

nausea

jean-paul sartre

*“The Nausea is not inside me: I feel it out there in the wall, in the suspenders, everywhere around me. It makes itself one with the café, I am the one who is within it.”*



# MONELL CHEMICAL SENSES CENTER

3500

CHAMBERS STREET



# *Acknowledgement*

Dr. Charles Horn

Marc Ciucci

Dr. Bart DeJonghe

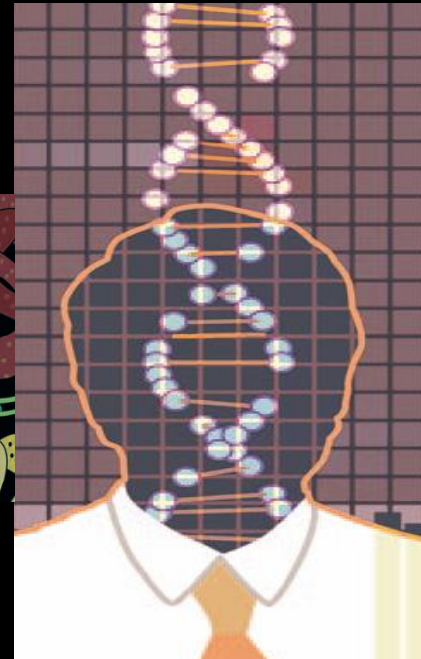
Dr. Kathakali Addya

Dr. John Tobias

Dr. Donald Baldwin



# Visceral Sickness: Insights into Pharmacology of Nausea



*Arun Chaudhury*

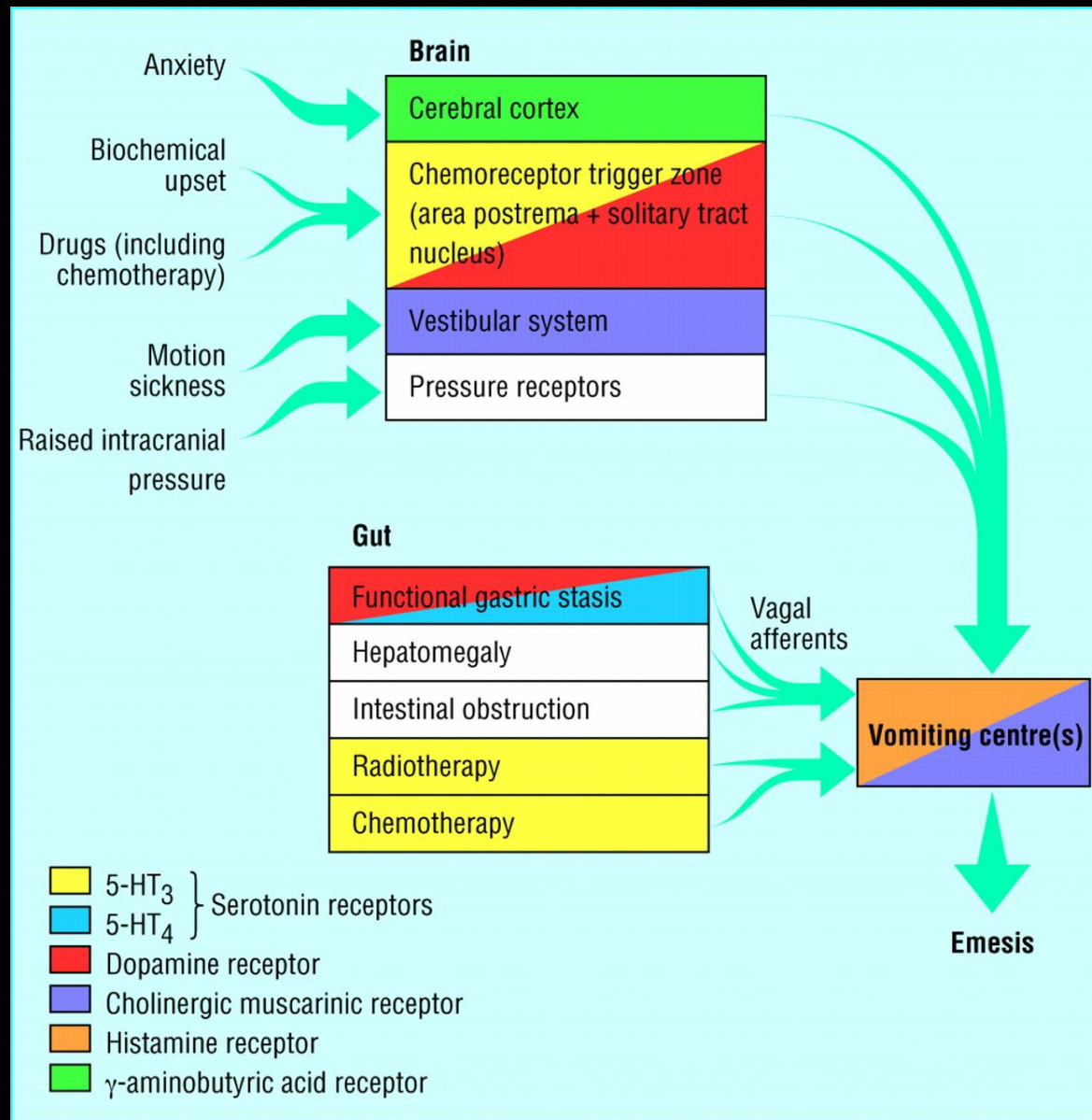
*Postdoctoral Fellow*

Puking slugs: Queasiness affects all



# Disorders of multiple systems cause vomiting

*Baines, M. J*  
*BMJ 1997;*  
*315:1148-1150*



# Bedside impact of vomiting

## Valsalva retinopathy



*Zhang & Mathura, NEJM: 352, 17, 2005*

# Socioeconomic impact of Nausea/Vomiting in USA

Symptom	N <sup>b</sup>	Missed work days, mean (SD)	N <sup>c</sup>	Missed leisure days, mean (SD)	N <sup>c</sup>	Missed household days, mean (SD)
<b>Nausea</b>	1498	2.2 (8.9)	883	3.3 (12.9)	860	6.6 (18.2)
<b>Vomiting</b>	522	4.4 (13.2)	180	5.7 (17.3)	171	13.1 (25.5)
Abdominal pain	443	1.9 (9)	710	2.7 (11.8)	694	4.6 (15.2)
Asymptomatic	4323	0.4 (3.2)	7932	0.3 (3.3)	7893	0.5 (4.8)

*Camilleri et al Clin Gastro Hepato 2005, 3: 543-552*

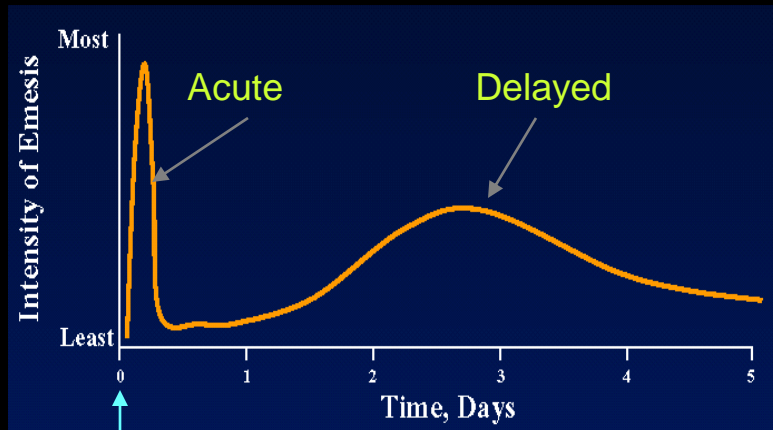


# Cancer therapy:

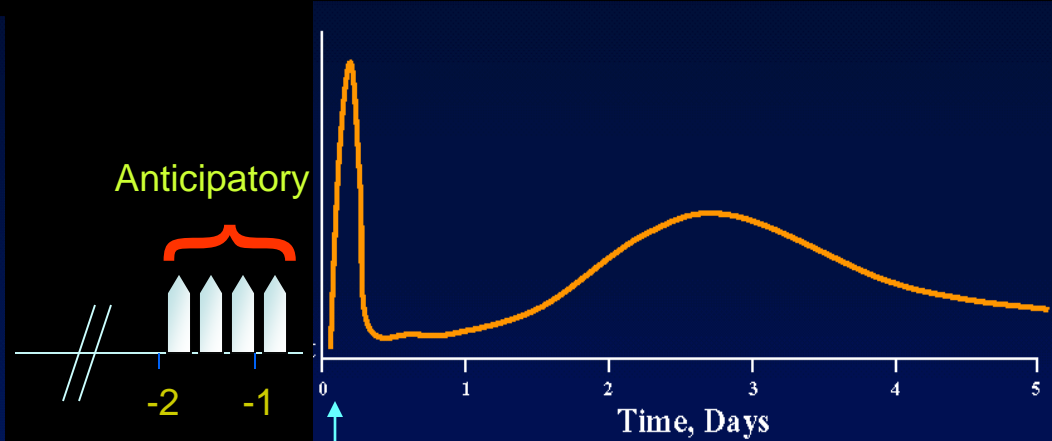
*Primum succerrere Or Primum non nocere?*

- Surgery
- Radiotherapy
- Biologicals
- Chemotherapy

# Patterns of emesis after chemotherapy



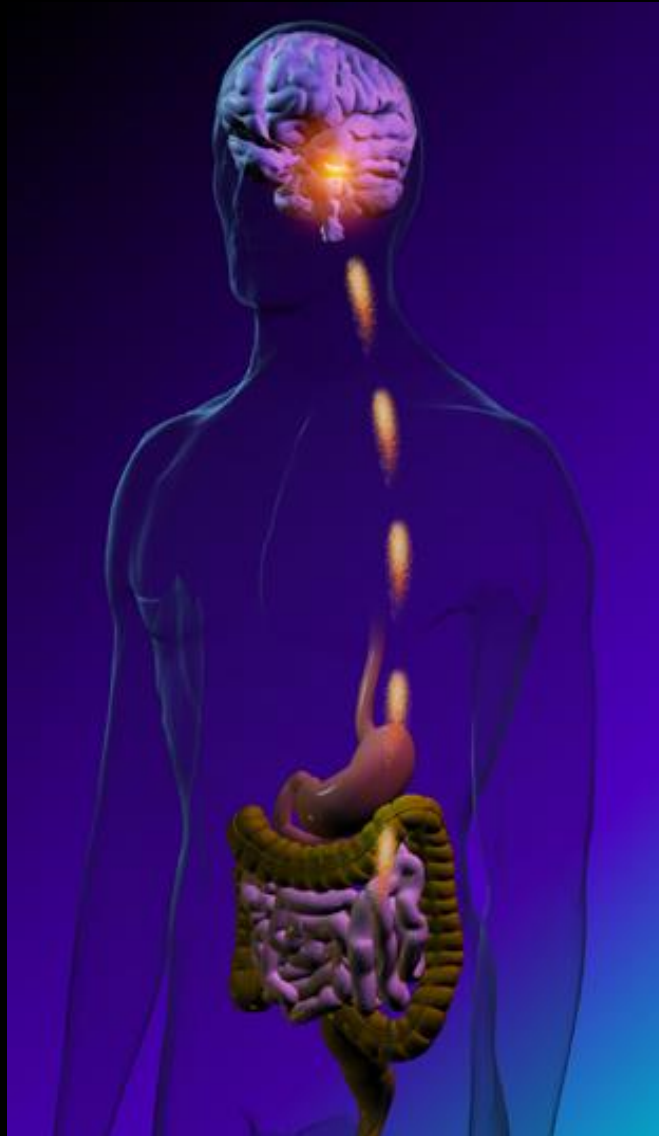
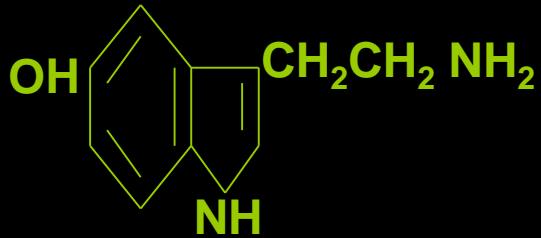
Course 1



Course X

*Adapted from Andrews PL & Davis CJ*

# Gut-Brain communication



CH<sub>2</sub>-Arg-Pro-Lys-Pro-Gln-  
Gln-Phe-Phe-Gly-Leu-Met-  
NH<sub>2</sub>

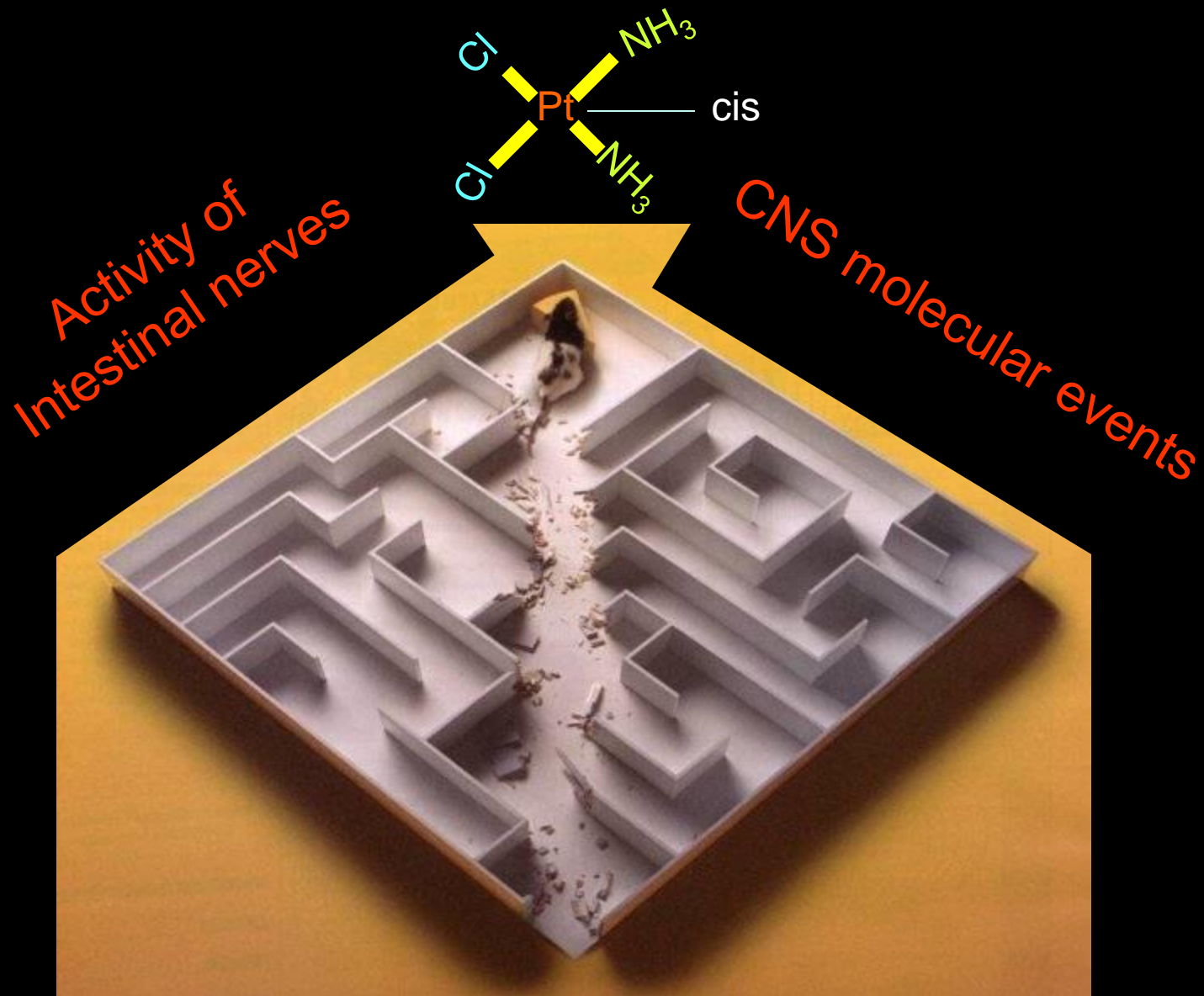
# Models for studying drug-induced sickness

