# Orexin neurons, reward and addiction: It all comes together in the lateral hypothalamus

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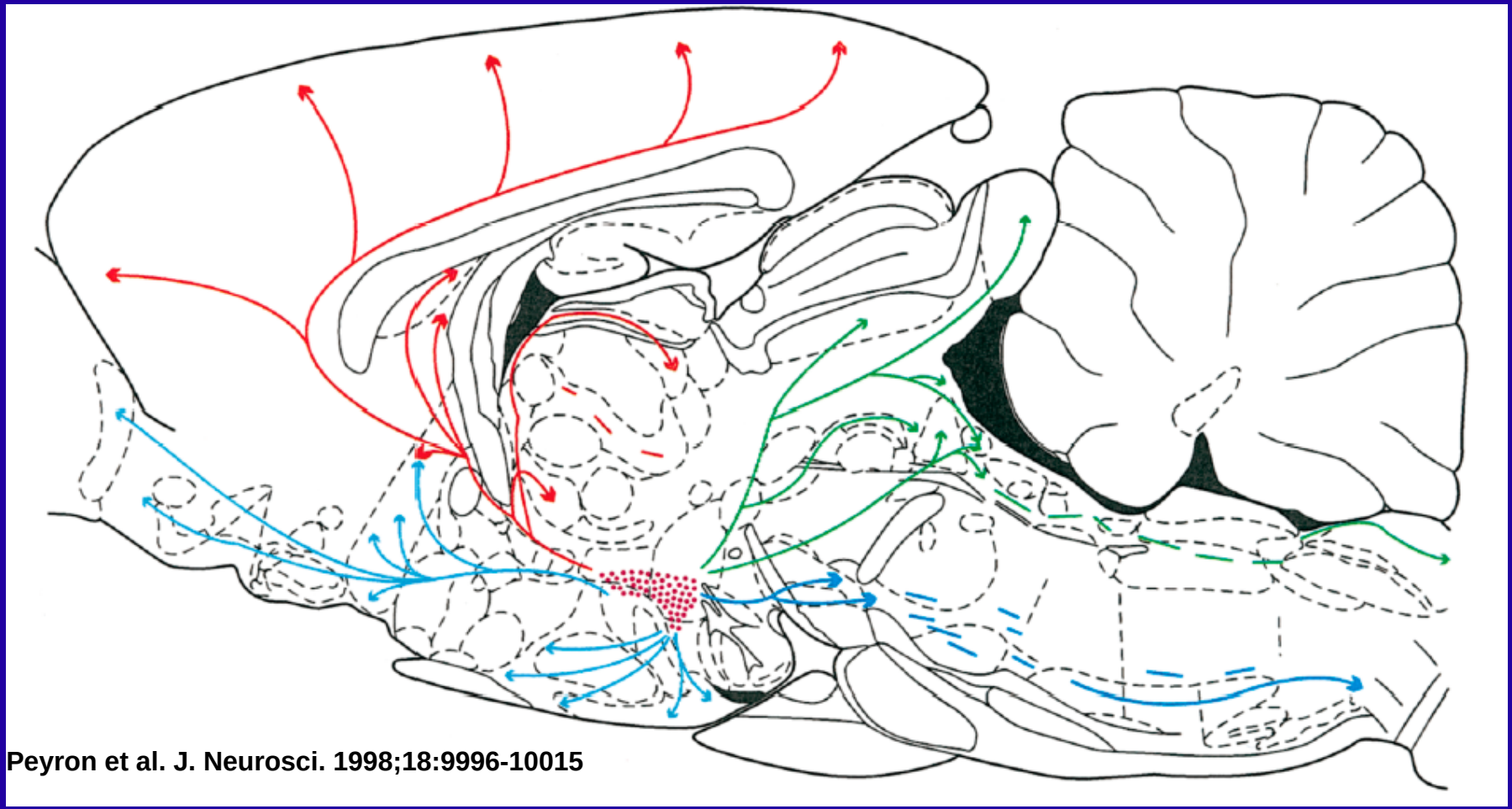
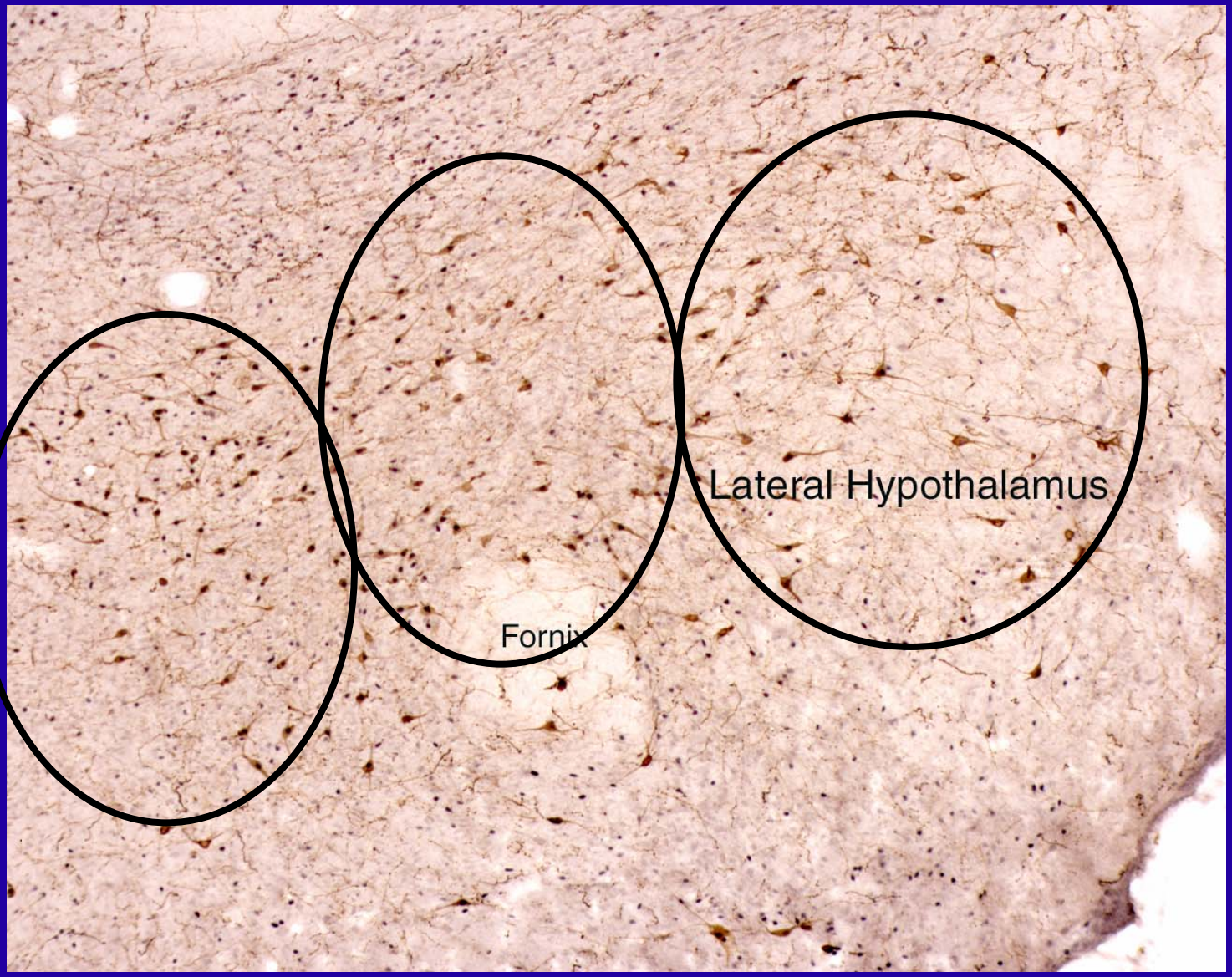
# Orexin (hypocretin) neurons:



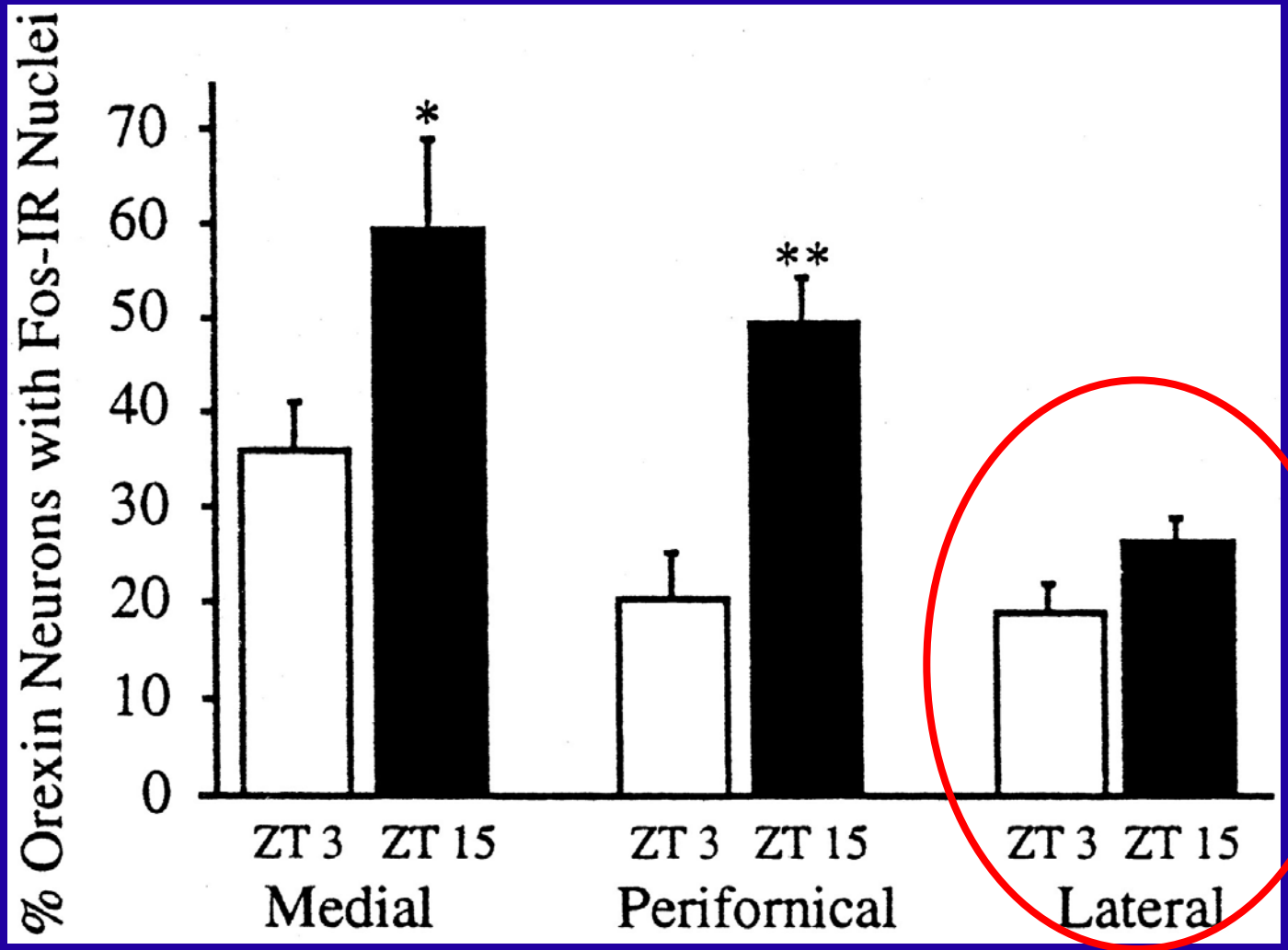
Peyron et al. J. Neurosci. 1998;18:9996-10015

- located only in hypothalamus
- widespread projections
- mutations produce narcolepsy symptoms
- prominent hypothesis: arousal

# Not all orexin neurons are created equal



# Activity of orexin neurons in LH does not correspond to arousal rhythm




Estabrooke, I. V. et al. J. Neurosci. 2001;21:1656-1662

# LH orexin neurons: Possible role in reward processing

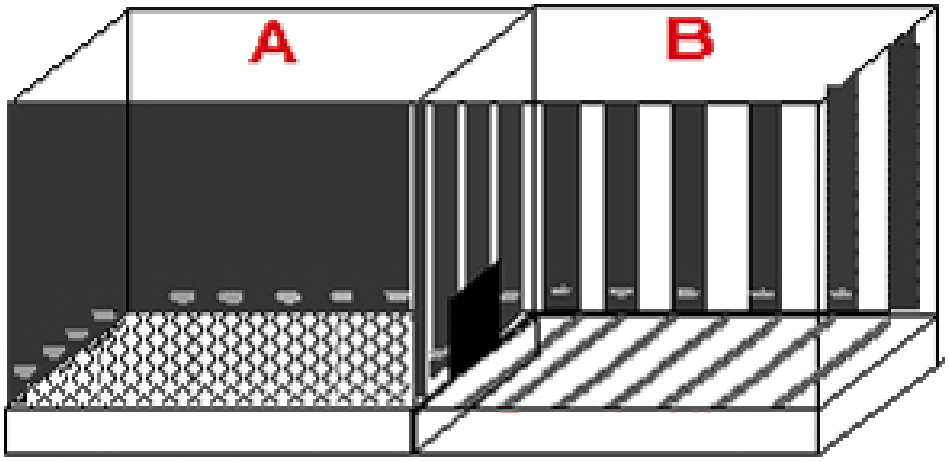
- Orexin administration increases feeding
- Orexin neurons send projections to brain areas involved in reward (e.g., PFC, Nac, VTA)
- Lateral hypothalamus long implicated in reward functions

- *Q: Are LH orexin neurons important in reward processing and addiction?*

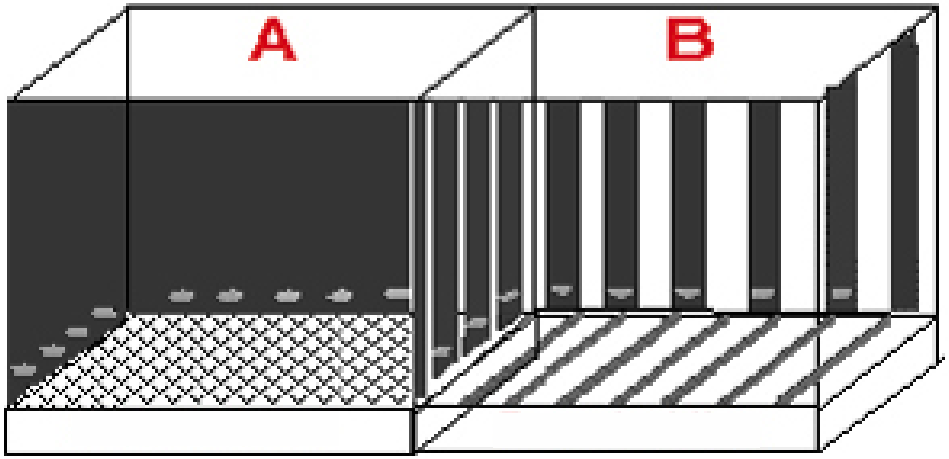
# Place conditioning procedure

## *Conditioned place preference (CPP)*

Preconditioning & Test Days
(Free Access to Both Chambers)

