Control of Ejaculation

What the Rat's Brain Tells the Clinician

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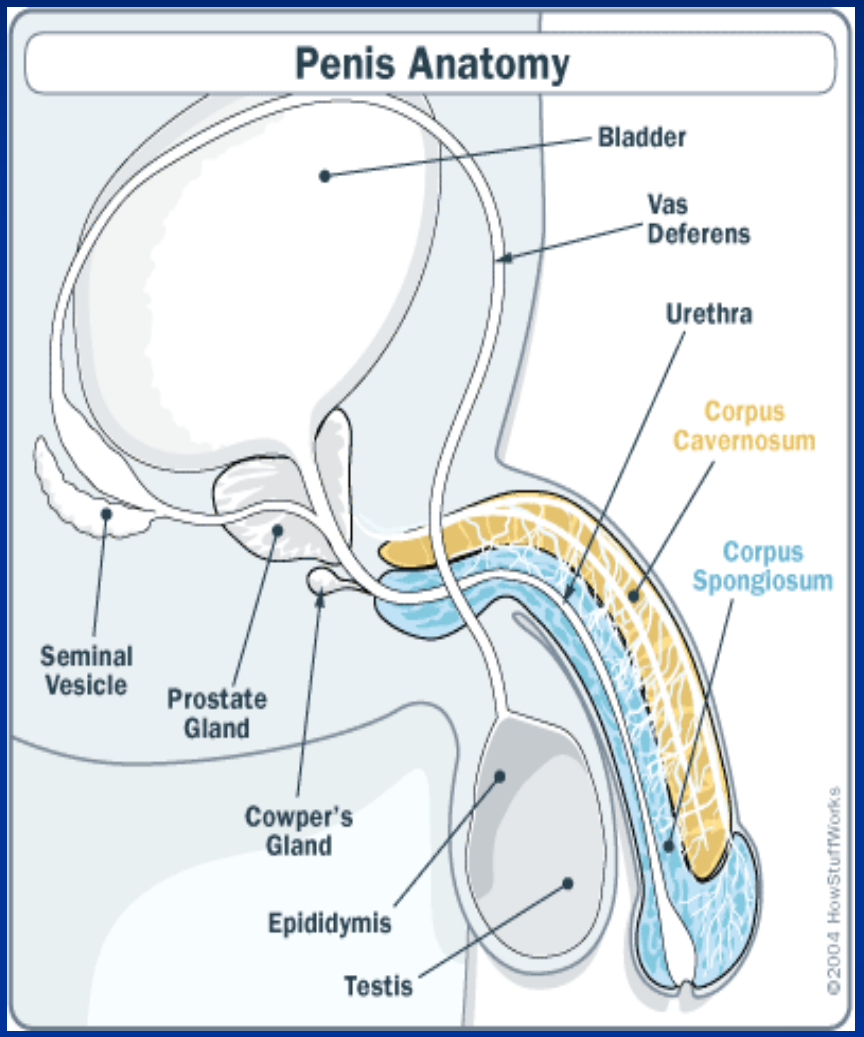
What is ejaculation?

2 phases:

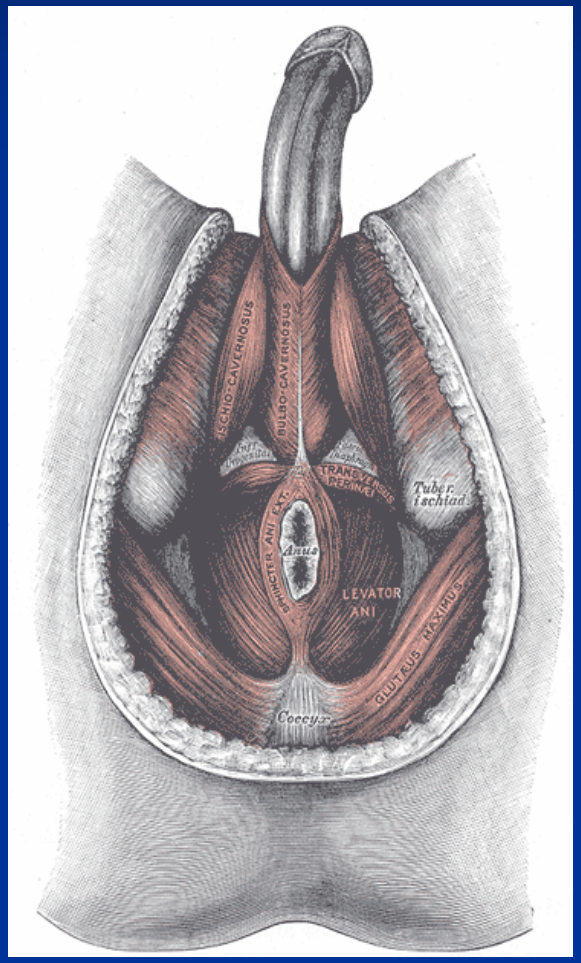
- Emission
- Expulsion

Seminal emission



- Sperm + fluids from seminal vesicle, prostate, & Cowper's gland → urethra (in prostate)
- Parasympathetic NS → secretion
- Sympathetic → movement

Expulsion, orgasm



Gray's anatomy

- Bulbospongiosus, ischiocavernosus, & pelvic floor muscles contract, bladder neck closes.
- Orgasm: cerebral process; does not require expulsion of semen

How is ejaculation coordinated and controlled?