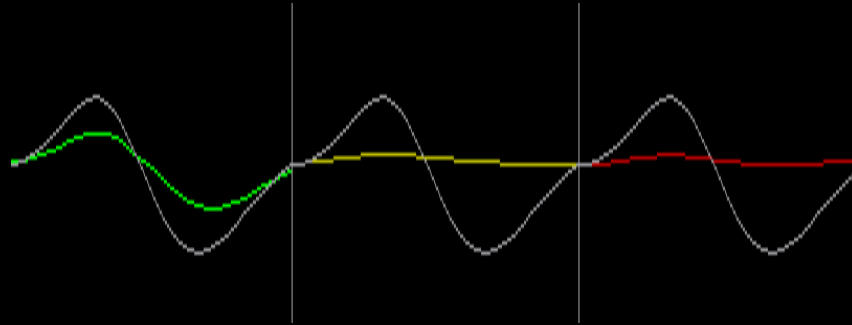
- House Musk Shrew
- Ferret
- Mice
- Rat

## Read-outs for visceral sickness

*Andrews & Horn 2006 Auton Neurosci. 2006 125(1-2):100-15*

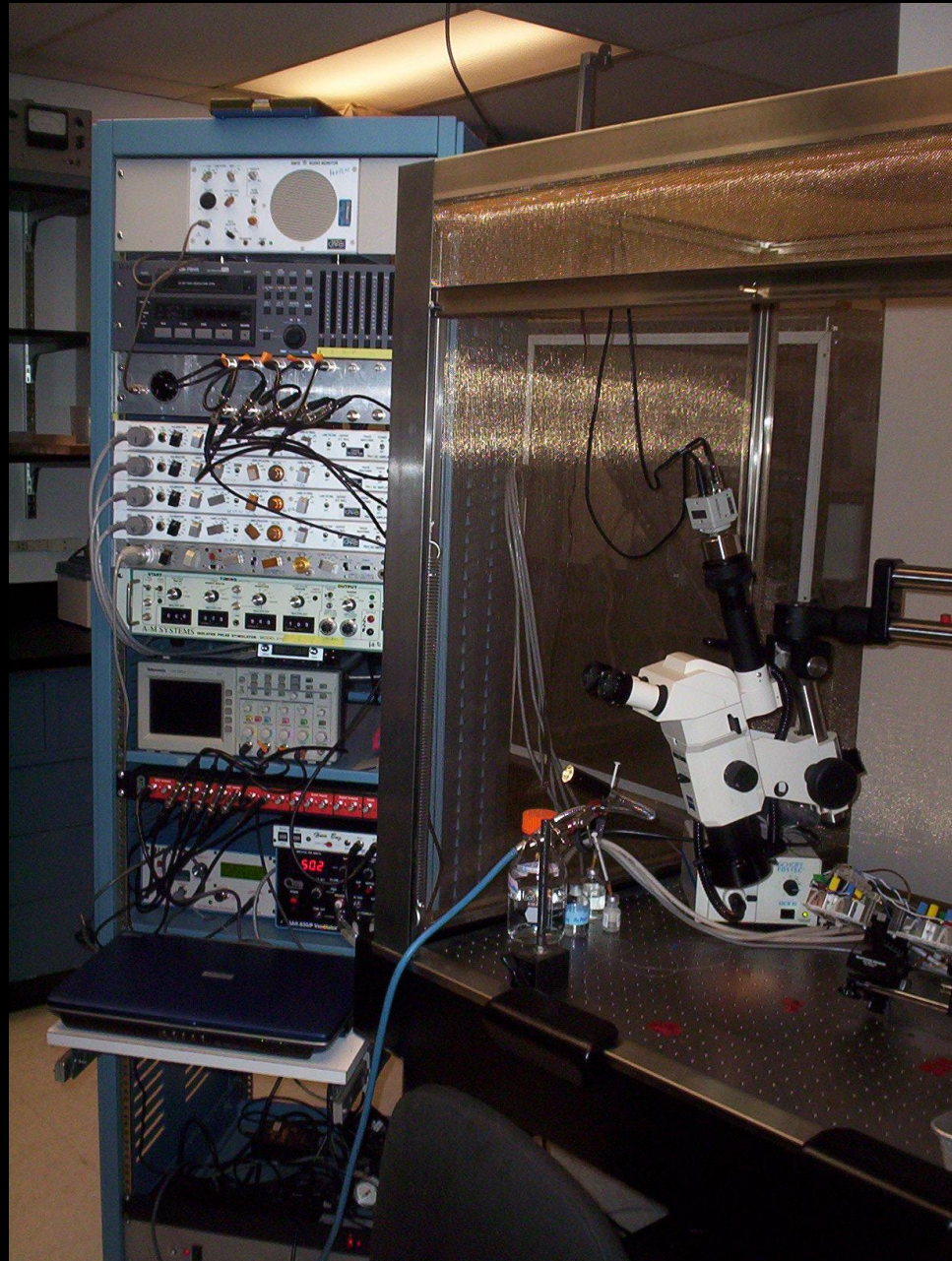
# Strategies for evaluating visceral sickness



