

2023 TSRI ARC Summer High School Mentorship Program:

Using animals to study the brain

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Use of laboratory animals in biomedical research

- Important contributions to medical progress
 - according to the American Medical Association, “Virtually every advance in medical science, from antibiotics and vaccines to antidepressant drugs and organ transplants, has been achieved either directly or indirectly through the use of animals in laboratory experiments.”
- Cause of heated public, scientific and philosophical discussion
- Animal welfare
 - ensure that research animals are treated as humanely as possible and are used only for important studies.



New concept: Animal Model

- A non-human species used in biomedical research because it can mimic aspects of a biological process or disease found in humans
- Animal models are sufficiently like humans in their anatomy, physiology or response to a pathogen that researchers can use the results of animal model studies to better understand human physiology and disease.
- By using animal models, researchers can perform experiments that would be impractical or ethically prohibited with humans.



MICE



RATS

History of the research rat

Notorious rat catcher, Jack Black



- Black plague (14th century)
- Rat catchers
- Rat baiting
- Breeding as pets for royalty
- First experiment: 1828 (effects of fasting on proteins)
- First supplier: Wistar Institute 1906

1909



1909

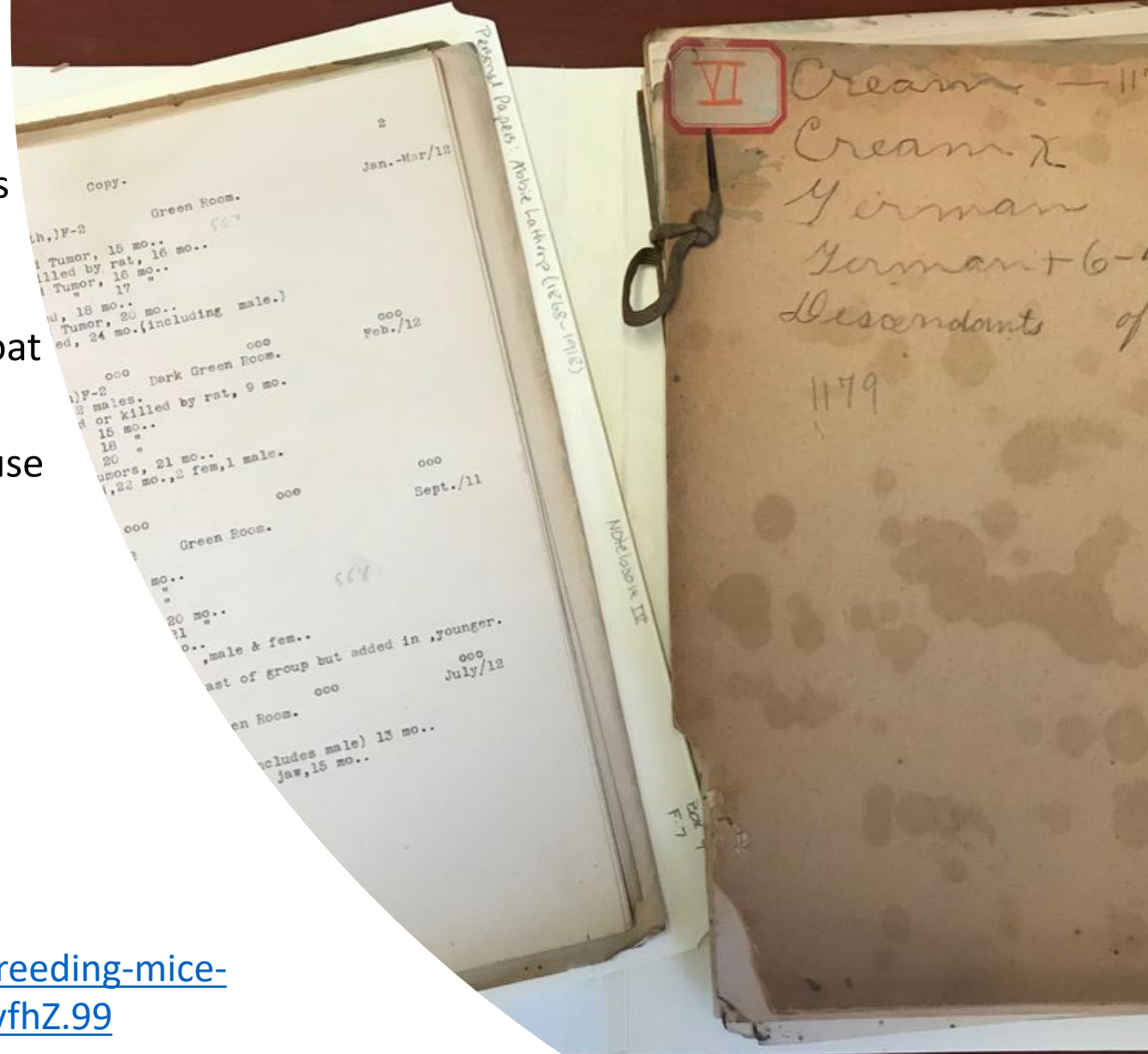
Helen Dean King

Helen Dean King, Ph.D., was The Wistar Institute's first female scientist and the first female research professor in the country. She worked at Wistar from 1909 until 1950 and bred the Wistar rat, which was the first standardized lab animal. Today, more than half of all laboratory rats trace their genealogy to the Wistar rat.

History of the research mouse

- The house mouse (*Mus musculus*) has followed humans across the globe and likely has one of the widest distributions of all mammals
- late 1800's-early 1900's: Fancy mice bred for unusual coat colors and behavioral patterns by hobbyists
- 1902: Abbie Lathrop helped establish the standard mouse model and pioneered research into cancer inheritance (sold mice to Harvard)
- 1929: Jackson Laboratory in Bar Harbor, Maine started and mouse strains became standardized

<https://www.smithsonianmag.com/science-nature/history-breeding-mice-science-leads-back-woman-barn-180968441/#4gh6ElcQTdJYvfZ.99>