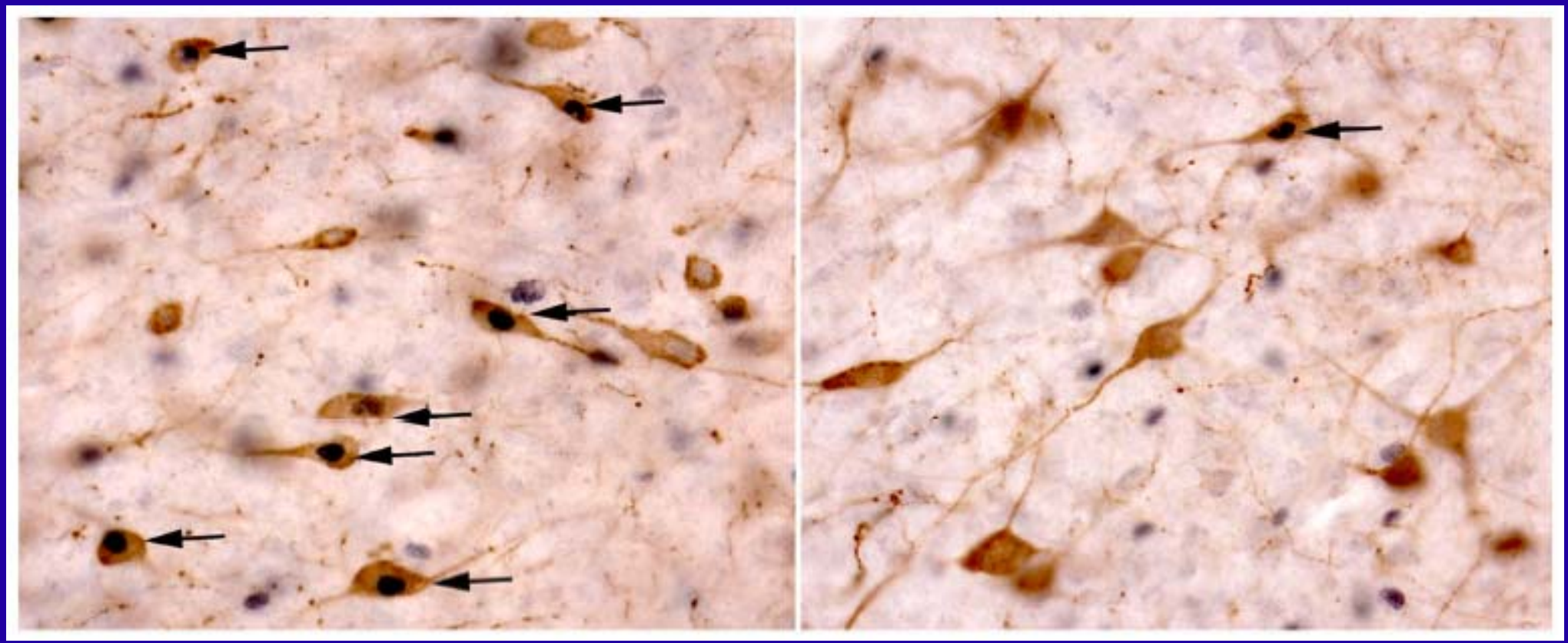



Pairing Days
(Confined to One Side)




**3 drug or food pairing days, balanced design**
**Preference tested next day, drug-free**
**Brains taken 2 hr after preference test for Fos measurements**

# Fos activation in orexin neurons with exposure to morphine environment



Morphine-conditioned

Non-conditioned

Harris, Wimmer and Aston-Jones, Nature 437: 556-9 (2005)

**Preference scores correlate with percentage of LH orexin cells that are Fos+**

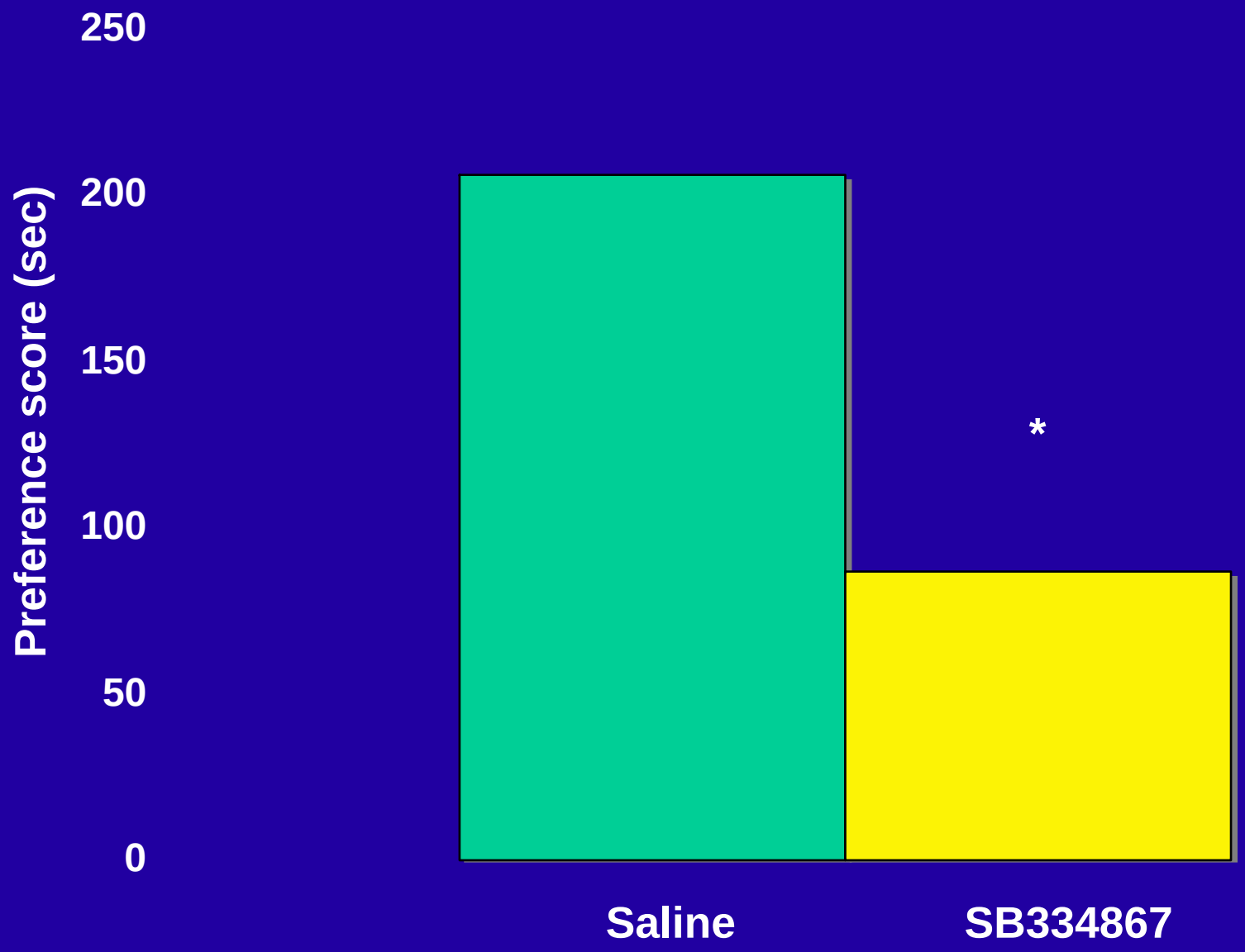
| Groups: | Cell Types: | Percentage Fos+ | Correlations R: | |
|---|---|---|---|---|
| Morphine Conditioned N=12 | **Orx LH** | **48±2*** | **.72** | **p<.01*** |
| | NonOrx LH | 55±6 | .30 | p=.34 |
| | Orx PFA | 62±2 | .04 | p=.91 |
| | Orx DMH | 67±4 | -.11 | p=.71 |
| Food Conditioned N=8 | **Orx LH** | **50±3*** | **.87** | **p<.01*** |
| | NonOrx LH | 47±5 | .20 | p=.64 |
| | Orx PFA | 42±3 | .26 | p=.54 |
| | Orx DMH | 47±6 | -.16 | p=.71 |
| Cocaine Conditioned N=8 | **Orx LH** | **52±5*** | **.90** | **p<.01*** |
| | NonOrx LH | 78±7 | .51 | p=.20 |
| | Orx PFA | 67±3 | .41 | p=.32 |
| | Orx DMH | 74±3 | .50 | p=.20 |
| Non-conditioned N=15 | **Orx LH** | **17±2** | **.11** | **p= .81** |
| | NonOrx LH | 43±6 | .30 | p=.53 |
| | Orx PFA | 52±4 | .42 | p=.36 |
| | Orx DMH | 59±4 | .02 | p=.96 |
| Naïve N=6 | **Orx LH** | **15±1** | | |
| | NonOrx LH | 29±8 | | |
| | Orx PFA | 52±3 | | |
| | Orx DMH | 57±6 | | |
| Novelty conditioned N=6 | **Orx LH** | **18±2** | **.09** | **p=.86** |
| | NonOrx LH | 50±1 | -.52 | p=.31 |
| | Orx PFA | 56±3 | .02 | p=.97 |
| | Orx DMH | 63±5 | .42 | p=.43 |