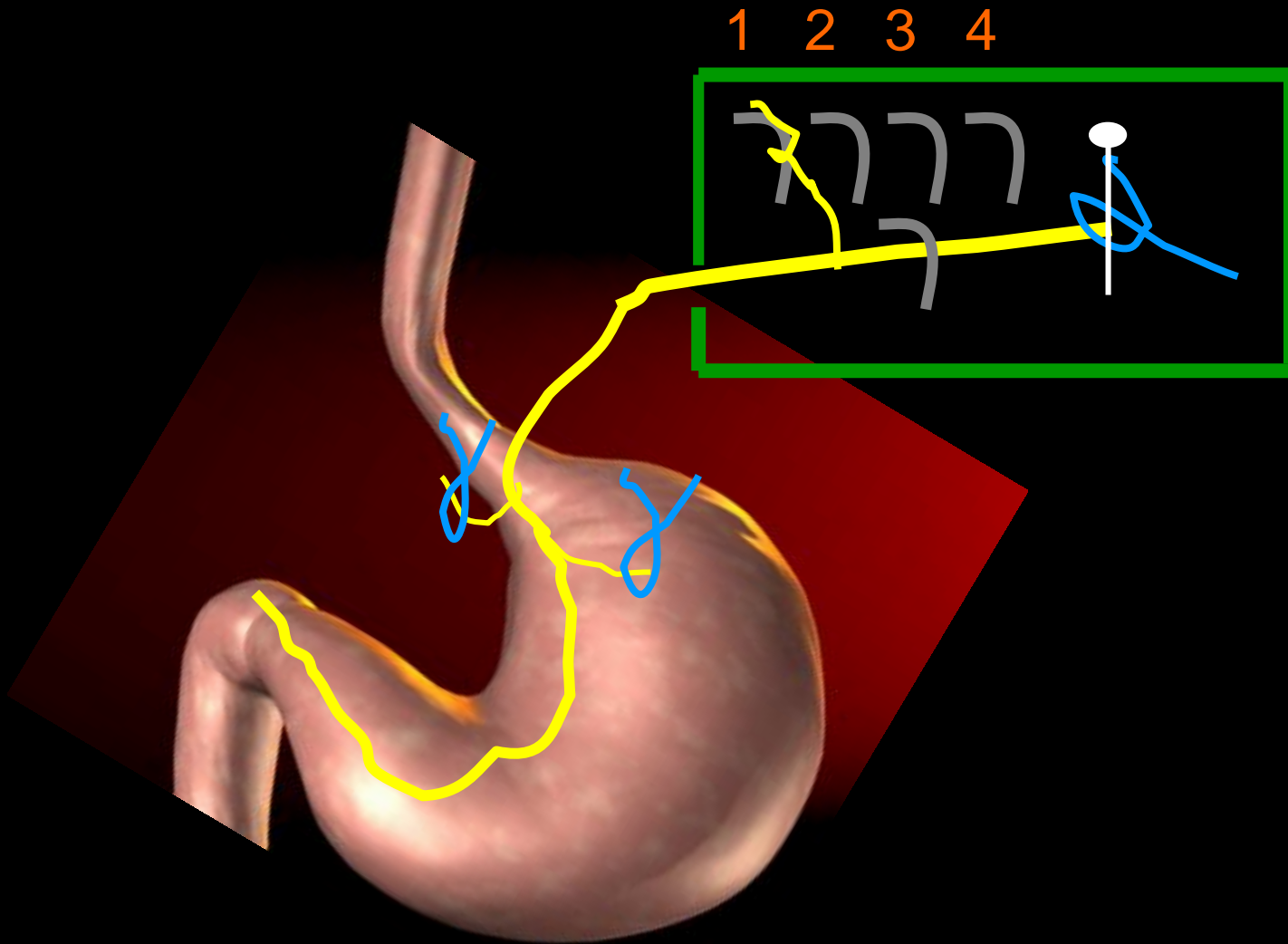


**Study 1: Afferent gastric vagal signaling in response to cisplatin**

# Rig setup



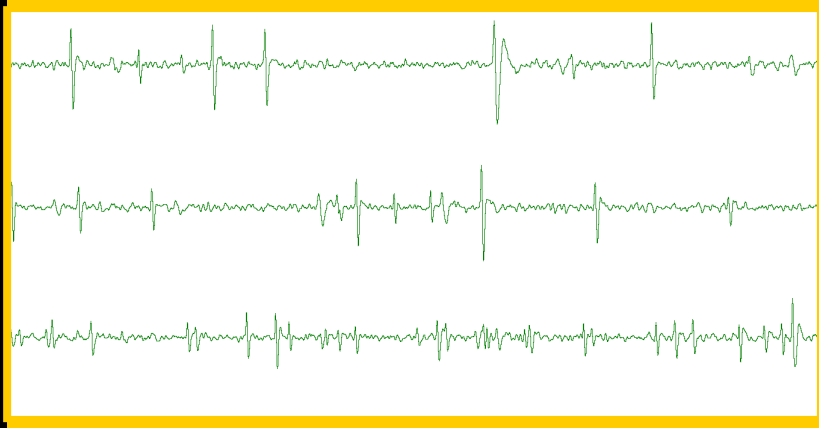
# Recording from gastric vagus



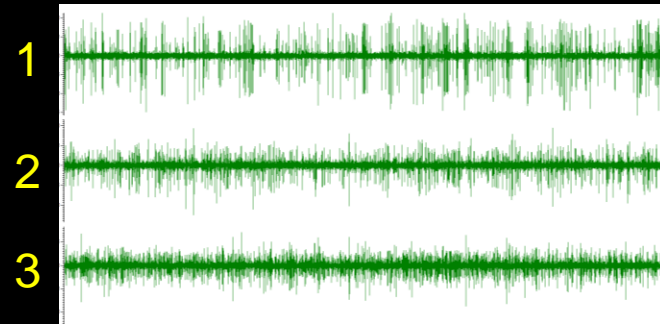


# Gastric vagal recordings

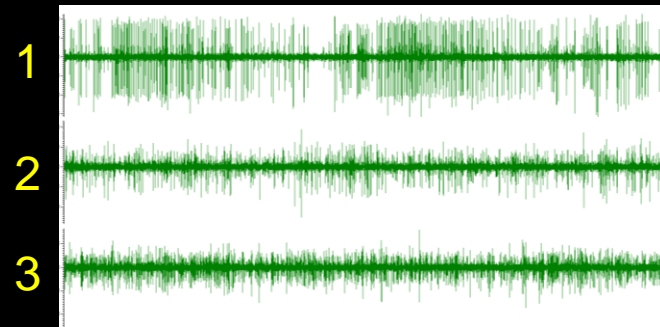
QC Issues



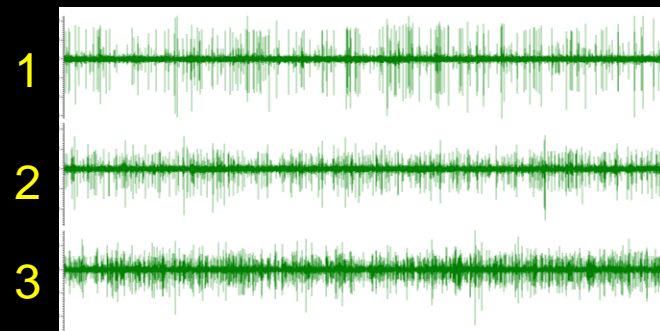
200  $\mu$ V  
40 ms



Baseline



Post-  
Cisplatin

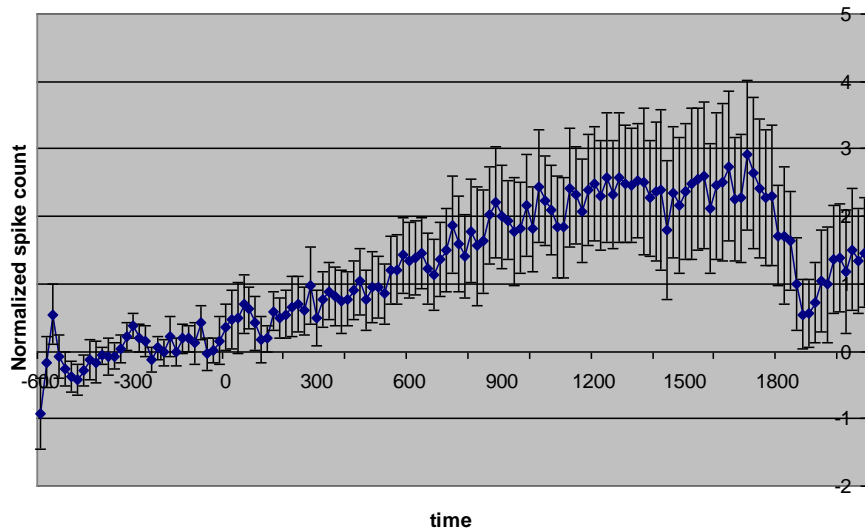


Post-  
Y25130

200  $\mu$ V  
1.25 s

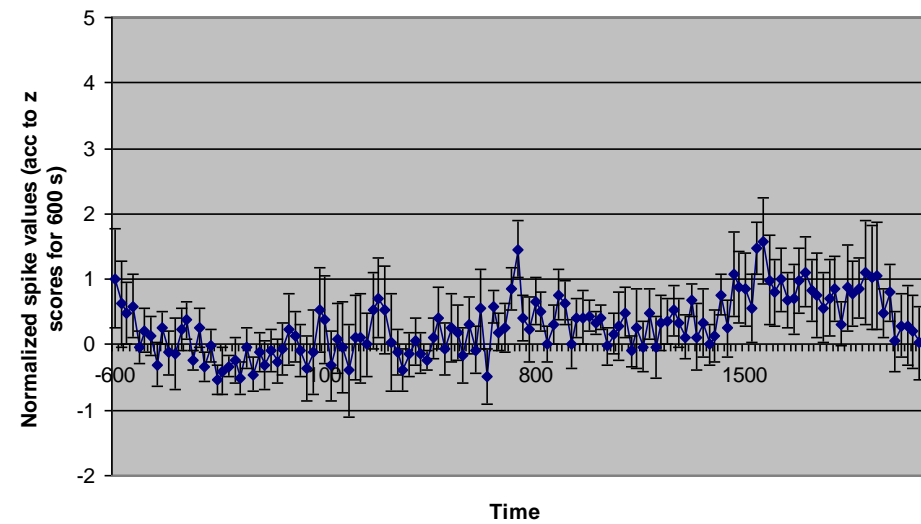
# Effect of cisplatin on gastric vagal activity

VT Vagus Cisplatin (Multiunit activity)



N=13 filaments

VT Vagus:saline controls

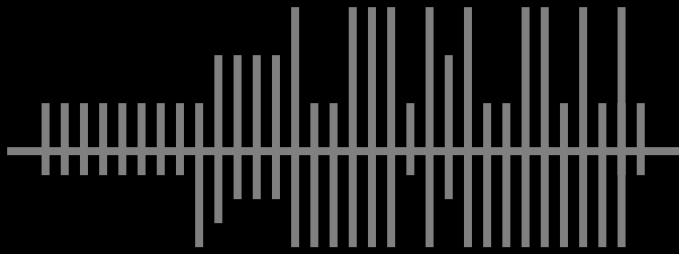


N=7 filaments

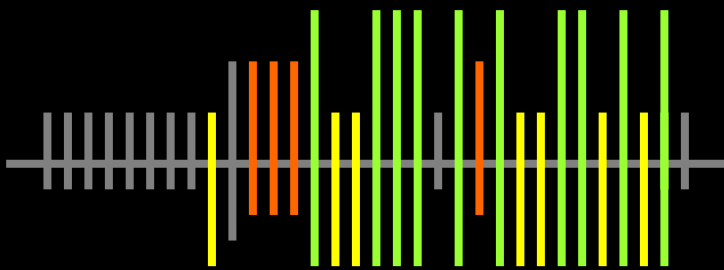
Time (s)

# How to look at single units?

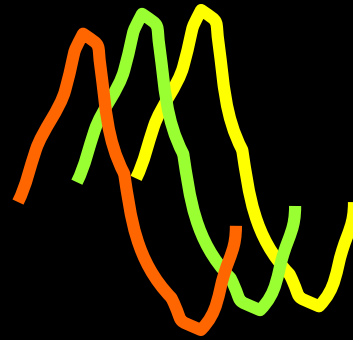
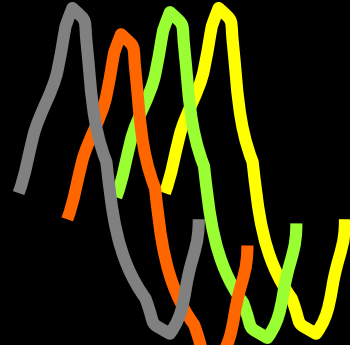
Unsorted spikes



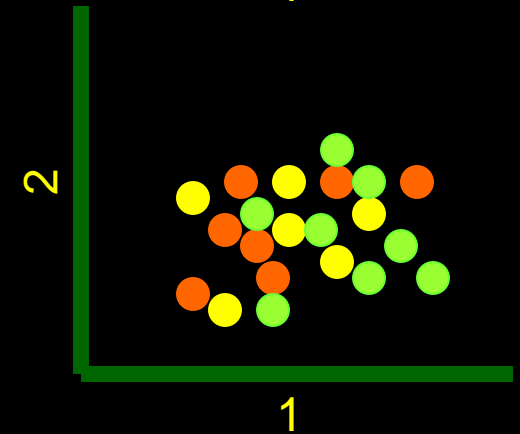
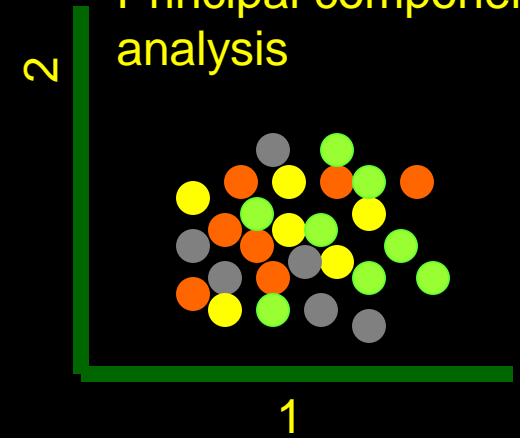
Sorted spikes



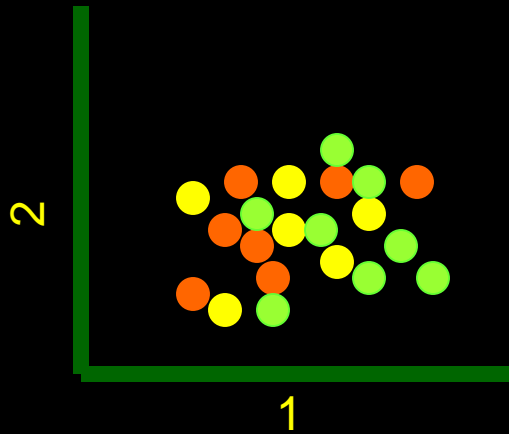
Template matching



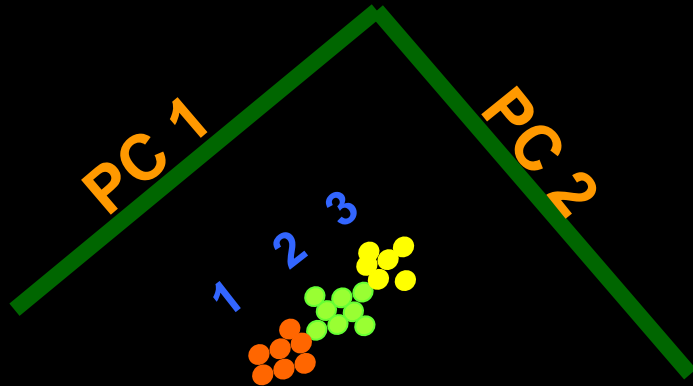
Principal component analysis



# How to look at single units?



Valley-seeking for clusters



Mahalanobis distance,  $d = 0.25 \times \Sigma^{-1} \times [Parzen]$



Calculate neighbors based on critical distance



Arrange neighbors based on "rank-order"



Find "seed-points" of clusters



Assign points to respective clusters based on multiple assignment (Fukunaga iterations)

# Properties of single units

In 2D Cluster Space:  $F(6,4246) = 10.085350$

In 3D Cluster Space:  $F(9,5165) = 8.278938$

$p = 4.26882e-011$

$p = 2.45752e-012$

Counts    ISI < 3000  $\mu$ S

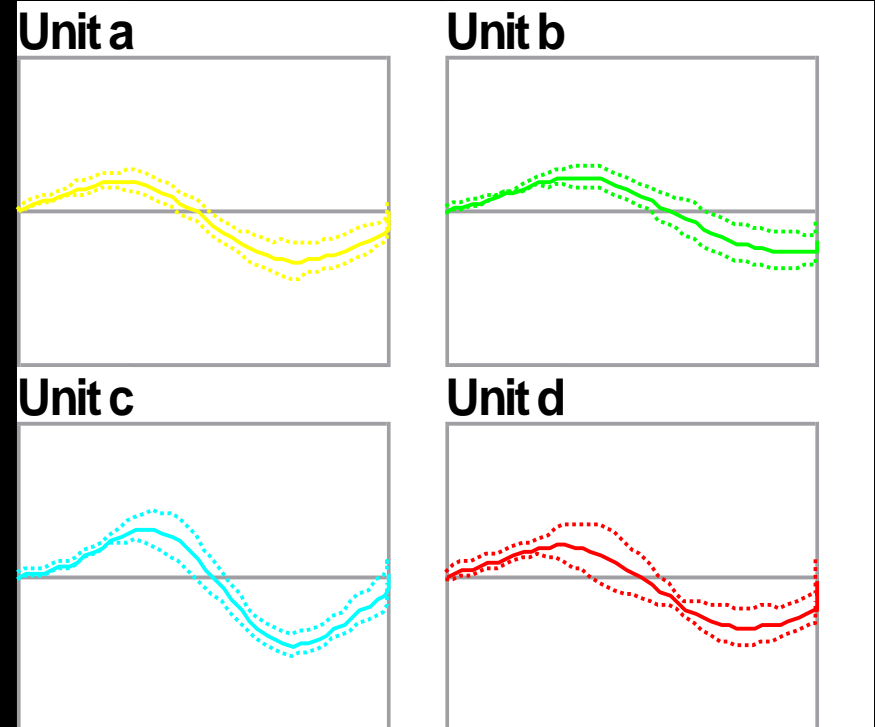
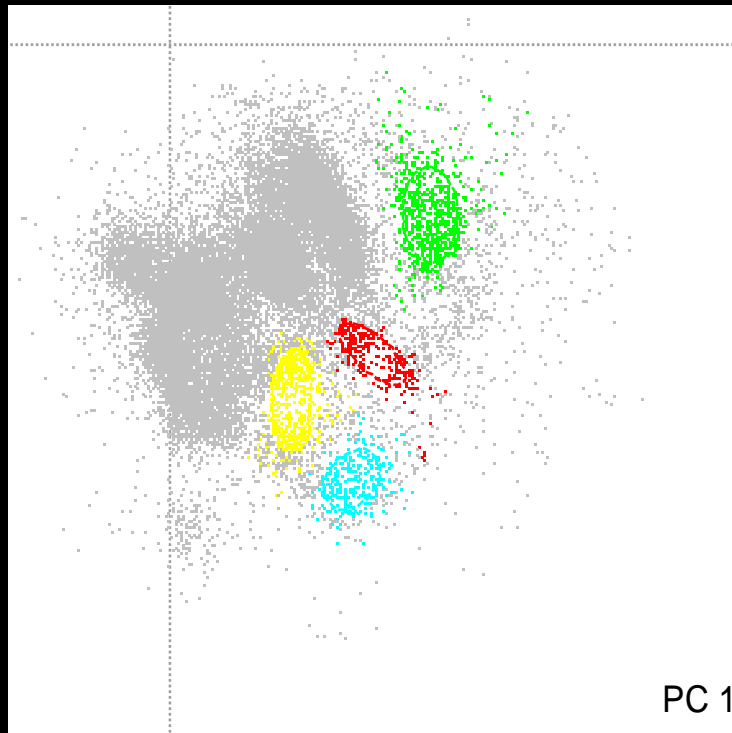
Unit a :    704    0%

Unit b :    806    0%

Unit c :    303    0%

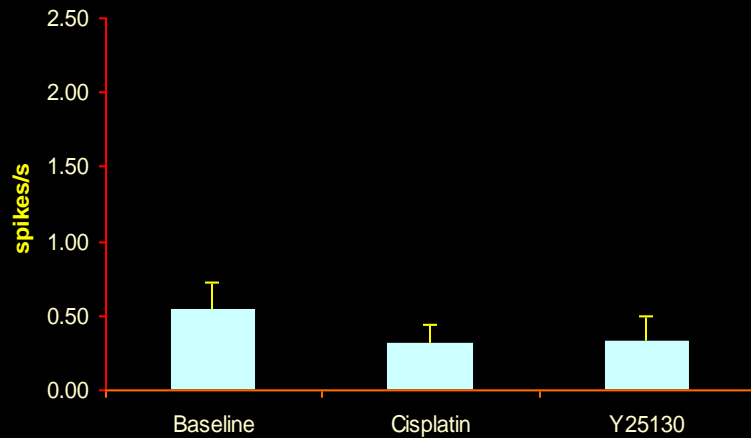
Unit d :    315    0%

2D feature space

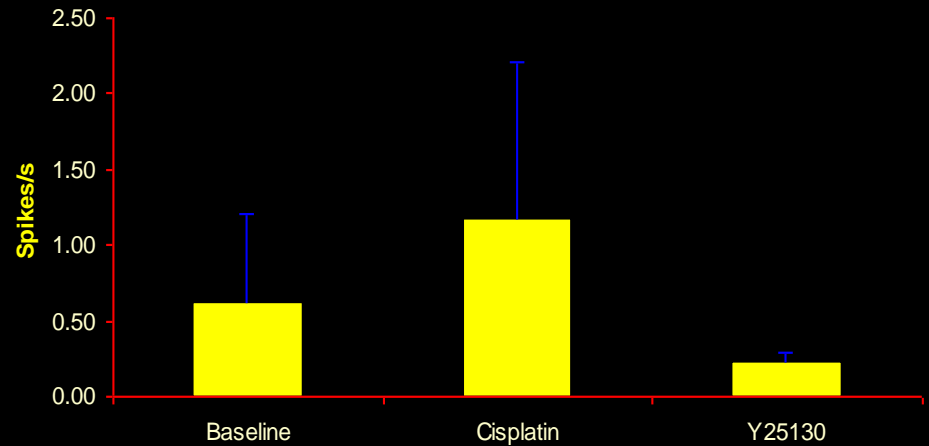


# Effect of cisplatin on single vagal units

Cisplatin-insensitive Units (14)



