

# **Panic Disorder and Agoraphobia: Novel Glutamate Mechanisms and Therapeutic Approaches from Preclinical Models**



**Anantha Shekhar, MD, PhD**

**Indiana University School of Medicine  
Indianapolis, USA**

# Disclosure



- Some of the studies were supported by a research grant from Janssen
- No other conflicts of interest

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## Collaborators

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  - Stephanie Fitz
  - Dr. William Truitt
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  - Amy Dietrich
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# Panic Disorder and Panic Attacks



- Panic disorder is characterized by recurrent “spontaneous” PANIC ATTACKS which are sudden onset of severe anxiety accompanied by multiple physical symptoms such as increases in respiration, heart rate, blood pressure.
- Panic Disorder begins in young adults; is a chronic illness; is a risk factor for suicide and many other cardiovascular and gastrointestinal illnesses

# Current Pharmacological Treatments for Panic Disorder are not Ideal



- The most commonly used treatments are antidepressants, but take a long time to work and often poorly tolerated
- Benzodiazepines [e.g., Xanax (alprazolam)] are effective with rapid effects, but side effects such as sedation and dependence are common

*(Nutt et al., 2002; Baldwin et al., 2005; Bandelow et al., 2008; Cloos and Ferreira, 2009).*

- ***Therefore, there is a great need for rapidly effective anxiolytic agents without the typical benzodiazepine side effects.***

# Panic Attacks can be elicited with specific stimuli

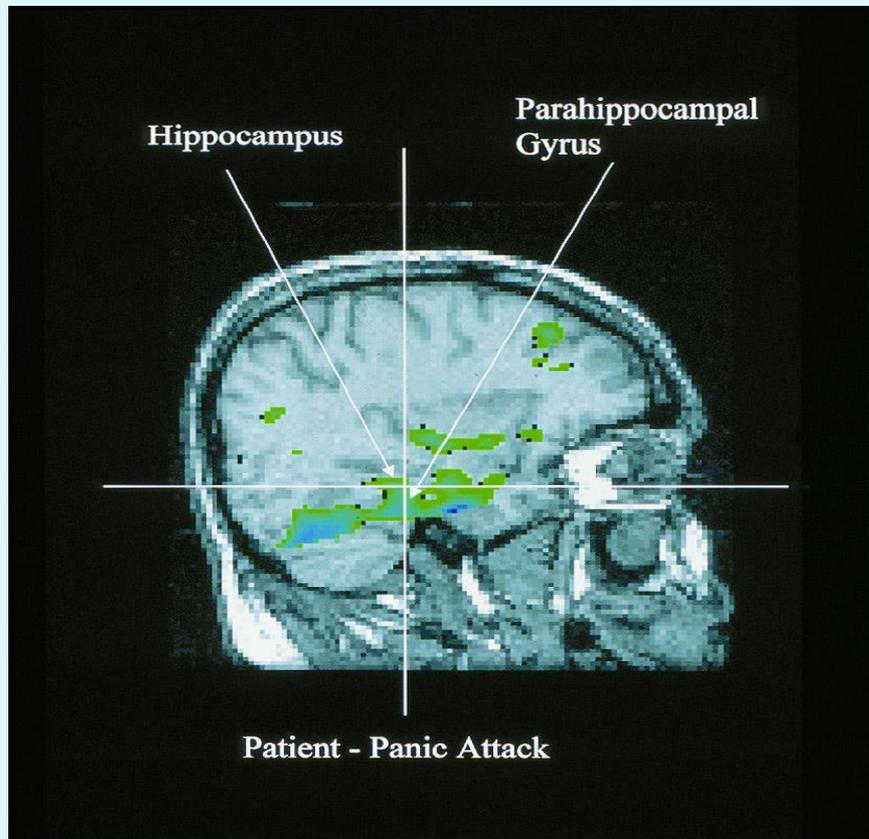


- Although considered “spontaneous”, panic attacks can be reliably provoked in panic disorder subjects by normally innocuous interoceptive stimuli (e.g., intravenous 0.5M sodium lactate, 7% CO<sub>2</sub> inhalations or CholecystokininCCK).

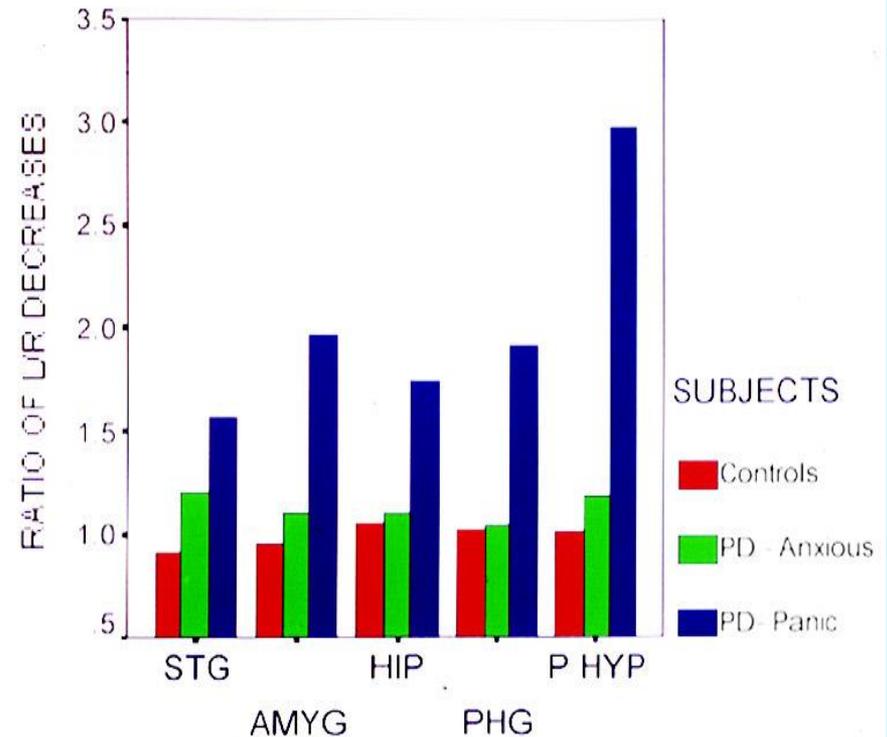
This suggests that global neural pathways which modulate normal panic are perturbed in these subjects.

