Addictions medicine: partnering with treatment for sustaining recovery~ an addiction psychiatrist's perspective

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Disclosures

- **Susan K. Blank, MD**
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- Consultant for BioScript
- President - Georgia Society of Addiction Medicine
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- Certified Medical Review Officer
- Chapter : Tobacco Addiction, 2013 ASAM Criteria
- Weekly Radio Show: *"Detailing Addiction with Dr. Susan Blank" on* America's Web Radio.

Topics for today

- Definition of Addiction
- Neurocognitive Effects of Addiction and how can you test in your office?
- Hormonal (Neuroendocrine) Effects of Addiction
- Why antidepressants don’t always work in our patients and what can we do?
- Stress in Relapse, especially for Women

Confusing Terms

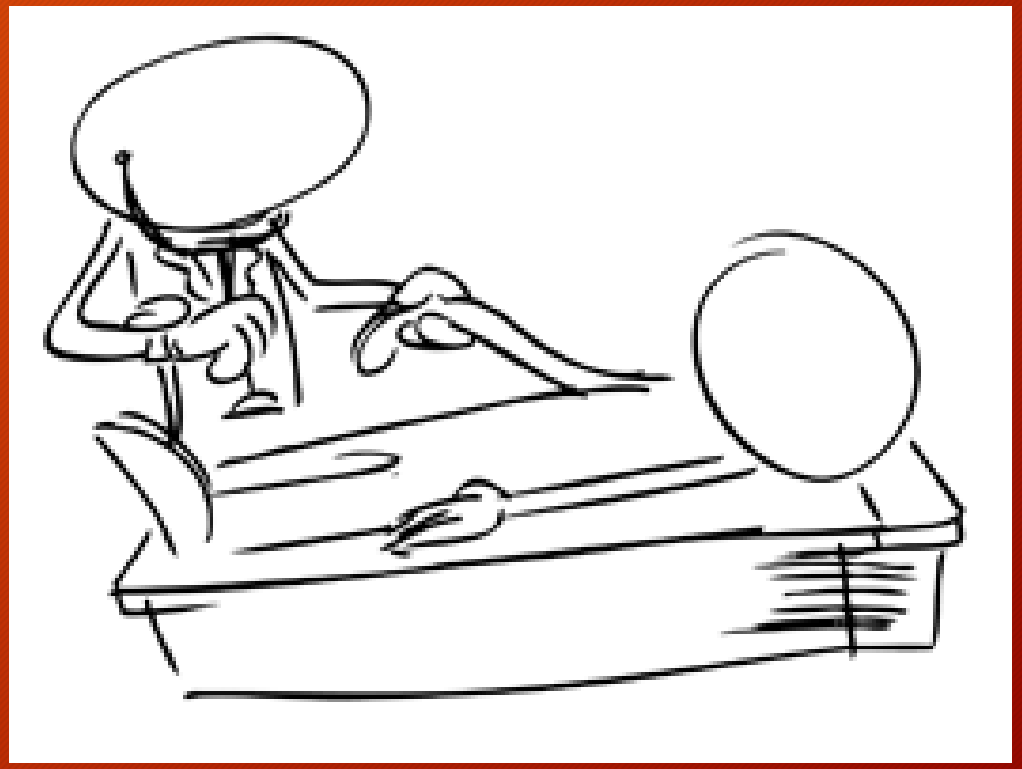
Definitions

- Proper Use
  - Taking Medications as per doctor's Instructions
- Drug MisUse
  - Taking a psychoactive substance for non-medical purposes, out of curiosity
- Drug Abuse
  - Drug use that leads to problems (e.g. loss of effectiveness in society; behavioral psychopathology, criminal acts)
- Drug Dependence
  - The state of needing a drug to function within 'normal limits'
- Addiction:
  - A maladaptive pattern of drug use leading to clinically-significant impairment or distress, associated with difficulty in controlling drug-taking behavior, withdrawal, and tolerance

Addiction: continued use in spite of consequences

Definitions

- Proper Use
  - Taking Medications as per doctor's Instructions
- Drug Dependence
  - The state of needing a drug to function within 'normal limits'



Definitions

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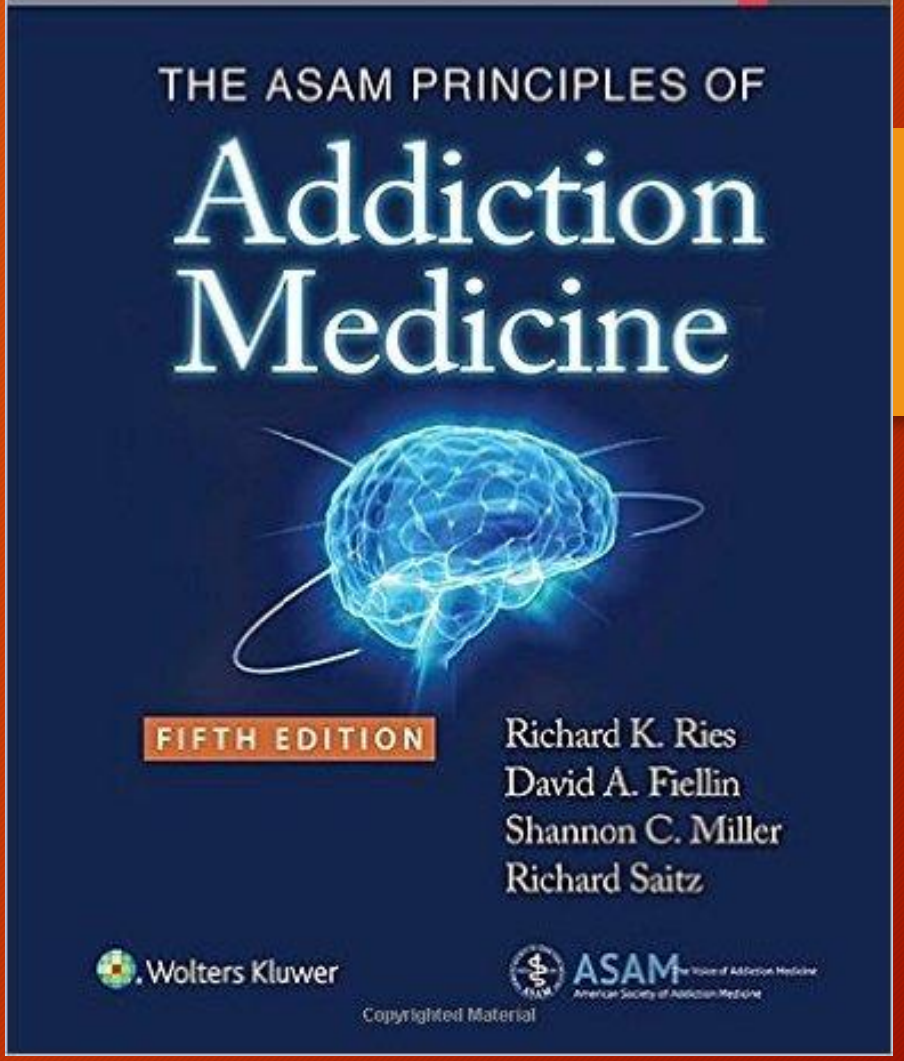
Classic Models of Addiction

Model	Emphasized Causes	Example Interventions
Moral	Personal responsibility; self-control	Moral suasion; social/legal sanctions
Spiritual	Spiritual defect	Prayer; 12-step faith-based treatment (e.g. AA)
Temperance	Drugs	Control of supply; calls for abstinence
Educational	Ignorance	Education
Conditioning	Classical/operant conditioning	Counterconditioning; extinction



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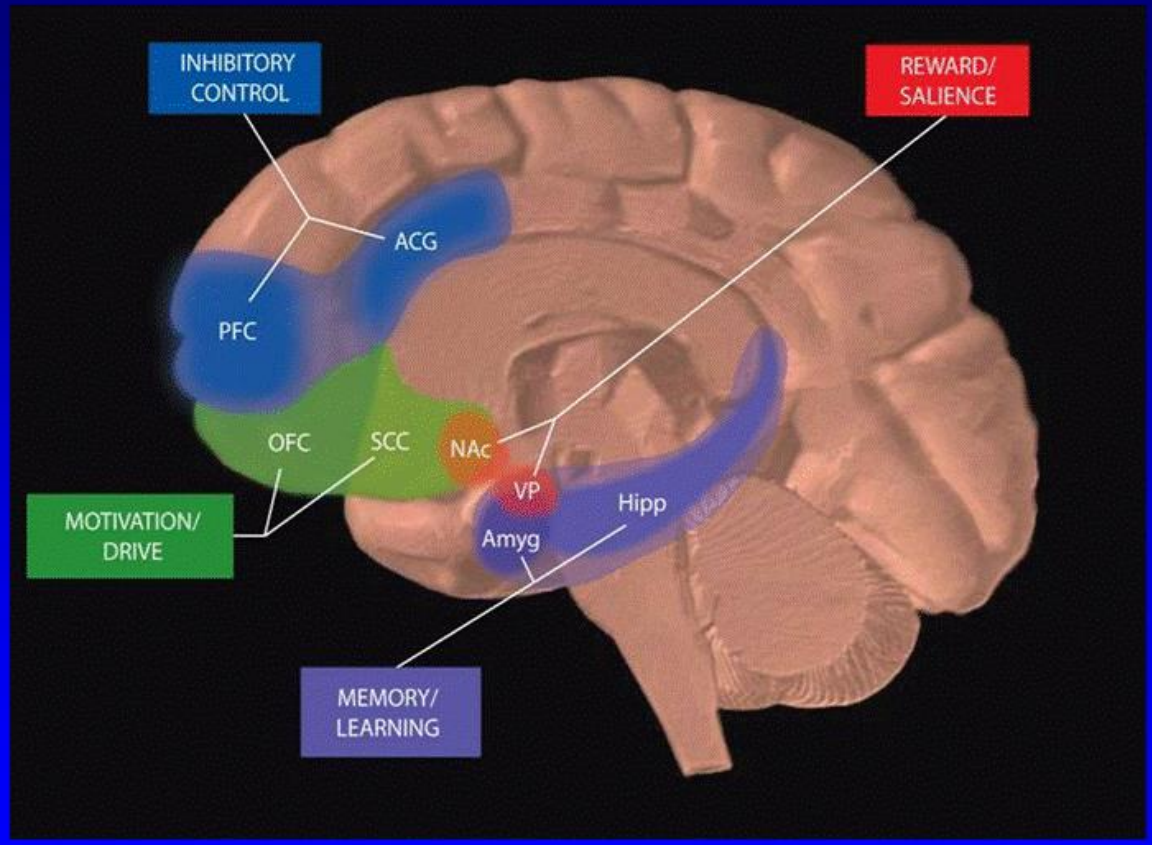
- Addiction is a Primary
- Chronic disease of brain
- Reward Pathway
- Motivation Pathway
- Memory Network and related circuitry.

Drug Addiction involves 4 circuits

1. Reward – nucleus accumbens(NAc)
   ventral pallidum
3. Motivation/drive- orbitalfrontal cortex (OFC)
   subcallosal cortex
5. Memory and learning- amygdala
   hippocampus
7. Control- prefrontal cortex
   anterior cingulate gyrus

Circuits Involved In Drug Abuse and Addiction



All of these brain regions must be considered in developing strategies to effectively treat addiction

NIDA

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- Dysfunction in these circuits leads to characteristic Biological
- Psychological
- Social
- Spiritual manifestations.

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- This is reflected in an individual pathologically pursuing Reward and/or
- Relief by substance use and other behaviors.

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- Addiction is characterized by inability to consistently abstain
- impairment in behavioral control
- craving
- diminished recognition of significant problems with one's behaviors and interpersonal relationships
- and a dysfunctional emotional response.

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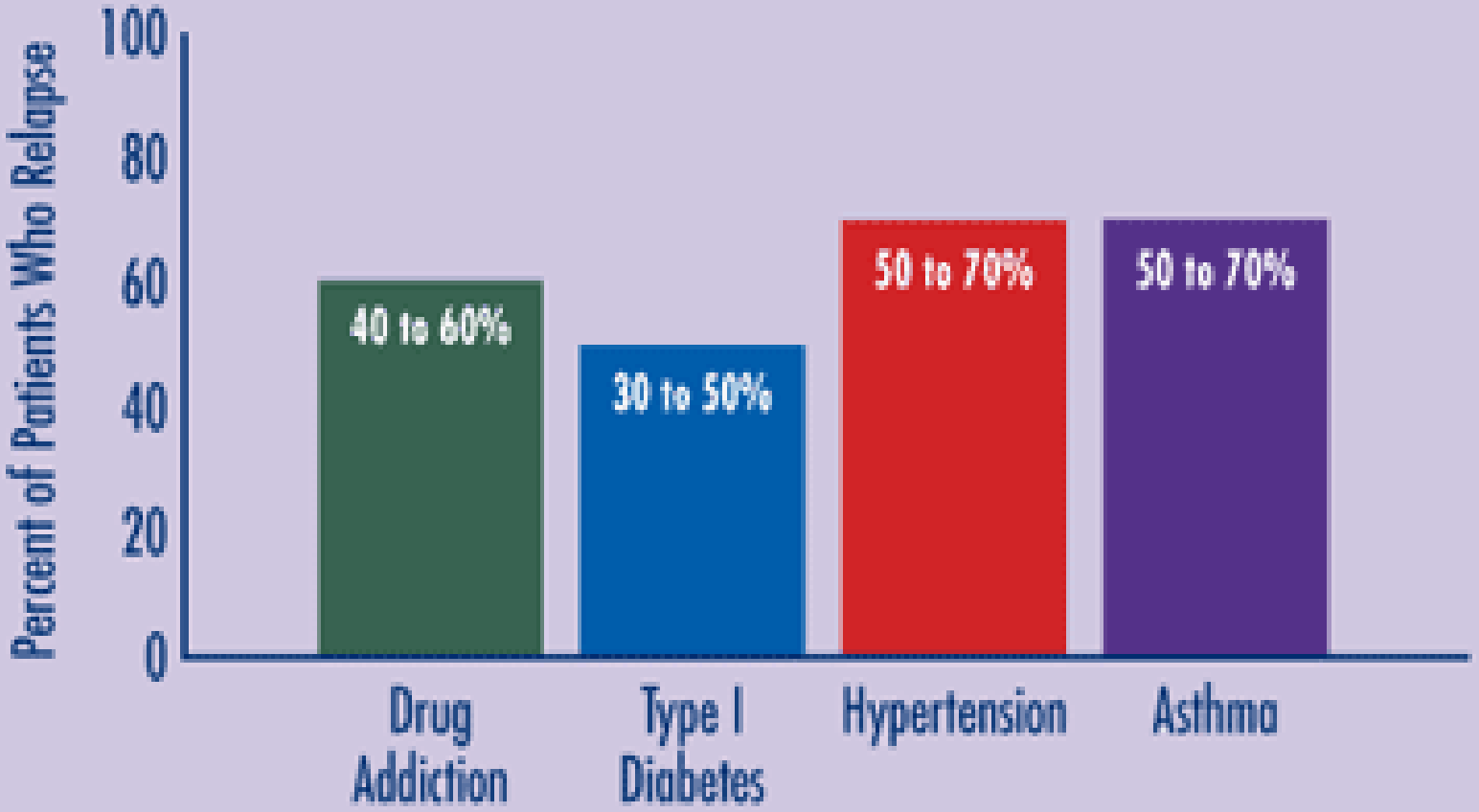
- Like other chronic diseases,
- Addiction often involves cycles of
- Relapse and Remission.

COMPARISON OF RELAPSE RATES BETWEEN DRUG ADDICTION AND OTHER CHRONIC ILLNESSES



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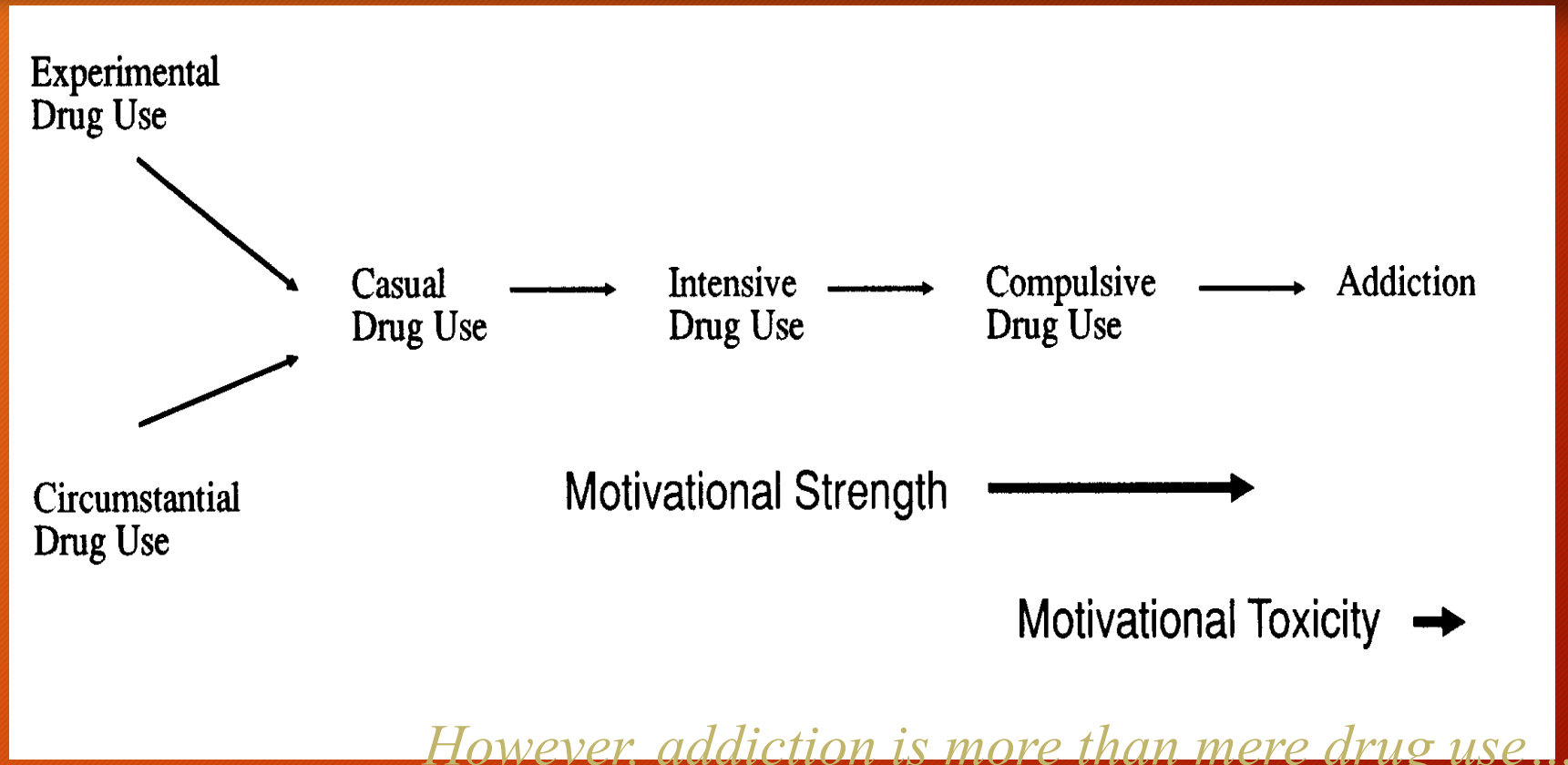
- Without treatment or engagement in recovery activities,
- Addiction is progressive and
- Can result in disability or premature death.