Harris, Wimmer and Aston-Jones, Nature 437: 556-9 (2005)

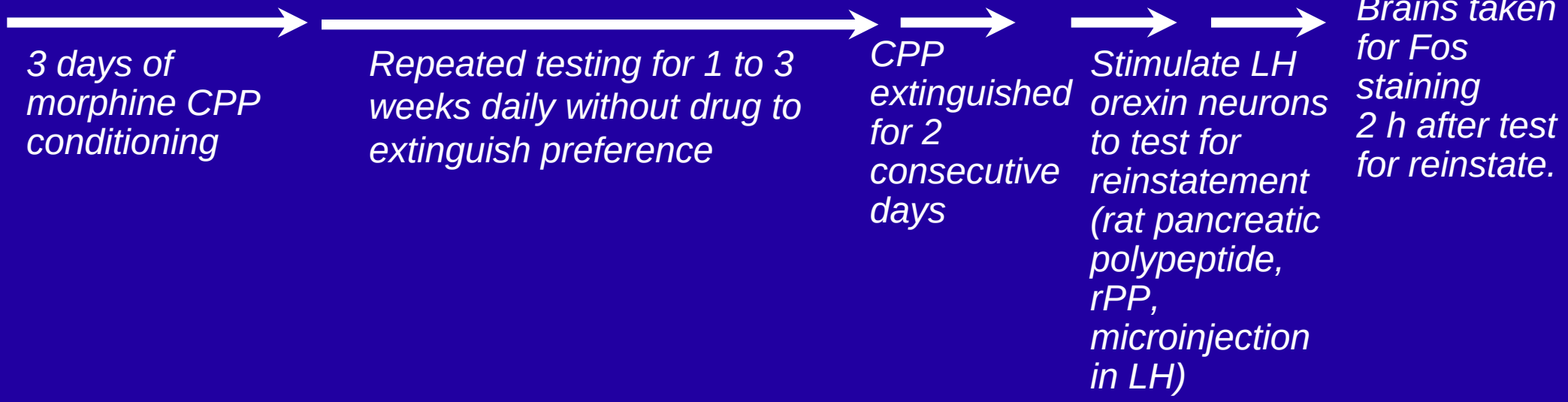
**Conclusion: LH orexin neurons are potently activated in proportion to reward preference**

***Q: Could activation of LH orexin neurons be involved in drug-seeking and relapse?***

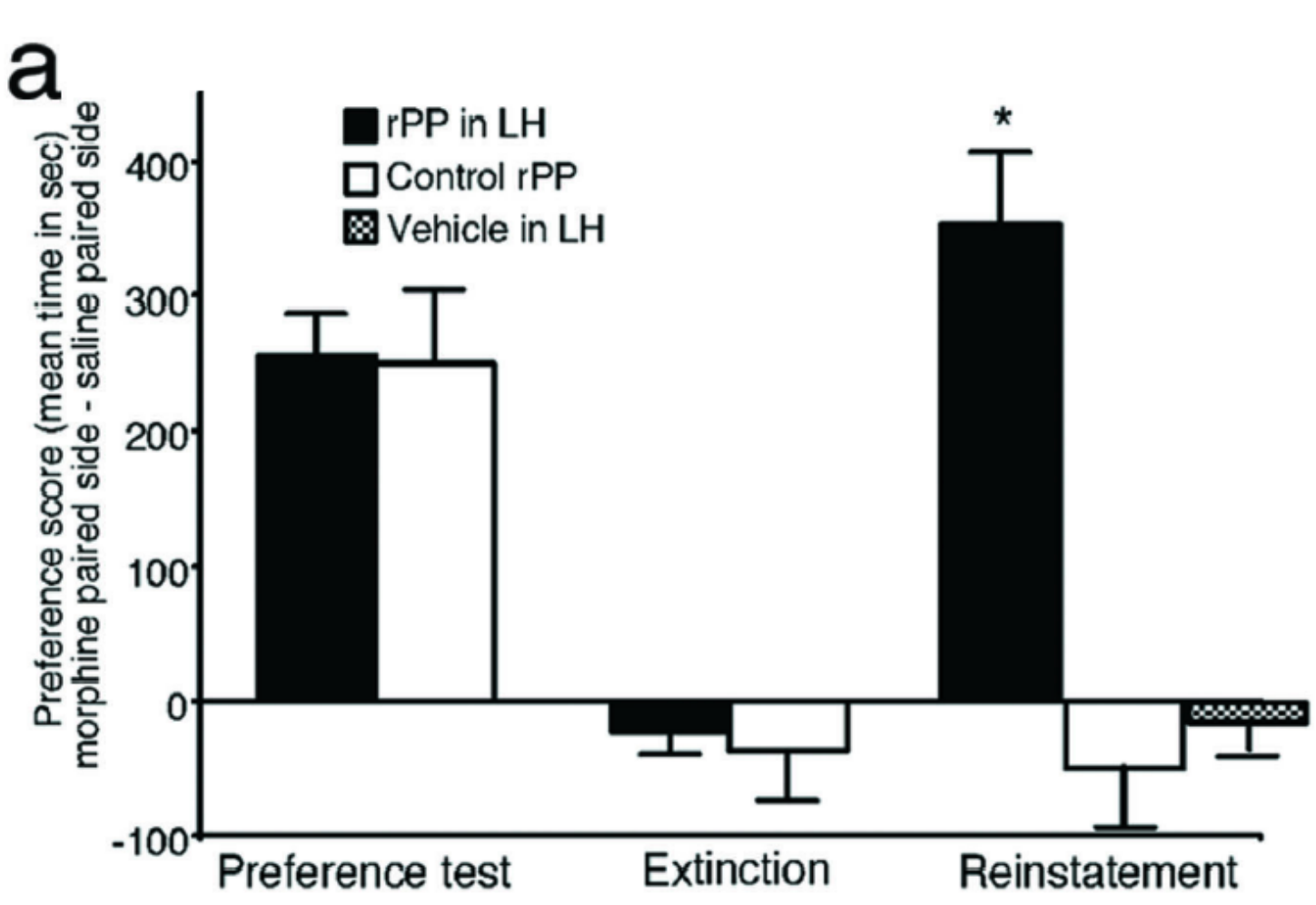
# Orexin antagonist attenuates expression of CPP



