Introduction to Neuroscience: Behavioral Neuroscience

Lecture 4

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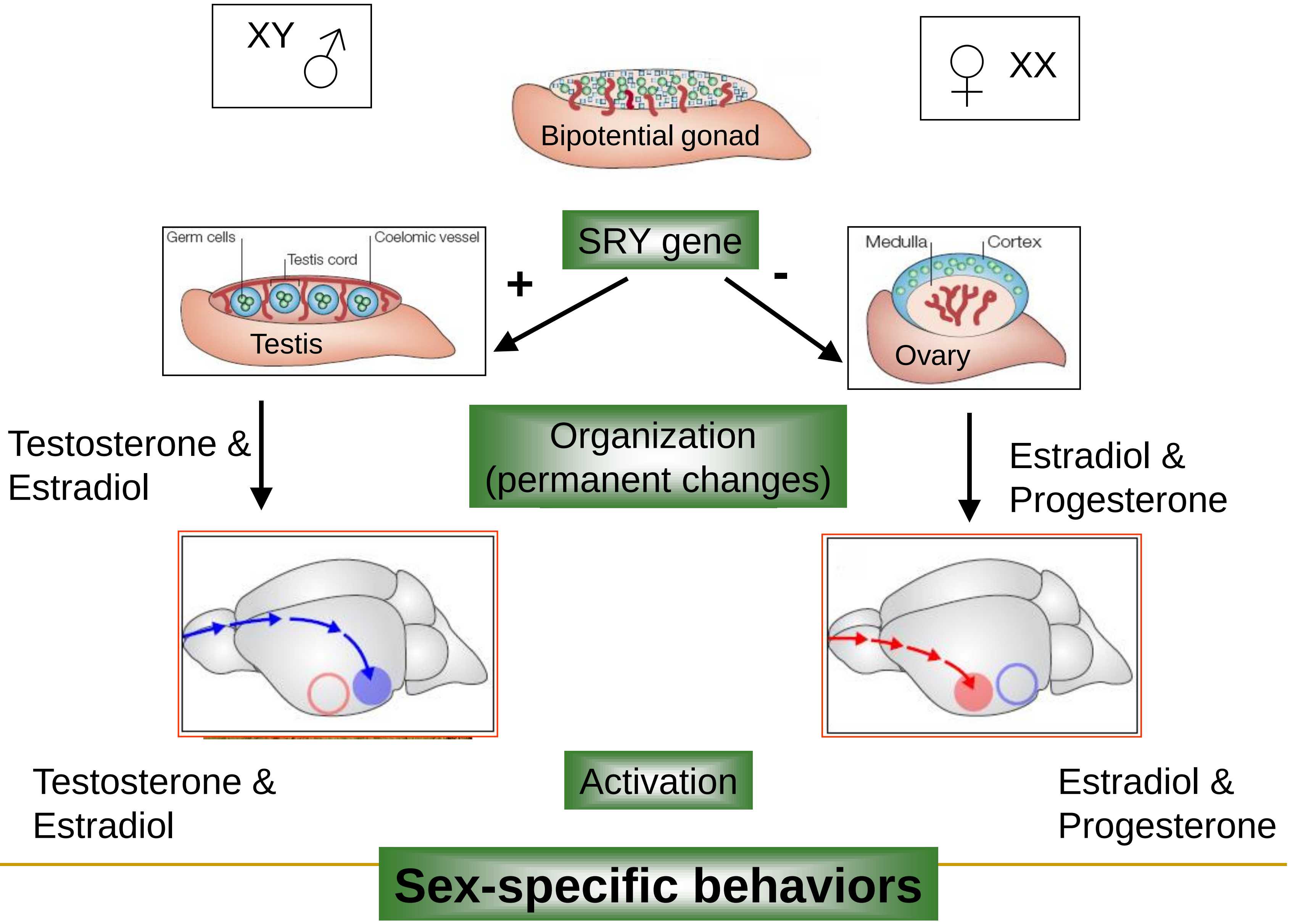
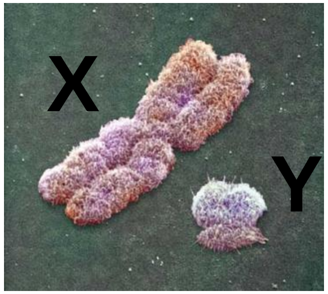
Sexual Dimorphism in Brain and Behavior-part II

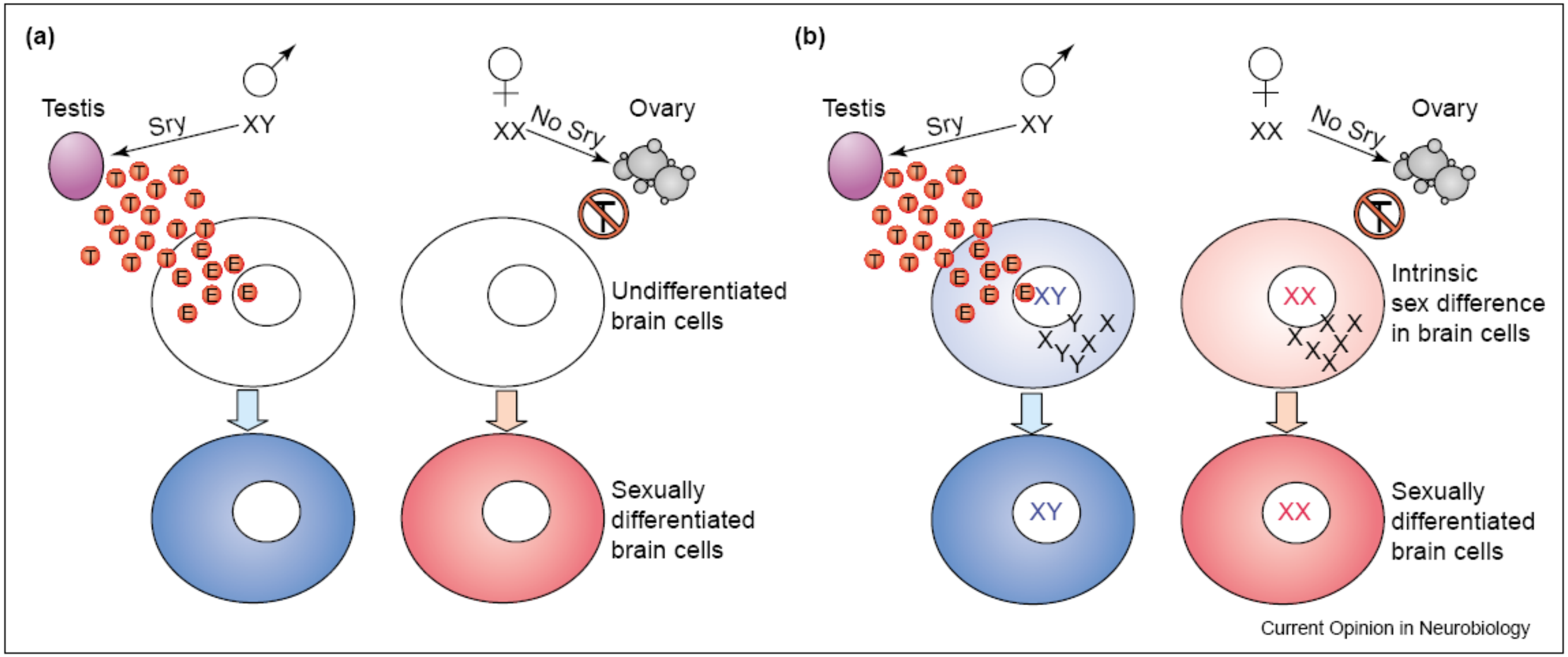
Studying Social-related Mental Disorders using Animal Models

Dimorphism of the brain: differentiation and activation

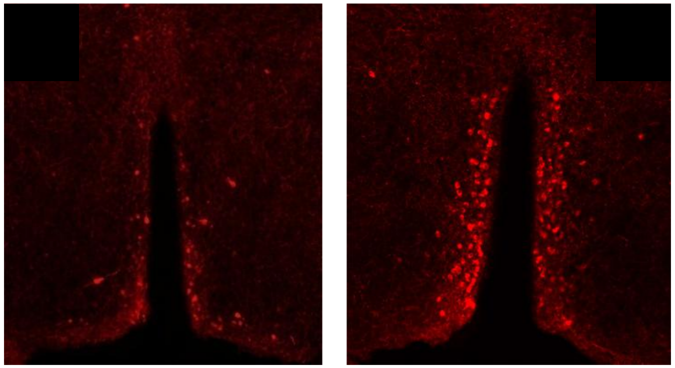


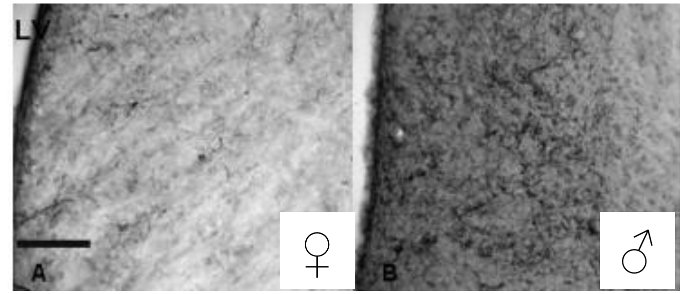
Sexual dimorphism can NOT be explained just by sex hormones organization affects

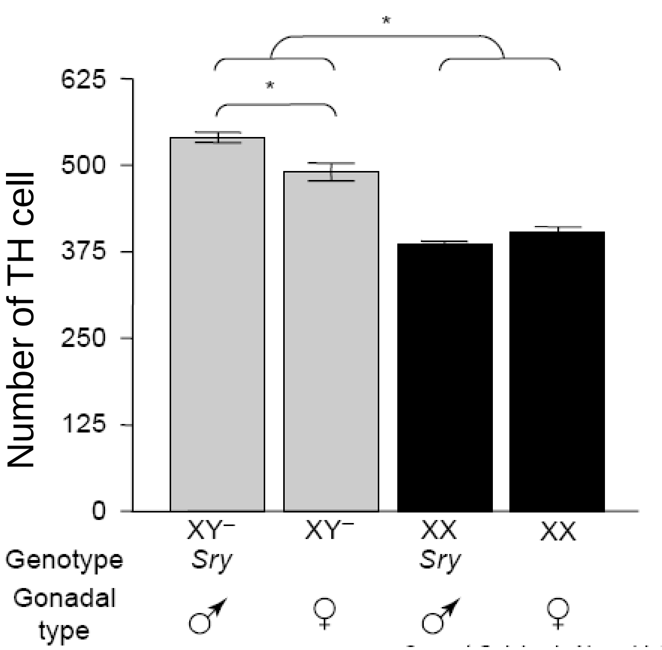


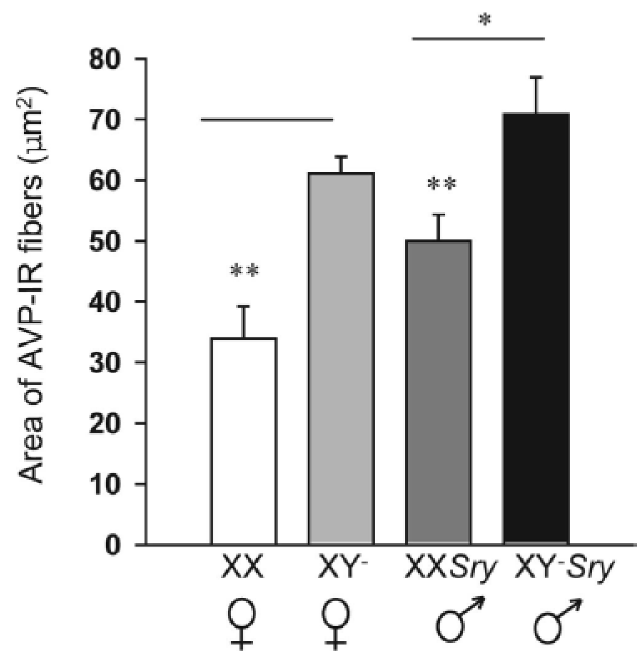


Evidence for the affect of Y-linked genes on sexual dimorphism of the brain







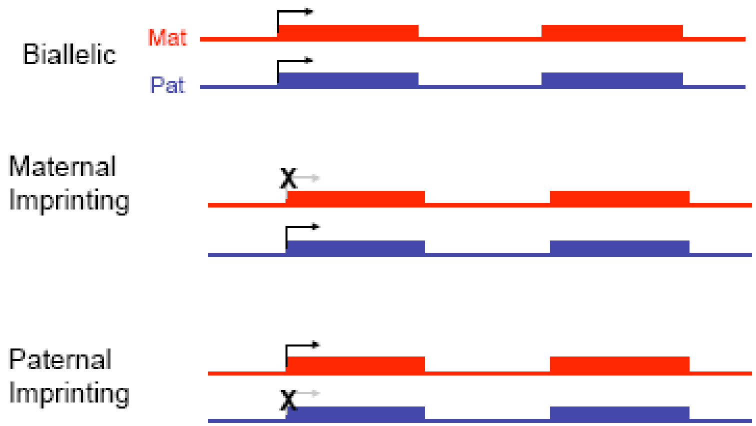


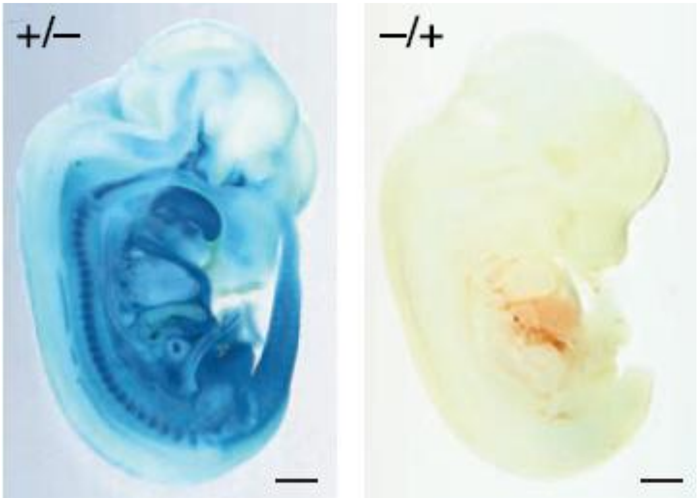
De Vries et al 2002 *J Neuroscience*

Imprinting genes

Definition:

A gene or chromosome region that is expressed when inherited from one (maternal or paternal) parent. But not when inherited from the other parent (i.e. parent-specific inactivation of a gene).





Imprinting genes

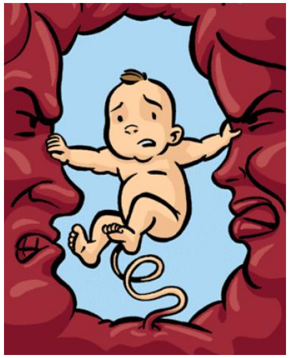
Mechanism:

•Imprinting is determined by allele-specific DNA methylation at critical sites (e.g. promoter region) which represses the expression of the gene.

•DNA methylation is the convalent attachment of methyl to the cytosine using DNA methylase enzyme.

Result: DNA methalation may inhibit transcription by mainly preventing the binding of transcription factors to the promoter region.

Imprinting genes



Biology function:
"The battle of the sexes theory" or "parental conflict theory"

- The father is more "interested" in the growth of the offspring, at the expense of the mother.
- The mother's interests is to conserve resources for her survival and provide sufficient nutrition to her pups.

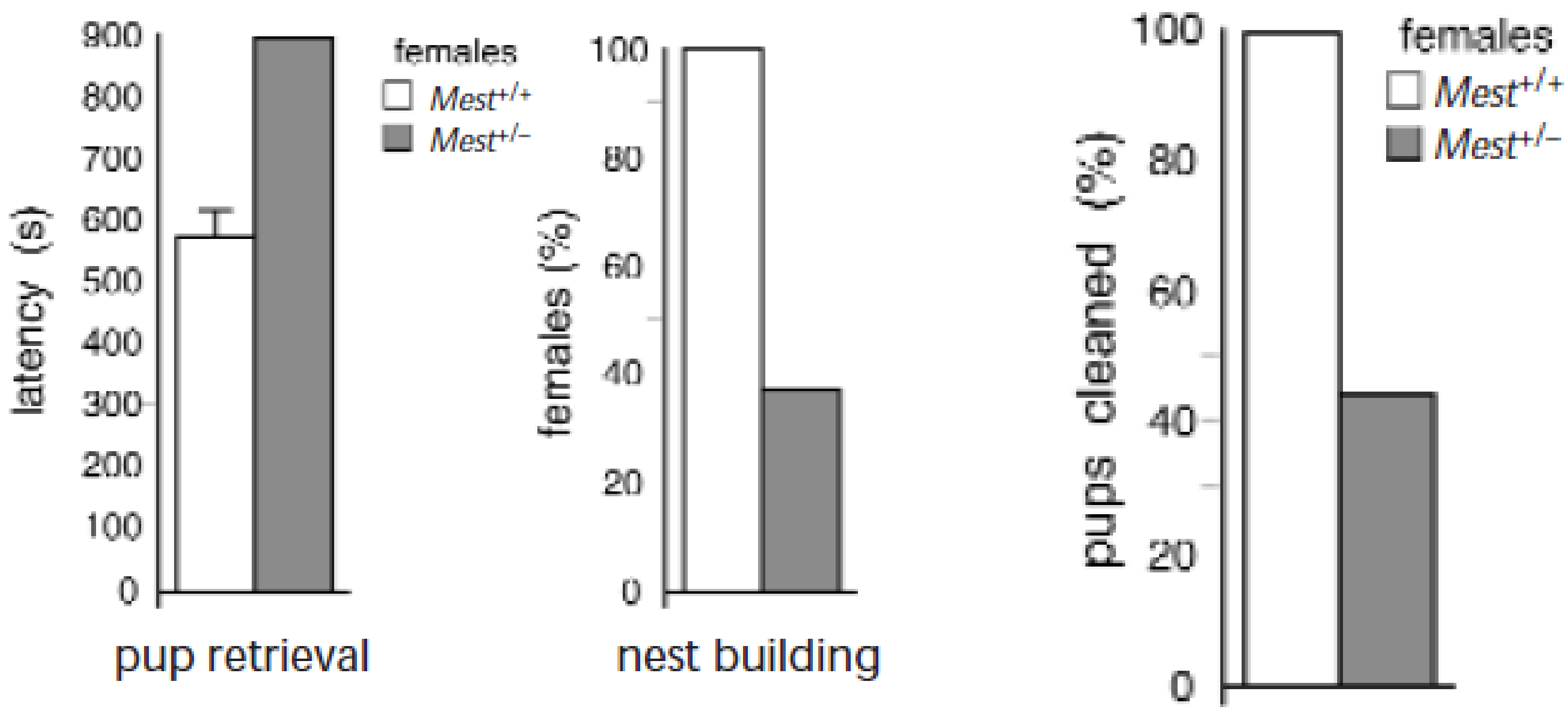
- Parental genes are selected to extract resources from the mother to give to the fetus, while maternal imprinting genes are selected to inhibit this transfer of resources.

Maternal imprinting genes will repress growth of pups and paternal imprinting genes will enhance growth.

Paternally expressed genes (Peg1/Mest)

Normal animal Peg1 enhance maternal care

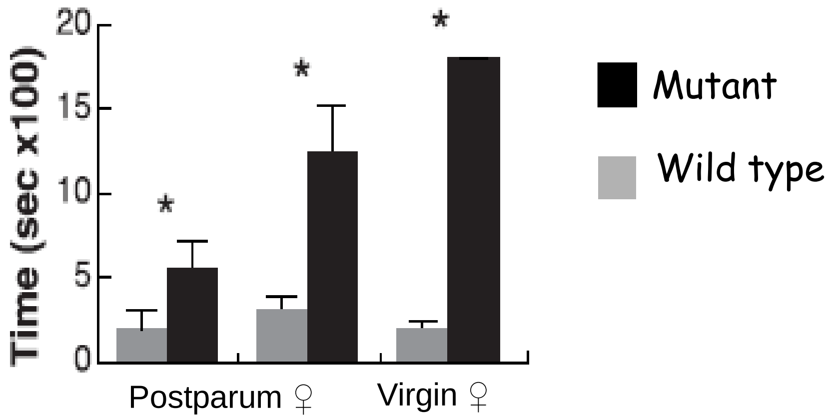
Peg1 mutant female will exhibit deficiency in maternal behaviors



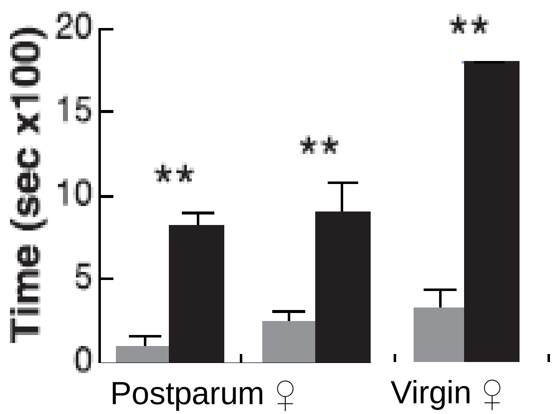
Curley et al 2004 *Proc R Soc B*

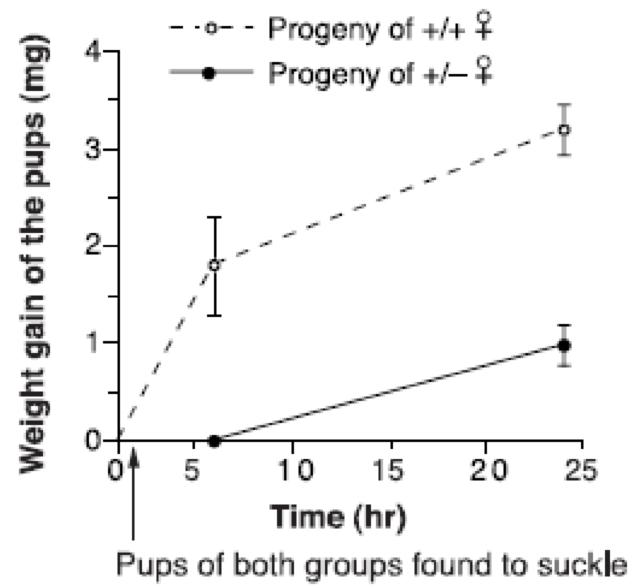
Paternally expressed genes (Peg3)