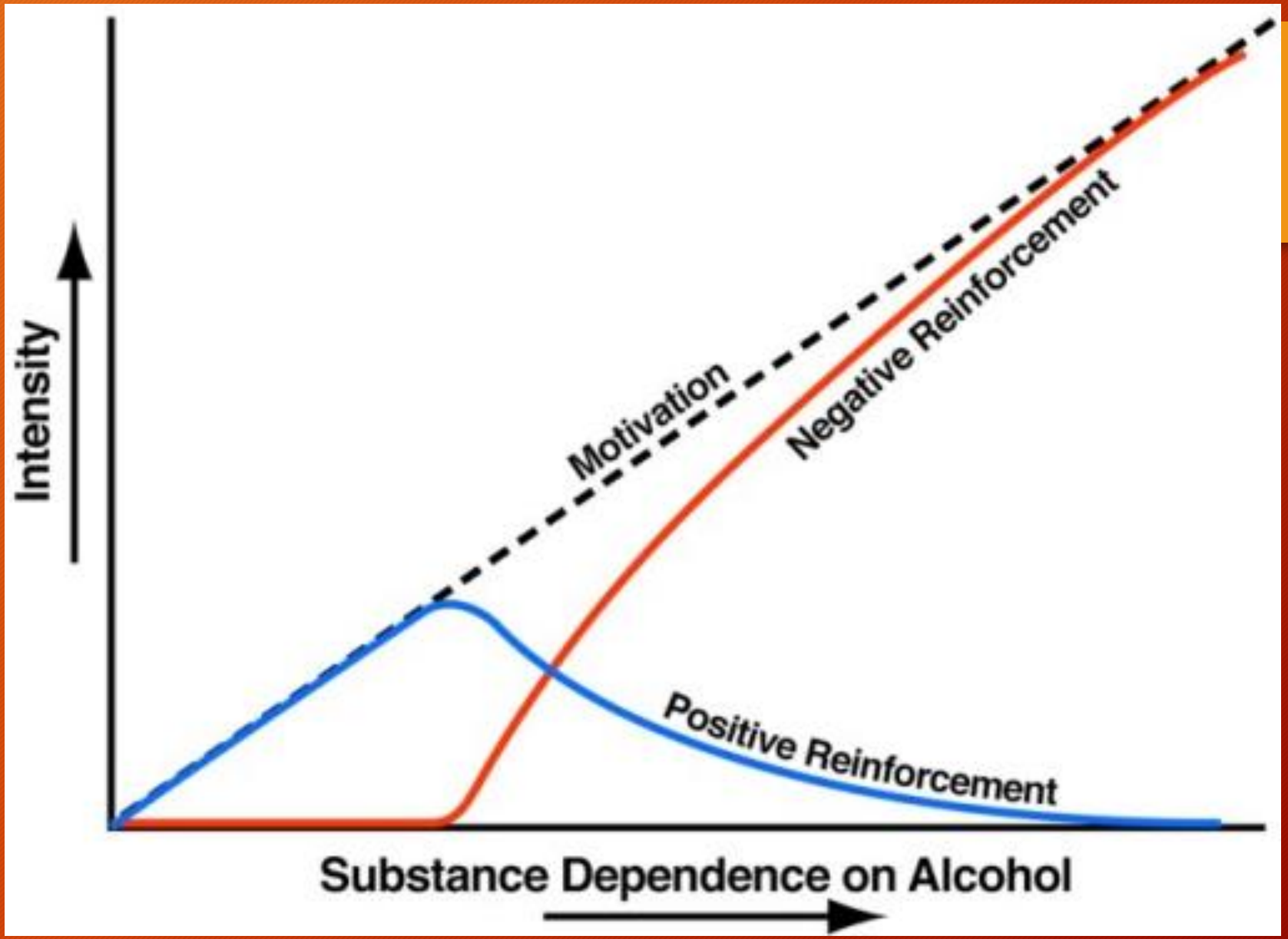
Nature of Addiction - a continuum of use?



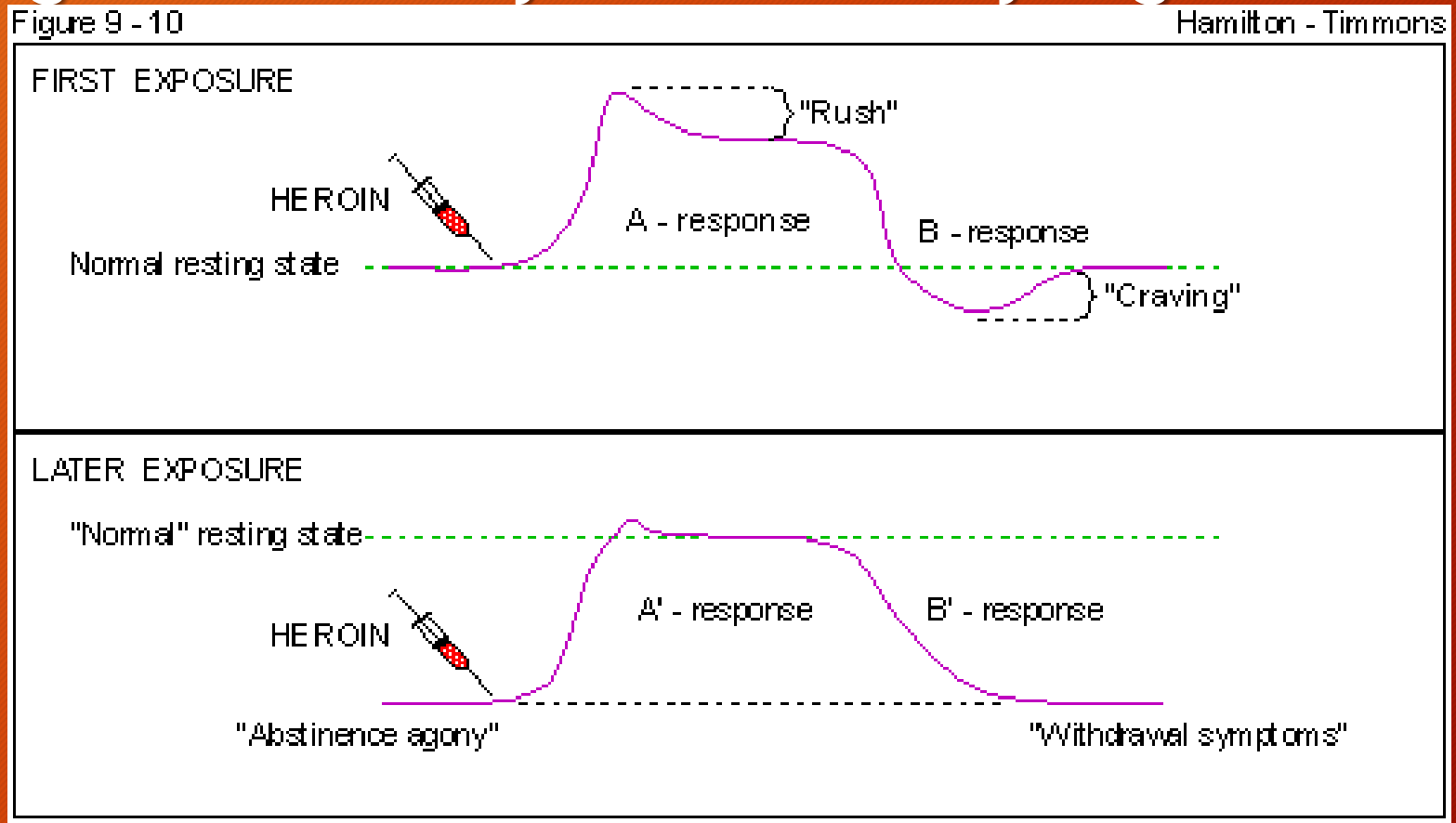
However, addiction is more than mere drug use…

Positive and Negative Reinforcement-

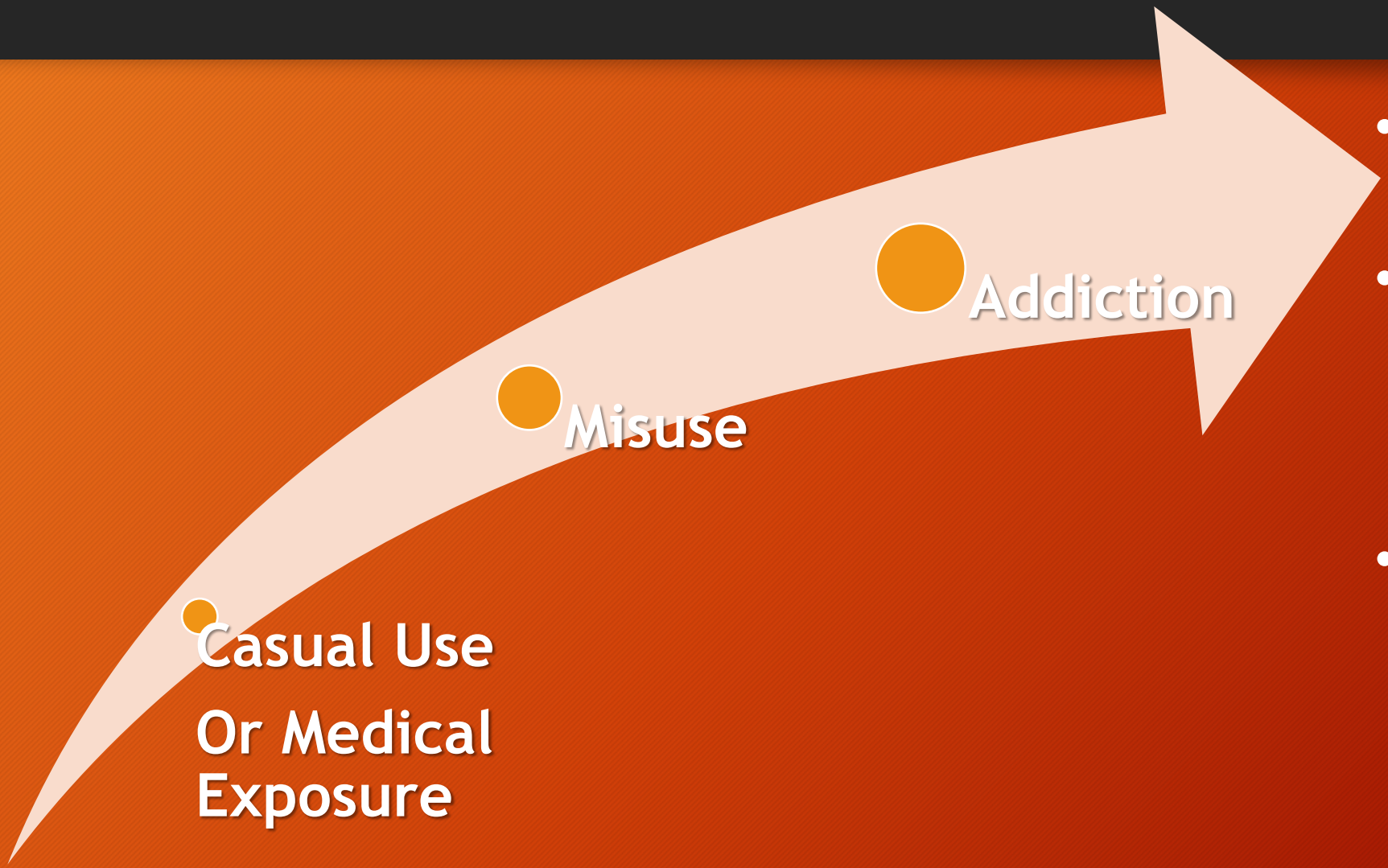
- Initial Use (for pleasure or pain relief) **Positive Reinforcement** – defined as the process by which presentation of a stimulus (drug) increases the probability of a response (non dependent drug taking paradigms-appropriate use, misuse, abuse).
- **Negative Reinforcement (addiction)**– defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)


Intensity
Motivation
Negative Reinforcement
Positive Reinforcement
Substance Dependence on Alcohol

- Drug-use initially motivated by positive reinforcement
- Over time, tolerance develops to rewarding effects
- Abstinence leads to withdrawal
- Drug use ultimately maintained by negative reinforcement

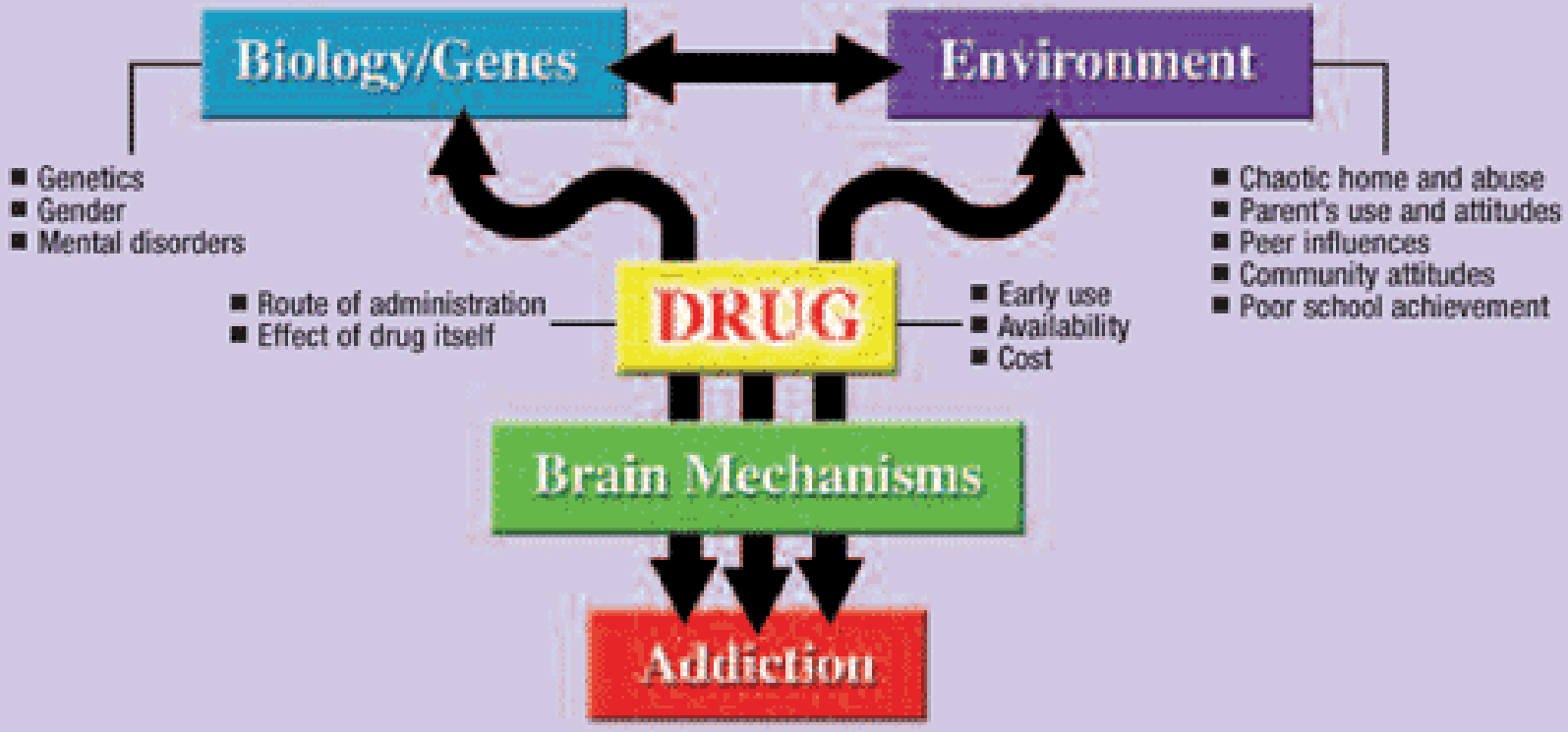


In Summary: Trajectory of Addiction

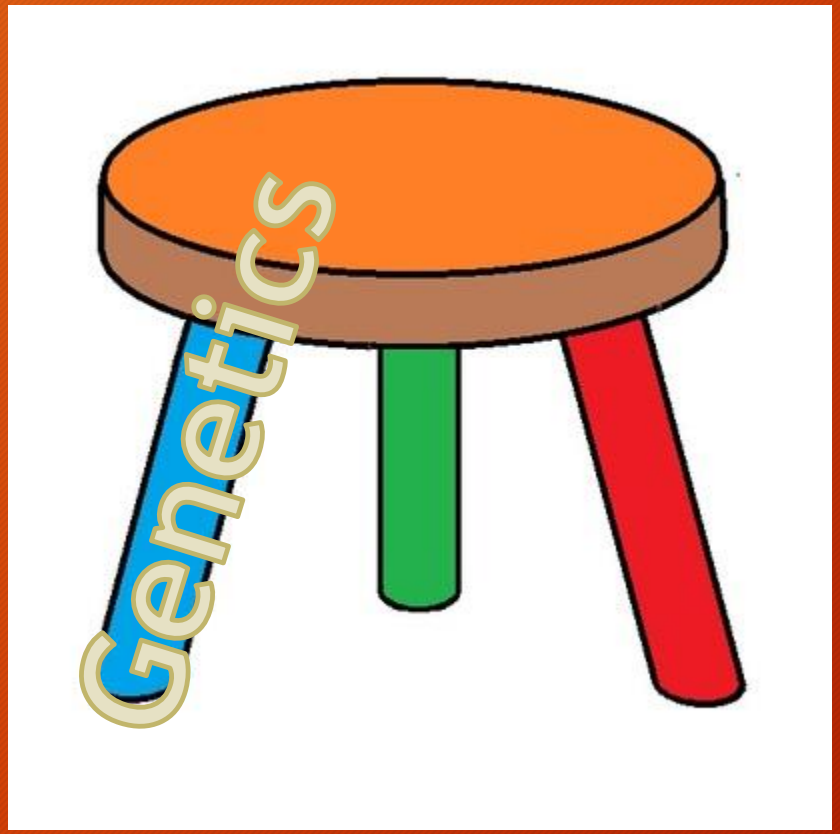


- Most people have no idea they are at risk
- Addiction is a genetically inherited, chronic brain disease.
- Addiction is not about the drugs or the behaviors, it is all about the brain.