# Drug-seeking during protracted withdrawal: *Animal Model of Relapse*



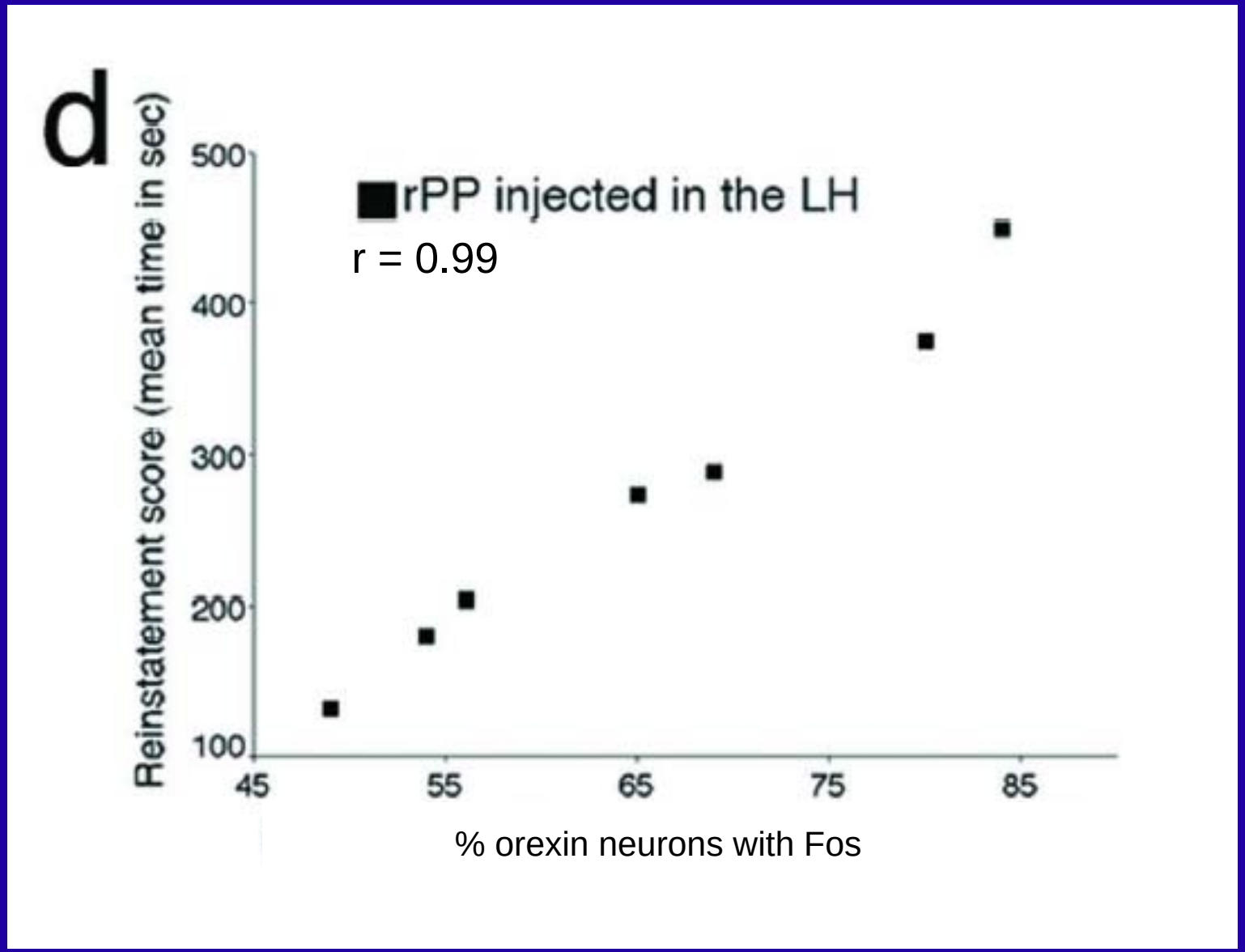
# rPP in LH reinstates morphine preference





Harris, Wimmer and Aston-Jones, Nature 437: 556-9 (2005)

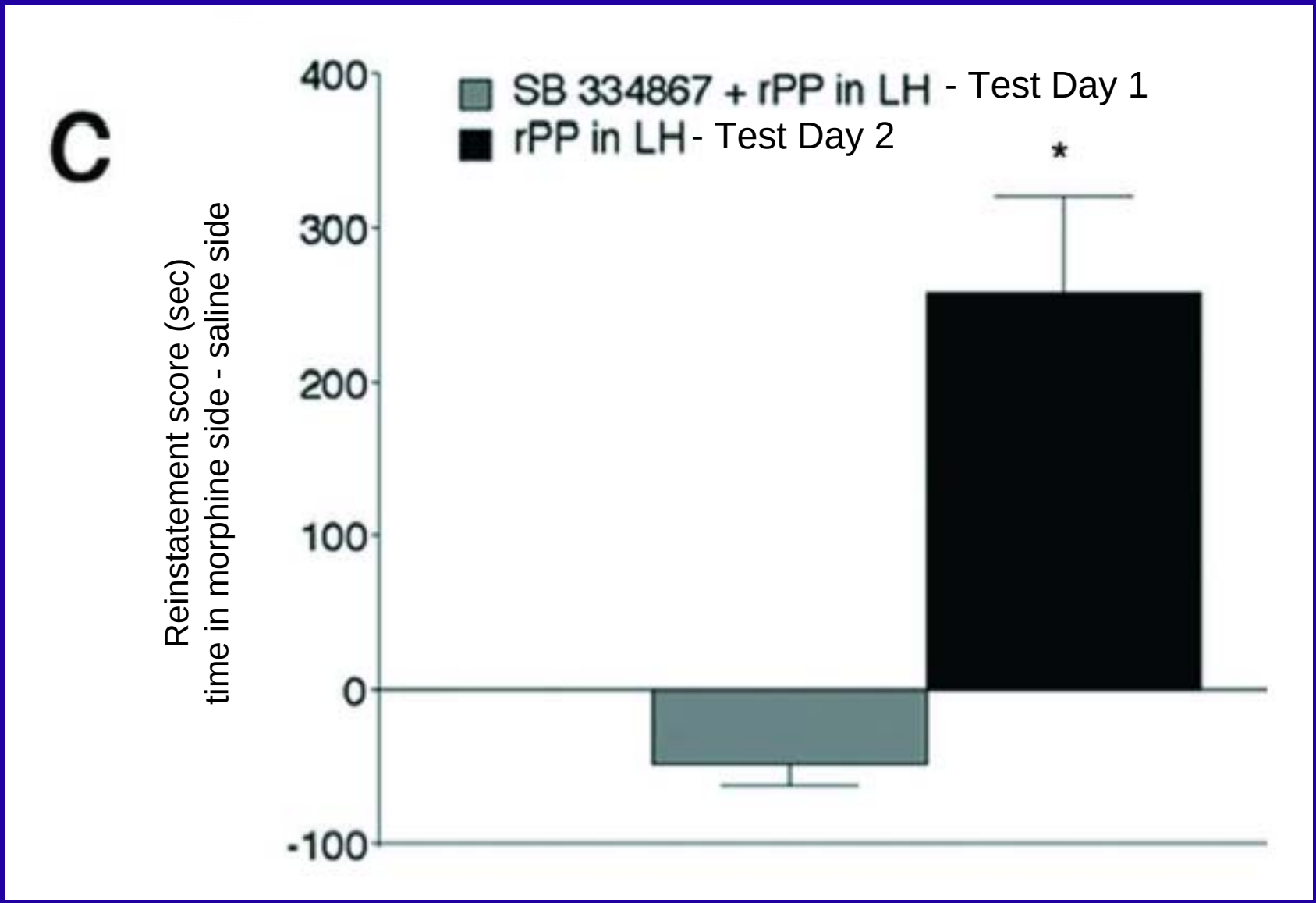
# Correlation: rPP-induced reinstatement and % LH orexin neurons with Fos