Cisplatin-sensitive Units (3)

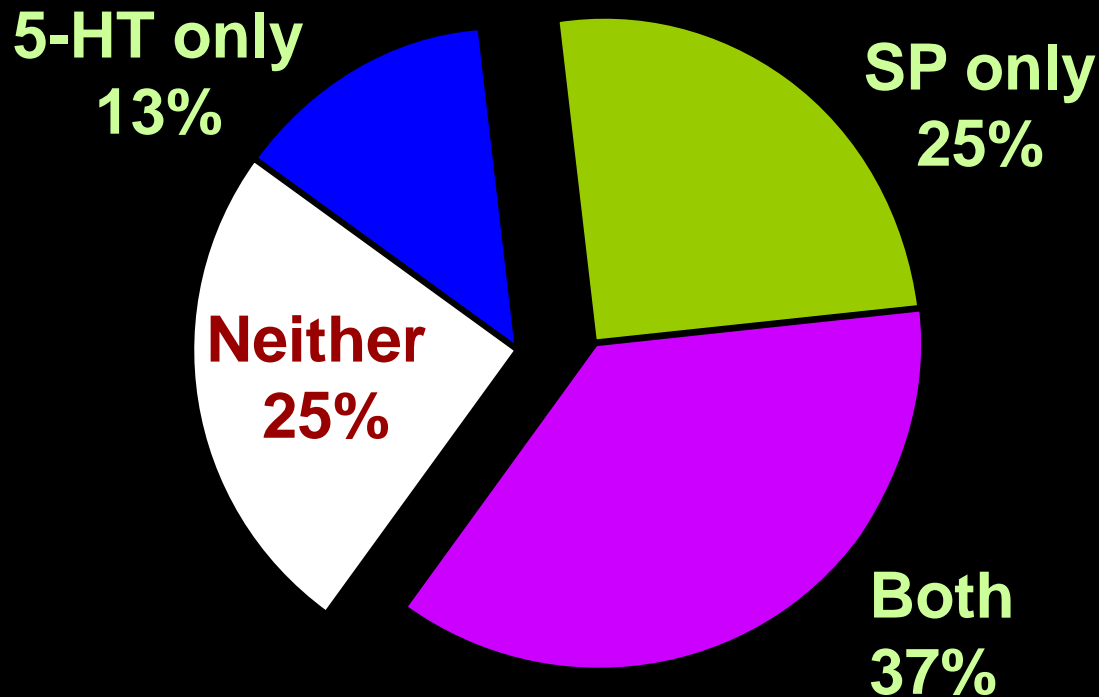


N=4 rats, 5 filaments

# Study 2: Neurochemical Interactions in Afferent Vagal Signaling

*Horn & Chaudhury, Neurogastroenterol Motil 18(8): 683, Aug 2006*

# Ventral vagal afferents sensitive to both 5-HT & SP

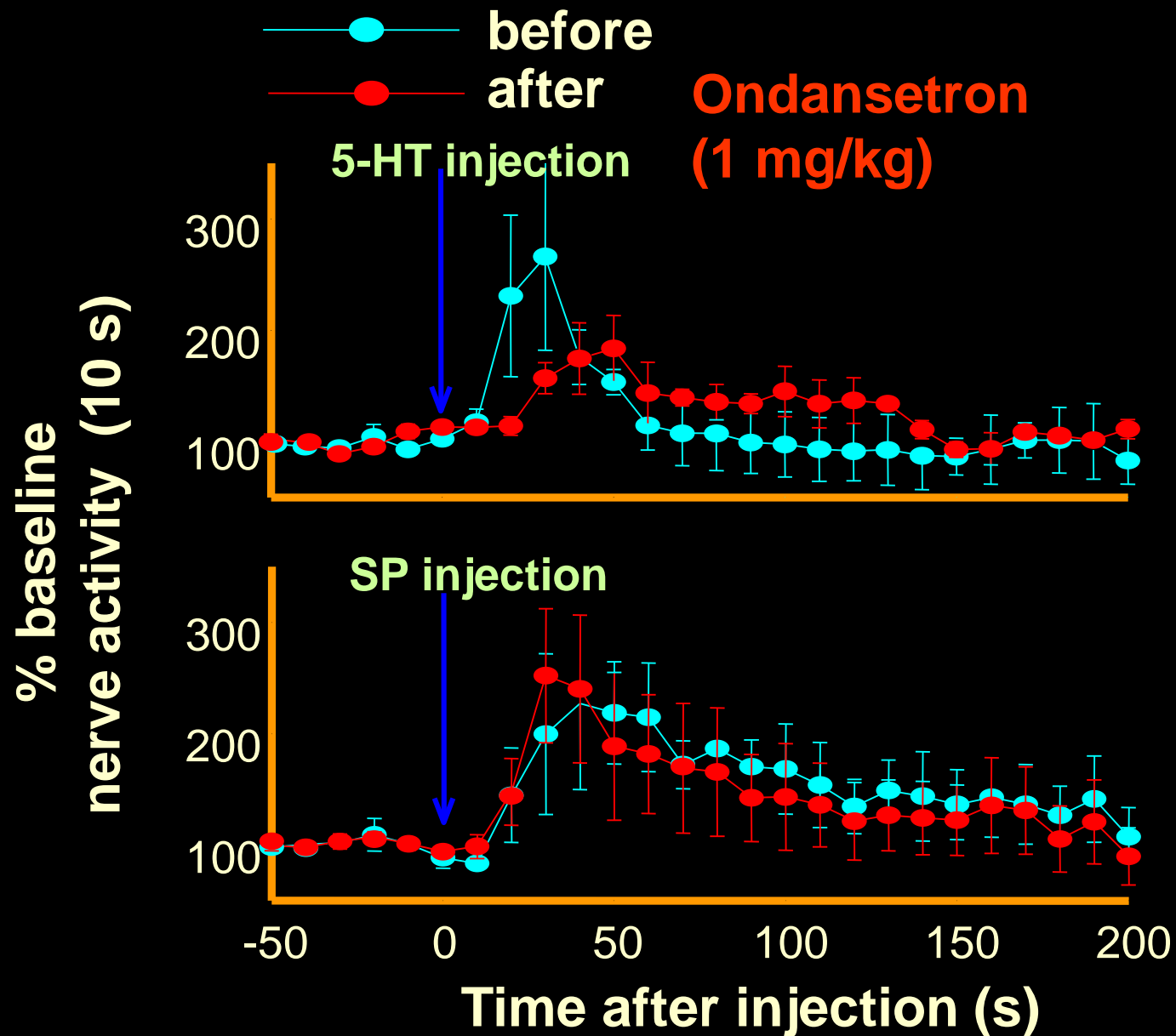


10 rats, ventral  
vagus

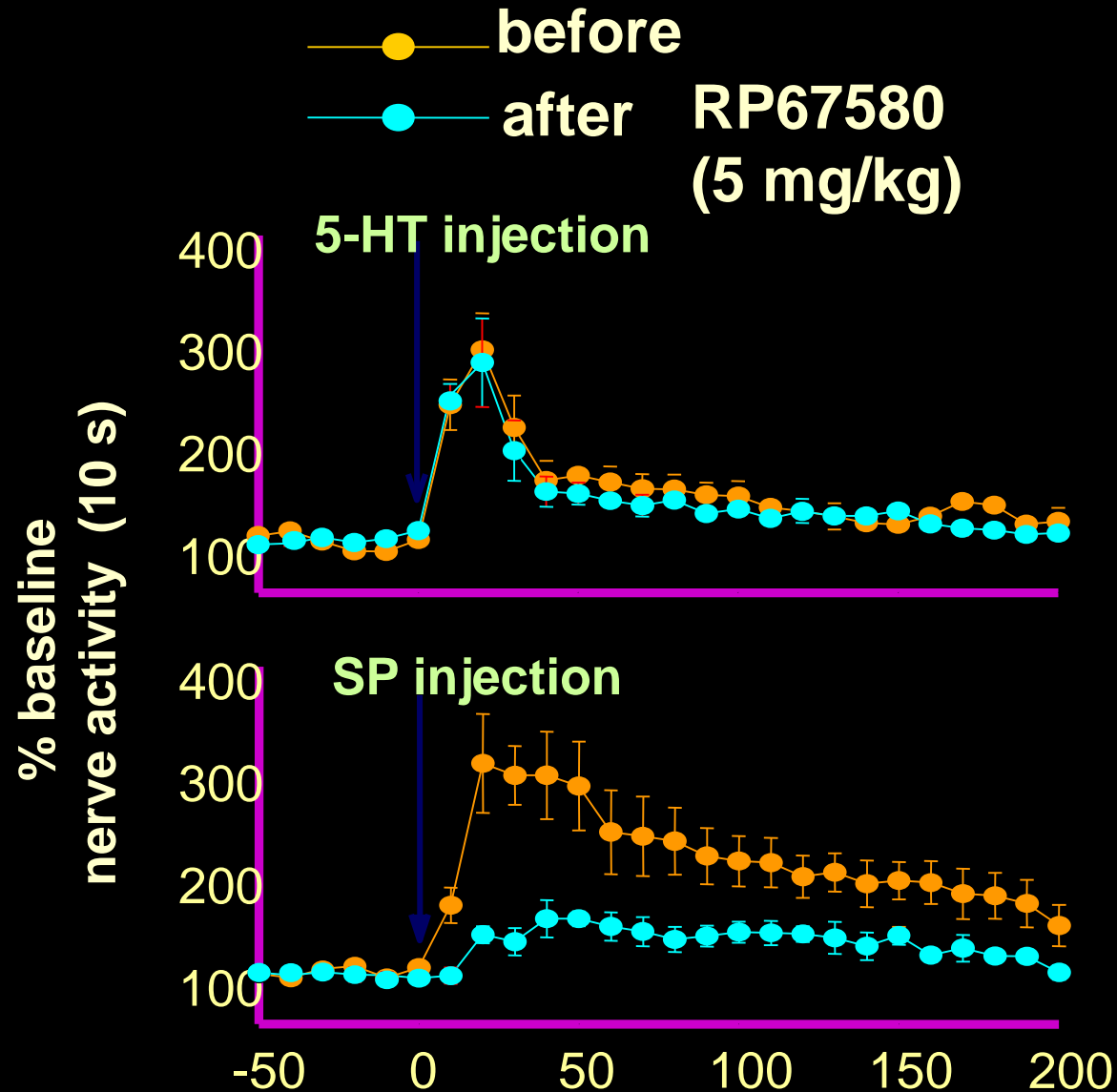
52 single units, 26  
filaments



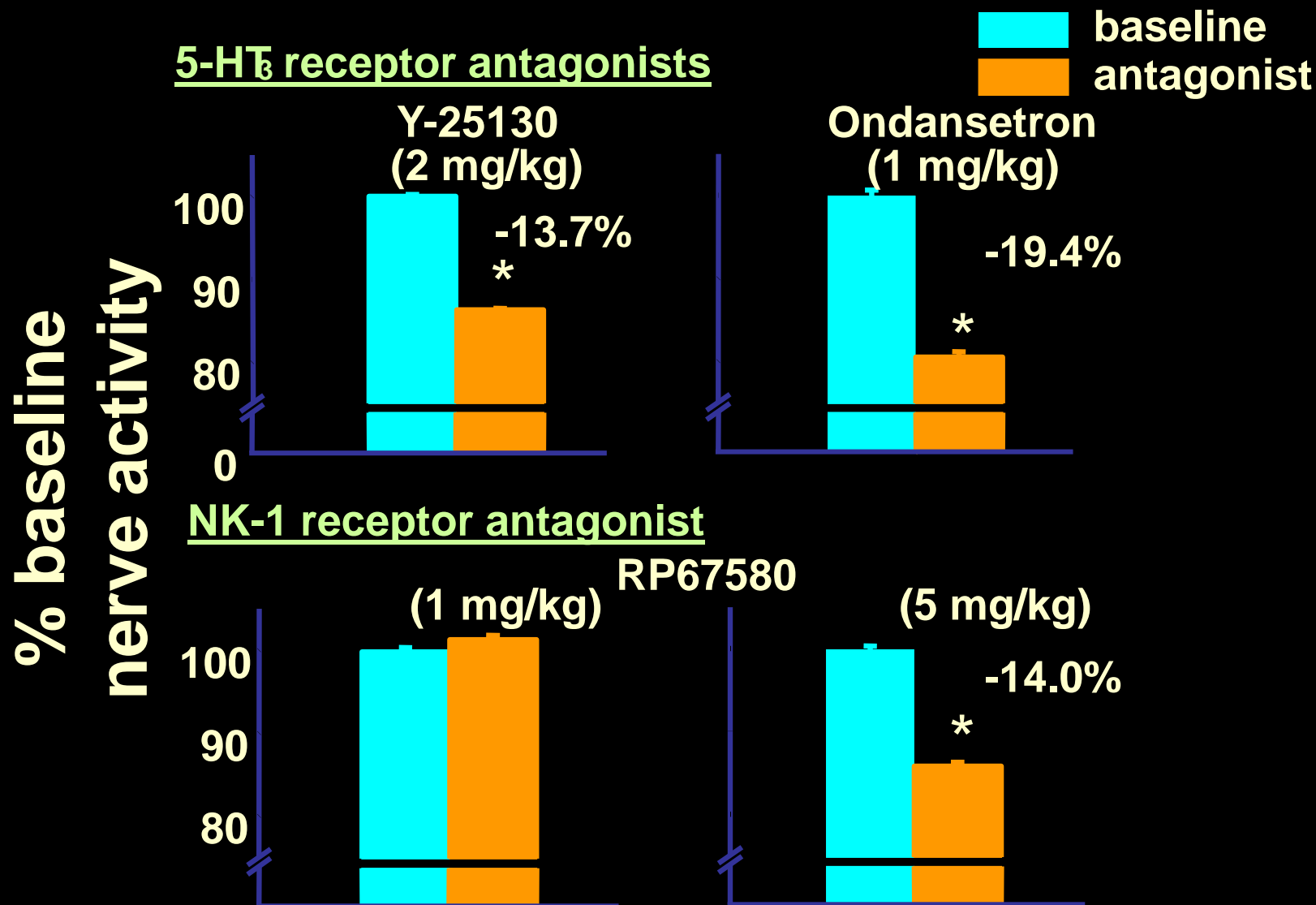
# 5-HT<sub>3</sub> Antagonist reduce Serotonin activity