RISK FACTORS



First Leg Essential to all Addiction: Genetics



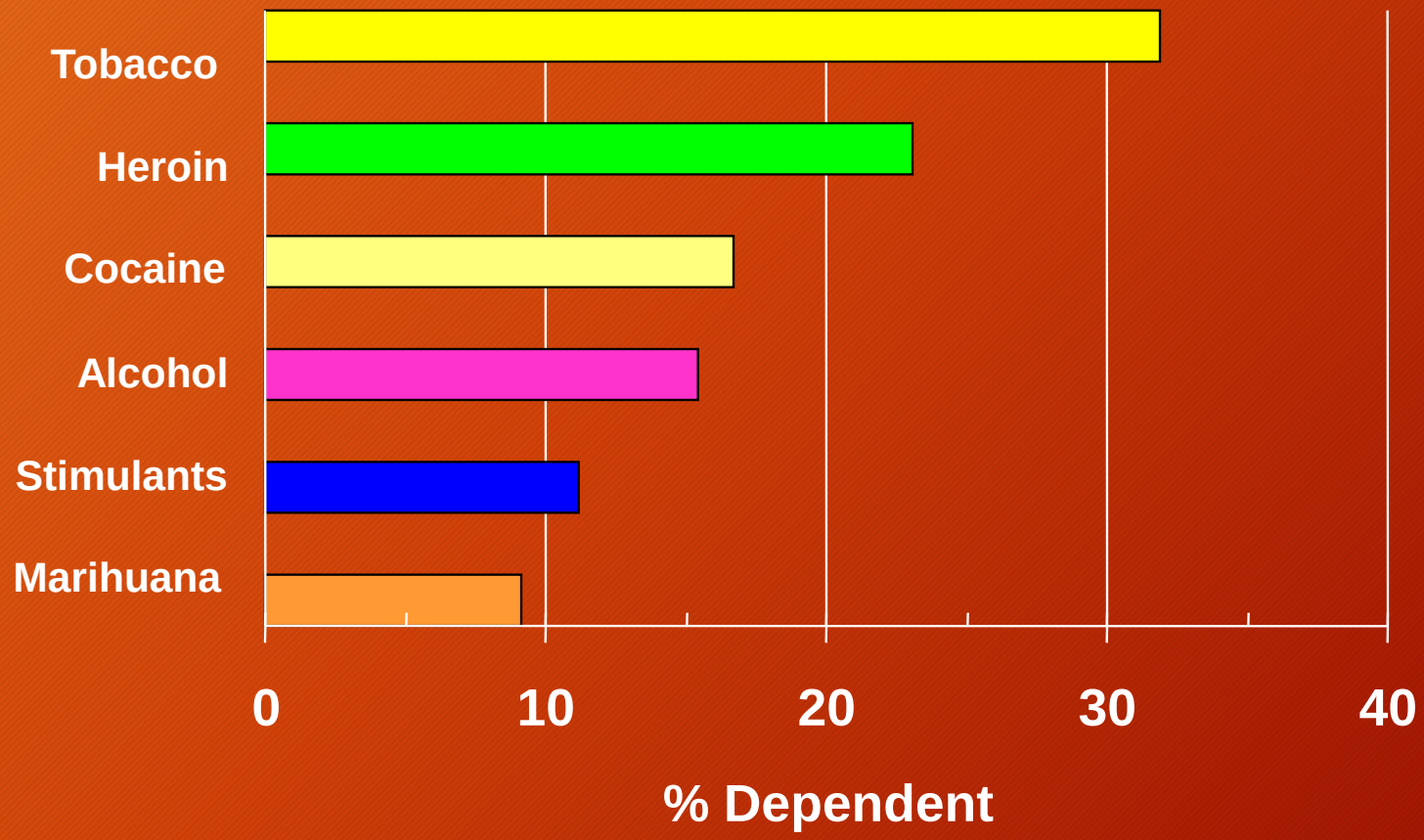
General Population DSM 5

- Any Substance Use Disorder (excluding Tobacco)
  - 1 month 3.8 %
  - 6 months 6.0 %
  - Lifetime 35.0 %
- Alcohol Use Disorder
  - 1 month 2.8 %
  - 6 months 4.7 %
  - Lifetime 29.1 %
- Other Drug Use Disorder
  - 1 month 1.3 %
  - 6 months 2.0 %
  - Lifetime 5.9 %

NSDUH 2013: Non-Medical Use Ages 12 & Older

Drug	Ever Used	Dependence
Tobacco	75.6%	24.1%
Cannabis	46.3	4.2
Cocaine	16.2	2.7
Stimulants	35.5	1.7
Anxiolytics	12.7	1.2
Hallucinogens	15.1	0.5
Analgesics	13.5	1.0
Inhalants	8.0	0.4
Heroin	1.8	0.3

Drug Dependence Among Ever-Users



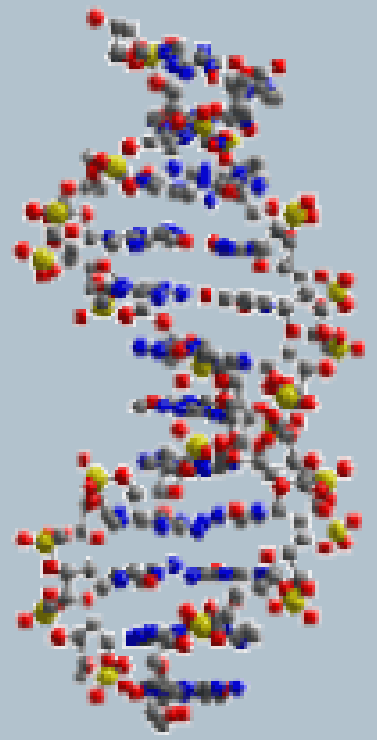
Addiction, Like Cardiovascular Disease, Has Genetic Contributions

Drug Abuse

CYP2A6 (nicotine metabolism) tobacco dependence

FAAH (endogencus cannabinoid regulator) problem drug use

Mu-opioid receptor in heroin addiction

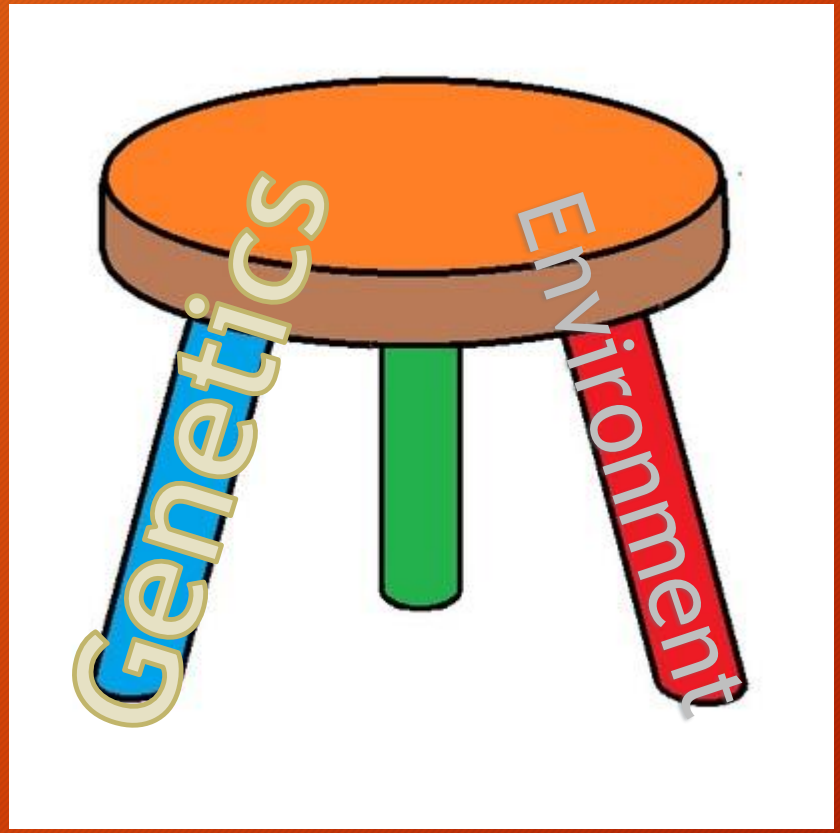


Cardiovascular Disease

APO-E (Apolipoprotein E) coronary artery disease

LOX 1 (lectin-like oxidized low density lipoprotein receptor) coronary artery disease in Caucasian women

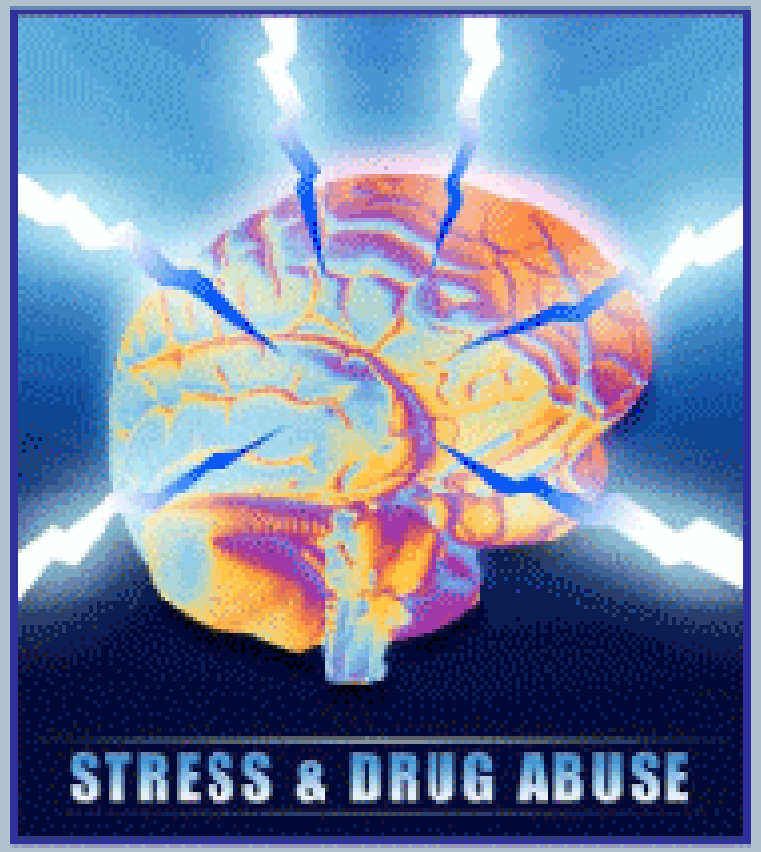
Second Leg Essential to all Addiction: Environment



Addiction, Like Cardiovascular Disease, Has Environmental Contributions

Drug Abuse:

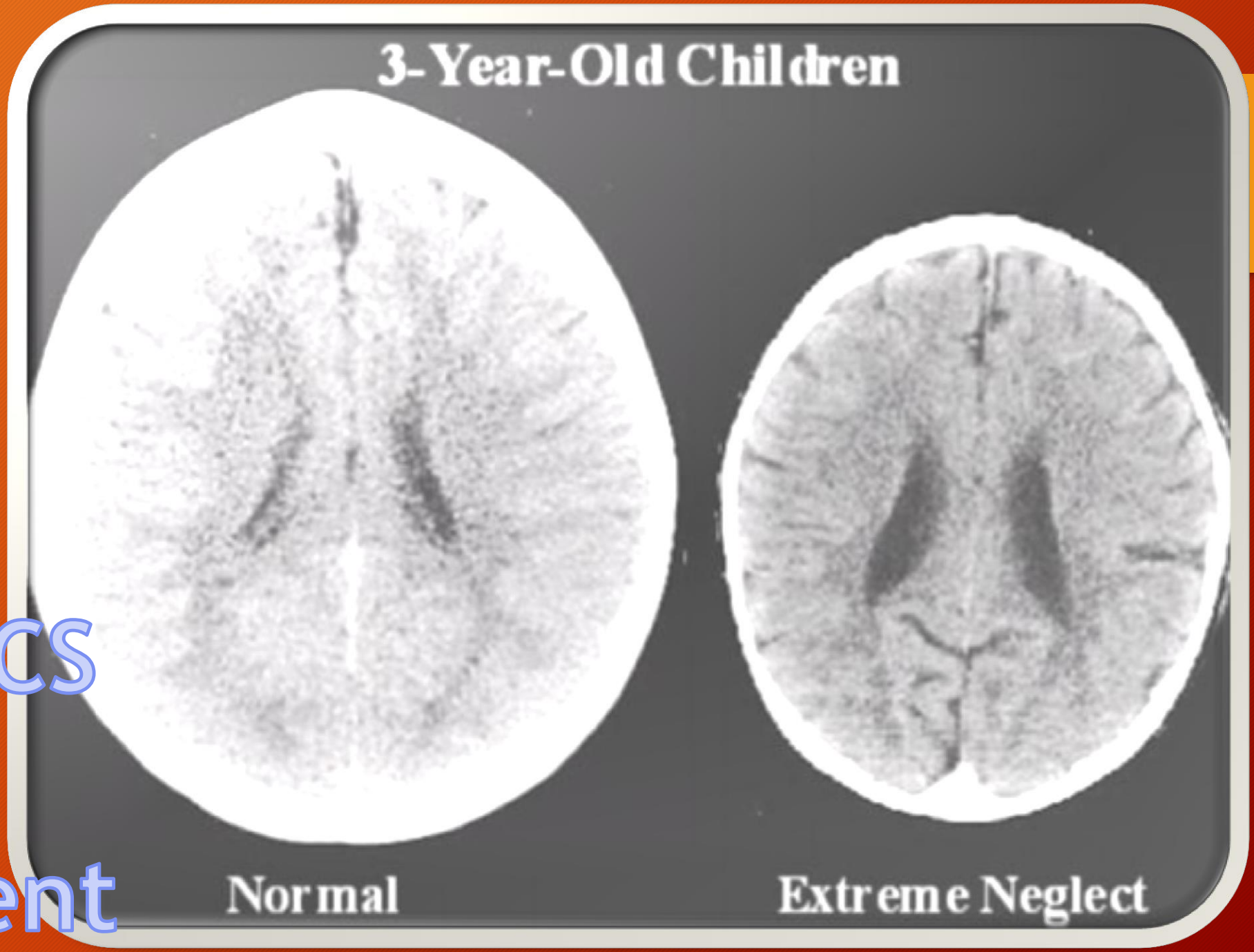
- Early Physical or Sexual Abuse
- Witnessing Violence
- Stress
- Peers Who Use Drugs
- Drug Availability



Cardiovascular Disease:

- Obesity
- Secentary Lifestyle
- Stress
- Drug and Alcohol Abuse

EPIGENETICS
or
Environment



urce: Randy Jirtle, Ph.D., Duke University Medical Center. Used with permission.

ese inbred mice are genetically identical. They are each about a year old and both a
male. Their different characteristics result from differences in the epigenome. The mot
of the mouse on the left received a normal mouse diet. The mother of the mouse on t
ght received a diet supplemented with genistein, the phytoestrogen found in soy pro
ts. Genistein increases the incidence of brown offspring by altering the epigenome rath
an mutating the genome — an example of nature via nurture.

Third Leg Essential to all Addiction: Stress

Why Do People Take Drugs in The First Place?

To Feel Good

To have novel:

feelings
sensations
experiences
AND
to share them

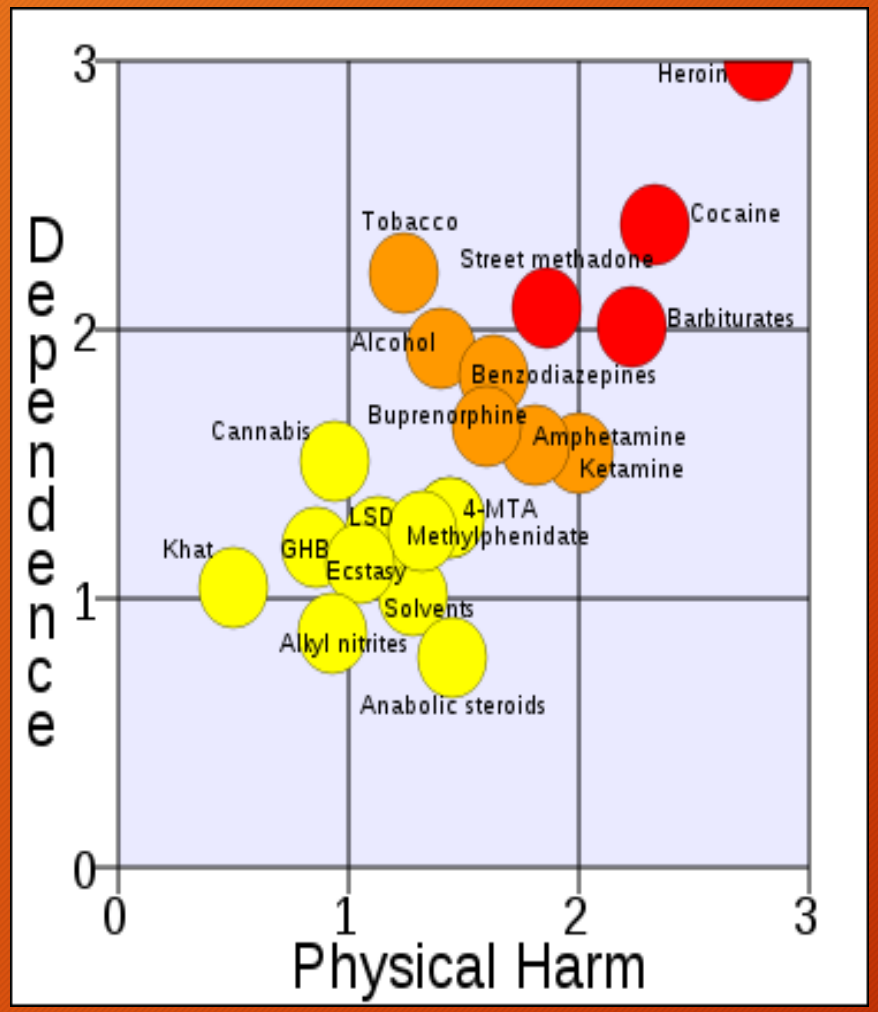
To Feel Better

To lessen:

anxiety
worries
fears
depression
hopelessness

NIDA

Heroin, Cocaine, Nicotine and Alcohol

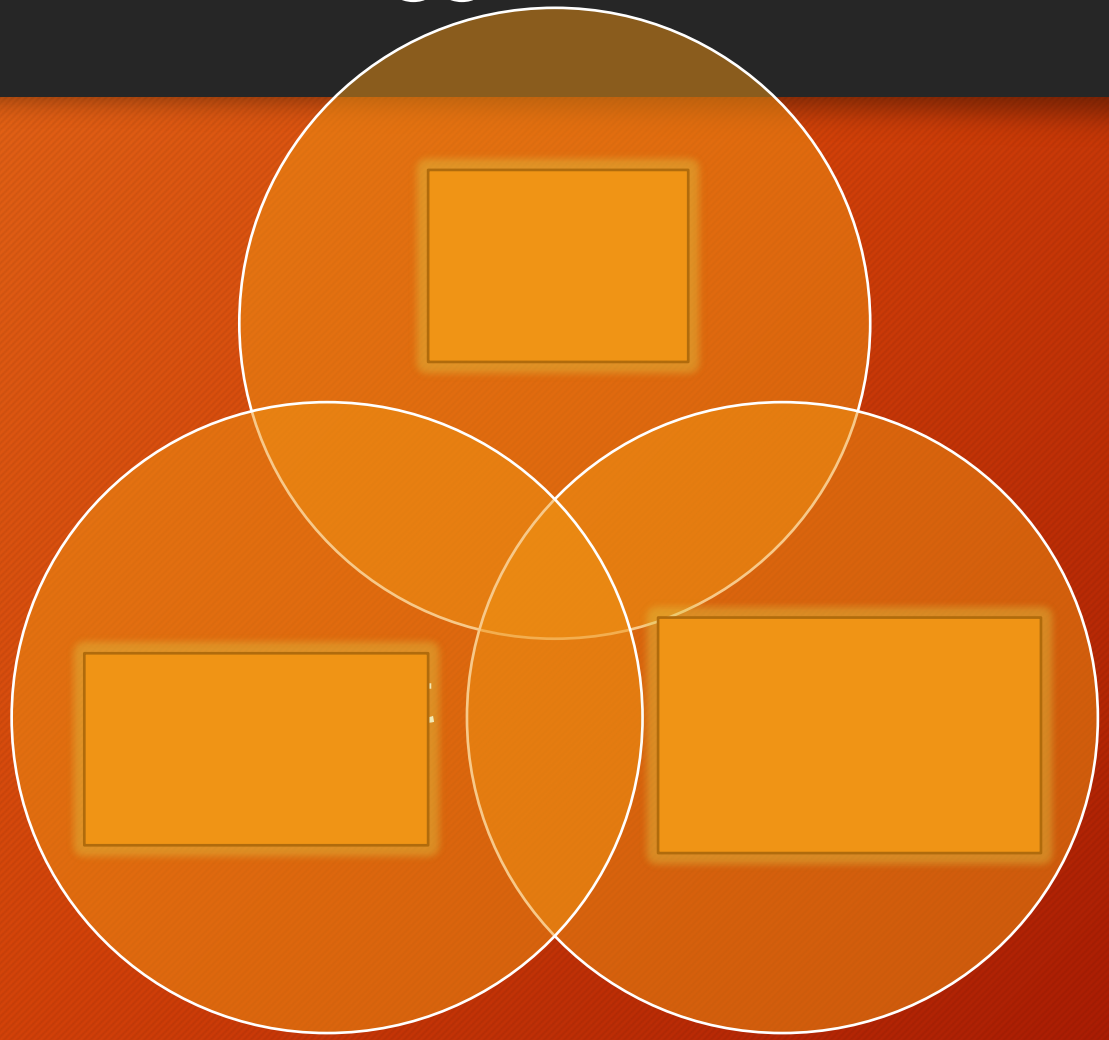


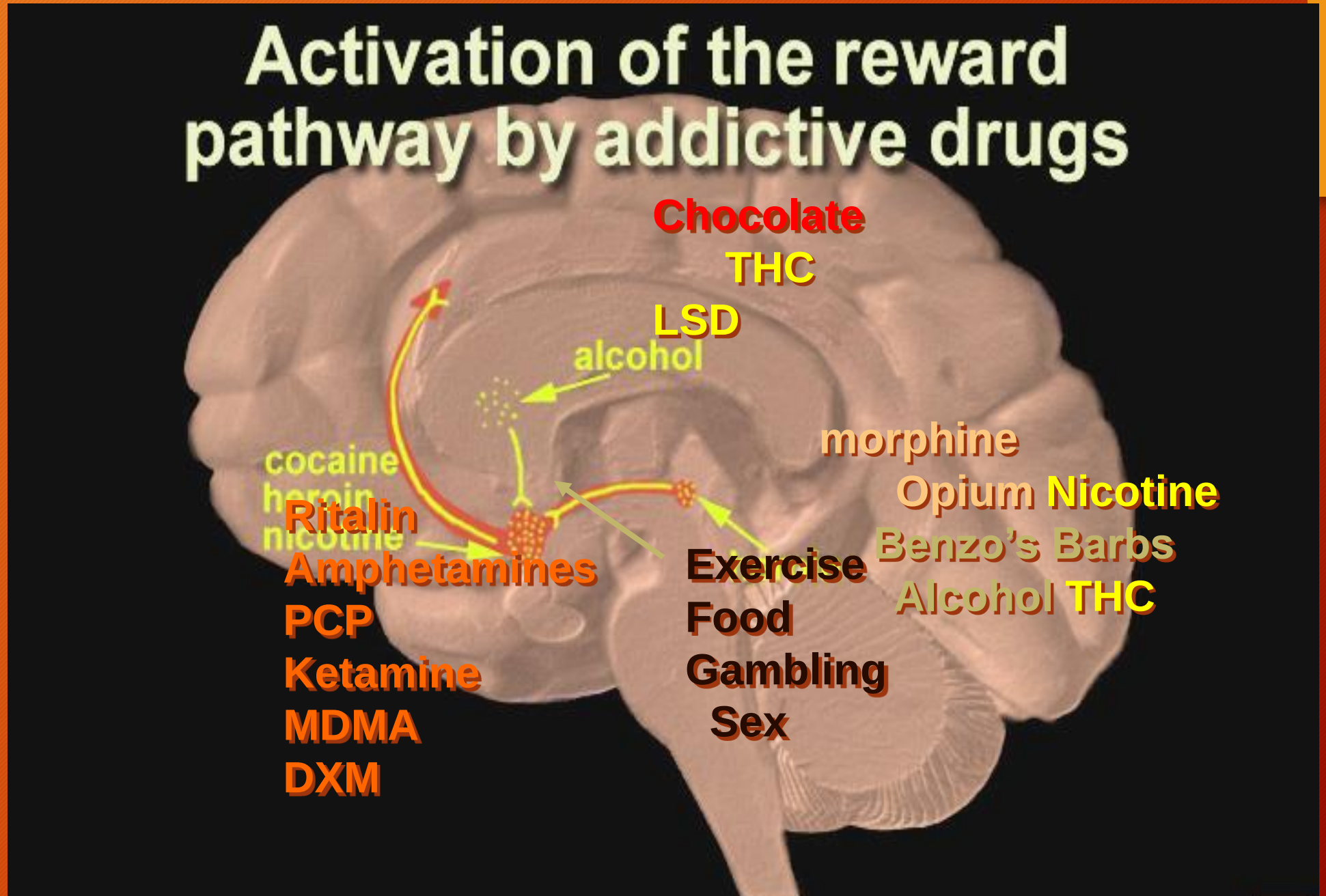
- Profoundly alter the Stress Response
- There are Acute Effects with use and opposite effects with withdrawal.
- These short acting substances cause the brain to be in constant flux creating a very unstable hormonal environment.

Case Study: Megan

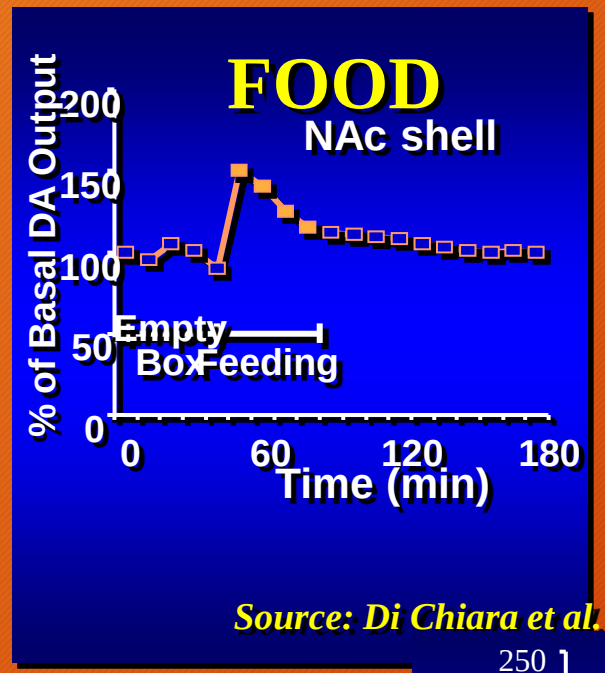
- Megan is a 45 year old woman, she is recently divorced, has 3 children and works 12 hour shifts as an ER Nurse
- Strong Family History of Addiction in both of her parents, so Megan vowed never to use drugs or alcohol
- Megan has some financial stress due to divorce
- Children are acting out at school and her oldest son has been caught stealing at the local convenience store
- Megan hurt her back at work…….Doctor prescribed Opia

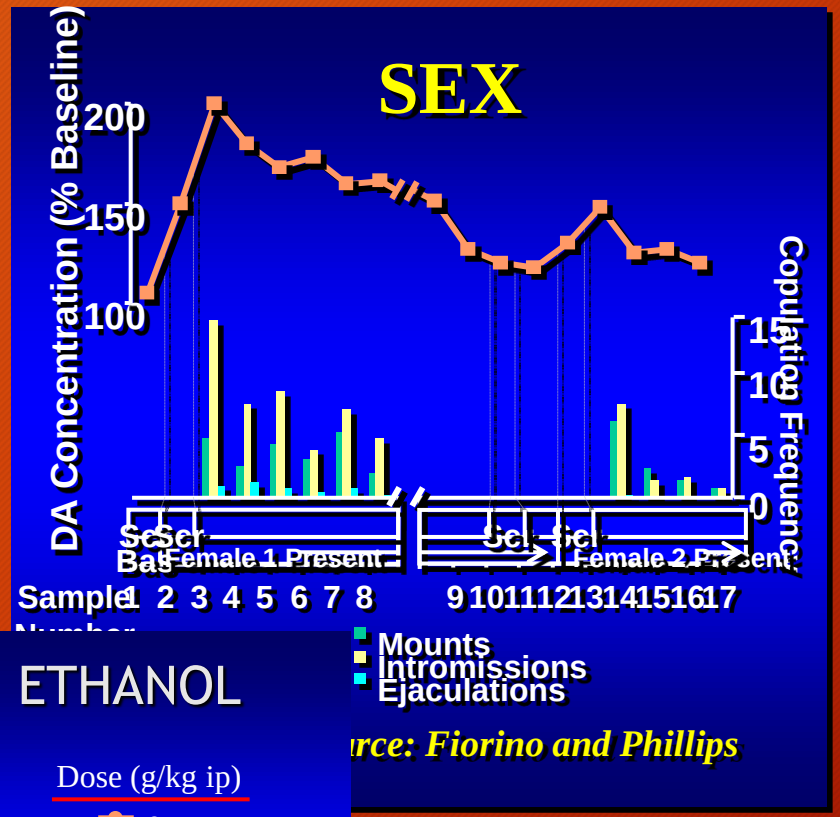
Megan’s The Three Legged Stool:

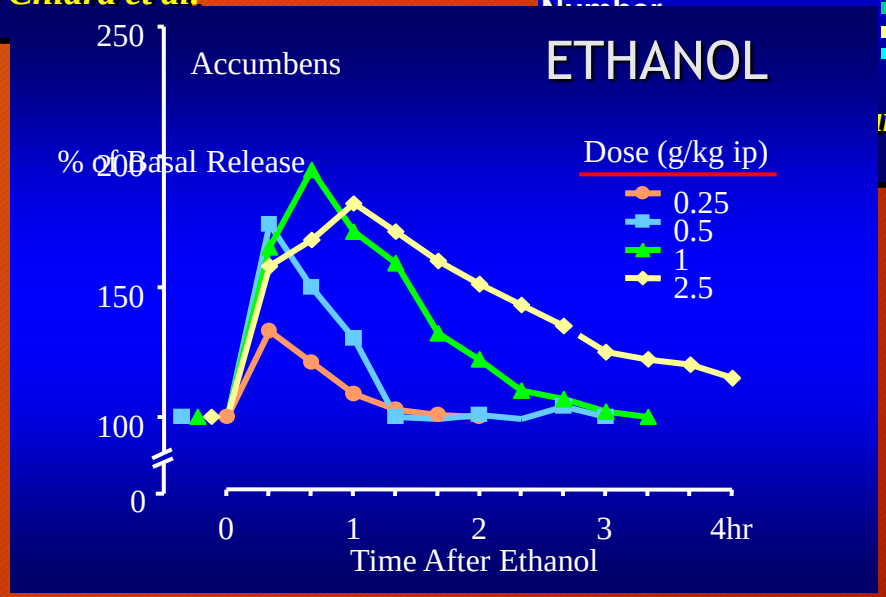



Activation of the reward pathway by addictive drugs
Chocolate
THC
LSD
alcohol
cocaine
heroin
nicotine
Ritalin
Amphetamines
PCP
Ketamine
MDMA
DXM
Exercise
Food
Gambling
Sex
morphine
Opium Nicotine
Benzo's Barbs
Alcohol THC