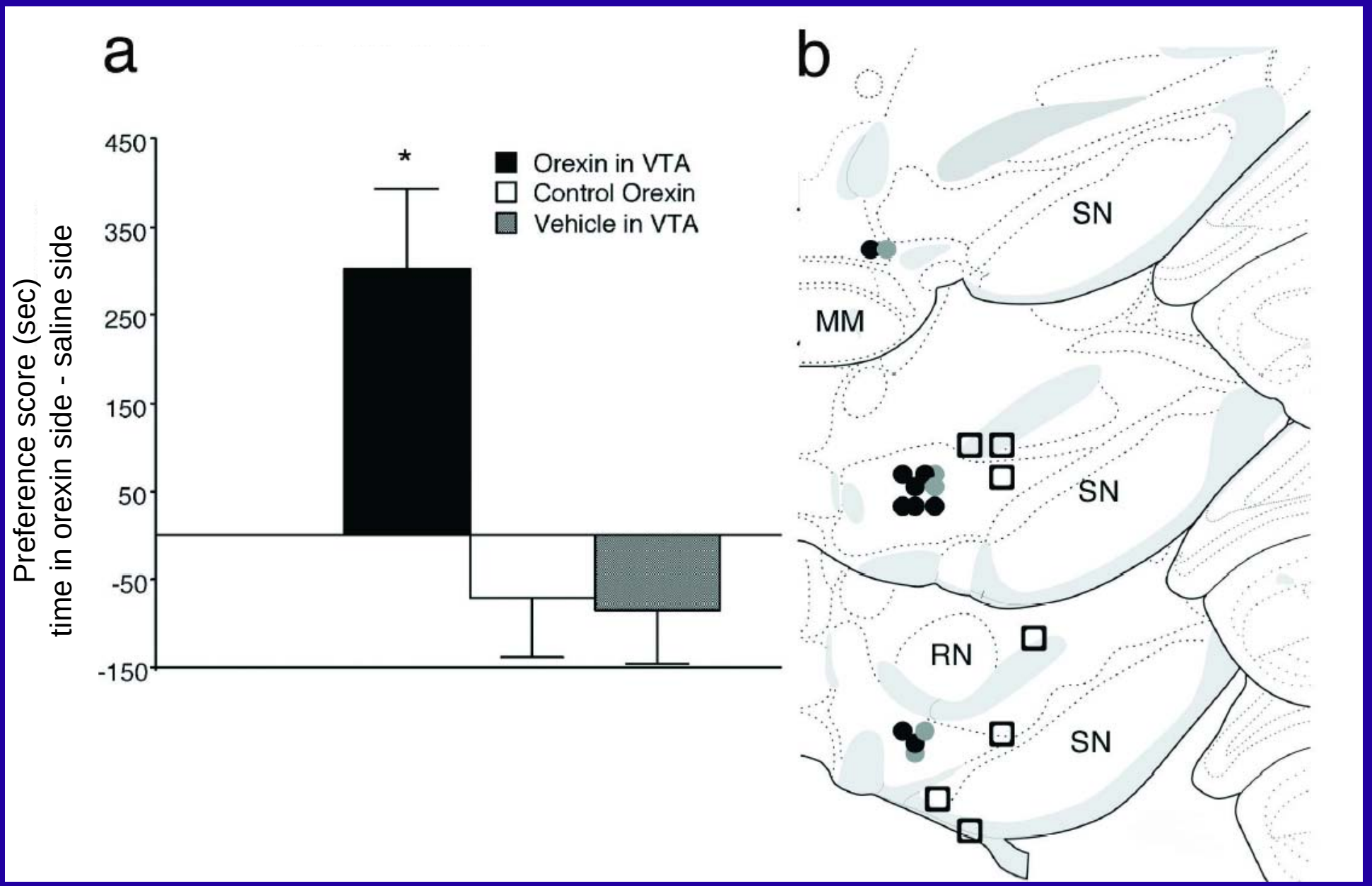

Harris, Wimmer and Aston-Jones, Nature 437: 556-9 (2005)

# rPP-induced reinstatement is blocked by selective orexin antagonist



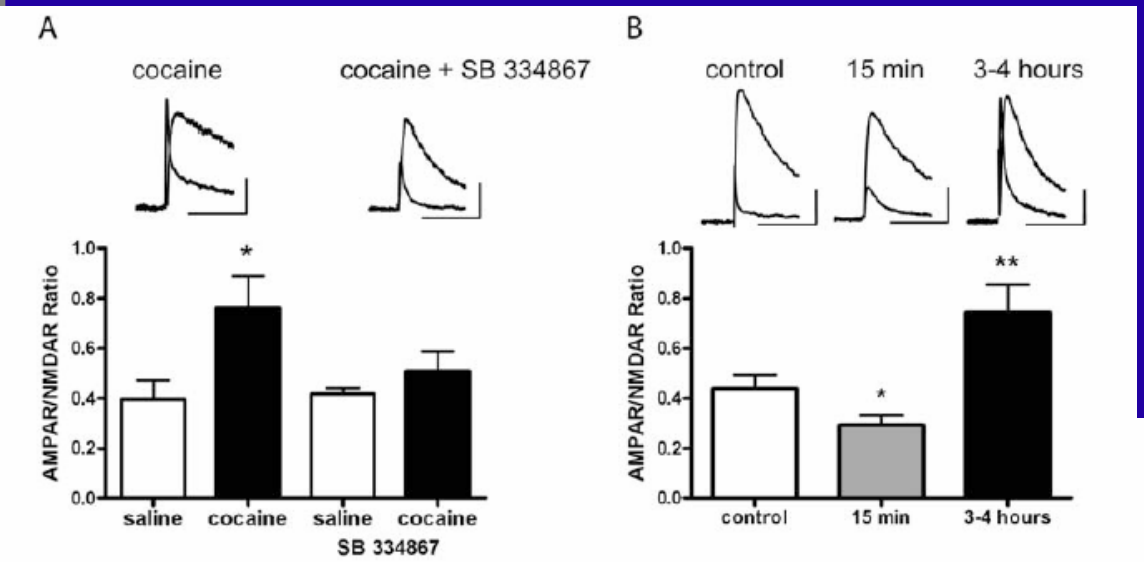

Harris, Wimmer and Aston-Jones, Nature 437: 556-9 (2005)

# Orexin injected into VTA reinstates morphine preference

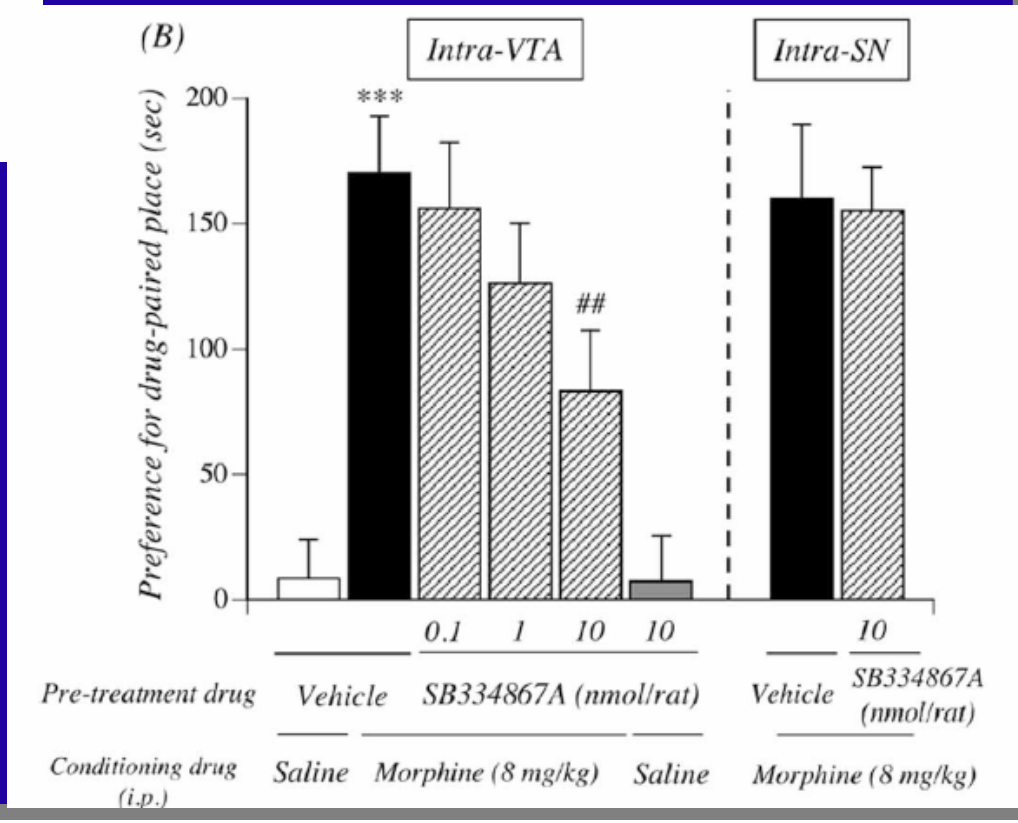



Harris, Wimmer and Aston-Jones, Nature 437: 556-9 (2005)