Time to retrieve pups



Latency of nest building

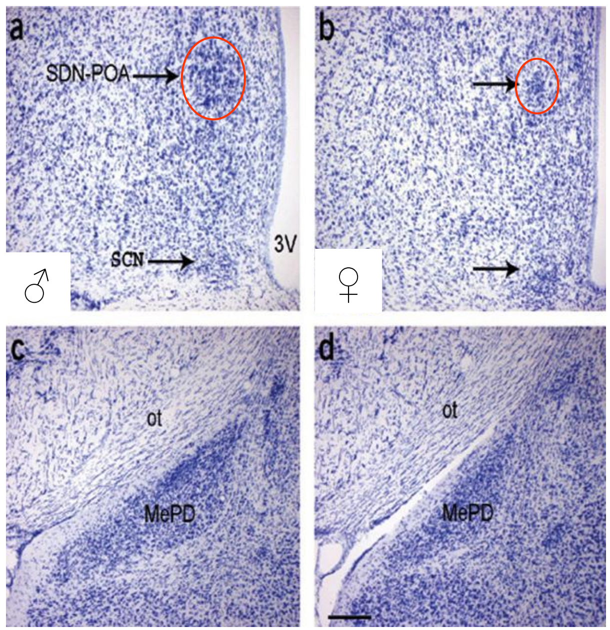




Lefebvre et al 1998; Nature Genetics
Keverne et al 1999; Science

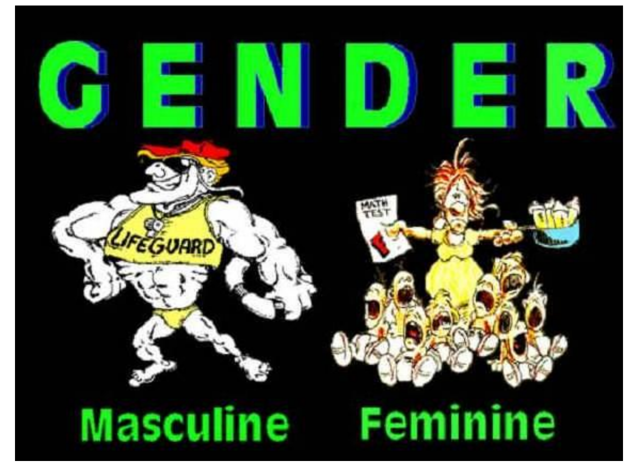
Hormones

Organization

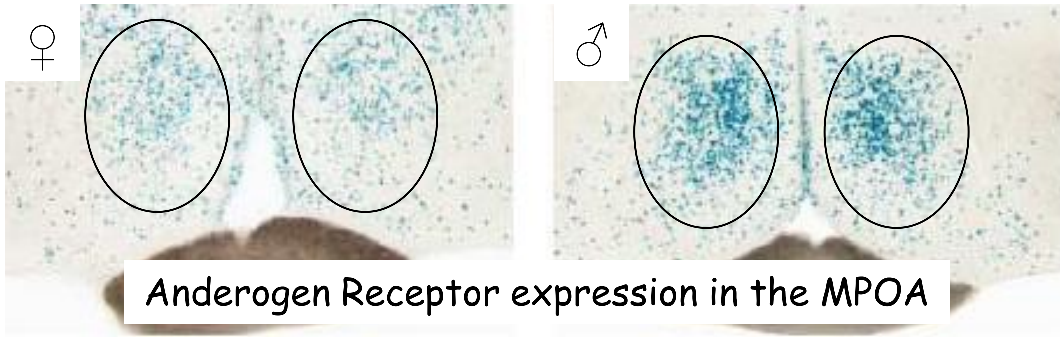


Hormones

Activation



The Medial Preoptic Area (MPOA) is activated by testosterone and is essential to the activation of male sexual behavior



Castration → Abolish of sexual behavior → Microinjection of testosterone into the MPOA → Reinstate sexual behavior

MPOA lesion → Abolish of sexual behavior

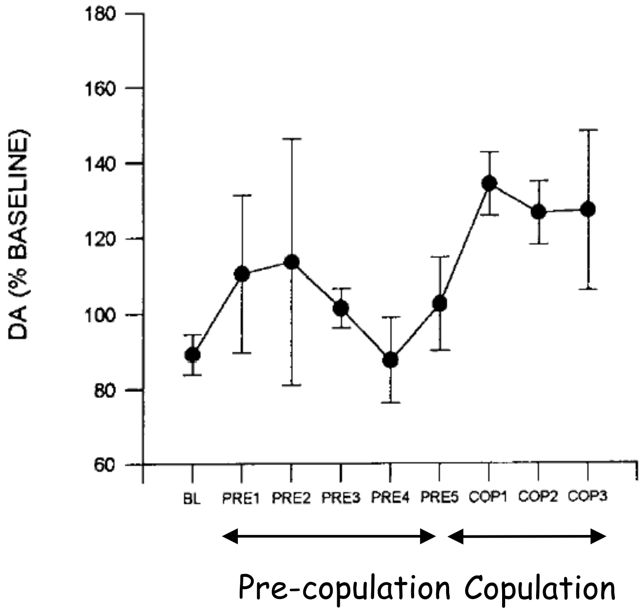
Intact male → Sexual behavior → Increase neuronal firing rate in the MPOA

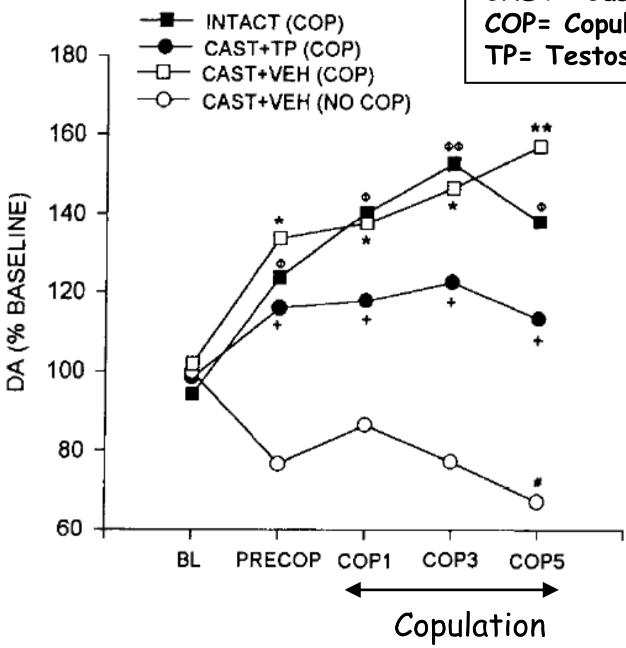
Sex-specific pheromone stimuli or mating behavior → Induce c-fos in MPOA of both males and females (c-fos is immediate early gene, indirect molecular marker of neuronal activity)

The Medial Preoptic Area (MPOA) is activated by testosterone and is essential to the activation of male sexual behavior

Intact male → Sexual (copulation) behavior → Increase of dopamine in the MPOA

Intact male → Microinjection of dopamine antagonist into the MPOA → Decrease in sexual behavior





INTACT= Non-castrated (normal)
CAST= Castrated
COP= Copulate
TP= Testosterone treatment

Hull et al. 1999; Behav. Brain Res

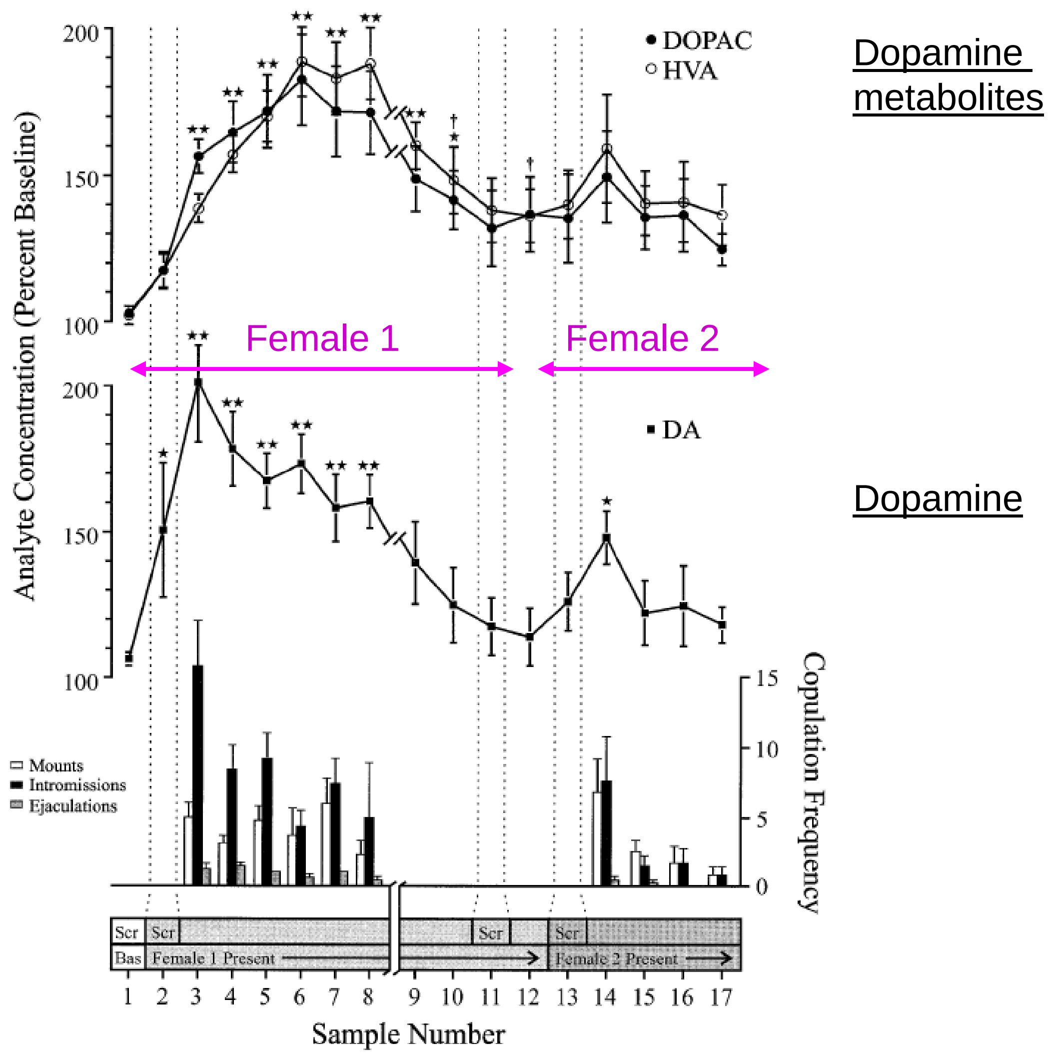
The Coolidge Effect

*According to the story, President Coolidge and his wife were visiting a farm in the Midwest and were given separate tours by the owners. Both President and Mrs. Coolidge noted during their tours that only one rooster was associated with the large flock of hens. Mrs. Coolidge asked the farmer how many times per day the rooster engaged in romance. "Several times a day," the farmer replied. "Please relay that information to the President," responded the First Lady, apparently impressed by the rooster's performance. Later, during his tour, President Coolidge was given this same information about the copulatory prowess of the rooster. The President pressed further, "Same hen each time?" "Oh no," replied the farmer, "A different hen each time." "Please relay that information to Mrs. Coolidge."

A male mice/rat has copulated to satiety can be induced to mate again if the initial female is replaced with a novel receptive female.

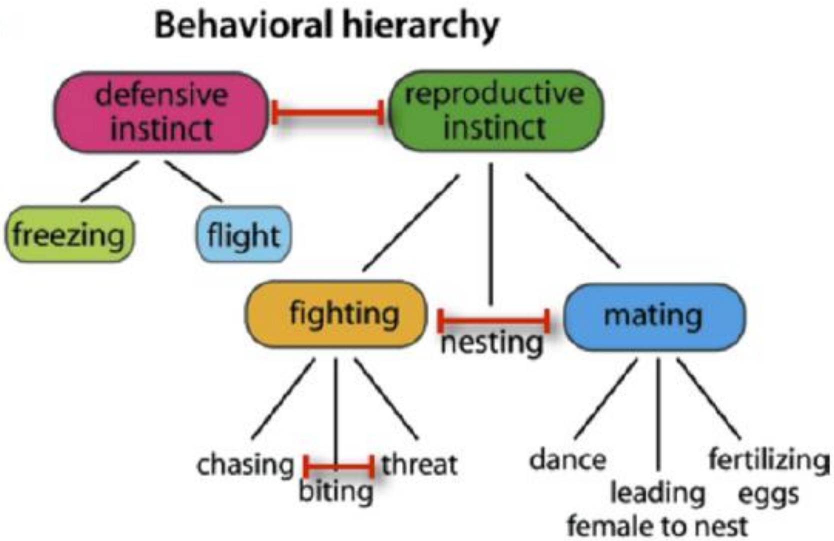
Novelty re-arouses sexual behavior

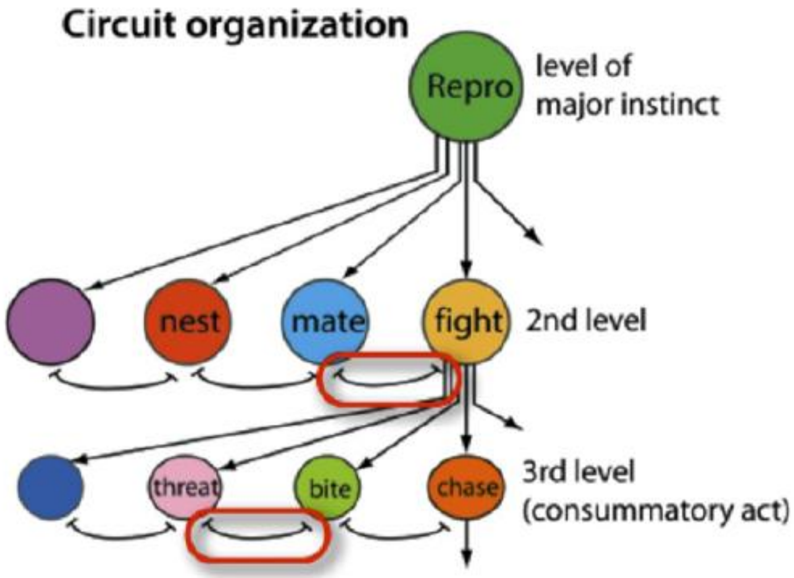
Dopamine fluctuations in MPOA during the "coolidge effect"



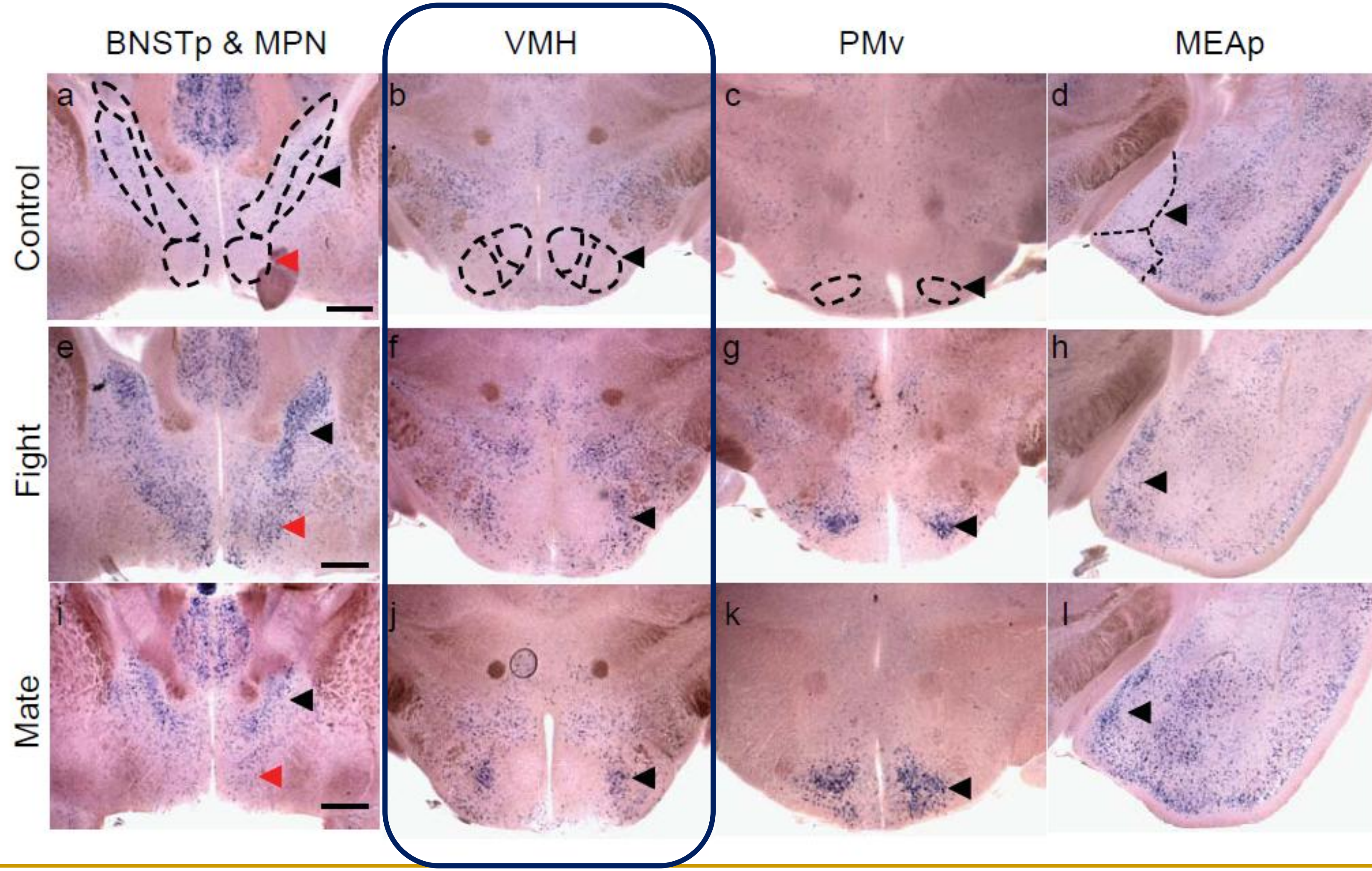
Fiorino et al 1997; J. Neurosci

Are the same brain regions regulate aggressive and sexual behavior?

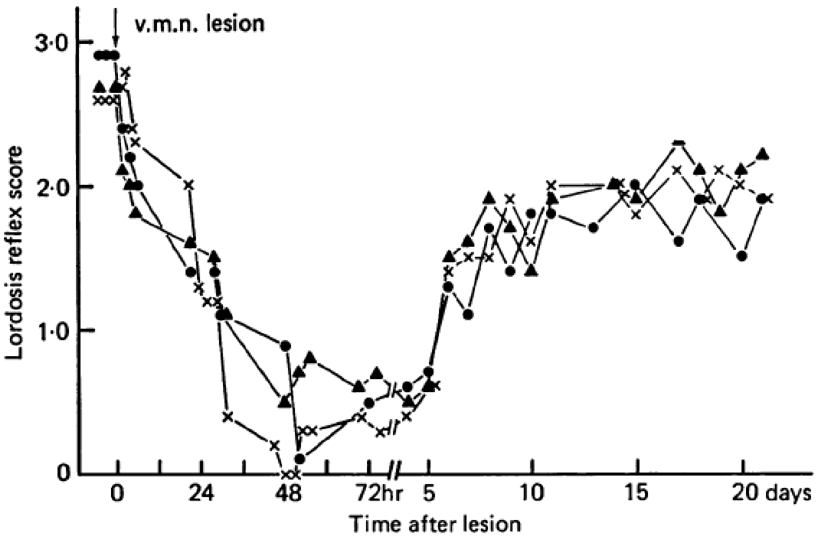


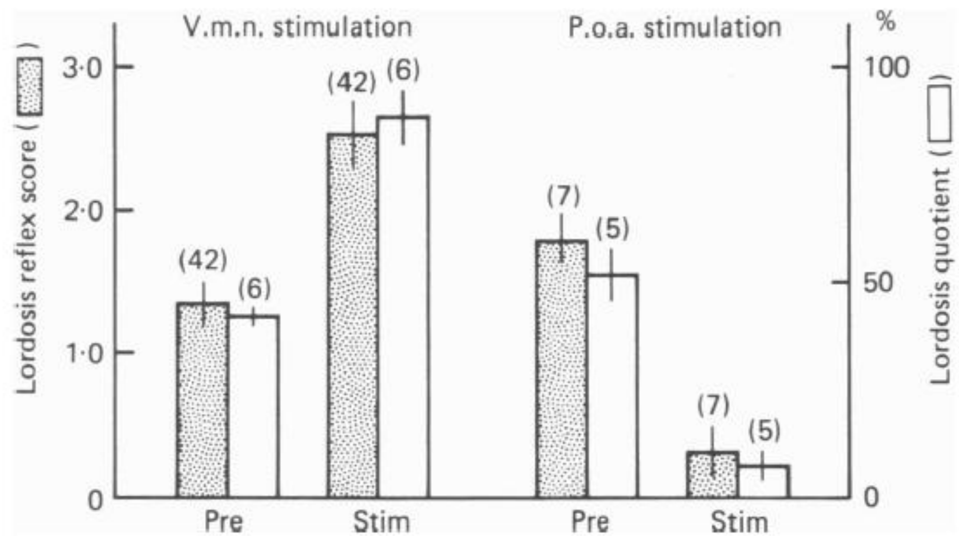


Labeling neuronal activity by measuring level of immediate early gene (cFOS) following sexual or aggressive behaviors in males



VMH brain region involve in female sexual receptivity (lordodisis behavior)