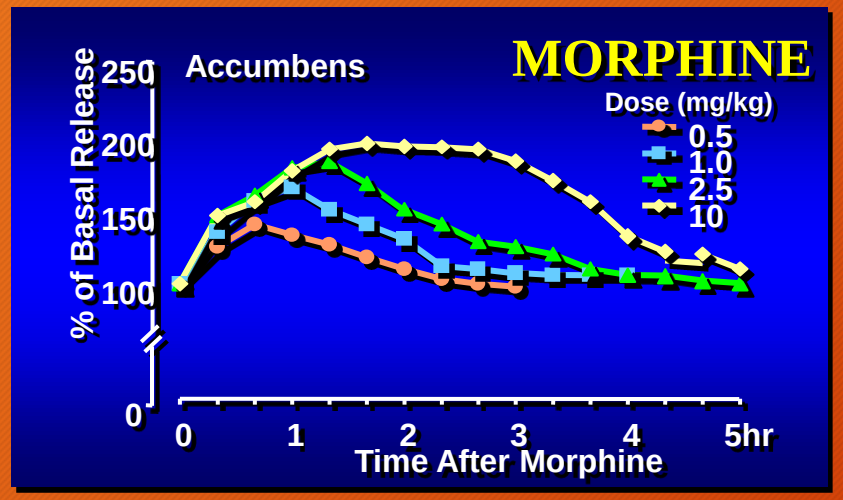
Natural Rewards Elevate Dopamine Levels

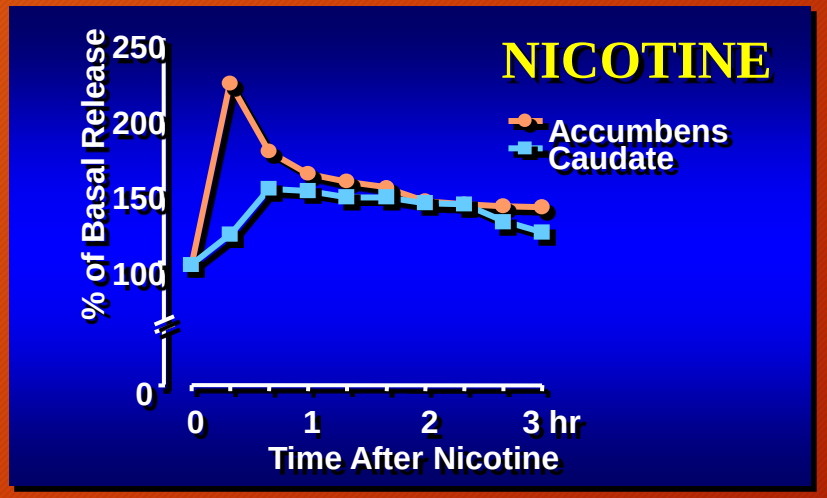


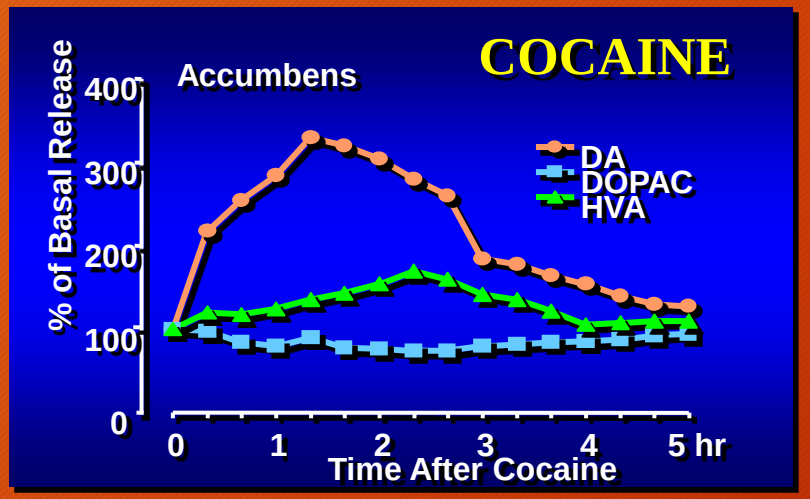


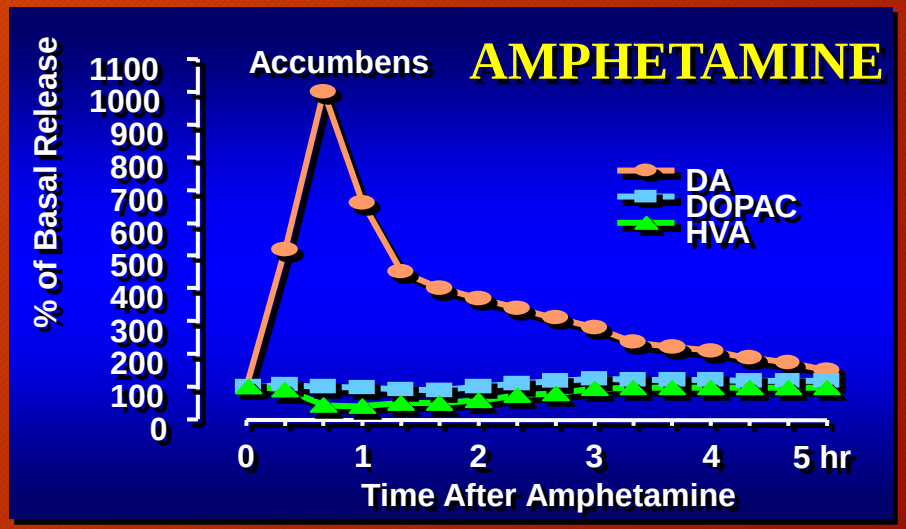


Effects of Drugs on Dopamine Levels



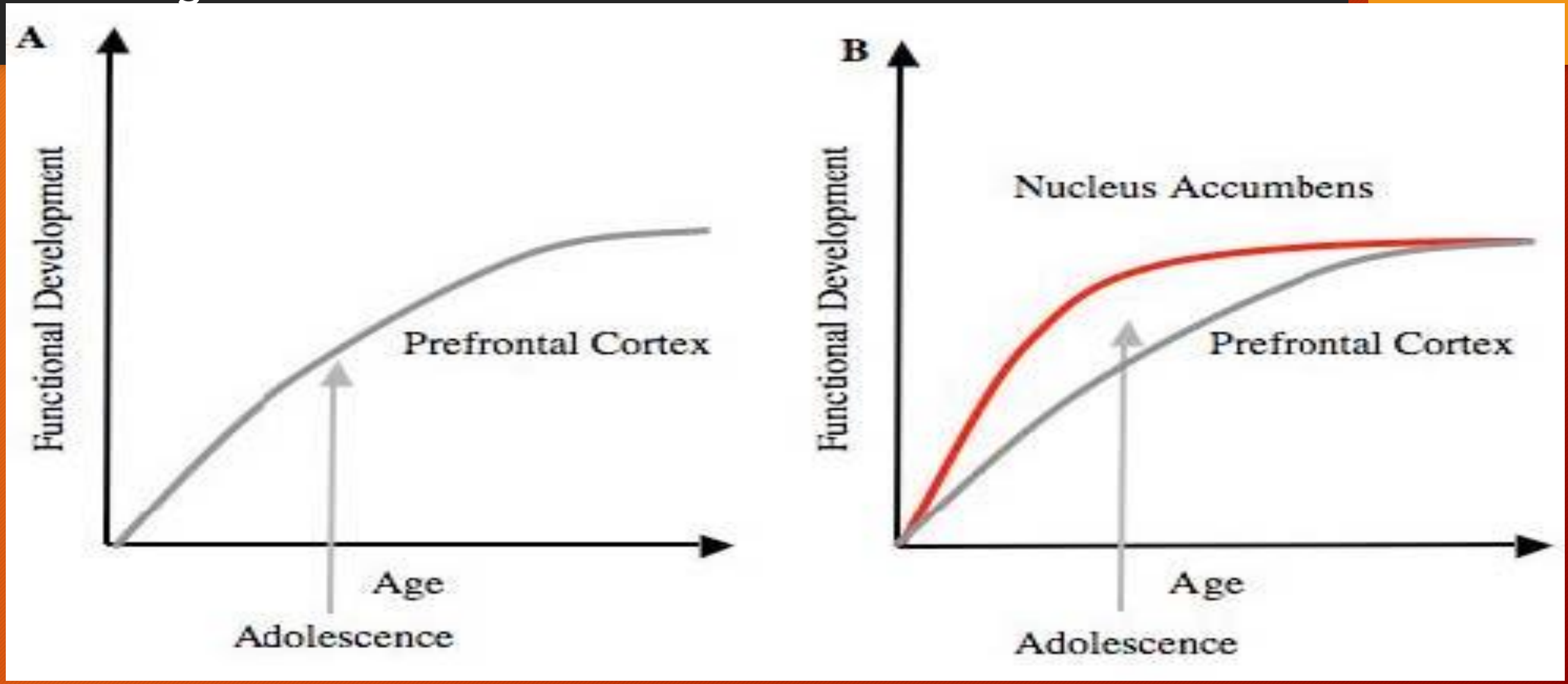


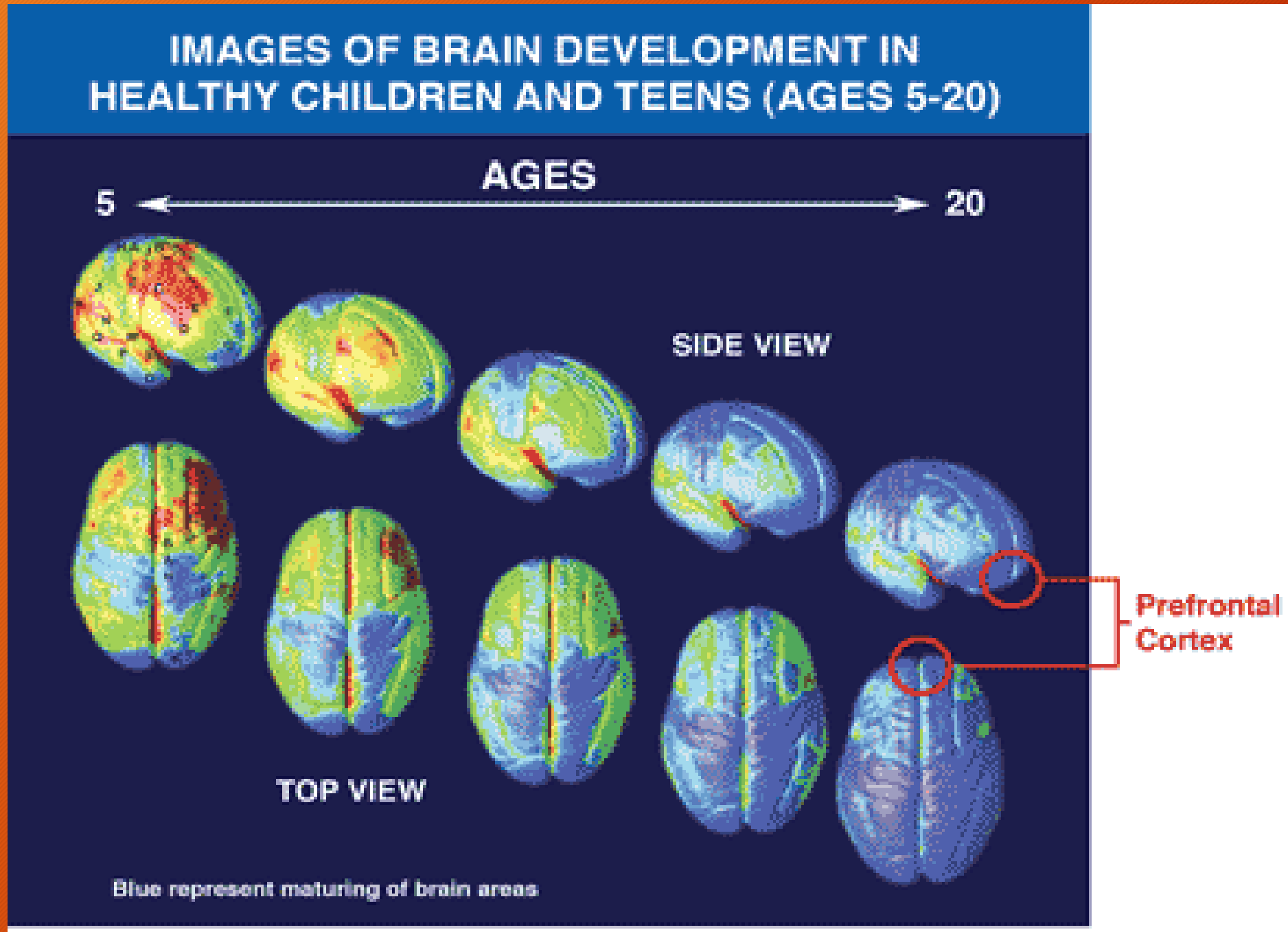




Source: Di Chiara and Imperato

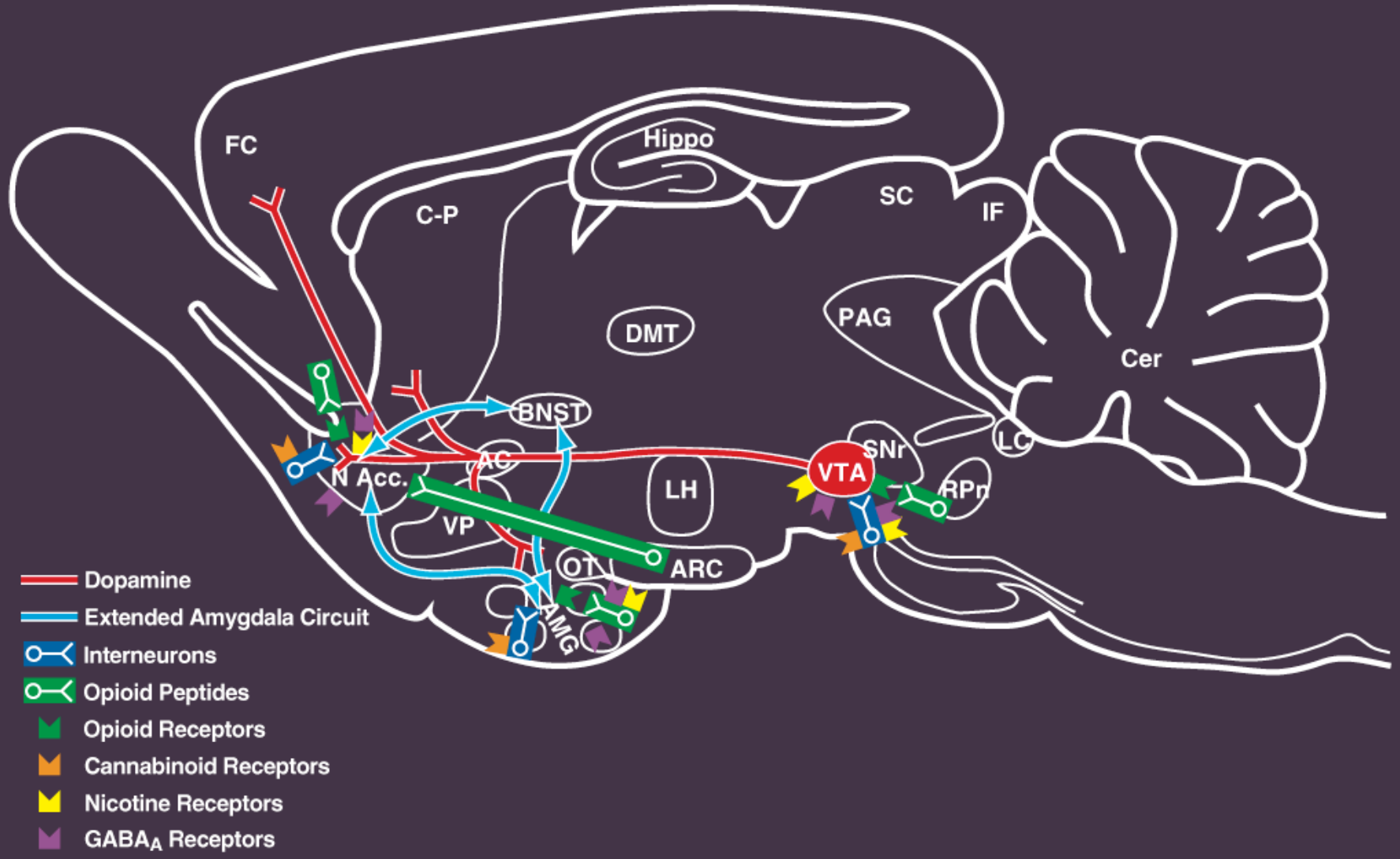
What causes Adolescents to experiment-role of early development of the Nucleus Accumbens-seek out exciting things



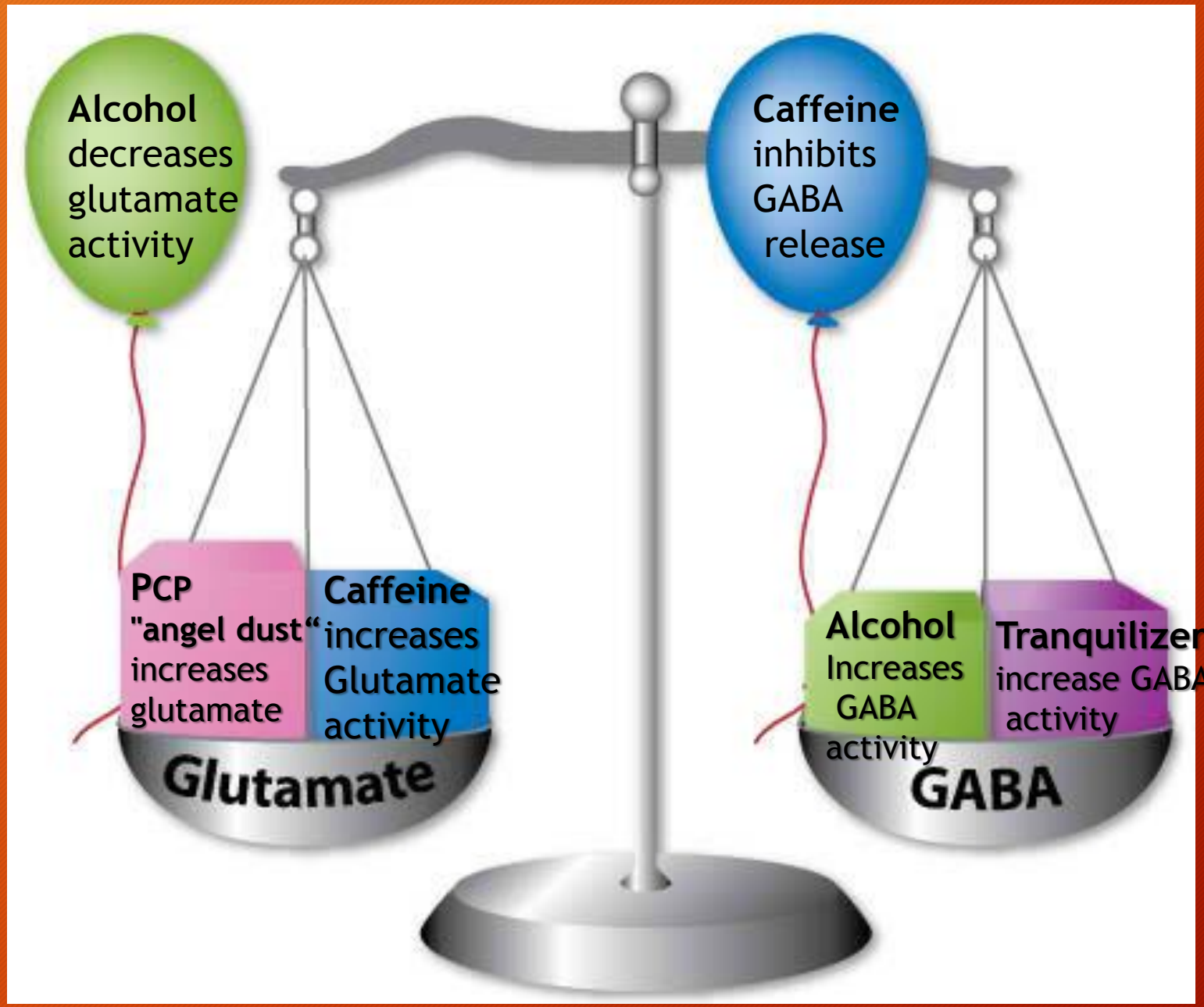


Source: Copyright PNAS ;101(21):8174-9. 2004

Neurochemical Circuitry in Drug Reward

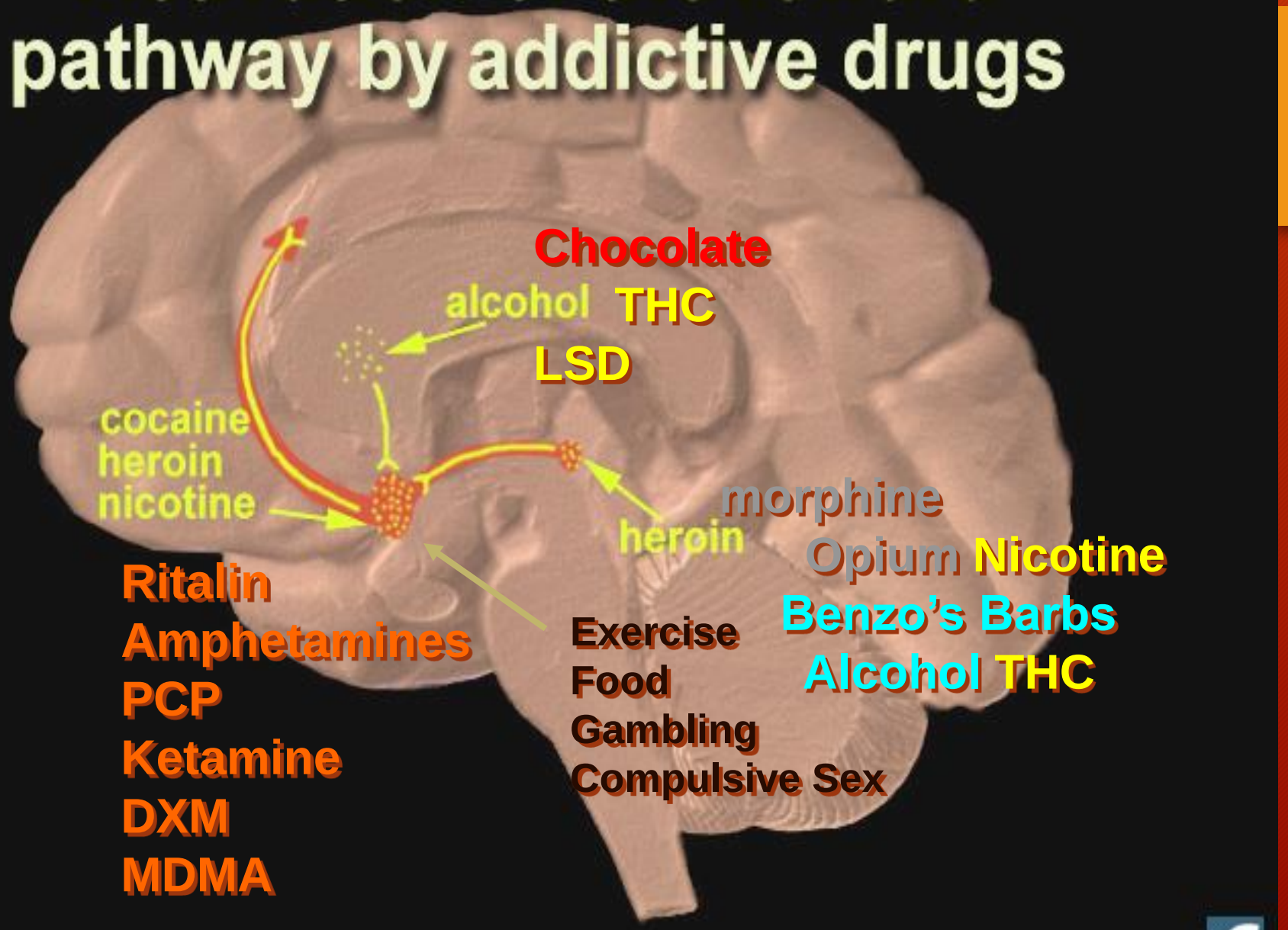


From: Koob GF, Clin Neurosci Res, 2005, 5:89-101.

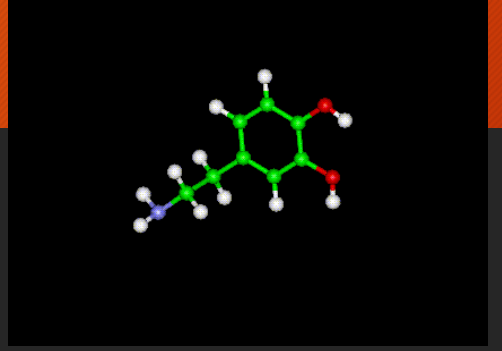


Genetic Science Learning Center (2011, January 24) Addiction Treatments Past and Present. http://learn.genetics.utah.edu/content/addiction/issues/treatments.html

Activation of the reward pathway by addictive drugs



Dopamine



- Found widely in many areas of the Brain
- Reinforcing effects of Drugs of abuse
- Effects immediate pleasure centers
- Lack of D2/5HT feedback loop results in the disease of Addiction

Dopamine Dysfunction

- Dopamine Feedback loop- Normal Brain

Dopamine produced

Dopamine production Stops, enough!!!!