# What is the 'panic' brain network?

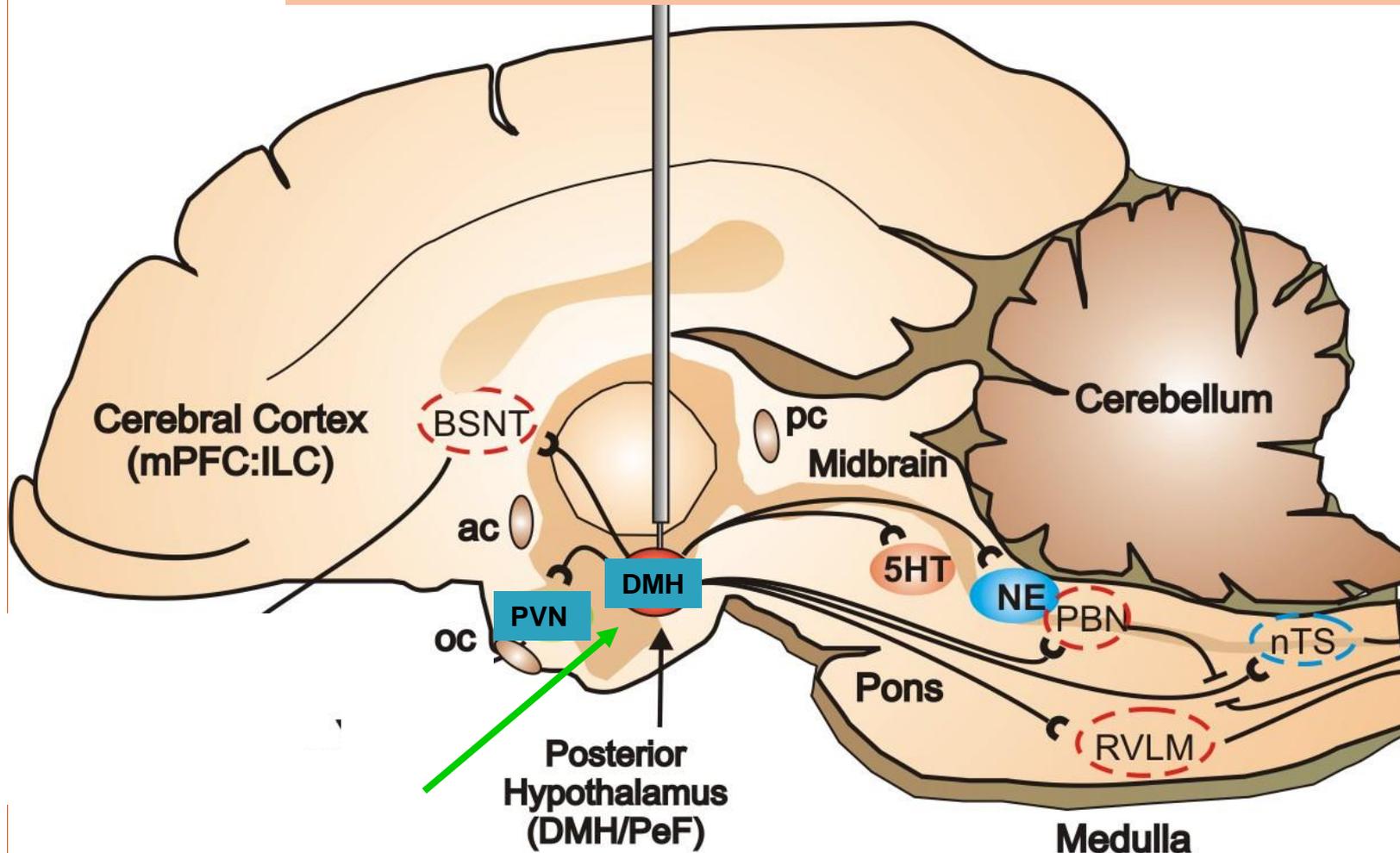
## PET image of Panic Attack



## Areas of significant change



**PRECLINICAL ANIMAL MODEL of PANIC:**  
Chronic Inhibition of GABA = Anxious and Panic-prone Rats



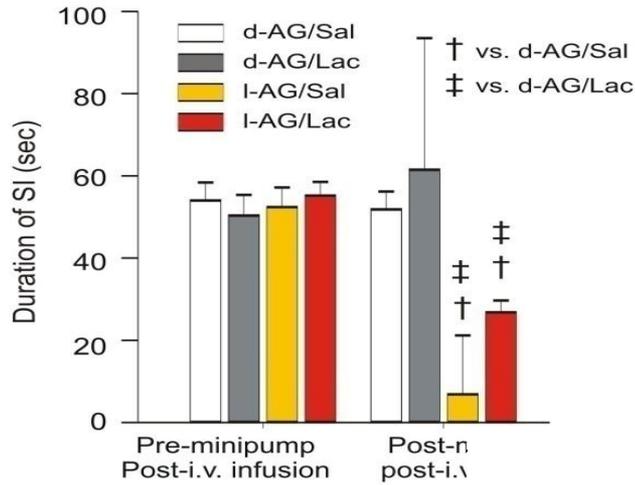
**0.5M Sodium Lactate (i.v.)**  
**An ordinarily mild**  
**Interoceptive stressor**