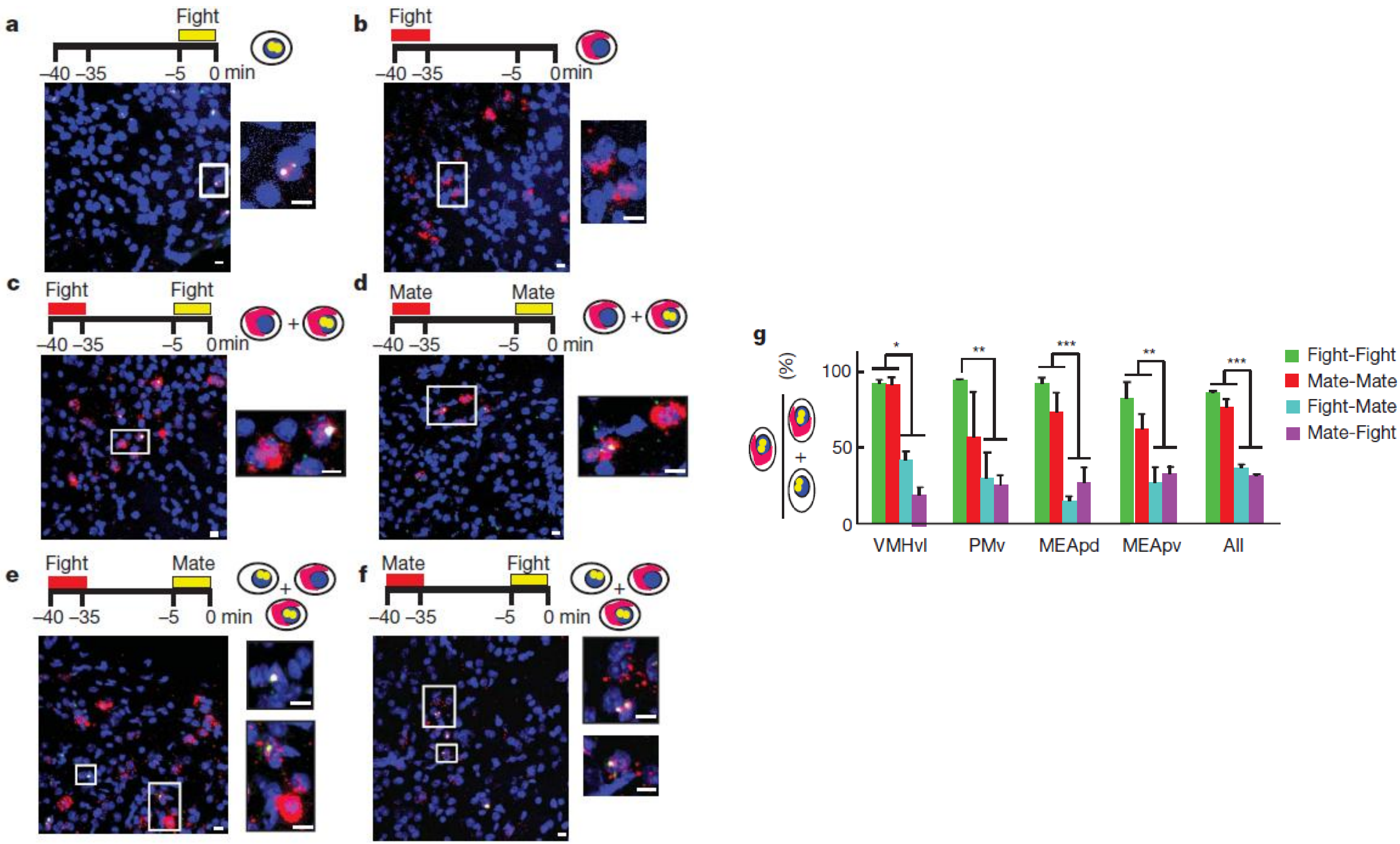
Pfaff and Sakuma 1979; J Physiol

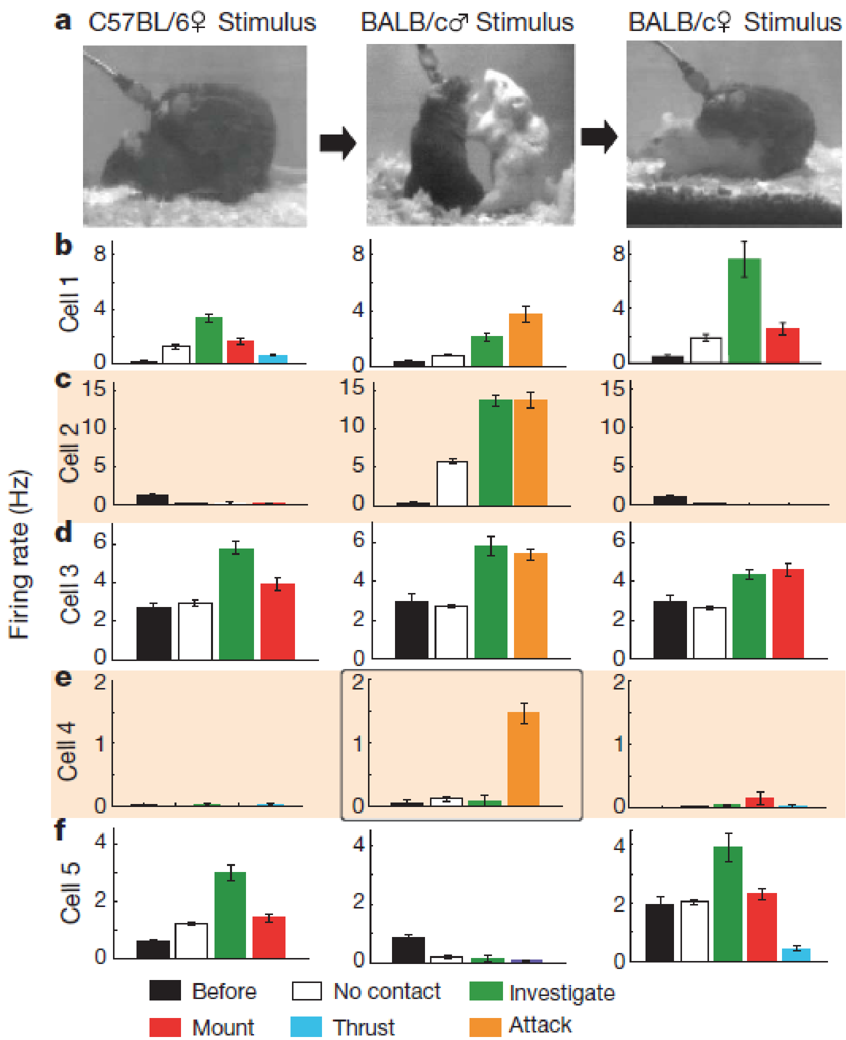
Functional identification of an aggression locus in the mouse hypothalamus

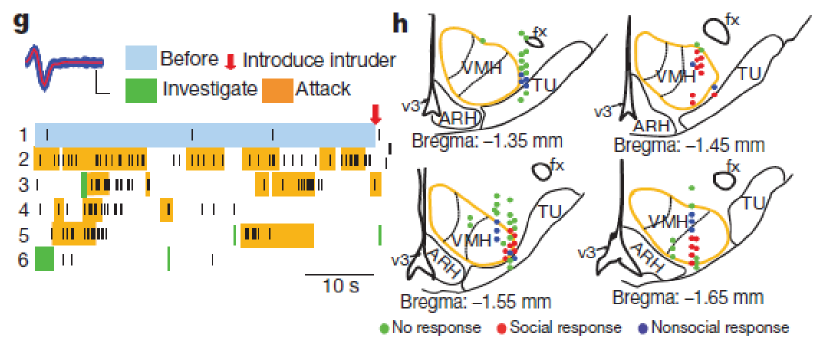
Dayu Lin[1,2], Maureen P. Boyle[3], Piotr Dollar[4], Hyosang Lee[1], E. S. Lein[3], Pietro Perona[4] & David J. Anderson[1,2]

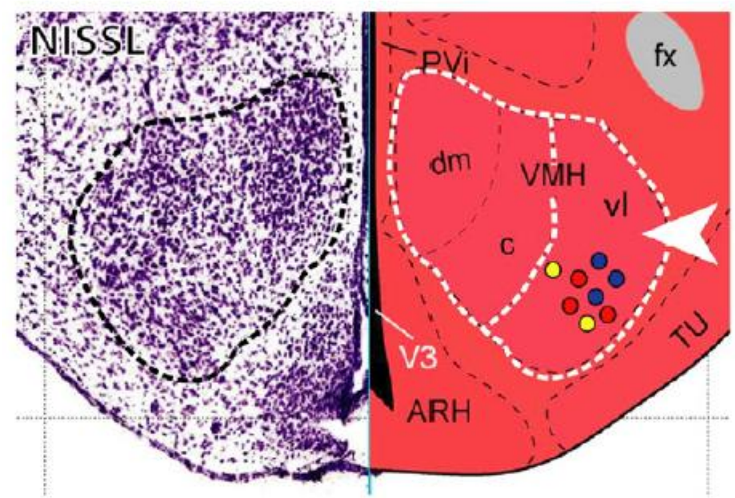
10 FEBRUARY 2011 | VOL 470 | NATURE

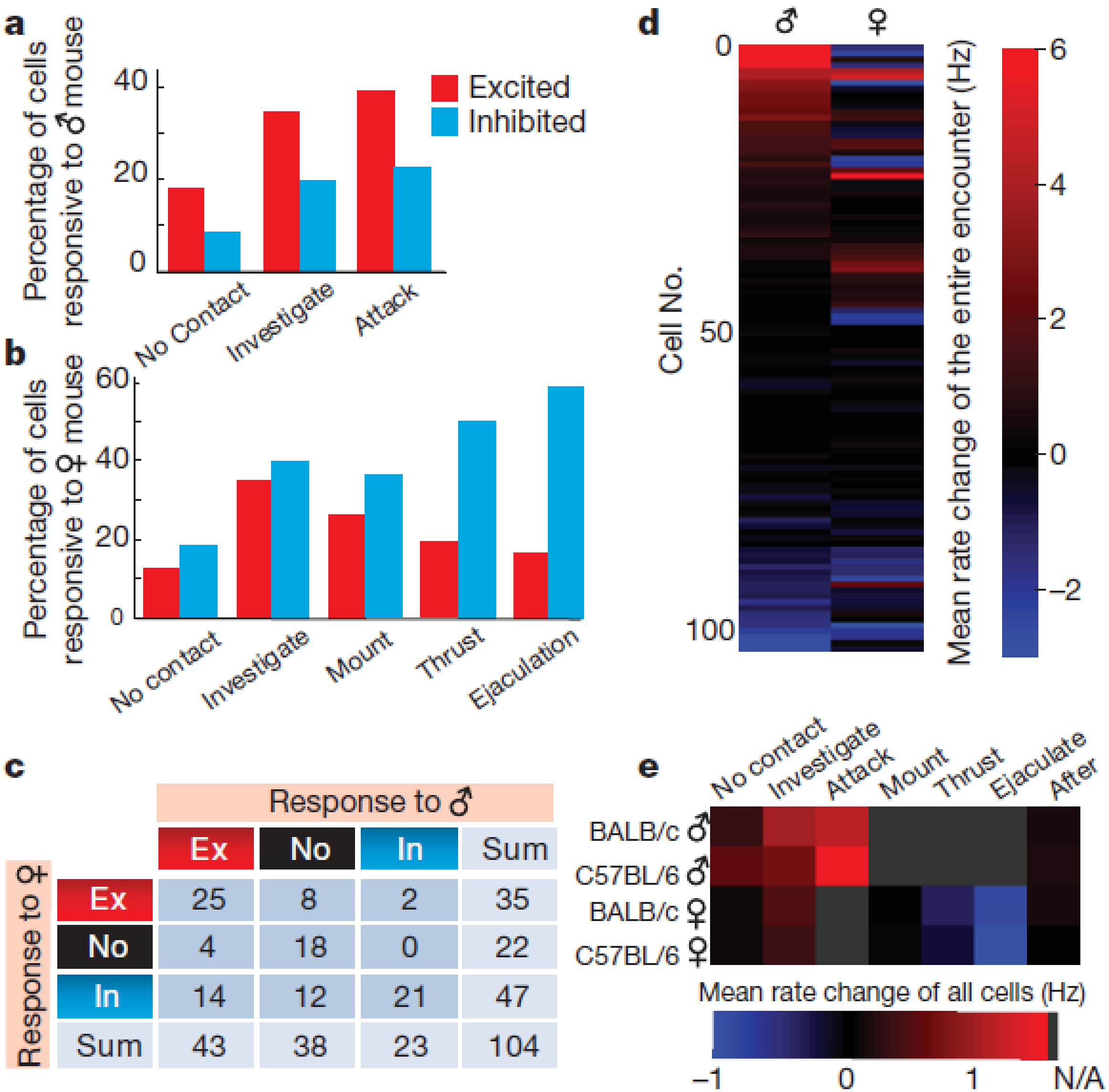
Labeling neuronal activity by measuring level of immediate early gene (cFOS) following sexual or aggressive behaviors in males




a C57BL/6♀ Stimulus
BALB/c♂ Stimulus
BALB/c♀ Stimulus
b
c
d
e
f
Cell 1
Cell 2
Cell 3
Cell 4
Cell 5
Firing rate (Hz)
Before
No contact
Investigate
Mount
Thrust
Attack

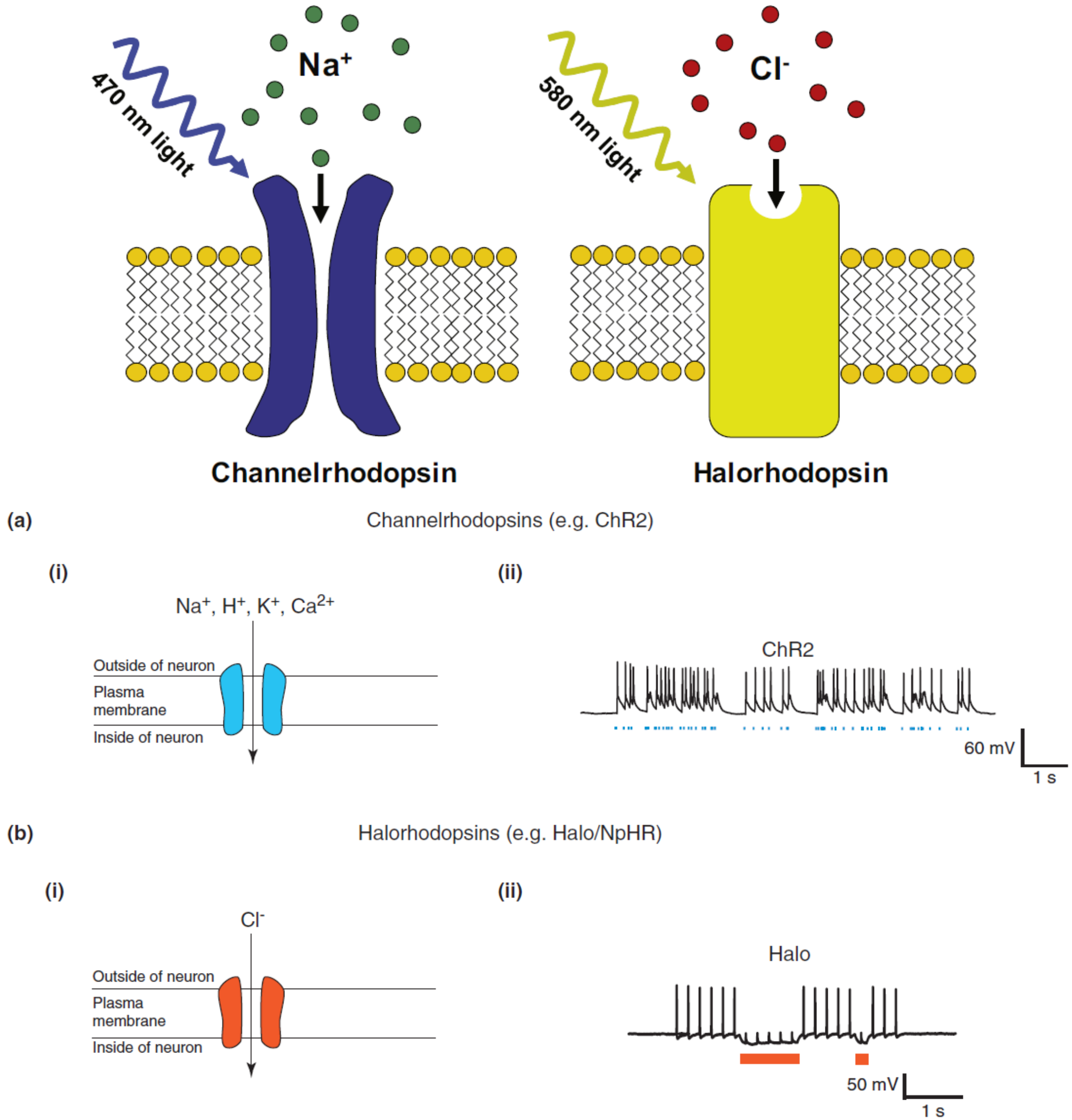

g
Before
Introduce intruder
Investigate
Attack
10 s
h
VMH
TU
ARH
fx
v3
Bregma: –1.35 mm
Bregma: –1.45 mm
Bregma: –1.55 mm
Bregma: –1.65 mm
No response
Social response
Nonsocial response

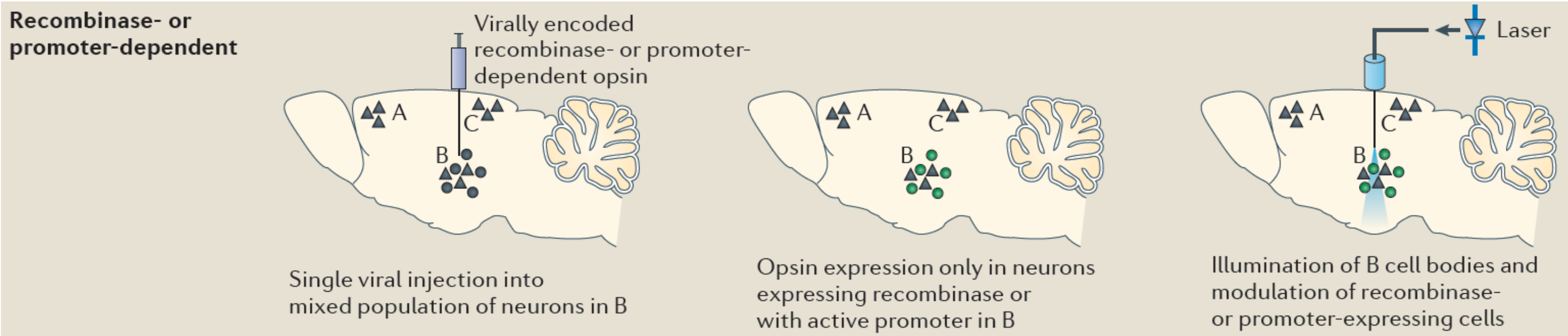

NISSL
PVi
fx
dm
VMH
vl
c
V3
ARH
TU

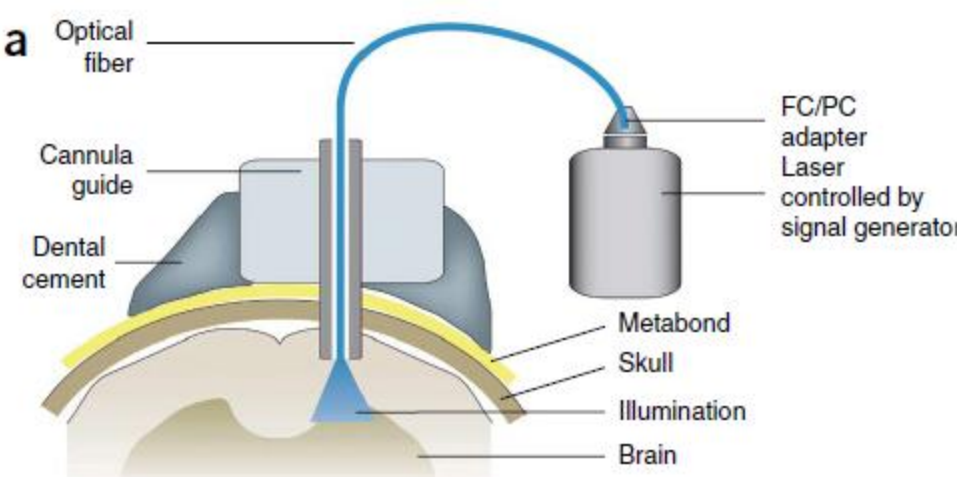


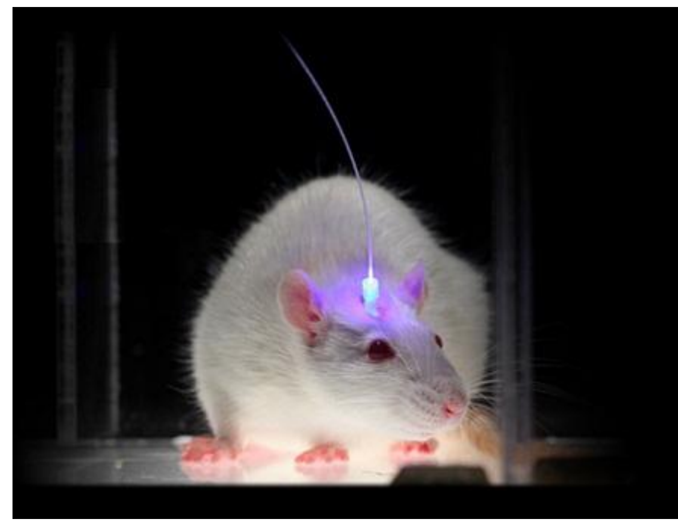
Response to ♀ \ Response to ♂	Ex	No	In	Sum
Ex	25	8	2	35
No	4	18	0	22
In	14	12	21	47
Sum	43	38	23	104

Neuronal manipulation using Optogenetic

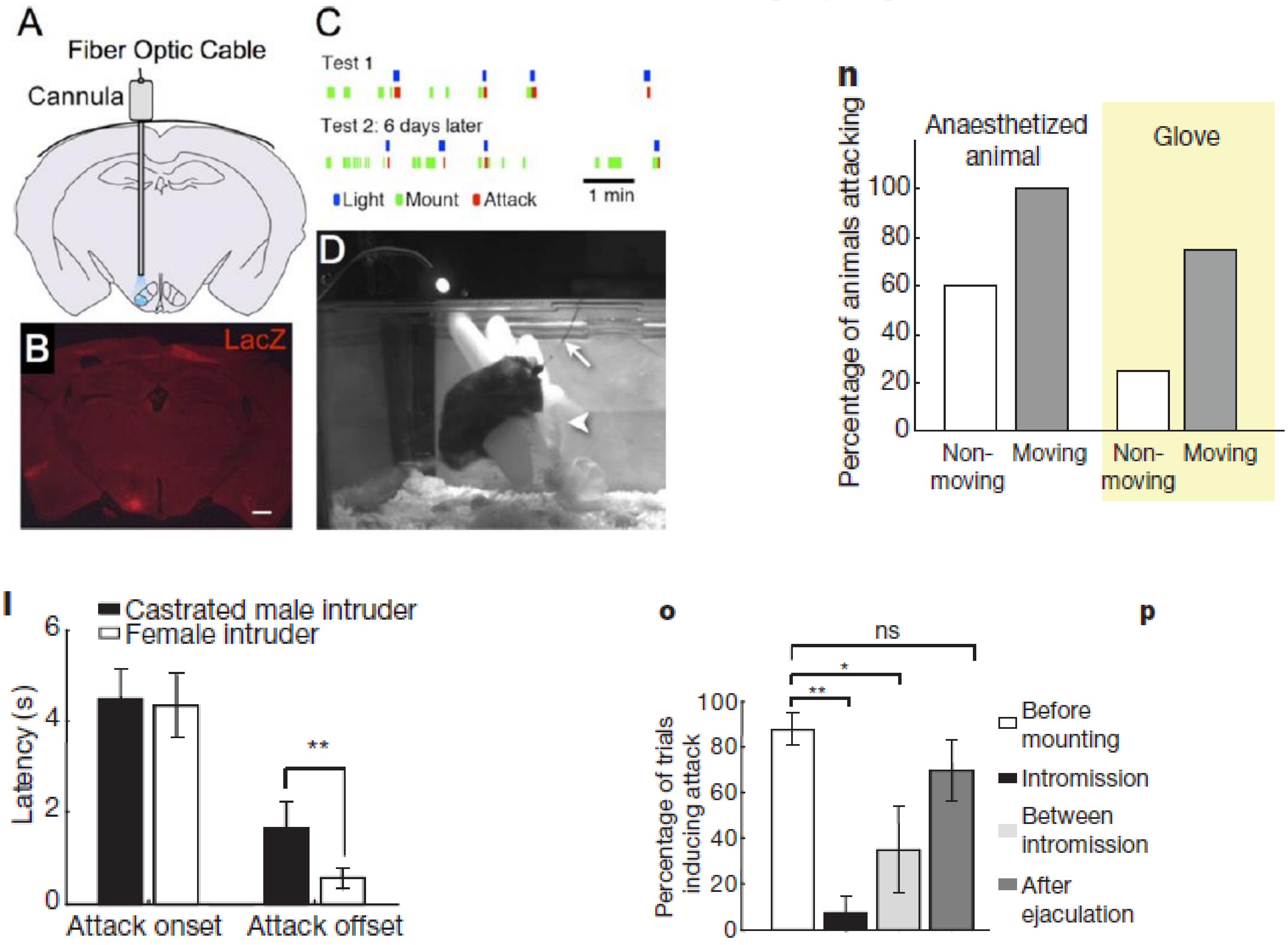



Recombinase- or
promoter-dependent
Virally encoded
recombinase- or promoter-
dependent opsin
Laser
A
B
C
Single viral injection into
mixed population of neurons in B
Opsin expression only in neurons
expressing recombinase or
with active promoter in B
Illumination of B cell bodies and
modulation of recombinase-
or promoter-expressing cells