Dopamine Dysfunction

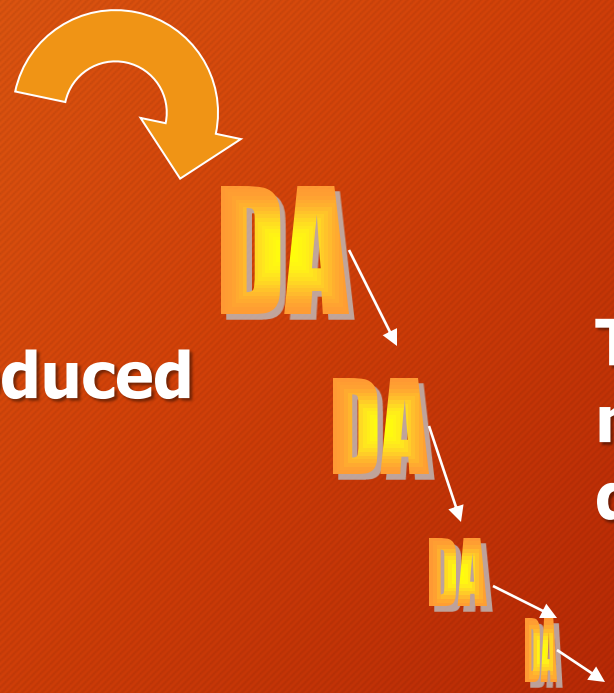
- **Dopamine Brain Diseases: Schizophrenia**

Dopamine produced

Too Much Dopamine: hallucinations, paranoia

Dopamine Dysfunction

- **Dopamine Brain Diseases: Parkinson's Disease**



Dopamine not produced

Too little Dopamine: movement disorders, depression,

Dopamine Dysfunction

- **Dopamine Brain Diseases: Addiction**

Dopamine produced

No Feedback: Dopamine production continues

*a little is good, more is better

Questions

Cognitive Impairment: A Seldom Discussed Complication of Substance Use Disorders

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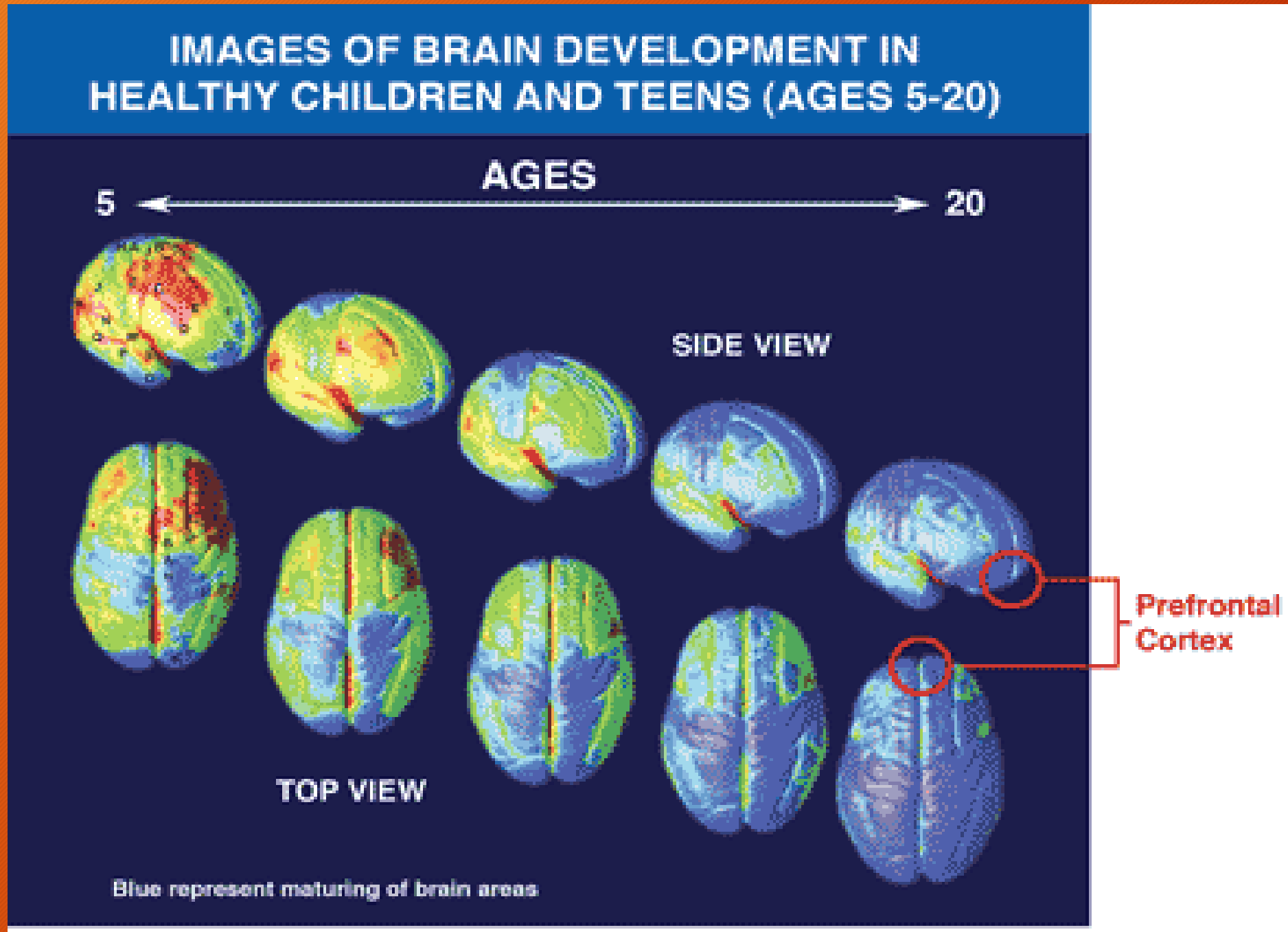


Source: Copyright PNAS ;101(21):8174-9. 2004

Brain: Most Complex Organ

- 100 Billion Neurons
- 1,000,000,000,000,000 connections in your brain
- 2% of body's weight
- Uses 20-30% of the total calories consumed


I AM THE
LEFT BRAIN
Decisive!
01100101
LOGIC
Accurate
ANALYTIC
REASON
1 3 5 7
2 4 6 8 9
PRACTICAL
Strategic
CONTROL
SCIENCE
Realistic
I AM the
Right BRain!
You are LOVE
thou art
Betty
FREE DOM
Passion
vivid
creative
YEARNING
PEACE

PreFrontal Cortex

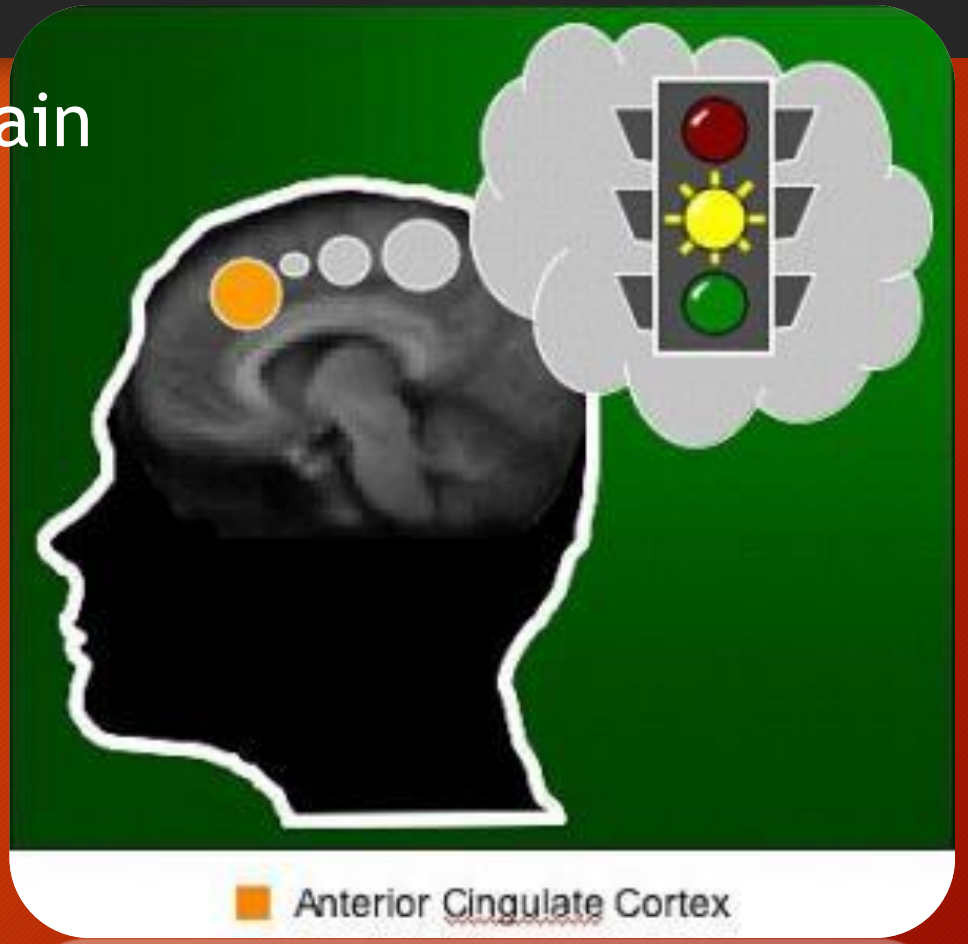
- Executive Functions
- “the Cop in your head”
- Focus
- Impulse control
- Planning &
  Organization
- Judgment
- Empathy
- Insight

PreFrontal Cortex Dysfunction

- Short Attention Span
- Impulsivity
- Disorganization
- Poor Judgment
- Procrastination
- Lack of Empathy and Insight

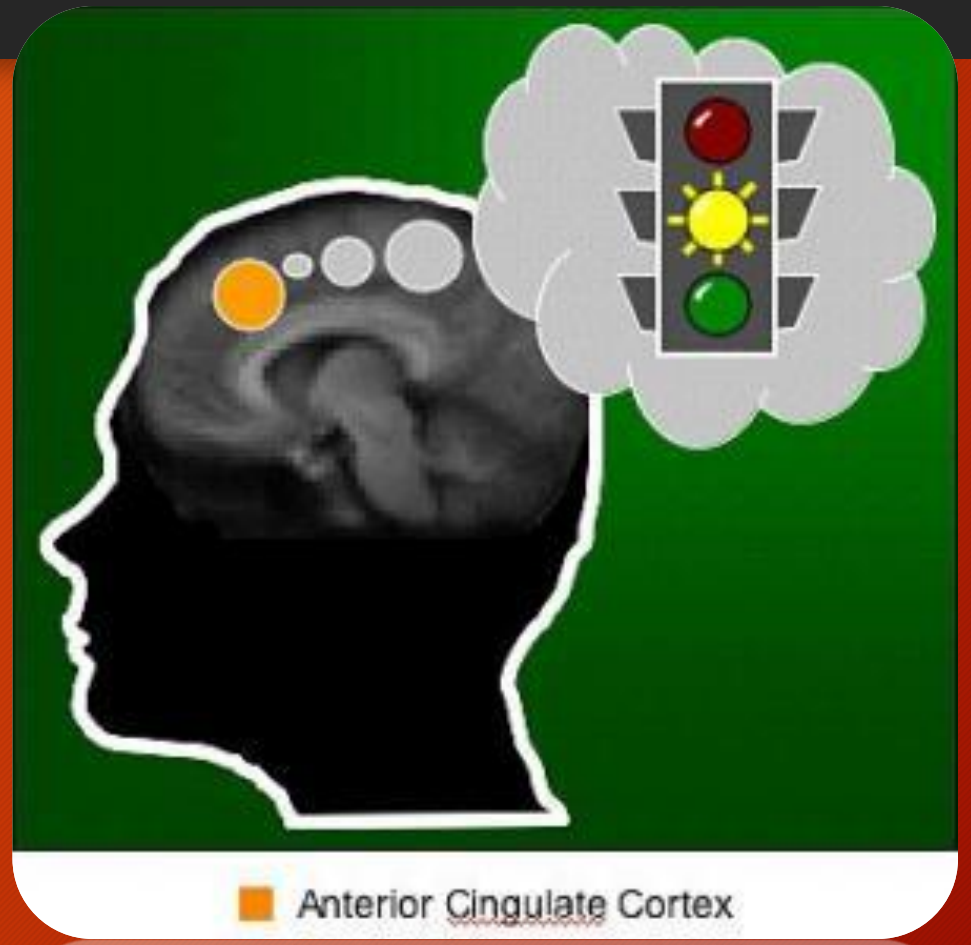
Anterior Cingulate

- Gear Shifter of the Brain
- Shifts Attention
- Sees Options
- Cooperation
- “go with the flow”
- Error Detection



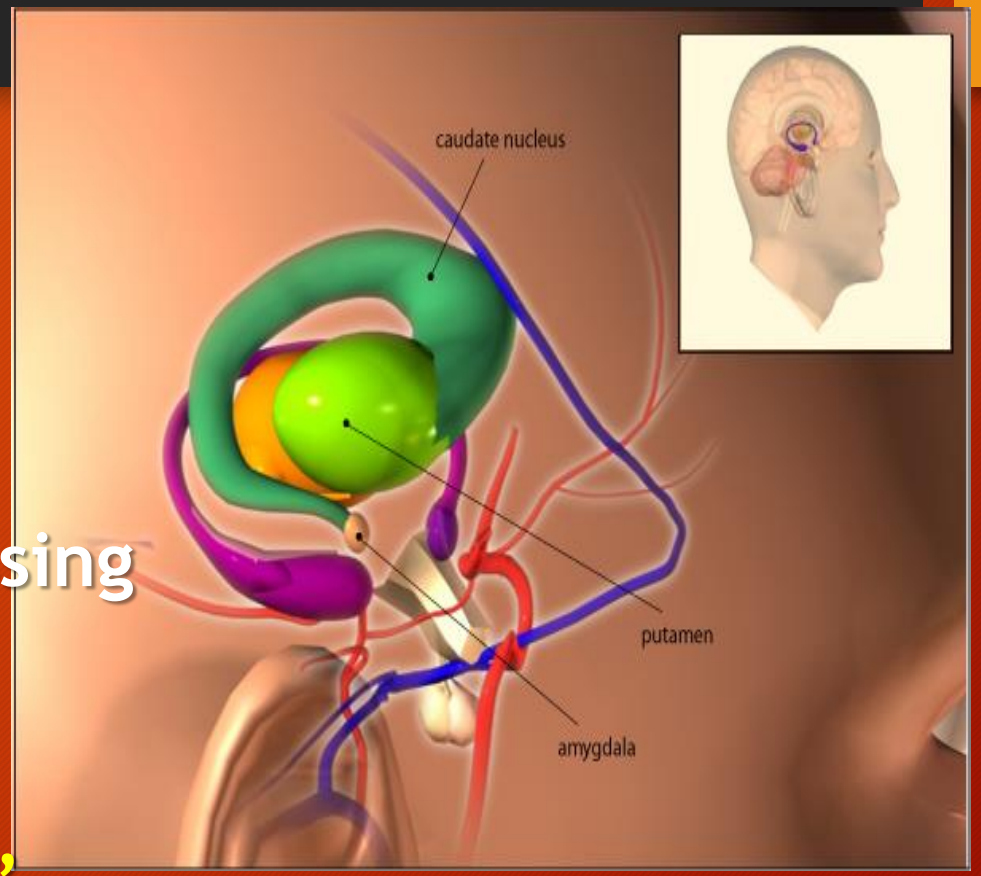
Anterior Cingulate Dysfunction

- Gets Stuck
- Worries
- Holds grudges
- Obsesses
- Compulsions
- Addiction
- Eating Disorders
- Oppositional
- Argumentative
- Sees Too many Errors



Basal Ganglia

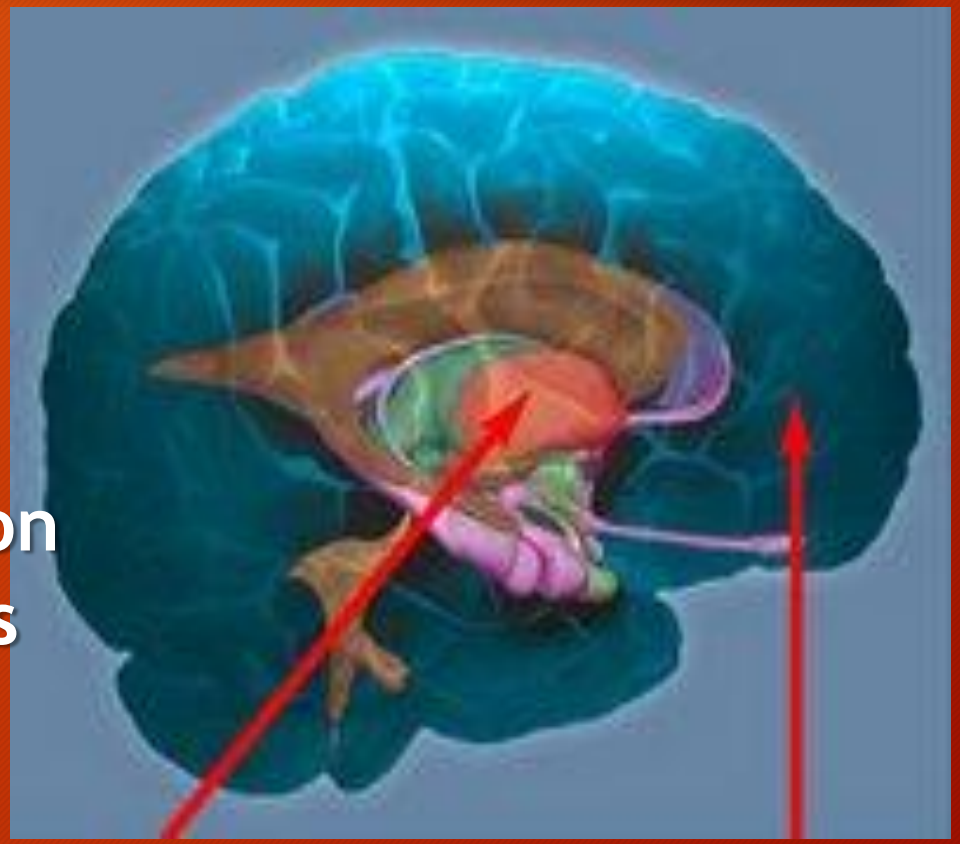
- **Movement, Anxiety and Motivation**
- Caudate
  - Thoughts
- Putamen
  - Motor
- Insula
  - Emotional Processing
  - Auditory/Visual processing
- Nucleus Accumbens
  - Pleasure
- **Amygdala="am I safe????"**



Basal Ganglia

Basal Ganglia

- Increased:
  - Anxiety/Panic Attacks
  - Conflict Avoidant
  - Excess motivation
  - Predicts the worst
- Decreased:
  - ADD Like Symptoms
  - Decreased Motivation
  - Movement Disorders (Parkinson's)