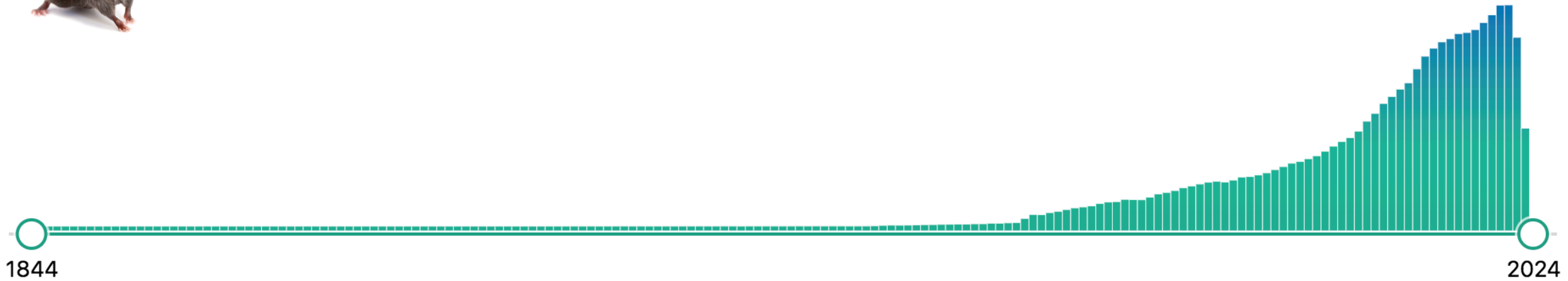


“Mouse” and “Rat” as a search terms in PubMed



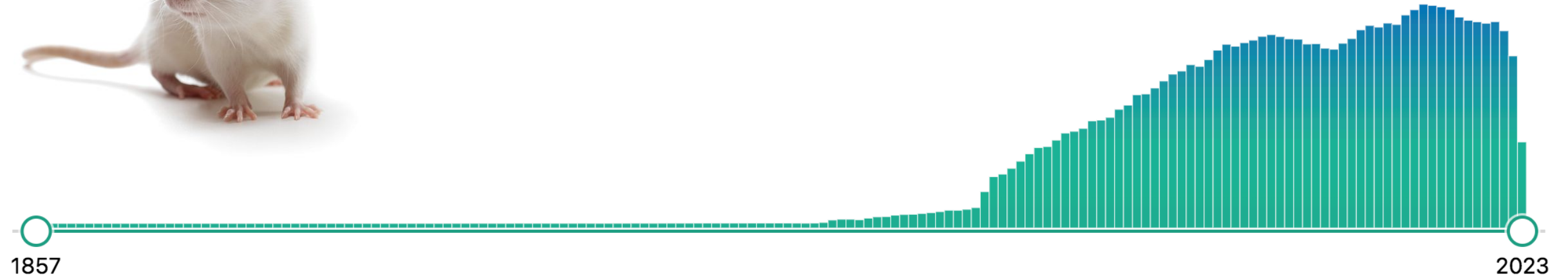
2,024,384 results

2021: 95,068 papers



1,857,418 results

2021: 39,986 papers



Animal welfare

- **Legislation**

- 1966: Animal Welfare Act
- 1985: Health Research Extension Act

- **Oversight**

- Office of Laboratory Animal Welfare (OLAW)
- Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC)
- Institutional Animal Care and Use Committees (IACUC)

“Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative.” U.S. Government Principle IV, 1985



National Institutes of Health
Office of Laboratory Animal Welfare



Scientists' responsibilities

The Three R's
Replacement
Reduction
Refinement

- Describing proposed use of animals in grant applications
- Obtaining approval of detailed protocol prior to using animals and prior to implementing significant changes
- Ensuring research is conducted according to this protocol
- Complying with institutional policies and procedures
- Addressing significant changes to the use of animals in progress reports

