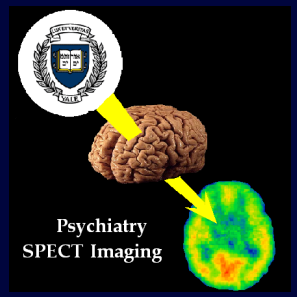
Neuroimaging of sex differences in structure, function, and chemistry in the healthy brain and implications for addiction.

Kelly P. Cosgrove, PhD
Assistant Professor, Psychiatry
Yale University School of Medicine



Department of Veterans Affairs

Outline

- **Introduction**
- **Sex differences in brain structure**
- **Sex differences in brain function**
- **Sex differences in brain chemistry**
- **Implications for addiction**
- **Where do we go from here?**

Why Study Sex Differences?

- **Sex differences exist in a variety of normal behaviors such as cognition and emotion.**
- **Sex differences in incidence, rate, and course of psychiatric diseases such as schizophrenia, depression, suicide, anxiety, and drug addiction.**

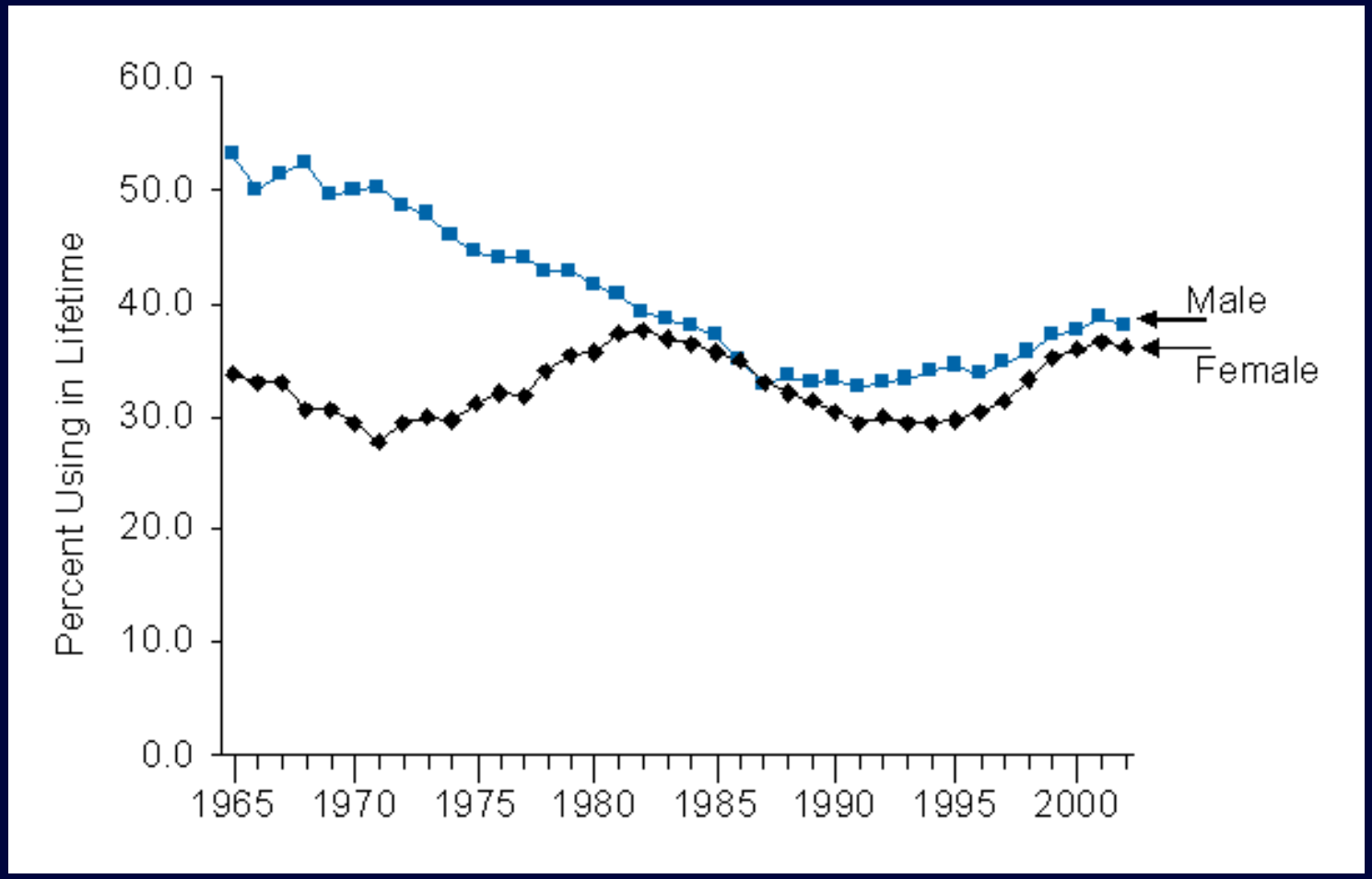
"Sex does matter. It matters in ways that we did not expect. Undoubtedly, it matters in ways that we have not yet begun to imagine." National Academy of Sciences report

Prevalence of alcohol/drug abuse by sex

	Adults (18+)		Adolescents (12-17)	
Current Use	Males	Females	Males	Females
Illicit:	4.1	3.0*	5.4	6.1*
Alcohol:	62.6	46.6*	17.4	18.3
Cigarette:	30.3	23.8*	12.2	12.5
Abuse				
Illicit:	0.6	0.3*	0.8	1.2*
Alcohol:	6.4	2.5*	3.8	4.1*
Dependence				
Illicit:	0.8	0.6*	0.7	0.8
Alcohol:	4.6	2.3*	2.0	2.1
Cigarette:	12.9	10.3*	3.1	3.0

Lynch, 2008

Prevalence of smoking by sex



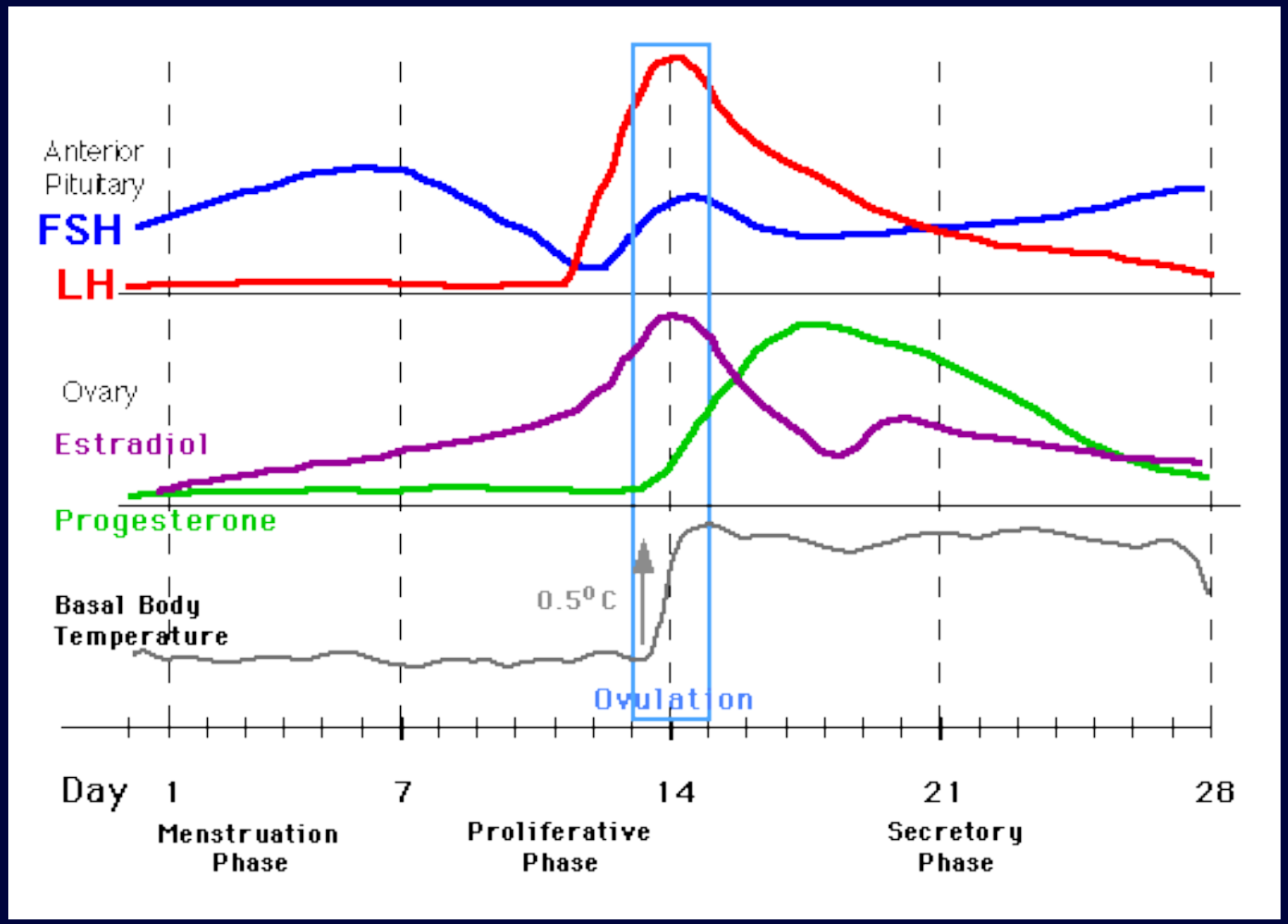
Results from the 2002 National Survey on Drug Use and Health (NSDUH)

Why Study Sex Differences in the Brain?

- **These differences may be accounted for by variations in underlying brain structure, function, and chemistry.**
- **Sexual differentiation of the brain begins during the second trimester of gestation and continues through puberty.**
- **Special consideration for impact of drugs during pregnancy.**

Menstrual Cycle

Follicular Luteal



http://embryology.med.unsw.edu.au/WWWHuman/MCycle/DnCMen.htm

Outline

- Introduction
- Sex differences in brain structure
- Sex differences in brain function
- Sex differences in brain chemistry
- Implications for addiction
- Where do we go from here?

Brain Structure

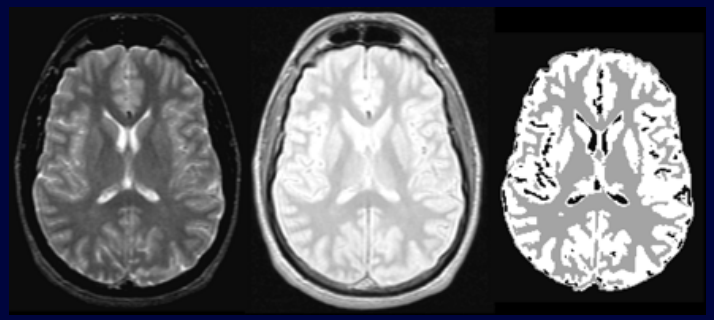
How we measure brain structure:

- **Computed Tomography (CT)**
- **Diffusion Tensor Imaging (DTI)**
- **Magnetic Resonance Imaging (MRI)**

Sex differences in adult brain volume

- **Men have larger brain volumes than women, approximately 1,260 cc for men and 1,130 for women.**

- **Men have greater CSF volume and white matter, while women have a greater percentage of gray matter.**



Segmentation process

(Gur et al., J Neuroscience, 1999)

Brain volume loss in normal aging differs by sex

- **MEN: whole brain, frontal and temporal lobe loss increases with age**
- **WOMEN: hippocampus and parietal lobe loss increases with age**
- **MEN: Steeper decline in gray matter loss**
- ***Relationship with sex steroid hormones, e.g., estrogen, estrogen replacement therapies?***

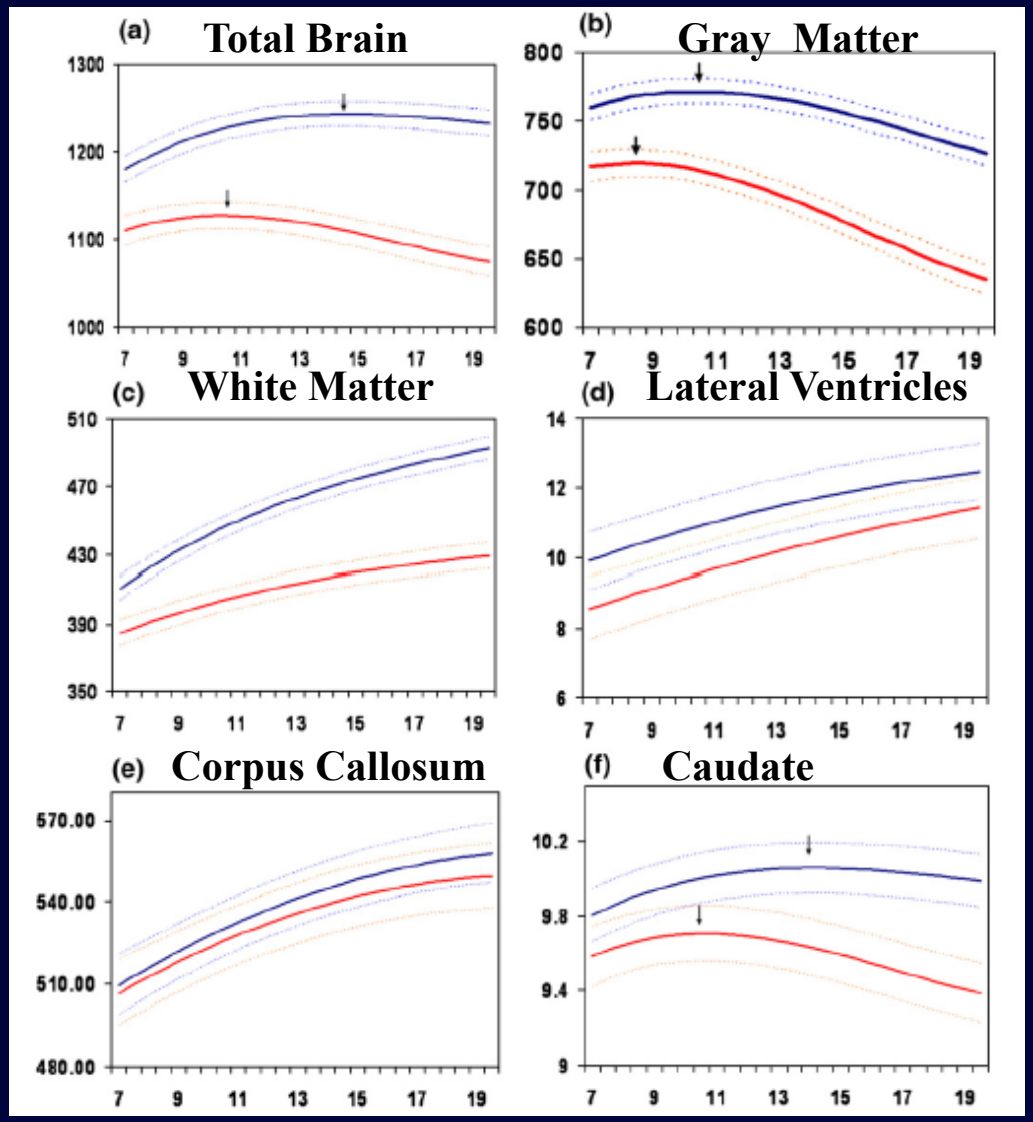
Brain size trajectories in children differ by sex