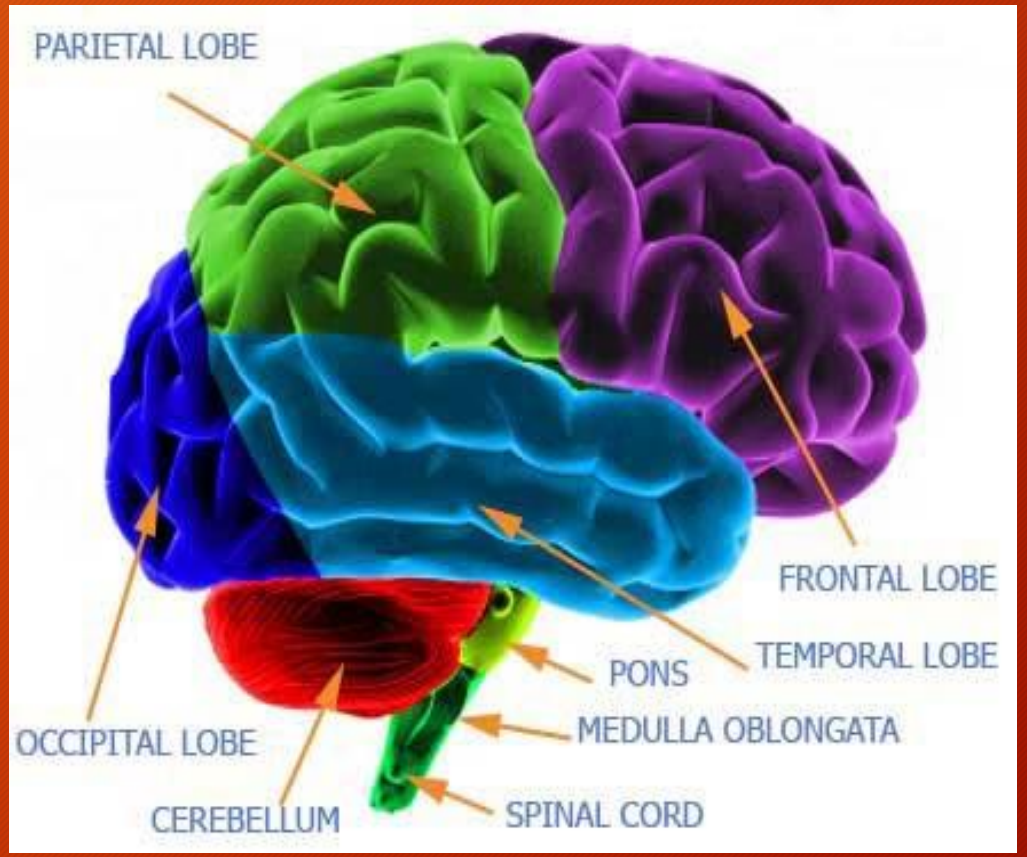


Basal Ganglia

PreFrontal Cortex

Temporal Lobes

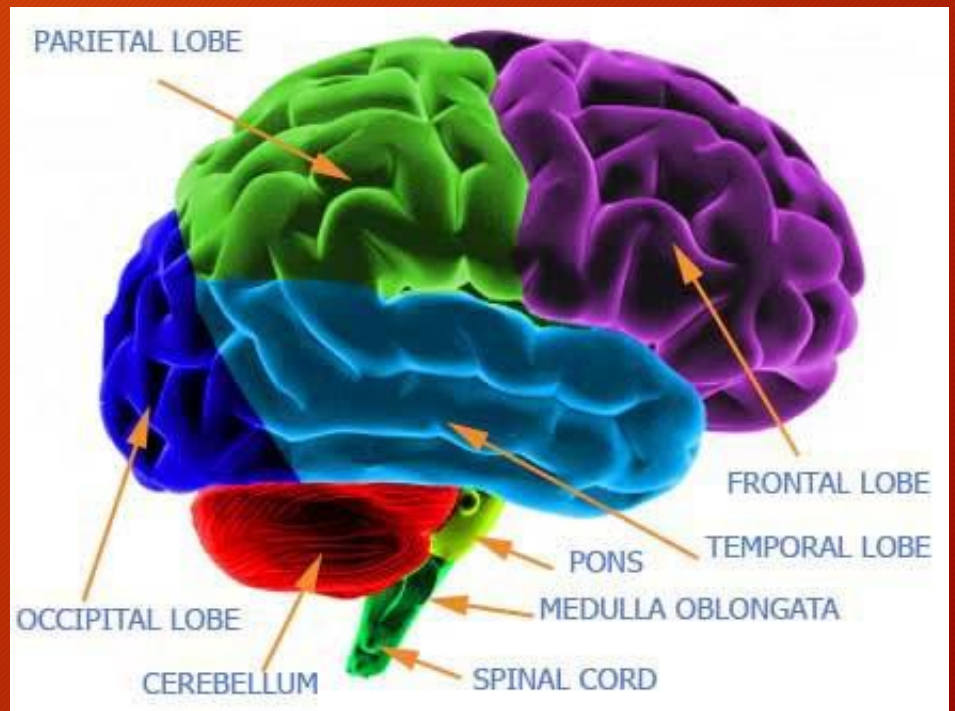
- Language
- Memory
- Retrieval of words
- Mood stability
- Read Social Cues
- Temper Control
- Spiritual Experience



Temporal Lobe Dysfunction

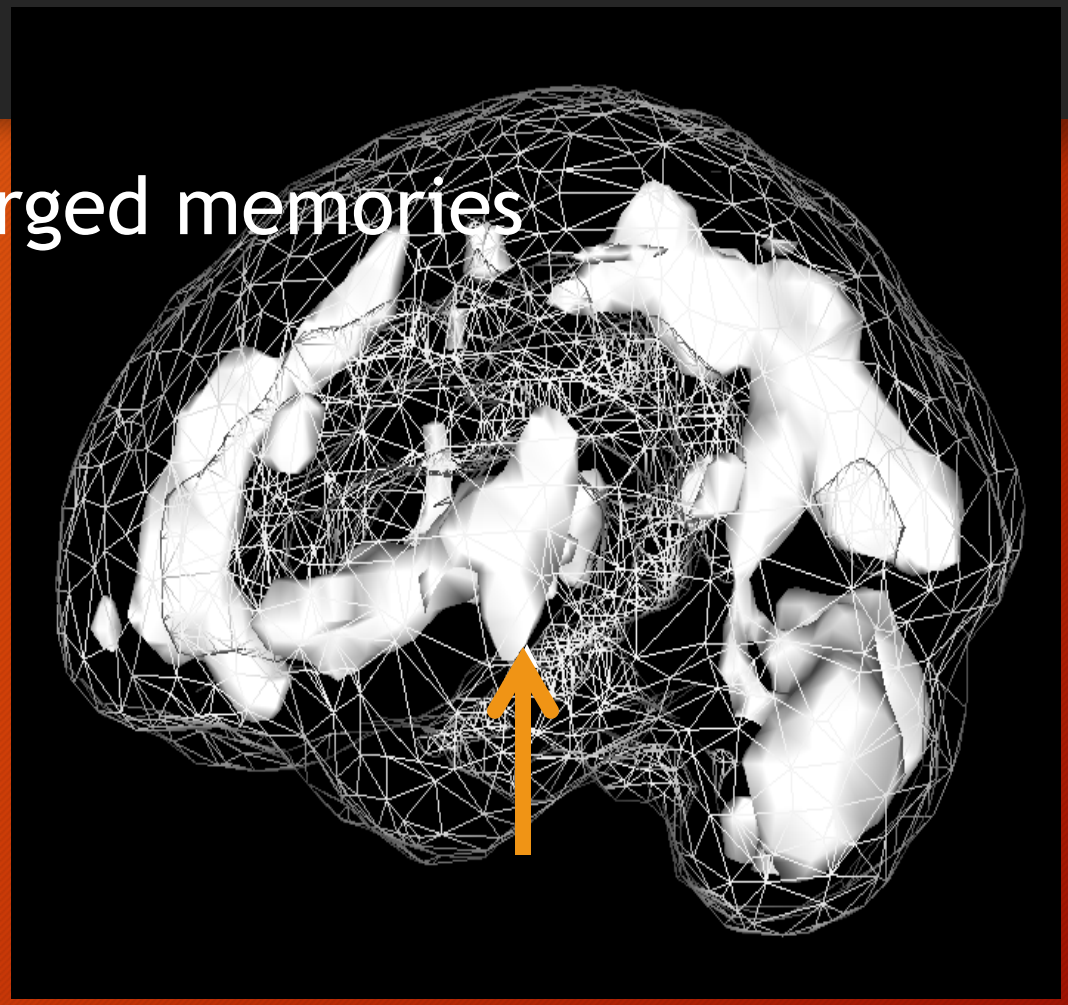
- The “what” Pathway
- Language Problems
- Memory Problems
- Dyslexia
- Word Finding Problems
- Panic/Anxiety
- Trouble with social cues

- Dark thoughts
- Aggression
- Illusions
- Hyper Religiosity



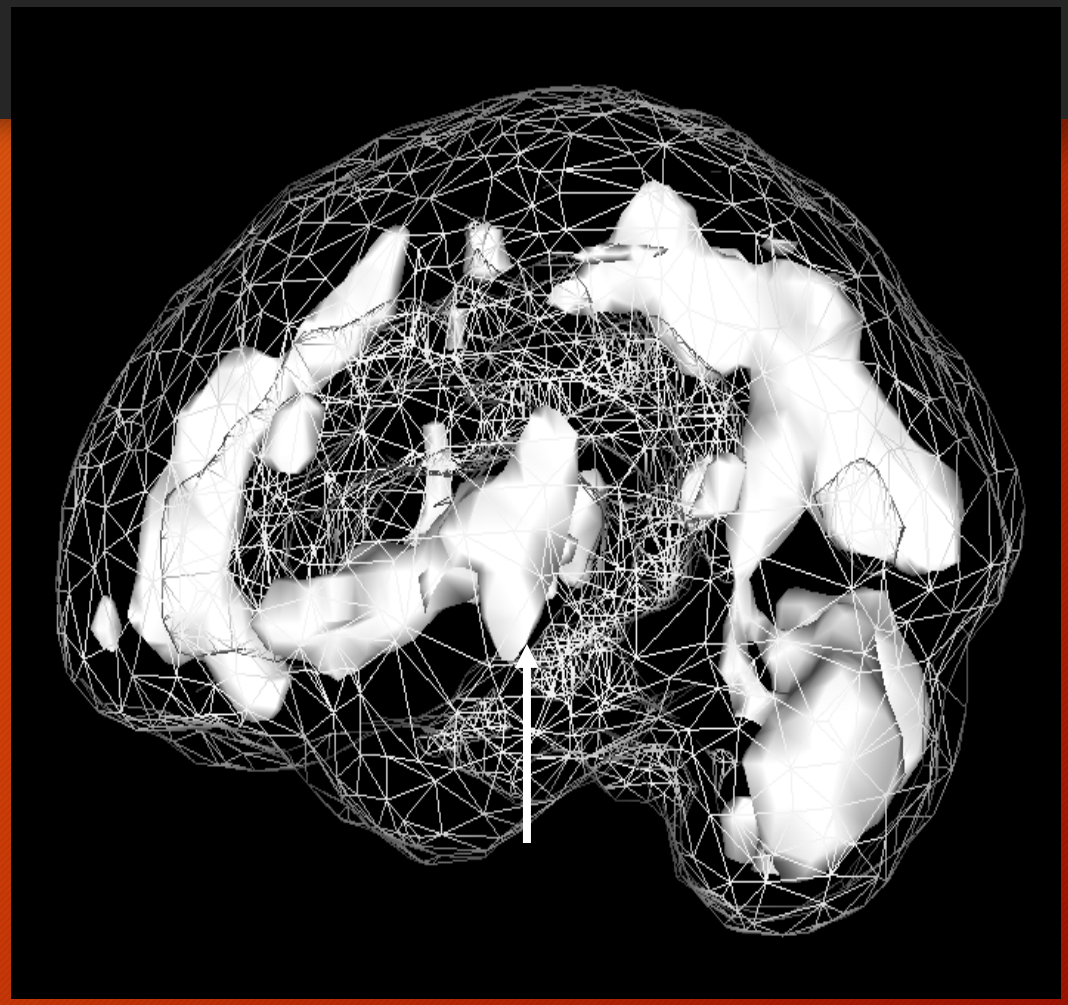
Deep Limbic System

- Emotional Tone
- Emotionally Charged memories
- Integration-
  - Sensory Info
- Sets emotional tone
- Bonding
- Sense of smell
- Libido
- Pain



Deep Limbic System Dysfunction

- Depression, sadness
- Negative, irritability
- Low motivation
- Negativity, blame
- guilt
- Social isolation
- Low self-esteem
- Low libido
- Low energy
- Decreased interest
- Worthlessness



Cerebellum

- Motor control
- Posture, gait
- Executive function, connects to PFC
- Speed of cognitive integration (like clock speed of computer)
- Impulse Control

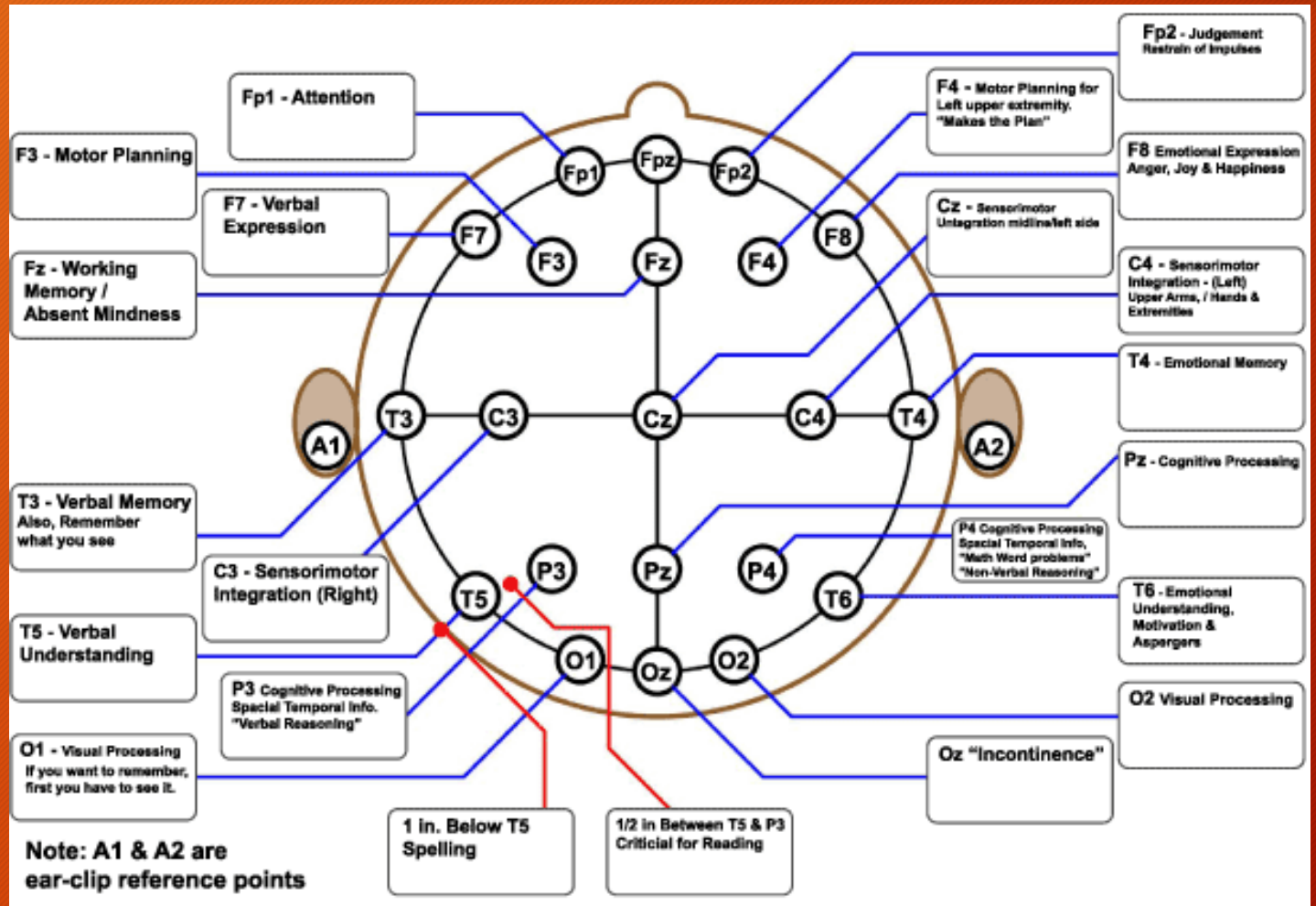
Cerebellum Dysfunction

- Gait/coordination problems
- Disorganization
- Slowed thinking
- Slowed speech
- Impulsivity
- Poor conditioned learning
- Autism/ Aspergers
- ADD

Effects Of Drugs of Addiction On the Brain

Director of the National Institutes of Health Dr. Francis Collins is a multiple-appearance guest on The Colbert Report and was on with the comedian last night to promote Barack Obama's BRAIN initiative. April 5, 2013

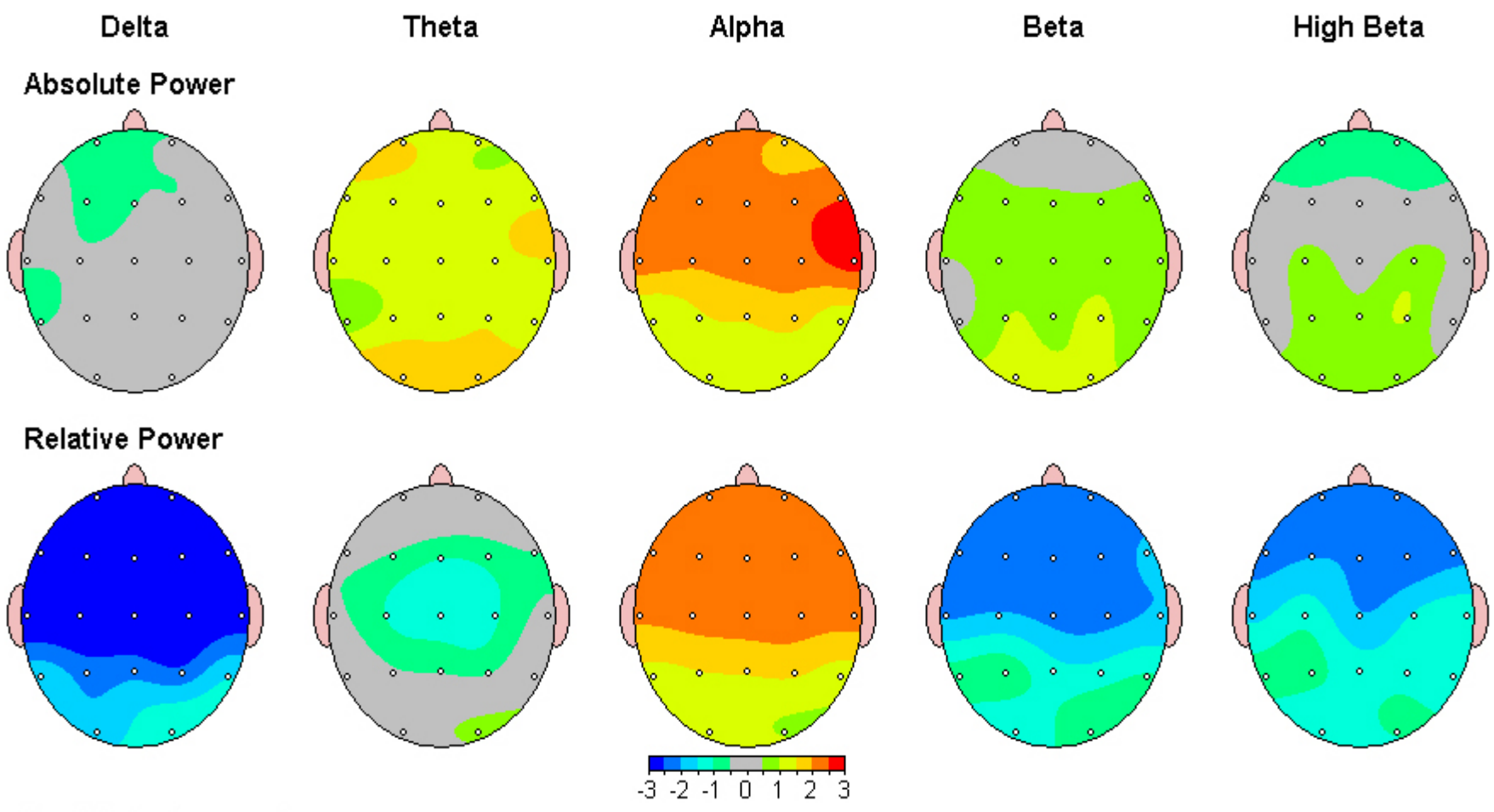
19 Channel Quantitative Electroencephagram