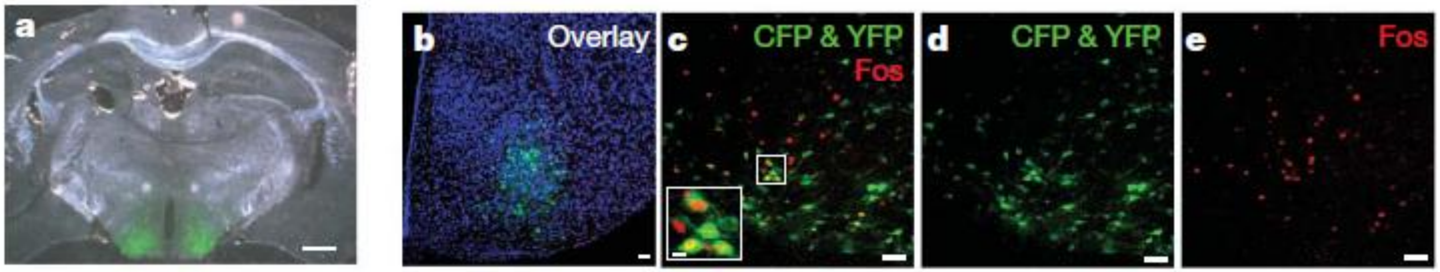

a
Optical
fiber
Cannula
guide
Dental
cement
FC/PC
adapter
Laser
controlled by
signal generator
Metabond
Skull
Illumination
Brain

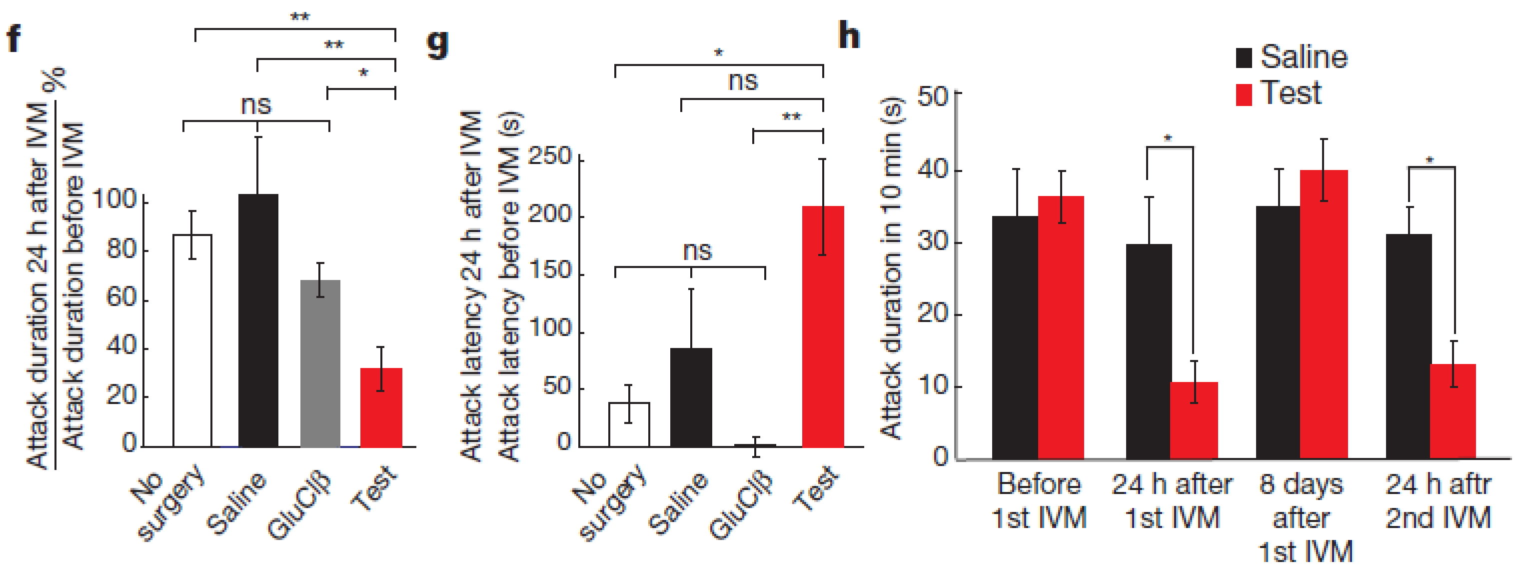


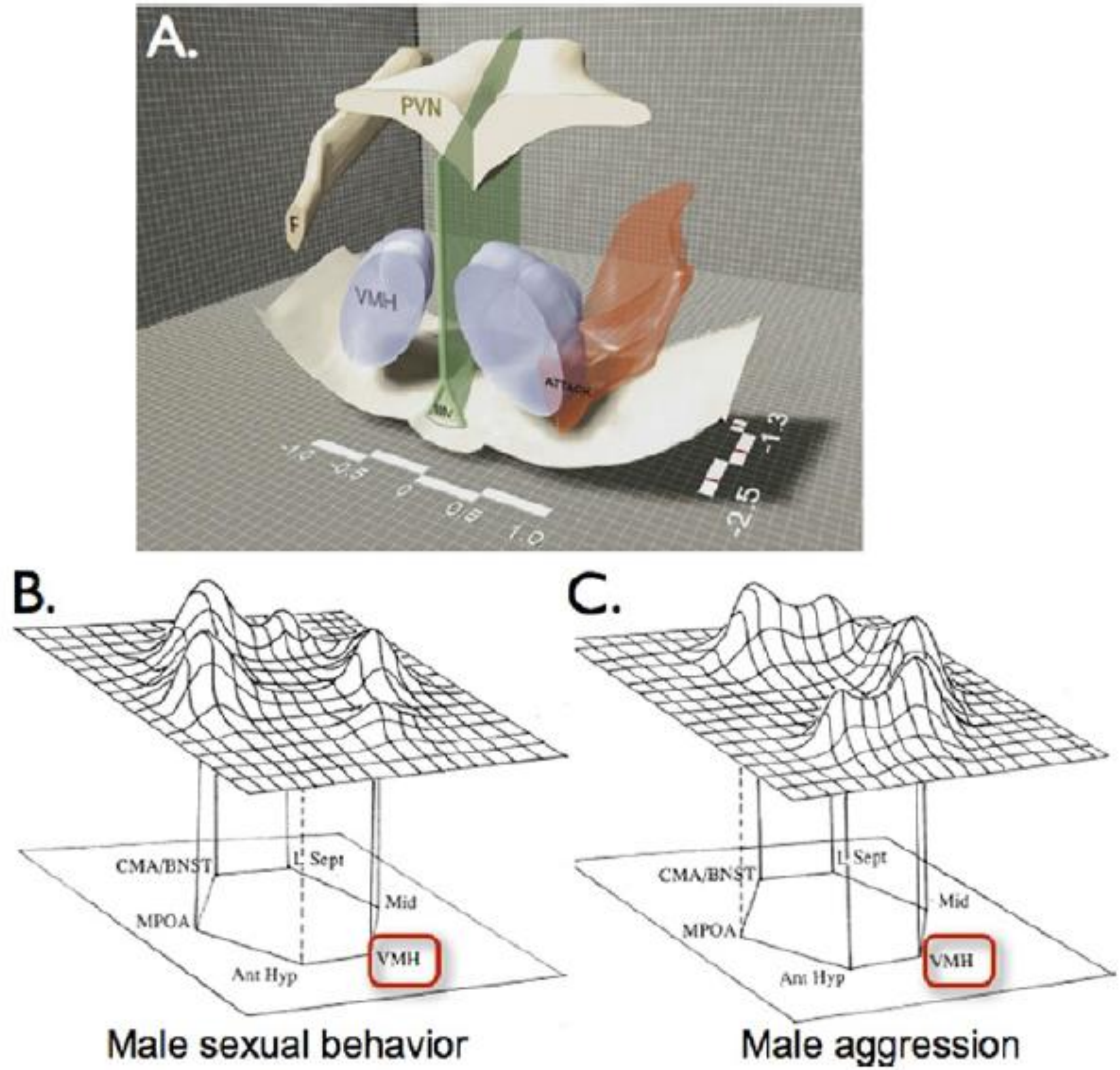
Activation of aggressive using optogenetic in the VMH



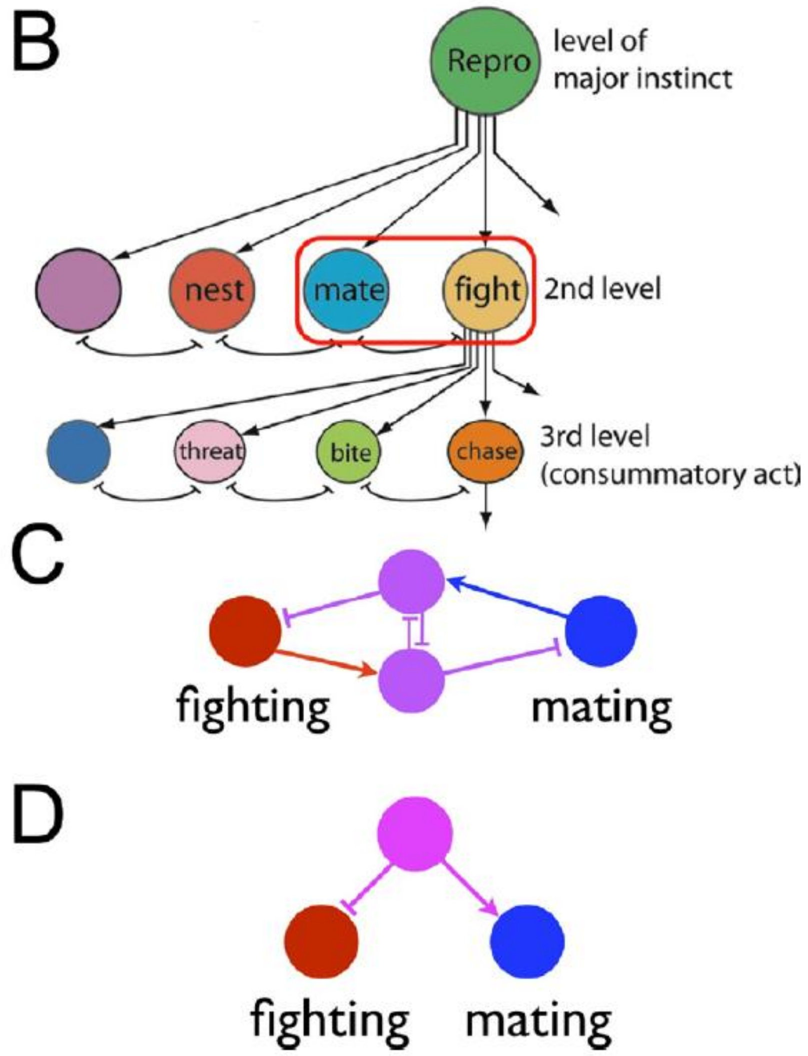
Reversible method to induce aggressive using optogenetic+pharamcolgy







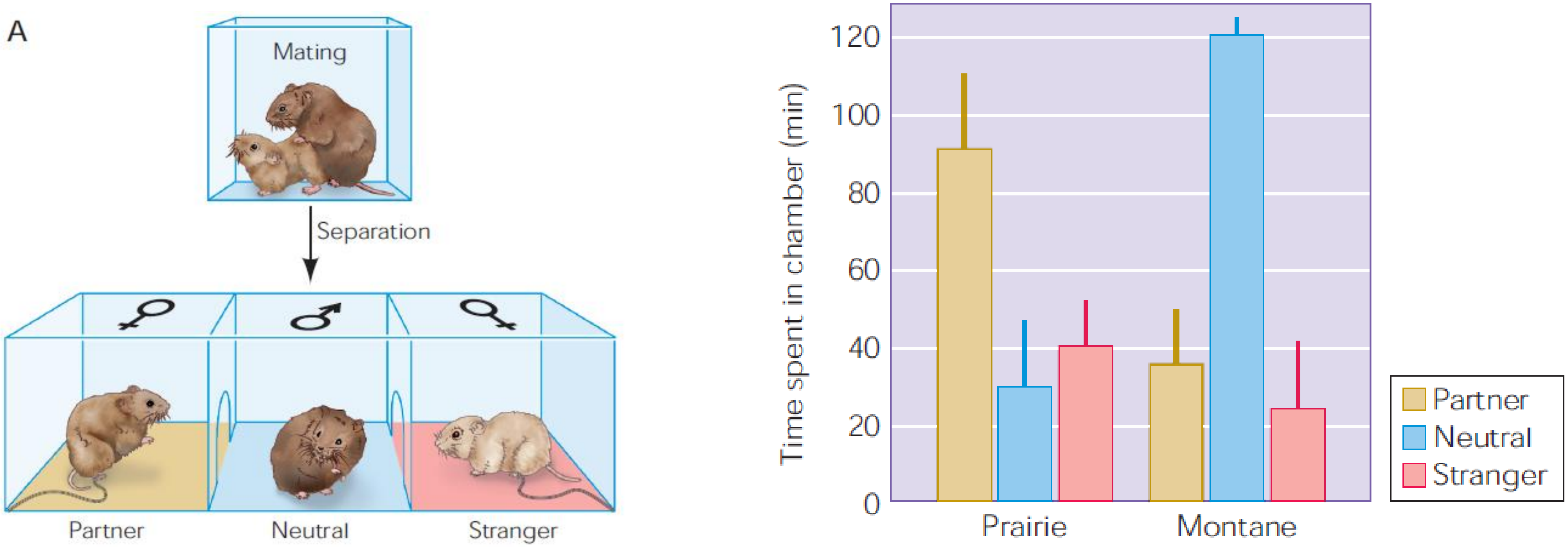
Anderson, 2012; Biol Psychiatry

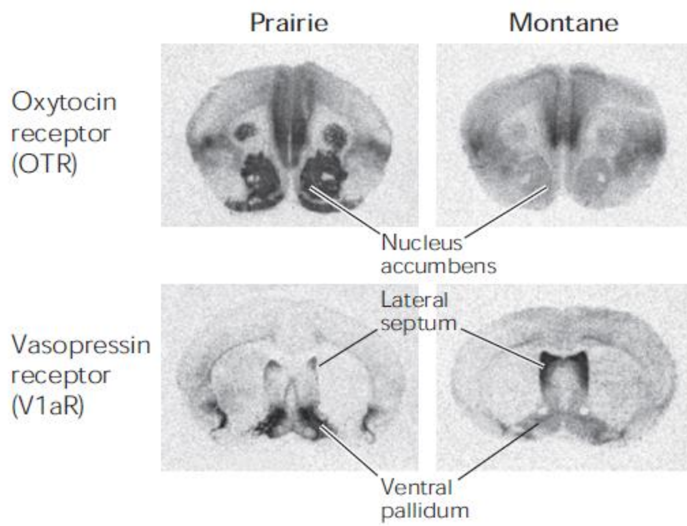

B
Repro
level of
major instinct
nest
mate
fight
2nd level
threat
bite
chase
3rd level
(consummatory act)
C
fighting
mating
D
fighting
mating

Pair bonding and social behavior in voles

- **Prairie voles**
- Highly social
- Monogamous
- Spend more than 50% of their time interacting with other prairie vole

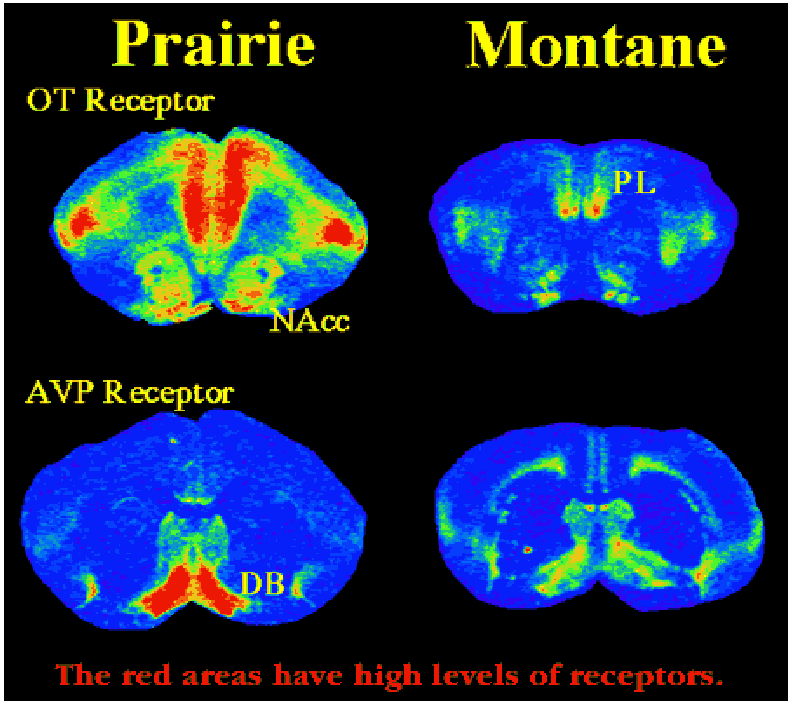
- **Montane voles**
- Avoid social contact except for the purpose of mating
- Polygamous
- Spend only around 5% of their time socially interacting.



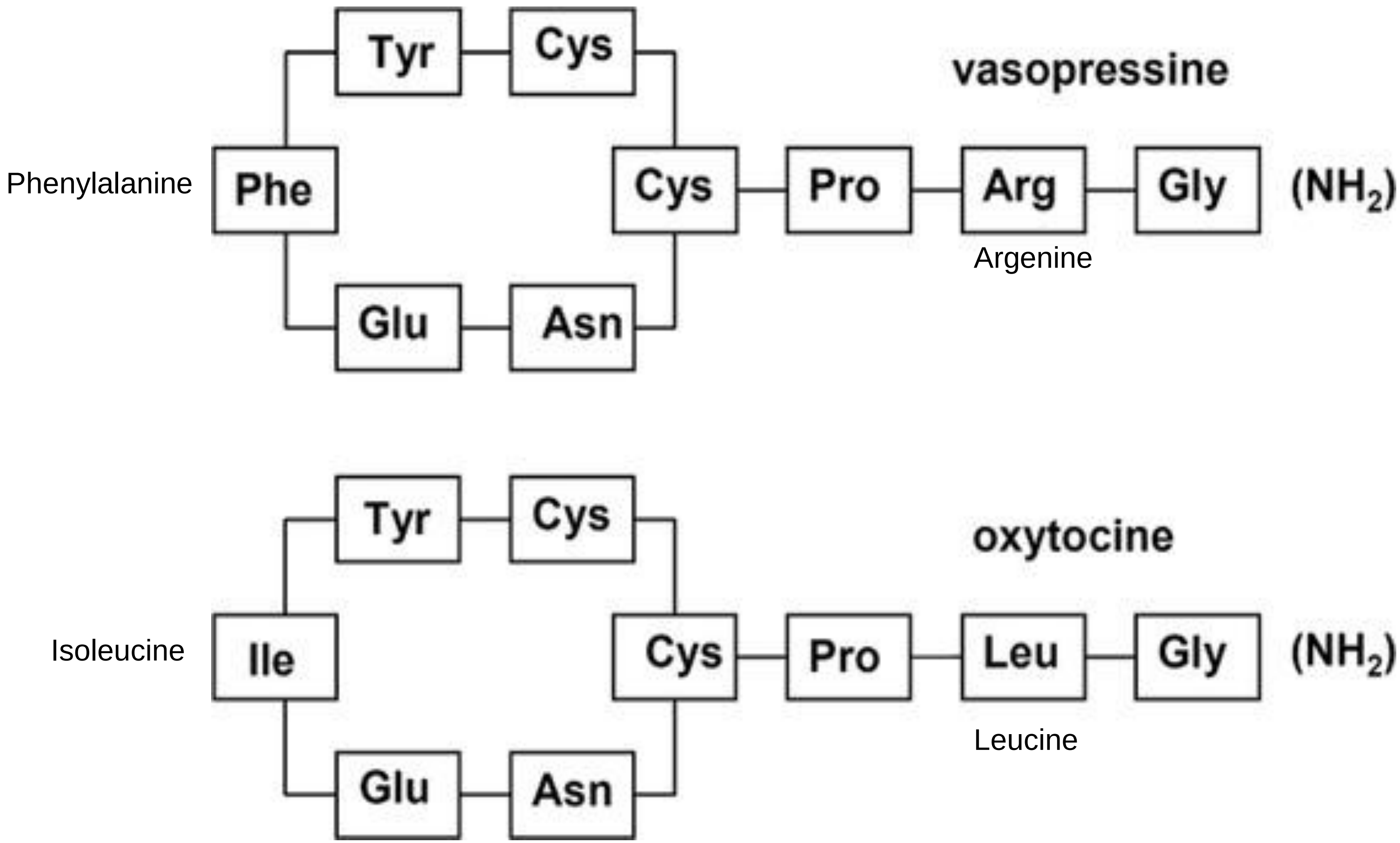


Hemanth et al 2006 *Physiology*

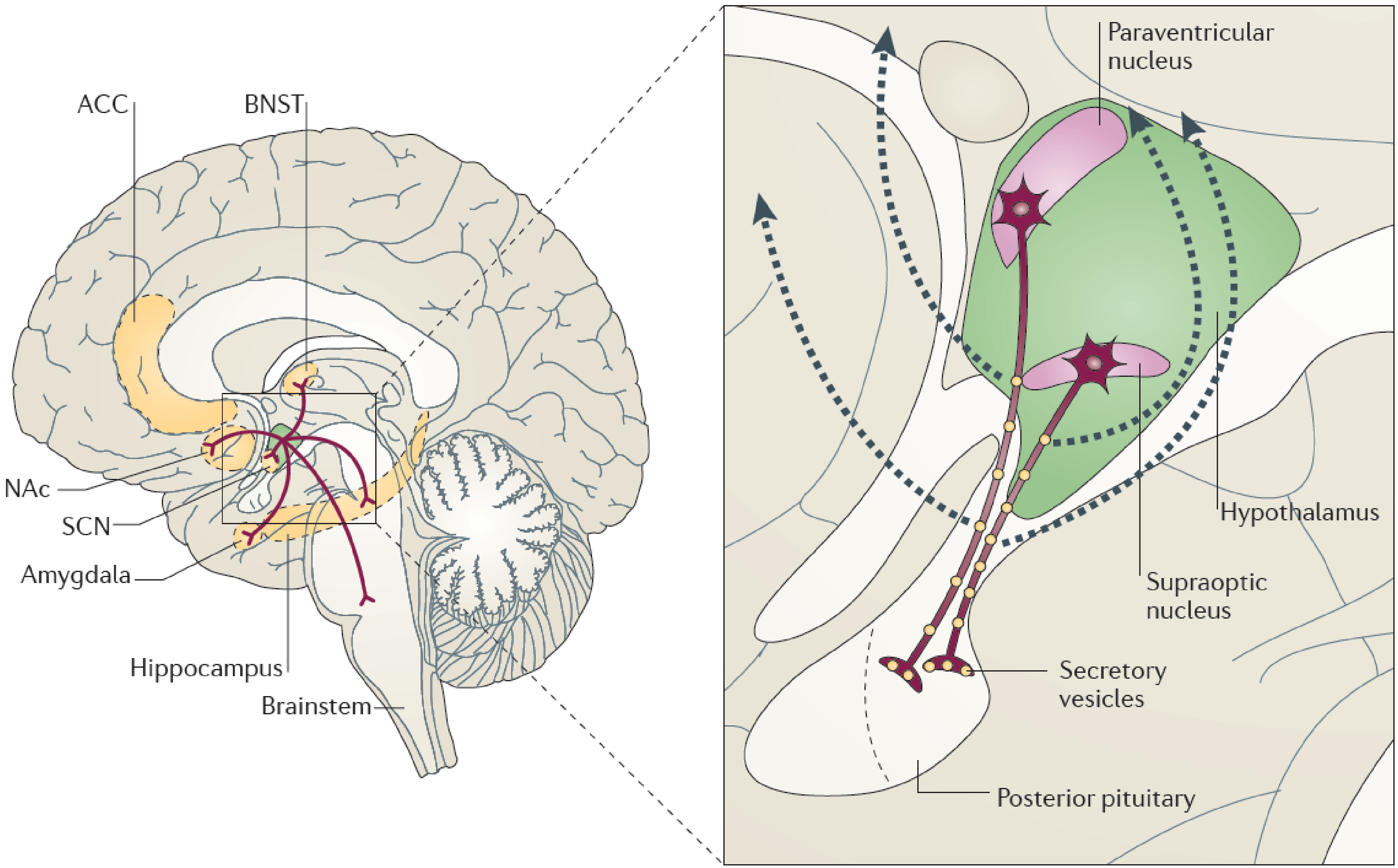
- Prairie voles have high levels of OT receptor in the nucleus accumbens and the basolateral amygdala relative to montane voles
- Montane voles have high levels of receptors in the lateral septum.
- Prairie voles have high densities of the V1a subtype of the AVP receptor in the ventral pallidum and the medial amygdala compared with montane voles.
- Montane voles have much higher levels of receptors in the lateral septum than do prairie voles.