*Shekhar and Keim 1997, J Neuroscience*

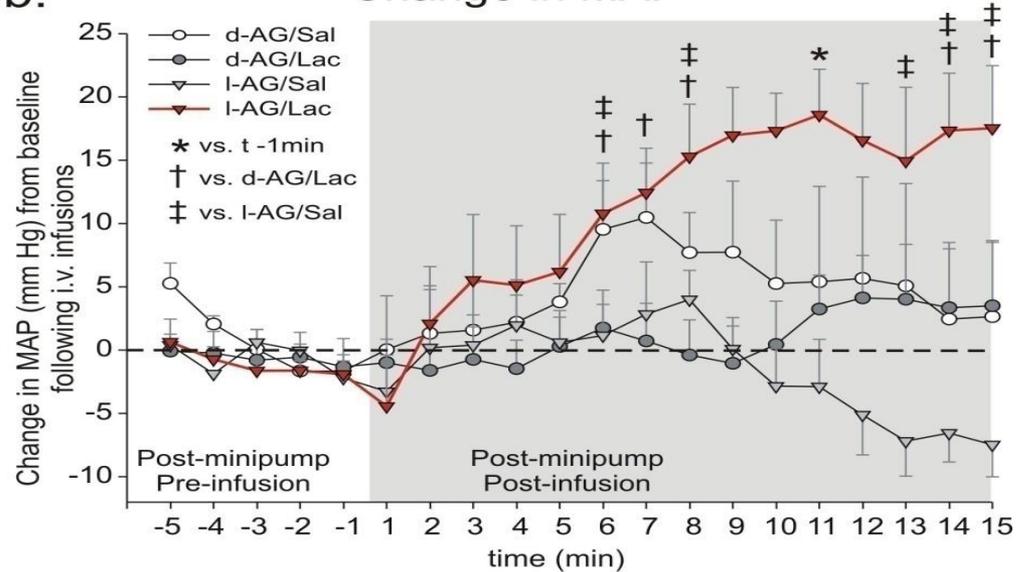
*Johnson and Shekhar 2006, J Neuroscience*

# Sodium lactate elicits panic response only in panic-prone rats

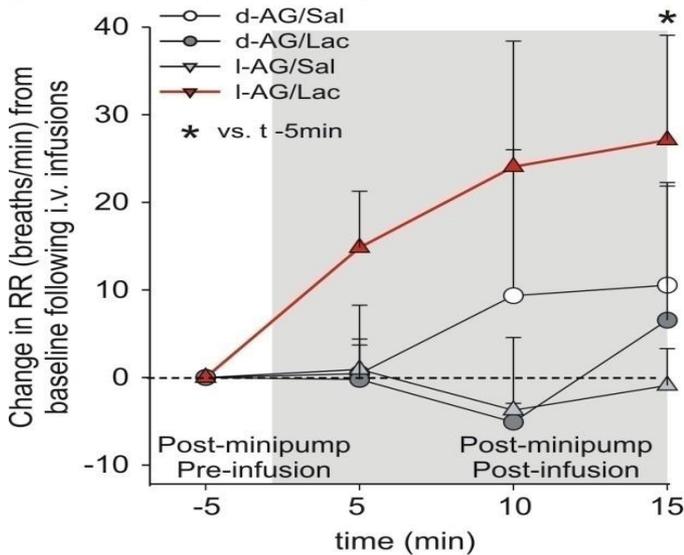
a. Social Interaction Time



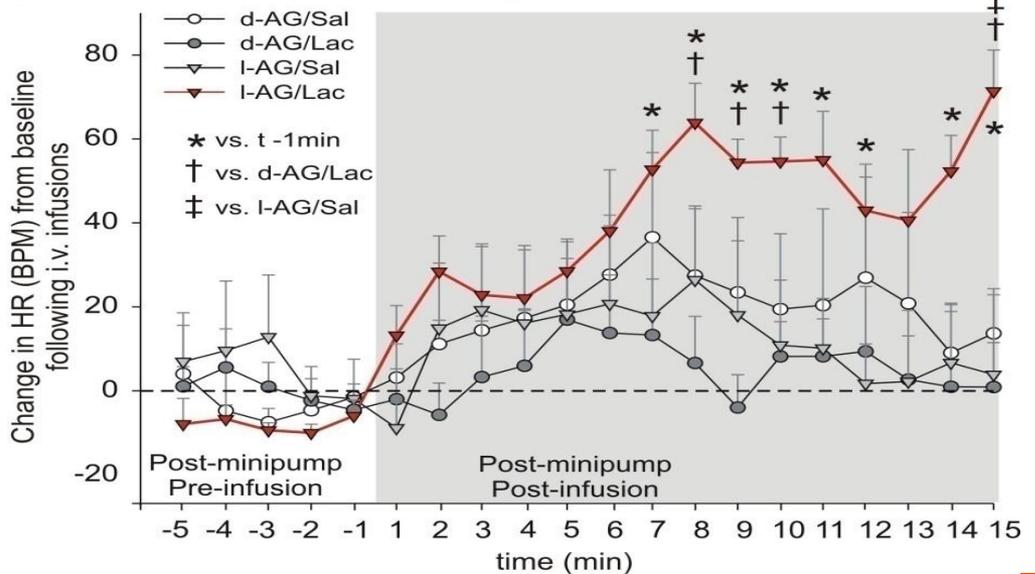
b. Change in MAP



c. Change in RR

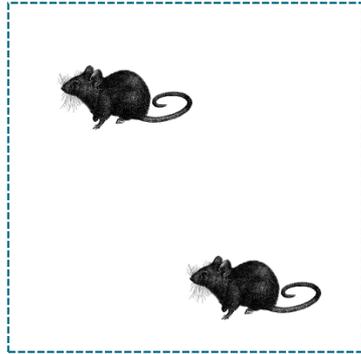


d. Change in HR

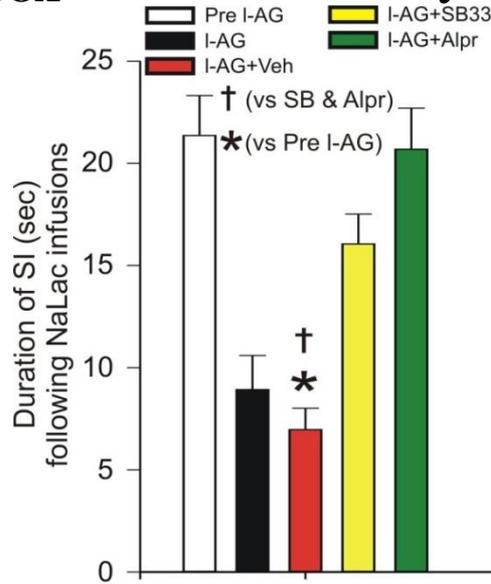


# Systemic Infusion of SB334867, an Orexin 1 Receptor Antagonist, or Benzodiazepine Attenuates Lactate-induced Panic-like Responses in Panic-prone rats