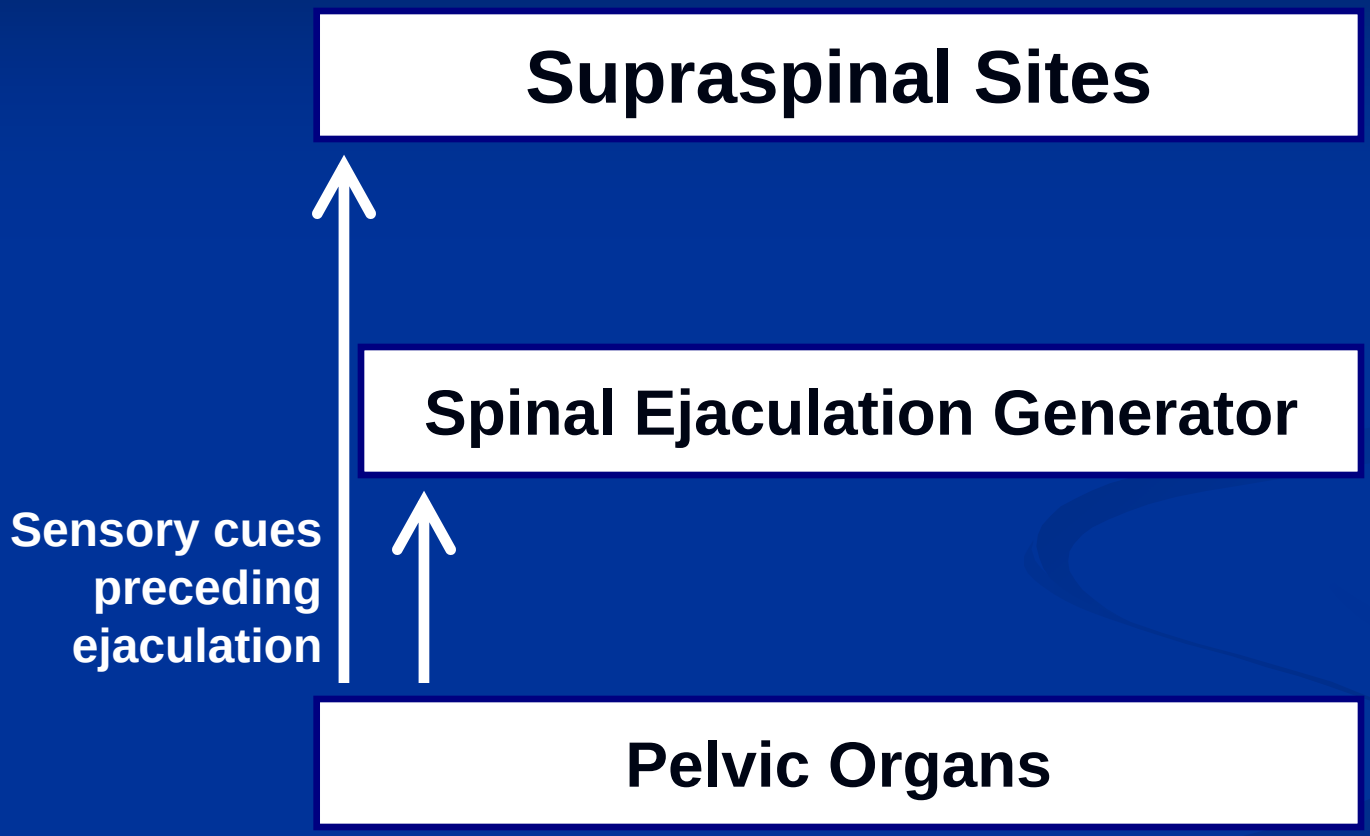
Neural Control of Ejaculation

Supraspinal Sites

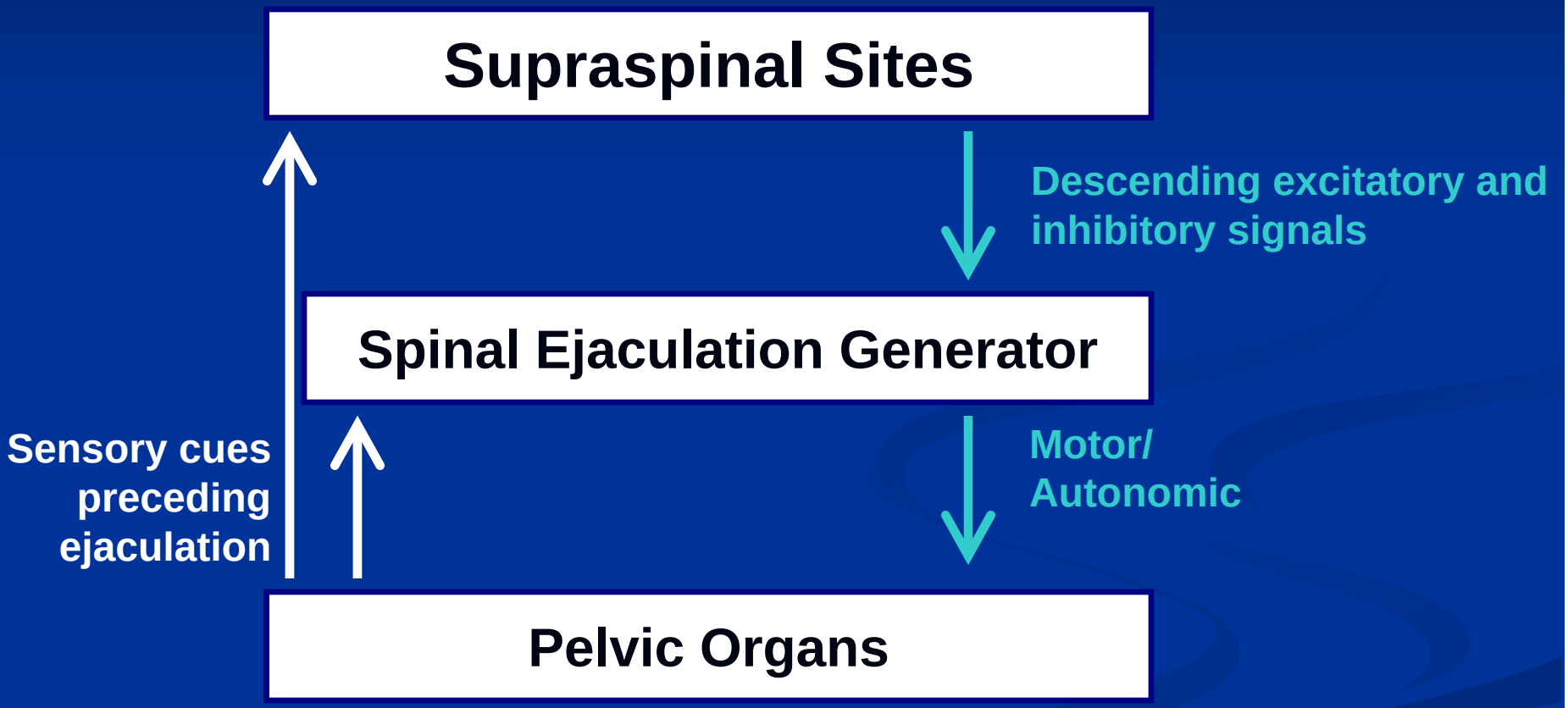
Spinal Ejaculation Generator

Pelvic Organs

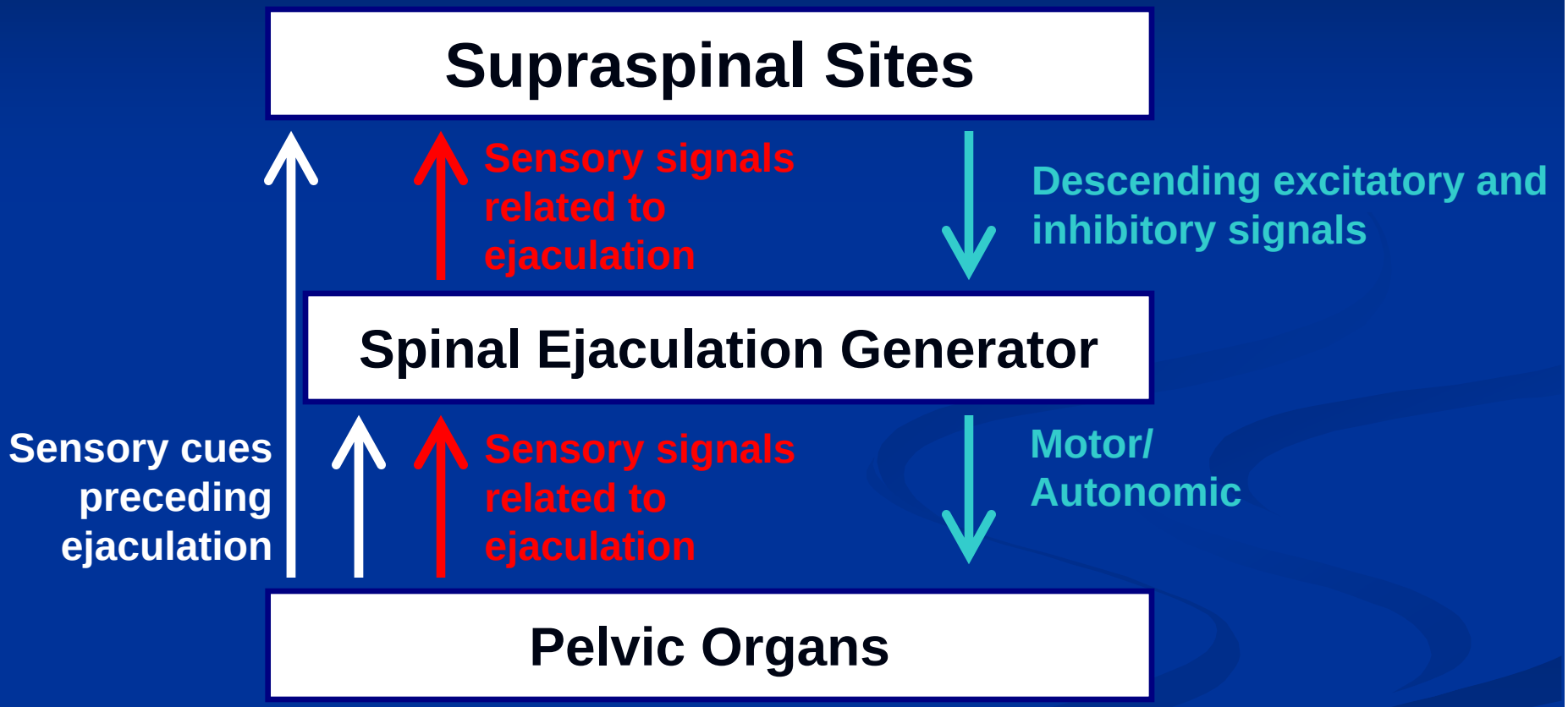
Neural Control of Ejaculation



Neural Control of Ejaculation



Neural Control of Ejaculation



A spinal ejaculation generator
Lumbar spinothalamic (LSt) neurons

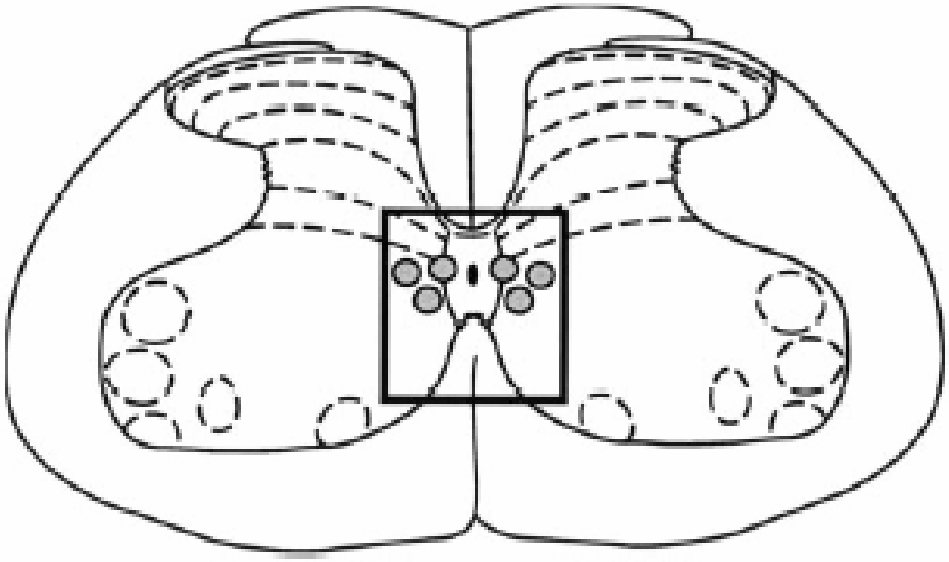


Figure 1. Schematic drawing of L4 illustrating the area of analysis (800 × 800 μm) for Fos-IR and activated LSt cells. *Gray circles* indicate the approximate location of LSt cells. This figure was modified from Paxinos and Watson (1998).

Truitt et al., 2003

LSt neurons

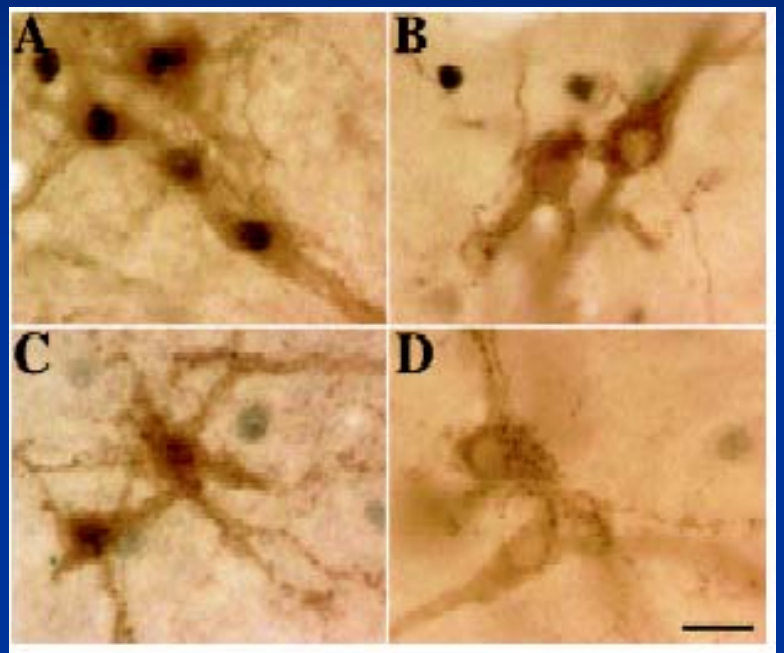
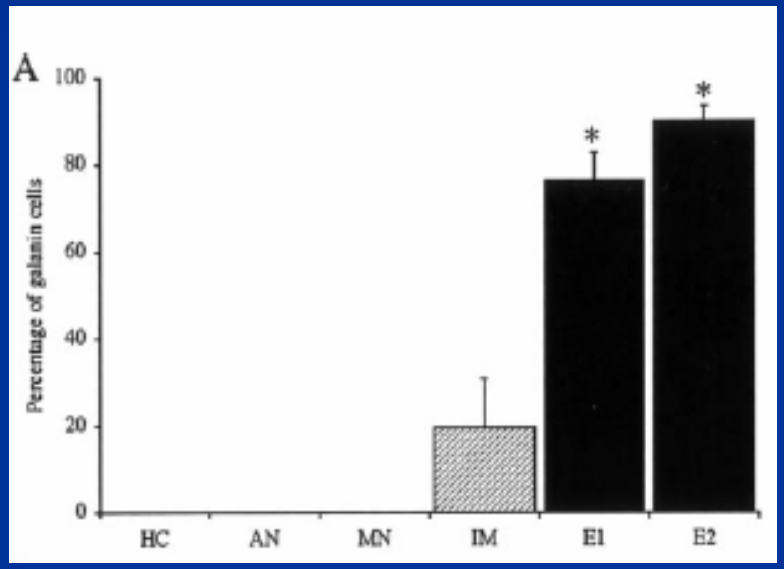


Figure 2. Neural activation of LSt neurons in male but not female spinal cord. *A*, Galanin neurons are Fos positive in a representative male after two ejaculations. *B*, Lack of colocalization of Fos and galanin in a male rat after intromissions but no ejaculation. *C*, Colocalization of galanin and Fos in an 8-OH-DPAT-treated male rat after one ejaculation. *D*, Lack of colocalization of Fos and galanin in a female rat after ejaculation by her male partner. Scale bar, 20 μm.

