SEX DIFFERENCES IN PRECLINICAL RESEARCH

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The importance of and rationale for including both male and female subjects in preclinical experiments

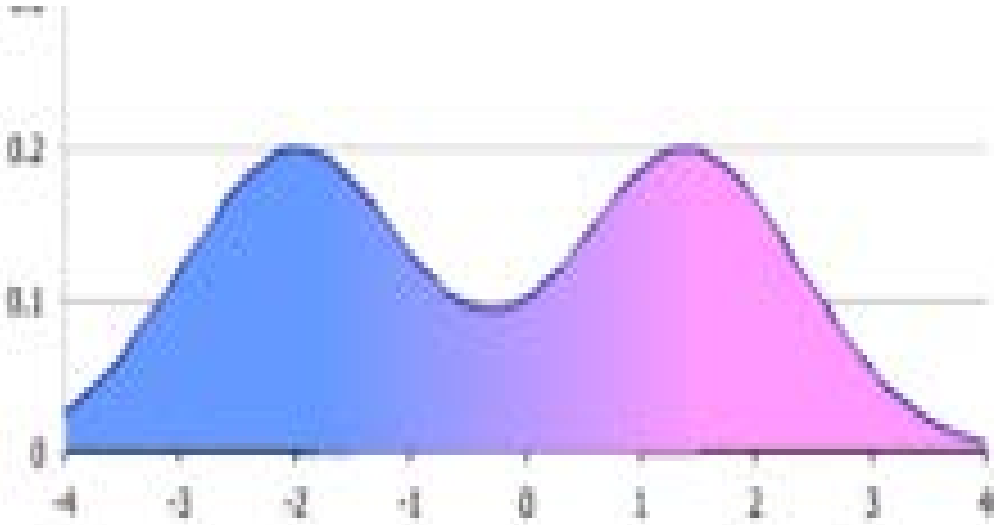
- "The over-reliance on male animals and cells in preclinical research obscures key sex differences that could guide clinical studies. And it might be harmful: women experience higher rates of adverse drug reactions than men do. Furthermore, **inadequate inclusion of female cells and animals in experiments and inadequate analysis of data by sex may well contribute to the troubling rise of irreproducibility in preclinical biomedical research**, which the NIH is now actively working to address."
- Clayton & Collins, NATURE,VOL 509,15MAY2014

What creates variability in data?

- Experimenter (multiple handlers, sex of handler, etc.)
- Testing conditions
- Housing conditions
- ***Individual Differences***
- ***Sex Differences***

What do we mean by Sex Differences?

- Sex Differences may be nuanced but we want them to be bimodal (or non-existent).



How do males and females differ?

- Qualitative Differences (e.g., during a sexual encounter females exhibit lordosis while males exhibit mounting).
- Quantitative Differences in the magnitude of the response (e.g., female rats show more activity in response to cocaine than do male rats).
- Distribution of incidence of a behavior (more female rats prefer cocaine to tasty pellets than do males).
- Different Mechanisms mediating the same outcome (e.g., different signaling pathways mediating response to CRF-R1).
- Combinations of the above mechanisms are also possible

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• Qualitative Sex Differences in Rat Behavior

A mother rat huddling over her pups.

Rats have provided a wide range of important insights into female reproductive physiology and behavior. Studies of maternal behavior in particular have helped us understand how neuroendocrine processes prepare pregnant mothers for parenting, and later regulate recognition, nurturance and lactation. Photo by Joe Lonstein.

Females exhibit lordosis and huddling over pups after parturition.

Males exhibit mounting and only huddle over pups after extensive experience with pups.

Studies of qualitative differences do not directly compare males and females and the study of only one sex may be justified.