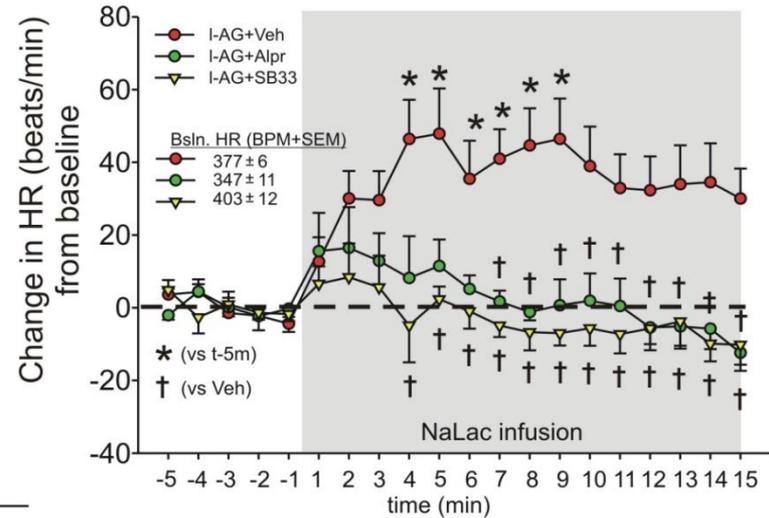
## Social interaction Box



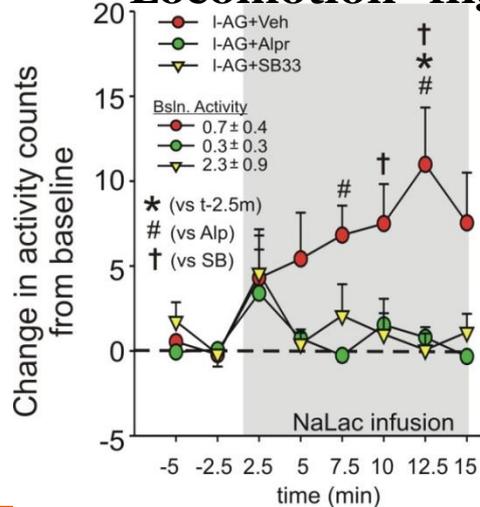
## Social Anxiety



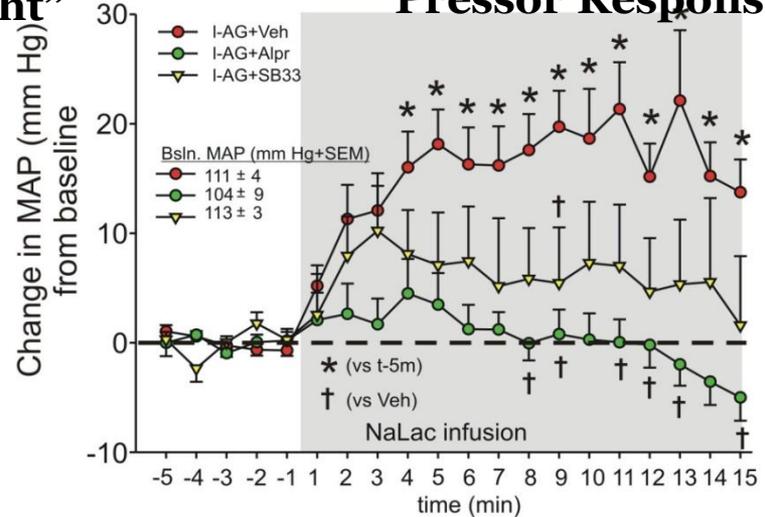
## Tachycardia



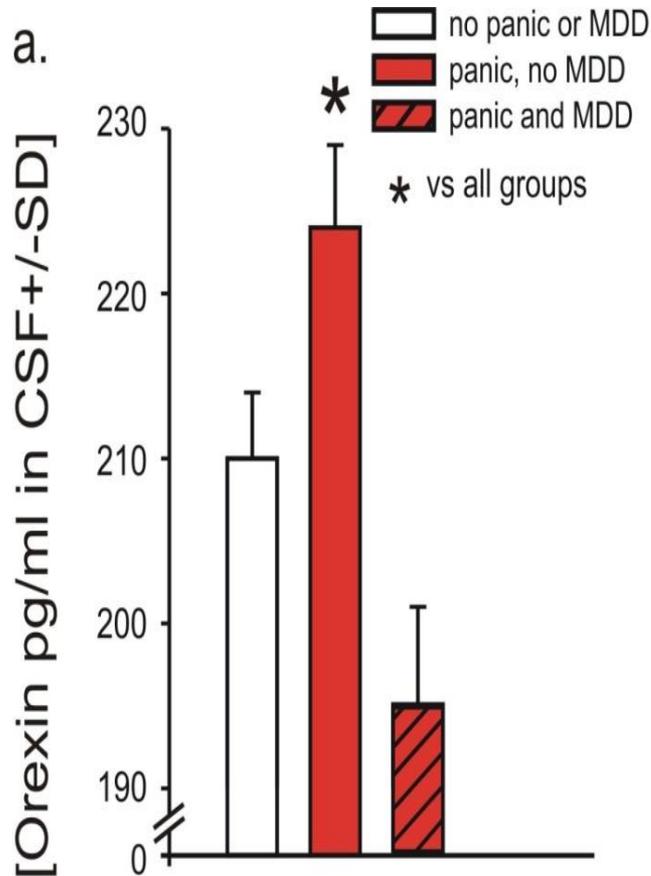
## Locomotion "flight"



## Pressor Response



# Panic Symptoms are associated with elevated CSF ORX in suicide attempters



b.