Truitt et al., 2003

- (A) Galanin-containing neurons are Fos-ir after 2 ejaculations,
- (B) but not after only intromissions.
- (C) They are Fos-ir after 8-OH-DPAT + I ejaculation.
- (D) No Fos-ir in a female after she received 1 ejaculation.

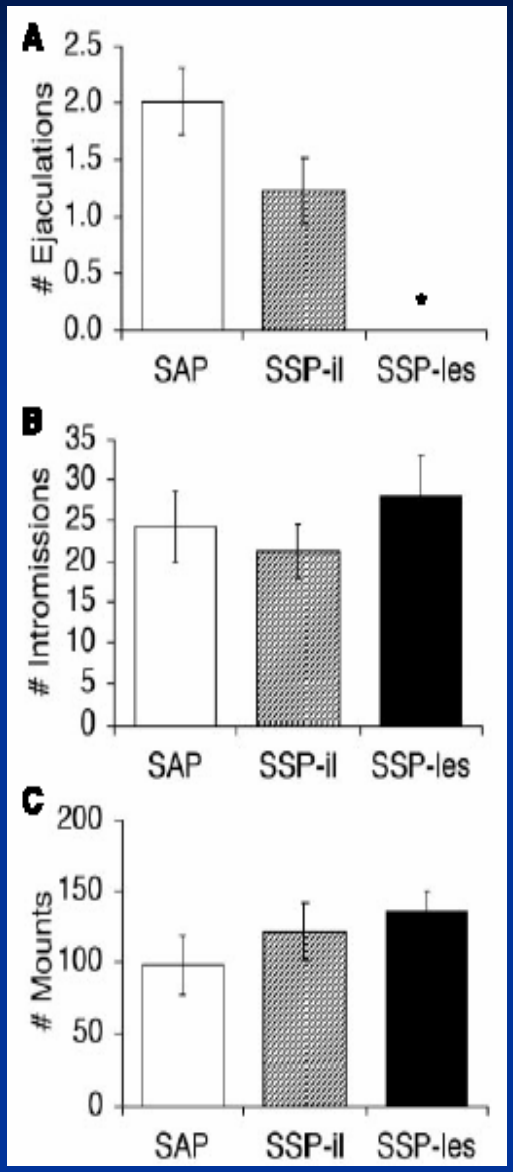
LSt neurons



Truitt et al., 2003

- Percentage of galanin cells that were Fos-ir after Home Cage, Anestrous Female, Mounts, M+I, 1 Ejac., 2 Ejacs

LSt neurons



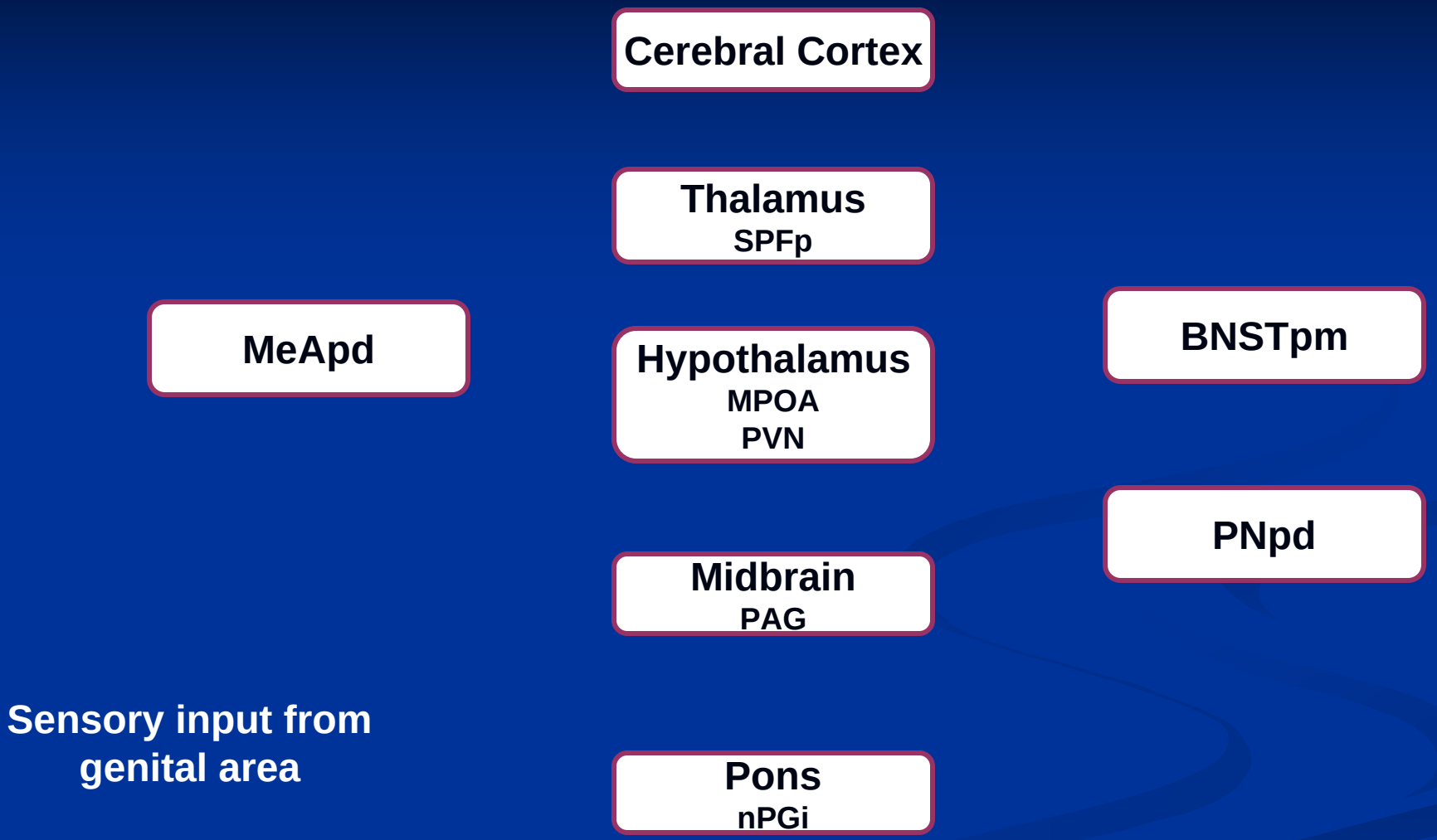
Truitt et al., 2003

- Destruction of LSt neurons by saporin conjugated to SSP abolished ejac., but mount & intro were normal.
- (SSP: analog of SP, agonist at NK1 receptors. Most LSt cells have NK1 rec.)

LSt Summary

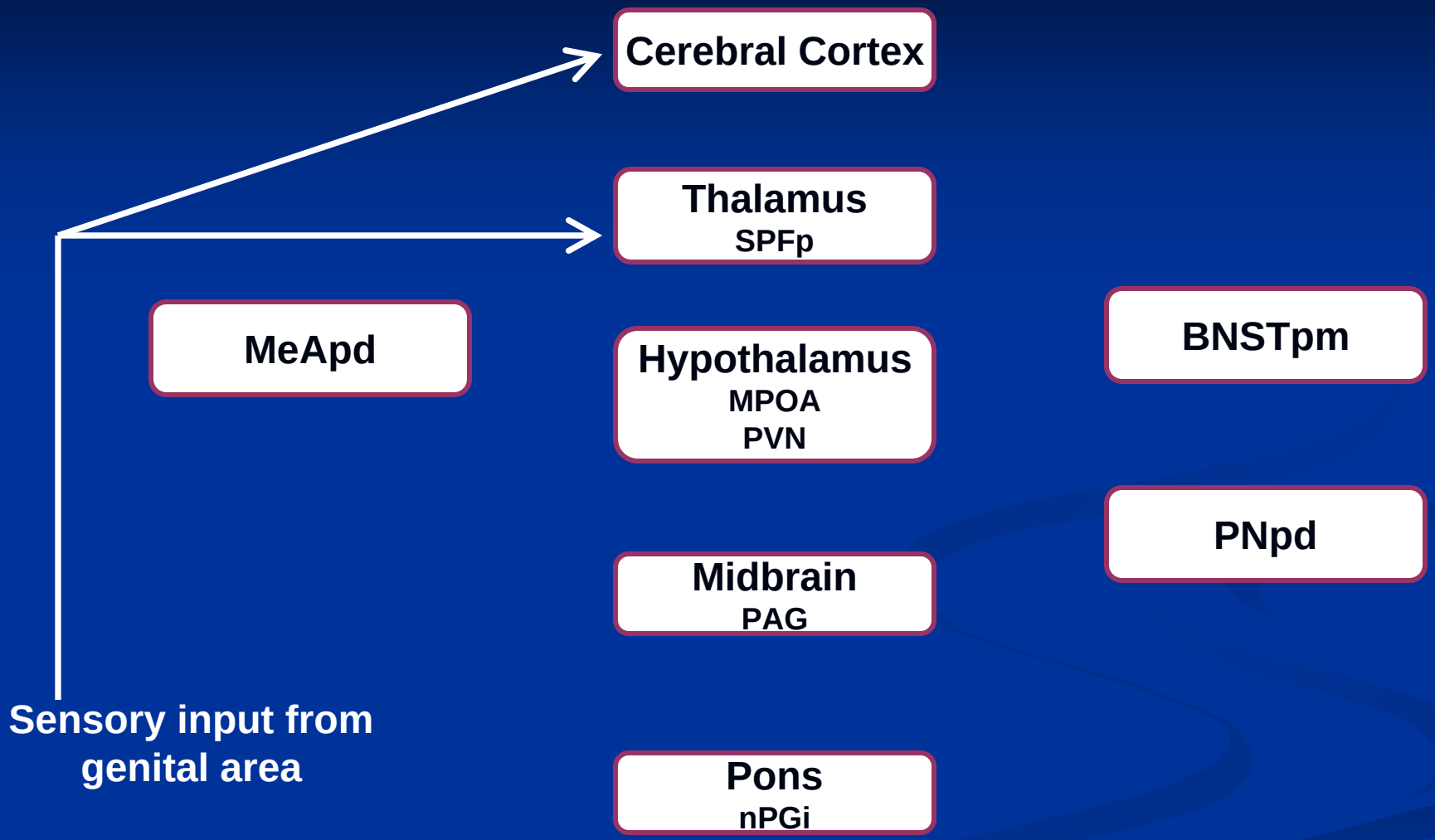
- LSt neurons are selectively activated by ejaculation and are necessary for ejaculation.
- Receipt of ejaculation by a female does not activate galanin-containing neurons in the same area.