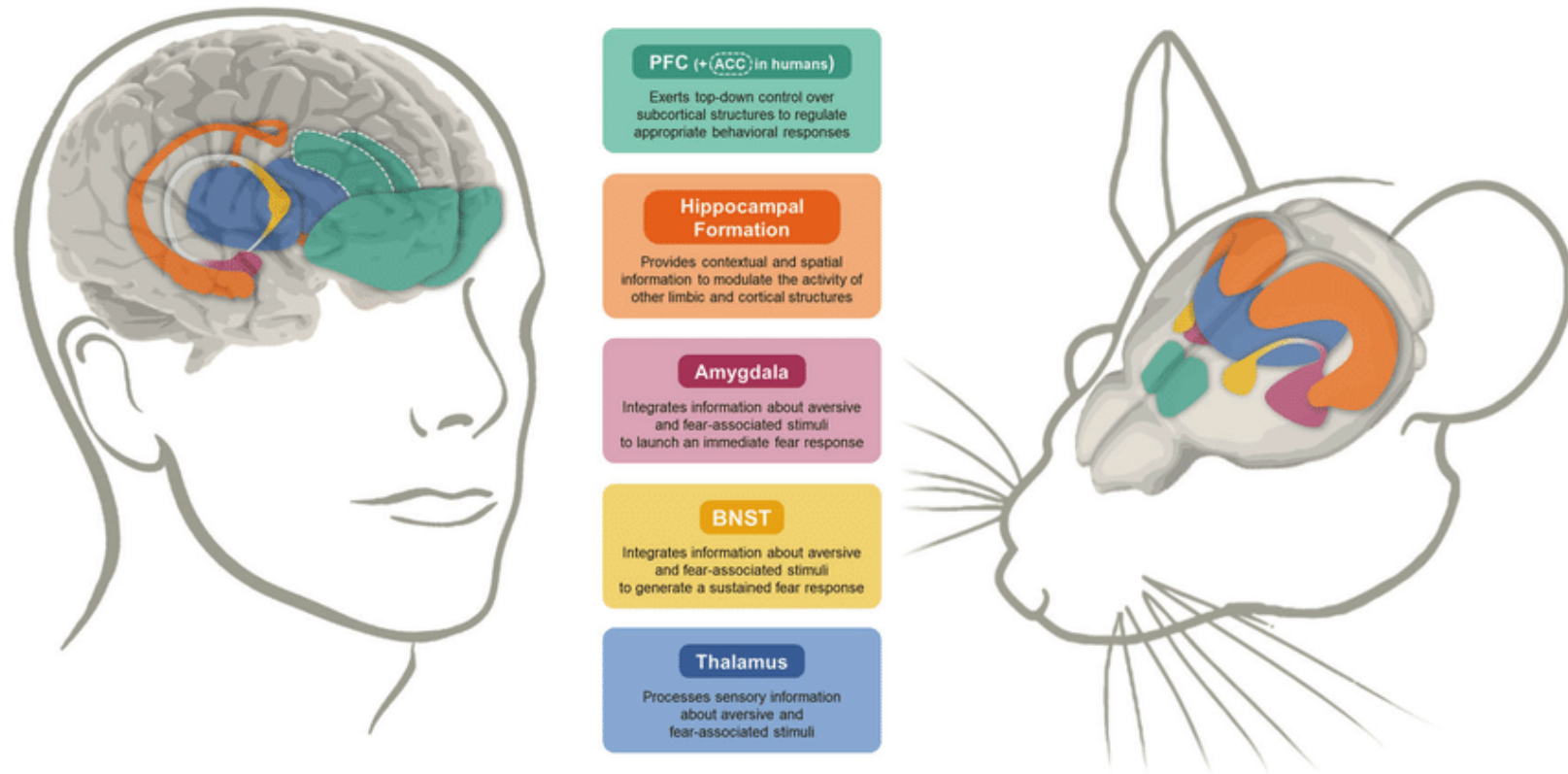


Rodent research: practical considerations

- Small
- Easy to transport
- Do well in laboratory settings
- Prolific breeders
- Short generation time
- Short life span – life cycle and disease progression ~2-3 yrs
- Social animals
- Control over genetic background
- Control over environment

Rodent research: biological considerations

- Similar to humans in anatomy, physiology, and genetics
- Will self-administer alcohol & drugs
- Reward circuitry similar
- Can manipulate
 - Genetics
 - Pharmacology
 - Circuitry



