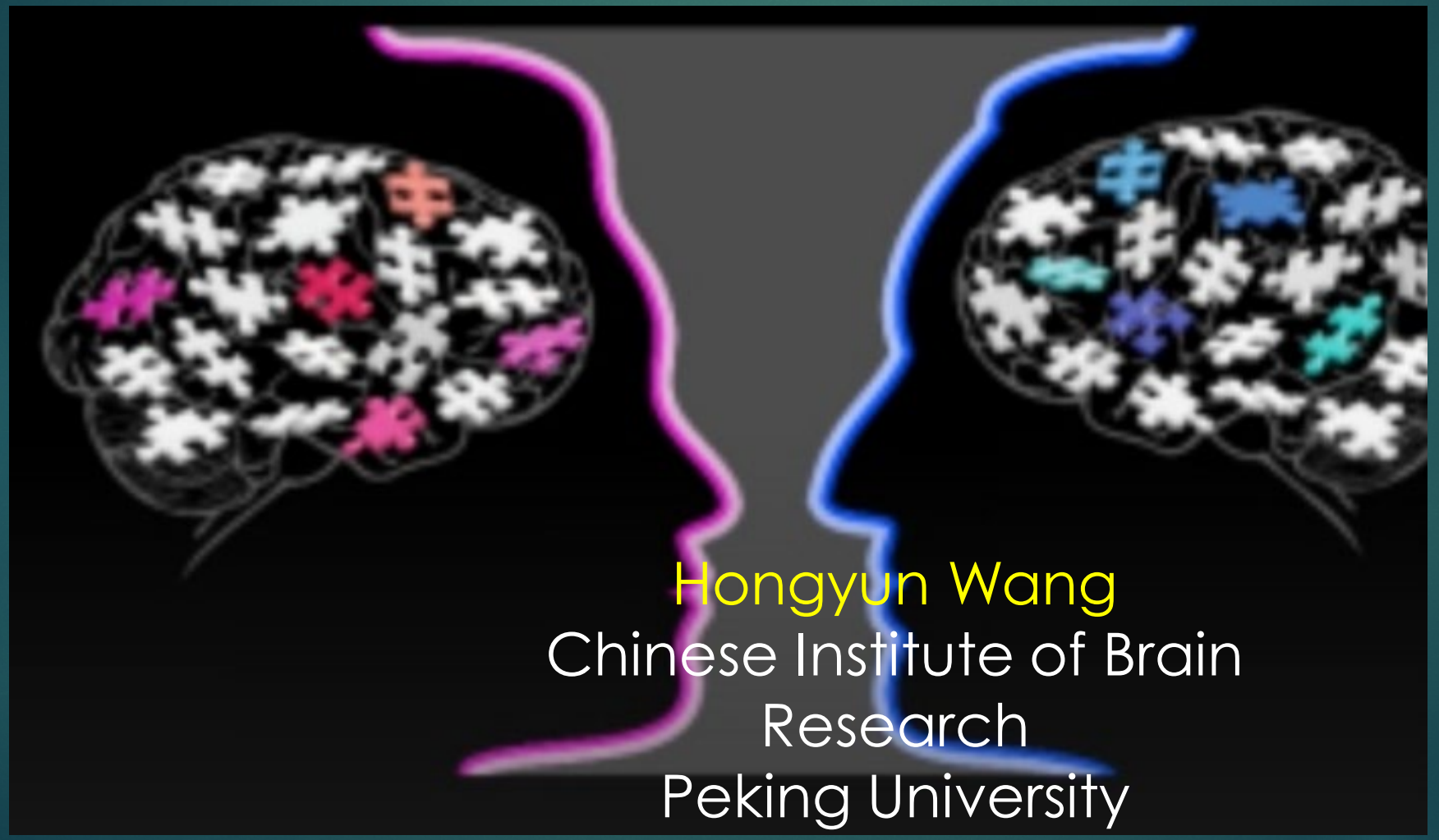
Exploring the sexual dimorphism of emotional disorders



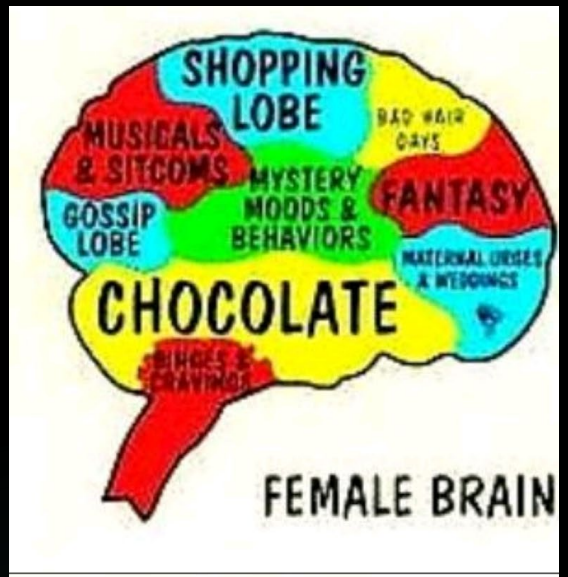
Hongyun Wang
Chinese Institute of Brain Research
Peking University

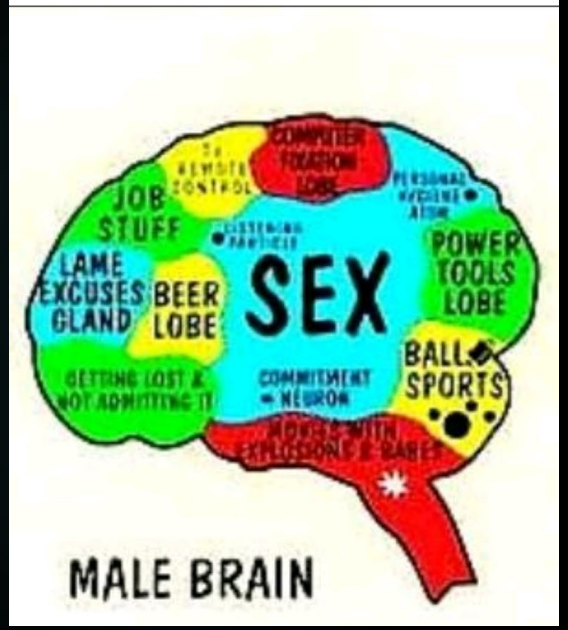
Yuhan Zhuo
Magdalena Koziol lab
Interested in a novel DNA modification in vertebrate genomes, called methylated deoxyadenosine

Lijuan Tang
Li Zhang lab
Exploring research interests

Hongyun Wang
Ying Li lab
Finding neural circuit mechanisms that mediate emotions and social behaviors

Hao Wu
Peace Cheng lab
Looking for possible targets for the treatment of mitochondrial diseases


SHOPPING LOBE
MUSICALS & SITCOMS
BAD HAIR DAYS
MYSTERY MOODS & BEHAVIORS
FANTASY
GOSSIP LOBE
CHOCOLATE
FEMALE BRAIN


JOB STUFF
POWER TOOLS LOBE
LAME EXCUSES GLAND
BEER LOBE
SEX
BALL SPORTS
COMMITMENT NEURON
MALE BRAIN

- Background

Sex differences in anxiety and depression clinical perspectives

Margaret Altemus[a,b,*], Nilofar Sarvaiya[c], and C. Neill Epperson[d,e,f]

Neurosteroid Biosynthesis Regulates Sexually Dimorphic Fear and Aggressive Behavior in Mice

Graziano Pinna · Roberto Carlos Agis-Balboa · Fabio Pibiri · Marianela Nelson · Alessandro Guidotti · Erminio Costa

Hormonal Cycles, Brain Network Connectivity, and Windows of Vulnerability to Affective Disorder

Joseph M. Andreano,[1,4,*] Alexandra Touroutoglou,[2,4] Brad Dickerson,[2,4] and Lisa Feldman Barrett[1,3,4]

www.who.int

Depression

30 January 2020

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Key facts

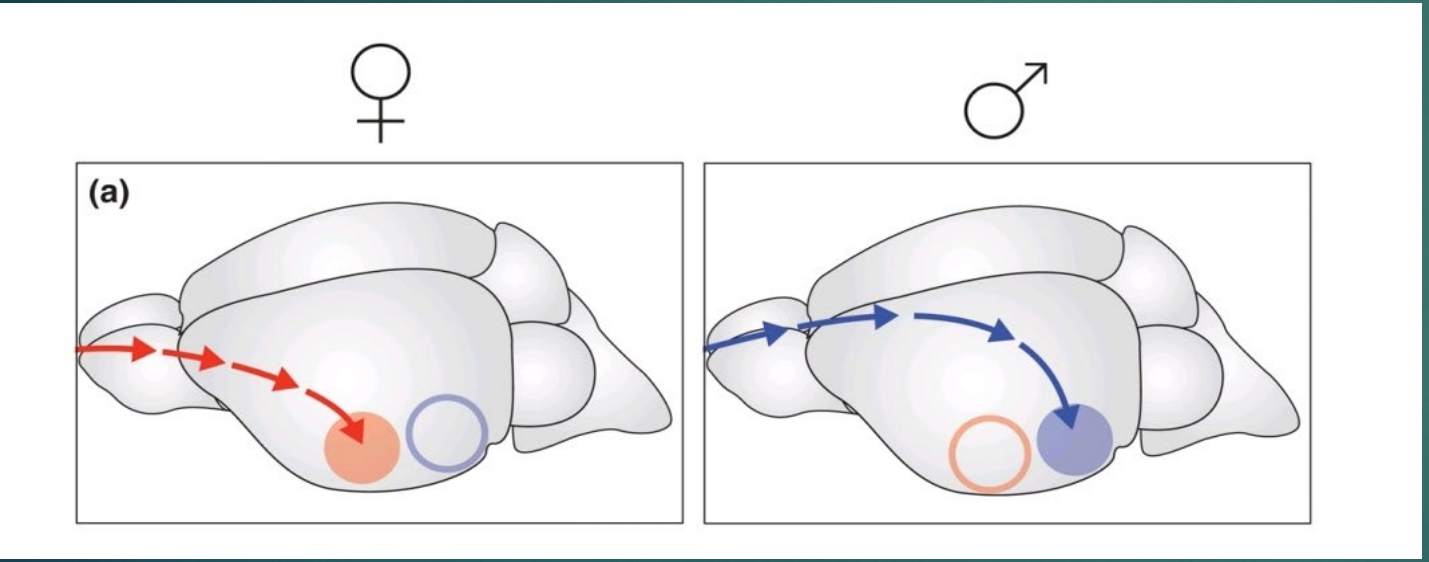
- Depression is a common mental disorder. Globally, more than 264 million people of all ages suffer from depression.
- Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease.
- More women are affected by depression than men.