Supraspinal control of ejaculation



Giuliano and Clement, 2005

Supraspinal control of ejaculation



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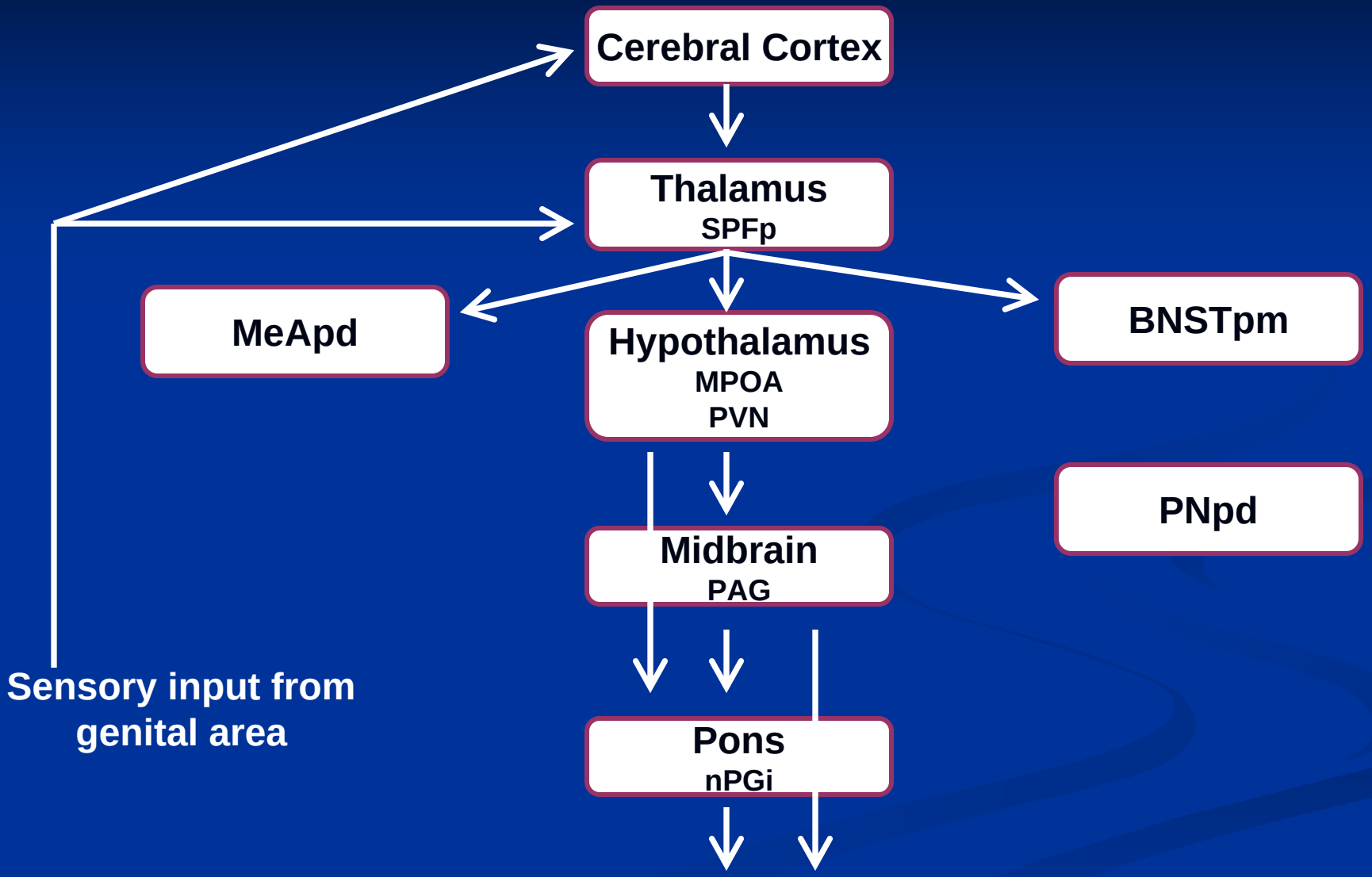

Giuliano and Clement, 2005

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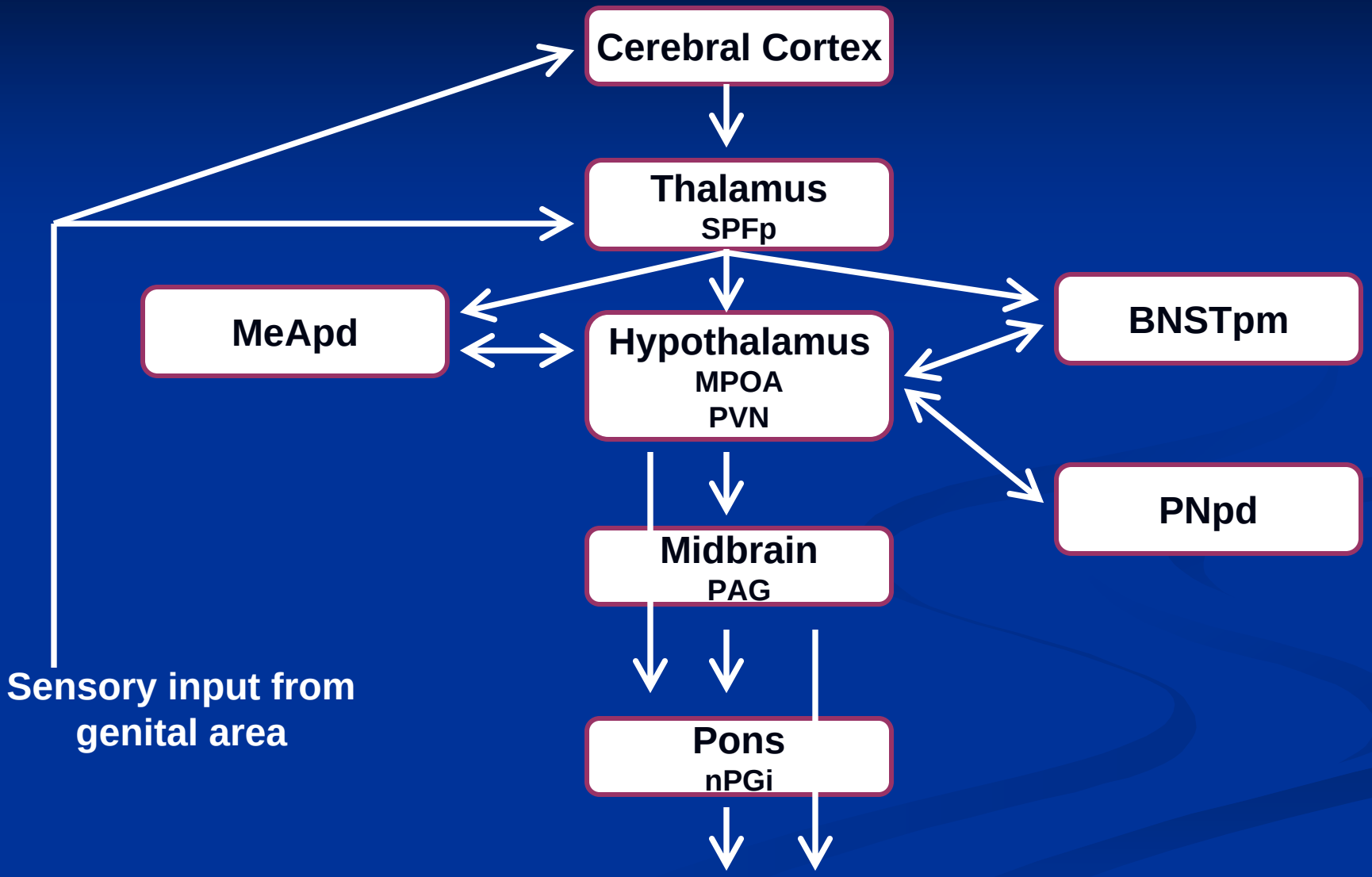
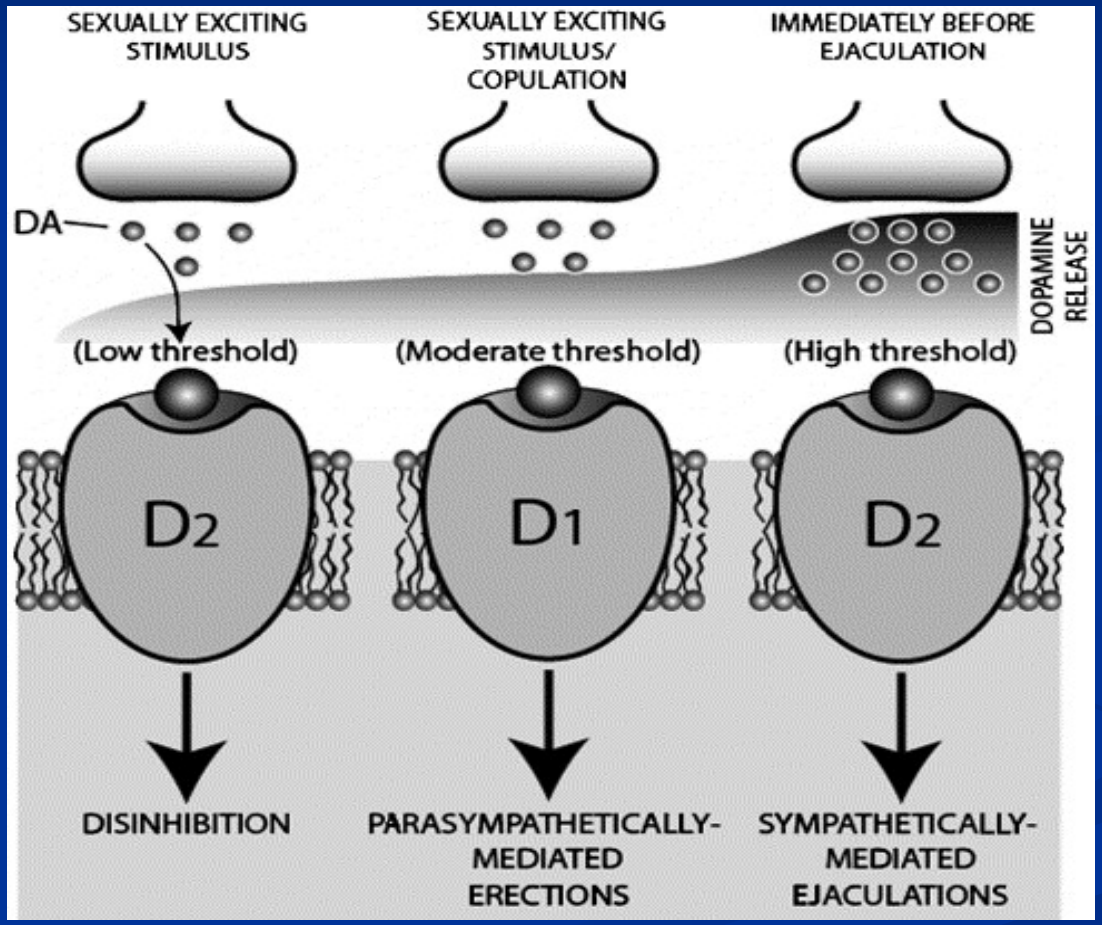