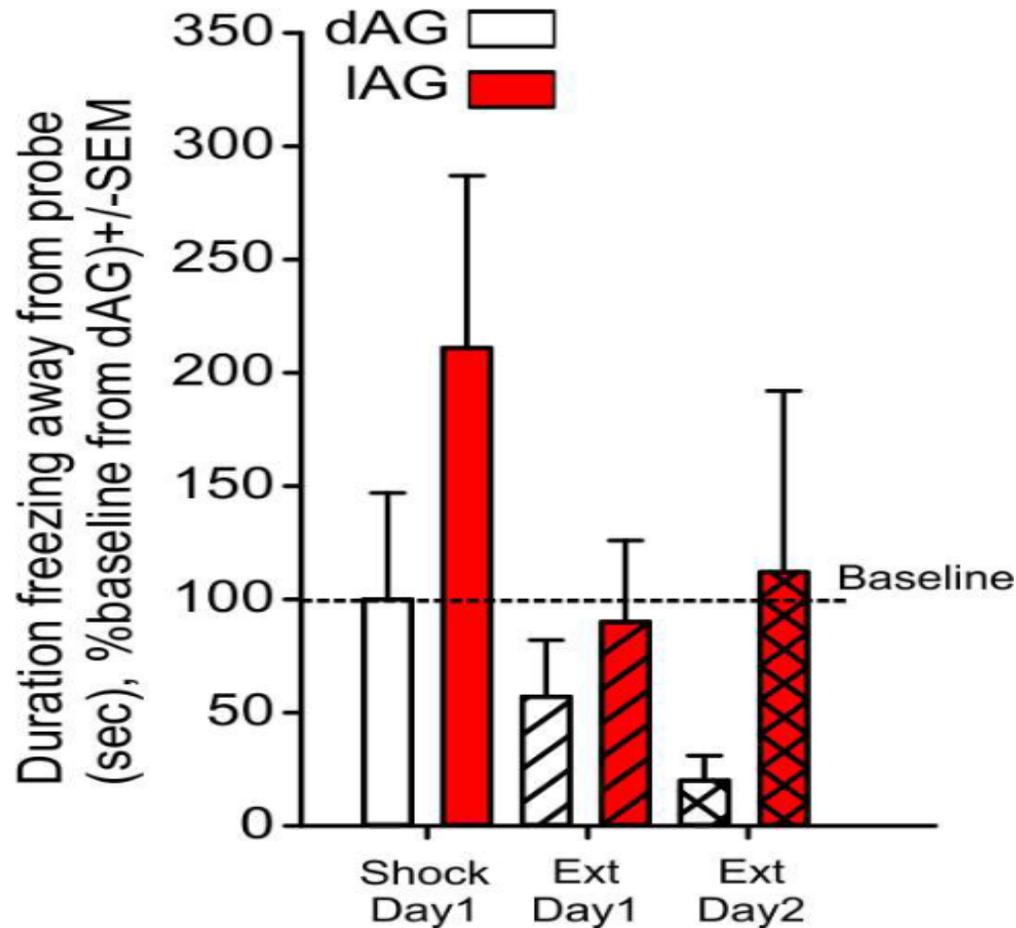
Subject group	No panic/No MDD (N=28)	Panic/No MDD (N=12)	Panic and MDD (N=13)
Age in years (mean+SD)	35+11	38+15	45+15
Gender (M:F)	17:11 61% :49%	3:9 25%:75%	7:6 54%: 46%
Co-morbid axis I diagnosis	Gen. Anxiety (3) Adjustment disorder (17) Dysthymia (4) Depressive syndrome NOS (4)	Gen. Anxiety (2) Adjustment disorder (2) Dysthymia (4) Depressive syndrome NOS (4)	MDD (13)

# Panic and Phobias

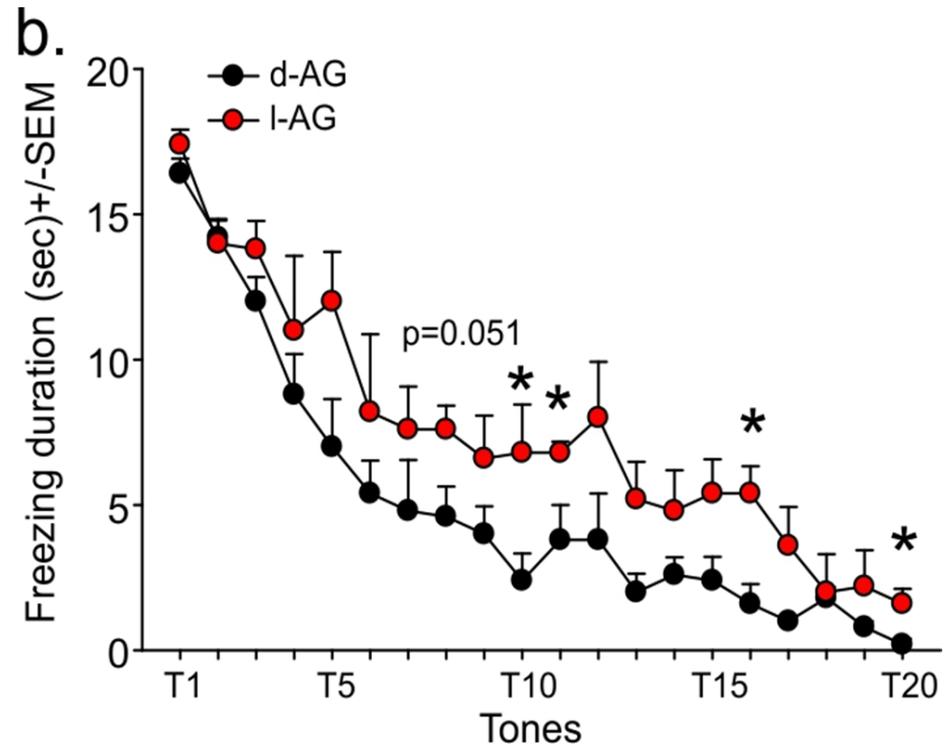
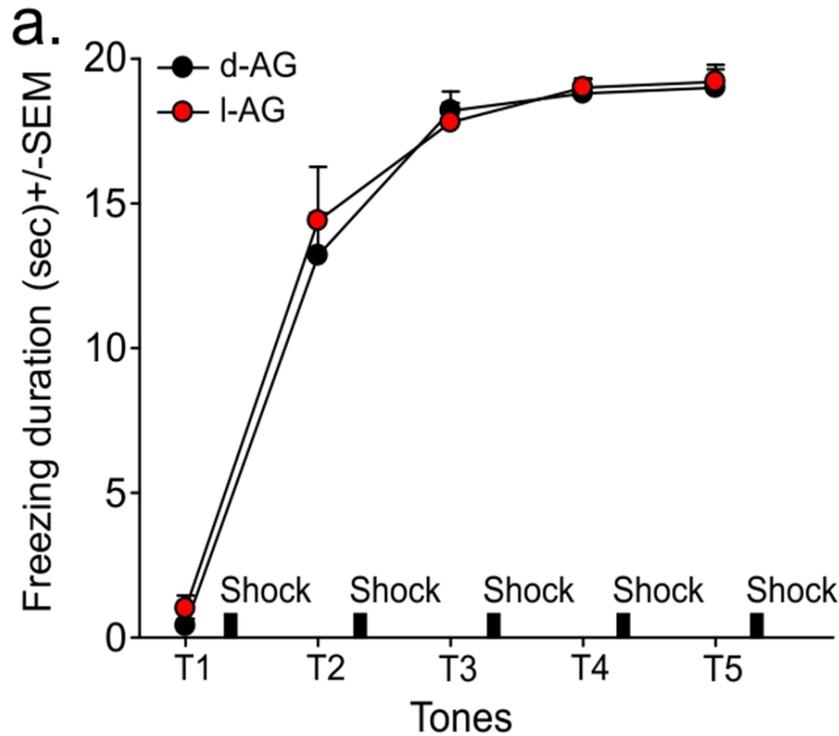