Autism spectrum disorder, which is characterized by impaired social communication and restrictive, repetitive behaviors, is severalfold more prevalent in males than females （Rubenstein et al.,2015）

Women have twice the lifetime rates of depression and most anxiety disorders （Kessler et al., 1994, 1995; Weissman et al., 1994, 1996; Gater et al., 1998）

Two recent meta-analyses found that when controlling for type of trauma, women do seem to be more likely than men to develop post-traumatic stress disorder（PTSD） in response to a number of stressors including combat (Crum-Cianflone & Jacoson, 2014), witnessing death and illness/injury (Freedman et al., 2002; Tolin and Foa, 2006)

But there is no significant difference in their learning and memory levels!

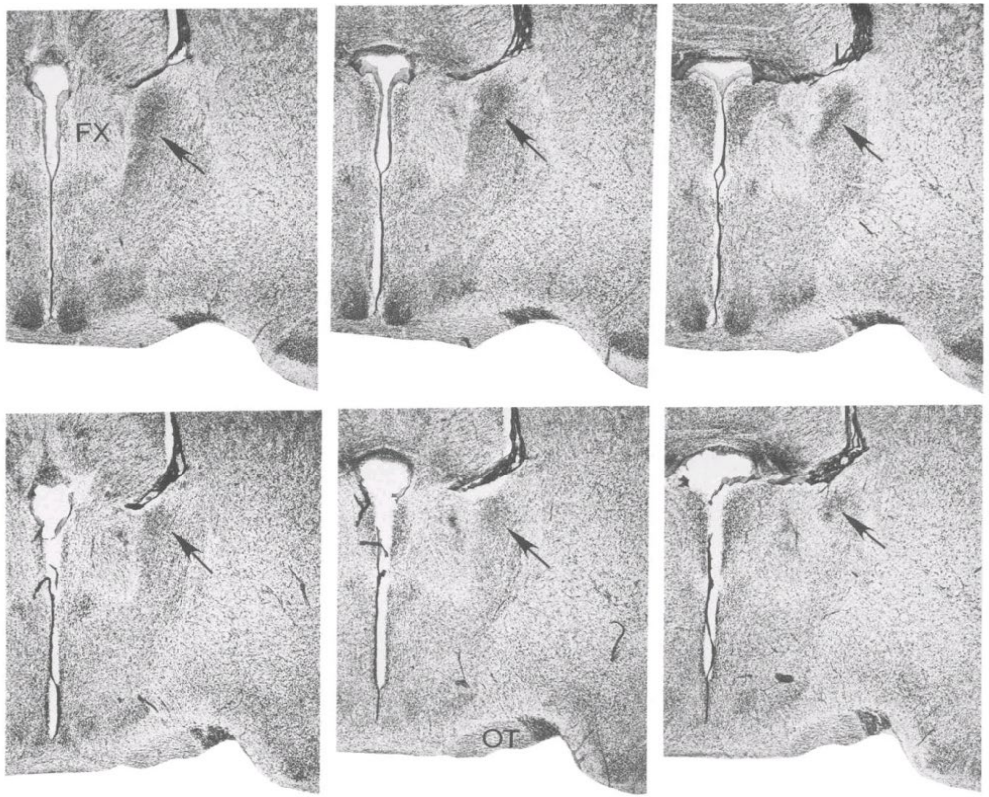


（Dulac & Kimchi , 2007）

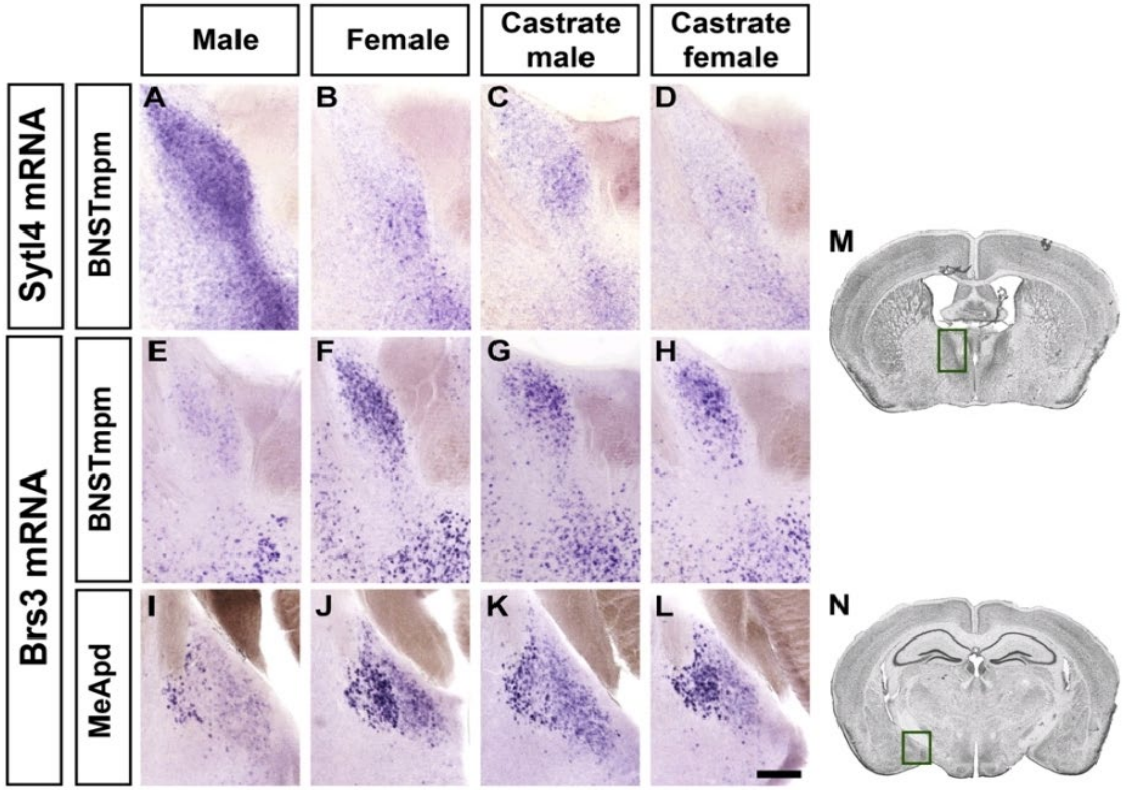
Accept the same sensory stimulation, why do male and female have different behaviors?

What is the source of the difference in susceptibility to emotional disorders between the sexes?

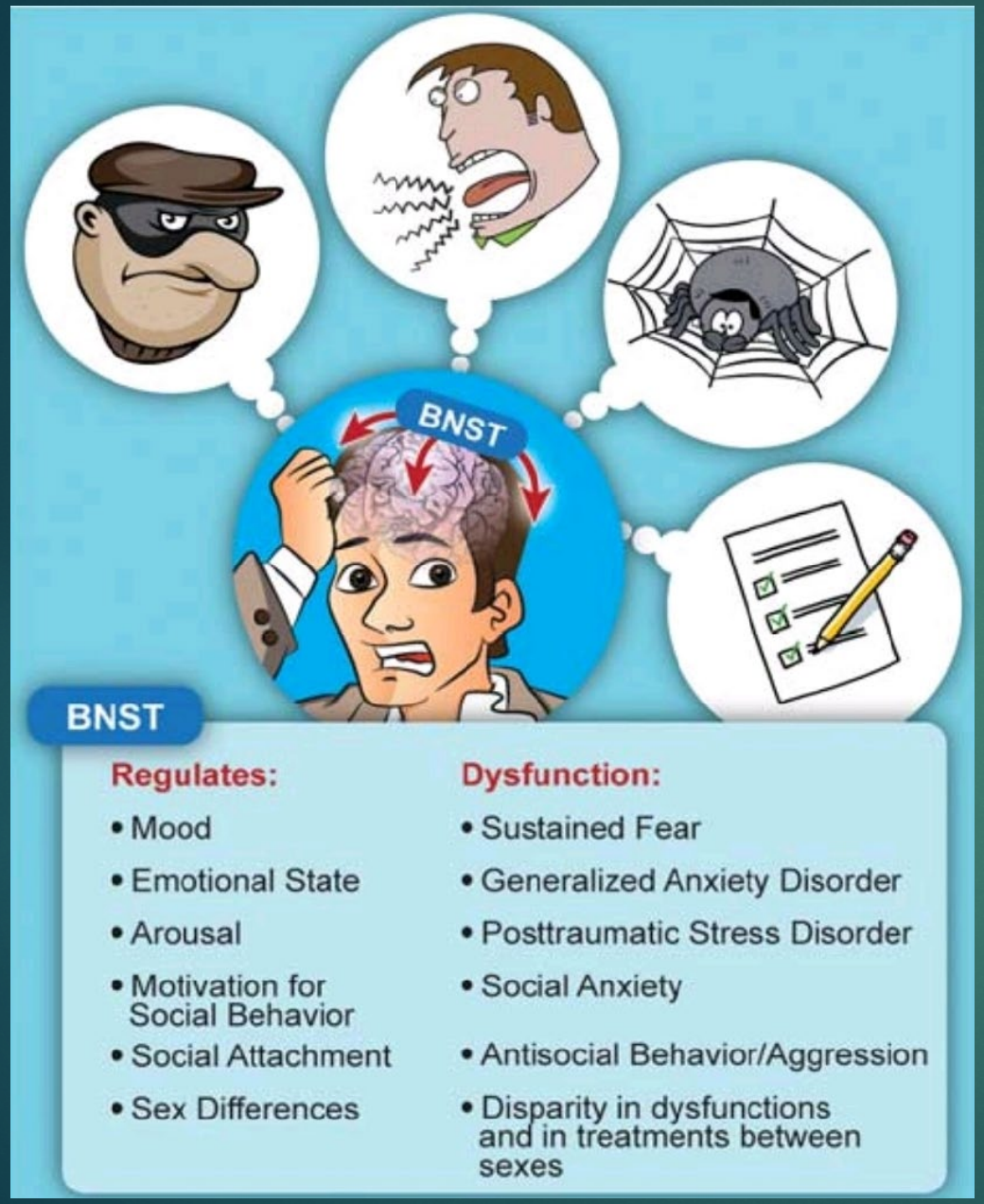
The Bed Nucleus of the Stria Terminalis （BNST） has obvious sexual dimorphism in anatomy and molecular expression



（Hinesa et al., 1992)