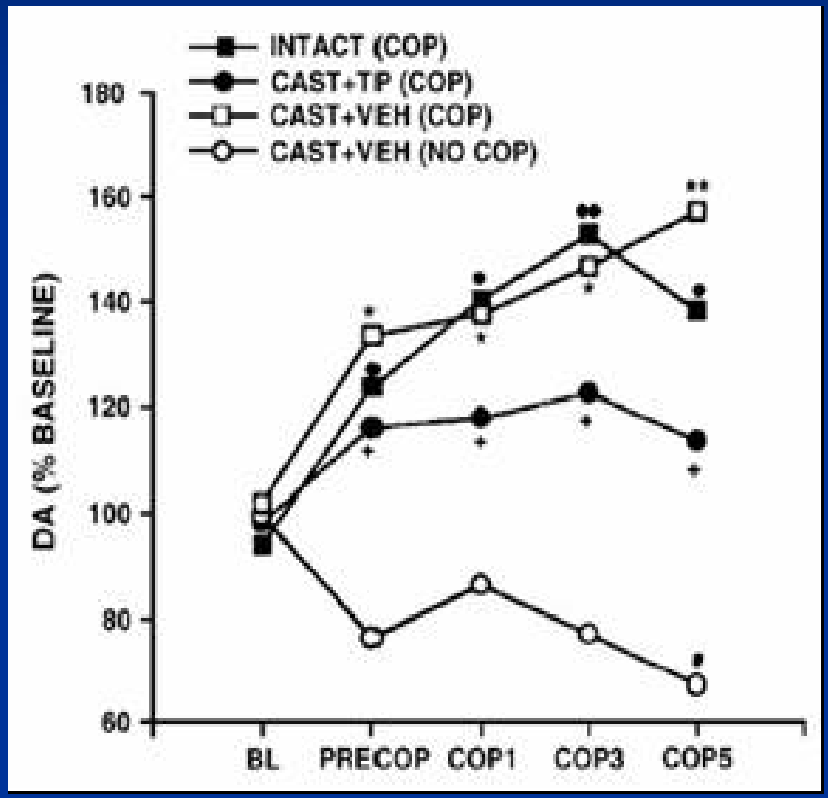
Giuliano and Clement, 2005

Roles of MPOA Dopamine



Dominguez and Hull, 2005

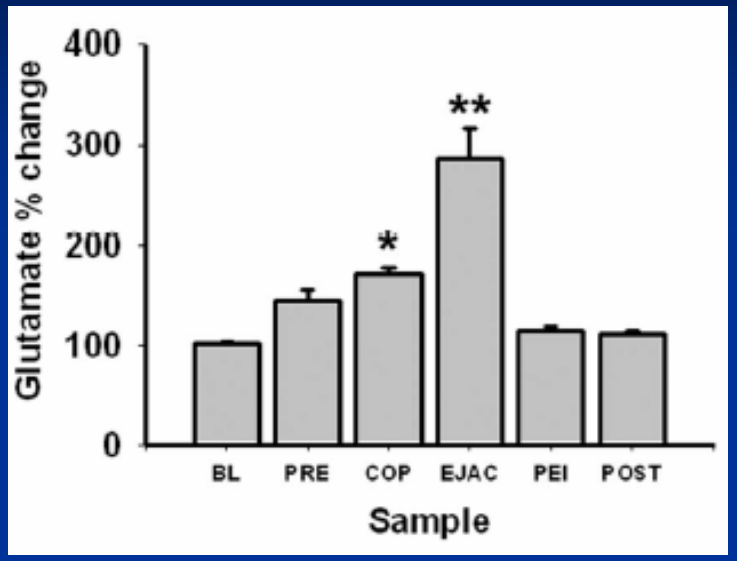
Dopamine is released in MPOA before and during mating

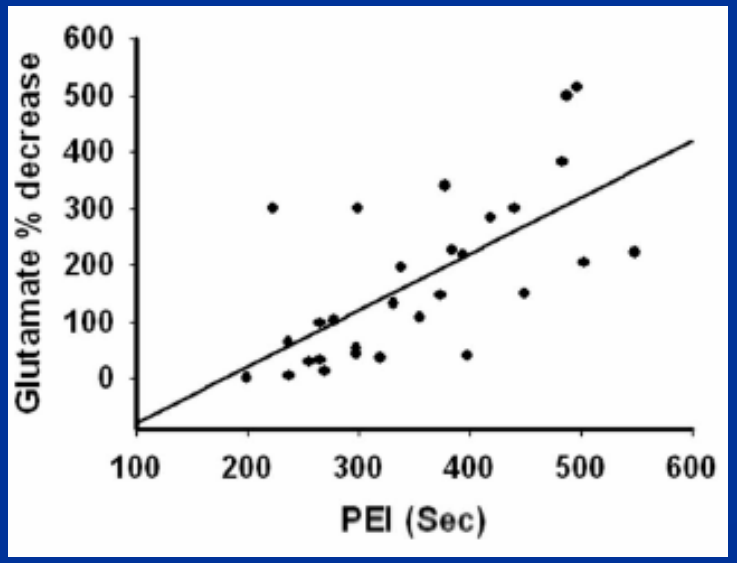


Hull et al., 1995

- DA increase from BL was correlated with ability to ejaculate

Role of MPOA glutamate

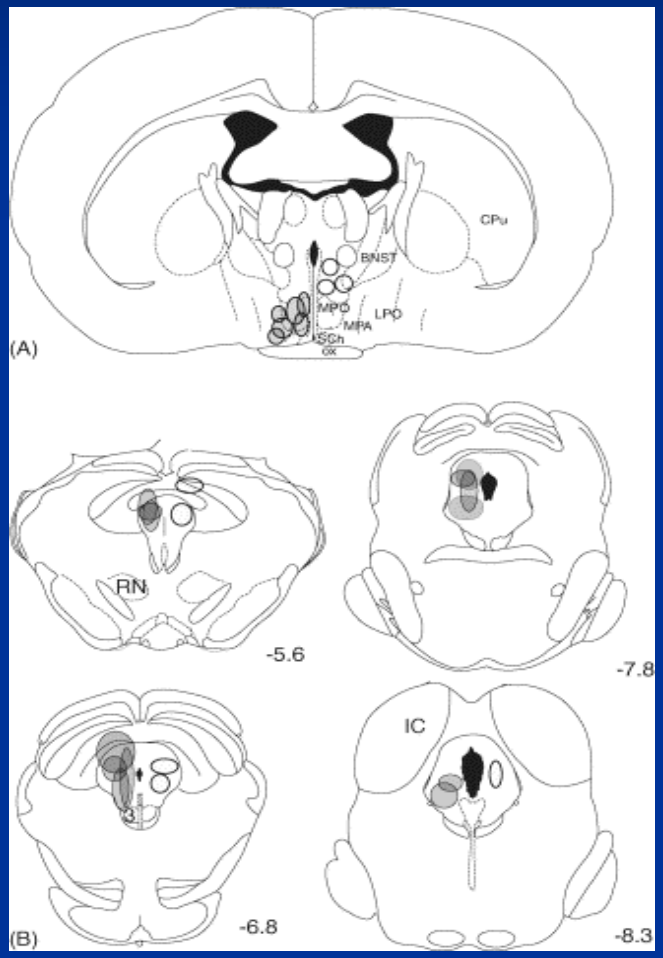


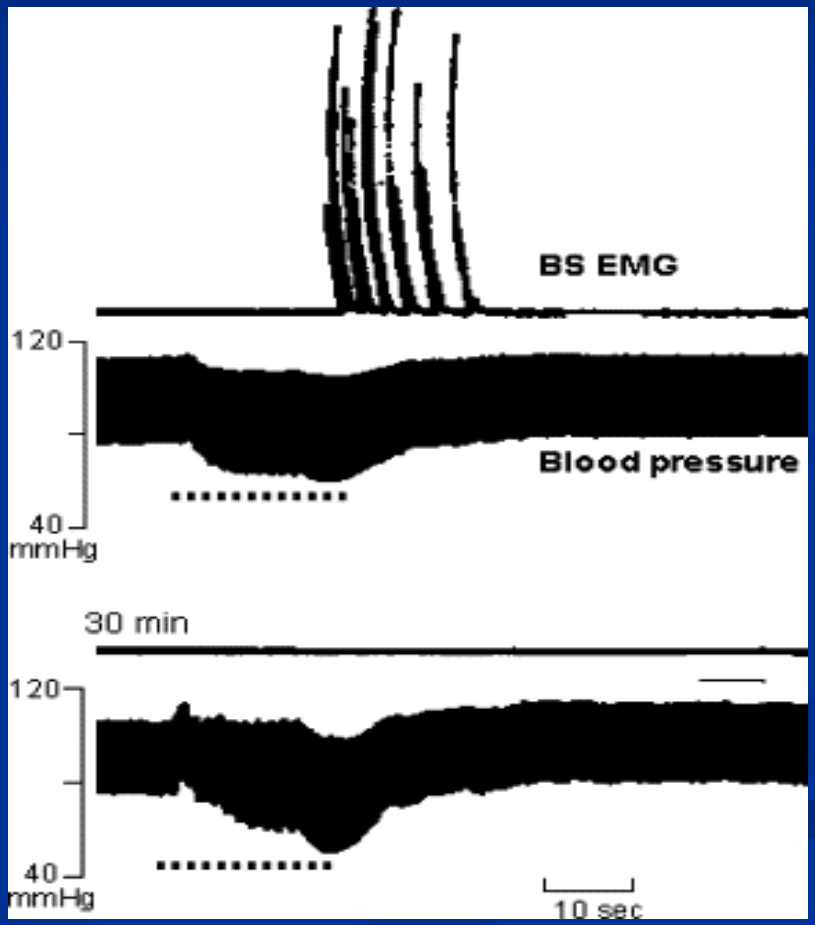


- Glut. increased during mating and
- Peaked with ejac.
- Post-ejac. decrease correlated with PEI
- Reverse-dialysis of uptake inhibitors increased ejacs., decreased EL, PEI.