- Agoraphobia is one of the most common consequences of panic disorder. It is a classic conditioned fear following an aversive experience.
- It affects over 50% of the PD subjects and results in the most severe disabling long-term consequences
- What specific mechanisms predispose people with panic attacks to develop phobias so frequently?

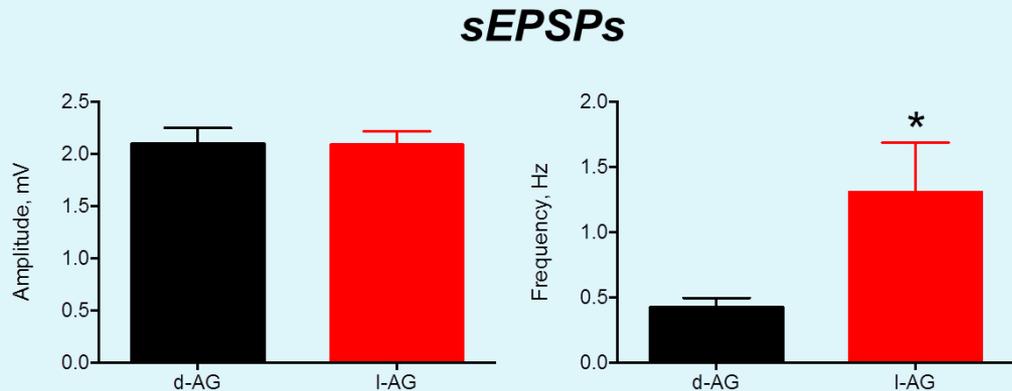
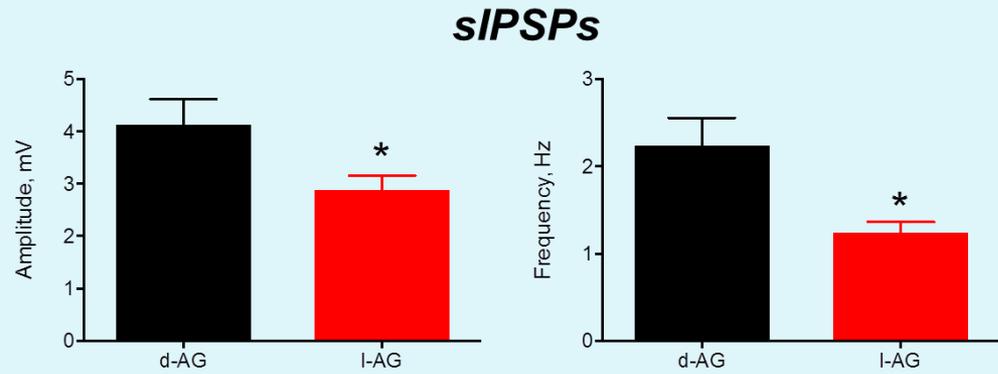
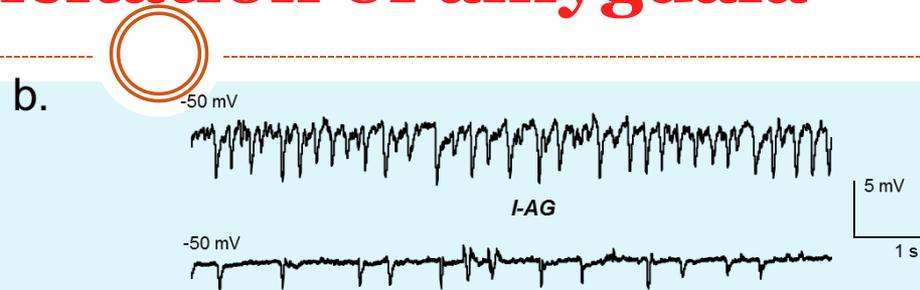
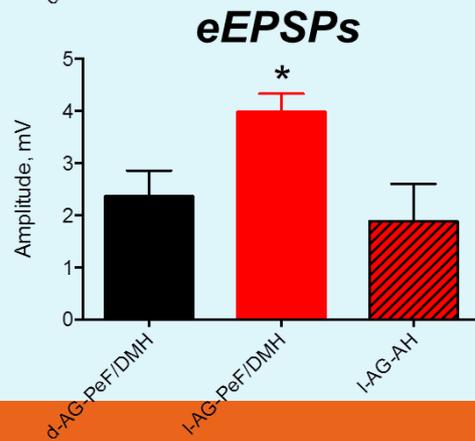
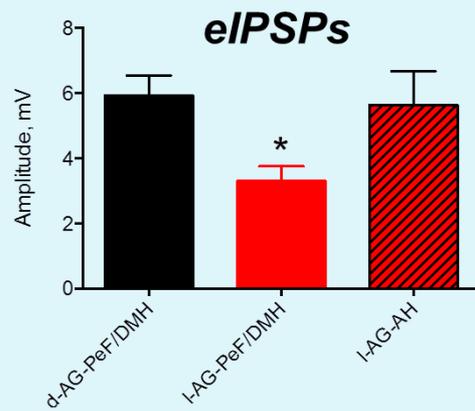
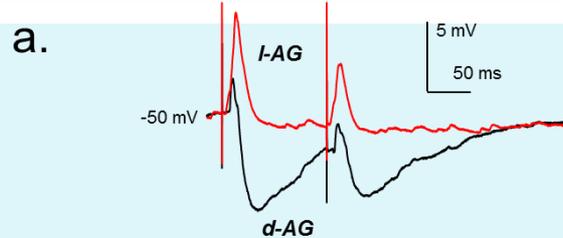
# Panic vulnerability enhances contextual conditioned fear and delays extinction