（Xu et al., 2012）



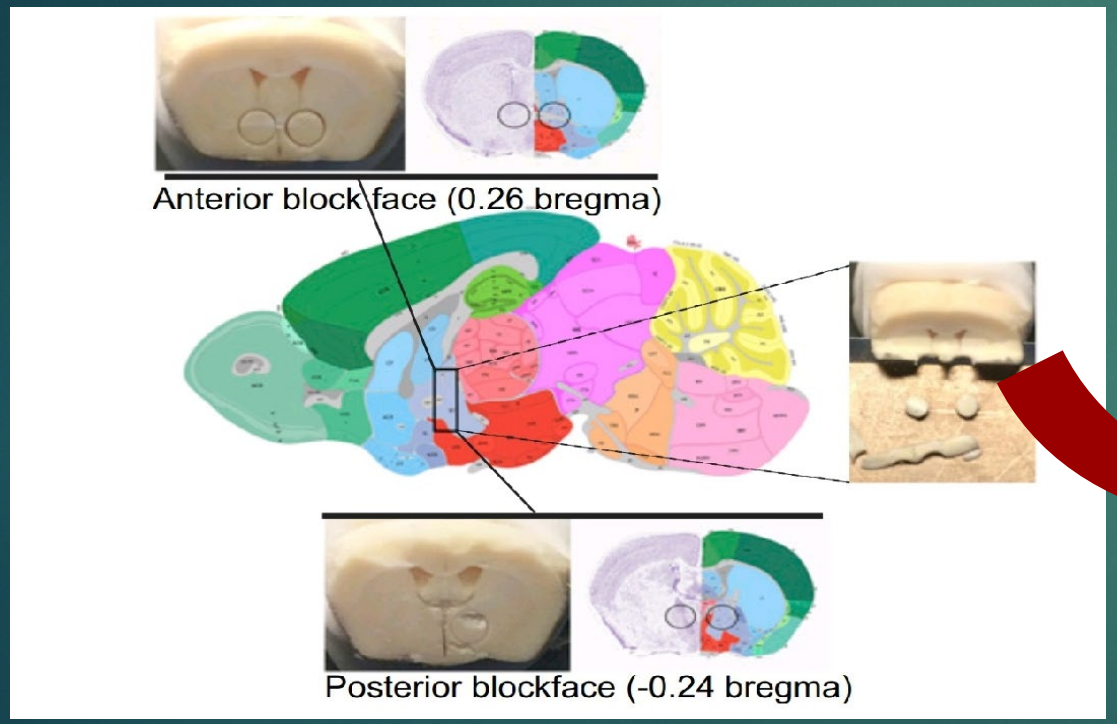
BNST is an important region modulating anxiety

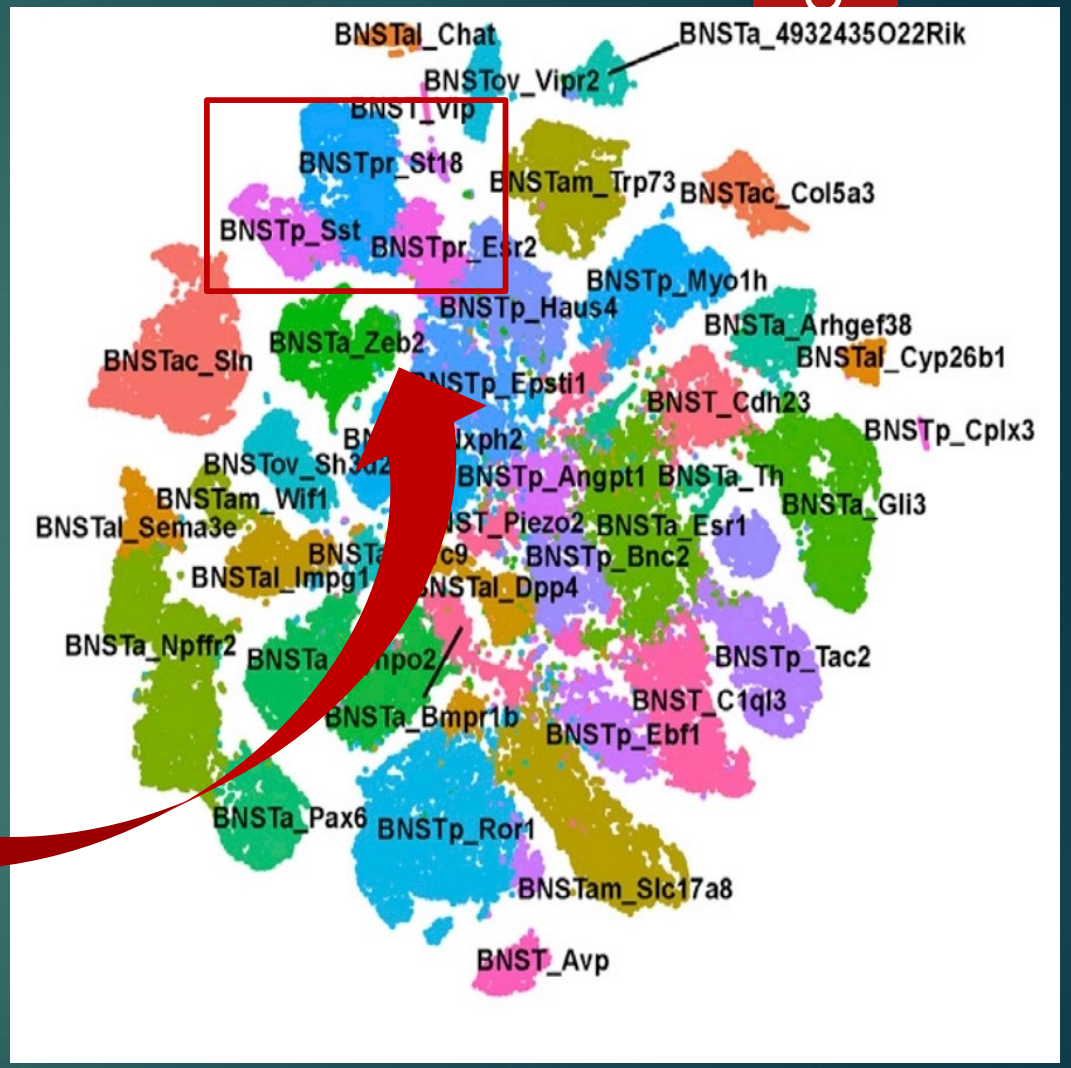
The human literature shows sex-specific changes in PTSD patients in SNPs of genes expressed in neurons in BNST subpopulations

This makes the BNST an excellent target for future research in PTSD and treatment for PTSD

（Lebow & Chen, 2016）

There is a group of neurons that highly express Suppression of tumorigenicity 18 protein （St18） in the posterior BNST