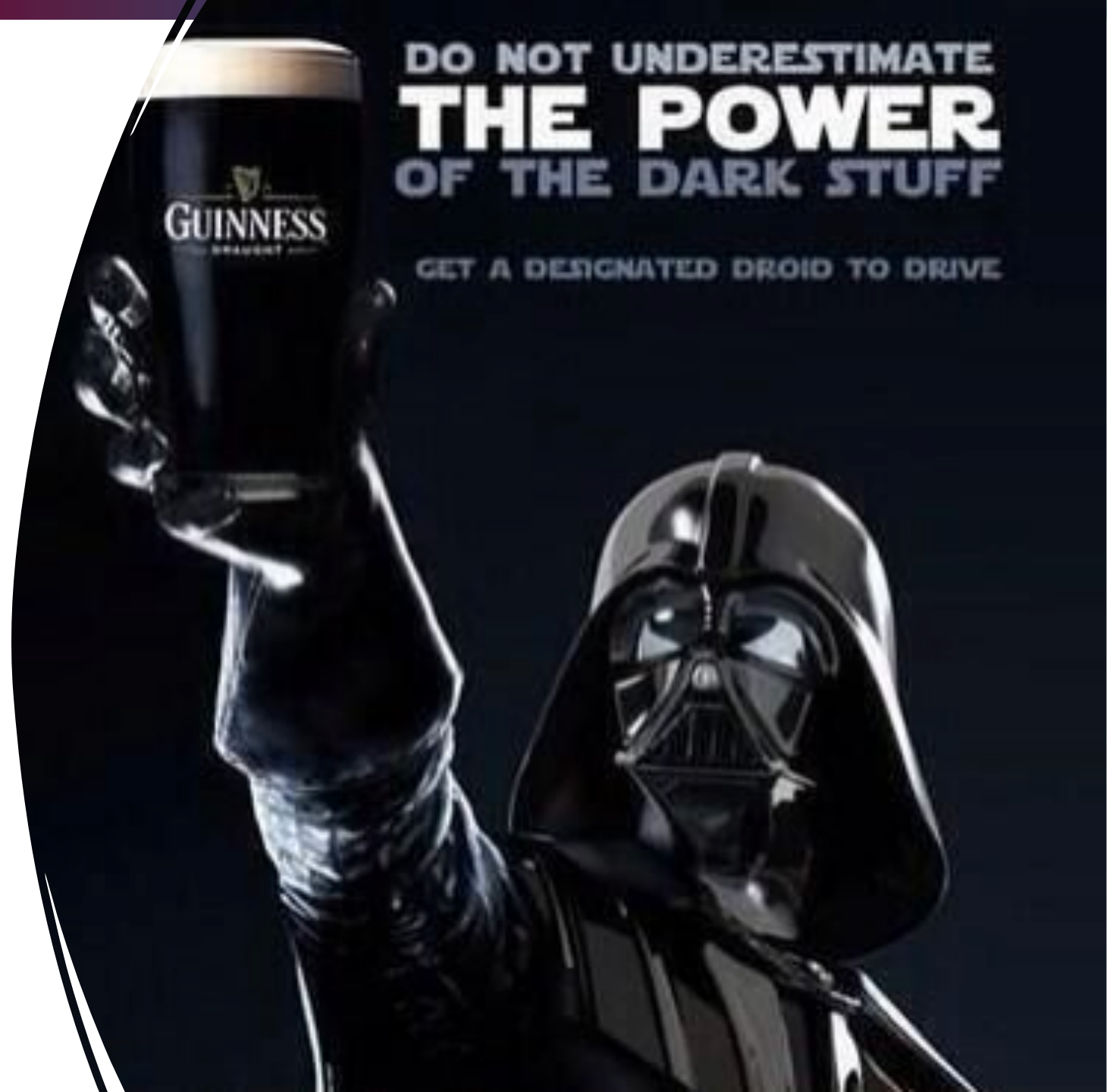


Experimental considerations

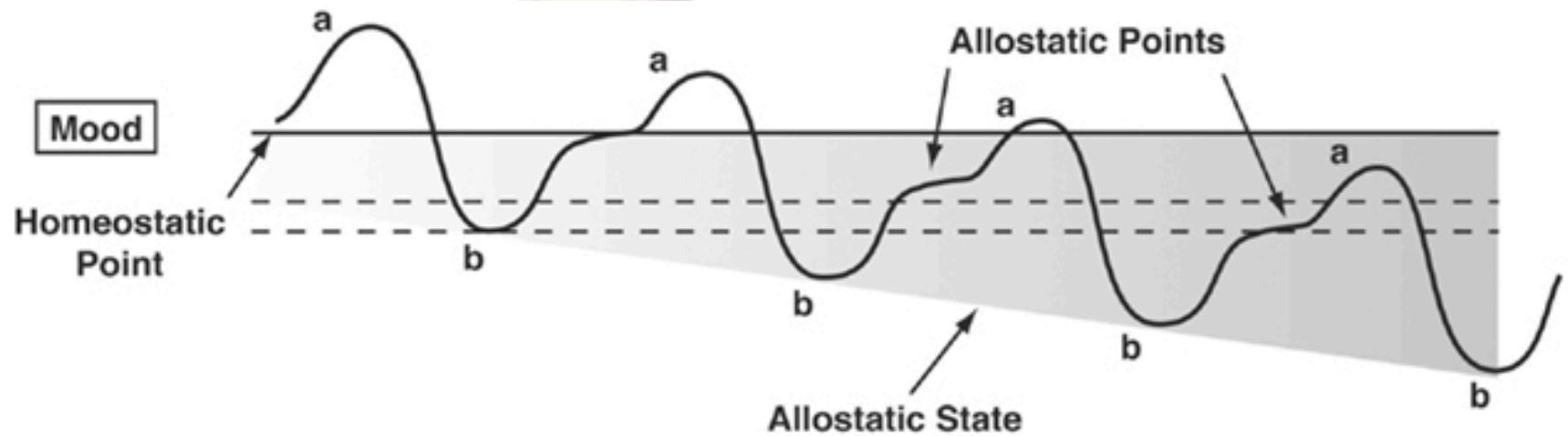
- Age
- Sex
- Group size
- Control groups
- Housing/environmental conditions
 - Light cycle
 - Temperature
 - Number per cage
 - Enrichment
 - Cage changing
 - Food and bedding
 - Microbial status of colony

The Scripps Research Institute's Alcohol Research Center (TSRI-ARC)