- **Boys total brain volume peaks at 14.5 years, in girls at 10.5 years.**
- **Males have a steeper rate of increase in WM in adolescence than females.**
- **Cortical and subcortical GM are inverted U-shaped and peak in females 1-2 years earlier.**

829 scans from 387 subjects aged 3-27

Lenroot…..Giedd, 2007, NeuroImage

Trajectories differ by sex



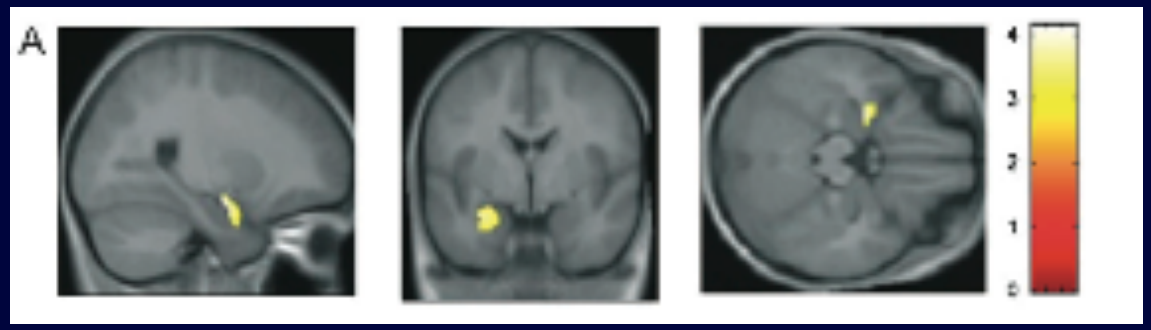
Blue = boys
Red = girls

Implications for developmental neuropsychiatry where disorders differ by age of onset, prevalence and symptoms by sex.

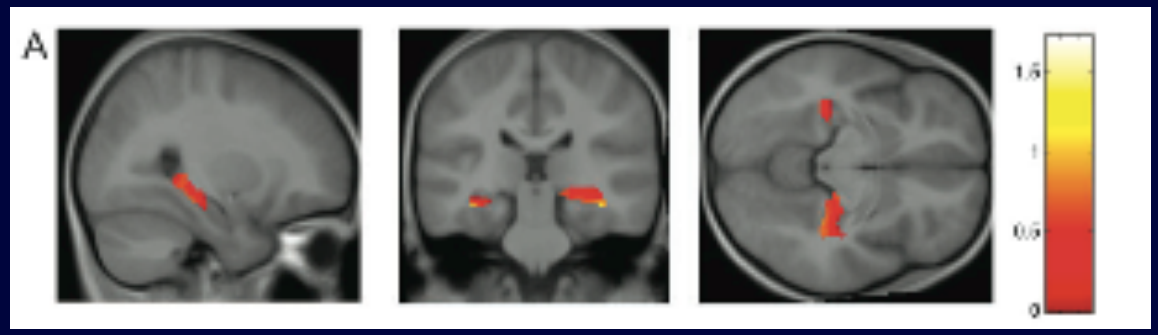
829 scans from 387 subjects aged 3-27

Lenroot…..Giedd, 2007, NeuroImage

Regional volume sex differences



Amygdala M>F



Hippocampus F>M

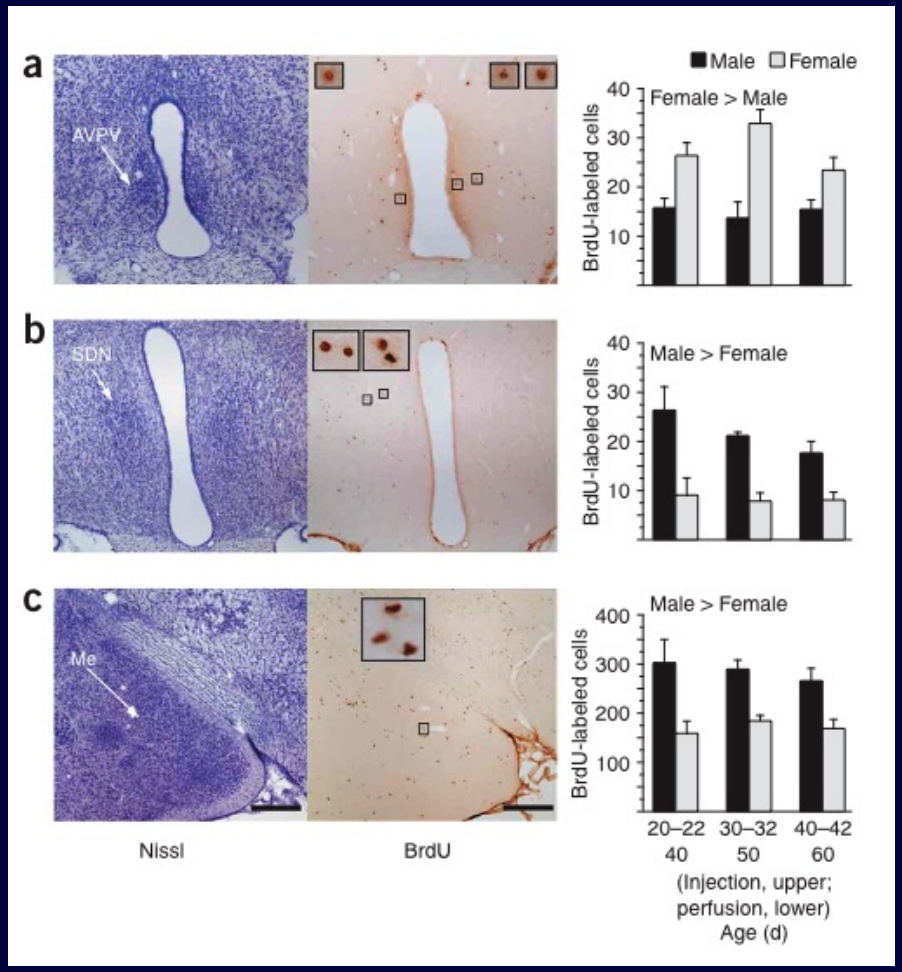
Aged 8-15

(Neufang et al., Cerebral Cortex, 2009)

Testosterone = positive association with diencephalon in boys
Estrogen = positive association with hippocampus in girls

Do differing developmental patterns in brain growth impact the course of psychiatric disorders?

Volume differences in adults may be driven by cell production in puberty



AVPV, anteroventral periventricular nucleus of the hypothalamus

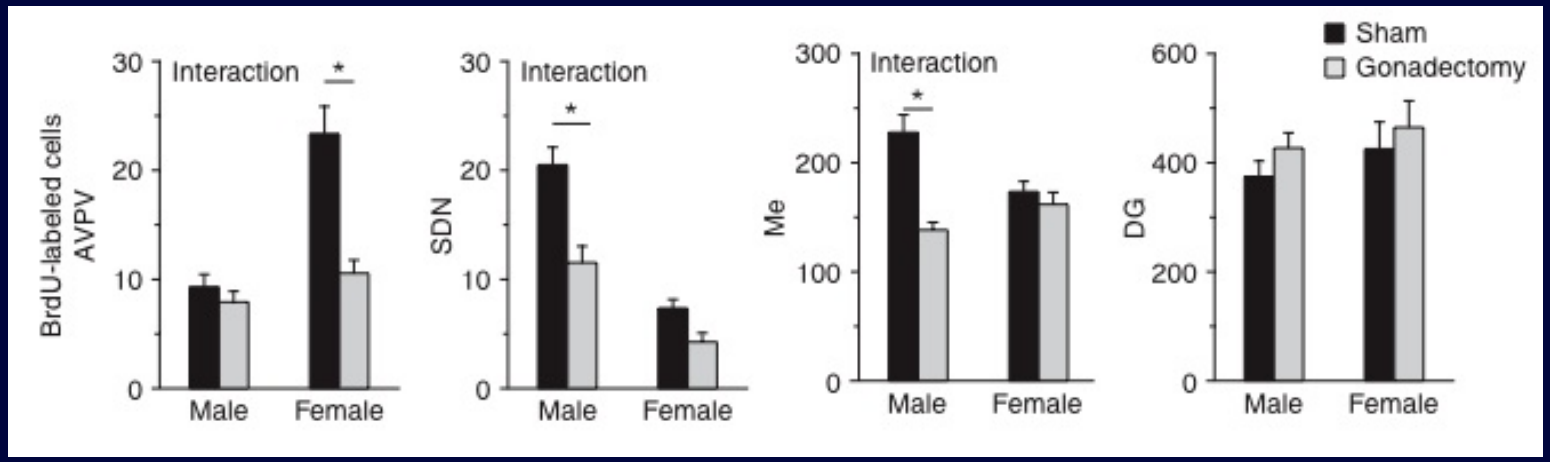
SDN, sexually dimorphic nucleus of the preoptic area

Me, medial amygdala

Ahmed et al., 2008 Nat Neuroscience

Cell production in these areas is driven by sex hormones

Gonadectomy abolishes the sex difference in cell numbers.



Ahmed et al., 2008 Nat Neuroscience

Outline

- Introduction
- Sex differences in brain structure
- Sex differences in brain function
- Sex differences in brain chemistry
- Implications for addiction
- Where do we go from here?

Brain Function

How we measure brain function:

Cerebral Blood Flow (CBF)

Cerebral Metabolic Rate of Glucose Utilization (CMRglu)

- **[^{18}F]FDG and PET - metabolism**
- **[^{15}O]H_2O and PET – blood flow**
- **[^{99m}Tc]HMPAO and SPECT – both**

fMRI and BOLD

Sex differences in brain perfusion

- **Cerebral Blood Flow (CBF): radiotracers follow the blood flow in brain**

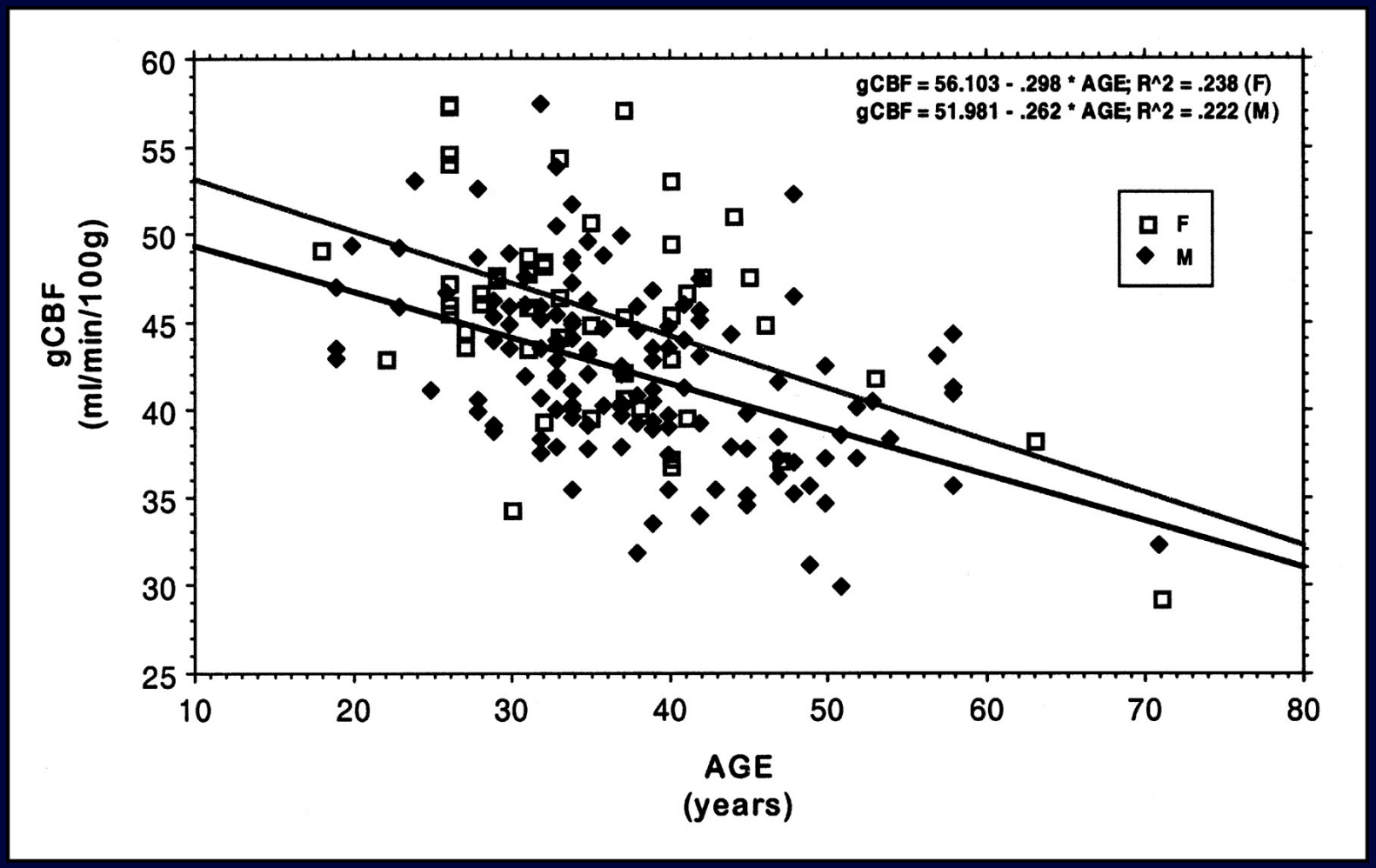
- **Women consistently have higher CBF than men.**

- **Regional differences:**

  F>M: R parietal cortex, R cerebellum

  M>F: cerebellum, L anterior temporal and orbital frontal cortex

Women have higher CBF than men



(Slosman et al., J Nuclear Medicine, 2001)