Dominguez et al., 2006

Stimulate MPOA → BS firing
PAG lesions abolish the effect





Marson, 2004

Summary of MPOA effects

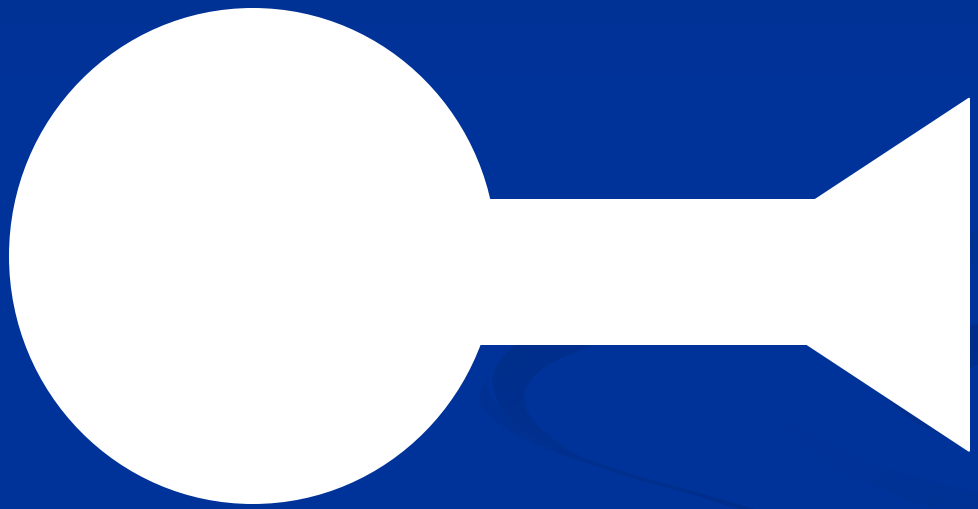
- High doses of D2 agonists → seminal emission *ex copula.*
- High doses of D2 agonists → ejaculation *in copula.*
- Electrical stimulation → BS firing.
- Lesions of PAG block that effect.

Role of the PVN

Reviewed in Argiolas & Melis, 2004

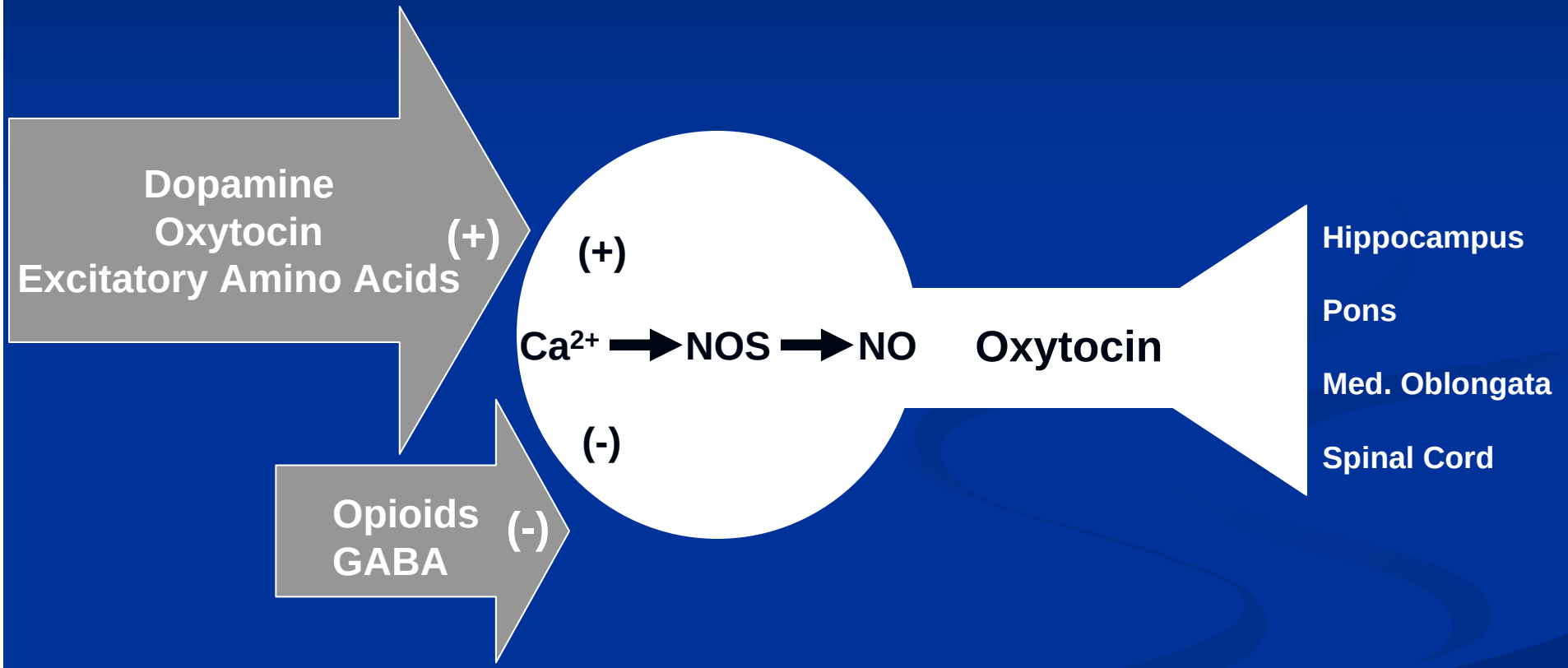
- D2 agonists, glutamate, NO in PVN → *ex copula* erection & seminal emission
- PVN lesions decrease amount of semen in ejaculate.
- Oxytocin fibers → lumbosacral cord, as well as hippocampus, other brain areas
- Oxytocin → systemic circulation via PP
  - (reviewed in Argiolas & Melis, 2004)

Role of the PVN



Argiolas and Melis, 2004

Role of the PVN



Argiolas and Melis, 2004

Role of nPGi

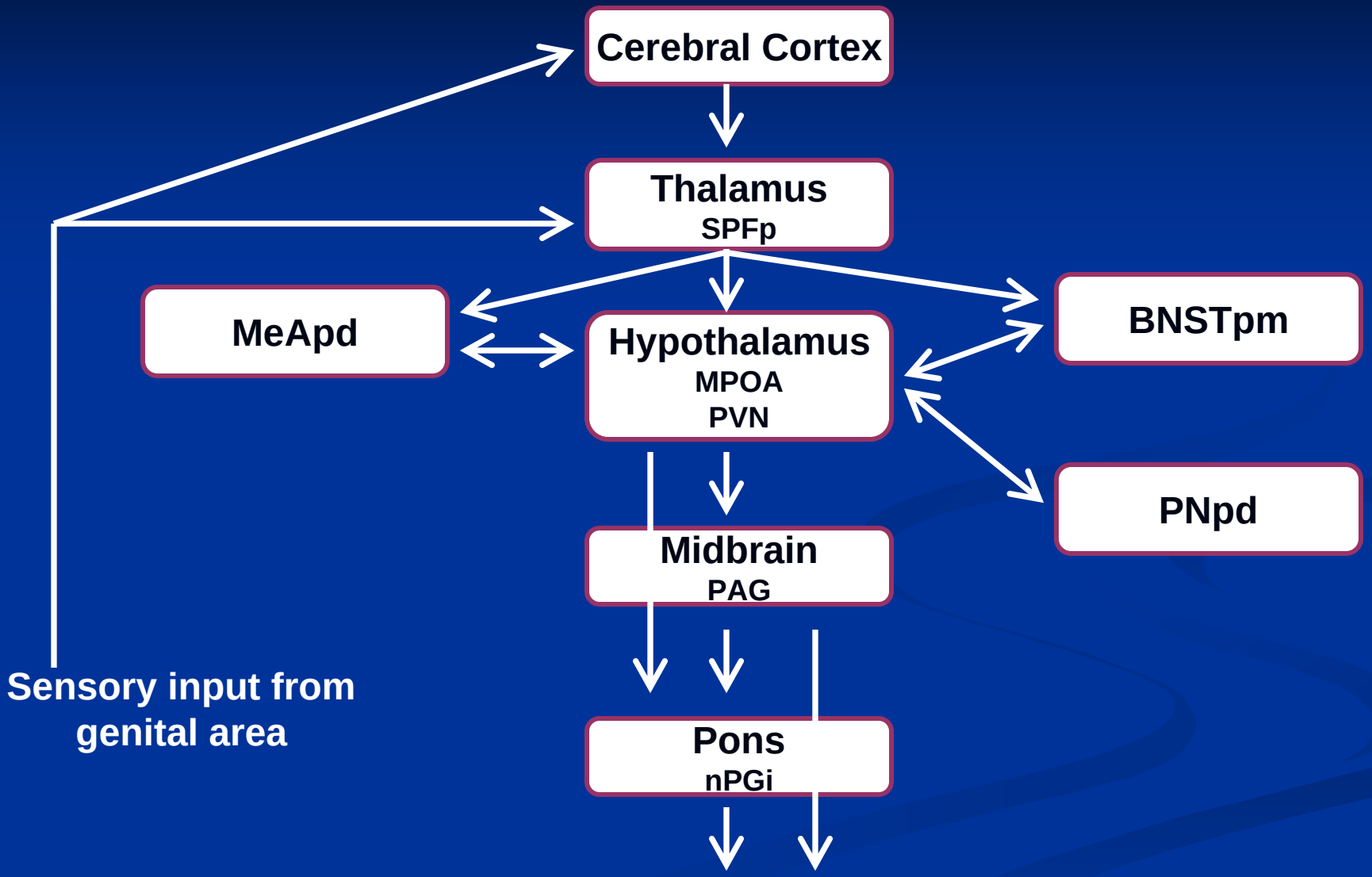
- Lesions of nucleus paragigantocellularis in medulla: as effective as spinal tran-section at releasing the urethrogenital reflex (model of orgasm) (Marson et al., ‘92).
- nPGi sends 5-HT axons to lower spinal cord; 5-HT lesions disinhibit UG reflex

  (Marson & McKenna, 1992, 1994).