- Exploring the “**DARK SIDE**” of alcohol use disorder
 - The “**LIGHT SIDE**” – using alcohol to increase good feelings – euphoria, relaxation, taste
 - The “**DARK SIDE**” – using alcohol to decrease negative feelings – stress, anxiety, depressed mood, sleep problems



Addressing the dark side of alcohol use disorder (AUD)

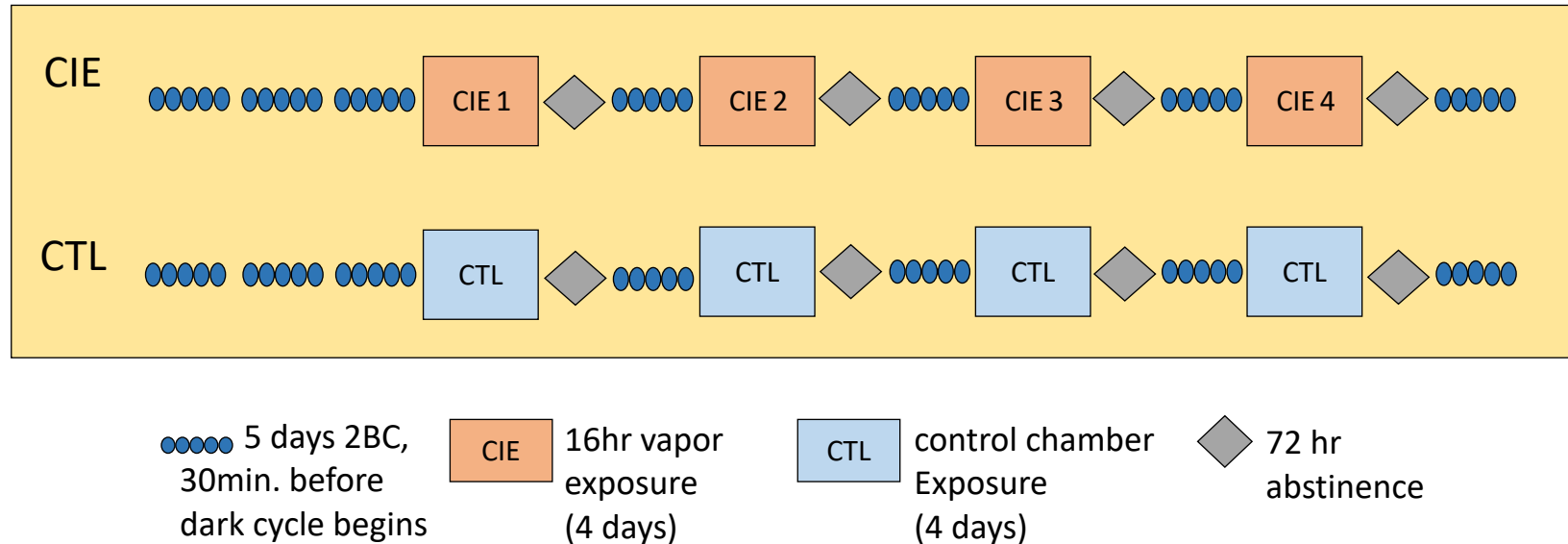


Animal Models of AUD

- Escalation in drinking
- Negative affect (anxiety, irritability) in abstinence
- Increased susceptibility to relapse (craving)



A mouse model of AUD



- 2BC = Two bottle choice. Mice get one bottle of water and one bottle of 15% alcohol (ethanol) for 2 hours Monday – Friday
- CIE = Chronic intermittent ethanol exposure in vapor chambers