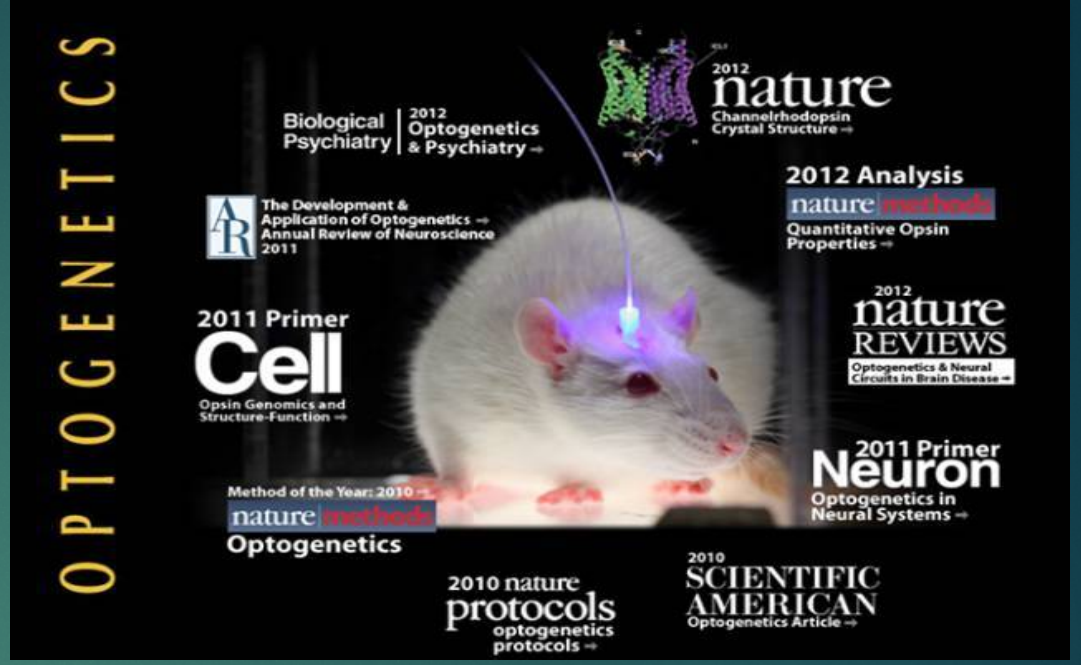


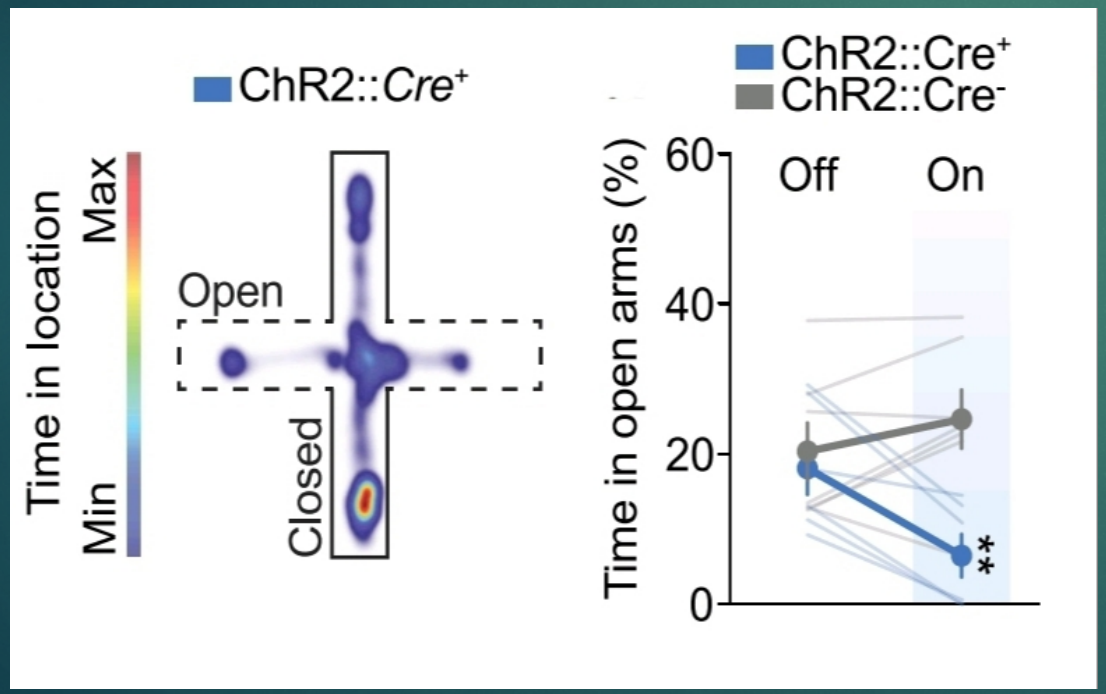


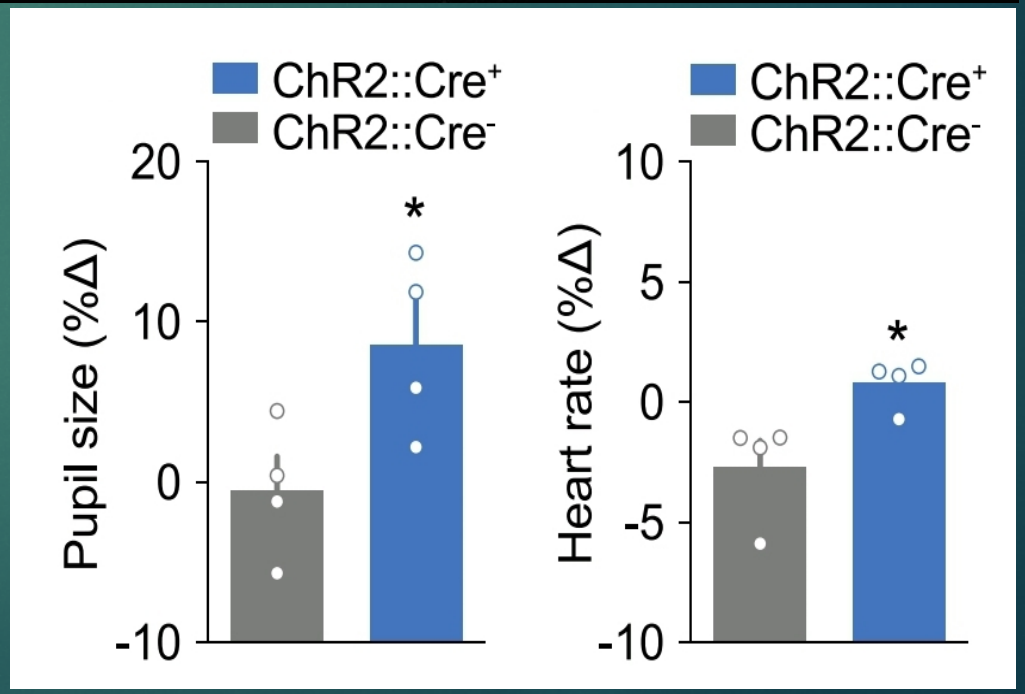
（Welch et al., 2019）

Optogenetic activation of the neurons can trigger anxiety-like behavior in mice

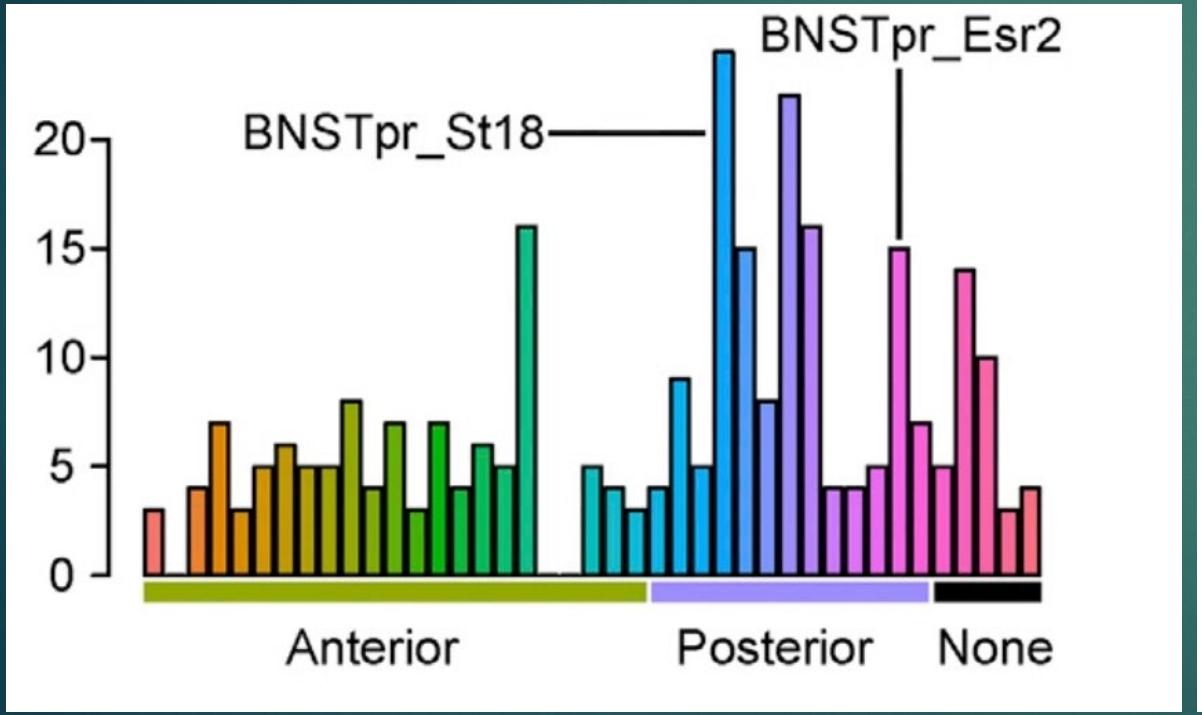
（Rodriguez-Romaguera et al., 2020）



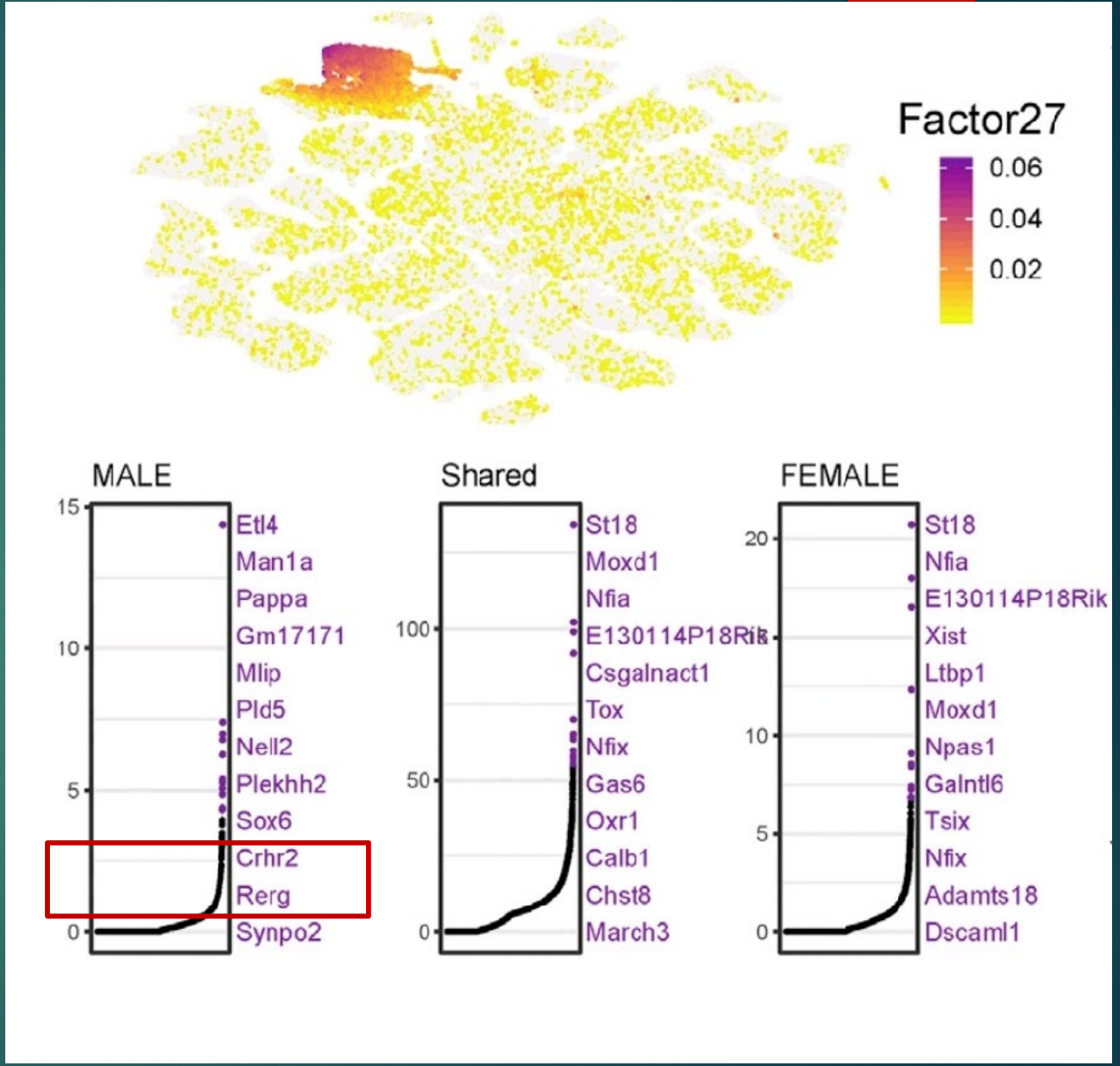




It is worth noting that the BNST St18 neurons of male mice highly express crfr2, while female mice hardly express this gene