# NK<sub>1</sub> antagonist reduce SP activity



# Antiemetics reduce basal vagal afferent activity



# Study 3: Effect of hepatic branch vagotomy on Pica

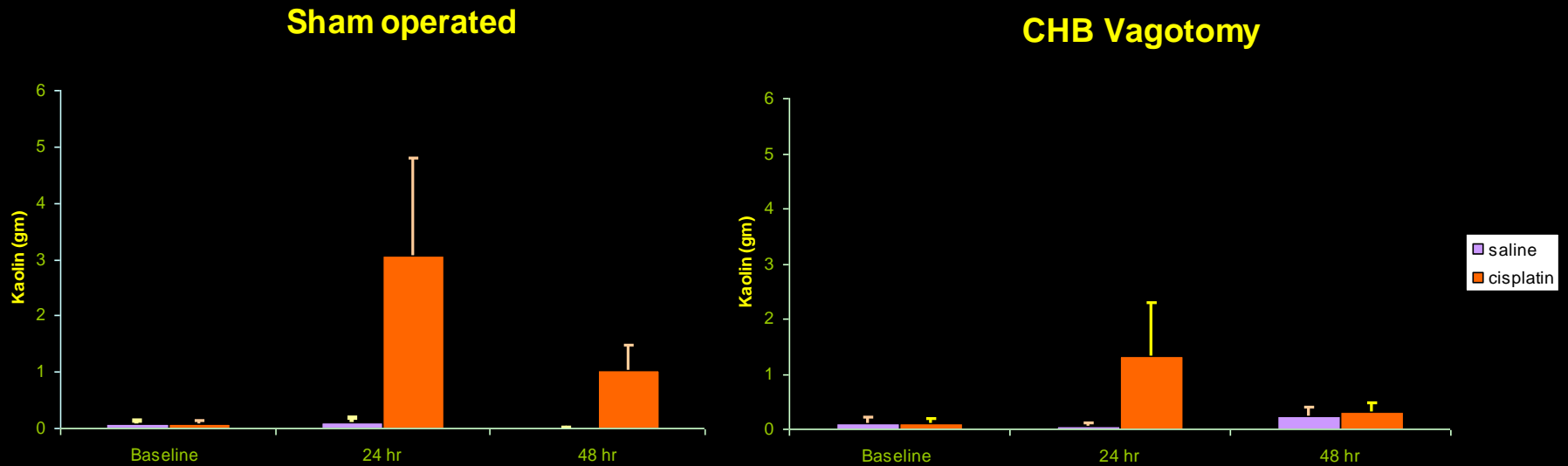
# Behavioral Experimental design

	Sham	CHB Vagotomy
saline	N=8	N=8
cisplatin	N=5	N=7



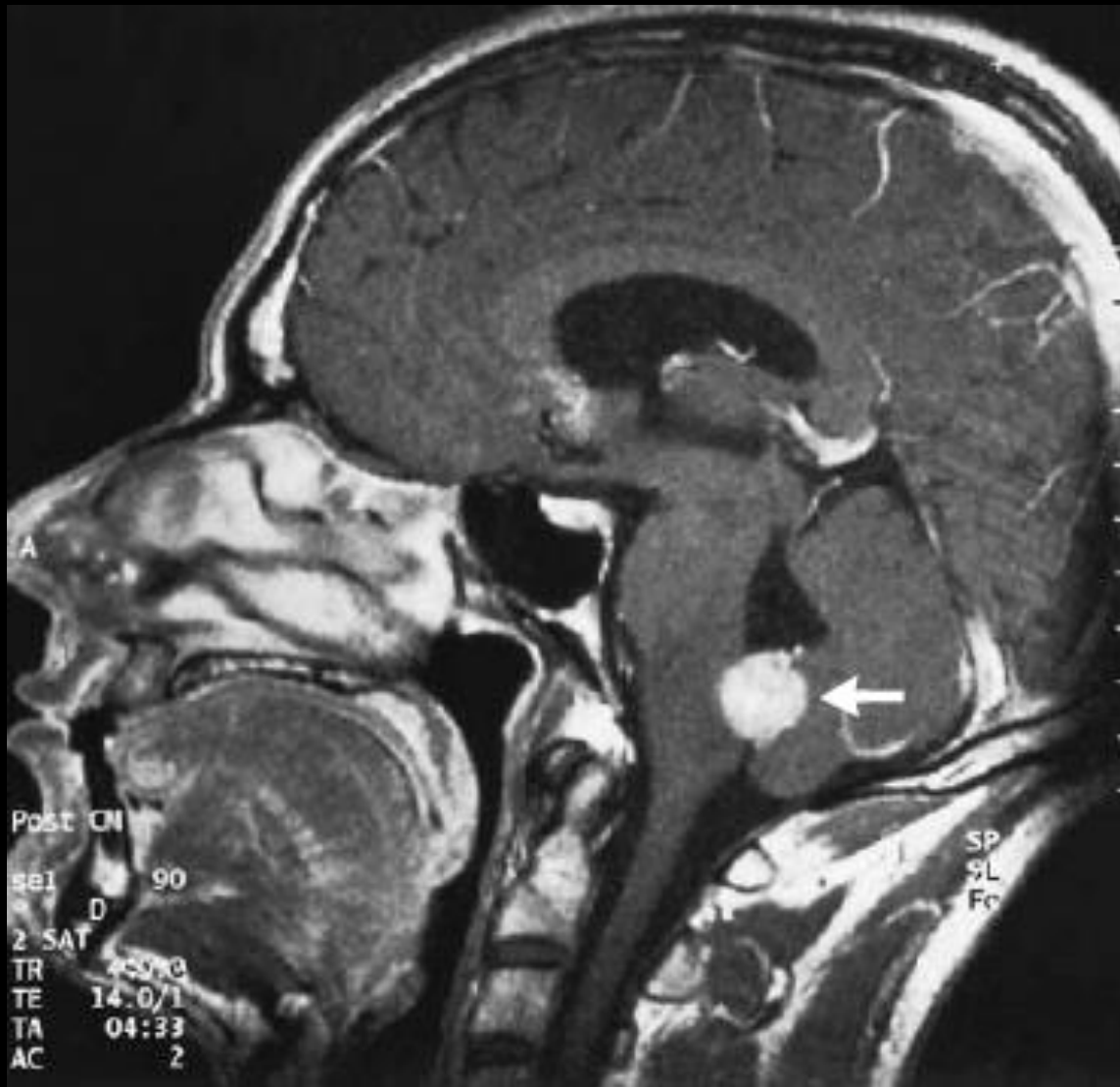
# Effect of CHB Vagotomy on Pica Behavior

## Kaolin



Which brain regions involved in sickness?

# Brainstem contribution to sickness



- 25 yr, male
- 7 mo H/O repeated, unprovoked, sudden vomiting
- Daily vomiting in previous 2 mo
- No headache, neurologic or other gastrointestinal symptom

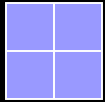
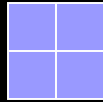


# Hints indicating forebrain involvement in nausea

Nausea: a conscious sensation

*(Sangers & Andrews Aut Neurosci , Aug, 2006)*

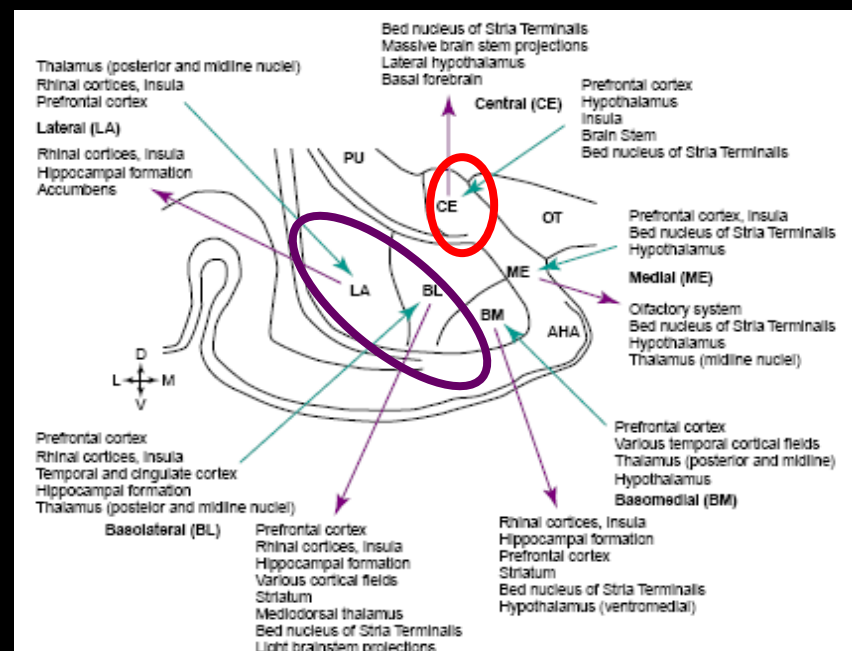
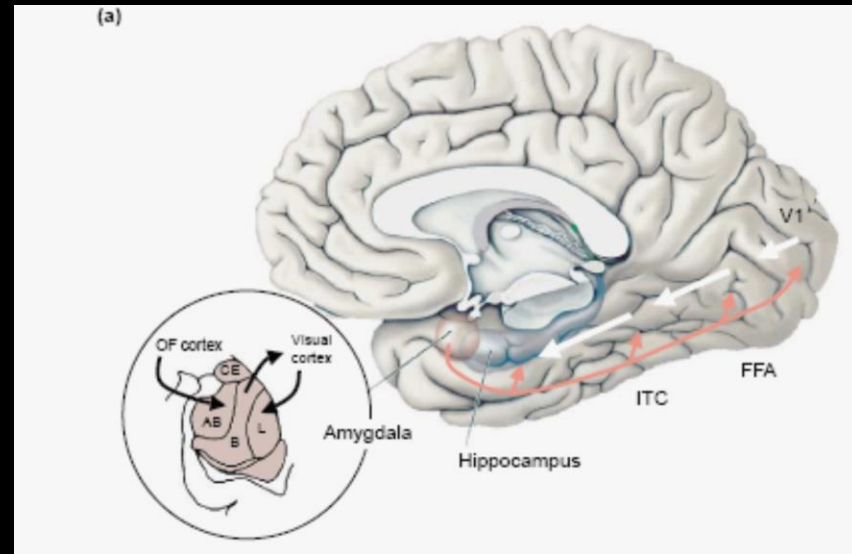
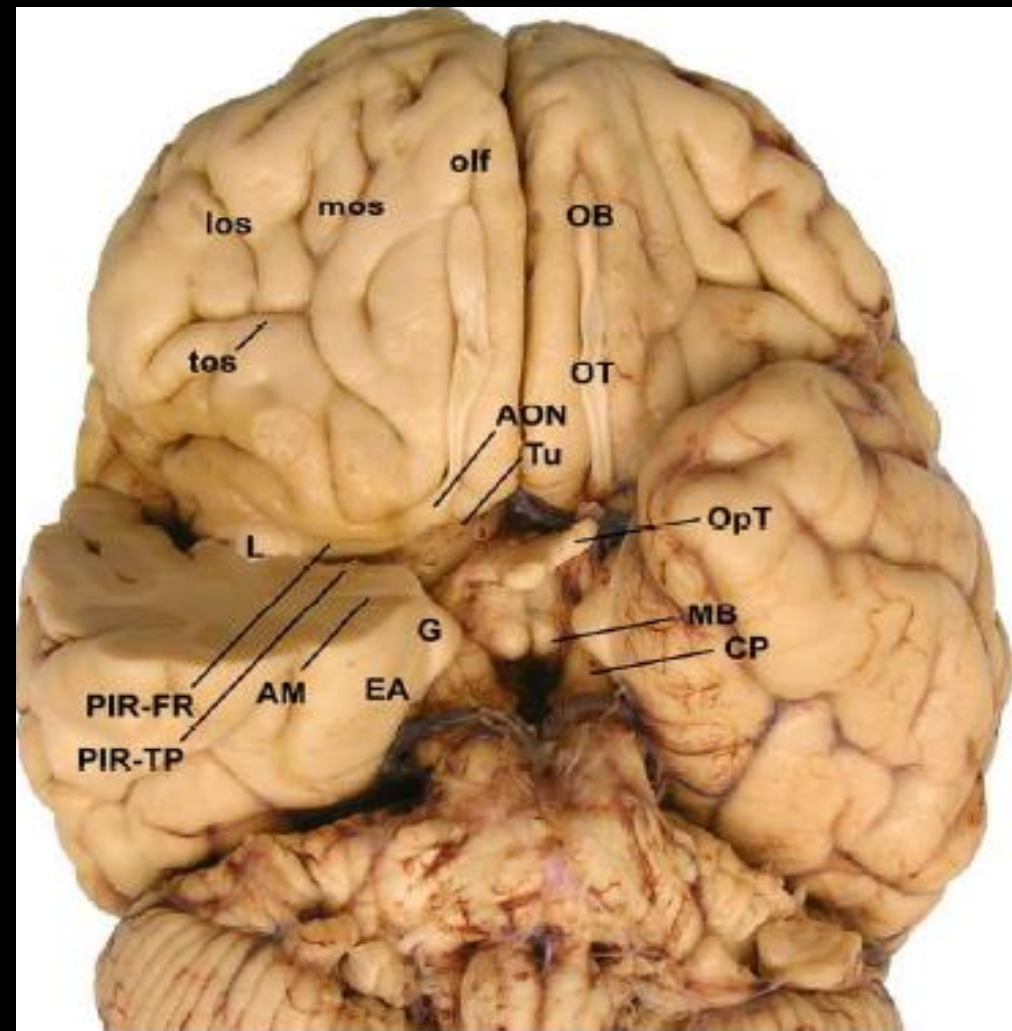
# What is conditioned flavor aversion?