N=187

No sex difference in brain metabolism

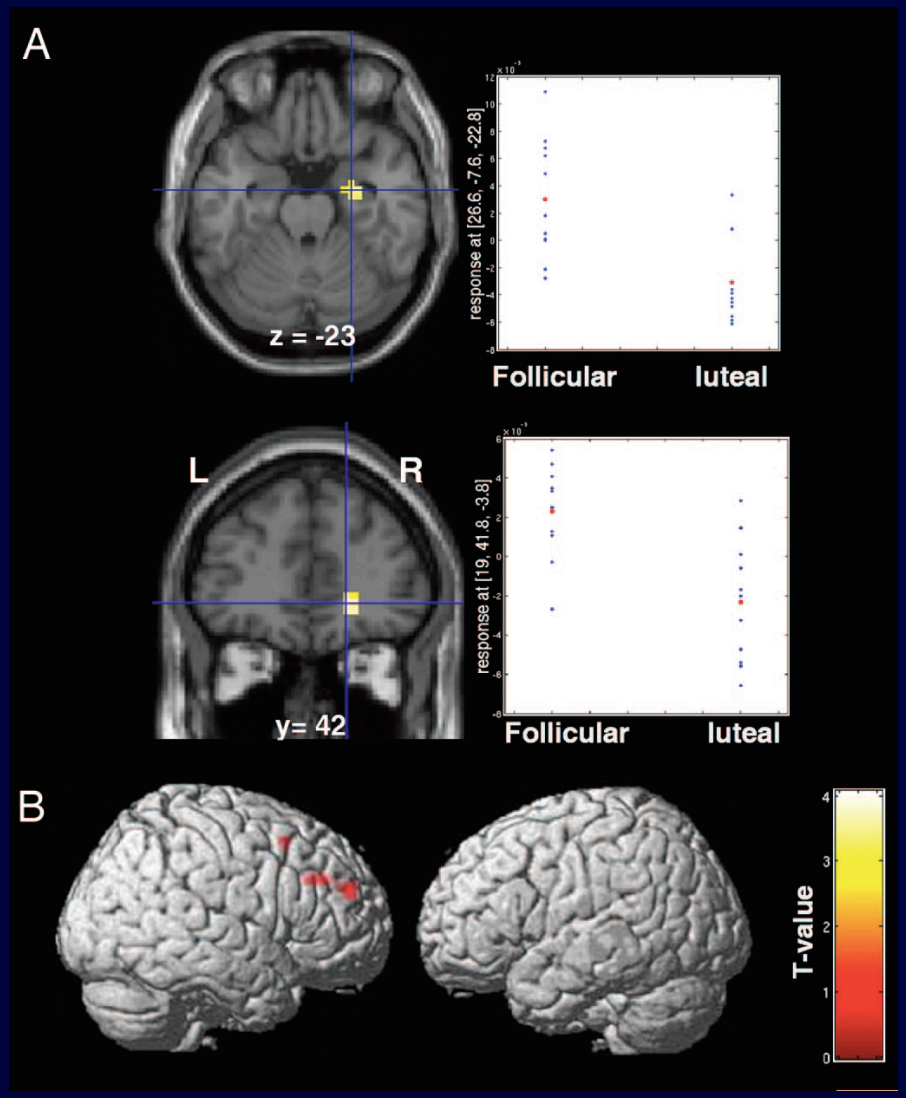
- **Initial studies found increased CMRglu in women.**

- **Glucose metabolism is inversely correlated with brain size, which would predict W>M. If this taken into account, there is no sex difference.**

Implications

- **Increased CBF in women = better distribution of drugs in the brain.**
- **Estrogen increases CBF – may underlie some of the sex differences.**
- **May contribute to increased subjective effects in women to drugs of abuse when estrogen is high, e.g., follicular phase.**

Cycle phase modulates reward in women



Dreher et al., 2007, PNAS

F>L in R amygdala

F>L in orbitofrontal

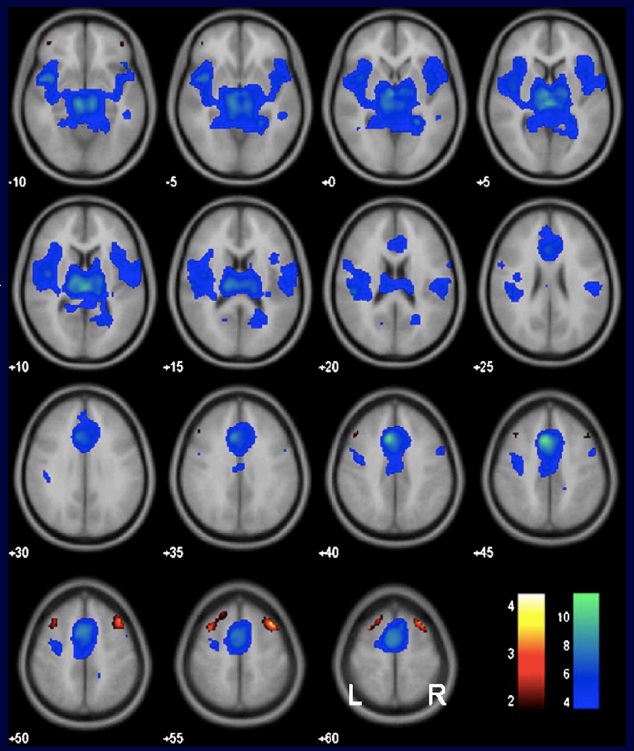
L>F in R dorsolateral prefrontal cortex

Implication: Women have greater subjective response to drugs during F vs. L phase?

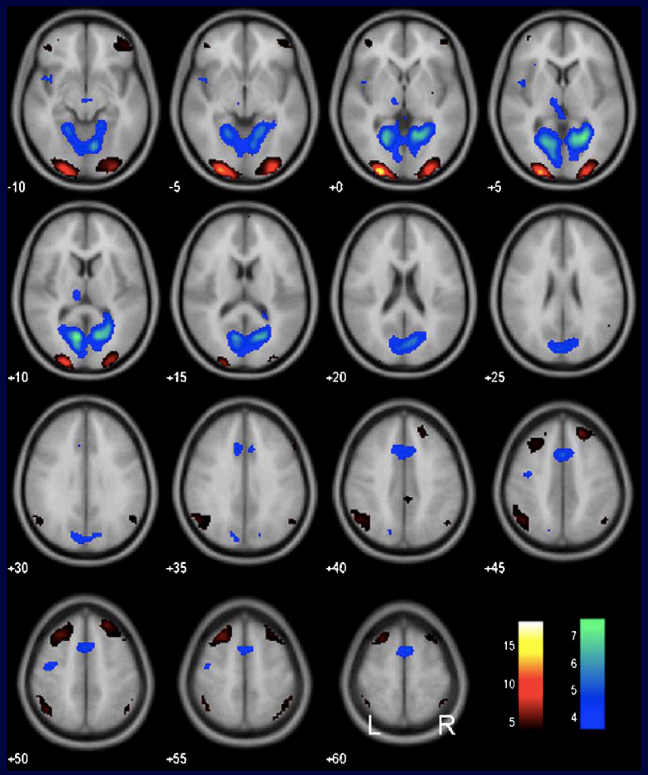
Men may be less efficient at inhibitory control

Greater activation in men vs. women during stop signal inhibition with equal performance – they use more "neural resources".

Women



Men



Implication: greater impulsivity in men vs. women?

Li et al., 2006

Outline

- Introduction
- Sex differences in brain structure
- Sex differences in brain function
- Sex differences in brain chemistry
- Implications for addiction
- Where do we go from here?

Brain Chemistry

PET and SPECT:

- **Low concentrations (nM – pM)**
- **Serotonin 1A, 2A, 1B, SERT; dopamine D1, D2, DAT; $GABA_A$-benzodiazepine; β_2-nAChR; mu- and kappa-opioid, cannabinoid, *estrogen receptor* , mGluR5**
- **Dopamine and serotonin**

PET & SPECT

Limitations:

Radiation exposure

In research – only age 18 and up

Limited spatial and temporal resolution vs MRI and fMRI

Expensive!!

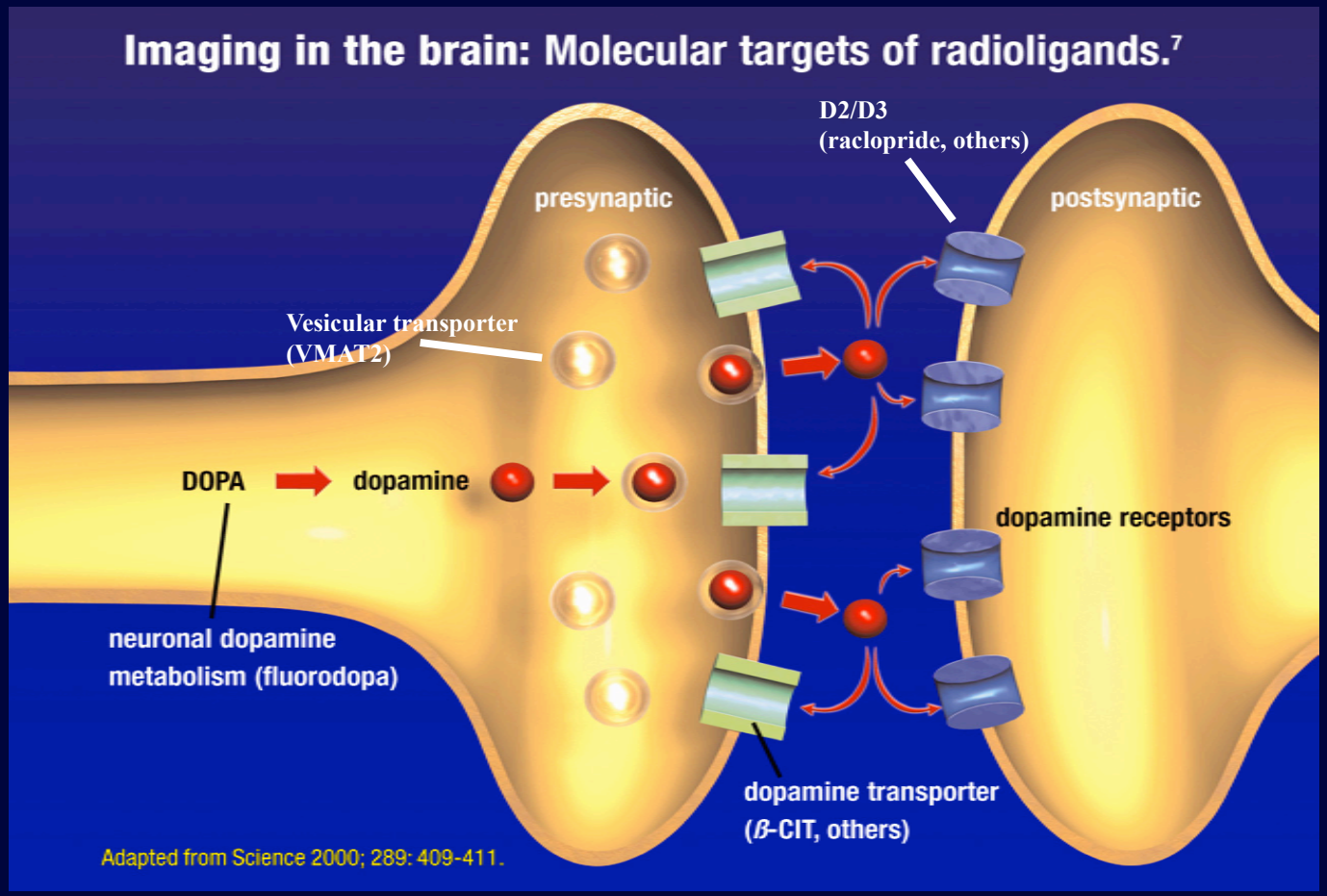
Brain Chemistry

MRS:

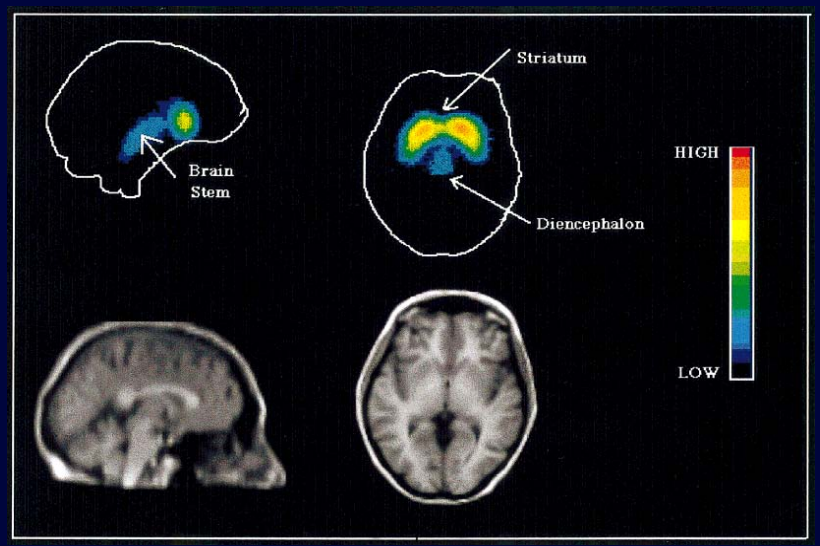
- **High concentrations (molar range)**
- **GABA, glutamate, glutamine, creatine, phosphocreatine, N-acetylaspartate**
- **Markers of neuronal integrity**

Dopamine

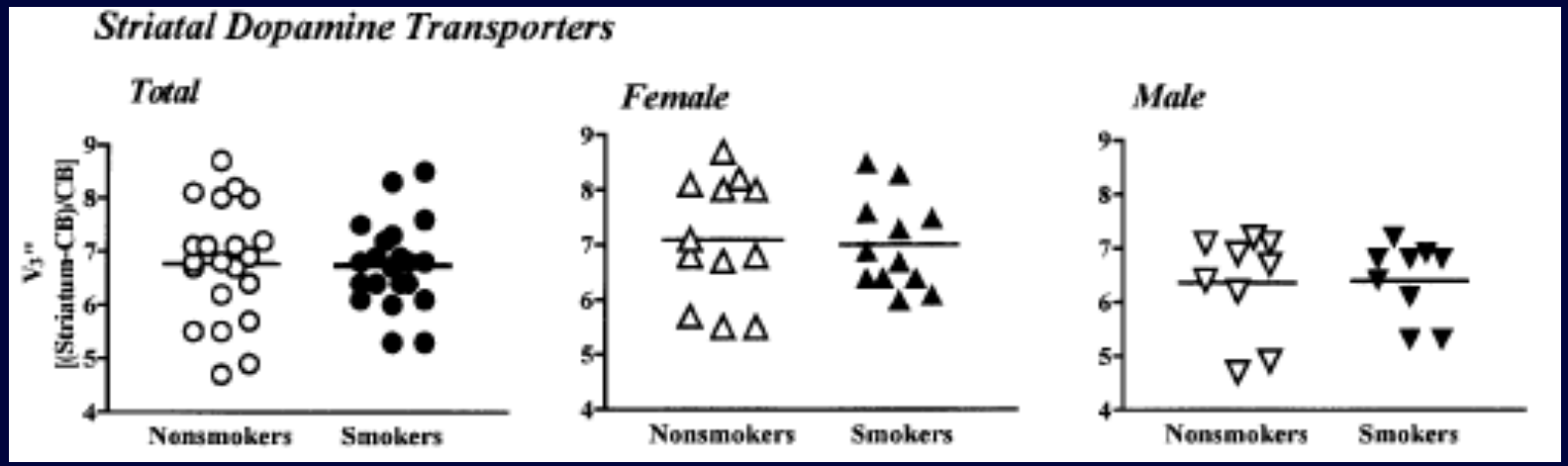
Important in reward processes, neuropsychiatric disorders, rewarding effects of all drugs of abuse.