Neurophysiology of Oxytocin (OXT) and arginine vasopressin (AVP)



Neurophysiology of Oxytocin (OXT) and arginine vasopressin (AVP)



Neurophysiology of Oxytocin (OXT) and arginine vasopressin (AVP)

- Oxt and Avp are synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus.

- Oxt and Avp are processed along the axonal projections to the posterior lobe of the pituritary, where they stored in vesicles and released into the blood circulation.

- In addition, there is dendritic release of the neuropeptide into the extracellular space, resulting local and diffuse action through the brain to reach distinct targets

- Smaller paraventricullar neurons in the paraventricullar nucleus also produce the neuropeptides and project directly to other brain regions.

- Mammals have 1 receptor of Oxt and 3 receptors of Avp (AVPR1A, AVP1B, AVPR2).

- In the brain, Oxt and Avp travel along the axonal projection of the paraventricular of the hypothalamus to different brain areas including: amygdala, hippocampus, striatum, supriachiamatic nucleus, bed nucleus of stria terminalis and brainstem

- Both peptides have peripheral and central functions

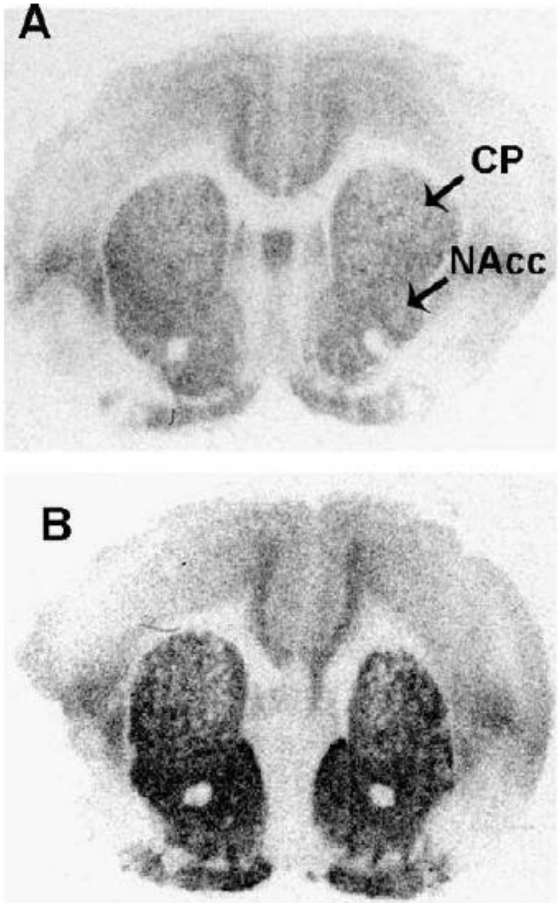
Oxytocin and parental behavior in Prairie voles

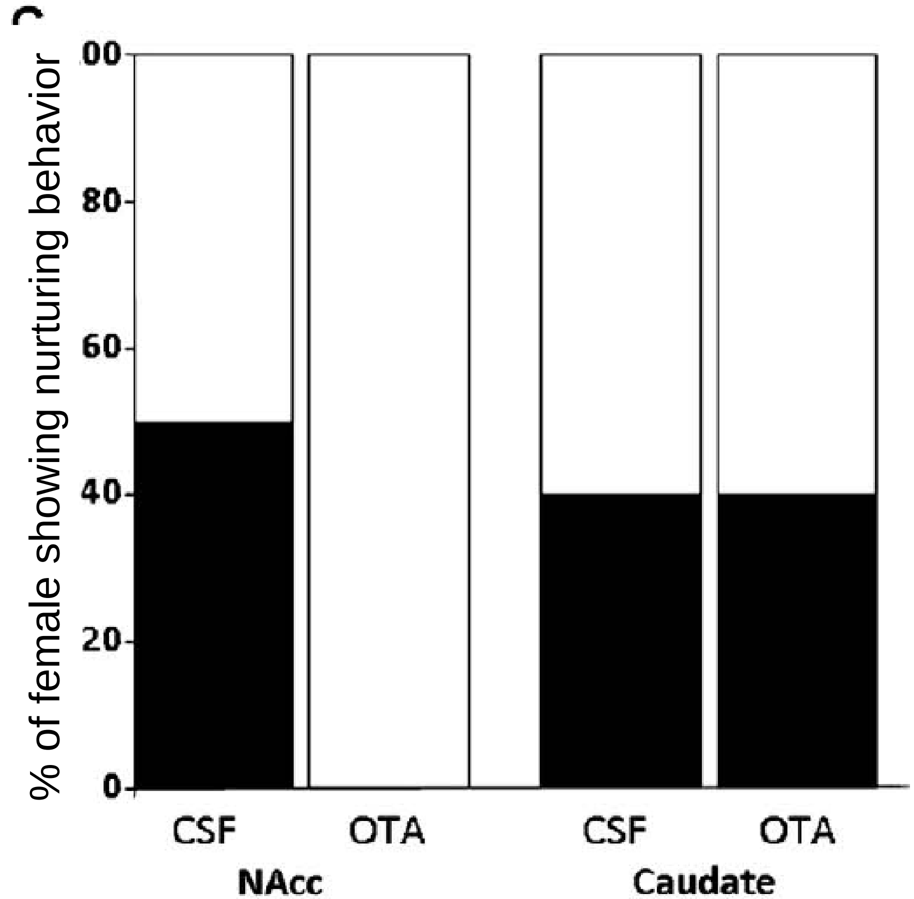
Parental behavior

Oxytocin receptor level

Low

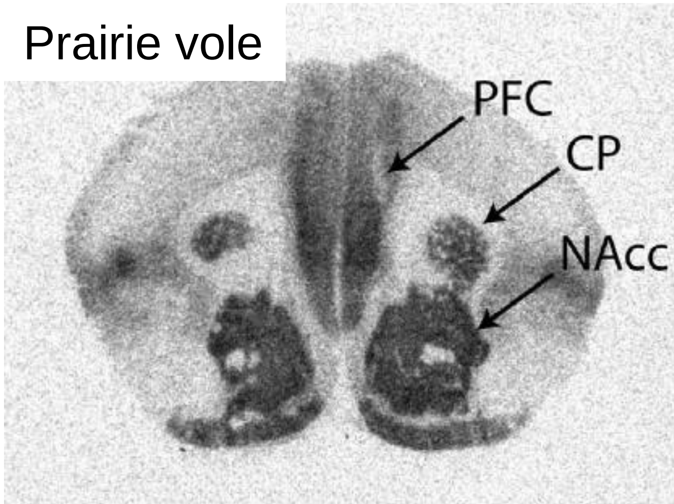
High

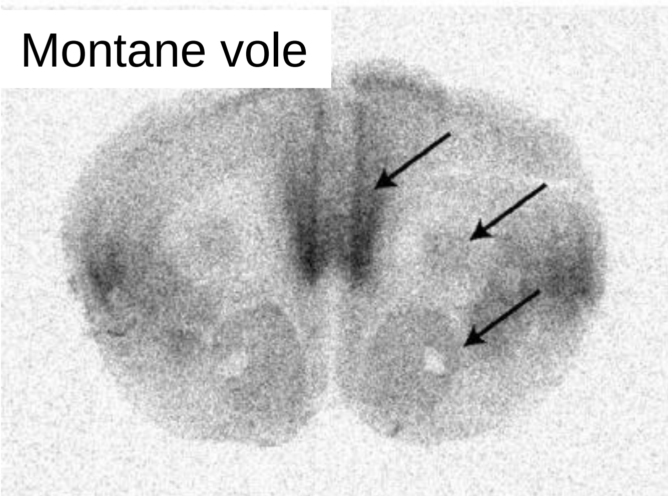


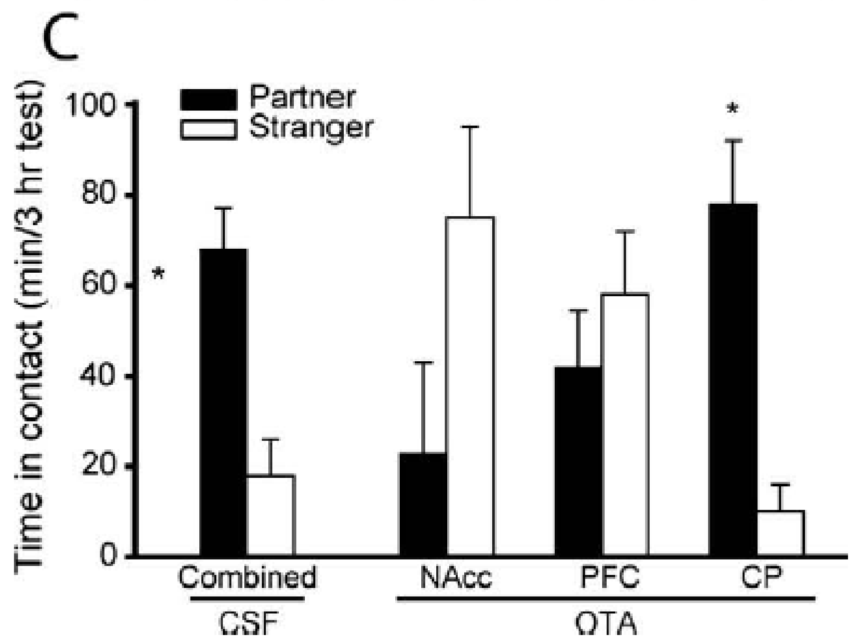


Ross and Young, 2009

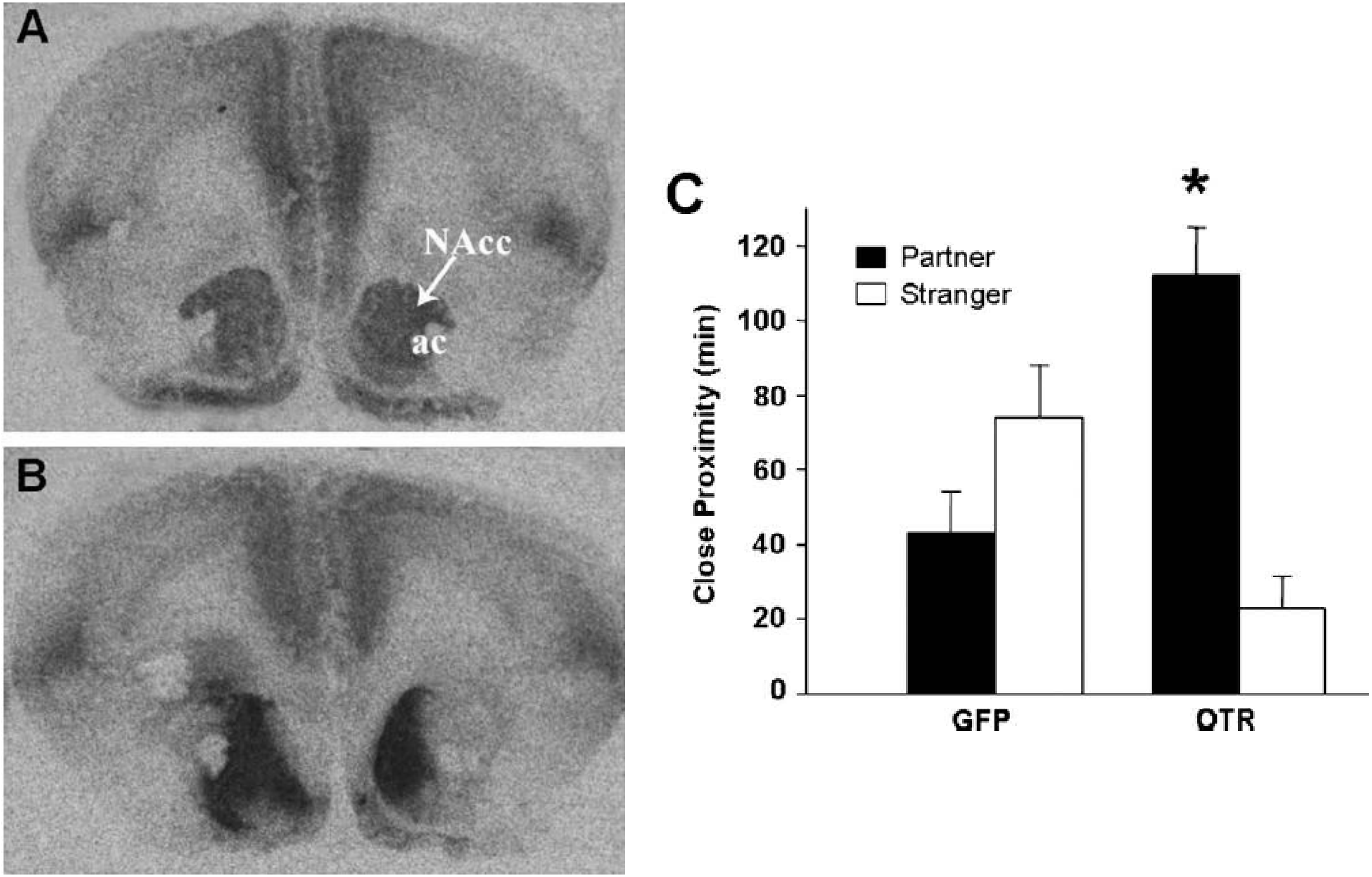
Oxytocin and partner preference in Prairie voles





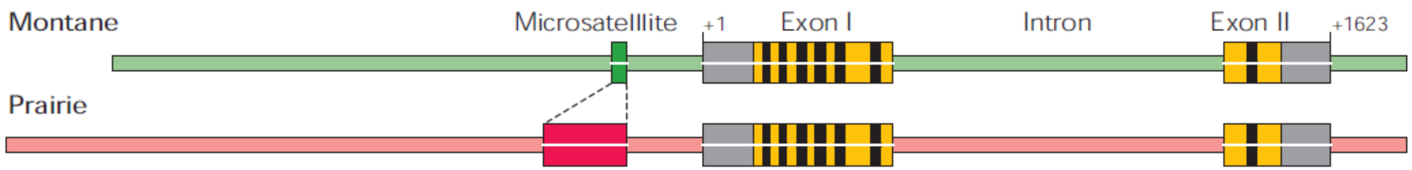


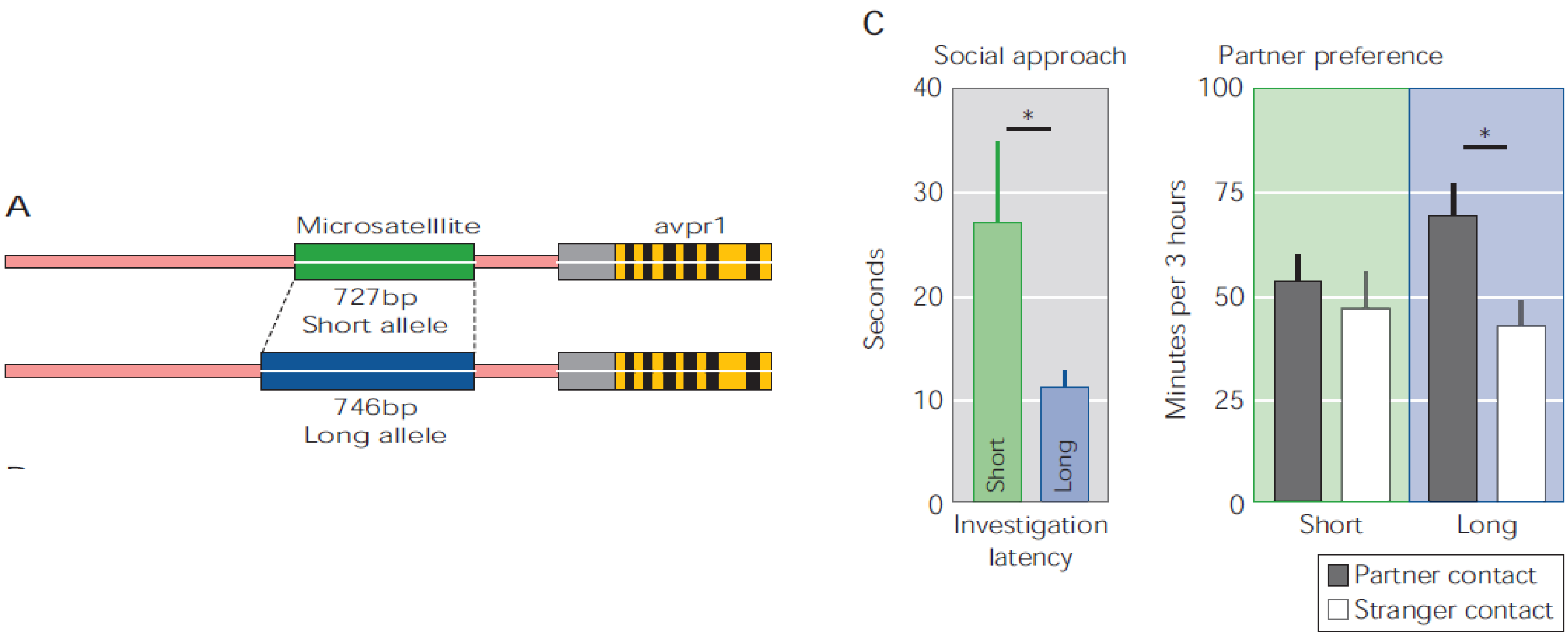
Viral over-expression of Oxytocin receptor in the NAc of female prairie voles



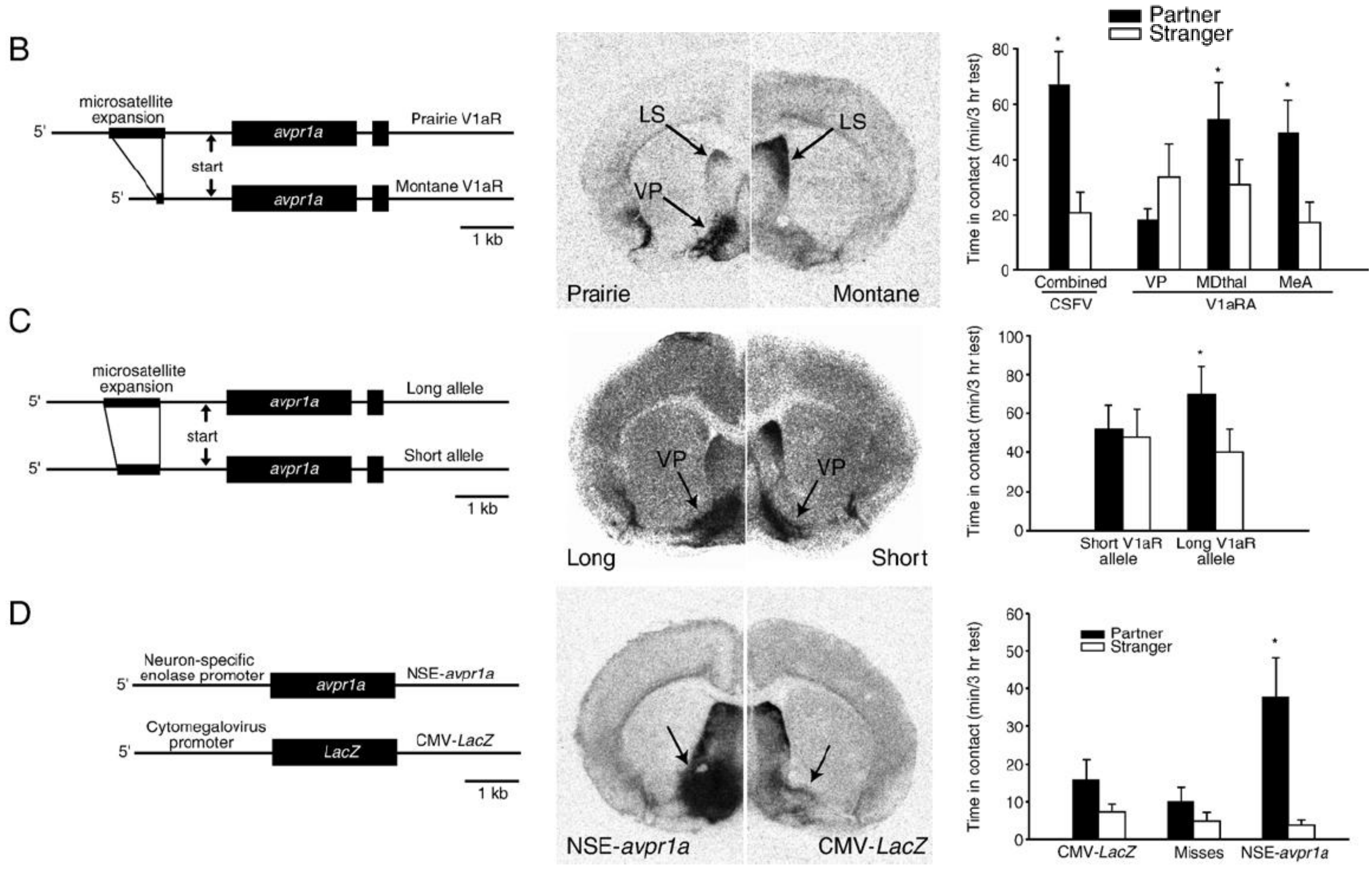
Vasopressin receptor and pair bonding in Prairie voles and Montane voles

V1aR





Hammock & Young, 2005 *Science*



Lim & Young 2006 Horm & Behav

The "Fidelity gene"

"A single gene can turn the Don Juan of voles into an attentive home-loving husband". BBC news

Meadow voles (*Microtus pennsylvanicus)*

Promiscuous social behavior

Prairie voles (*Microtus ochrogaster*)

Monogamous social behavior

Young et al. 1999 *Nature*

The "Fidelity gene" in human

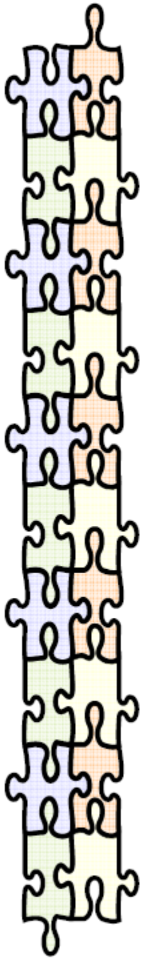
?