# ? Amygdala & Visceral Illness

- Conditioned flavor aversion
- Visceral epilepsy: Ictus vomiticus

# Where is the amygdala?

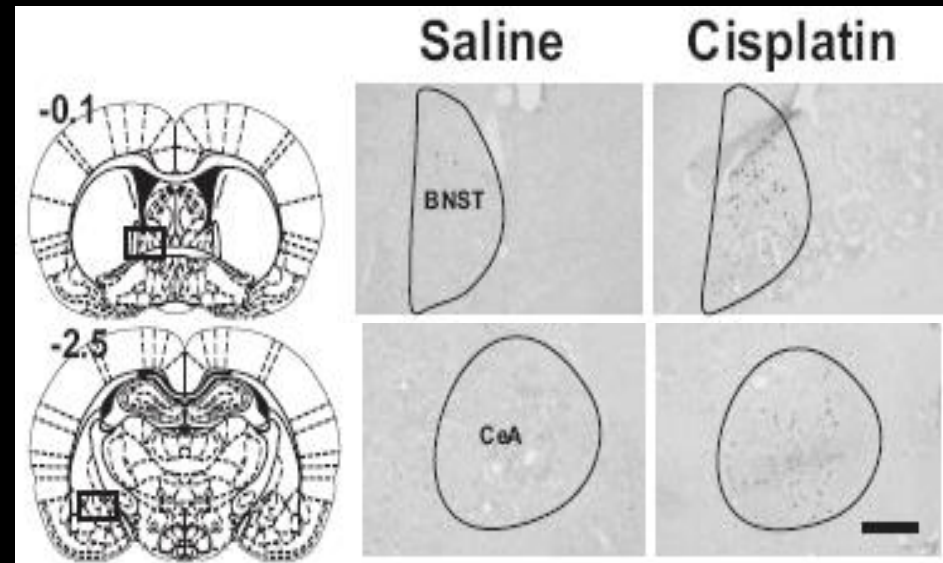
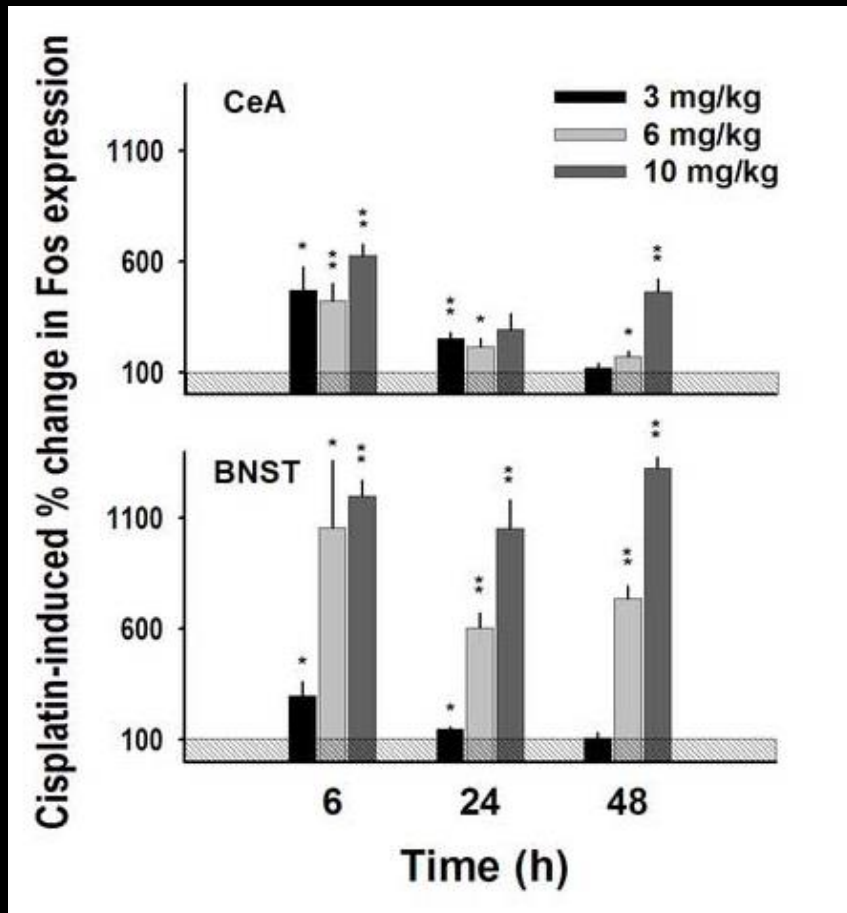


*Vuilleumier, TICS, 9: 585, 2005*

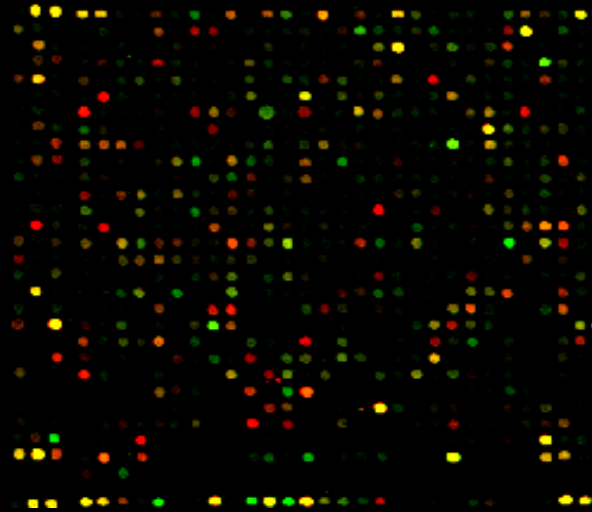
# Study 4: Brain Fos expression during 48 h after cisplatin treatment