Women have higher DAT than men

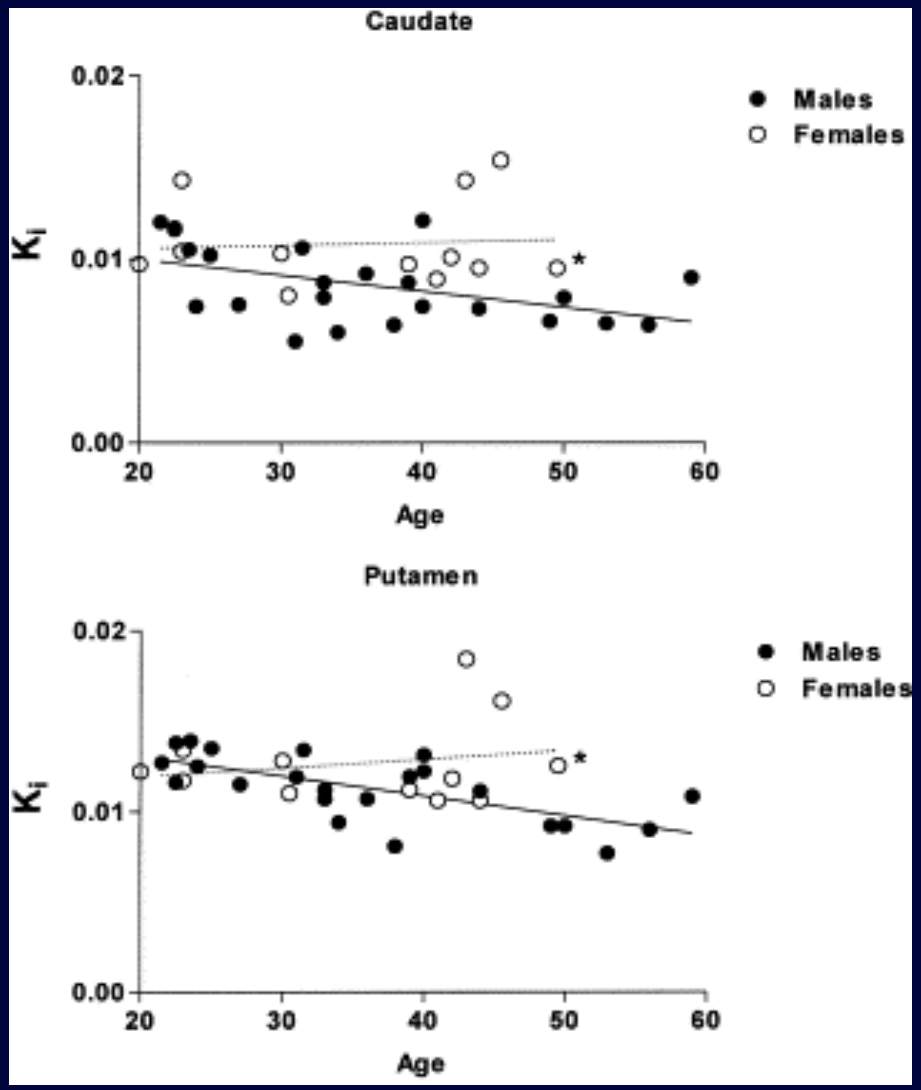


DAT not regulated by the menstrual cycle ***(Best et al., 2005)*****.**



(Staley et al., Synapse, 2001 also Lavalaye et al., 2000; Mozley et al., 2001)

Sex differences in DA synthesis

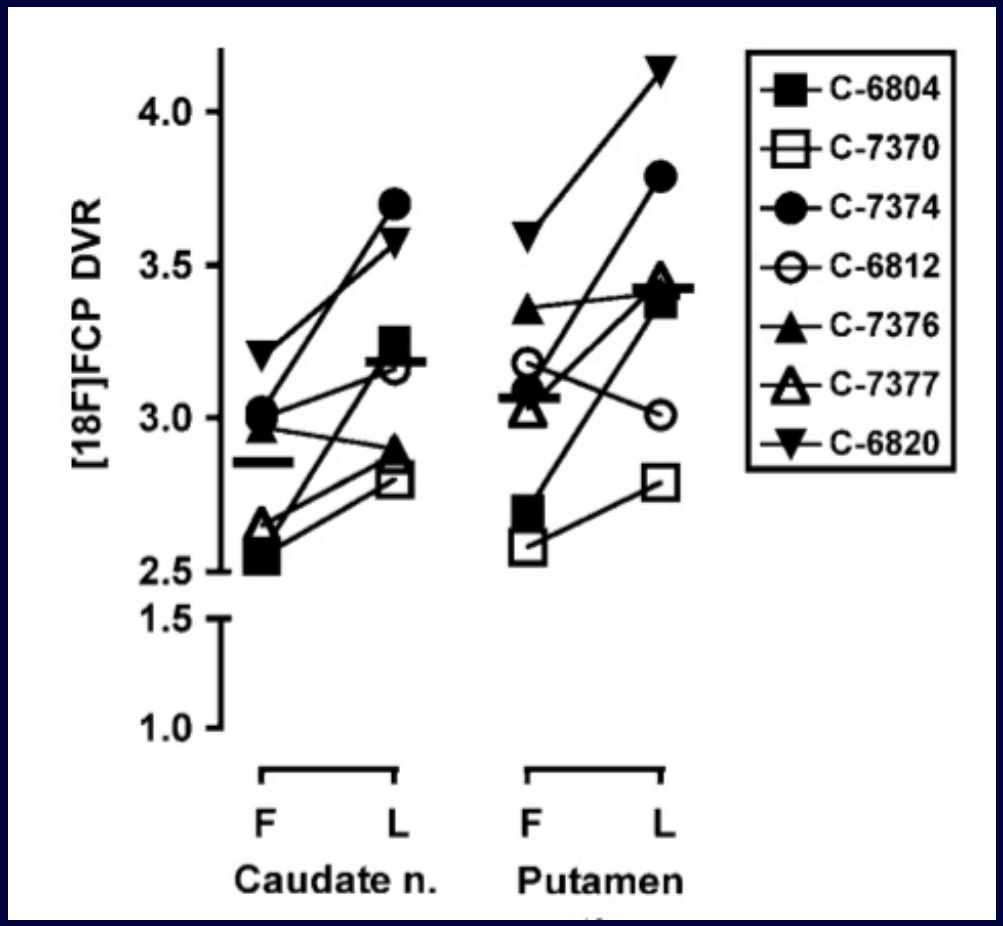


Higher striatal DA uptake in premenopausal women vs. men, indicating higher presynaptic DA synthesis capacity, enhanced DA turnover in women.

DA uptake decreased with age in men.

Laakso et al., Biological Psychiatry, 2002

No sex difference in dopamine receptor (D2/3) numbers in humans or NHPs



Menstrual cycle may regulate the receptor in nonhuman primates.

OR

Could be due to synaptic dopamine levels changing over the cycle.

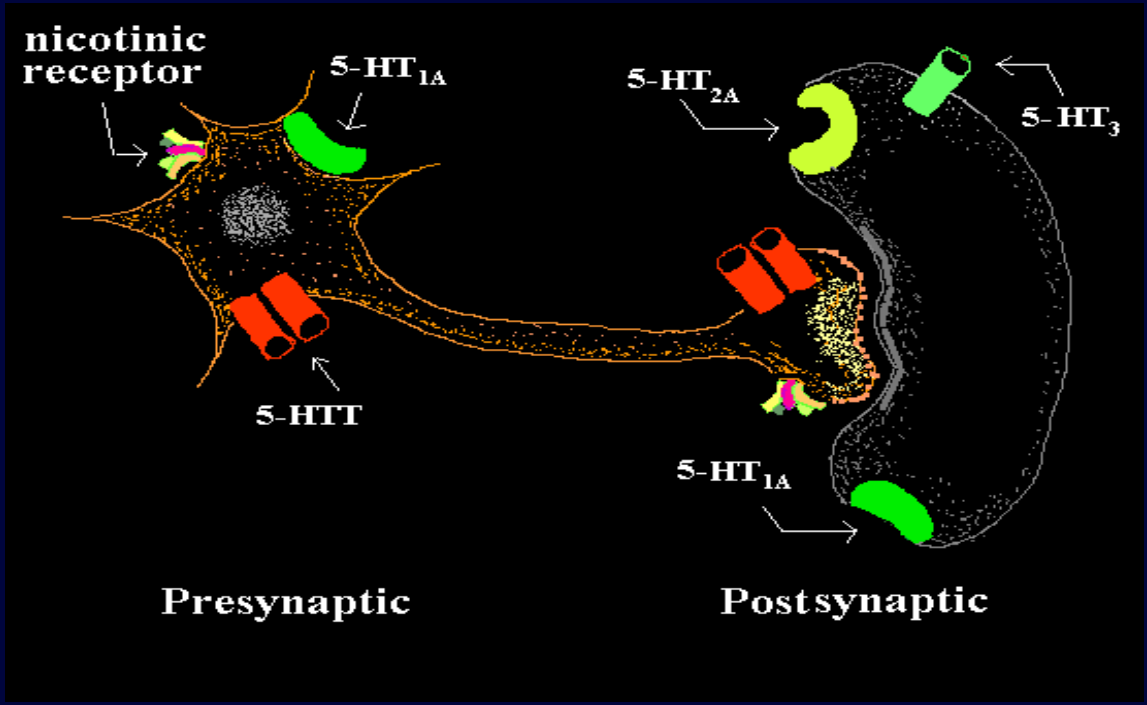
Czoty et al., 2009 NPP

Implications of sex differences in DA

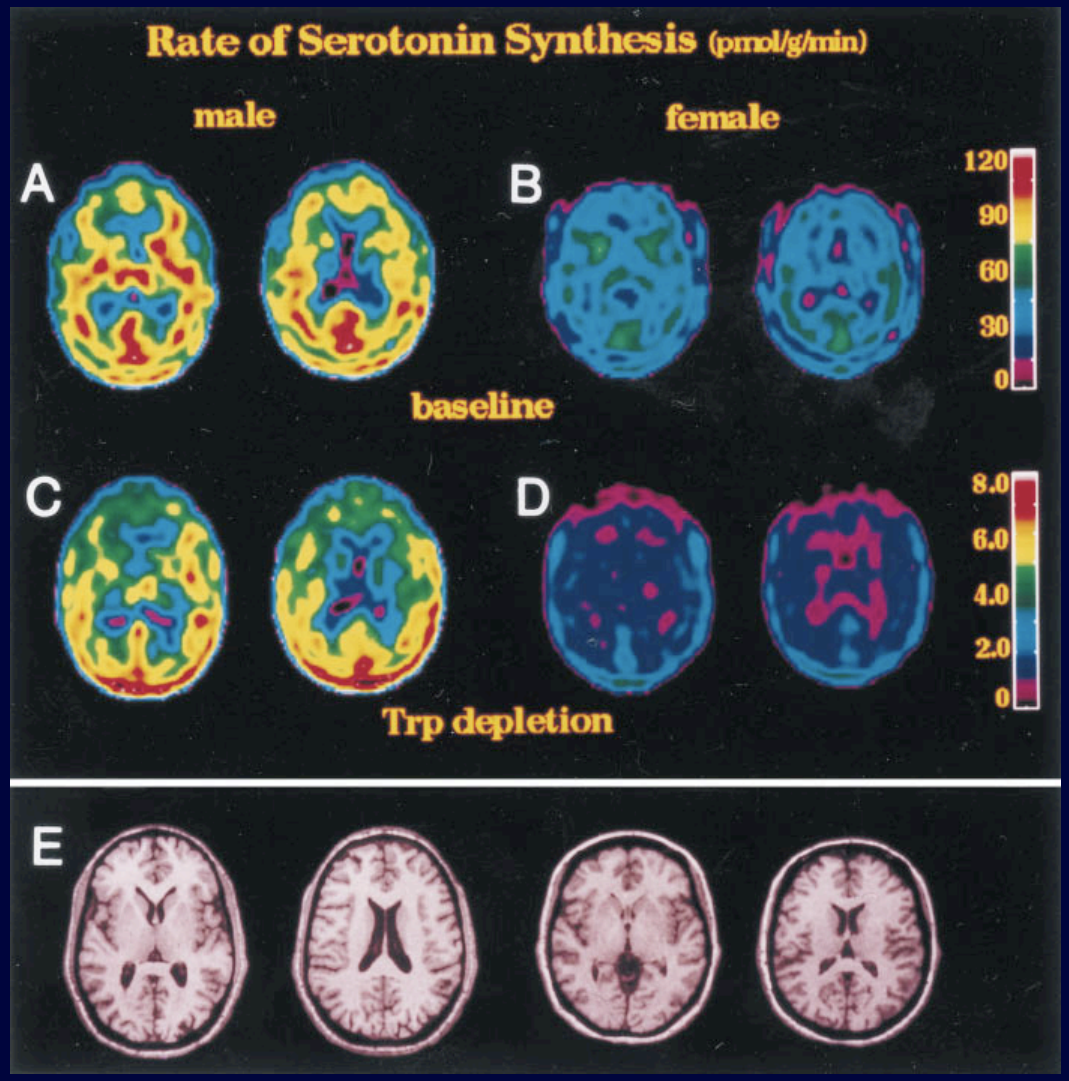
- **Increased estrogen is associated with increased dopamine and may be protective in women.**
- **Changes in estrogen over the menstrual cycle and life span may coincide with increased/decreased risk times for developing addiction and other disorders.**
- **Dopamine related disorders, e.g., OCD, Tourette's syndrome, Parkinson's Disease, Schizophrenia, are all more prevalent in men.**

Serotonin

Coordinates complex sensory and motor patterns during many behavioral states. Implicated in pathology of mood, sleep, eating and substance disorders.



Men have faster (52%) serotonin synthesis



A reduced capacity for serotonin synthesis in women may underlie a vulnerability to depression.