# Orexin is also involved in plasticity and learning

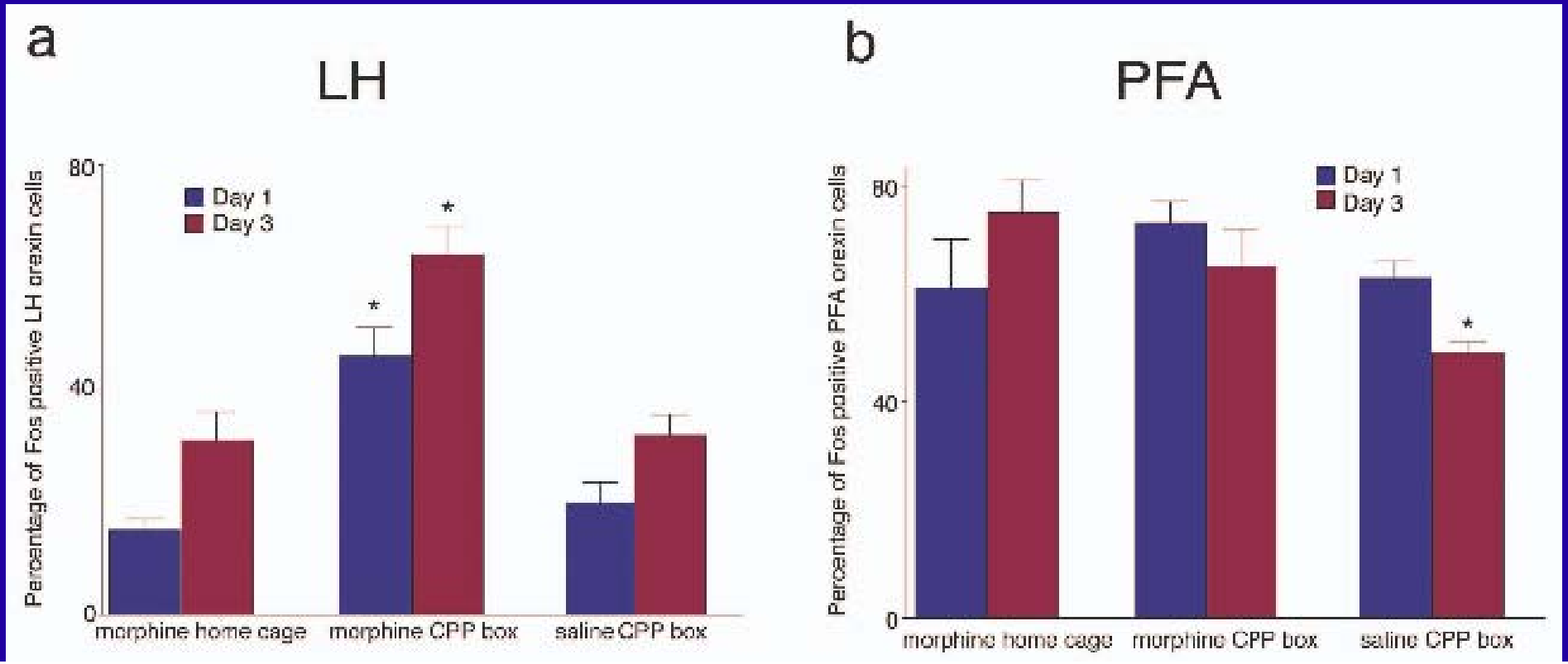



Borgland et al, Neuron 49 (2006)




Narita et al, J. Neurosci 29 (2006)

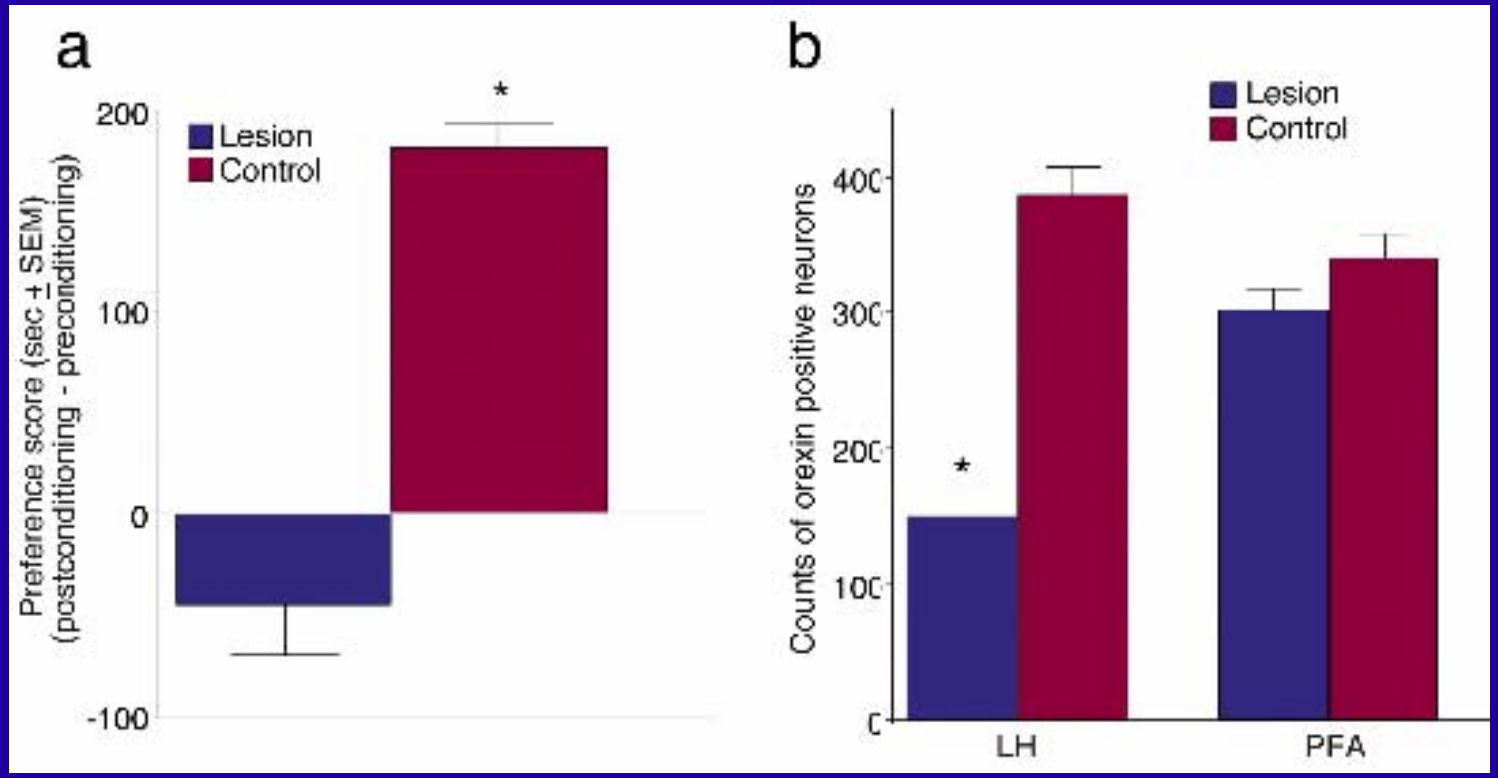
# LH orexin neurons are stimulated during drug pairing

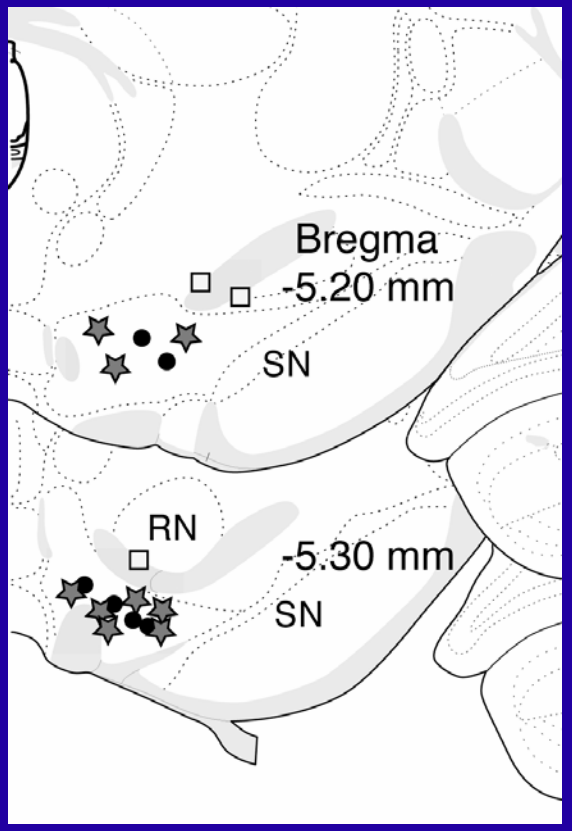



QuickTime™ and a TIFF (LZW) decompressor are needed to see this picture.