Genetic variation in the vasopressin receptor 1a gene (*AVPR1A*) associates with pair-bonding behavior in humans

Pair-bonding has been suggested to be a critical factor in the evolutionary development of the social brain. The brain neuropeptide arginine vasopressin (AVP) exerts an important influence on pair-bonding behavior in voles. There is a strong association between a polymorphic repeat sequence in the 5′ flanking region of the gene (*avpr1a*) encoding one of the AVP receptor subtypes (V1aR), and proneness for monogamous behavior in males of this species. It is not yet known whether similar mechanisms are important also for human pair-bonding. Here, we report an association between one of the human *AVPR1A* repeat polymorphisms (RS3) and traits reflecting pair-bonding behavior in men, including partner bonding, perceived marital problems, and marital status, and show that the RS3 genotype of the males also affects marital quality as perceived by their spouses. These results suggest an association between a single gene and pair-bonding behavior in humans, and indicate that the well characterized influence of AVP on pair-bonding in voles may be of relevance also for humans.

Walum et al 2008, *PNAS*

A (brief) history of autism



1908 Bleuler's initial identification of autism in adults

1943 Kanner describes 11 children with childhood autism

1944 Asperger describes "little professor" syndrome

1967 Bettelheim's *The Empty Fortress* published

1968 DSM-II lists autism as type of childhood schizophrenia

1980 Wing conceptualizes triad of autistic symptoms

1987 *DSM-IIIR* places among personality disorders

1994 *DSM-IV* places autism among clinical disorders

1999 Federal autism research initiatives launched

2000 DSM-IV-TR clarifies PDD-NOS

2002 Vaccine/MMR controversy

2011 DSM-V: clarified better the symptoms

American Psychiatric Association DSM-5 Development (Jan, 2011)

Autism Spectrum Disorder
Must meet criteria A, B, C, and D:

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. Deficits in social-emotional reciprocity; ranging from abnormal social approach and failure of normal back and forth conversation through reduced sharing of interests, emotions, and affect and response to total lack of initiation of social interaction,

2. Deficits in nonverbal communicative behaviors used for social interaction; ranging from poorly integrated- verbal and nonverbal communication, through abnormalities in eye contact and body-language, or deficits in understanding and use of nonverbal communication, to total lack of facial expression or gestures.

3. Deficits in developing and maintaining relationships, appropriate to developmental level (beyond those with caregivers); ranging from difficulties adjusting behavior to suit different social contexts through difficulties in sharing imaginative play and in making friends to an apparent absence of interest in people .

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:

1. Stereotyped or repetitive speech, motor movements, or use of objects; (such as simple motor stereotypies, echolalia, repetitive use of objects, or idiosyncratic phrases).

2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change; (such as motoric rituals, insistence on same route or food, repetitive questioning or extreme distress at small changes).

3. Highly restricted, fixated interests that are abnormal in intensity or focus; (such as strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment; (such as apparent indifference to pain/heat/cold, adverse response to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects).

C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)

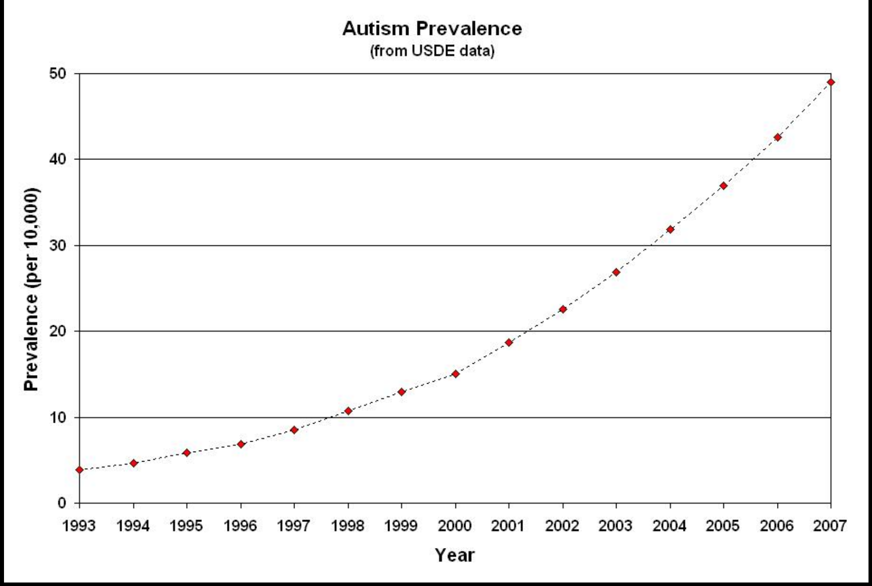
D. Symptoms together limit and impair everyday functioning.

Autism Spectrum Disorders

Main characteristics:

- Social and Communication Deficits
- Fixed Interests (Rigidity in habits)
- Stereotypic (repetitive) Behaviors
- Symptoms must be present in early childhood

Prevalence



- 1 in 130-160 (**1 in 94 boys)**
- Present cross-culturally and cross-nationally
- 4:1 male to female ratio

- Complex genetic disorders (i.e. interactions between many genes and environmental factors)

- Few hundreds of genes were associated with autism

- No biomarker for autism diagnostic:
diagnostic is based only behavioral smyptoms (~1.5-3years old)

Autism Spectrum Disorders

Pervasive Developmental Disorders

Pervasive Developmental Disorders (DSM-IV)

- Autistic disorder (Kanner autism, 1943)
  - Impaired social interaction, impaired communication, restricted/repetitive patterns of behavior and interests
- Asperger syndrome (Hans Asperger, 1944)
  - Impaired social interaction and restricted/repetitive/stereotyped behaviors and interests, but less difficulty with verbal communication (normal IQ and no clinically significant delay in language development)
- Rett syndrome
  - Only in girls, apparently normal development for the first 5 months of life, then deceleration of head growth, loss of previously acquired purposeful hand skills, development of stereotyped hand movements, decreased social interaction, mental retardation
- Childhood disintegrative disorder
  - Normal development in first 2 years of life, including normal language development, followed sometime between the ages of 2 and 10, by loss of skills in language, social behavior, bowel or bladder control, play, or motor skills
- PDD not otherwise specified

Associated Brain Phenotypes

- Abnormal acceleration in growth of brain in first few years of life. Larger, heavier brains, including forebrain (10% larger) in toddlerhood.
- Overgrowth of white matter, but underdeveloped interconnectivity in the brain (e.g. underdevelopment of corpus callosum)
- Reduced number of cerebellar Purkinje cells
- Small and densely packed neurons in limbic regions, including amygdala, hippocampus, and entorhinal cortex
- Decreased serotonin synthesis left frontal cortex and thalamus in childhood
- High blood serotonin
  - 25% of patients
  - 30-50% increase in platelet serotonin levels
- Decreased activation of fusiform gyrus (“face area”) during facial recognition tasks

Concordance rates suggest high heritability and many susceptibility genes

- Narrow phenotypic definition (classical autism)
  - 60% concordance for monozygotic twins
  - 0% concordance for dizygotic twins
- Broad phenotypic definition (including Asperger syndrome and other communication and social disorders)
  - 92% concordance for monozygotic twins
  - 10% concordance in dizygotic twins
- ~5% sibling (non-twin) recurrence rate
- Other family members have relatively high rates of social and communication difficulties and obsessive-compulsive traits ("broader autism phenotype")

Studying autism using mouse models

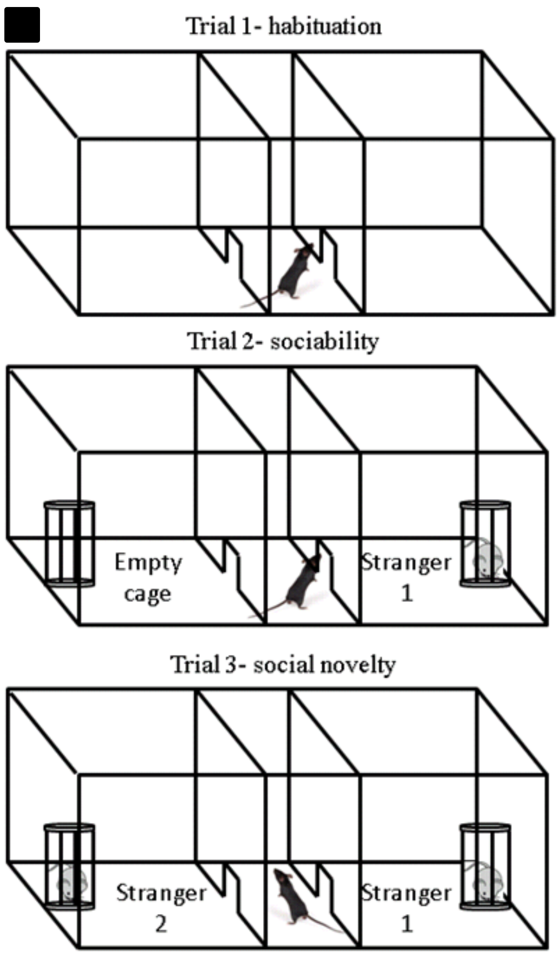
• Multiple genetic modified mouse models

• Multiple behavioral assays and paradigms for studying autistic-related behavioral phenotype

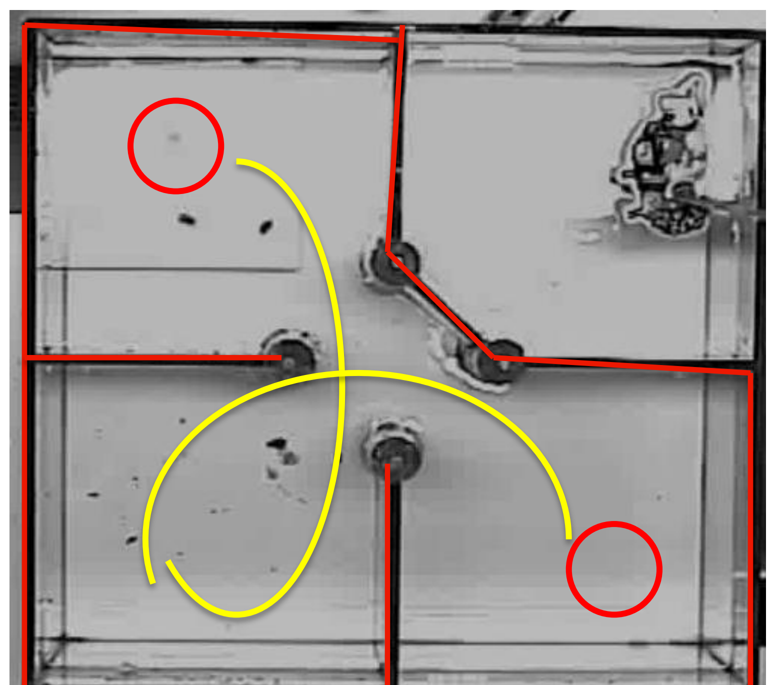
• Autistic-related behaviors are largely scored by human observer
(in particularly social interactions)

Commonly used tests

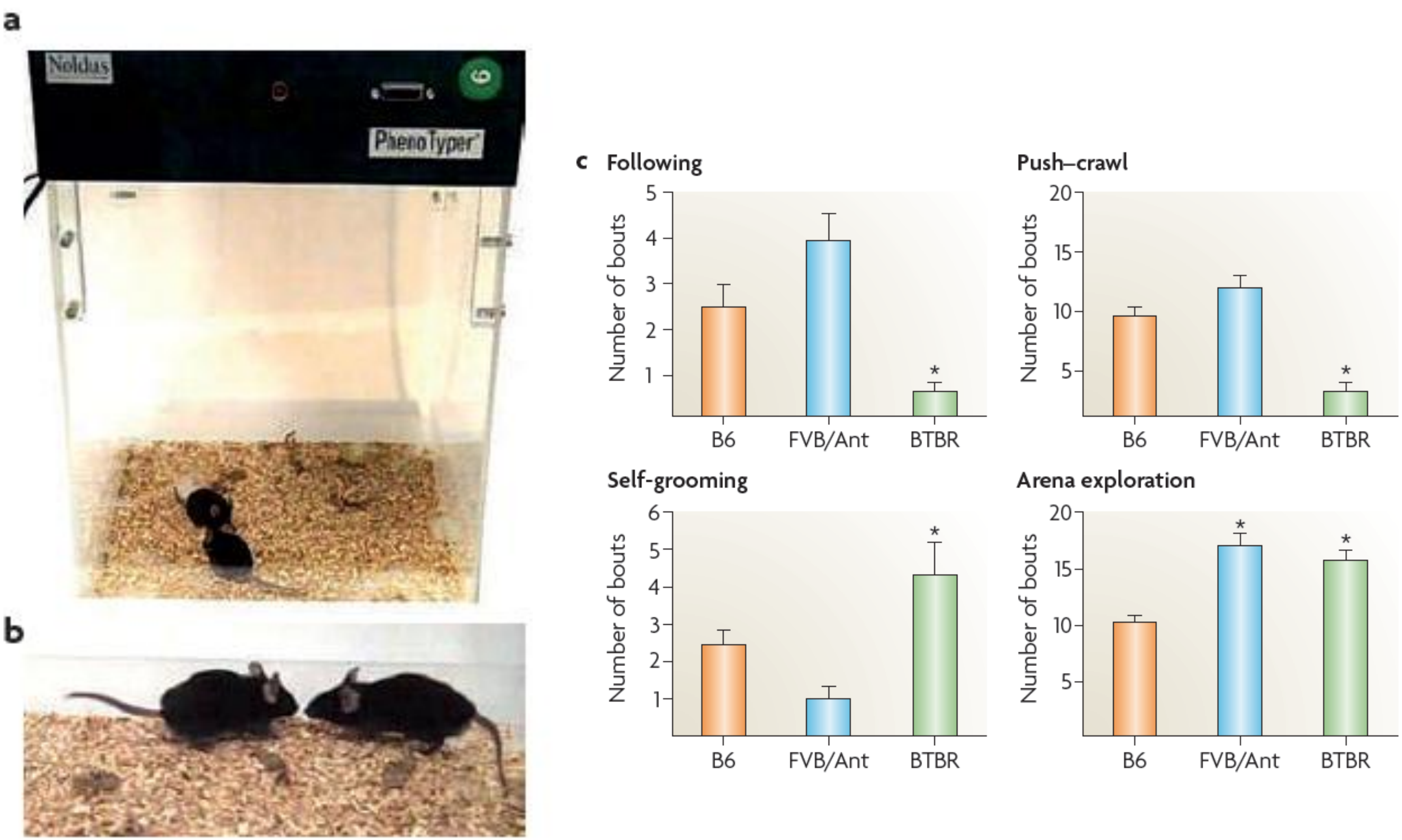
Sociability

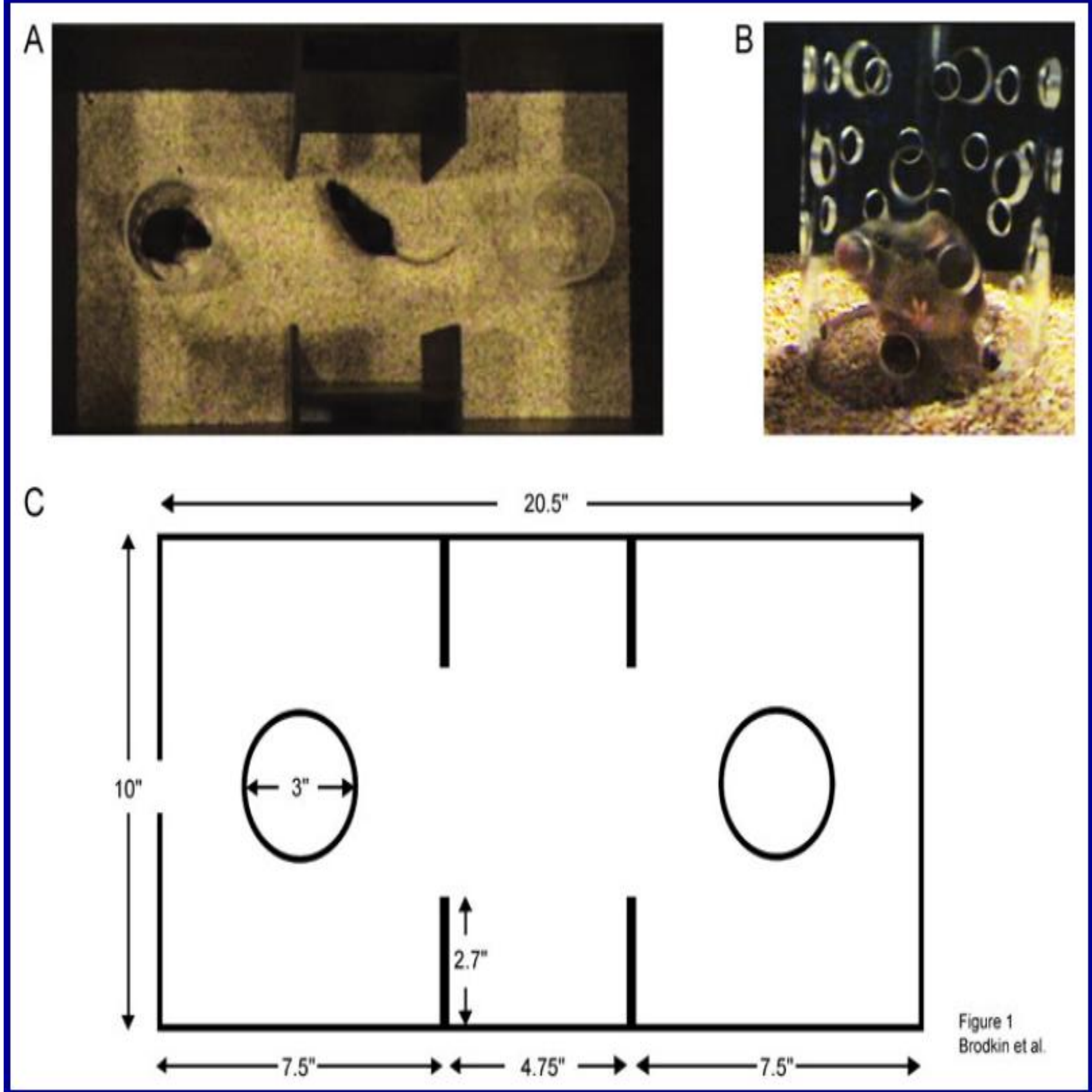


Cognitive rigidity



Stereotypical behavior


a
Noldus
PhenoTyper
b
c
Following
Number of bouts
5
4
3
2
1
B6
FVB/Ant
BTBR
*
Push–crawl
Number of bouts
20
15
10
5
B6
FVB/Ant
BTBR
*
Self-grooming
Number of bouts
6
5
4
3
2
1
B6
FVB/Ant
BTBR
*
Arena exploration
Number of bouts
20
15
10
5
B6
FVB/Ant
BTBR
*
*

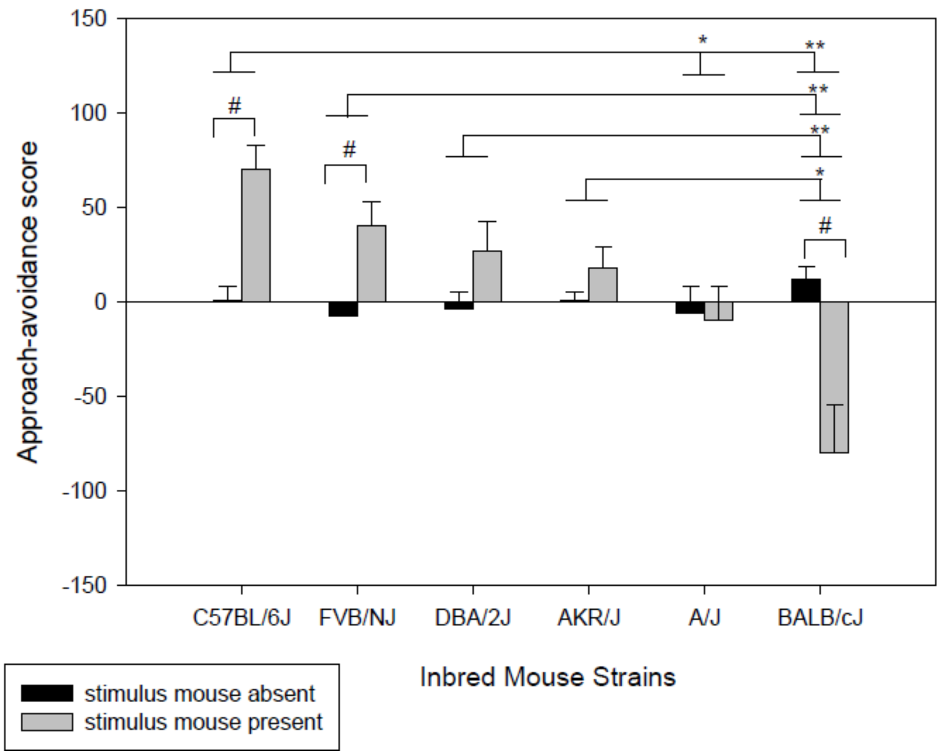


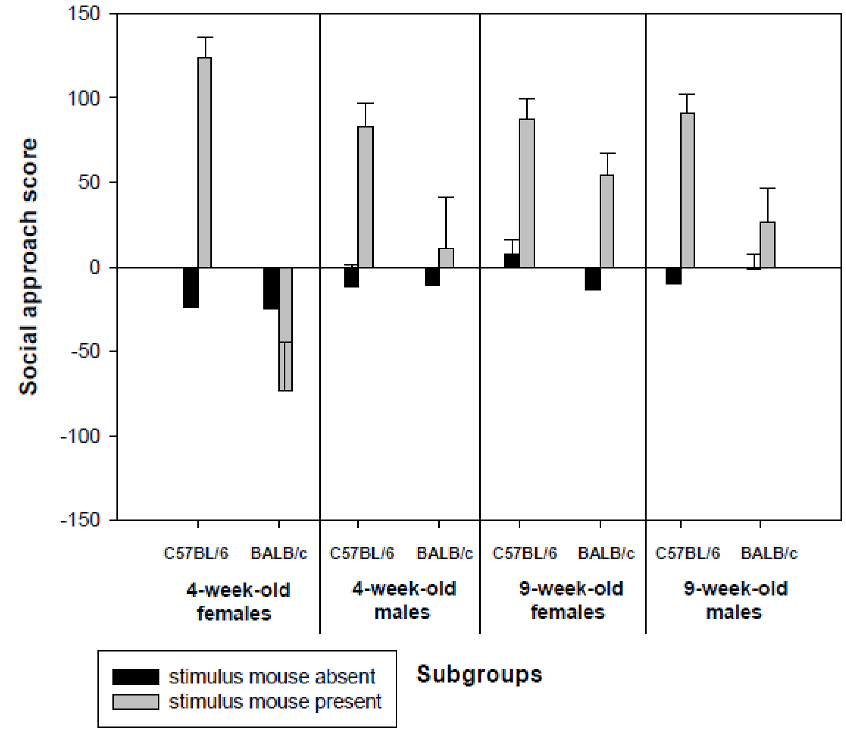
<u>Sociability = tendency to seek social interaction</u>