Nishizawa et al., 1997, PNAS

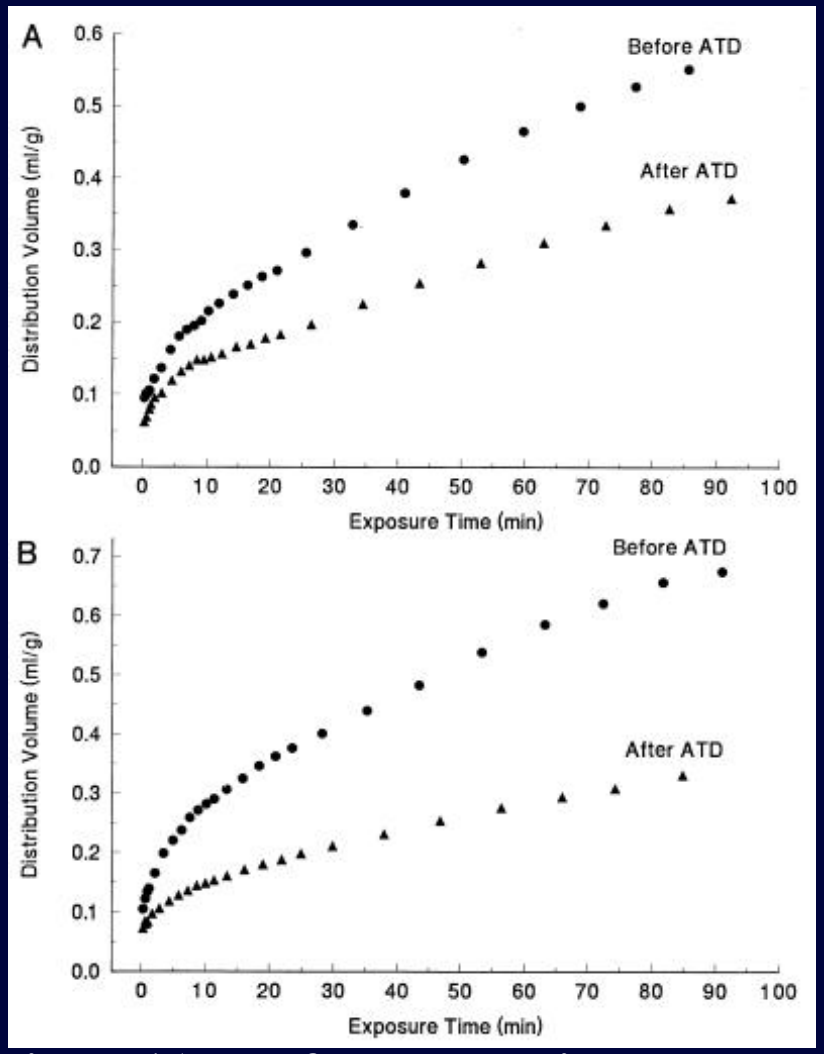
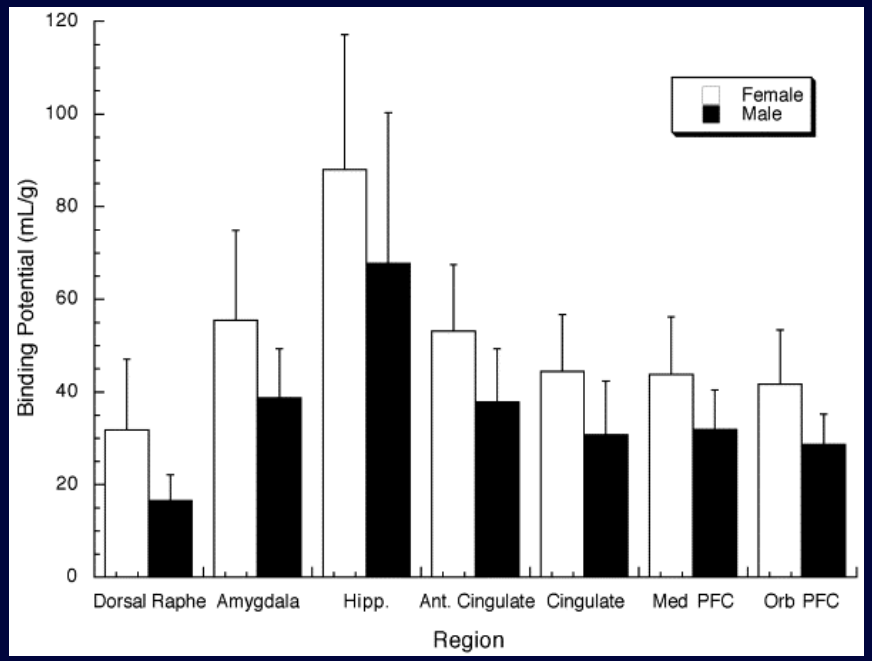
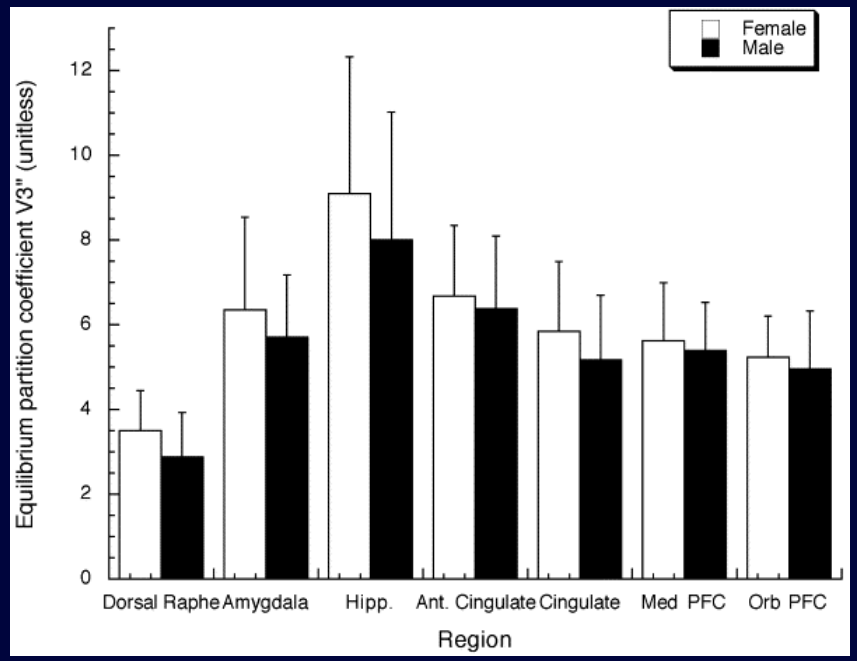


Figure 1A set of representative plots exemplifying the tissue distribution volume (ml/g) in the frontal cortex of a male (*A) and female (B) subjects as a function of the exposure time θ [$\theta = \int_0^T C_p^*(t)\, dt / C_p^*(T)$; min]. The upper curves in A and B were obtained at baseline, and the lower curves were obtained after tryptophan depletion.*

Women have higher 5-HT$_{1A}$ receptor availability than men

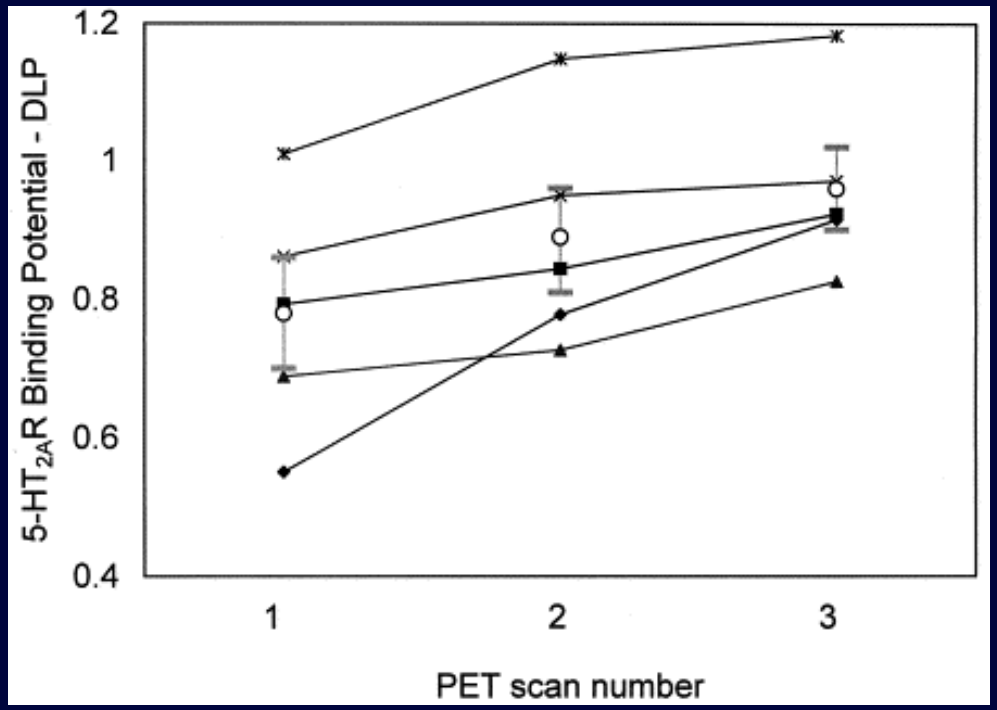




Parsey et al., Brain Research, 2002

No difference when measure women in days 3-10 of cycle ***(Stein et al., 2008).***

Sex hormones influence 5-HT$_{2A}$ receptor availability



1 – baseline
2 – estradiol *(8-14 wk)*
3 – estradiol + progesterone *(2-6 wk)*

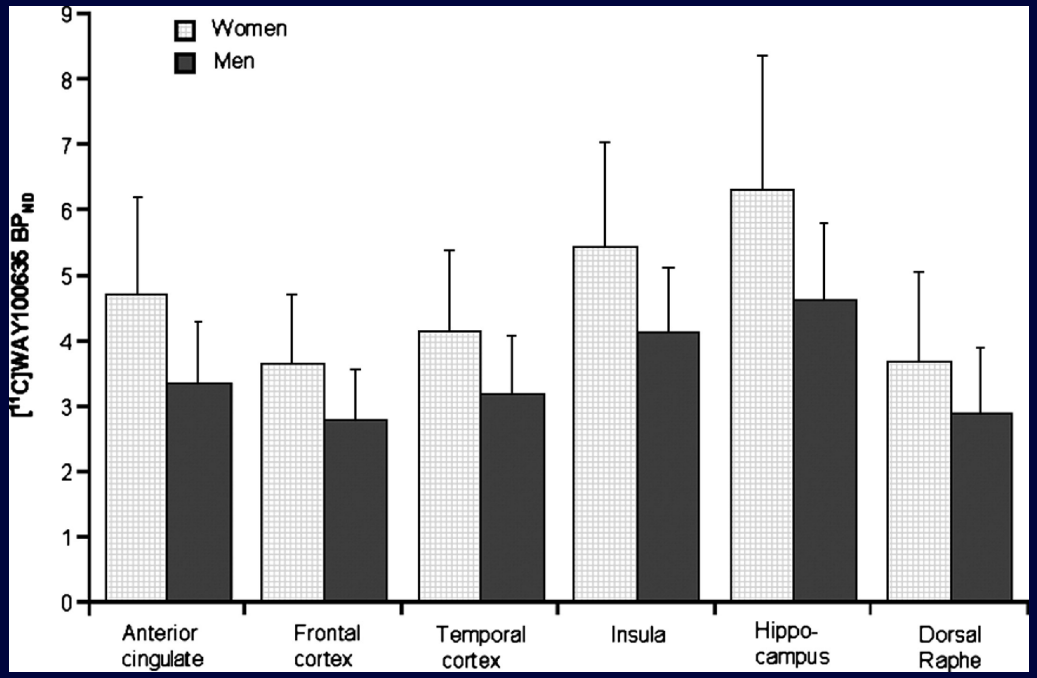
(Moses et al., Biological Psychiatry, 2000)

- **Estrogen replacement therapy in PM women was associated with increased 5-HT$_{2A}$ receptor availability in prefrontal cortex *(Kugaya et al., 2003)*.**
- **No difference in 5HT-$_{2A}$ receptors in men vs. women *(Lewis et al., 1999; Adams et al., 2004)*.**

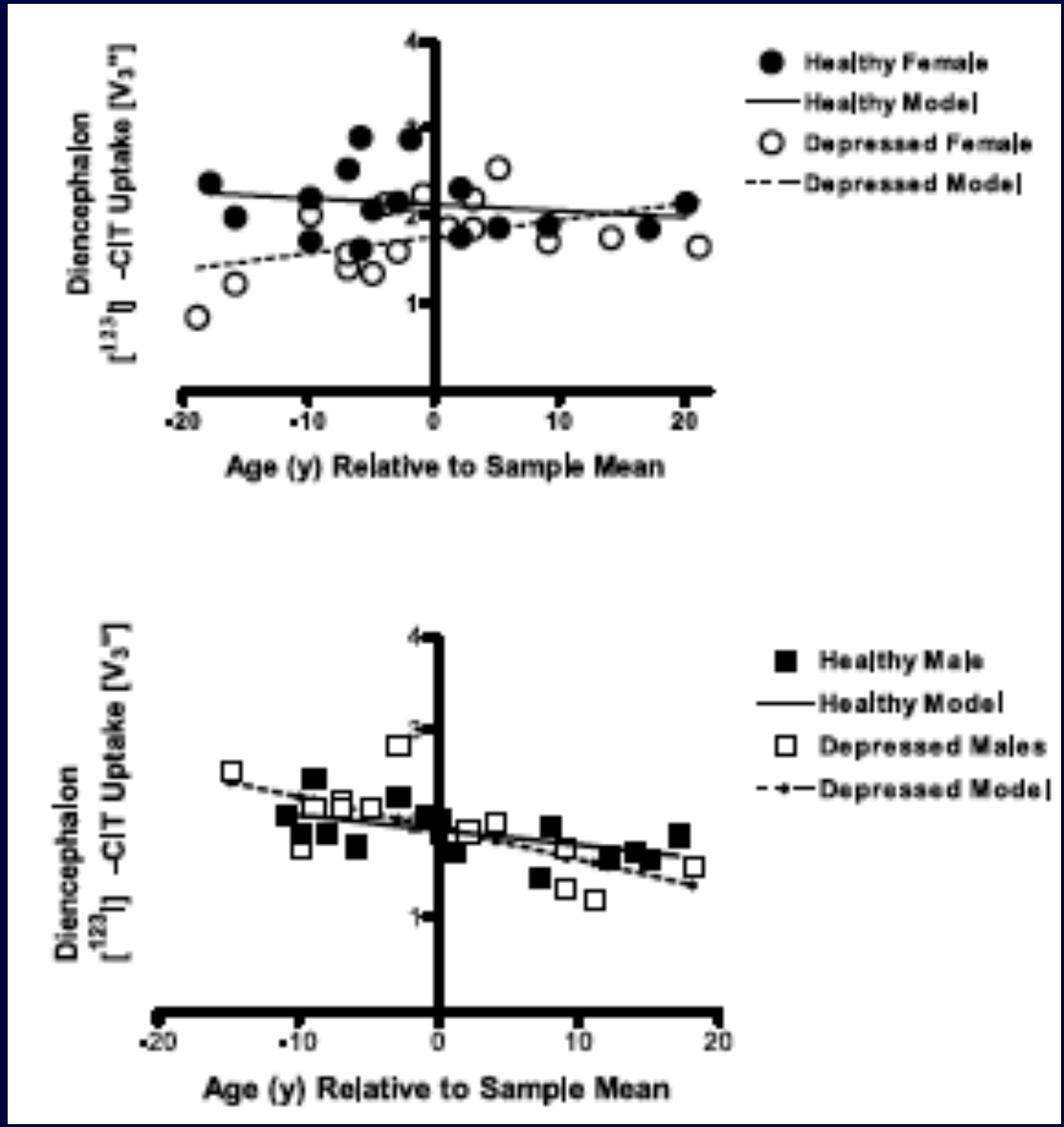
Women have higher SERT than men

W>M in SERT availability in diencephalon and brainstem measured with [^{123}I]ß-CIT SPECT.
(Staley et al., Synapse, 2001)