（Welch et al., 2019）

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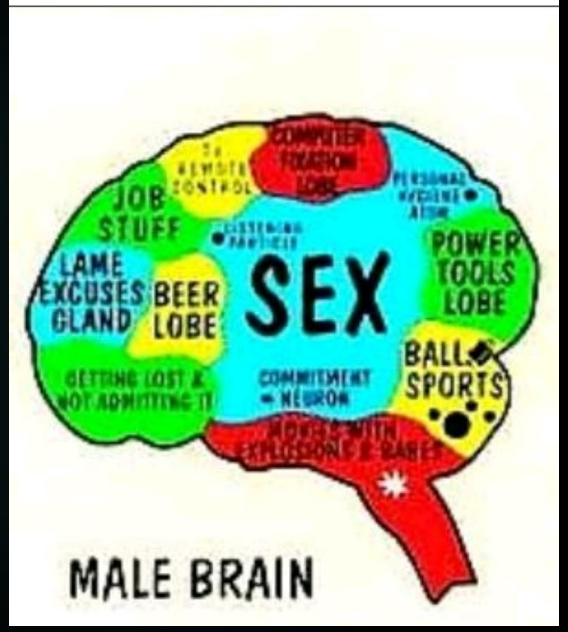
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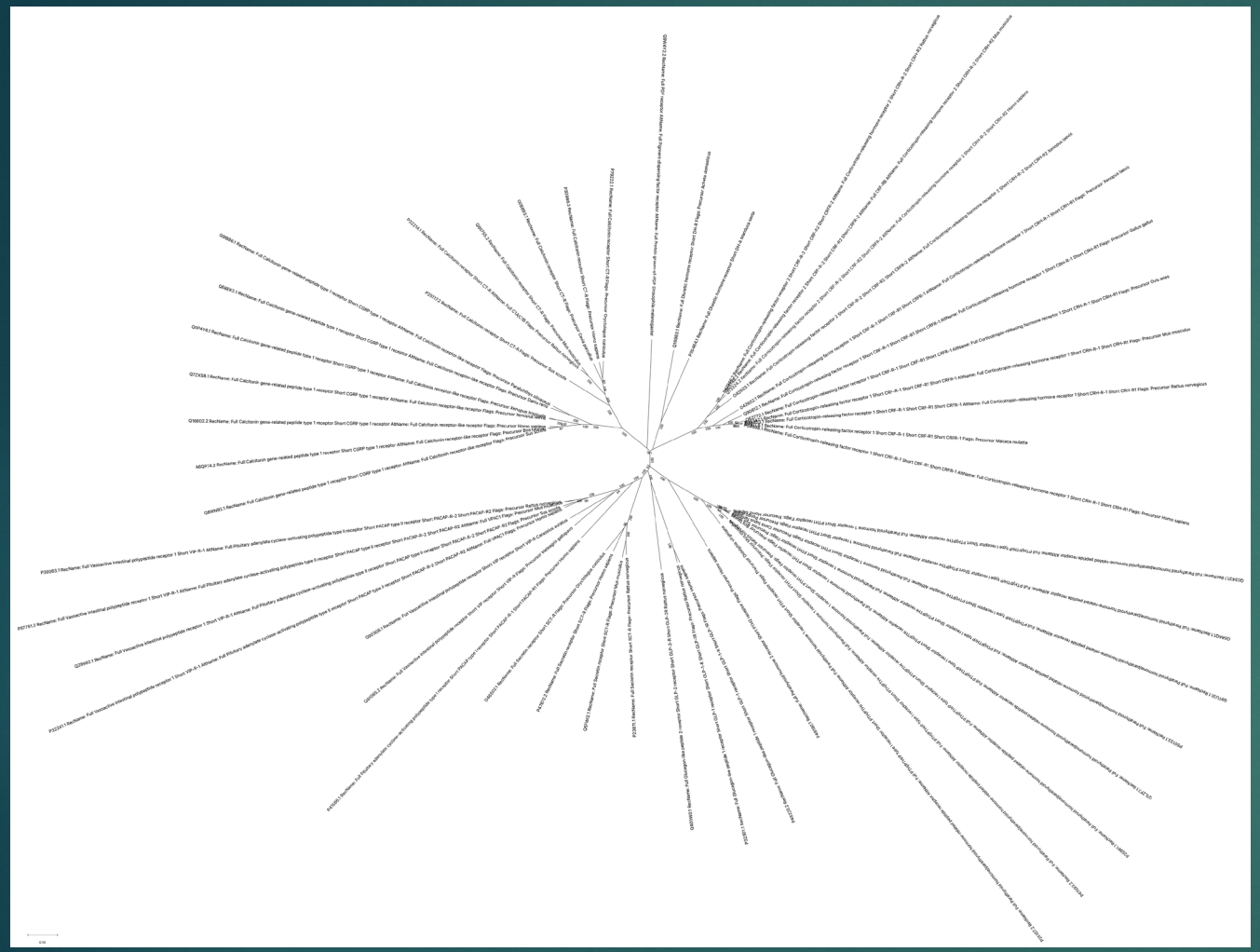
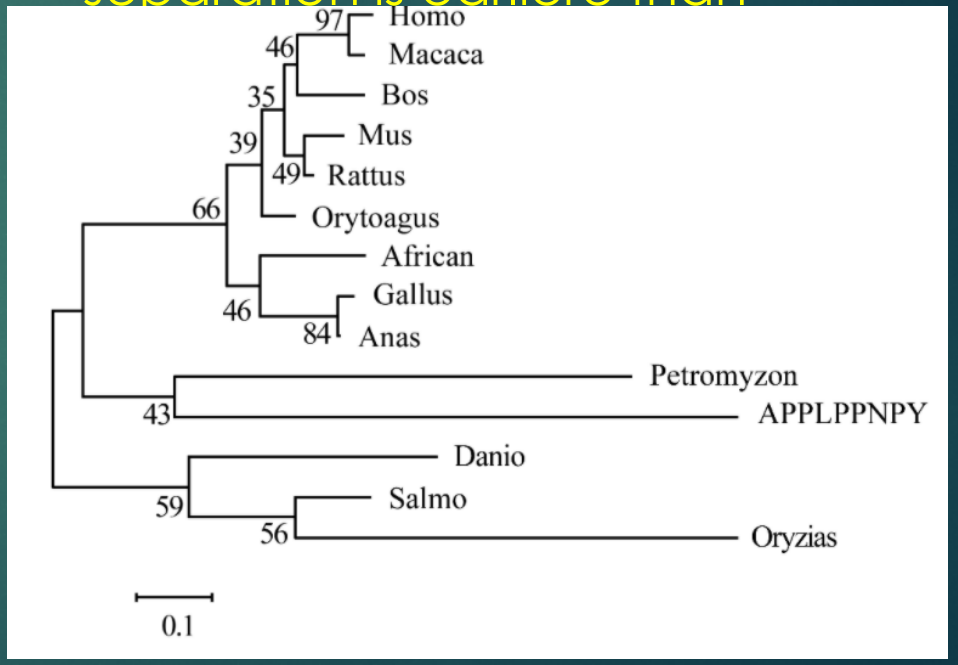
- Results



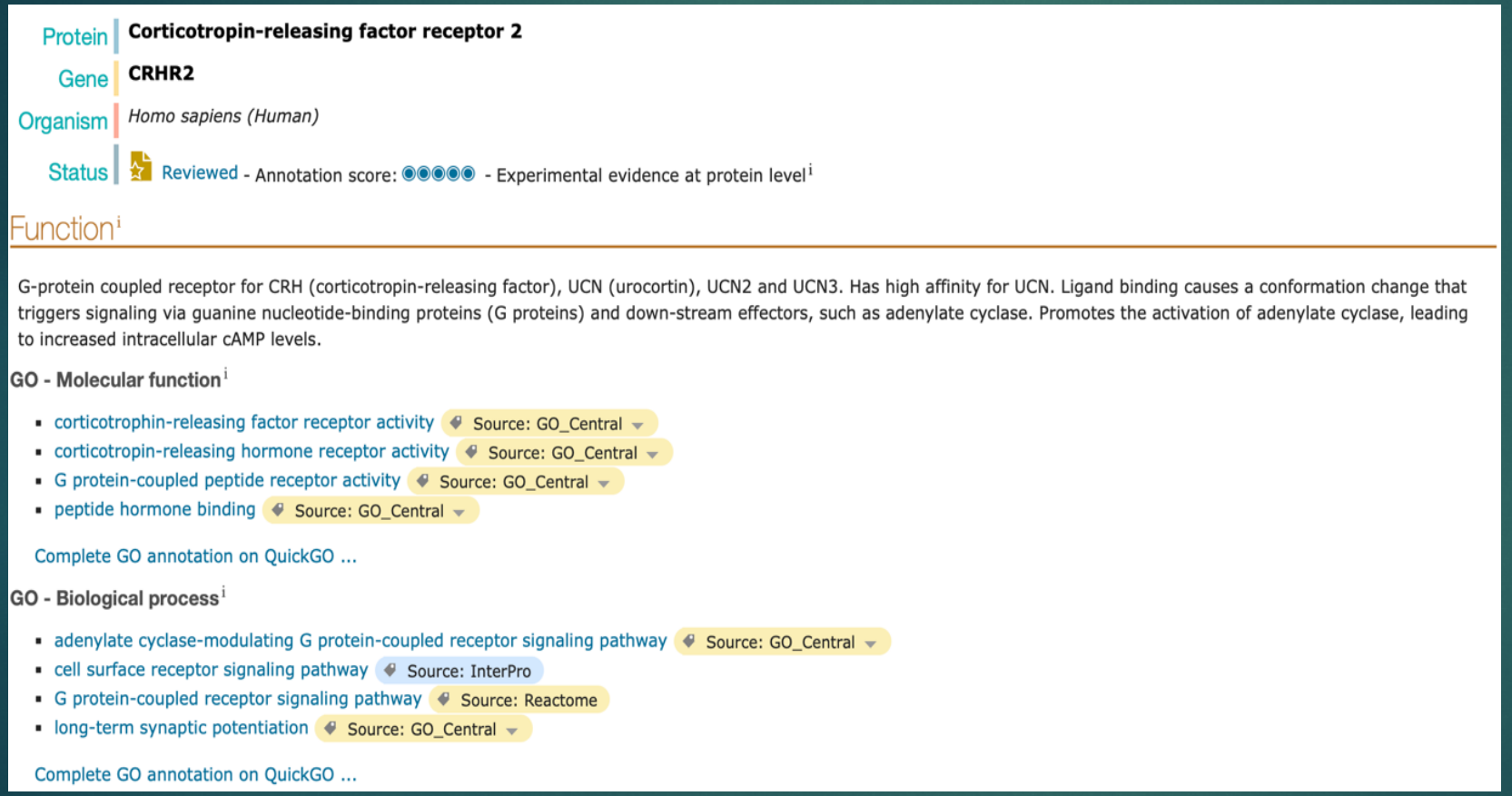
Devided into: CRHR1, CRHR2, calcitonin receptor, calcitonin receptor-like receeeptor, PTH1 receptor and SCT-R

It indiactes CRHR is a ancient protein, and CRHR separation is earliere than



Fundamental information about CRHR2:

search uniport with gene:crhr2 AND organism:"Homo sapiens (Human) [9606]"



Protein **Corticotropin-releasing factor receptor 2**

Gene **CRHR2**

Organism *Homo sapiens (Human)*

Status Reviewed - Annotation score: ●●●●● - Experimental evidence at protein level[i]

Function[i]

G-protein coupled receptor for CRH (corticotropin-releasing factor), UCN (urocortin), UCN2 and UCN3. Has high affinity for UCN. Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and down-stream effectors, such as adenylate cyclase. Promotes the activation of adenylate cyclase, leading to increased intracellular cAMP levels.