# Panic vulnerable rats shows delayed extinction of conditioned fears

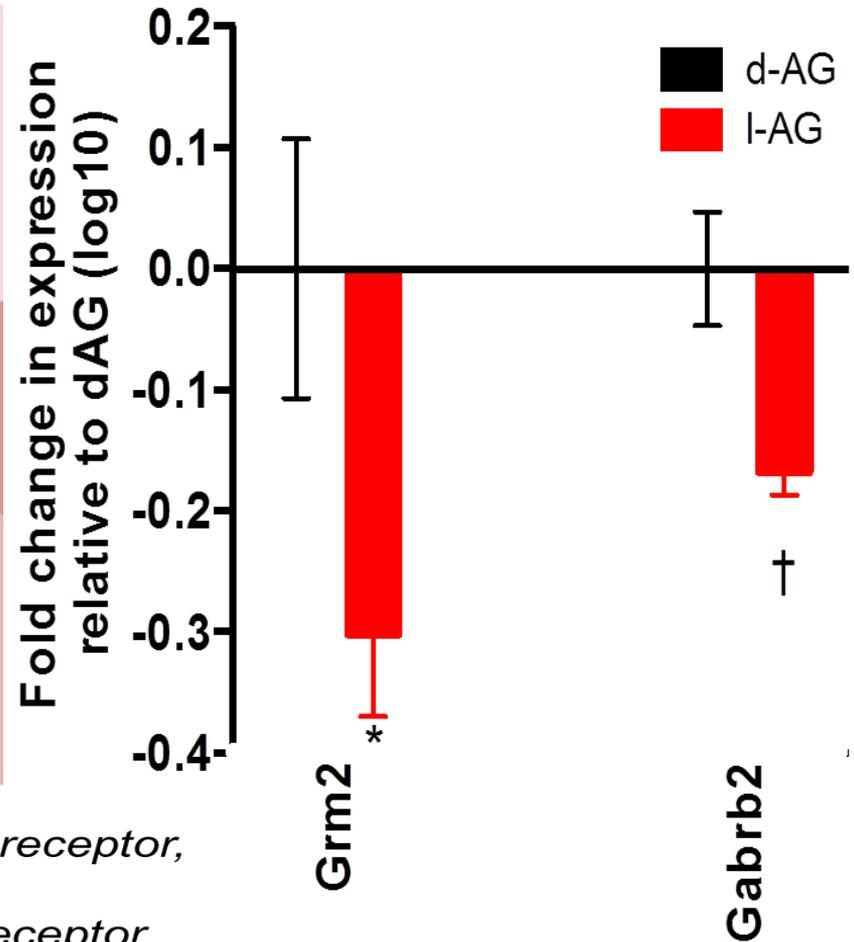


# Panic prone rats show reduced inhibition and increased excitation of amygdala



# Gene Changes in Central Nucleus of Amygdala

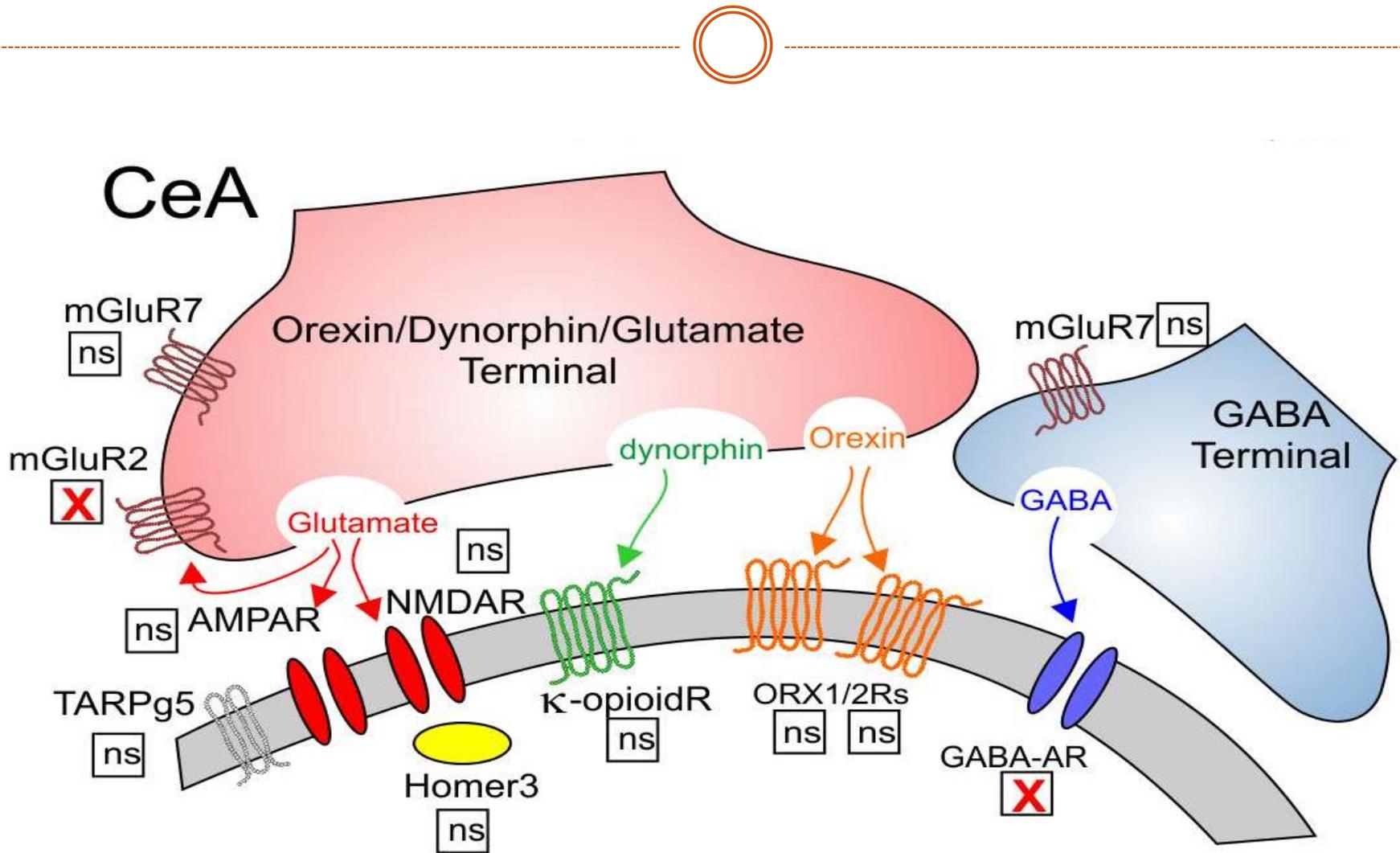
rec. & subunits	Gabra1	Gabra2	Gabra3	Gabra4	Gabra5	Gria1	Gria2	Gria3	Gria4	Grid1	Grid2	
	Gabra6	Gabrb1	Gabrb2	Gabrb3	Gabrd	Gri1	Gri2a	Gri2b	Gri2c	Gri2d	Gri3a	Gri3b
	Gabrg1	Gabrg2	Gabrg3	Gabre	Gabrq	Gri4	Grik1	Grik2	Grik3	Grik4	Grik5	Gri5
	Gabbr1	Gabbr2	Gabbr3			Gri6	Gri7	Gri8				
reg.	Gira1	Gira2	Gira3	Gira4	Girb	Cacng1	Cacng2	Cacng3	Cacng4	Cacng5	Cacng6	Cacng7
	Gabarap	Gabarap2	Ah4	Dbi		Cacng8	Homer1	Homer2	Homer3	Grip1	Grip2	Gripap1
enz.	Gad1	Gad2	Abat			Slc1a1	Slc1a2	Slc1a3	Slc1a4	Slc1a6		
transport	Slc6a1	Slc6a11	Slc6a12	Slc6a13	Slc32a1	Slc17a6	Slc17a7	Slc17a8	Slc7a11			