W>M in SERT with selective PET tracer.
(Jovanovic et al., 2008)



Depressed W<M in SERT availability (22% vs 1%) in diencephalon



(Staley et al., Biol Psych, 2006)

Implications of SERT

- **If women have higher SERT but lower 5HT synthesis? than men.**
- **Dysregulation of this in younger women may explain a mechanism underlying depression in women.**
- **Young women are more responsive to SSRIs vs tricyclics compared to older women and men *(Kornstein et al., 2000).***
- **Women receiving estrogen – accelerated response to sertraline *(Rasgon et al., 2007).***

Outline

- **Introduction**
- **Sex differences in brain structure**
- **Sex differences in brain function**
- **Sex differences in brain chemistry**
- **Implications for addiction**
- **Where do we go from here?**

Sex differences in drug addiction

- **The majority of studies on sex differences in drug addiction are preclinical.**

- **To date studies examining sex differences using brain imaging technology in drug addiction have focused on cocaine and alcohol dependence and tobacco smoking.**

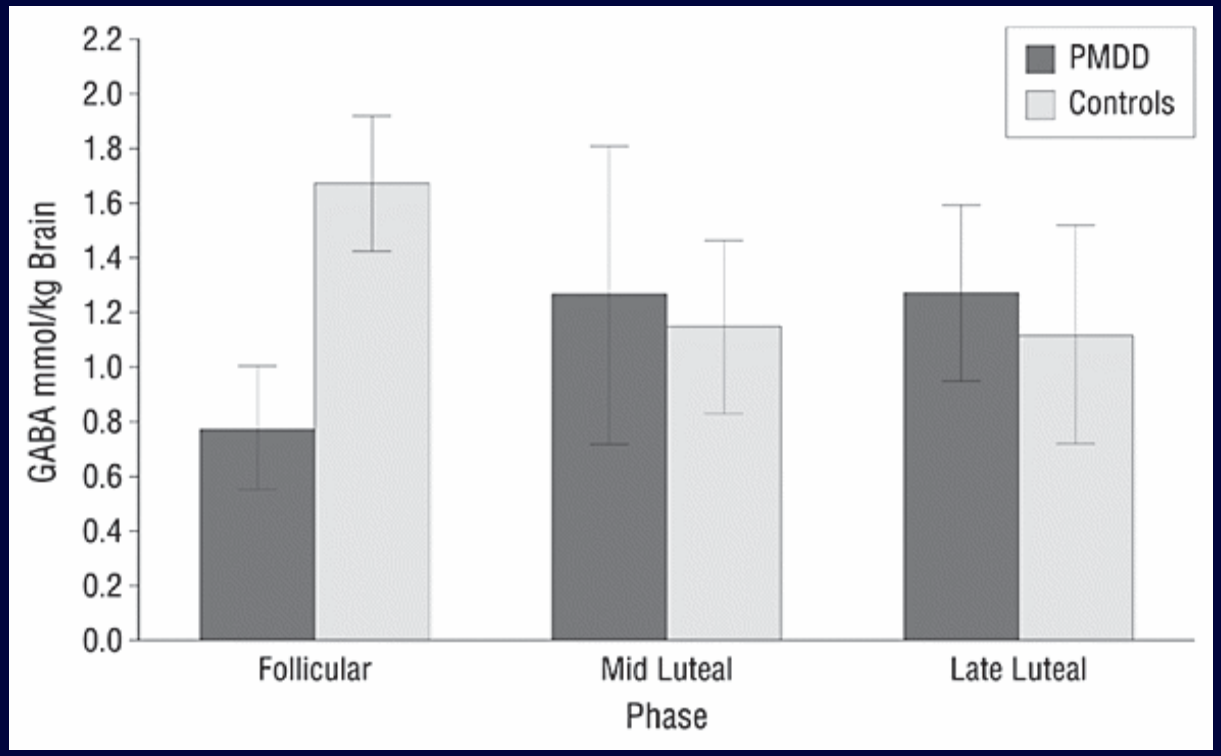
Sex difference in tobacco smoking

- **Limited research on sex differences in the brains of tobacco smokers.**

- **However, tobacco smoking in both men and women is associated with significant brain changes and should be considered due to high comorbidity with other drug abuse.**

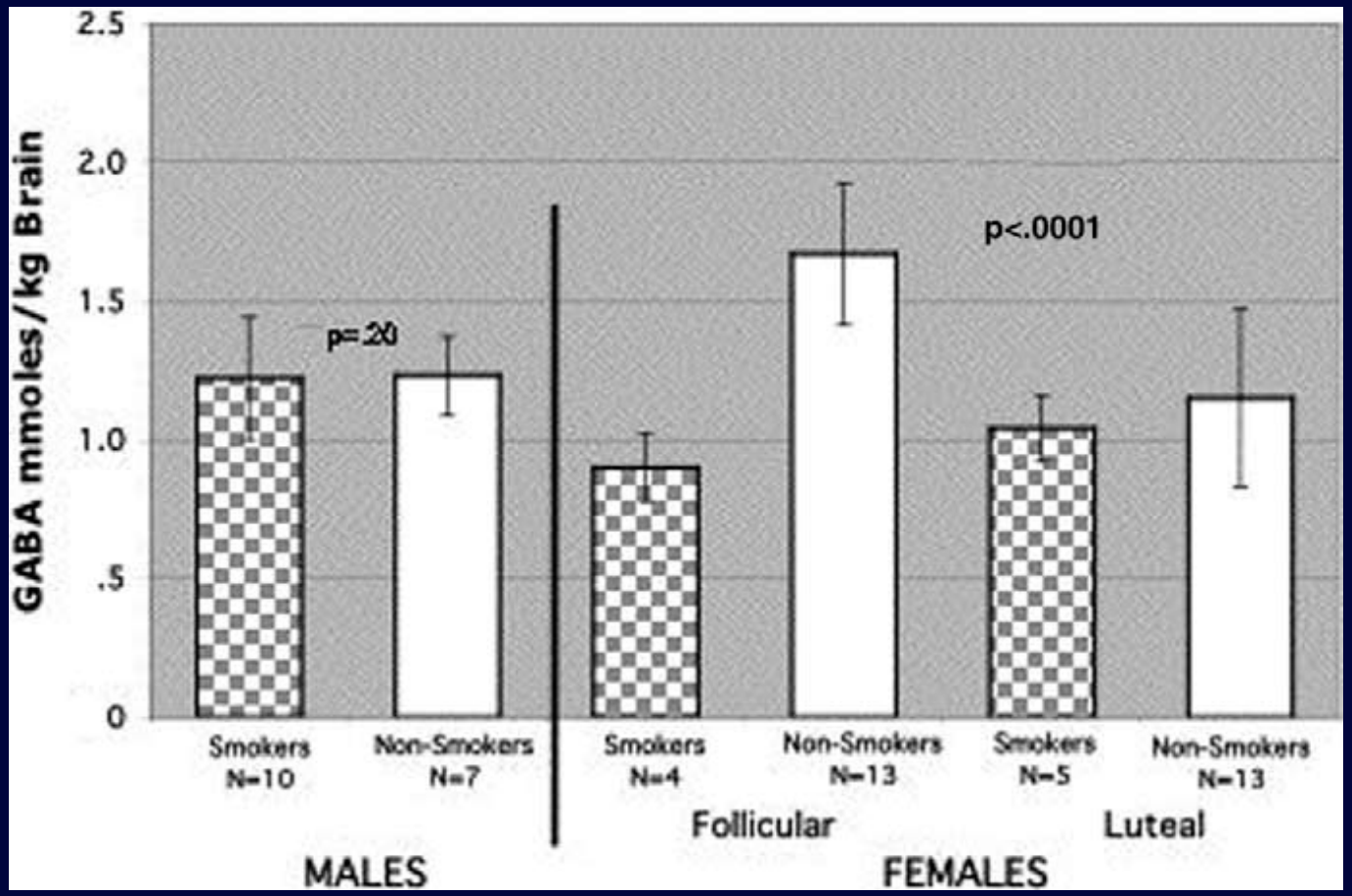
Sex hormones influence cortical GABA levels with ^{1}H-MRS

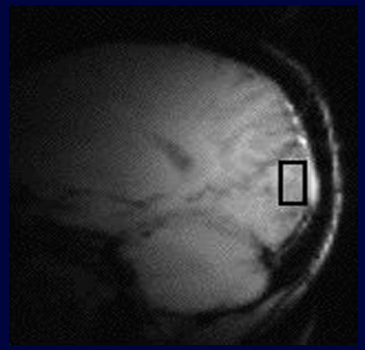
GABA levels decrease over the course of the menstrual cycle in healthy women.



(Epperson et al., Arch Gen Psychiatry, 2002)