GO - Molecular function[i]

- corticotrophin-releasing factor receptor activity — Source: GO_Central
- corticotropin-releasing hormone receptor activity — Source: GO_Central
- G protein-coupled peptide receptor activity — Source: GO_Central
- peptide hormone binding — Source: GO_Central

Complete GO annotation on QuickGO ...

GO - Biological process[i]

- adenylate cyclase-modulating G protein-coupled receptor signaling pathway — Source: GO_Central
- cell surface receptor signaling pathway — Source: InterPro
- G protein-coupled receptor signaling pathway — Source: Reactome
- long-term synaptic potentiation — Source: GO_Central

Complete GO annotation on QuickGO ...

Functions:
G-protein coupled receptor for CRH (corticotropin-releasing factor), UCN (urocortin), UCN2 and UCN3.

Review > Nat Rev Neurosci. 2016 Oct;17(10):636-51. doi: 10.1038/nrn.2016.94.
Epub 2016 Sep 2.

Region-specific roles of the corticotropin-releasing factor-urocortin system in stress

Marloes J A G Henckens [1 2 3], Jan M Deussing [2], Alon Chen [1 2]

Affiliations + expand

PMID: 27586075 DOI: 10.1038/nrn.2016.94

Abstract

Dysregulation of the corticotropin-releasing factor (CRF)-urocortin (UCN) system has been implicated in stress-related psychopathologies such as depression and anxiety. It has been proposed that CRF-CRF receptor type 1 (CRFR1) signalling promotes the stress response and anxiety-like behaviour, whereas UCNs and CRFR2 activation mediate stress recovery and the restoration of homeostasis. Recent findings, however, provide clear evidence that this view is overly simplistic. Instead, a more complex picture has emerged that suggests that there are brain region- and cell type-specific effects of CRFR signalling that are influenced by the individual's prior experience and that shape molecular, cellular and ultimately behavioural responses to stressful challenges.

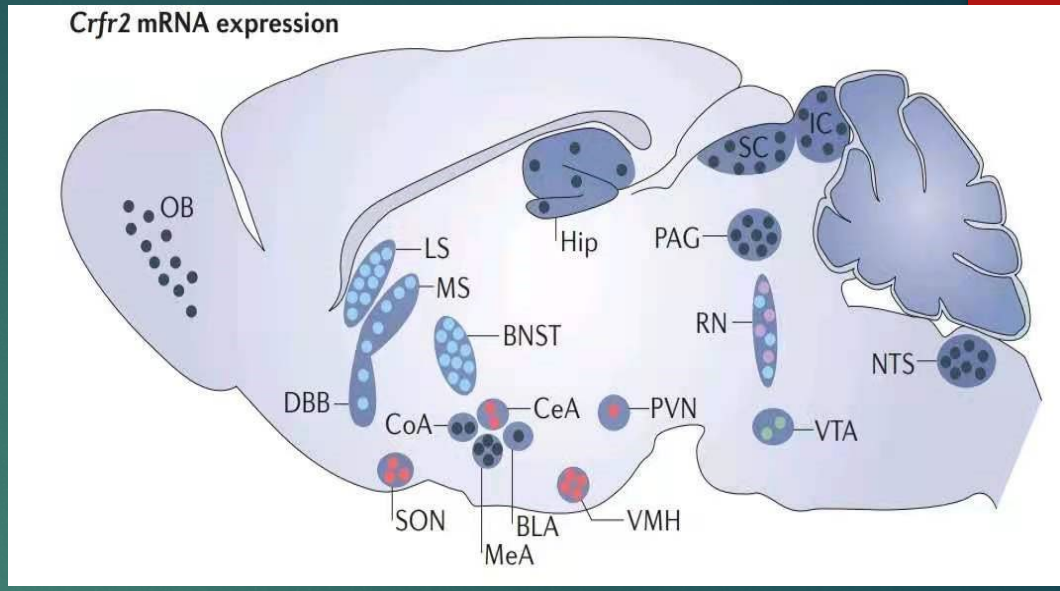


Figure 2: Hypersensitivity of HPA axis to stress in mutant animals.

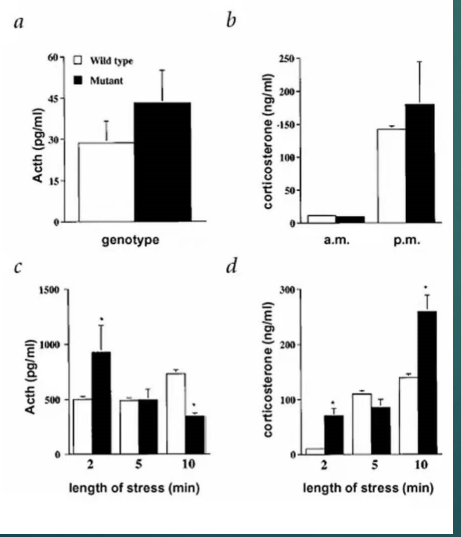
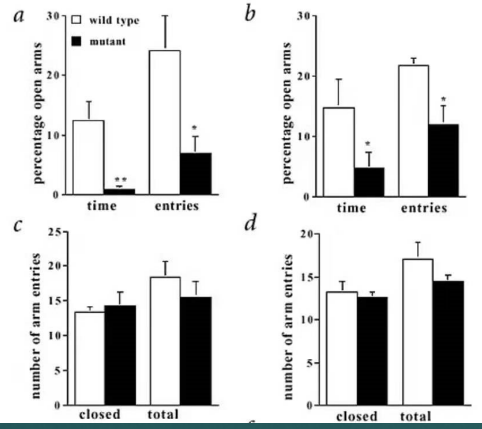
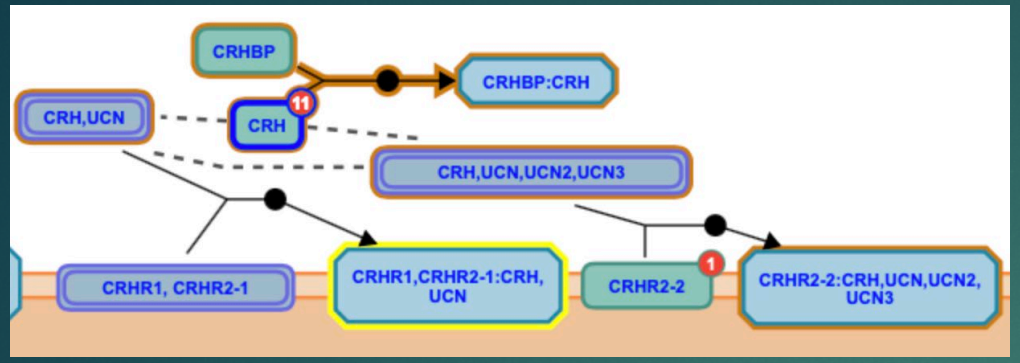


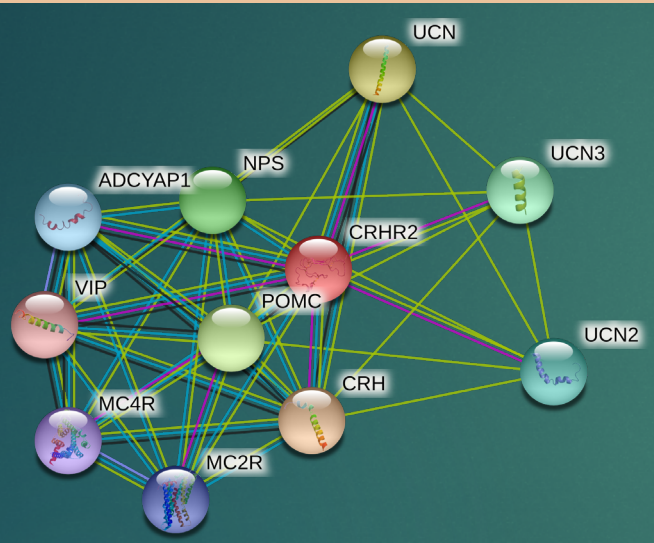
Figure 4: Increased anxiety-like behaviour of mutant animals as measured in the elevated plus maze and open-field test.