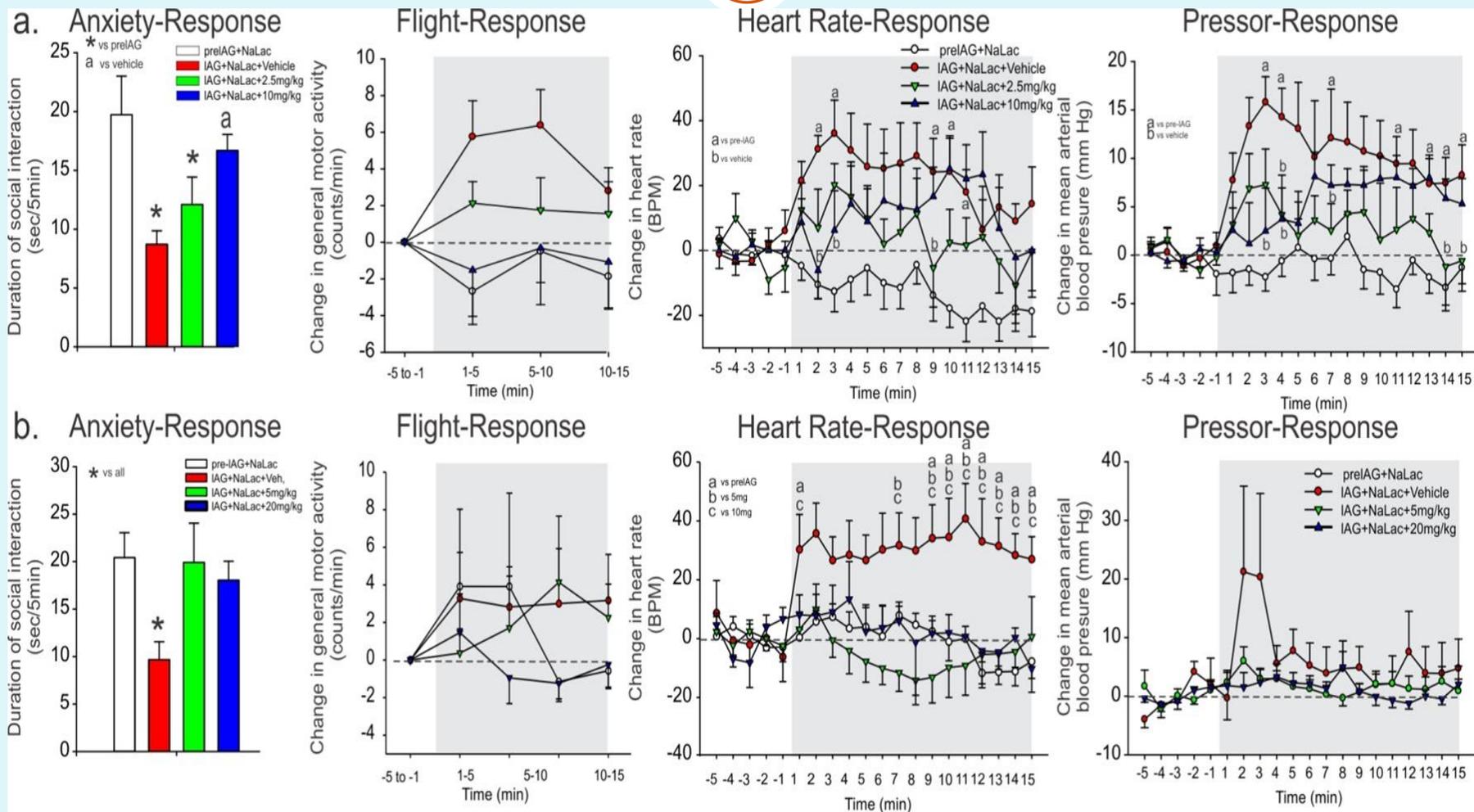
**Gabrb2** – GABA(A) receptor, beta 2

**Grm2** – glutamate receptor, metabotropic 2

# Synaptic gene Changes in Panic-prone animals



# mGluR2 receptor positive allosteric modulator (PAM) as panic therapy



# CONCLUSIONS



- Reduced MGluR2 receptors may be novel target implicated in panic attacks and agoraphobia
- MGluR2 receptor positive allosteric modulators (PAMs) may provide novel therapeutic approach for panic disorder

# Questions?