Smoking disrupts the regulation of GABA over the menstrual cycle



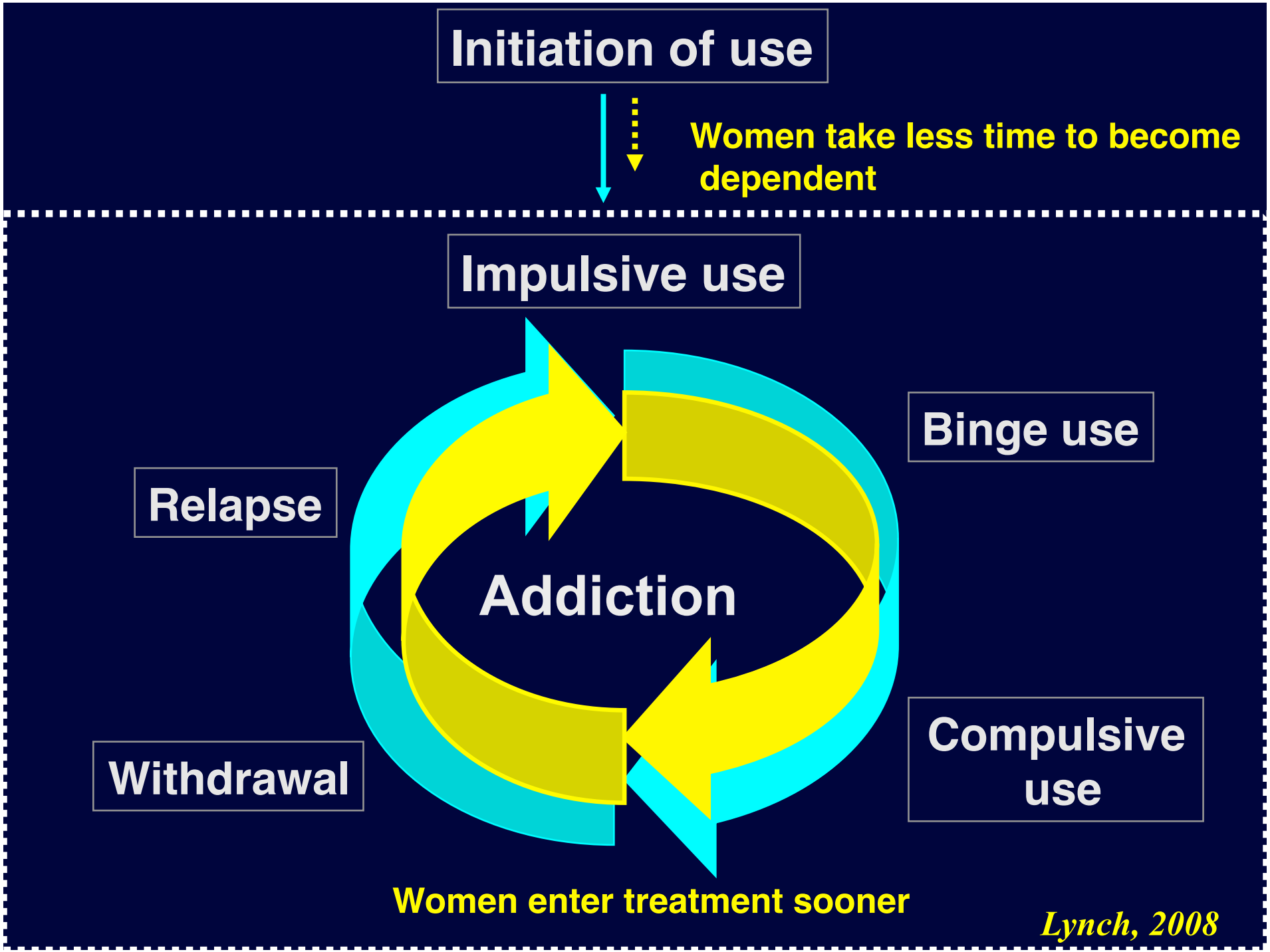


Epperson et al., 2005

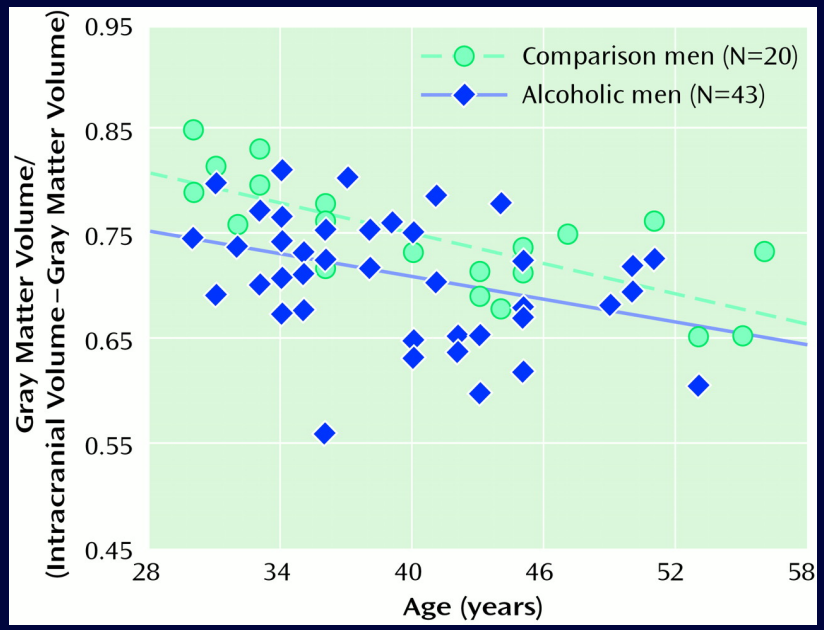
Sex differences in alcoholism

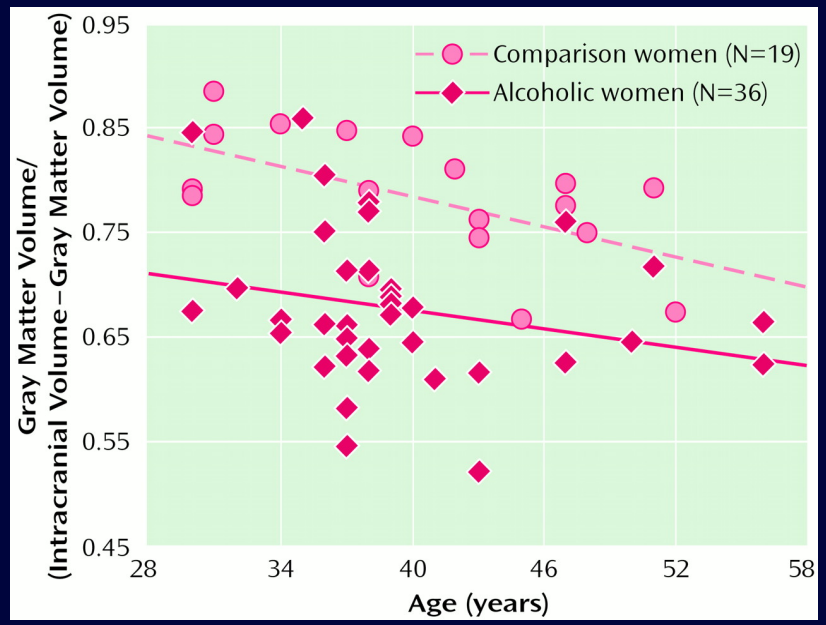
- **Main Finding: Although women report shorter histories of drinking and less intake compared to men, women have similar or worse brain atrophy compared to men.**

- **This is consistent with the "telescoping" phenomenon.**


Initiation of use
Women take less time to become dependent
Impulsive use
Binge use
Relapse
Addiction
Compulsive use
Withdrawal
Women enter treatment sooner
Lynch, 2008

Sex differences in effects of alcohol with MRI at 3 weeks abstinence





Alcoholic women had smaller GM, WM, CSF than control women, and proportion of GM volume to total intracranial content was smaller in women vs. men.

(Hommer et al., Am J Psychiatry, 2001)

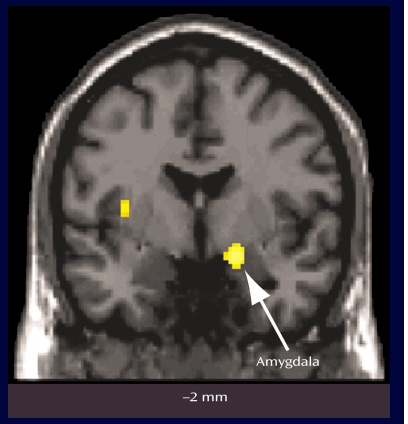
Sex difference in cocaine addiction

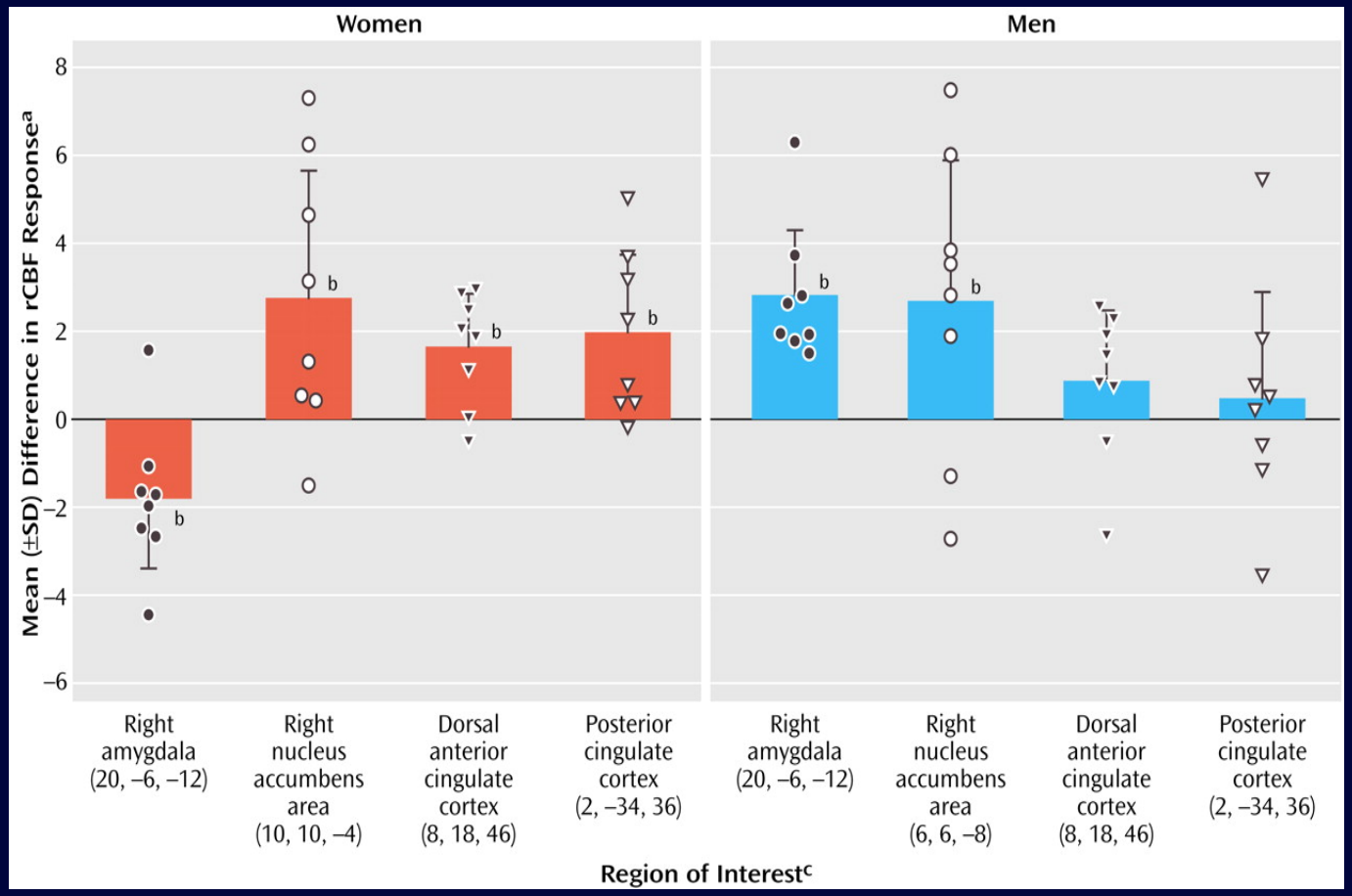
- **Main Finding: Effects of cocaine on the brain are more pronounced in men versus women.**

- **Estrogen may play a role, i.e., have a neuroprotective effect on the vasoconstrictive effects of cocaine.**

- **Cerebral blood volume by cocaine was unchanged in women in follicular phase, reduced 10% in luteal phase, reduced 20% in men *(Kaufman et al., 2001)*.**

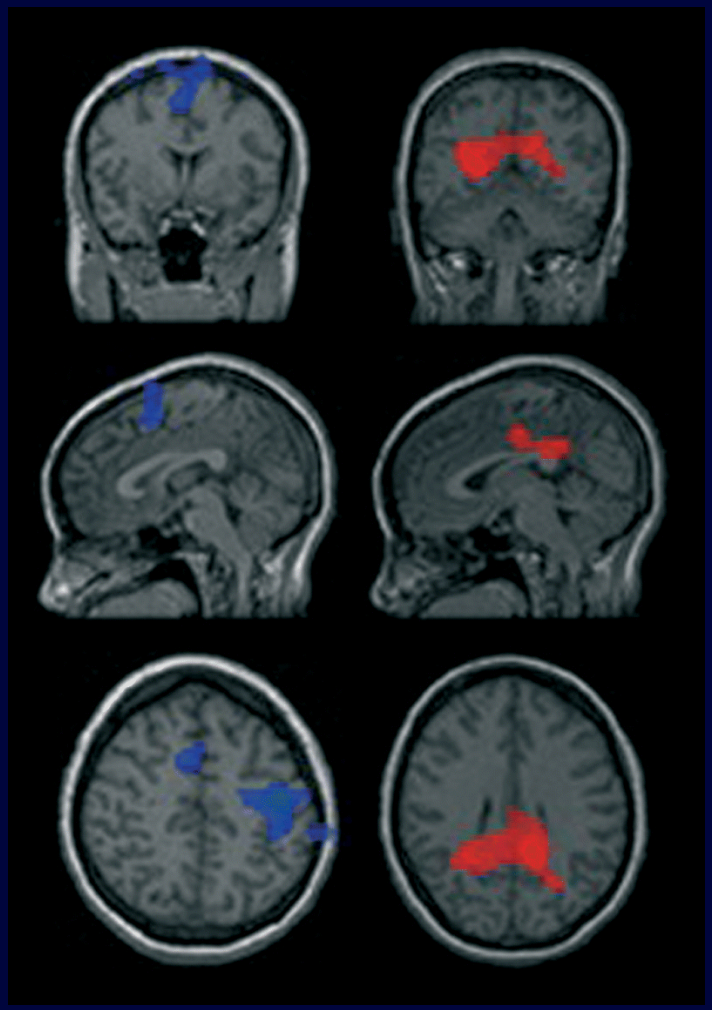
Less amygdala activation in women to cue-induced craving





(Kilts et al. Am J Psychiatry, 2004)

Men have greater perfusion deficits during cocaine withdrawal

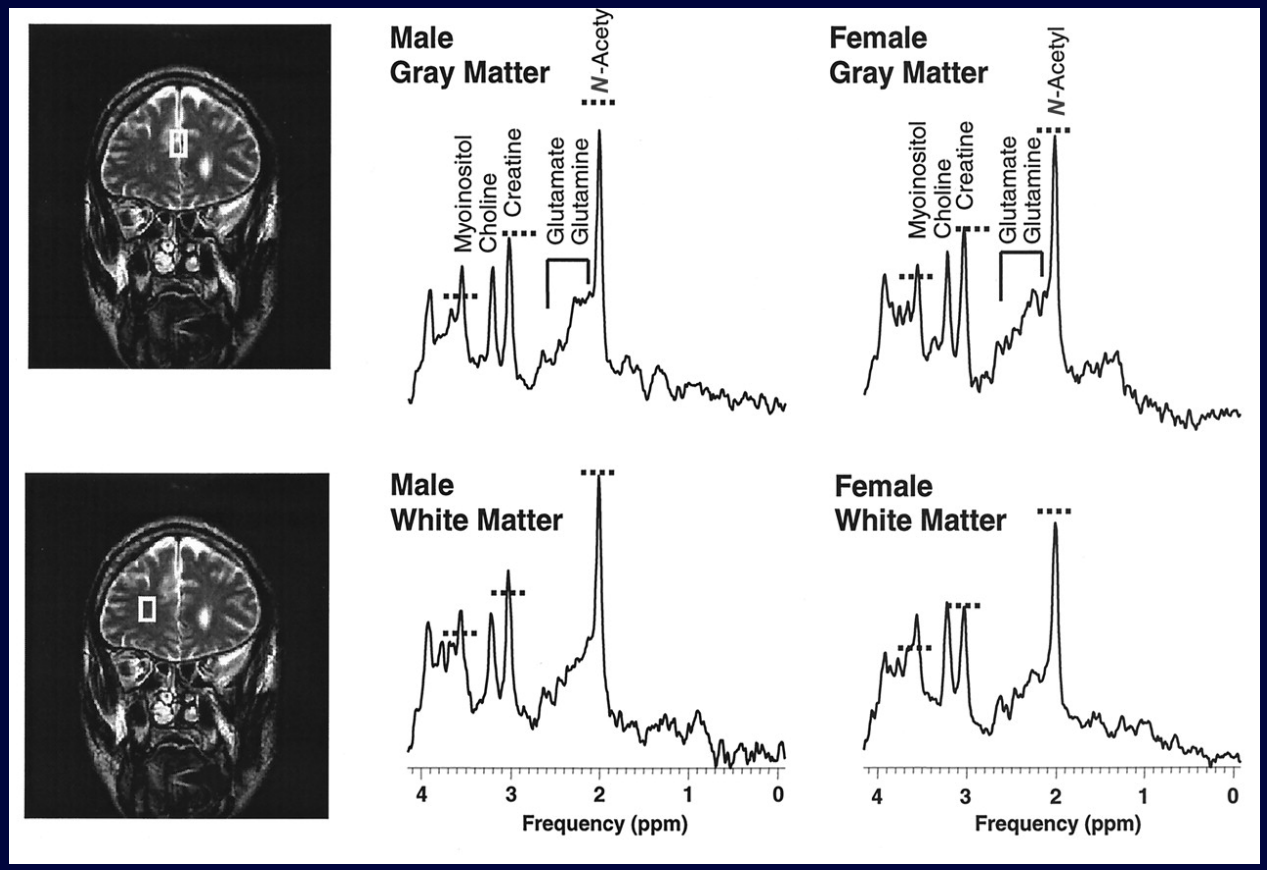


Males (blue) have *decreased* CBF in R precentral gyrus, R superior and medial frontal gyri, and anterior cingulate cortex.

Females (red) have *increased* CBF in the posterior cingulate.