An ejaculation circuit

- Selective activation (Fos-ir) by ejaculation:
- Subparafascicular nucleus of thalamus (SPFp)
- Posteromedial bed nucleus of stria terminalis (BNSTpm)
- Posterodorsal medial amygdala (MeApd)
- Posterodorsal preoptic nucleus (PNpd)

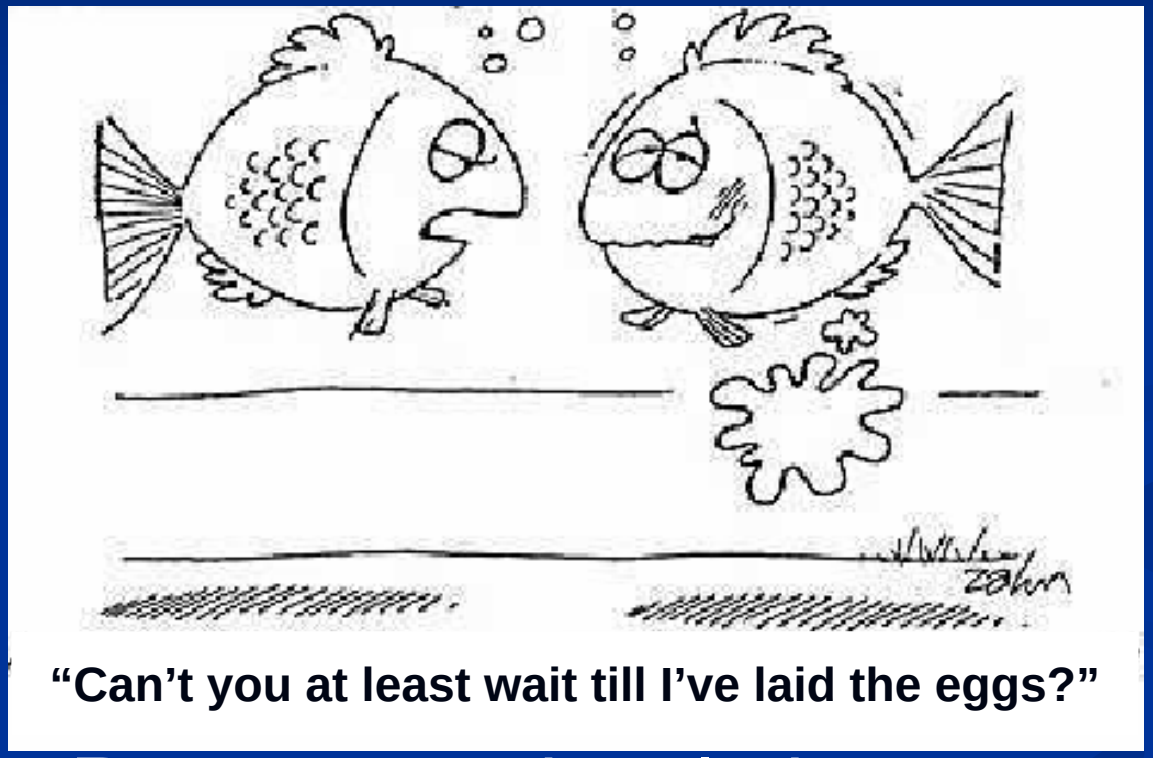
Supraspinal control of ejaculation



Giuliano and Clement, 2005

So, what DOES the rat's brain tell the clinician?

So, what DOES the rat's brain tell the clinician?



"Can't you at least wait till I've laid the eggs?"

- Premature ejaculation
- Delayed or absent ejaculation

Role of norepinephrine (NE)

- Sympathetic NS transmitter → seminal emission & ejaculation; also in CNS.
- Dose-dependent effects of NE drugs
- α2 autoreceptors decrease NE release
  - α2 antagonists (e.g., yohimbine) increase NE release, facilitate copulation in rats
- But too much NE → inhibits erection

Role of dopamine (DA)

- Rats:
  - Dopamine agonists facilitate copulation and reflexes
  - D2 agonists → ejaculation
- Humans:
  - DA agonists have been used for erectile dysfunction, but not for ejac. disorder.
  - DA antagonists (antipsychotics) block ejac.

Role of serotonin (5-HT) in rats

- Neurotoxic lesions facilitate copulation
- 5-HT is released in LH at ejaculation
  - SSRI in LH delayed onset of copulation
  - 5-HT in LH decreased DA in Nuc. Accumb.
  - Mechanism for PEI quiescence
- 5-HT1A agonist (8-OH-DPAT) → ejac.
- 5-HT1B agonist inhibits ejaculation
- 5-HT2C agonist → erection, inhibit ejac.

Effects of SSRIs in rats

- Chronic Prozac inhibited ejaculation
  - Systemic oxytocin restored it (Cantor et al., '99).
  - 8-OH-DPAT (5-HT1A agonist) also restored it (Faulring et al., 2002, SfN).

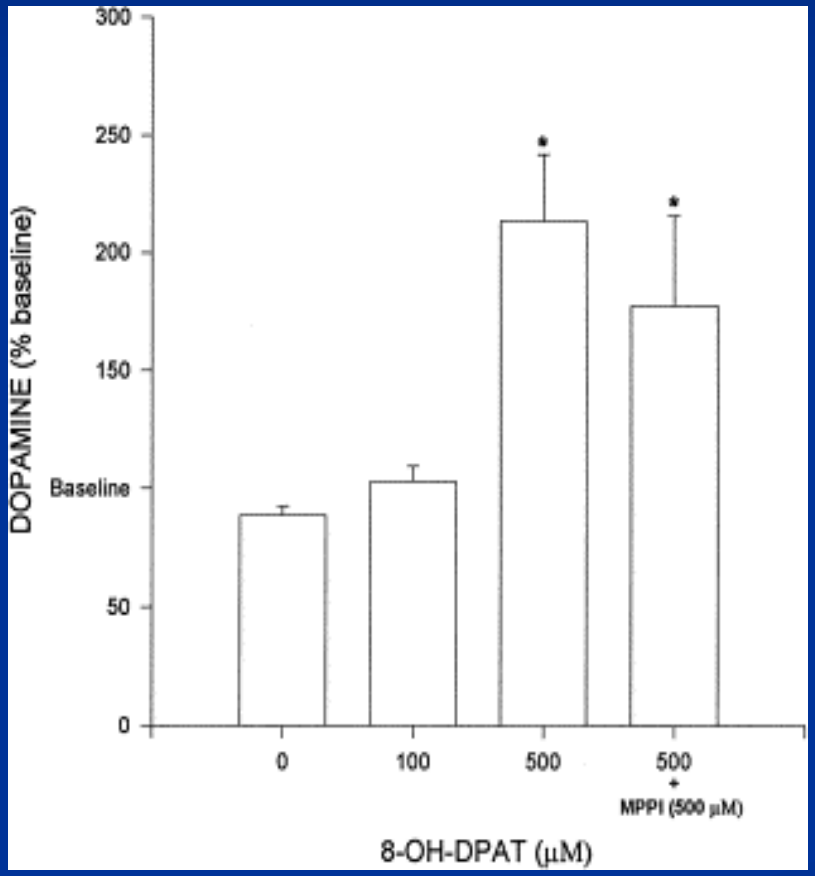
8-OH-DPAT → ejac. How does it work?

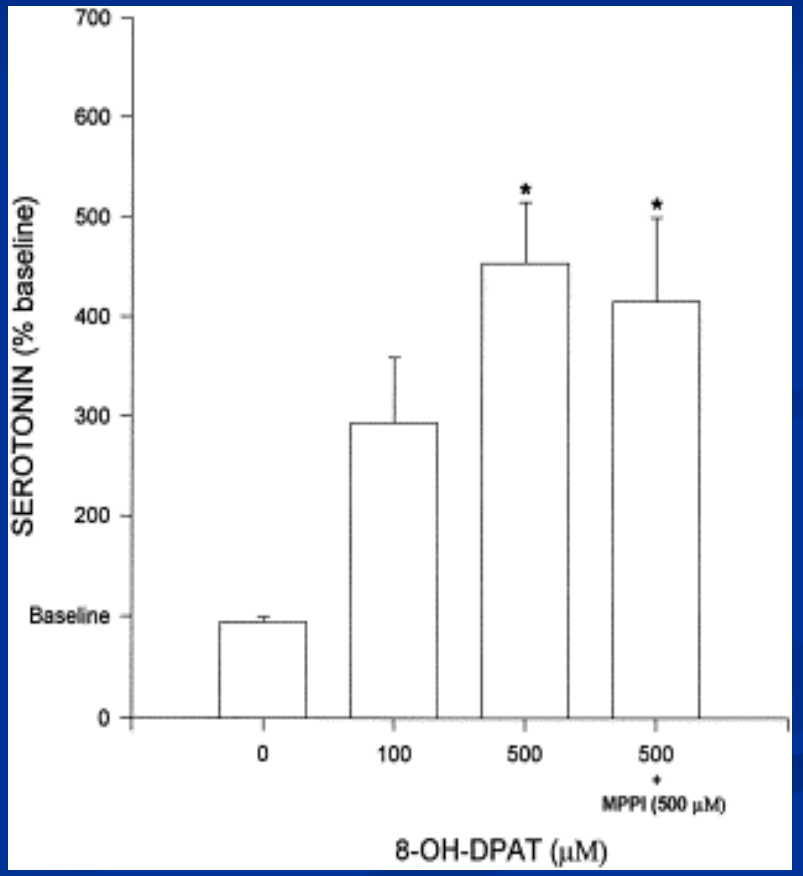
Autoreceptor on 5-HT somas

Postsynaptic receptor

Uptake inhibitor?

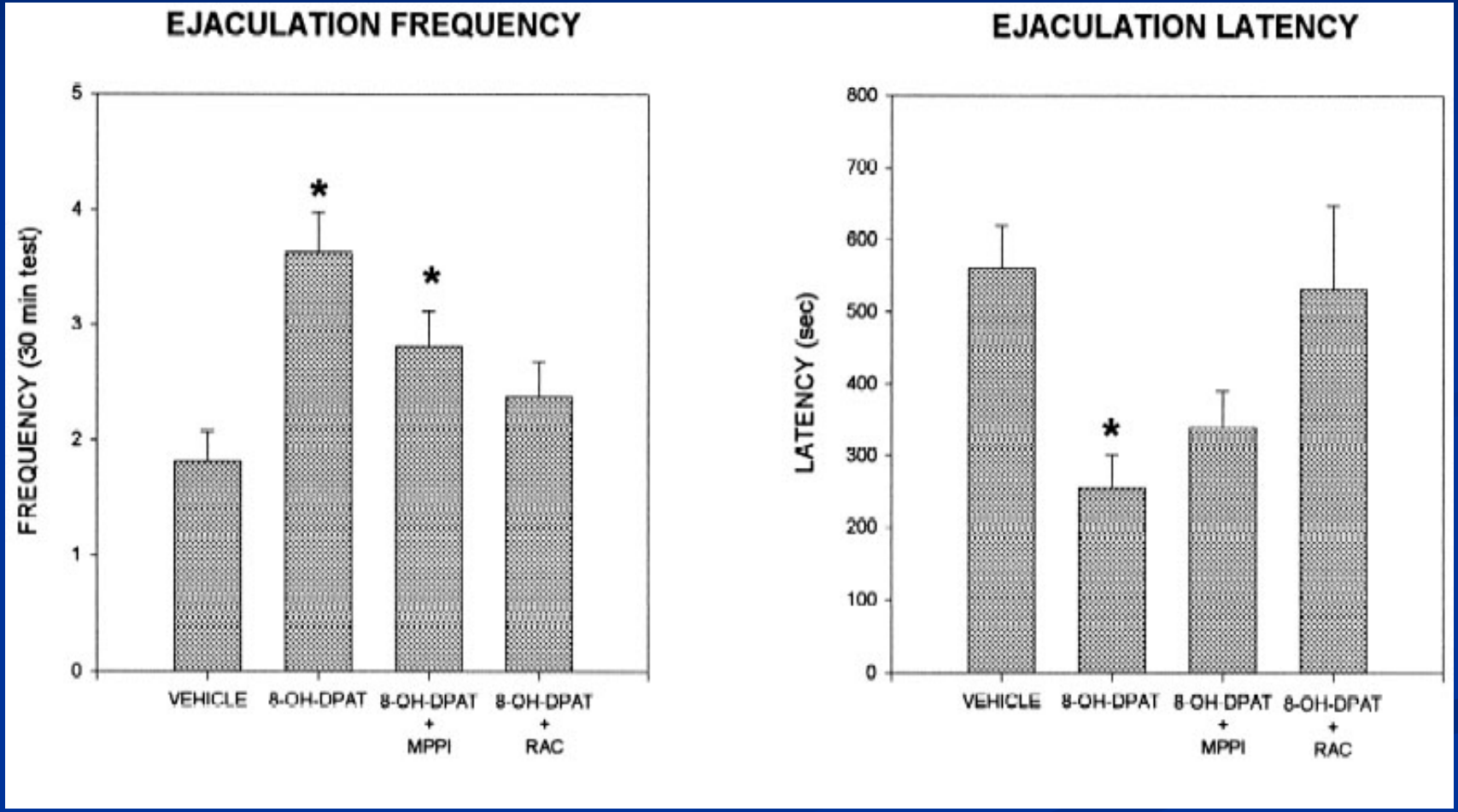
DPAT increased both DA and 5-HT in MPOA Effects not blocked by 5-HT1A antagonist