The two bottle choice set-up

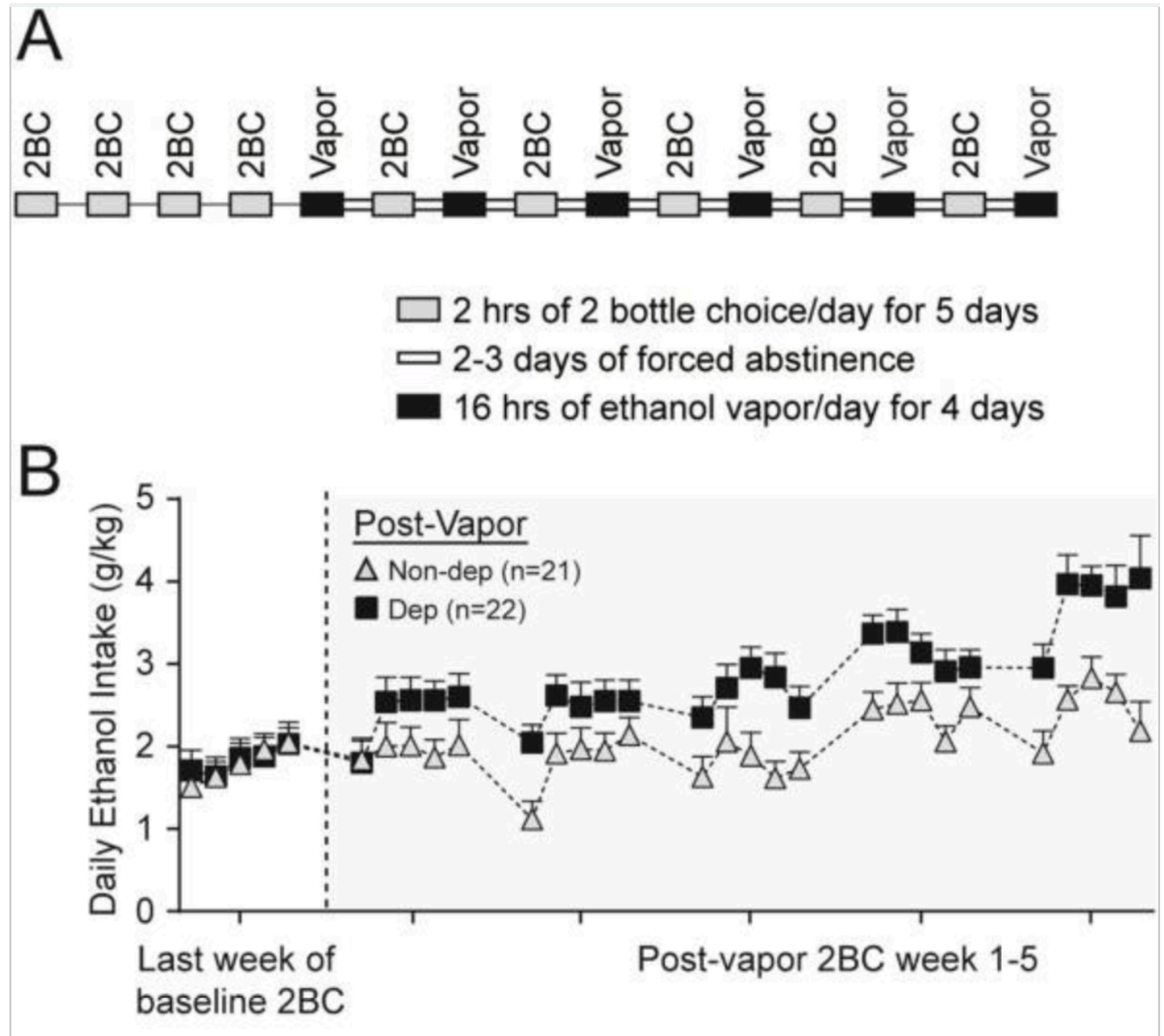


Alcohol vapor chambers: for chronic intermittent ethanol (CIE) exposure



Example data

Athanason AC, Nadav T, Cates-Gatto C, Roberts AJ, Roberto M, Varodayan FP. Chronic ethanol alters adrenergic receptor gene expression and produces cognitive deficits in male mice. *Neurobiol Stress*. 2023 Apr 27;24:100542. doi: 10.1016/j.ynstr.2023.100542. PMID: 37197395; PMCID: PMC10184141.



Take Home Messages

- While there is understandable controversy about using animals in research, human health has been very much improved because of it!
- Scientists are required to justify their use of animals and follow strict guidelines
- Rats and mice have quite similar reward circuitry to humans and have been very important for furthering our understanding of the effects of alcohol and drugs on the brain