<u>Phase 1:</u>
Test mouse habituation

<u>Phase 2:</u>
Stimulus mouse in cylinder on social side

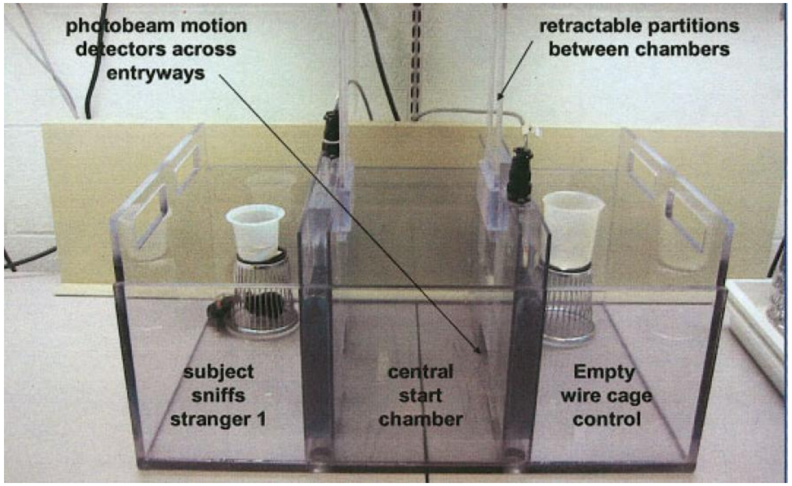
<u>Phase 3:</u>
Free interaction between test and stimulus mouse

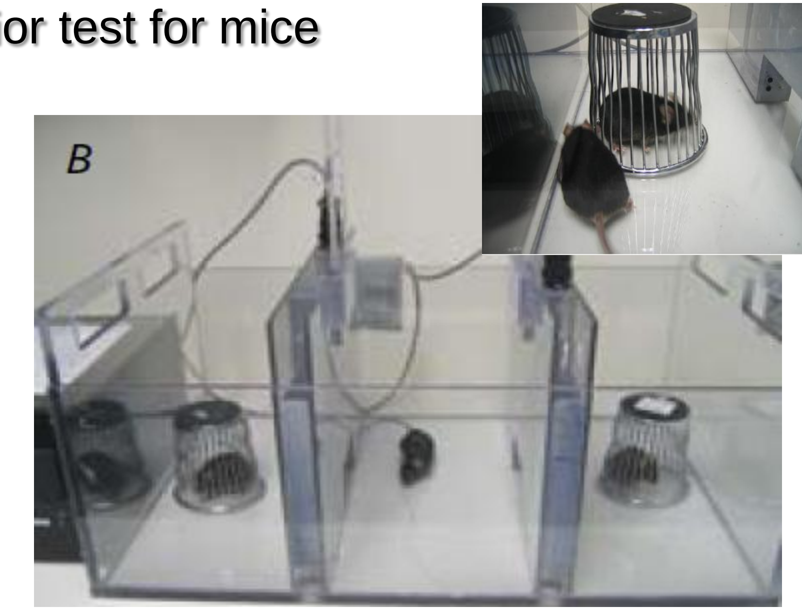


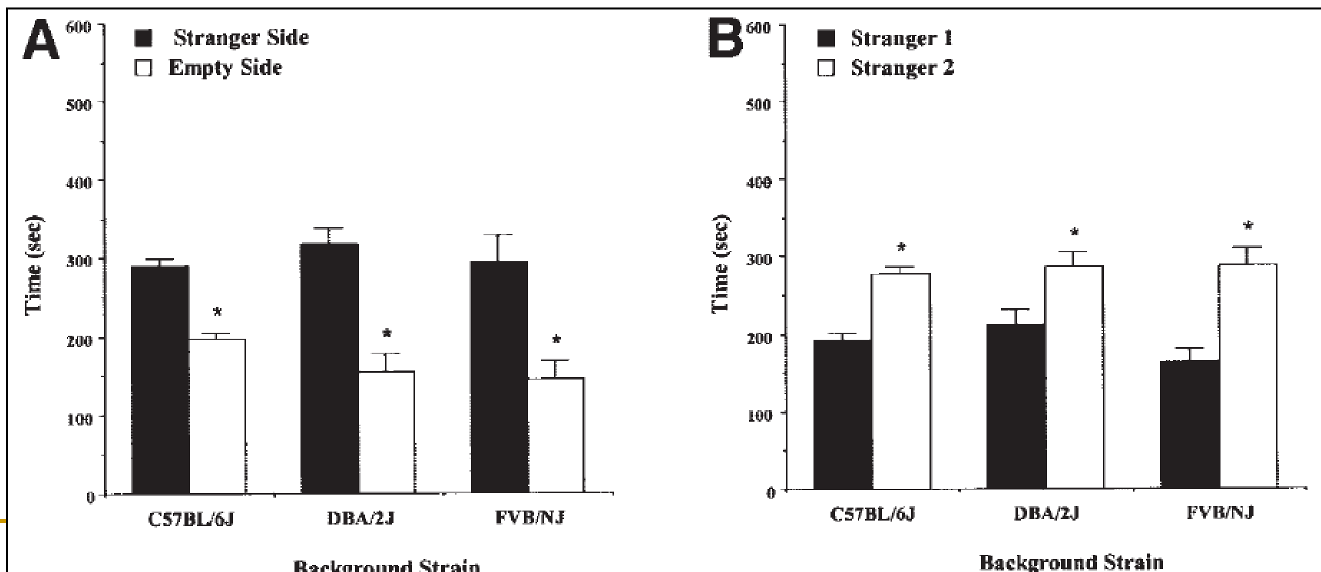


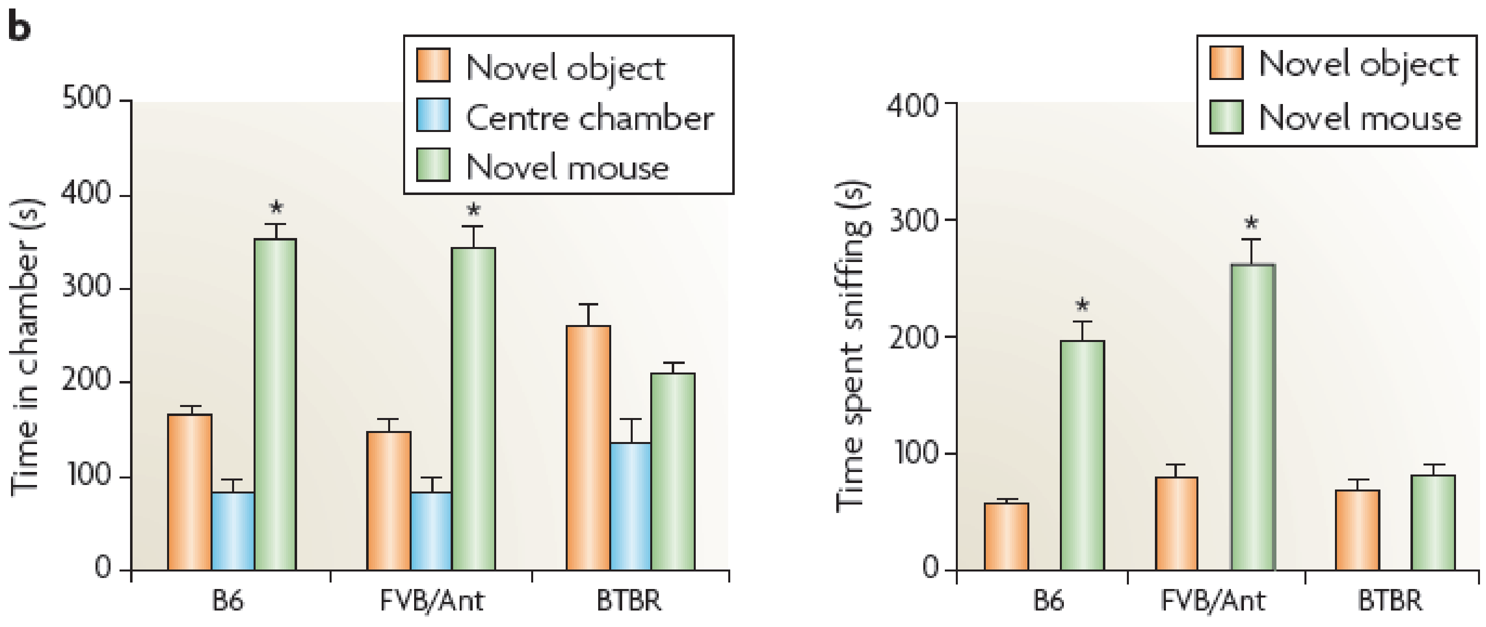
Brodkin et al 2004 Brain Research

Social behavior test for mice

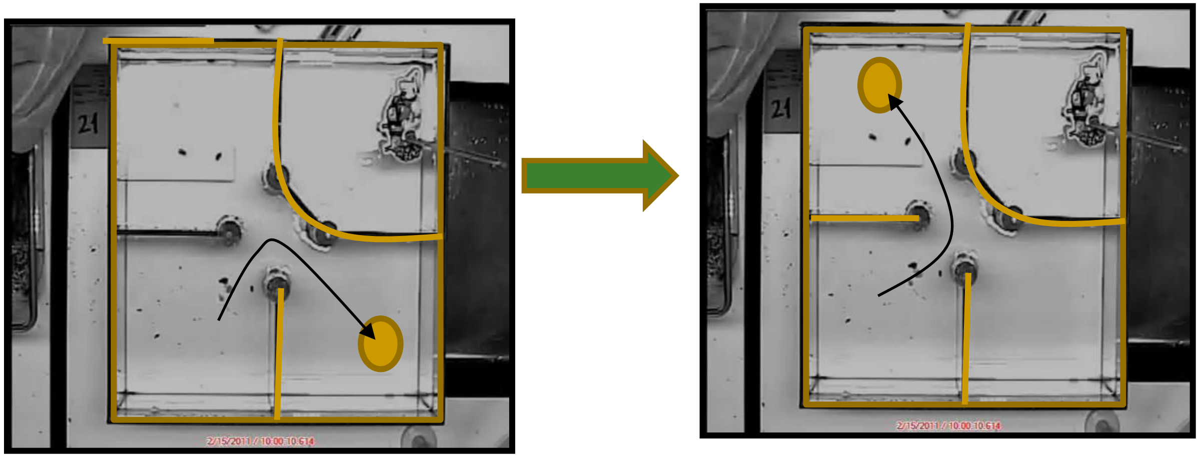


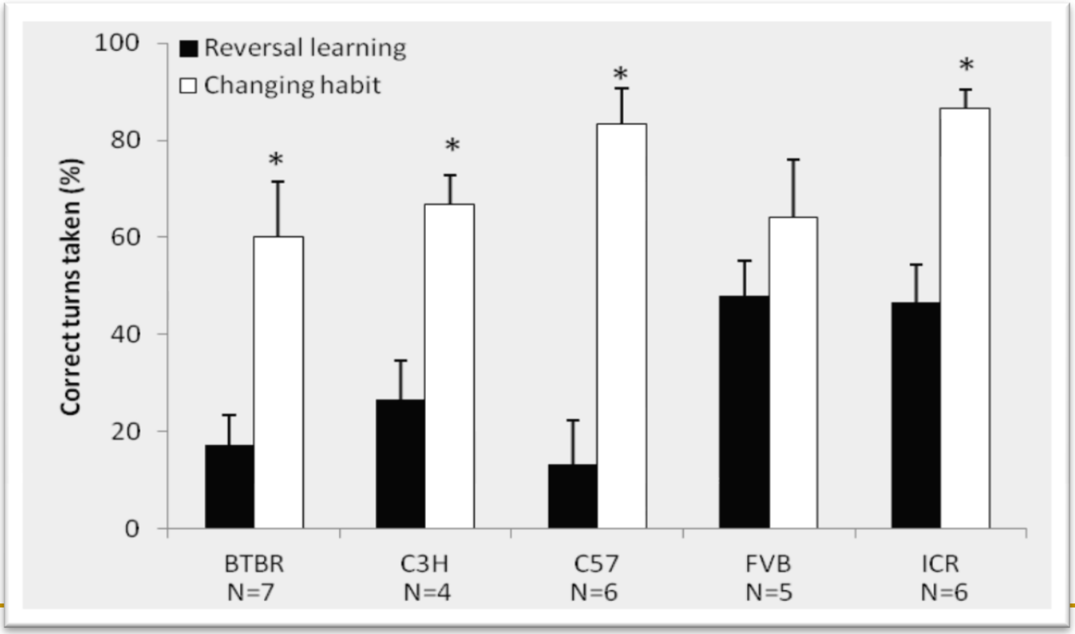




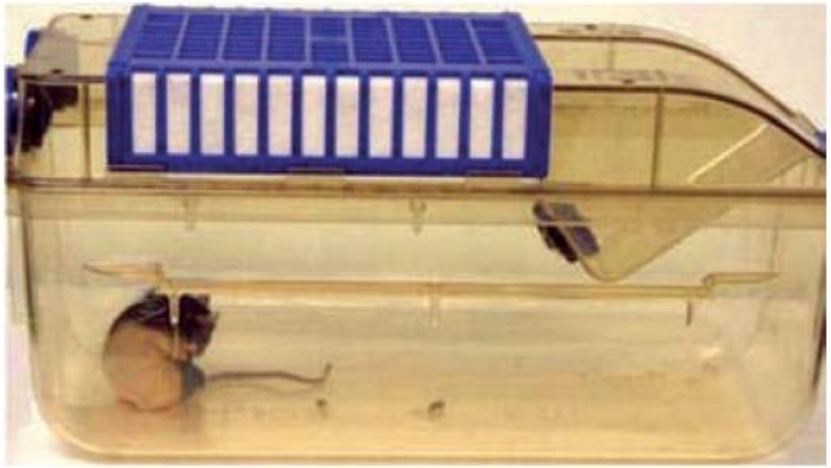

b
Novel object
Centre chamber
Novel mouse
Time in chamber (s)
500
400
300
200
100
0
B6
FVB/Ant
BTBR
*
*
Novel object
Novel mouse
Time spent sniffing (s)
400
300
200
100
0
B6
FVB/Ant
BTBR
*
*

Cognitive rigidity Wet T-maze assay





Stereotypic behavior



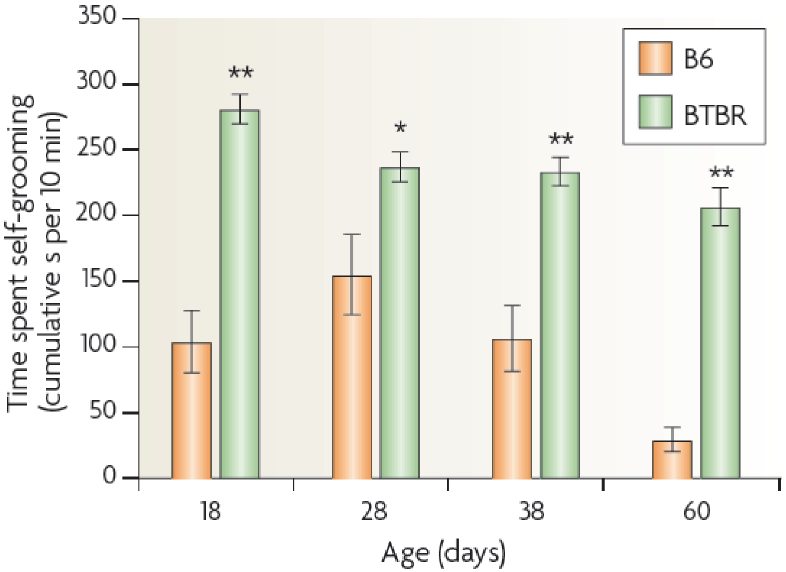


Table 1 | **Examples of autism-relevant behaviours in genetic mouse models of autism spectrum disorders**

Mouse model	Genetic characteristics	Behavioural phenotypes relevant to the symptoms of autism*
Nlgn4	Null mutation in the murine orthologue of the human *NLGN4* gene[43]	• Reduced reciprocal social interactions[43] • Low sociability[43] • Lack of preference for social novelty[43] • Reduced ultrasonic vocalizations[43]
Nlgn3	Homozygous mutation of humanized R451C mutation of the *Nlgn3* gene[44,45]	• No genotype differences in reciprocal social interactions[44,45] • No genotype differences in sociability[44,45] • No genotype differences in preference for social novelty[44] • Reduced ultrasonic vocalizations[44]
	Null mutation in the murine orthologue of the human *NLGN3* gene[41]	• No genotype differences in reciprocal social interactions[41] • Reduced preference for social novelty[41]
Neurexin 1α	Null mutation in the murine *neurexin 1α* generated by deleting the first exon of the gene[46]	• No genotype differences in reciprocal social interactions[46] • No genotype differences in sociability[46] • Impaired nest-building behaviour[46] • Increased repetitive self-grooming[46]
Nlgn1	Null mutation in the murine orthologue of the human *NLGN1* gene[47]	• No genotype differences in reciprocal social interactions[47] • No genotype differences in sociability[47] • No genotype differences in preference for social novelty[47] • Impaired nest-building behaviour[47]
Pten	Conditional null mutation, inactivated in neurons of the cortex and hippocampus, mouse orthologue of the human *PTEN* gene[68]	• Reduced reciprocal social interactions[68] • Low sociability[68] • Impaired nest-building behaviour[68] • Impaired social recognition[68]
	Pten haploinsufficent mutant line in which exon 5, and thus the core catalytic phosphatase domain, is deleted[48]	• Low sociability in females[48]
En2	Null mutation in the murine orthologue of the human *EN2* gene[49,50]	• Reduced reciprocal social interactions[49] • Increased repetitive self-grooming[49] • No genotype differences in sociability, confounded by low activity levels[50]
15q11–13	Duplication in the genomic region on the mouse chromosome 7 homologous to the human genomic region 15q11–13 (REF. 29)	• Low sociability[29] • Ultrasonic vocalizations elevated in pups and reduced in adults[29] • Impaired reversal learning[29]
17p11.2	Duplication in the genomic region of murine chromosome 11 homologous to the human genomic region 17p11.2 (REF. 51)	• Low sociability[51] • No genotype differences in preference for social novelty[51] • Impaired nest-building behaviour[51]
Gabrb3‡	Null mutation in the murine orthologue of the human *GABRB3* gene[52]	• Low sociability‡ (REF. 52) • Lack of preference for social novelty‡ (REF. 52) • Repetitive stereotyped circling patterns‡ (REF. 52) • Impaired nest-building behaviour‡ (REF. 52)
Slc6a4	Null mutation in the murine orthologue of the human serotonin transporter (*SLC6A4*) gene[50]	• Low sociability[50] • Lack of preference for social novelty[50]
	Haploinsufficient mutant line of the human serotonin transporter *SLC6A* gene[48]	• Impaired social recognition[48]
Oxt	Null mutation in the murine *Oxt* gene generated by either a deletion in the first exon[40,53,54] or by deletions in the last two exons[40]	• Impaired social recognition[53] • Reduced pup ultrasonic vocalizations[54] • No genotype differences in sociability[40] • No genotype differences in preference for social novelty[40]
Avpr1b	Null mutation of the murine vasopressin receptor 1b *Avpr1b* gene[55,56]	• Impaired social recognition[55] • Reduced pup ultrasonic vocalizations[56]
Mecp2	Heterozygous mutation in methyl-CpG-binding protein 2 (REFS 39,57,58,59)	• Hindlimb clasping[57,58] • Social avoidance[39] • Impaired social recognition[59] • Reduced social interest in an arena[59]

Table 1 (cont.) | **Examples of autism-relevant behaviours in genetic mouse models of autism spectrum disorders**

Mouse model	Genetic characteristics	Behavioural phenotypes relevant to the symptoms of autism*
Foxp2	Homozygous and heterozygous mutations in the mouse homologue of the *FOXP2* gene[64] Knock-in mice for the mouse homologue of *FOXP2* (REF. 67)	• Reduced pup ultrasonic vocalizations[64,67]
Fgf17	Null mutation in the murine *Fgf17* gene generated by deletion of the sites that encode the signal peptide[66]	• Reduced reciprocal social interactions[66] • Lack of preference for social novelty[66] • Reduced pup ultrasonic vocalizations[66]
Cadps2	Null mutation in murine orthologue of the *Cadps2* gene[25]	• Reduced reciprocal social interactions[25]
BTBR	BTBR T + tf/J (BTBR strain) is a genetically homogenous inbred strain that displays behavioural traits with face validity to all three diagnostic symptoms of autism	• Reduced reciprocal social interactions[78,81,90,91,111] • Low sociability[81,83,88,90,91,111] • Increased repetitive self-grooming[81,88,90,111] • Reduced social transmission of food preference[81] • Ultrasonic vocalizations elevated in pups and reduced in adults[87,89] • Unusual ultrasonic vocalization call categories in pups and adults[87,135]
BALB	BALB/cJ and BALB/cByJ are genetically homogenous inbred strains that display relatively low social behaviour in various settings, reduced ultrasonic vocalizations and reduced empathy-like behaviour	• Low sociability[79,83] • No genotype differences in preference for social novelty[83] • Reduced reciprocal social interactions[84] • Reduced ultrasonic vocalizations in adolescent same-sex social interaction[84] • Reduced place-conditioned social reward[85] • Reduced social learning during social distress‡ (REFS 80,145)
C58/J	C58/J is a genetically homogenous inbred strain that displays low sociability, primarily in males, and high levels of two distinct repetitive behaviours that emerge early in development	• High level of repetitive motor stereotypies[82,86] • Low sociability[82,86] • Increased repetitive self-grooming[86]

