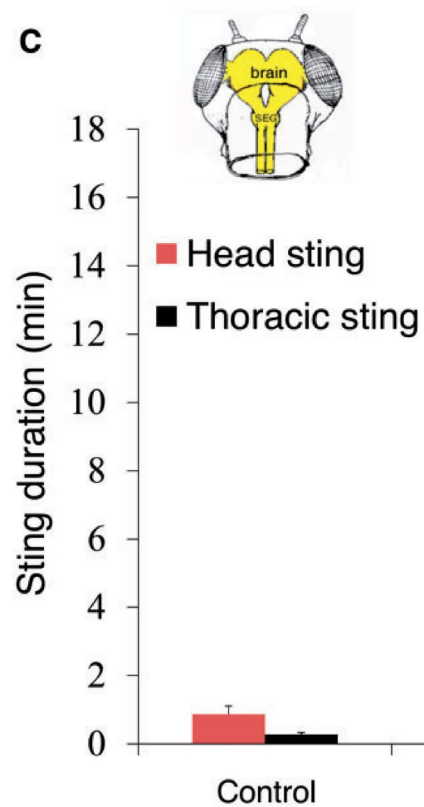
Gal, et al
jewel wa



Radioactive
venom shows
location of
sting delivery



SEM of tip of
sting showing
sensory hairs -
arrows



Do quiescence and wasp venom-induced lethargy share common neuronal mechanisms in cockroaches?



White spot =
head stung

Potential drug leads ...

Head sting venom: > 250 proteins, including newly found ampulexins and precursors which are only activated once injected, hijacking control of the host's brain by introducing a 'storm' of the host's own neurochemicals.

Long term interest – Parkinson's disease

Arvidson et al, (2019) Parasitoid jewel wasp mounts multipronged neurochemical attack to hijack a host brain. *Molecular & Cellular Proteomics* 18: 99.

Moore et al (2018) Ampulexins: A New Family of Peptides in Venom of the Emerald Jewel Wasp, *Ampulex compressa*. *Biochemistry*.

Cockroaches fight back



Catania, KC (2018) How not to be turned into a zombie. *Brain Behavior and Evolution* 92: 32-46.

Parasites *can* manipulate behaviour of their hosts

- ‘puppet-masters’
- ‘evolutionary neuroscientists’
- ‘evolution’s neurobiologists’
- ‘neuroparasitology’

But still many questions

- Does it *really* increase transmission?
- *How* does it work? Mechanisms?

Herbison, R, Lagrue, C & Poulin, R (2018) The missing link in parasite manipulation of host behaviour. *Parasit Vectors* 11: 222.

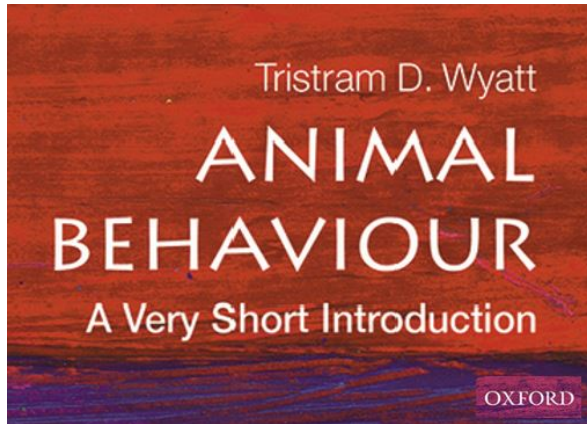
Adamo, SA (2013) Parasites: evolution’s neurobiologists. *J Experimental Biology* 216: 3-10.