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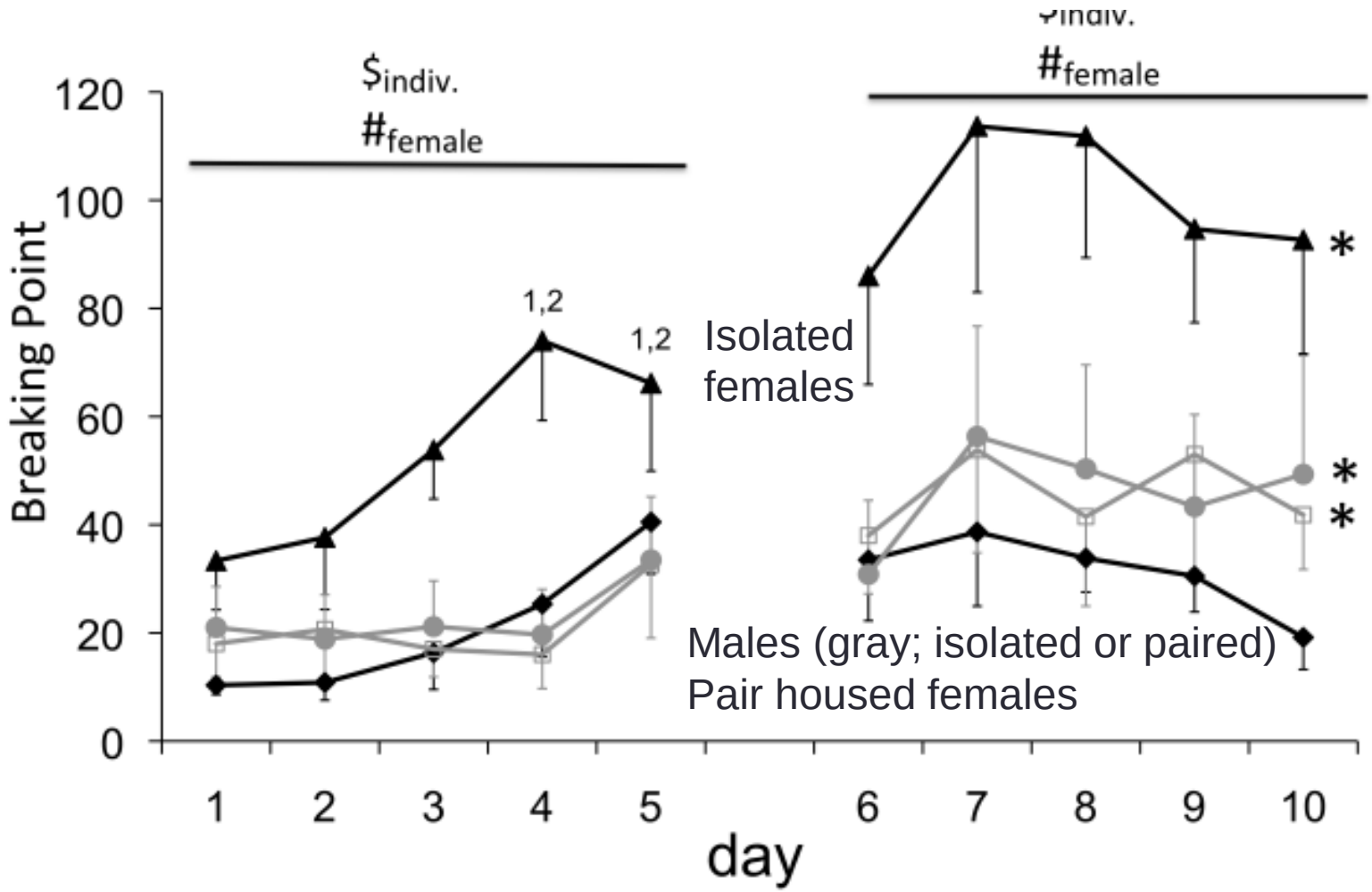
Isolated females have greater motivation for cocaine than males or paired females



Westenbroek, Perry, & Becker (Behav Brain Res, 2013)