*Horn, Ciucci & Chaudhury, In Press, Autonomic Neurosci, 2006.*

# Cisplatin induce Fos in amygdala



N=90 rats



## Study 5: Global gene expression profiling in amygdala in response to cisplatin

*Chaudhury & Horn, Neurogastroenterol Motil 18(8): 682, Aug 2006.*

*Chaudhury & Horn, Submission, Oct 2006.*

# Experimental design for gene expression analysis

Cisplatin ip

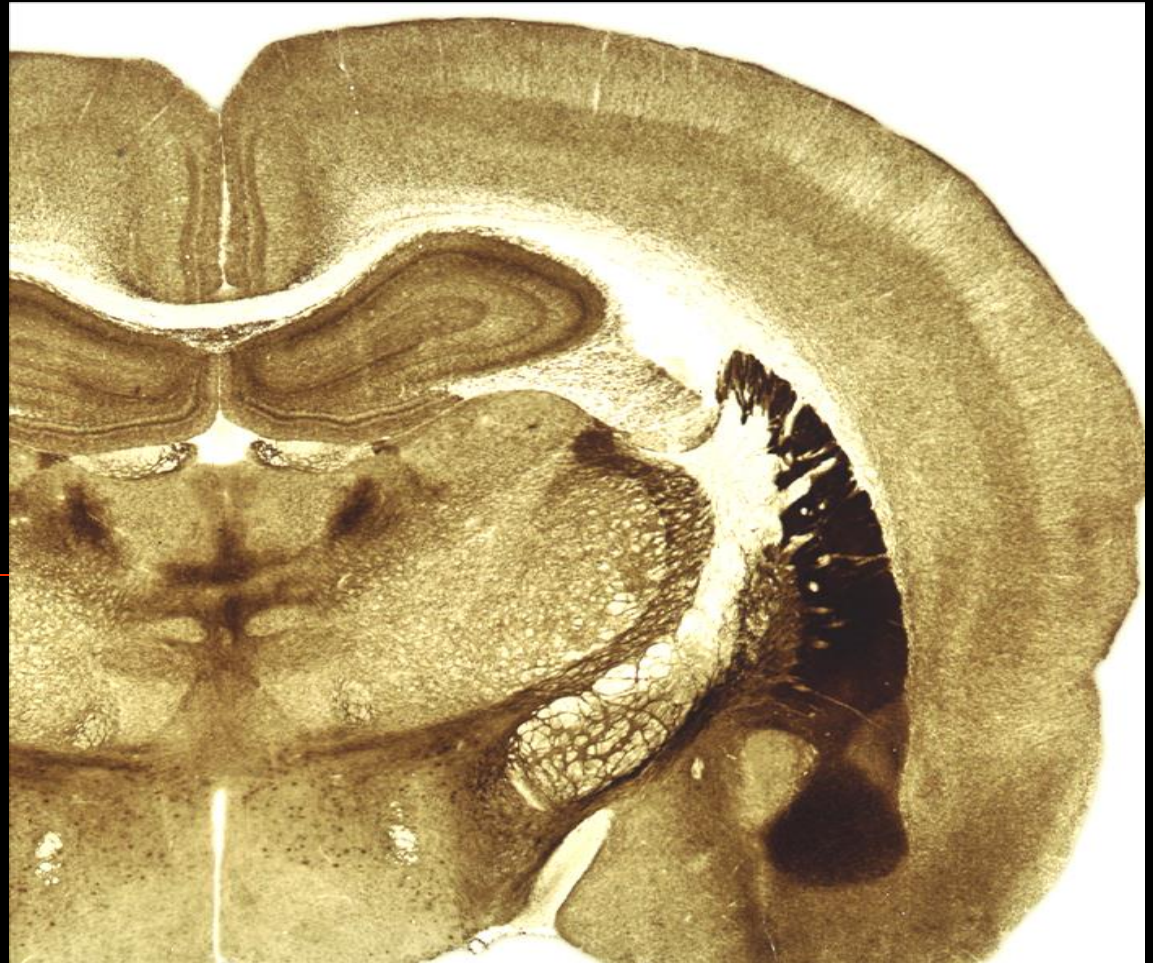
10 mg/kg/ml



24 hrs



Saline ip

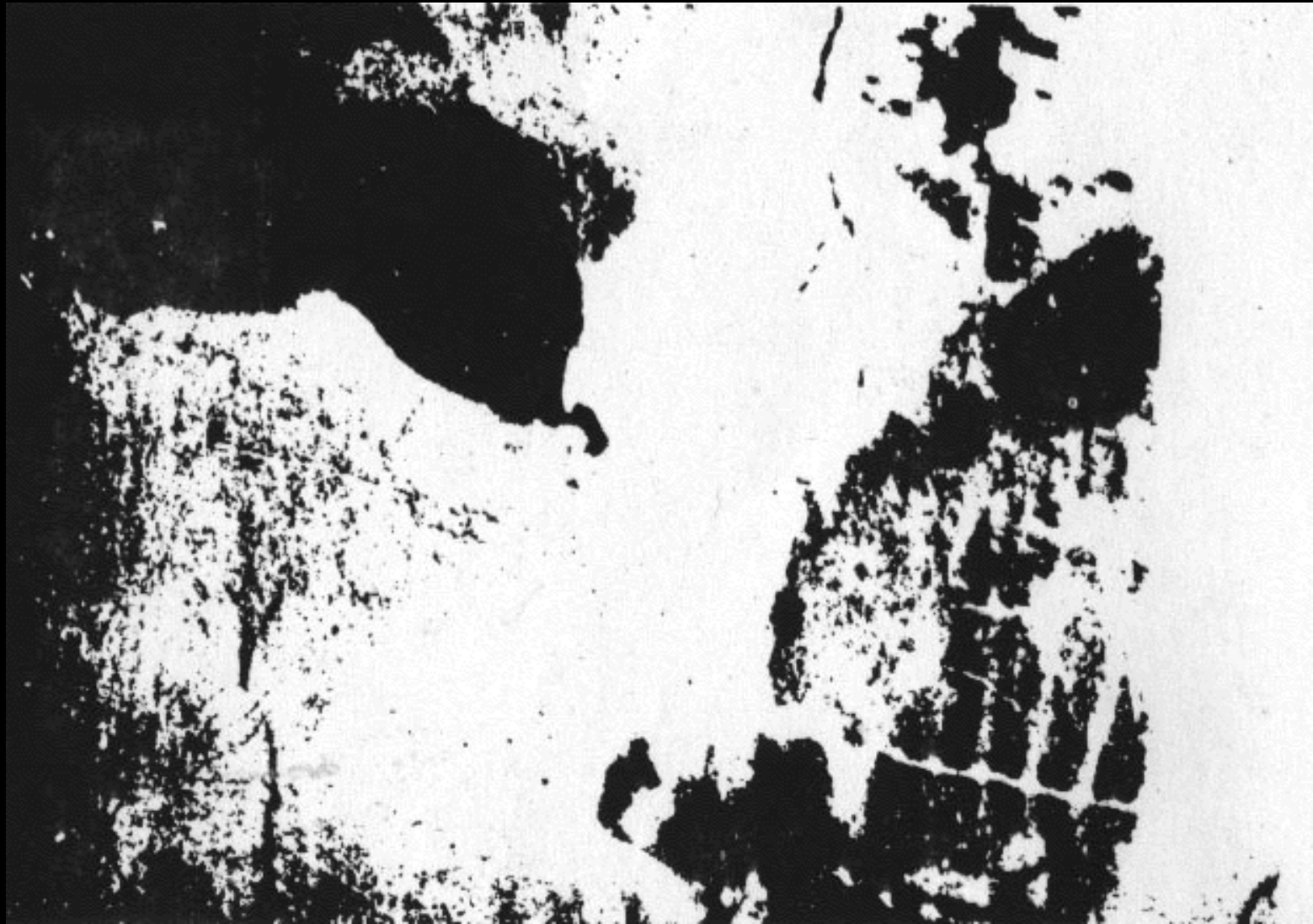


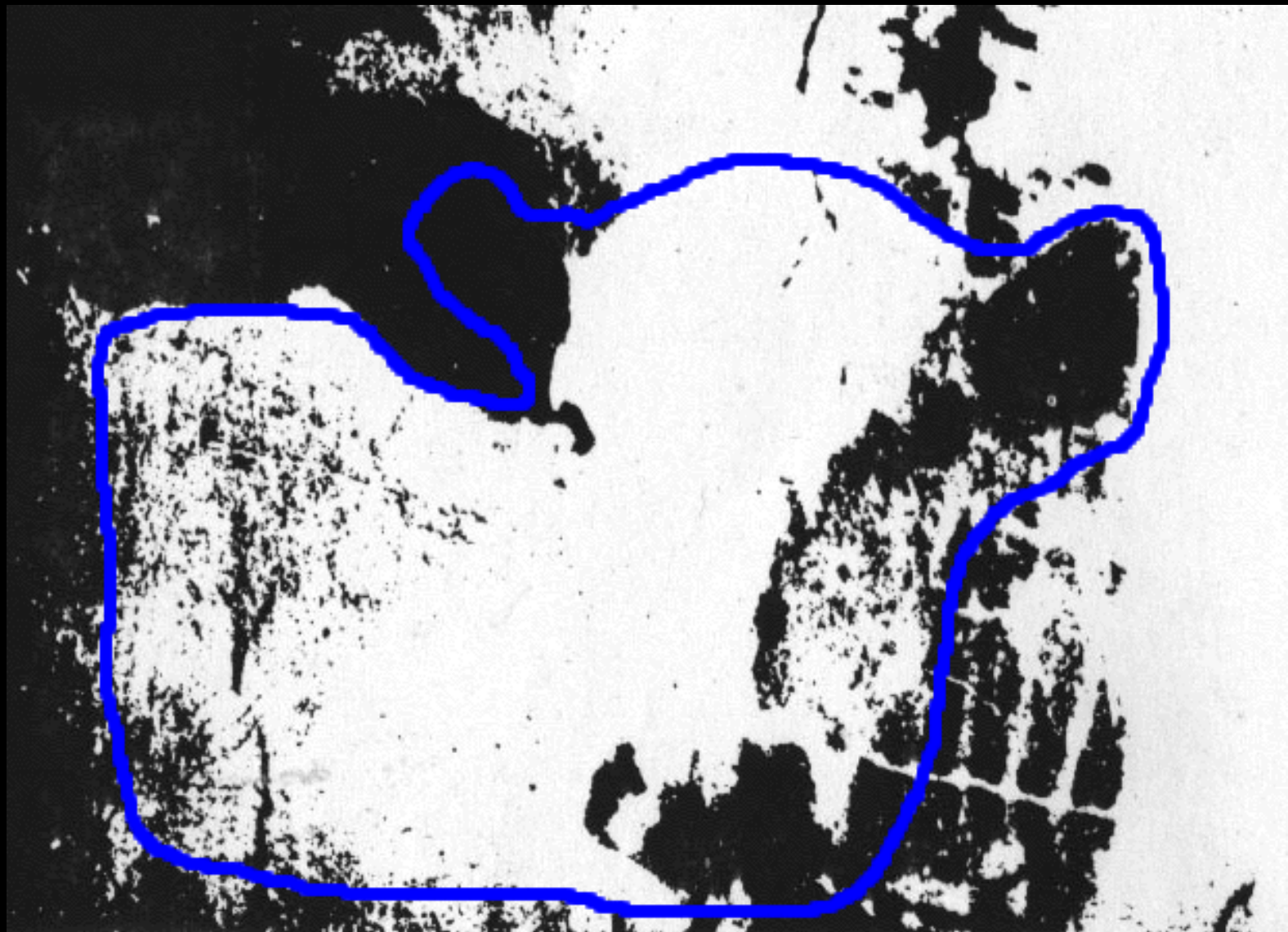
*Adapted from*

*Paxinos & Watson*

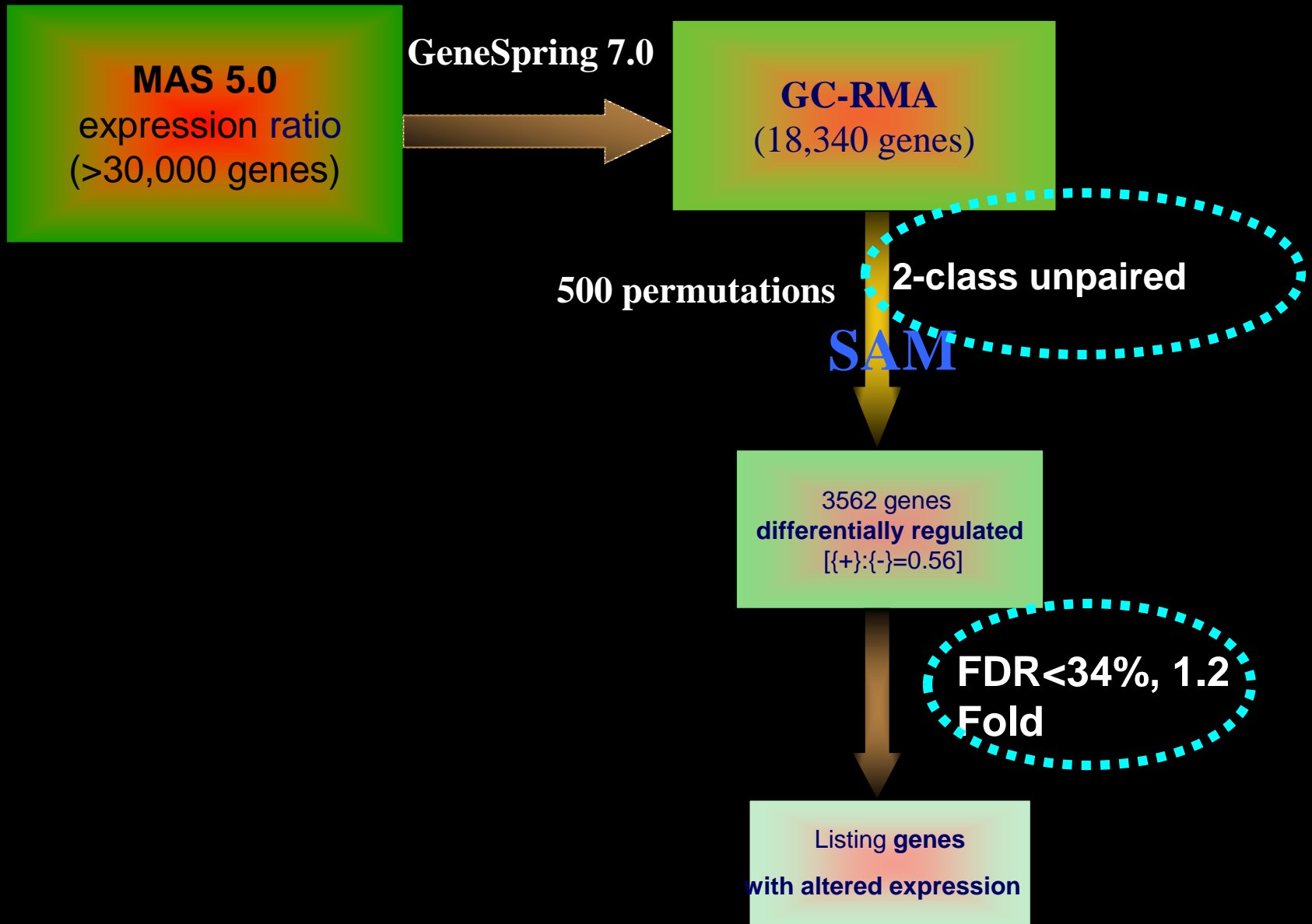


# Pattern recognition in a complex dataset

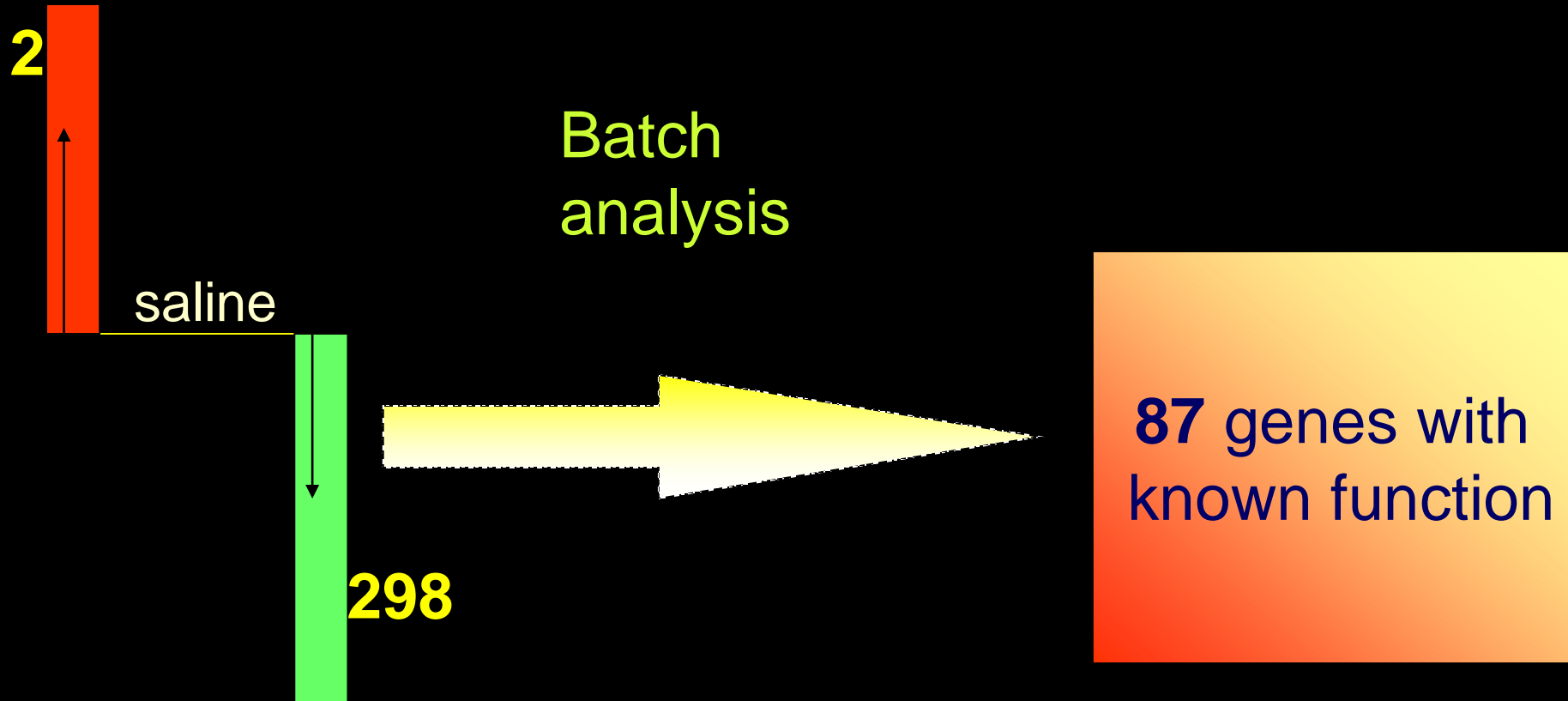




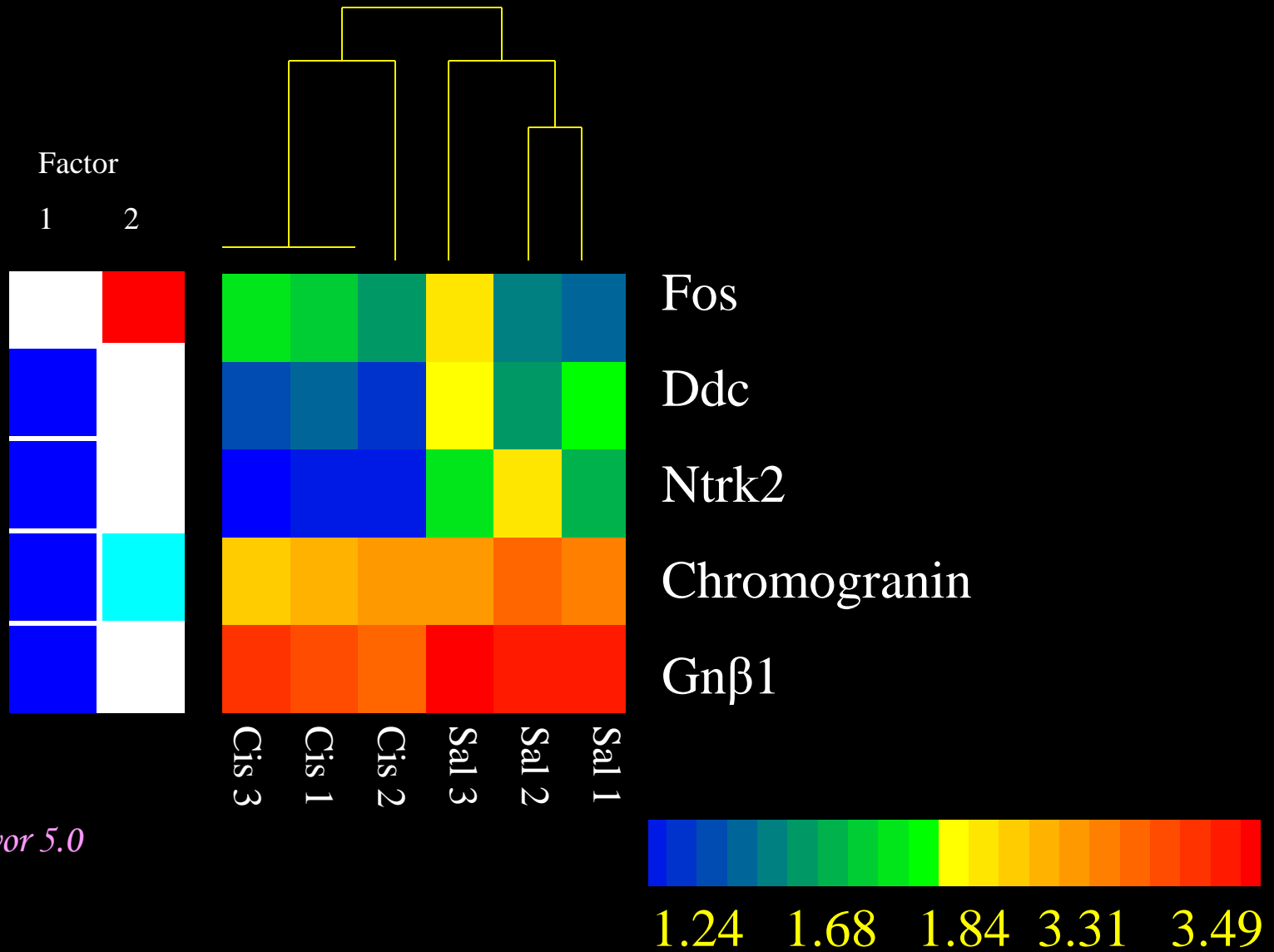
# Test for significant genes



# List of amygdalar genes affected by cisplatin

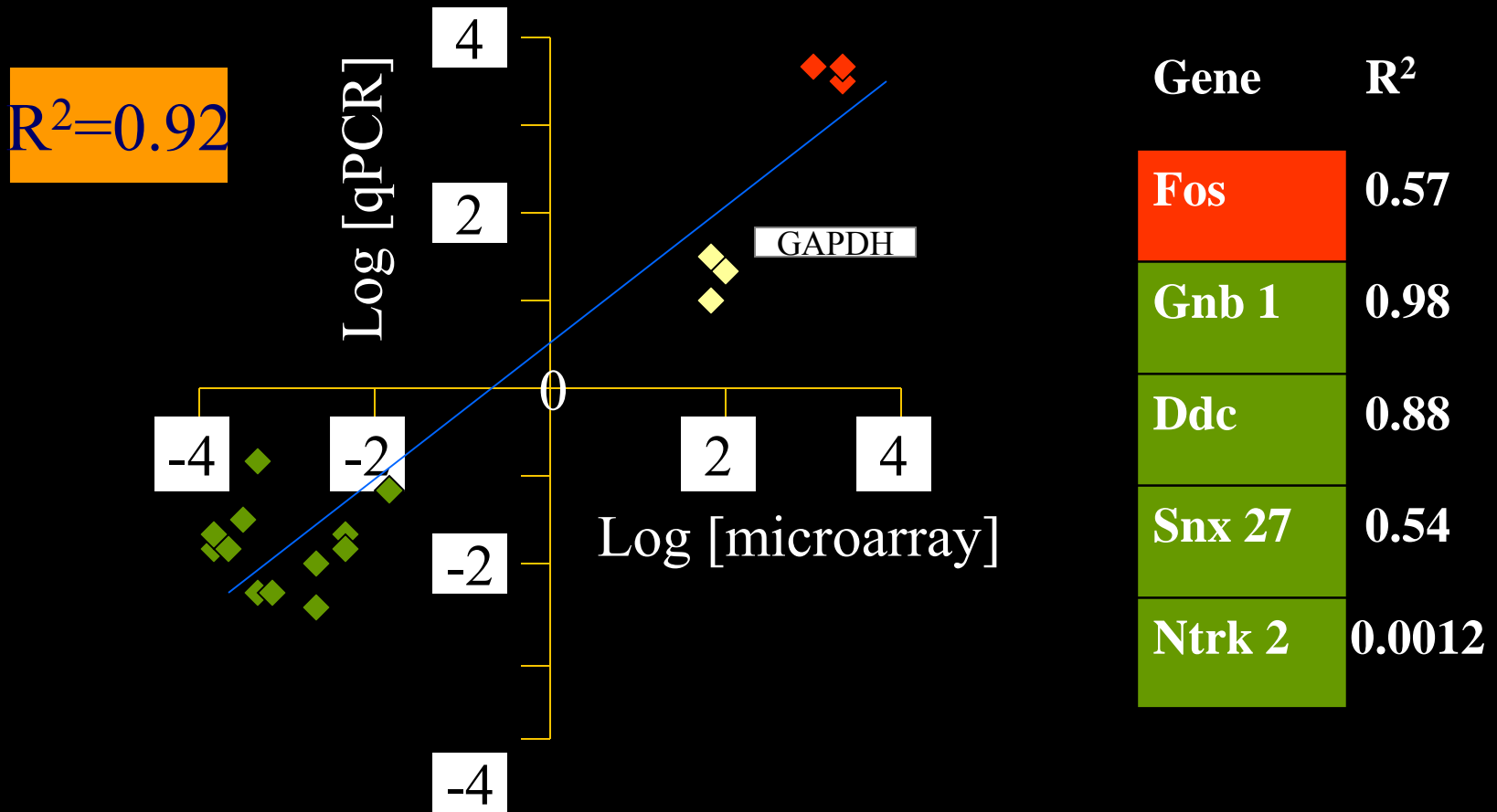


# Heatmap of genes related to sickness/feeding behavior

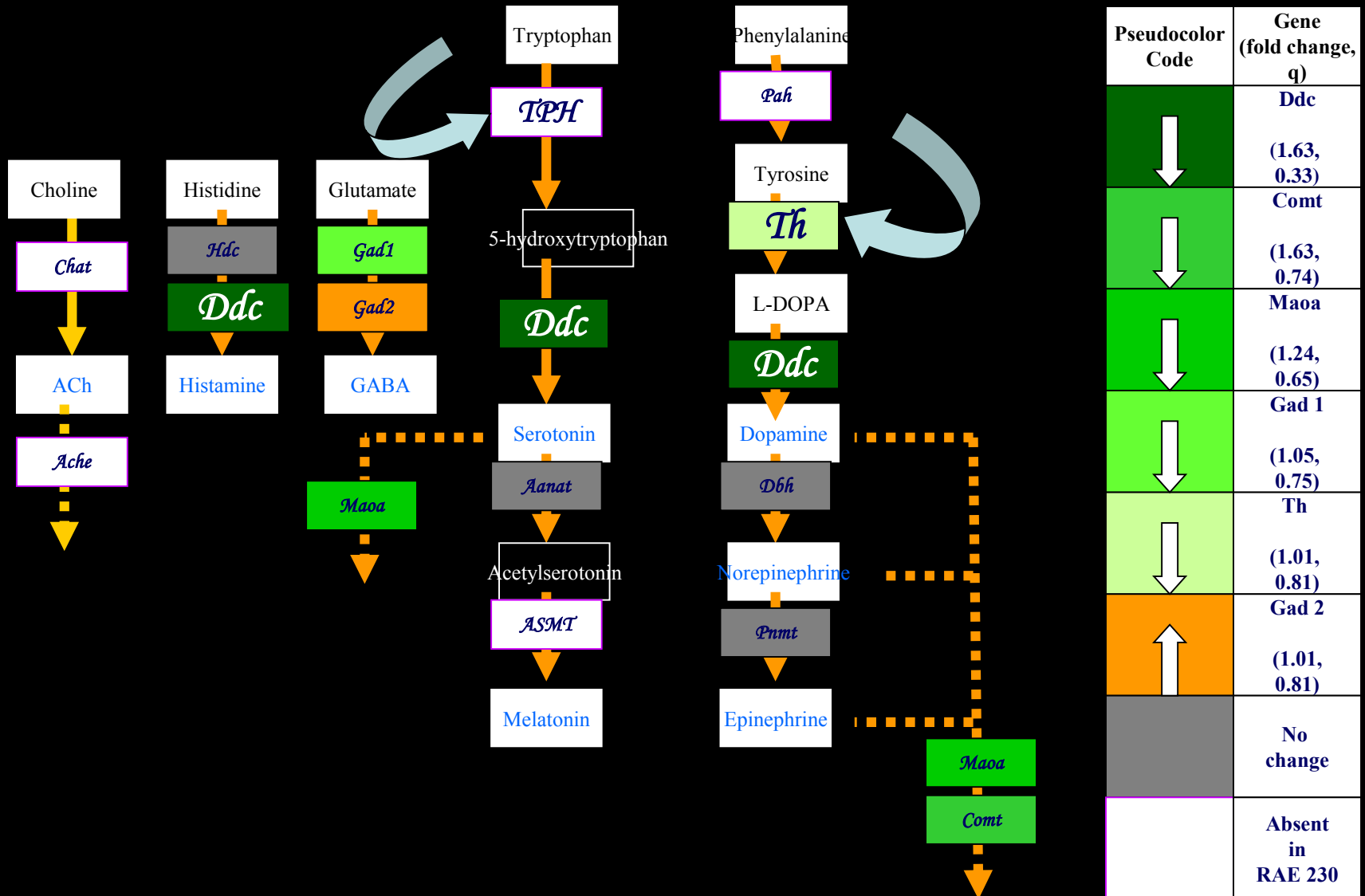


Clusfavor 5.0