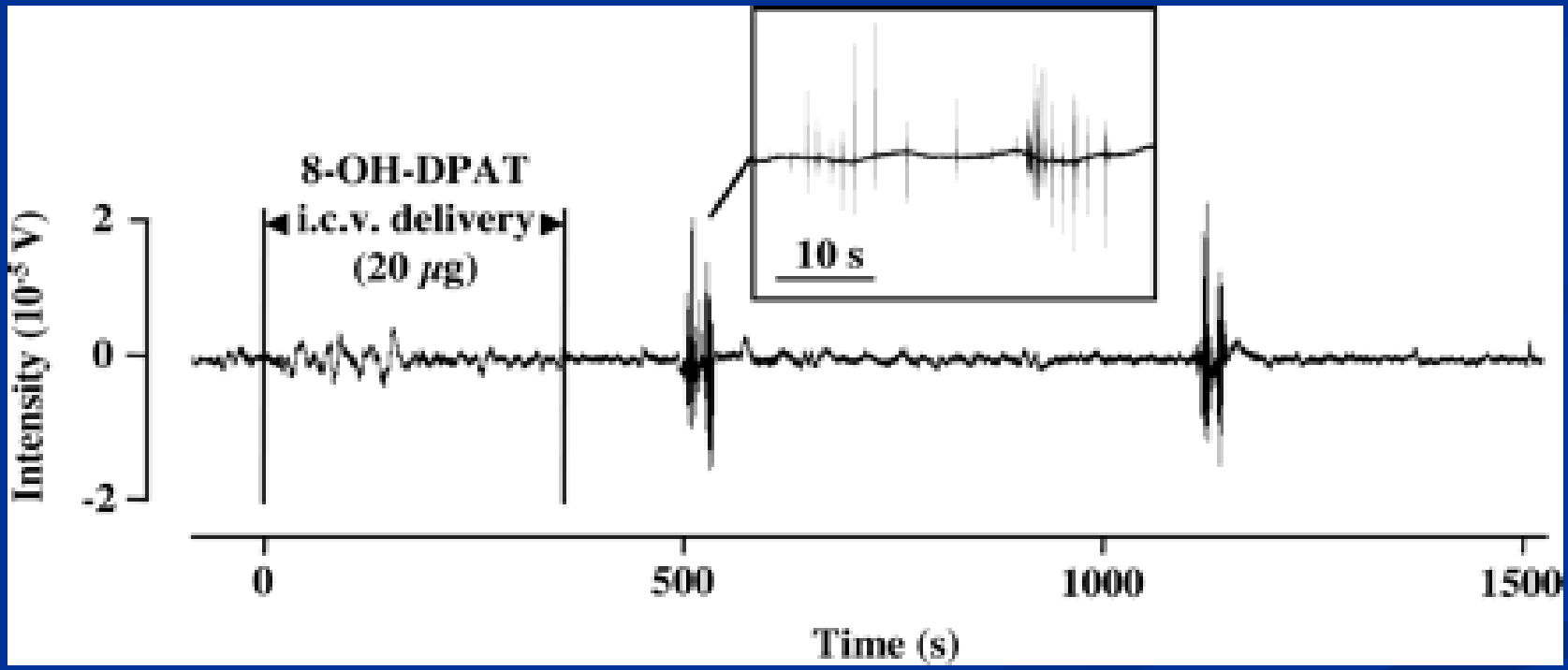
Lorrain et al., 1998

Rat: DPAT in MPOA



Matuszewich et al., 1999

8-OH-DPAT → burst firing of rat bulbospongiosus muscle



Clement et al., 2006

8-OH-DPAT → burst firing of rat bulbospongiosus muscle

Clement et al., 2006 JPET

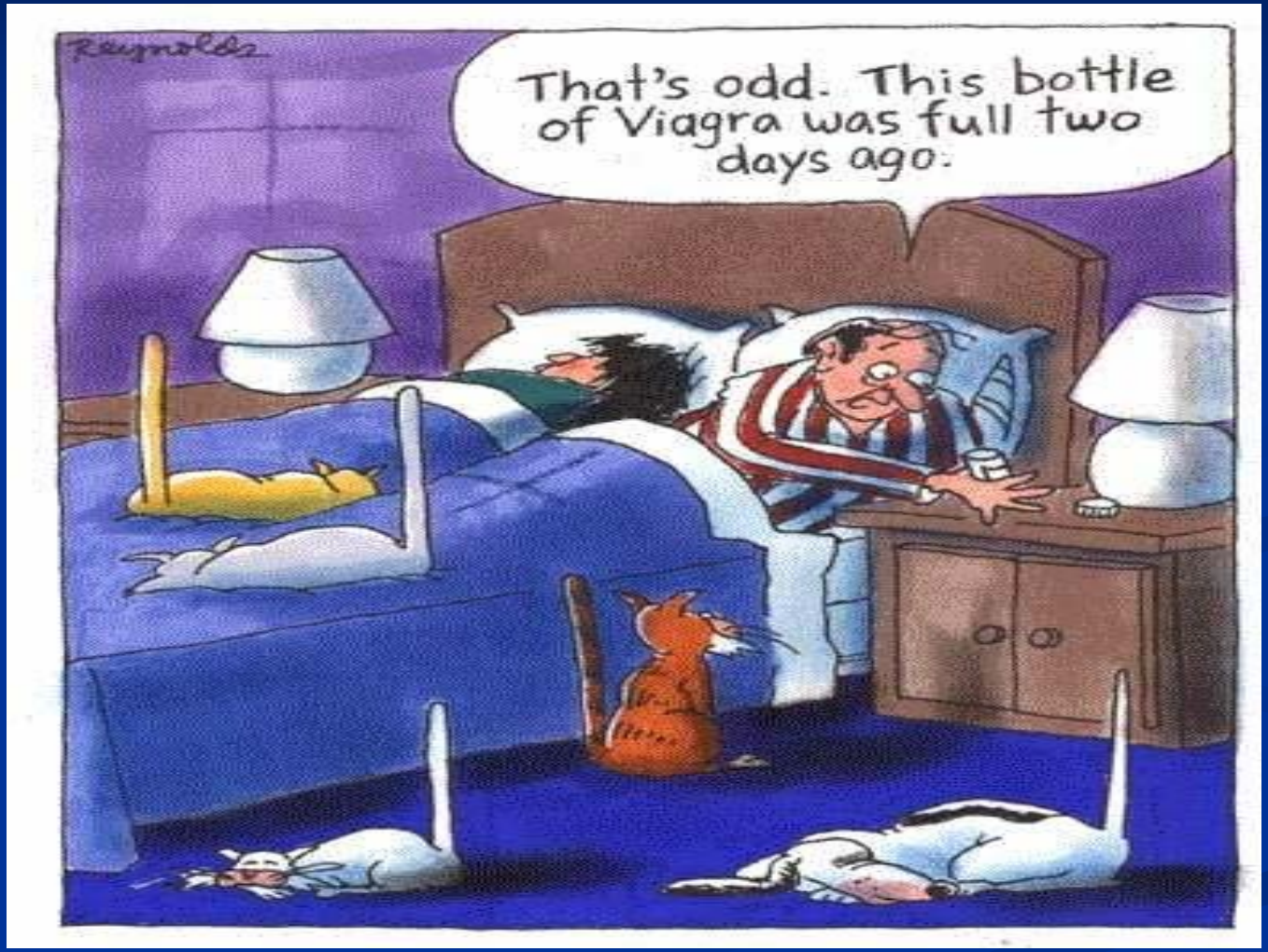
- D2 antagonists blocked DPAT's effect. A 5-HT1A antagonist did not.
- D2 agonist → more clusters of firing than did DPAT

Therefore, at least some of DPAT's effects are mediated by D2 receptors

Effects of SSRIs in humans

- Most SSRIs delay or block ejaculation
- No ejac. delay by some SSRIs
  - Nefazodone: blocks 5-HT2 receptors
  - Mirtazapine: blocks 5-HT2 & α2 autoreceptors
  - Bupropion: inhibits reuptake of DA & NE, also 5-HT1A agonist

How about the little blue pill?



Effects of nitric oxide (NO) in rats

- NO → GC → cGMP → transmitter release: DA in MPOA, oxytocin from PVN.
- NO → GC → cGMP → vasodilation, erection
  - Parasympathetic, anti-sympathetic
  - NOS antagonist increases seminal emission

Effects of NO in men

- Phosphodiesterase 5 (PDE 5) catalyzes the degradation of cGMP.
- Sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) inhibit PDE 5 → increase erection (parasympathetic effect)
- But, they also delay/inhibit ejaculation
  - Dilates smooth muscle in vas deferens & seminal vesicles: can't squeeze fluids
  - Used to treat premature ejac.

Summary

- MPOA & PVN → ejac.
  - D2 receptors, NO, glutamate
  - Oxytocin from PVN
- NO → erection, inhibits ejaculation
- 5-HT inhibits ejac., via 1B, 2C receptors
  - 5-HT1A → ejac., partly via D2 receptors

Summary

- SSRIs inhibit desire, erection, & ejac.
- Less inhibition from SSRIs that also inhibit DA & NE reuptake &/or are 5-HT2 or α2 antagonists.
- SSRIs and NOS inhibitors used to treat premature ejaculation, but can be TOO effective.

Thanks!

- My lab, especially Dr. Juan Dominguez
- The rats and patients who provided the information
- NIMH grants R01 MH 40826, K02 01714
- You for your attention!