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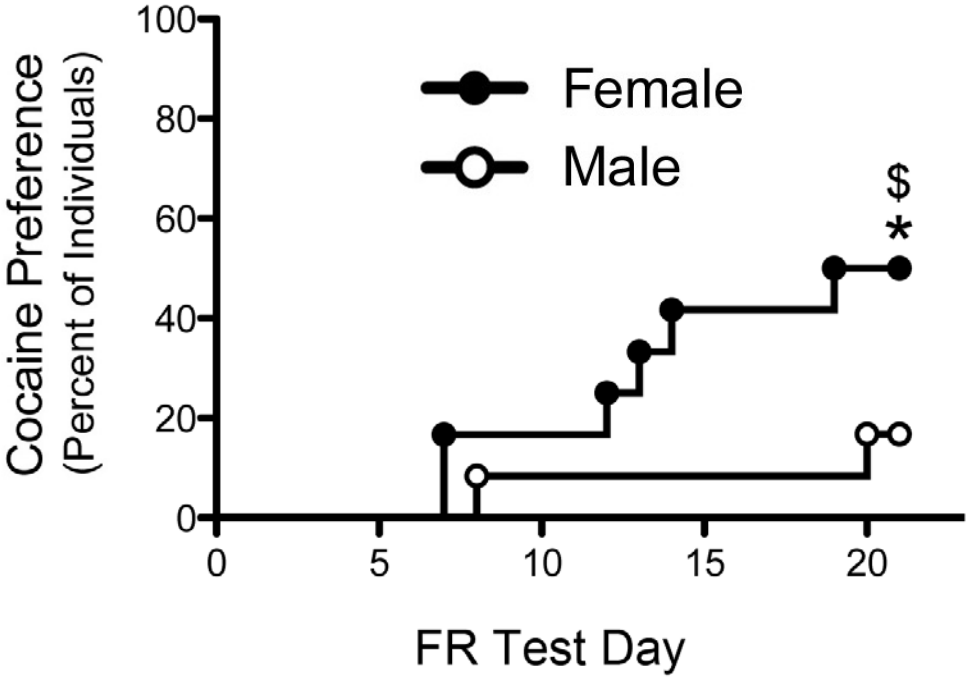
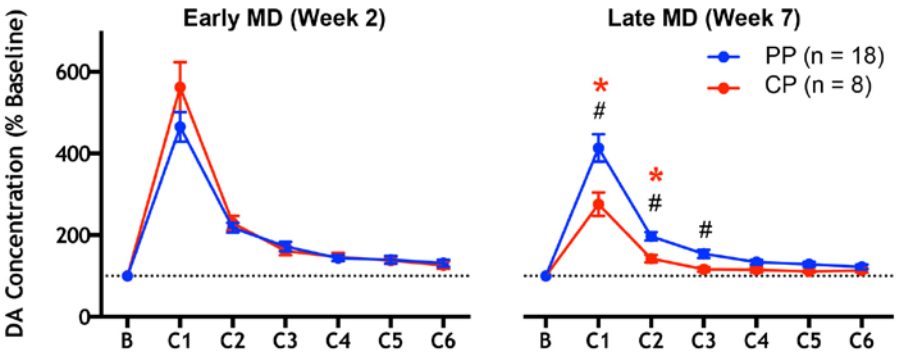
More females choose cocaine over pellets and they choose cocaine more rapidly than do male rats

Perry et al PLOSOne 2014.





Both females and males who prefer cocaine (CP) have lower cocaine-induced DA in accumbens after preference formation than they did early during self-administration Perry et al (submitted).