Further reading – see online

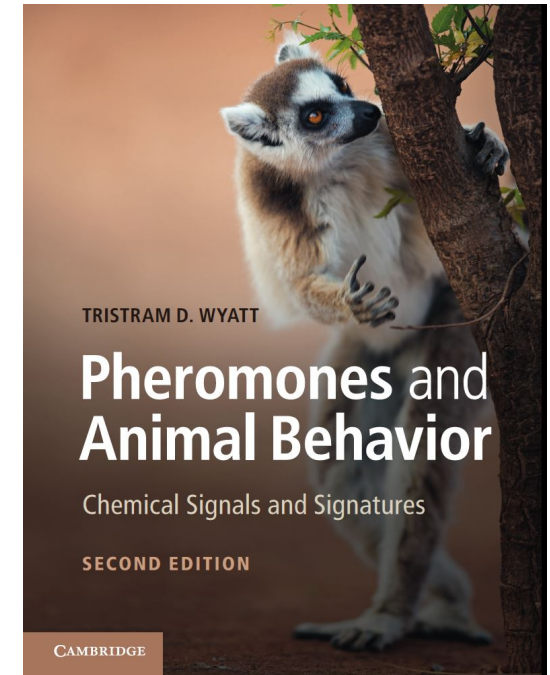
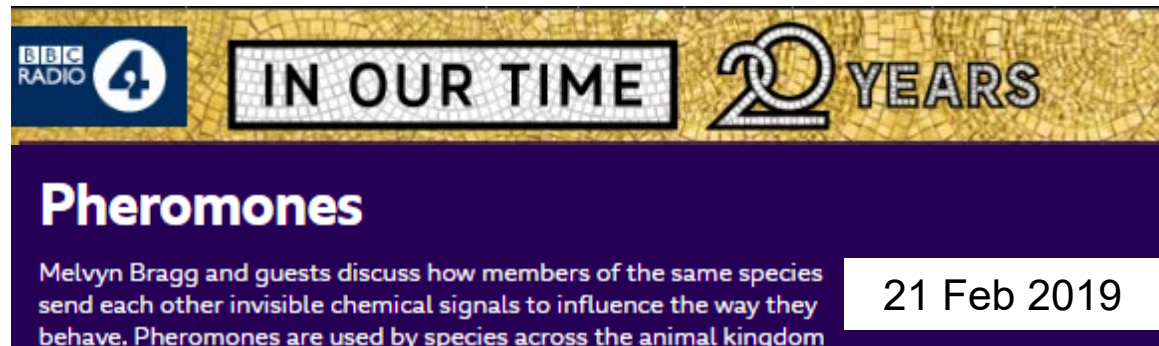
- Popular science books
 - Simon, M (2018) *Plight of the Living Dead: What real-life zombies reveal about our world--and ourselves*. Penguin.
 - Wyatt, TD (2017) *Animal behaviour: A very short introduction*. OUP
 - Zimmer, C (2003) *Parasite Rex: Inside the bizarre world of nature's most dangerous creatures*. Arrow.
 - Zuk, M (2008) *Riddled with Life: Friendly worms, ladybug sex, and the parasites that make us who we are*. Houghton
- Science journalism on the web, many authors including:
 - Ed Yong e.g. (2017) How the zombie fungus takes over ...
www.theatlantic.com/science/archive/2017/11/how-the-zombie-fungus-takes-over-ants-bodies-to-control-their-minds/545864/
 - Carl Zimmer e.g. (2014) Mind suckers. www.nationalgeographic.com/magazine/2014/11/mindsuckers/
- Books and special collections of papers
 - Special issue of *Integrative and Comparative Biology*, Vol 54, Issue 2. Parasitic manipulation of host phenotype, or how to make a zombie. Free, available at www.academic.oup.com/icb/issue/54/2
 - Dawkins, R (1982) *The extended phenotype*. San Francisco, CA: WH Freeman.
 - Hughes, DP, Brodeur, J & Thomas, F (eds.) (2012) *Host manipulation by parasites*. Oxford: Oxford University Press.
 - Moore, J (2002) *Parasites and the behavior of animals*. New York: Oxford University Press.

Thanks for listening

@pheromoneEvo
@BehavingAnimals



(2017) OUP



Winner, Royal Society of Biology
Postgrad Textbook Award 2014

2 edn. fully updated & rewritten.