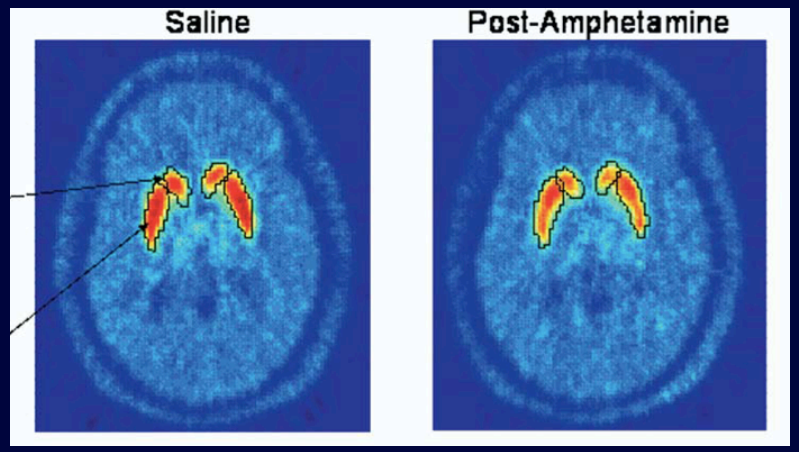
(Tucker et al., NeuroReport, 2004)

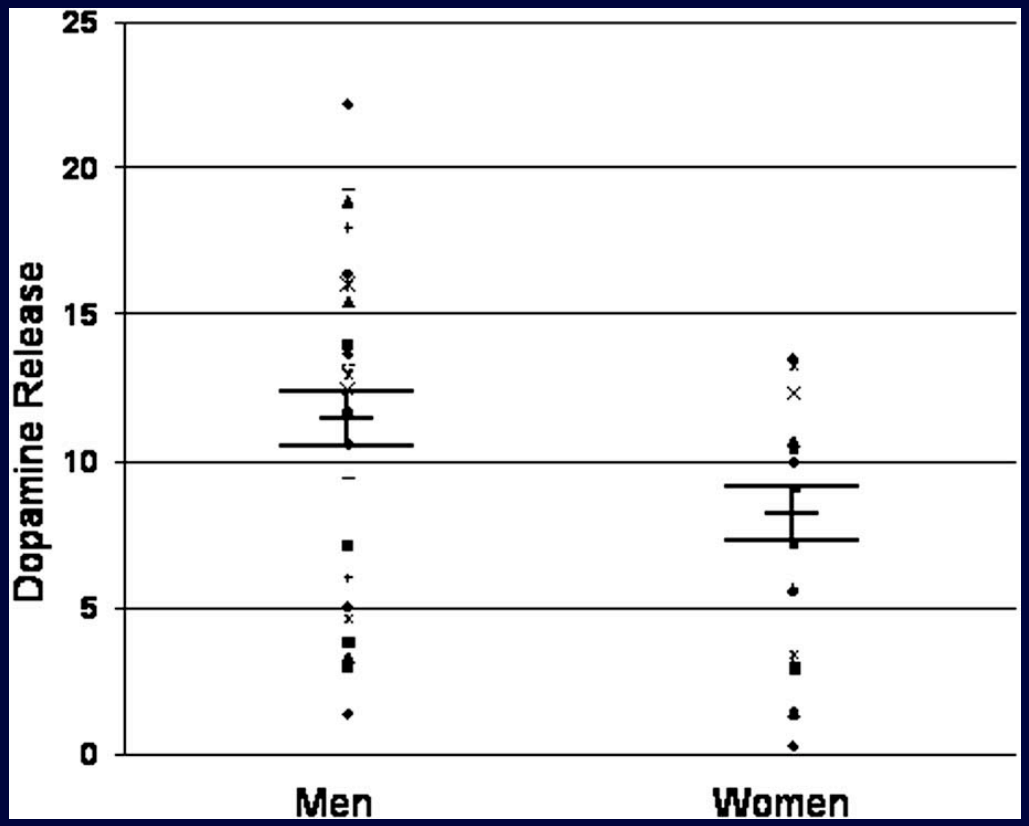
Men have more pronounce neuronal damage after chronic crack cocaine



Abstinent (5 mo) cocaine-dependent women have less neuronal damage in frontal cortical GM and WM than men measured by MRS. ***(Chang et al., Am J Psychiatry, 1999)***

Men have greater amphetamine -induced dopamine release





Munro et al., 2006, Biol Psychiatry

This correlated with greater subjective responses to amphetamine in the men vs. women.

Table 3. Raclopride Binding Potentials During Placebo and Amphetamine PET Scans[a]

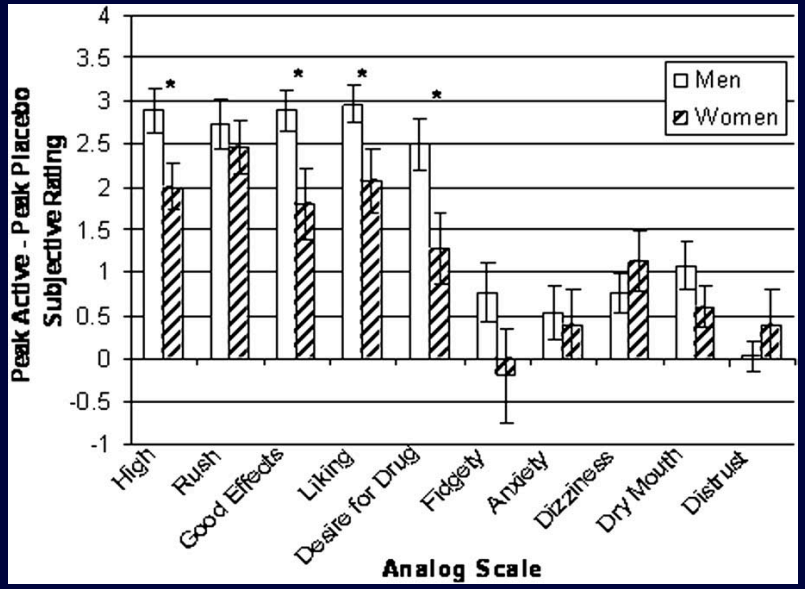
Region	Placebo	Amphetamine	Dopamine Release[b]
aPU			
Men	3.06 ± 0.33	2.67 ± 0.31	12.59 ± 6.30
Women	3.09 ± 0.25	2.84 ± 0.27	8.19 ± 3.56
p value	.777	.091	.017
pPU			
Men	3.04 ± 0.40	2.43 ± 0.33	19.94 ± 6.59
Women	3.19 ± 0.27	2.65 ± 0.20	16.97 ± 4.56
p value	.185	.021	.128
aCN			
Men	2.63 ± 0.30	2.45 ± 0.28	6.58 ± 5.62
Women	2.70 ± 0.25	2.64 ± 0.26	2.20 ± 3.72
p value	.409	.032	.010
pCN			
Men	1.86 ± 0.40	1.68 ± 0.34	9.59 ± 7.09
Women	1.95 ± 0.30	1.86 ± 0.29	4.16 ± 5.00
p value	.463	.079	.012
VS			
Men	2.12 ± 0.32	1.88 ± 0.31	11.64 ± 5.52
Women	2.08 ± 0.21	1.94 ± 0.22	7.13 ± 4.54
p Value	.686	.512	.010

aCN = anterior caudate nucleus; aPU = anterior putamen; pCN = posterior caudate nucleus; PET = positron emission tomography; pPU = posterior putamen; VS = ventral striatum.

[a]Values represent mean ± SD.

[b]Dopamine release = ((placebo BP − amph BP)/placebo BP) * 100.

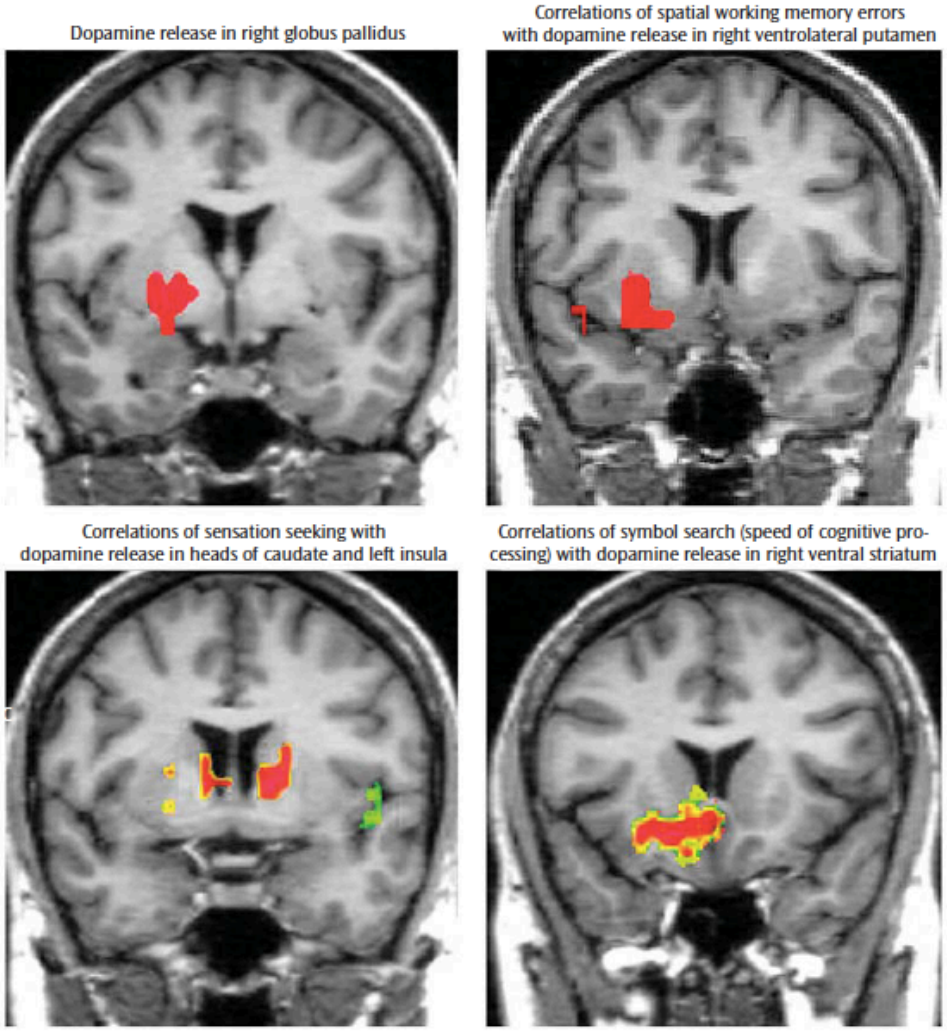
Subjective Analog Scale Responses by Sex



W>M
R GP
R FC
TC
PC

M>F
Dorsal Stri

FIGURE 1. Coronal Images Demonstrating Significant Clusters of Gender Differences in (A) Dopamine Release in the Right Globus Pallidus, (B) Correlations of Spatial Working Memory Errors With Dopamine Release in the Right Ventrolateral Putamen, (C) Correlations of Sensation Seeking With Dopamine Release in the Heads of the Caudate and Left Insula, and (D) Correlations of Symbol Search (speed of cognitive processing) With Dopamine Release in the Right Ventral Striatum



Riccardi et al., Am J Psych, 2006

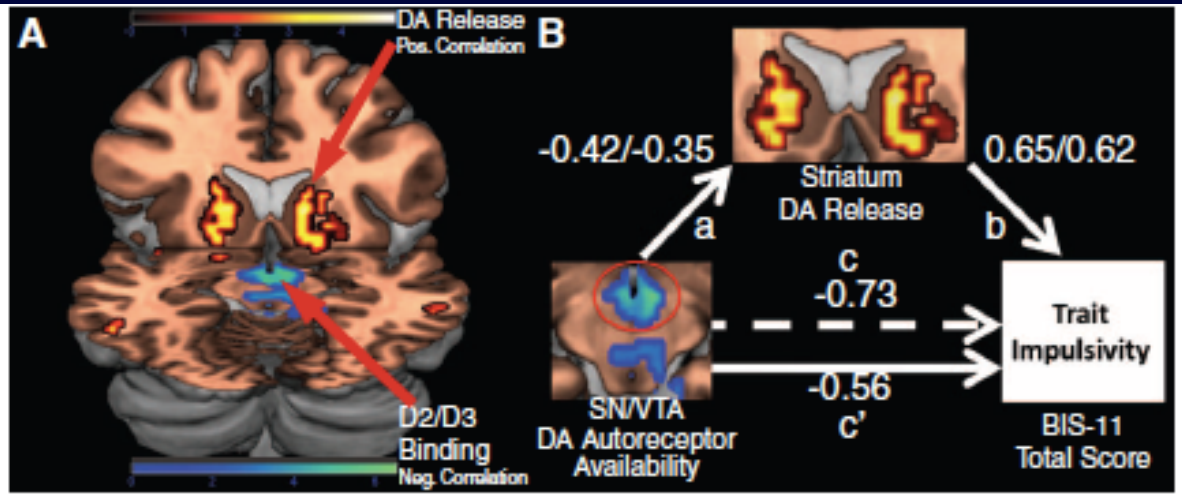


Fig. 1. (**A**) Rendering of two separate SPMs depicting negative correlations between BIS-11 scores and D2/D3 BP_{ND} (cool colors) and positive correlations between BIS-11 scores and AMPH-induced DA release (warm colors) ($P_{corrected} < 0.05$; image thresholded at $t > 3$). For D2/D3 BP_{ND}, inverse associations emerged in the DA midbrain [anteriorly in the VTA, centered at 6, −3, −11 (x, y, z; Montreal Neurological Institute space)]. Peak coordinates for the striatal AMPH-induced DA release correlations are −16, 15, 5 (left) and 20, 23, −3 (right); cluster sizes are 167 voxels (left) and 216 voxels (right). Color bars represent z-statistic values. SPMs rendered on a T1-weighted magnetic resonance image template brain, with cuts at $z = -11$ and $y = 16$. (**B**) Path analysis demonstrating that the influence of midbrain D2/D3 availability on trait impulsivity is mediated through an impact on striatal AMPH-induced DA release. Path a shows coefficients for the effect of midbrain D2/D3 BP_{ND} (cluster outlined with red circle) on right and left striatal DA release. Path b shows the coefficients for the effect of striatal DA release on trait impulsivity. Paths c and c′ show coefficients for the total (dashed line) and direct (solid line) effects of midbrain D2/D3 BP_{ND} on trait impulsivity. All coefficients standardized. Sobel test for mediation: $Z = -1.94$, $P = 0.05$.

Buckholtz et al., 2010

General Conclusions

- **There are a variety of sex differences in normal brain structure and function that may impact or underlie observed sex differences in psychiatric disorders.**

- **Women have**
  - **Smaller brains, but more gray matter**
  - **Higher CBF**
  - **Equivalent CMRglu**
  - **Higher dopaminergic and serotonergic tone**
  - **More vulnerable to alcohol and (?) tobacco smoking**
  - **Some protection from cocaine, other dopaminergic disorders**
  - **Vulnerability to depression, stress**

Where do we go from here?

- **Effects of fluctuating sex hormones need to be carefully examined.**
- **Differences in pre- vs. post-menopausal women and men.**
- **The development of new radiotracers will allow investigations of neurochemistry in new areas.**
- **Combine imaging with genetics**
- **Target medications, therapy as sex-specific**
- **Brain chemistry changes during adolescence are somewhat limited to animal studies due to issues with radioactivity**