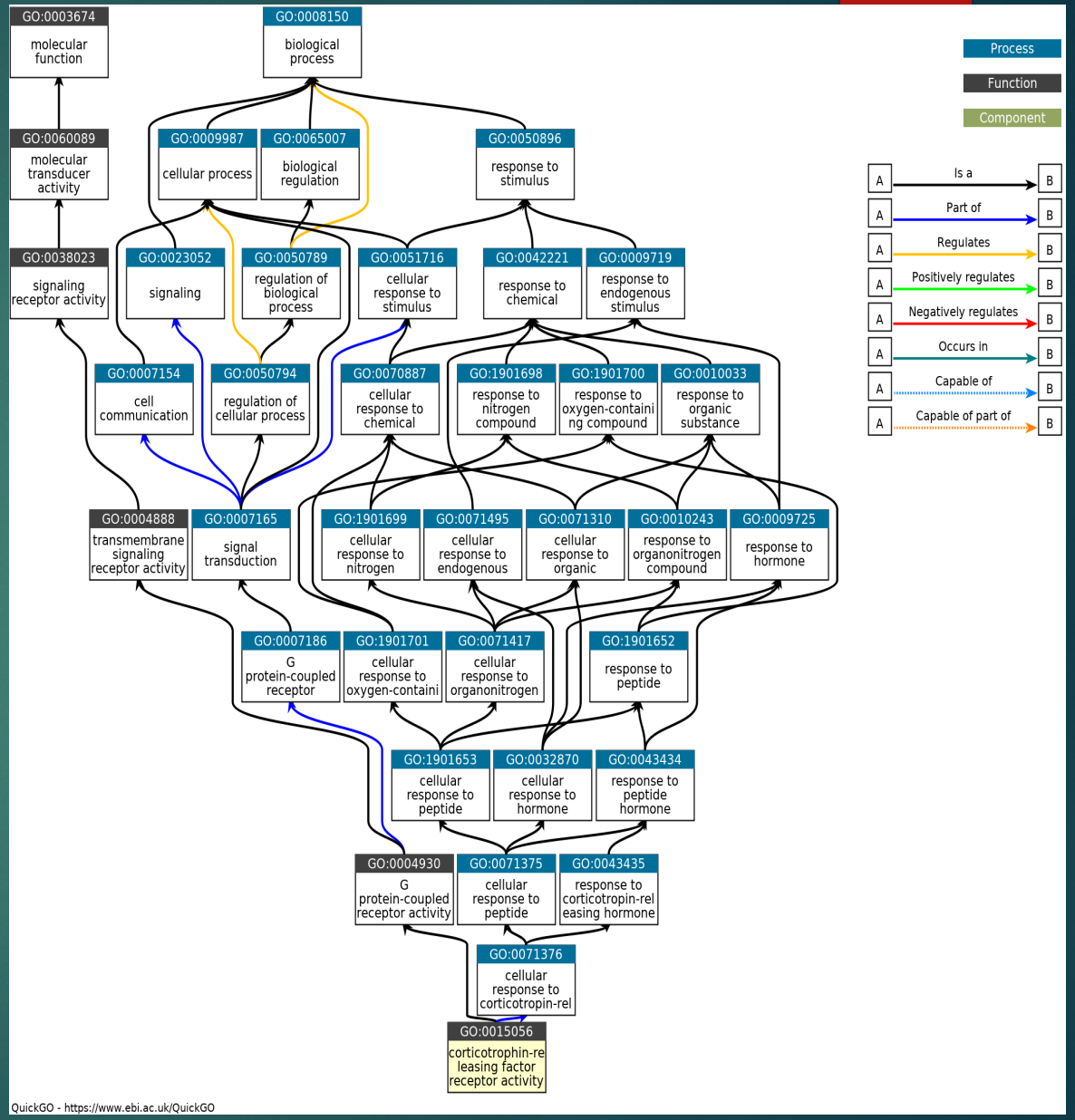
CRHR2 activation is responsible for ensuring physiological and psychological homeostasis and counteracts the initial stress-response-provoking effects and anxiety-like behaviors

What is the molecular basis for CRFR2 to function?



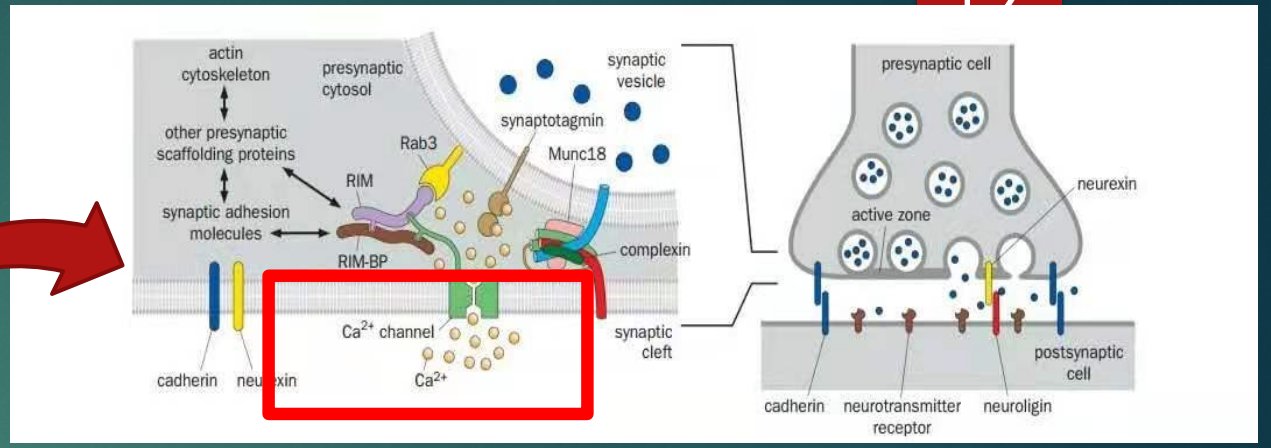


CRHR2 belongs to a category of CRHR receptors, and its main ligands are CRH and UCN families When CRHR are bound by natural ligands, they can activate downstream signal transduction pathways

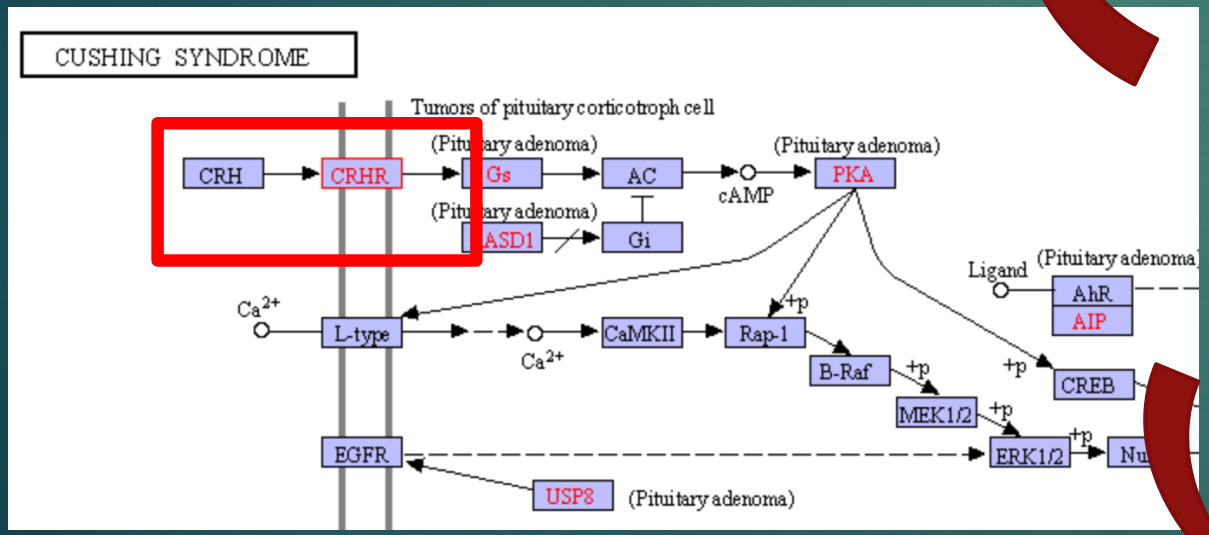


Calcium signal is especially important

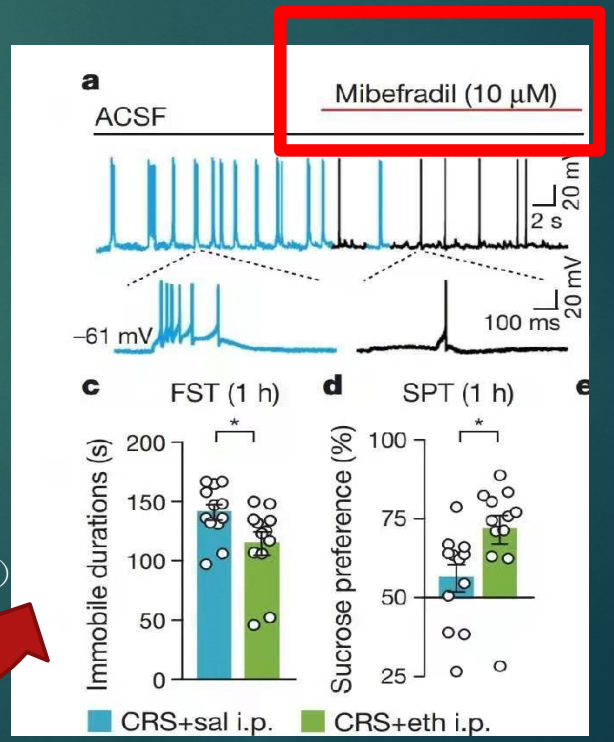
How CRHR2 affects the activities of St18 can be considered from two directions, but both require subsequent electrophysiological and pharmacological experiments to verify



（Luo, 2015）



（Cui et al., 2018）



Agonists of CRHR2 & Three mutation sites related to drug-response in human

Agonists

Key to terms and symbols | View all chemical structures | Click column headers to sort

Ligand	Sp.	Action	Value	Parameter	Reference
[^{125}I]urocortin 1 (mouse, rat)	Hs	Full agonist	10.0	pK_d	28
[^{125}I]sauvagine (frog)	Hs	Full agonist	9.6 – 9.8	pK_d	8,12
urocortin 1 {Sp: Human}	Hs	Full agonist	9.0 – 9.6	pK_d	8,12
urocortin 2 {Sp: Human}	Mm	Full agonist	9.3	pK_d	21,29
urocortin 2 {Sp: Mouse}	Mm	Full agonist	9.2	pK_d	21
urocortin 1 {Sp: Mouse, Rat}	Mm	Full agonist	8.7 – 9.4	pK_d	12,14,21,28,36
urocortin 1 {Sp: Mouse, Rat}	Hs	Full agonist	8.6 – 9.4	pK_d	12
urocortin 1 {Sp: Human}	Mm	Full agonist	8.8	pK_d	14
urocortin 2 {Sp: Human}	Rn	Full agonist	8.8	pK_d	21
urocortin 1 {Sp: Human}	Rn	Full agonist	8.7	pK_d	14
urocortin 2 {Sp: Mouse}	Rn	Full agonist	8.7	pK_d	21
urocortin 3 {Sp: Mouse, Rat}	Mm	Full agonist	8.7	pK_d	21
urocortin 2 {Sp: Human}	Hs	Full agonist	8.5 – 8.6	pK_d	8
sauvagine	Mm	Full agonist	8.4 – 8.7	pK_d	14,28,36
urotensin 1 (fish)	Mm	Full agonist	8.5	pK_d	36
sauvagine	Hs	Full agonist	7.6 – 9.3	pK_d	8,12
sauvagine	Rn	Full agonist	8.0 – 8.8	pK_d	14,28
urocortin 3 {Sp: Mouse, Rat}	Rn	Full agonist	8.3	pK_d	21