# Bilateral disconnection of LH orexin projections to VTA blocks acquisition of a morphine CPP

***Unilateral excitotoxic lesion of LH + SB in contra VTA***



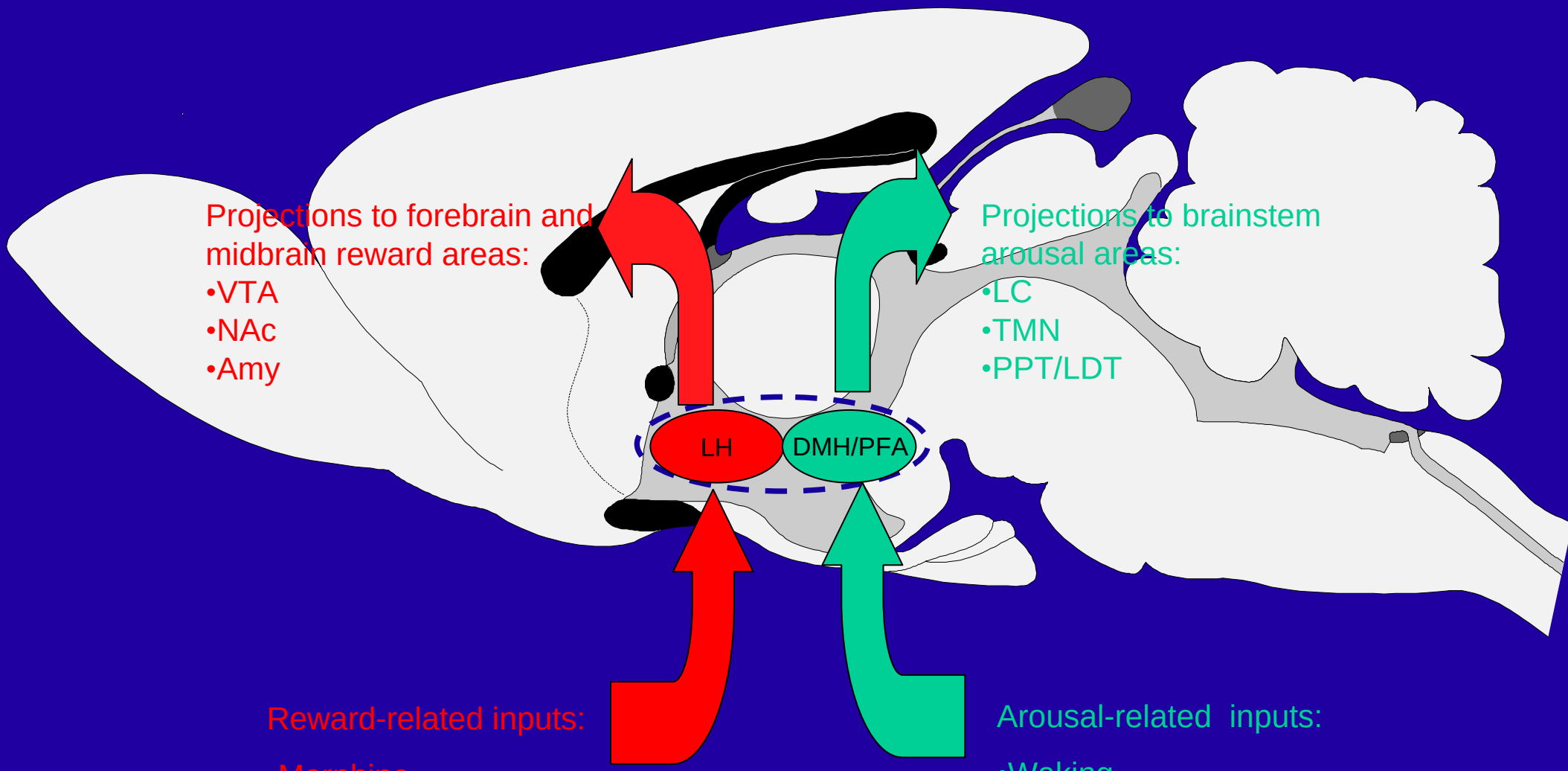

***Go see: Wimmer et al., poster 00-74***
***Monday PM***

# SUMMARY

- LH orexin neurons (but not other orexin neurons) are stimulated in proportion to reward preference.
- Blockade of orexin receptors attenuates expression of drug preference.
- Exogenous stimulation of LH orexin neurons reinstates extinguished drug preference (relapse).
- Orexin in VTA dopamine neuron area reinstates extinguished drug preference (relapse).
- Orexin projections from LH to VTA are critical for learning stimulus-drug relationships.

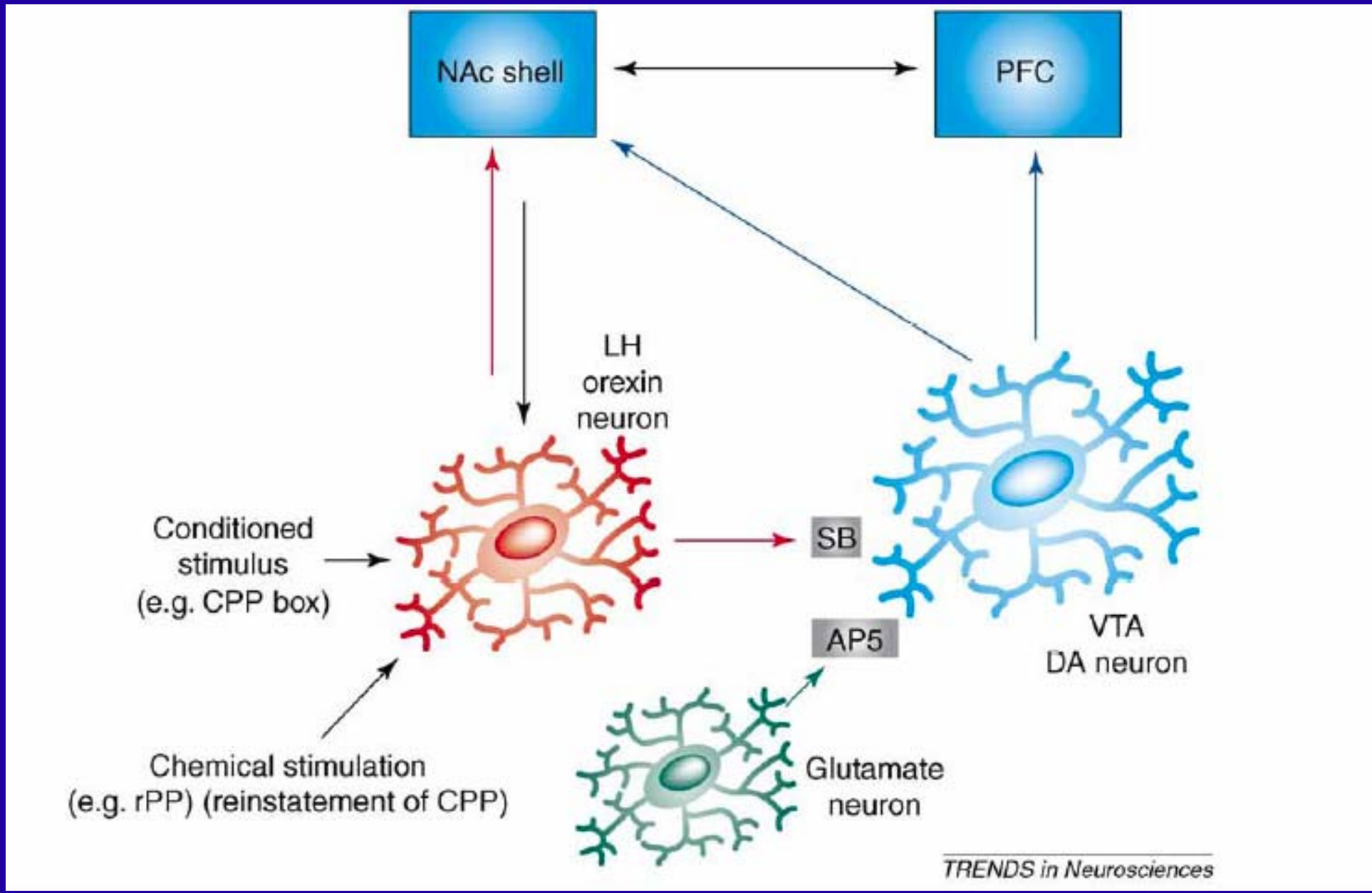
*Hypothesis: LH orexin neurons are involved in reward-based learning and memory*

# Functionally distinct orexin neuron groups



# Collaborators

# Role of LH orexin neurons in reward-based learning and memory circuitry




Harris and Aston-Jones, TINS 29: 571-7 (2006)

# Bilateral neurotoxic lesions of LH orexin neurons blocks acquistion of a morphine CPP