***Studying female rats may prove to be a morecost-effective model of the addicted phenotype*.**

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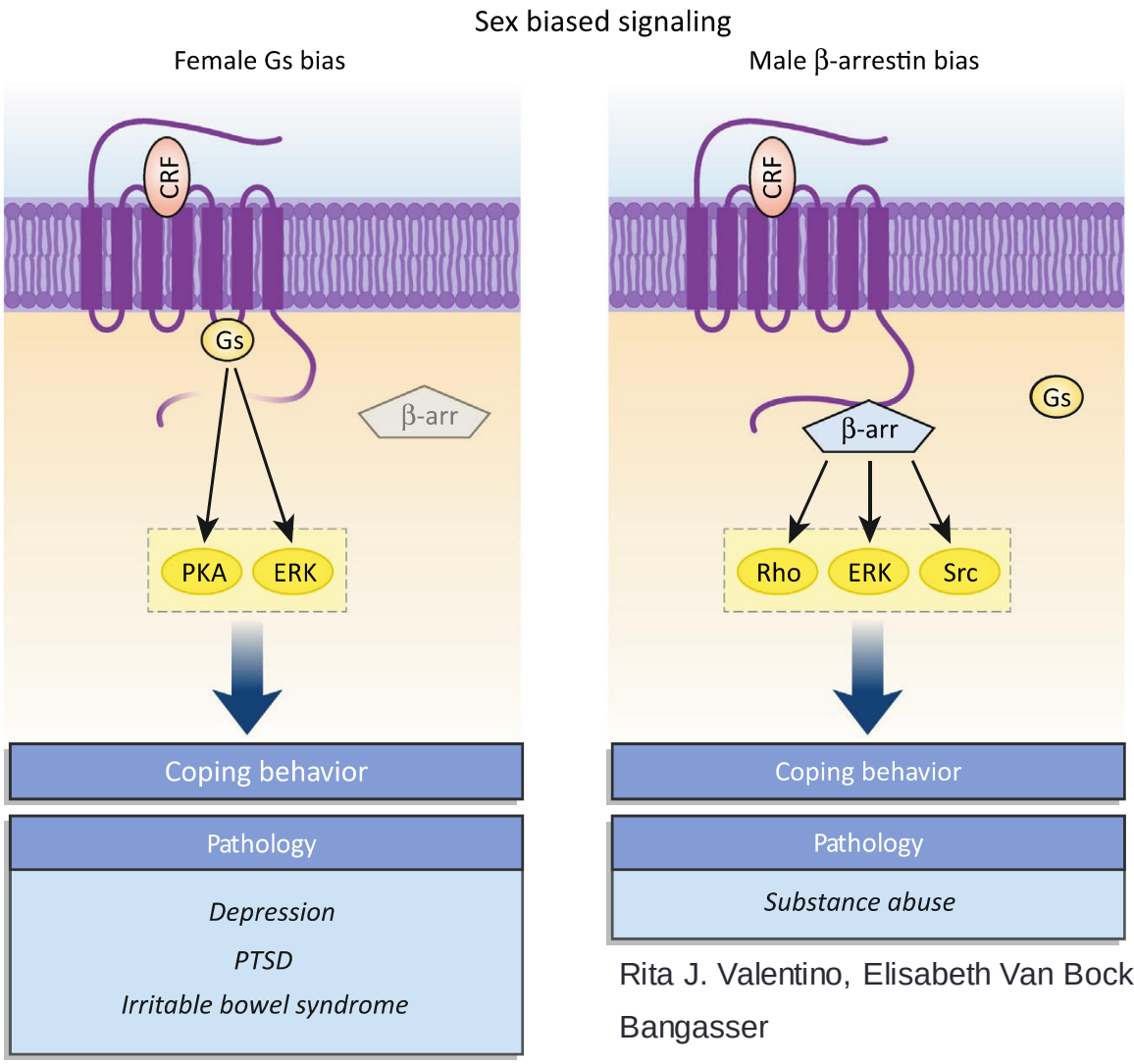
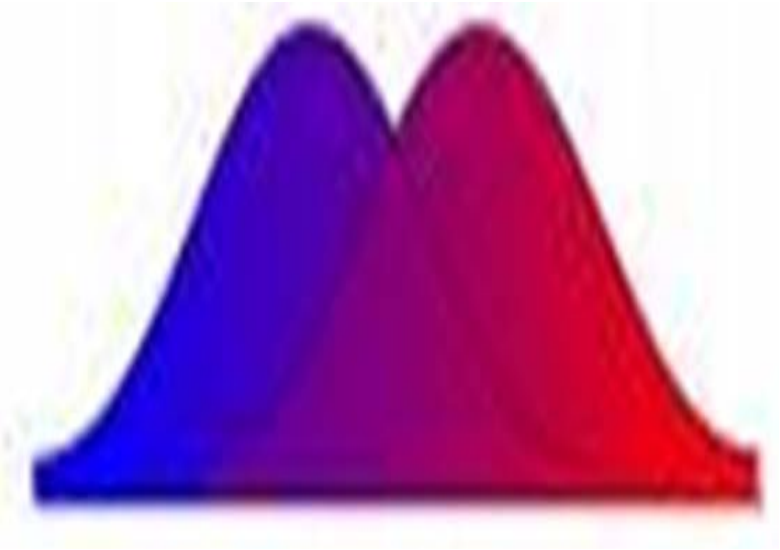
Sex-specific cell signaling: the corticotropin-releasing factor receptor model



Rita J. Valentino, Elisabeth Van Bockstaele, and Debra Bangasser

TRENDS in Pharmacological Sciences

Combinations of Mechanisms



Female rats exhibit greater amphetamine-induced behavior than males and the regions of the striatum activated by amphetamine are different in males and females (Castner & Becker, 1996; Castner et al., 1993).

Once a sex difference has been described then the mechanism(s) and causes for the sex difference can be studied.

Making sense of Sex Differences

- **What makes males and females different?**
- Males and females may exhibit sex differences because they **secrete different hormones**.
- Males and females may exhibit sex differences because **males and females have different brains/bodies due to developmental influences.**
- Males and females may exhibit sex differences because they secrete **different hormones *and*** because **males and females have different brains/bodies due to developmental influences.**

WhenTalking About Sex Differences: biology is not destiny

What Does it Mean if there are Sex Differences in the Brain? (a cautionary note)

- Neuroscience perspective – the brains are different
- Biological Determinism – it's all due to the brain
- When we talk about biological sex differences we need to remember that there are people who will assume that the biology is causal: even when we know that there are environmental influences that affect the development.

It's Official: Being Fat is not Your Fault National Post 6/25/2013

A study found that overweight men and women who are told obesity is a disease are less interested in going on a diet to improve their health.
28 January 2014 : http://www.dailymail.co.uk/health/article-2547768/Labelling-obesity-disease-excuse-not-diet.html#ixzz2z52yMC77

Conclusions

- Variability in data can originate from many sources, but when experimenter-dependent variability is controlled, individual differences and sex differences need to be examined.
- Knowledge of the ways that males and females can differ will inform how we construct our experiments to study both sexes in our research. For some types of studies females may prove to be more cost-effective as an animal model.
- Knowledge of the mechanisms mediating the development and expression of sex differences will advise our science and the translation of that knowledge for the benefit of both men and women.