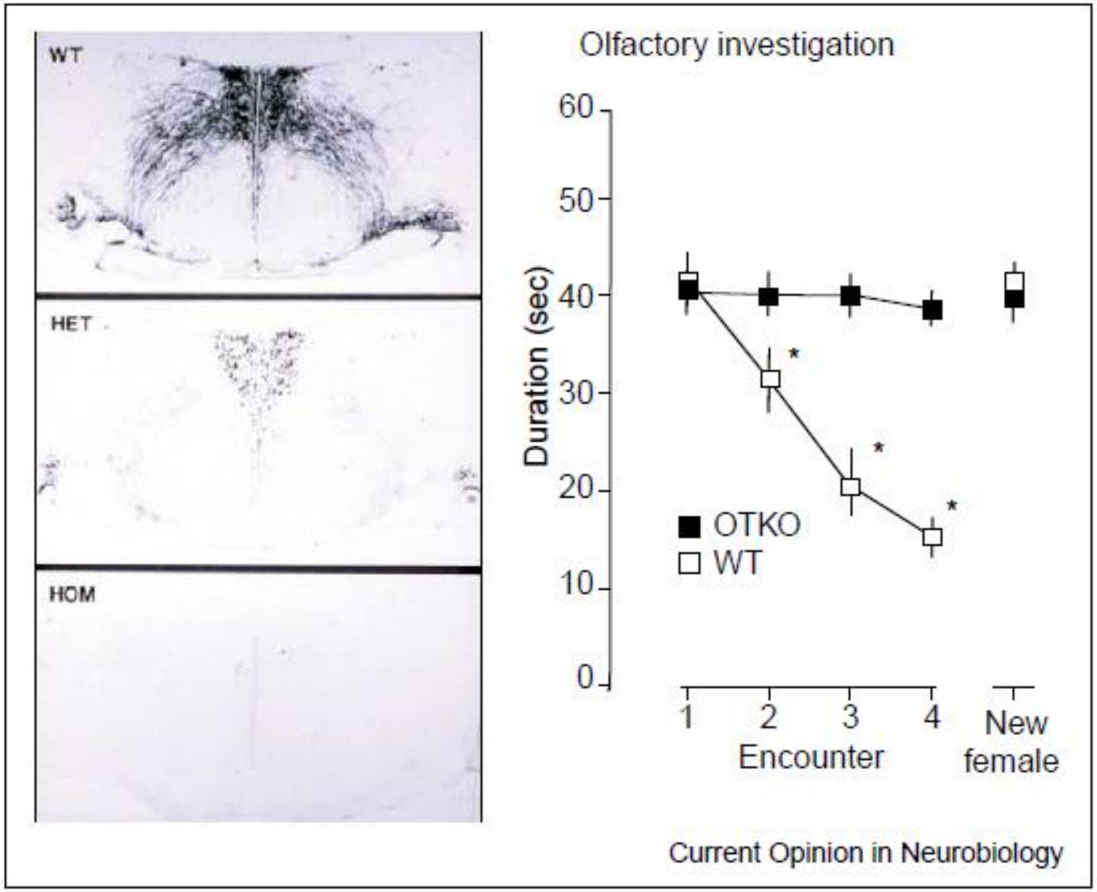
Table 2 | **Examples of treatments that prevented or reversed phenotypes in mouse models of neurodevelopmental disorders**

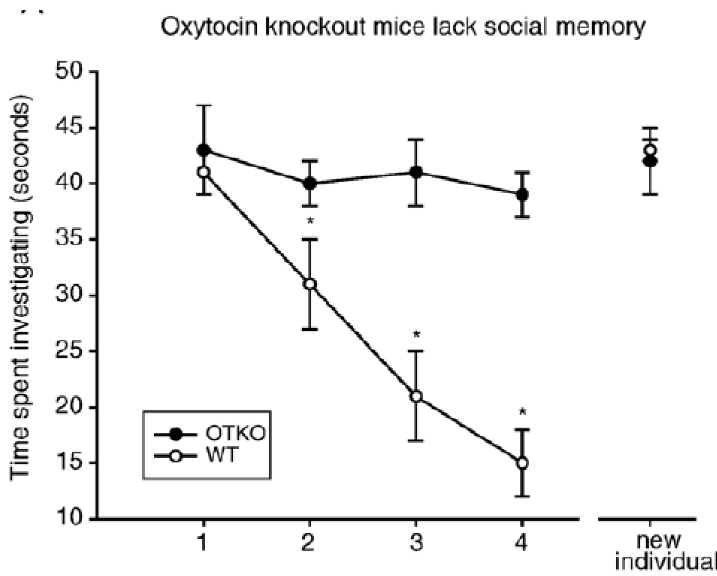
Treatment	Mouse model	Phenotypic improvement
mGluR antagonists, MPEP[88,161,162], fenobam[162]	*Fmr1*$^{-/-}$	• Susceptibility to audiogenic seizures is prevented[161] • Decreased open field hyperactivity[161] • Rescued prepulse inhibition of startle deficit[162] • Rescued abnormal spine morphology[162]
	BTBR	• Reduced repetitive behaviour[88]
mTOR inhibitors, rapamycin[63,77,177,178], RAD001 (REF. 177)	*Pten*	• Prevented and reversed macrocephaly, dendritic and axonal hypertrophy[77] • Improved social interaction time[77] • Increased open field centre time[77] • Reduced duration and frequency of seizures[77]
	Tsc1 null-neuron inactivated in neurons[63,177]	• Improved survival rates[63,177] • Improved neuronal morphology, reduced enlarged neurons and restored myelination[177]
	Tsc1^{GFAP} inactivated in glia[178]	• Improved survival rates and weight gain[178] • Prevented seizures and electroencephalography (EEG) abnormalities[178]
	Tsc2$^{+/-}$ (REF. 63)	• Improved learning and memory on Morris water maze and fear conditioning[63]
Oxytocin[114]	*OXT*$^{-/-}$	• Rescued deficits in social recognition[114]
BDNF[75]	*Fmr1*$^{-/-}$	• Rescued long-term potentiation abnormality[75]
Ampakines, CX546 (REF. 73)	*Mecp2*$^{-/-}$	• Reversed respiratory deficits[73]
mGluR genetic reduction[74]	*Fmr1*$^{-/-}$	• Prevented susceptibility to audiogenic seizures[74] • Rescued abnormal spine morphology[74] • Rescue of exaggerated inhibitory avoidance learning[74]
FMR1 gene replacement[60,61,76]	*Fmr1*$^{-/-}$	• Normalized open field activity[60] • Normalized light–dark anxiety-like behaviour[60] • Rescued abnormal social responses[61] • Rescued increased prepulse inhibition[76]
PAK genetic reduction[92]	*Fmr1*$^{-/-}$	• Normalized open field centre time[92] • Rescued fear-conditioning deficit[92] • Rescued long-term potentiation deficit[92]
MECP2 gene replacement[174,176]	*Mecp2*$^{-/+}$ is an inducible heterozygous transgenic[176]	• Rescued open field deficits[176] • Increased survival and lifespan[174]
	Mecp2/Stop is an *Mecp2* mutant with *Mecp2* conditional activation[174]	• Normalized weights, breathing, gait and activity[174]

Silverman et al 2010; Nature Reviews Neuroscience

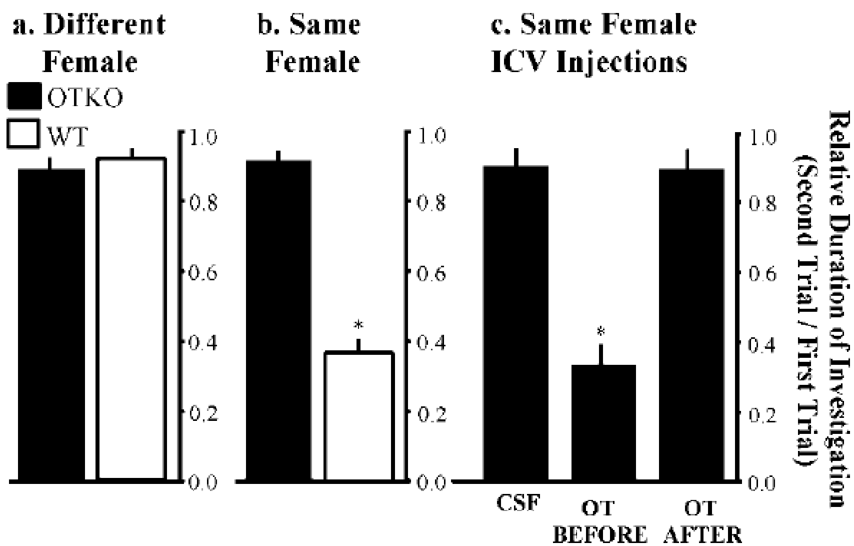
Studying the role of oxytocin in autism using mouse models

Oxytocin KO mouse model

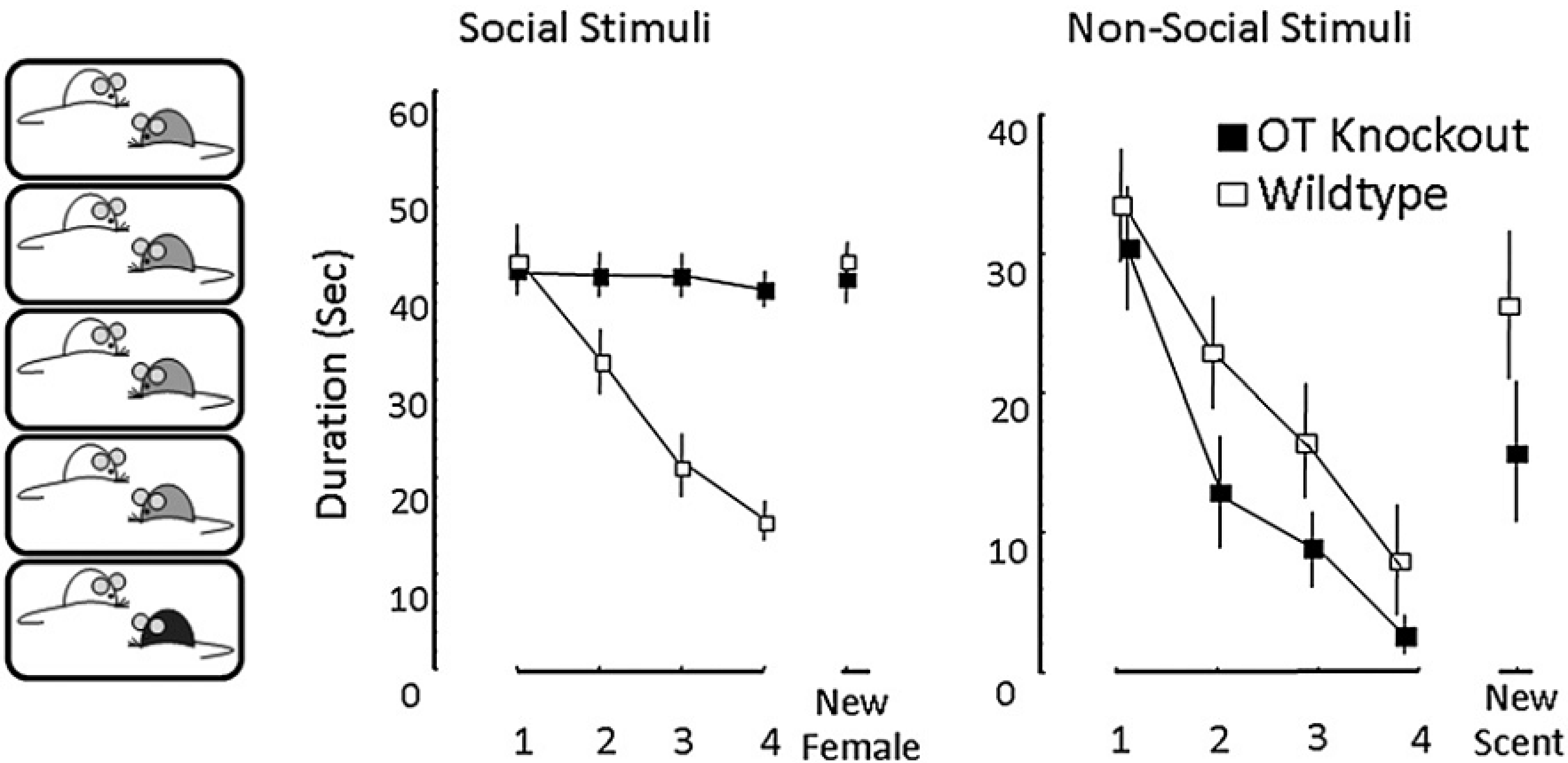




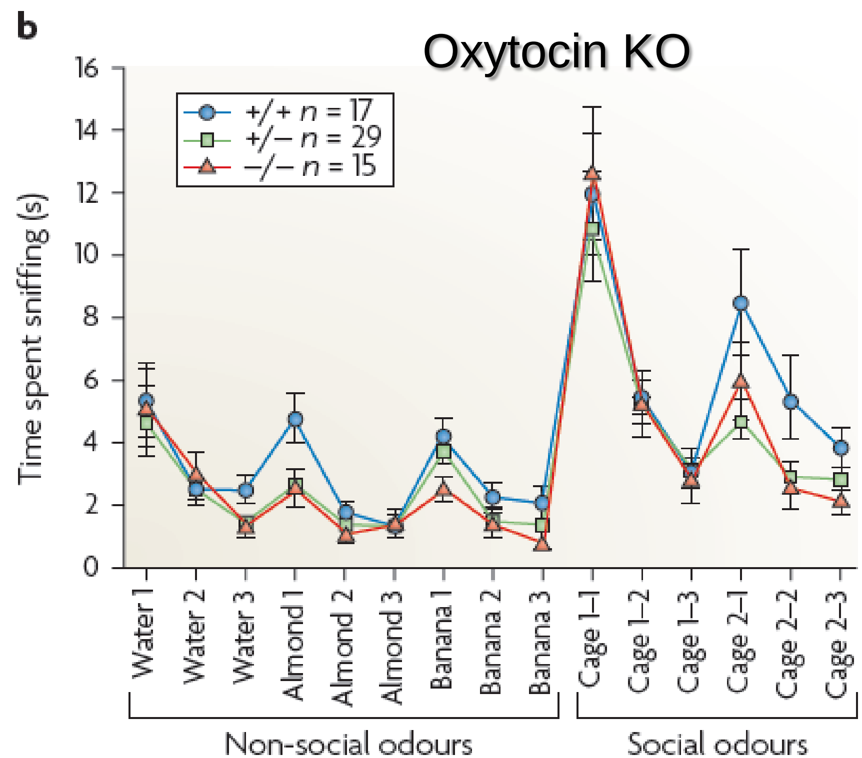
Oxytocin knockout mice lack social memory
Time spent investigating (seconds)
50
45
40
35
30
25
20
15
10
OTKO
WT
*
1
2
3
4
new individual

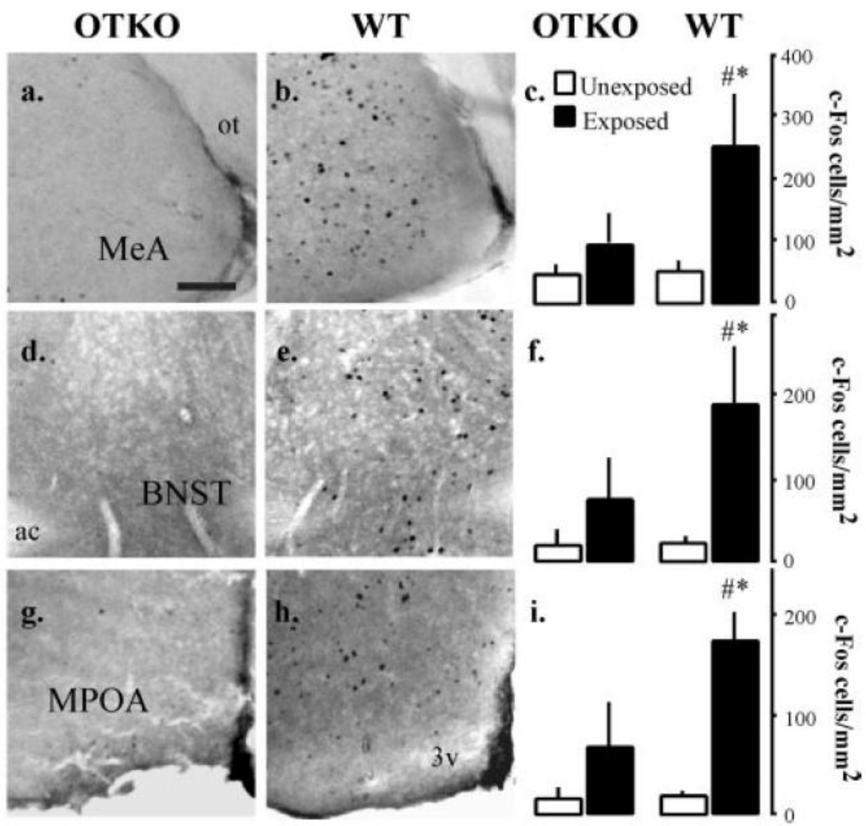


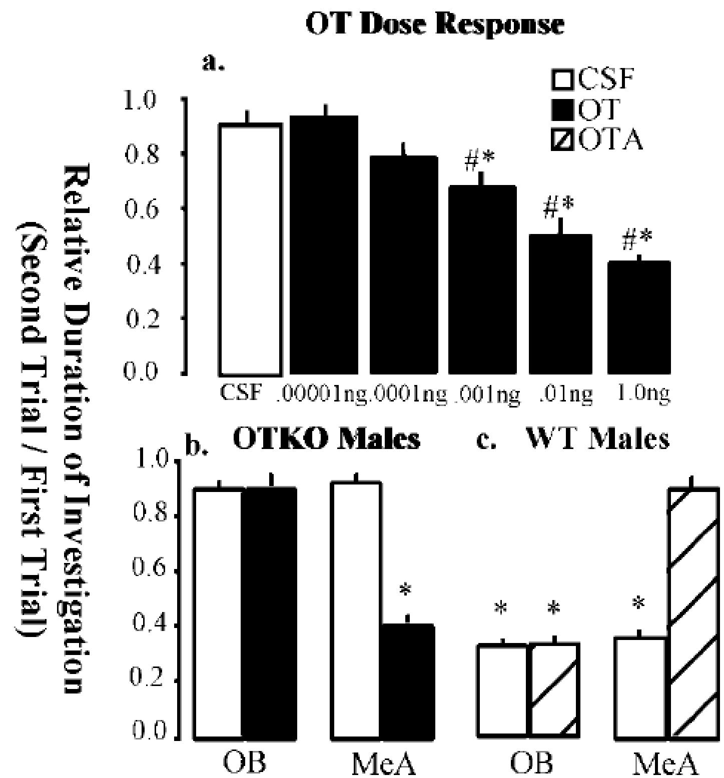
a. Different Female
b. Same Female
c. Same Female ICV Injections
OTKO
WT
1.0
0.8
0.6
0.4
0.2
0.0
*
CSF
OT BEFORE
OT AFTER
Relative Duration of Investigation (Second Trial / First Trial)


Social Stimuli
Non-Social Stimuli
Duration (Sec)
60
50
40
30
20
10
0
1
2
3
4
New
Female
40
30
20
10
0
OT Knockout
Wildtype
New
Scent

Olfactory habitutation/dishabituation

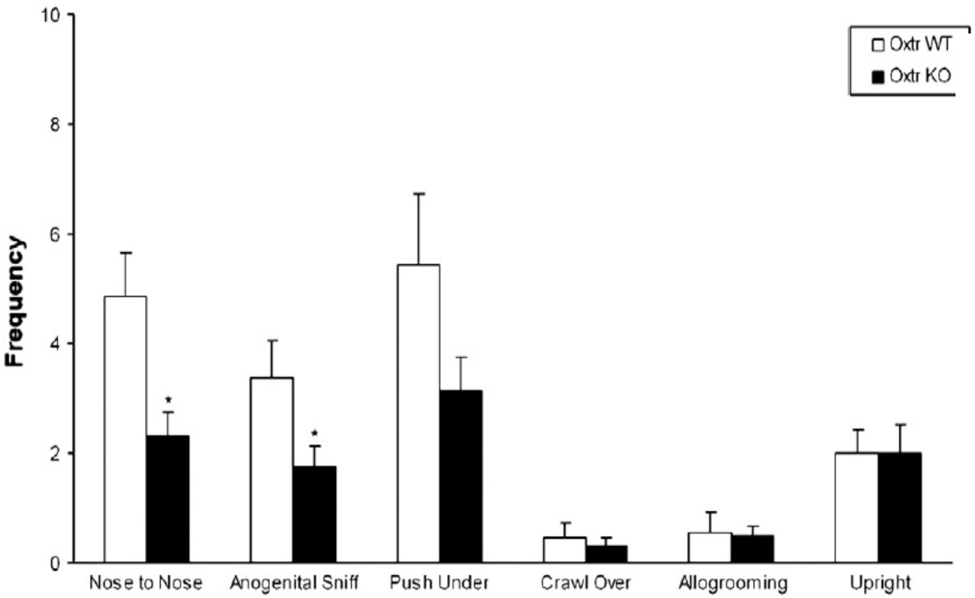


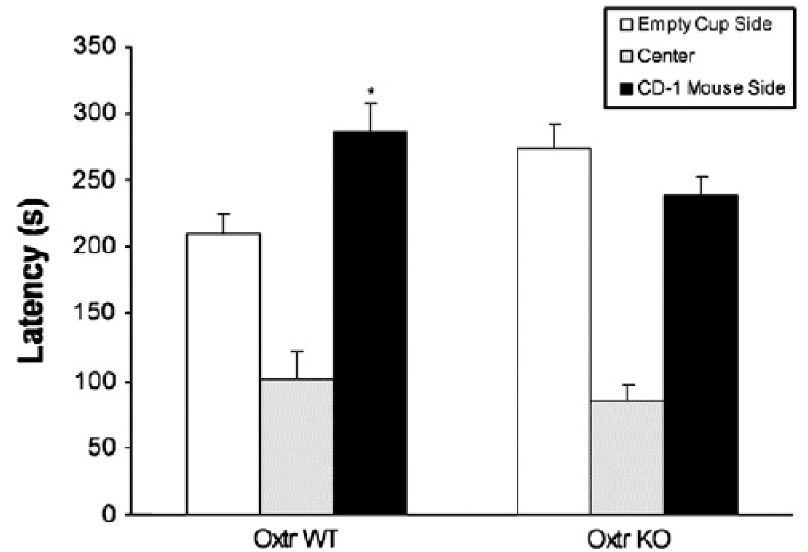




Ferguson et al 2001; J Neuroscience

Oxytocin Receptor Knockout and Autism





Pobbe et al 2012; Hormones and Brhavior

Summery:

- OTKO mouse fail to habituate to, or recognize, a stimulus mice even after repeated exposures.

- The deficit in social recognition in OTKO mice represents a defect in the initial processing of olfactory cues and not in the recall of the previously stored memory.

- OT must be present in the MeA during the initial social exposure for the proper processing of the olfactory information and the development of the social memory.

Oxytocin effects on humans

Oxytocin Improves "Mind-Reading" in Humans

Gregor Domes, Markus Heinrichs, Andre Michel, Christoph Berger, and Sabine C. Herpertz

Oxytocin increases trust in humans

Michael Kosfeld[1]*, Markus Heinrichs[2]*, Paul J. Zak[3], Urs Fischbacher[1] & Ernst Fehr[1,4]

Vol 435|2 June 2005|doi:10.1038/nature03701 nature

Oxytocin Modulates Neural Circuitry for Social Cognition and Fear in Humans

Peter Kirsch,[1] Christine Esslinger,[1] Qiang Chen,[2,4] Daniela Mier,[1] Stefanie Lis,[1] Sarina Siddhanti,[3,4] Harald Gruppe,[1] Venkata S. Mattay,[2,4] Bernd Gallhofer,[1] and Andreas Meyer-Lindenberg[2,3,4]

The Journal of Neuroscience, December 7, 2005 • 25(49):11489–11493 • 11489