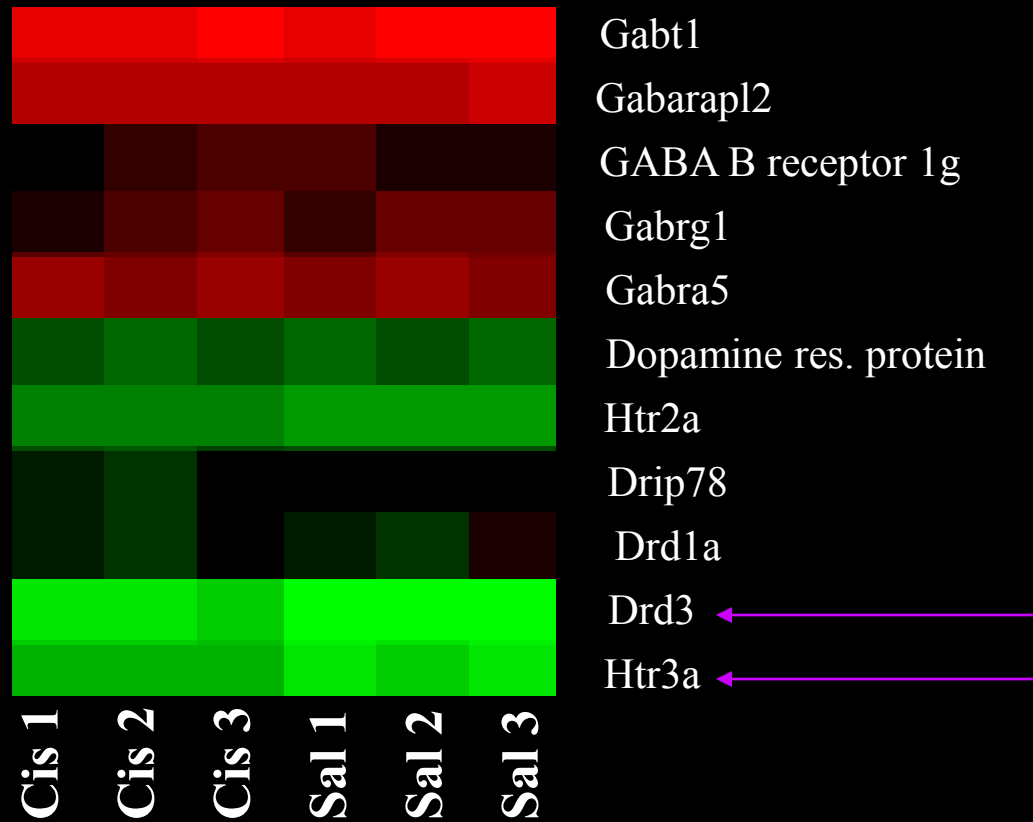
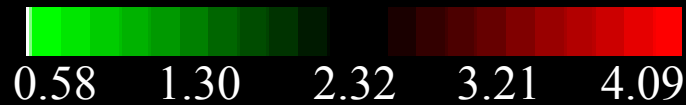
# Correlogram of microarray & qPCR gene expression



# Alterations in amine biosynthetic enzymes



# Changes in monoamine-receptor gene expression





# Future experiments: Top-down approach to consolidate power of microarray study

Pretreatment  
with saline

Pretreatment  
with “anti-  
emetic”

Saline

N=5

N=5

cisplatin

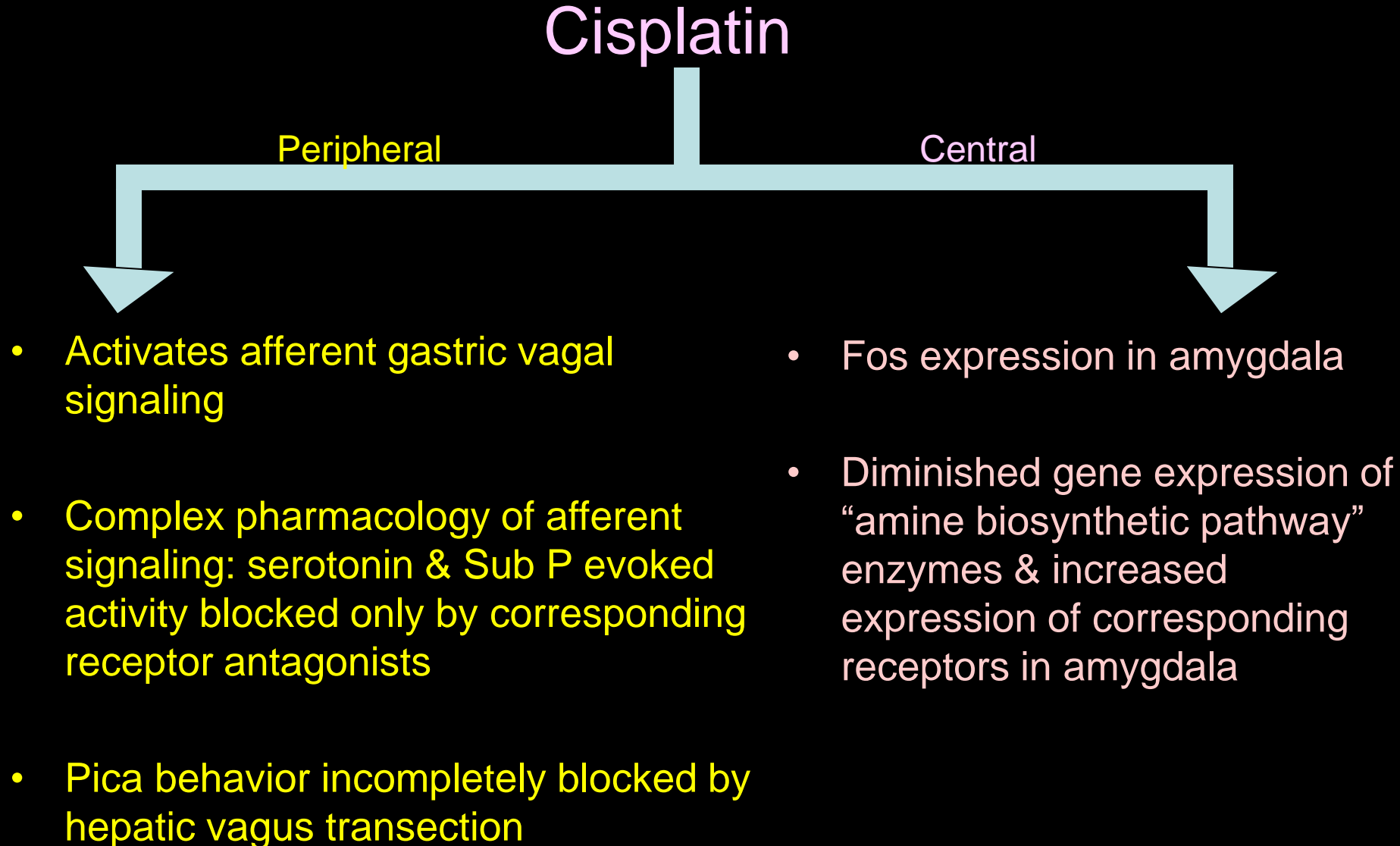
N=5

N=5



Look at “common players” in Amygdala & NTS

# Clues for visceral sickness: Gut-Brain integration



# Future plans

- a. Local serotonin dynamics: stoichiometry of luminal composition & quantal release
- b. Splanchnic nerve contribution to toxin signaling
- c. Inflammation, visceral sickness & vagal signaling
- d. Time domain of NT release (at periphery & CNS) in response to toxins: Rationale for choice of antiemetics
- e. Forebrain pharmacology
- f. ?Vaccine for emesis

*In search for “Merlin” of gut-brain crosstalk*

*Thank you!*