1. rs7793837 *[Homo sapiens]*

Variant type:	SNV
Alleles:	A>C,T [Show Flanks]
Chromosome:	7:30687161 (GRCh38) 7:30726777 (GRCh37)
Canonical SPDI:	NC_000007.14:30687160:A:C,NC_000007.14:30687160:A:T
Gene:	CRHR2 (Varview)
Functional Consequence:	genic_upstream_transcript_variant,intron_variant,5_prime_UTR_variant
Clinical significance:	drug-response
Validated:	by frequency,by alfa,by cluster
MAF:	T=0.271481/594 (ALFA) T=0.166667/100 (NorthernSweden) T=0.171943/315 (Korea1K) ...more
HGVS:	NC_000007.14:g.30687161A>C, NC_000007.14:g.30687161A>T, NC_000007.13:g.30726777A>C, NC_000007.13:g.30726777A>T, NG_029169.1:g.17943T>G, NG_029169.1:g.17943T>A, XM_017011752.2:c.-712T>G, ...more

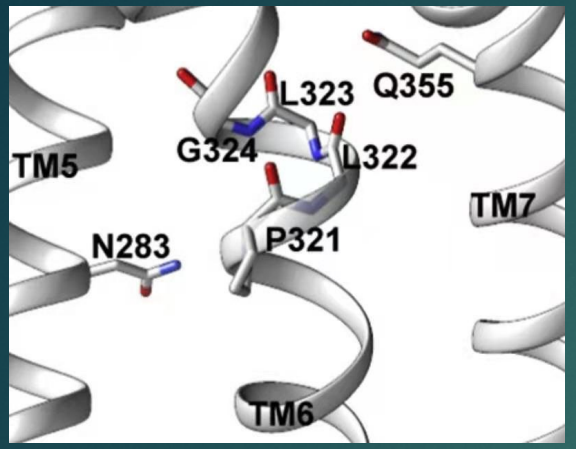
PubMed LitVar

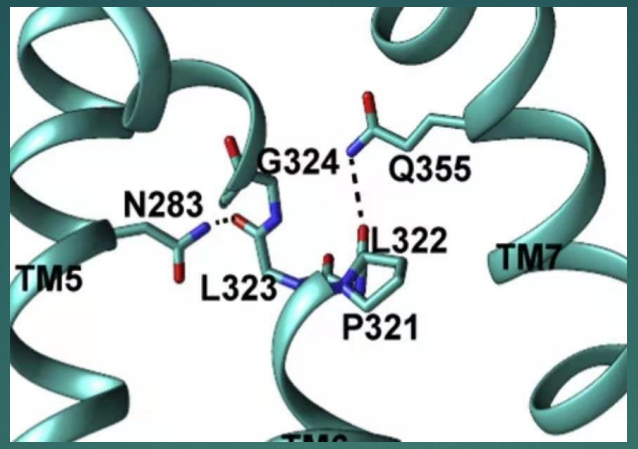
2. rs58713119 has merged into rs7793837 *[Homo sapiens]*

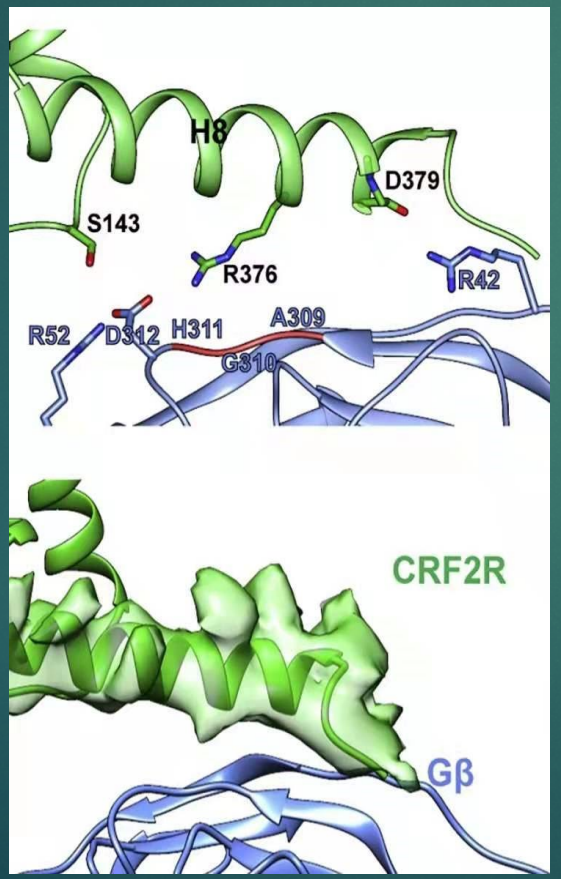
Variant type:	SNV
Alleles:	A>C,T [Show Flanks]
Chromosome:	7:30687161 (GRCh38) 7:30726777 (GRCh37)
Canonical SPDI:	NC_000007.14:30687160:A:C,NC_000007.14:30687160:A:T
Gene:	CRHR2 (Varview)
Functional Consequence:	genic_upstream_transcript_variant,intron_variant,5_prime_UTR_variant
Clinical significance:	drug-response
Validated:	by frequency,by alfa,by cluster
MAF:	T=0.271481/594 (ALFA) T=0.166667/100 (NorthernSweden) T=0.171943/315 (Korea1K) ...more
HGVS:	NC_000007.14:g.30687161A>C, NC_000007.14:g.30687161A>T, NC_000007.13:g.30726777A>C, NC_000007.13:g.30726777A>T, NG_029169.1:g.17943T>G, NG_029169.1:g.17943T>A, XM_017011752.2:c.-712T>G, ...more

3. rs10384543 has merged into rs7793837 *[Homo sapiens]*

Variant type:	SNV
Alleles:	A>C,T [Show Flanks]
Chromosome:	7:30687161 (GRCh38) 7:30726777 (GRCh37)
Canonical SPDI:	NC_000007.14:30687160:A:C,NC_000007.14:30687160:A:T

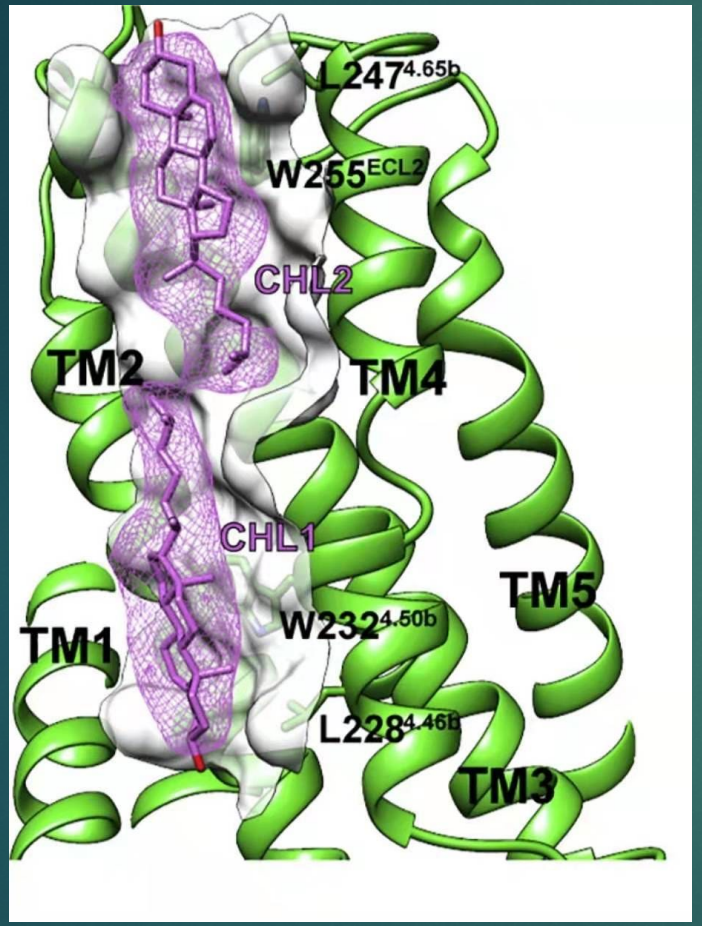




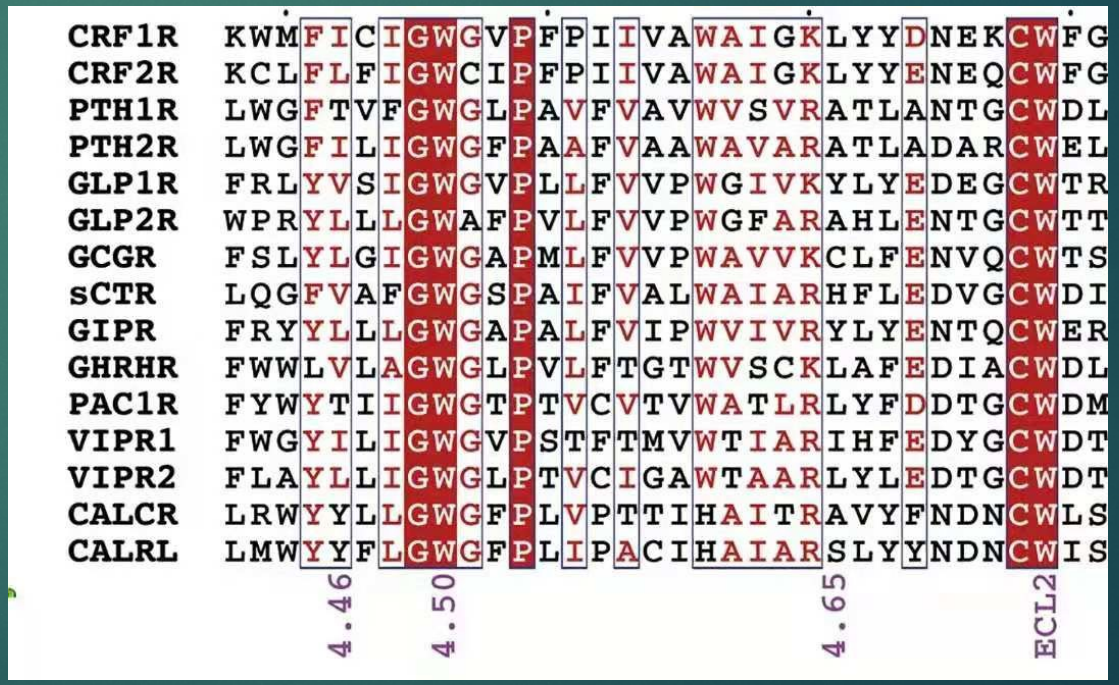


After CRFR2 is activated, the conformational changes are mainly concentrated in TM5, TM6, and TM7. TM6 unwinds at P3216.47b-G3246.50b and forms a 90° twist.

The interaction between the Helix 8 helix of the receptor and the N-terminus of Gβ is the main interface between the receptor and the Gs protein



The amino acids acting on these two cholesterol molecules are highly conserved in class B GPCRs



All criticisms are accepted