Montage: LinkEars

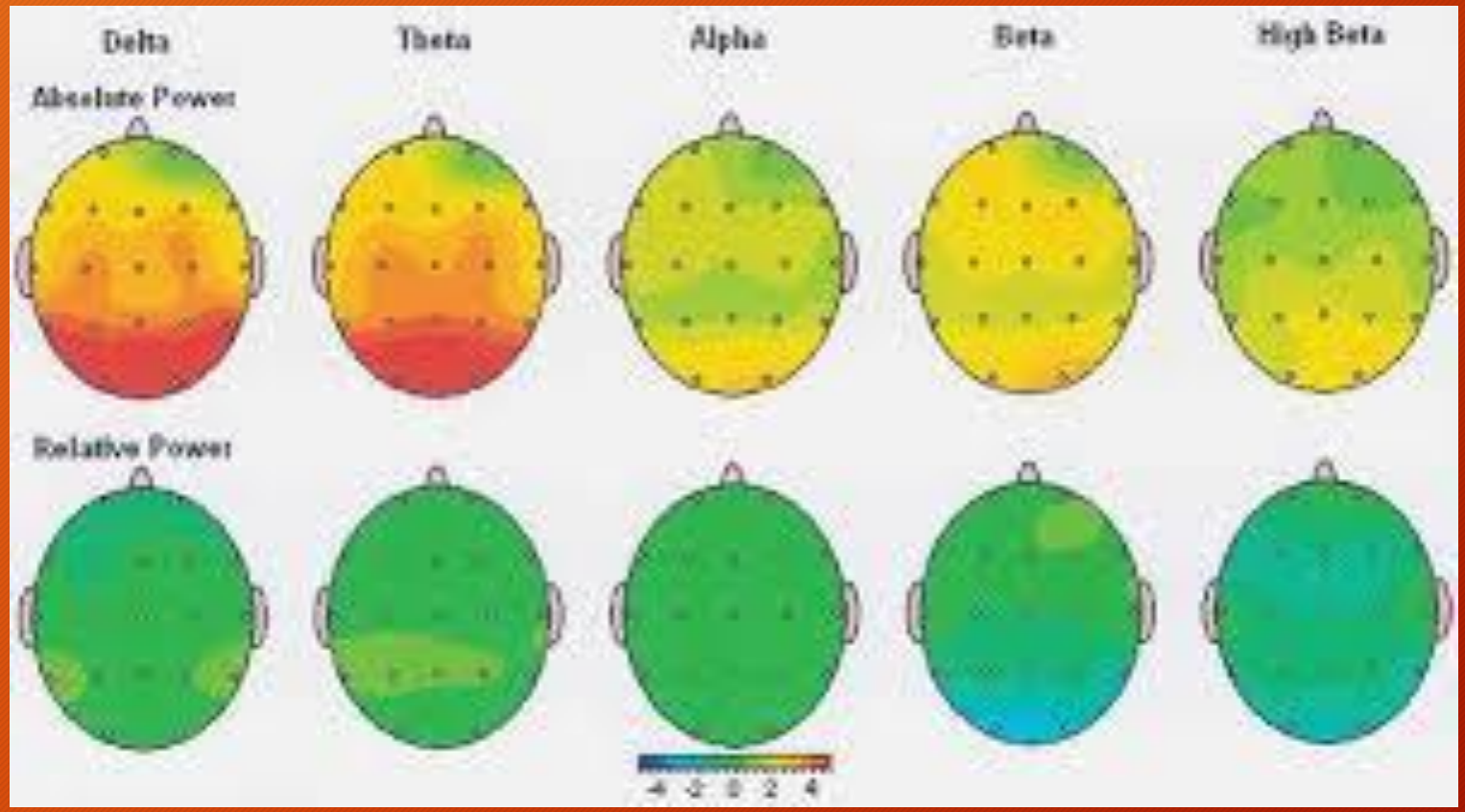
EEG ID: ECa

Z Scored FFT Summary Information



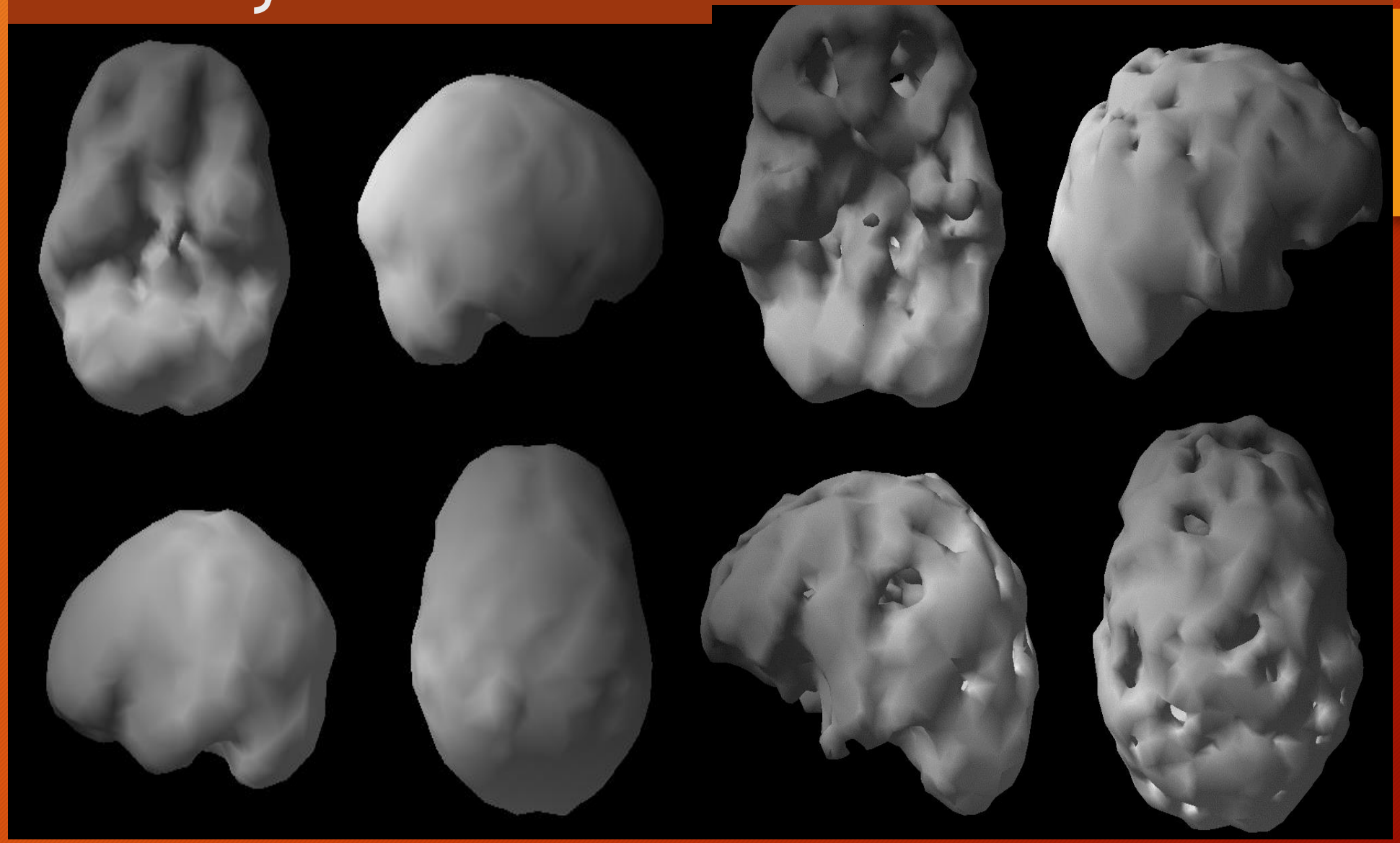
QEEG of Fetal Alcohol Syndrome-Cory Hammond

Journal of Neurotherapy, 16:47–52, 2012

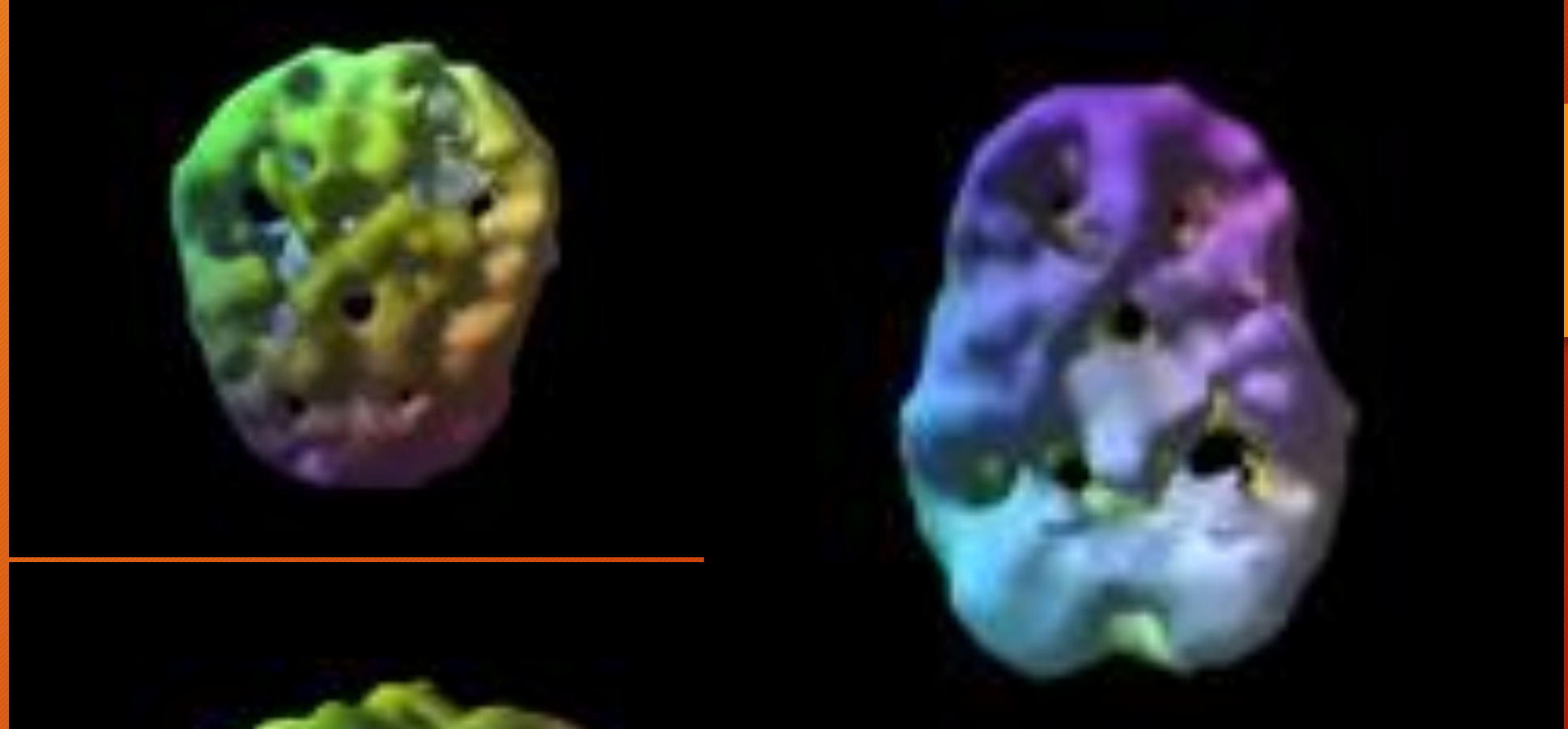


Healthy Brain

Alcohol Damaged Brain



Unchain your brain, Amen, D and Smith D; 2010, Mindworks Press.



38 y/o – 17 years of heavy alcohol weekend use (binge type drinking)

Table 2.

Scores from the individual neuropsychological tasks from which outcome scores were derived

	Controls (*n* = 58)	Alcohol-dependent (*n*=43)	Uncorr. *P*-value
WAIS-R tests			
Vocabulary: age scaled scores	14.1 ± 2.7	12.5 ± 3.3	0.006
Arithmetic: age scaled scores	12.0 ± 2.7	11.9 ± 3.1	NS
Picture arrangement: age, scaled scores	13.7 ± 2.8	12.6 ± 3.4	NS
Block design: age scaled scores	12.7 ± 3.3	12.1 ± 2.9	NS
Digit symbol: age scaled scores	10.9 ± 2.5	**9.3 ± 2.7**	0.002*
Pro-rated verbal IQ	114.6 ± 12.2	109.7 ± 15	NS
Pro-rated performance IQ	114.5 ± 11.4	109.8 ± 13.3	NS
Pro-rated full scale IQ	117.0 ± 12.0	110.9 ± 14.7	0.024
Trail-Making Tests			
Trail A (s)	33.0 ± 10	36.9 ± 12.8	NS
Trail B (s)	66.1 ± 23.9	**84.4 ± 42.9**	0.007
Total: Trail A ± B (s)	99 ± 28	121 ± 51	0.007
WMS: logical memory test			
Immediate recall	13.3 ± 3.0	12.0 ± 3.5	0.05
30-min recall	11.7 ± 3.2	10.1 ± 3.9	0.03
Total Wechsler memory score: (immediate + recall).	25.0 ± 6.0	22.2 ± 7.1	0.033

Cognitive Effects of Chronic Alcohol Use

- Both smoking and alcoholism were related to impaired executive function.
- However, the effect of alcoholism was not independent of IQ
- Suggesting a generalized effect, perhaps affecting a wide range of cognitive abilities of which executive function is a component.

Glass, J, et al. Addiction. 2009 Jan;104(1):38-48.***Effects of alcoholism severity and smoking on executive neurocognitive function.***

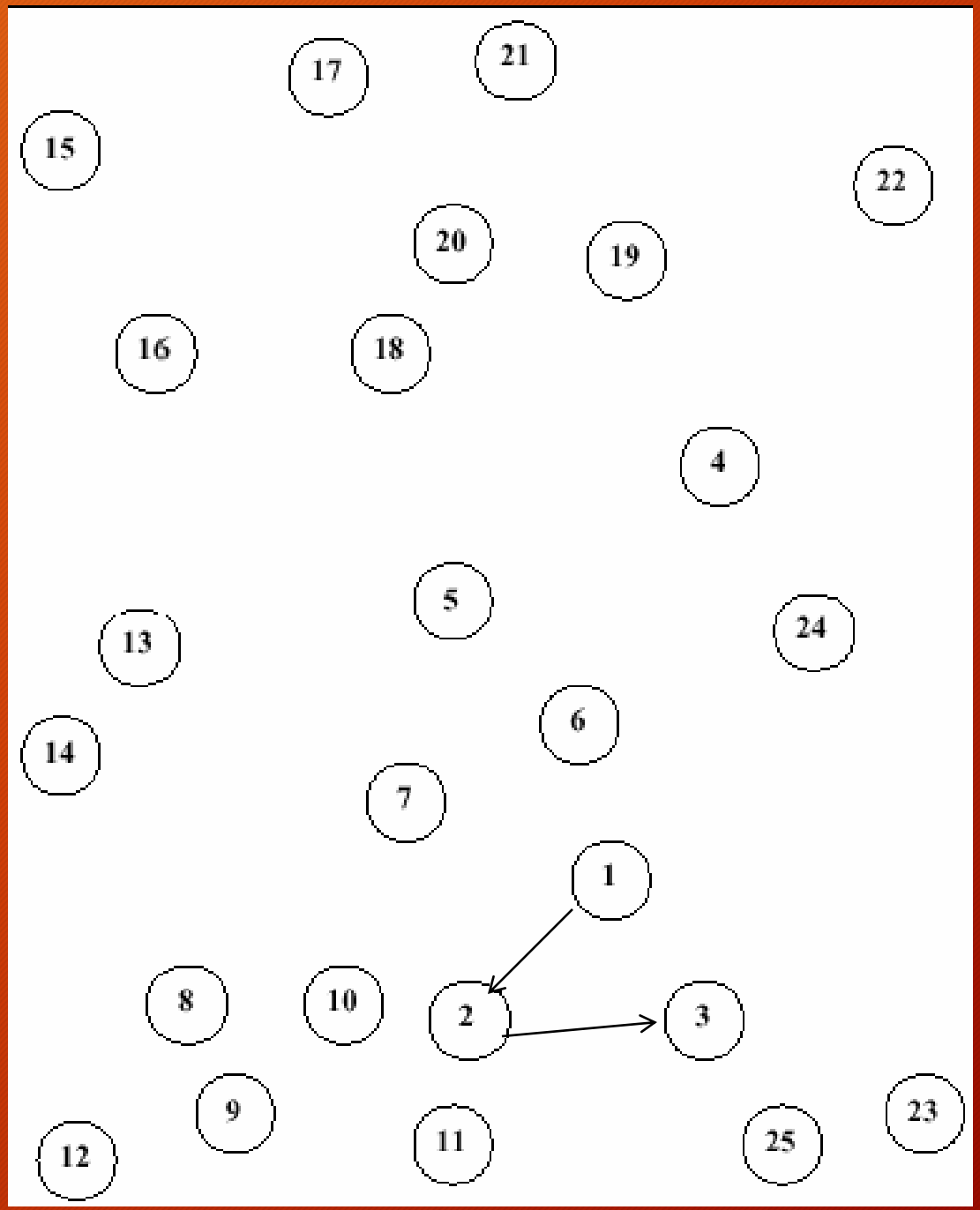
SIMON J. C. DAVIES, et al..University of Bristol London, recommend:

- Trail A and B test, in particular the Trail B section, and the digit symbol test should be considered for routine clinical use in the assessment and treatment of alcohol dependence, even in apparently cognitively, mentally, and physically healthy patients.
- The Trails test requires minimal training, can be easily used by a range of workers, takes about 5 min to complete, and requires no special equipment

Trails: Part A

Trail A
Controls 33 ± 10 seconds
Average: 29

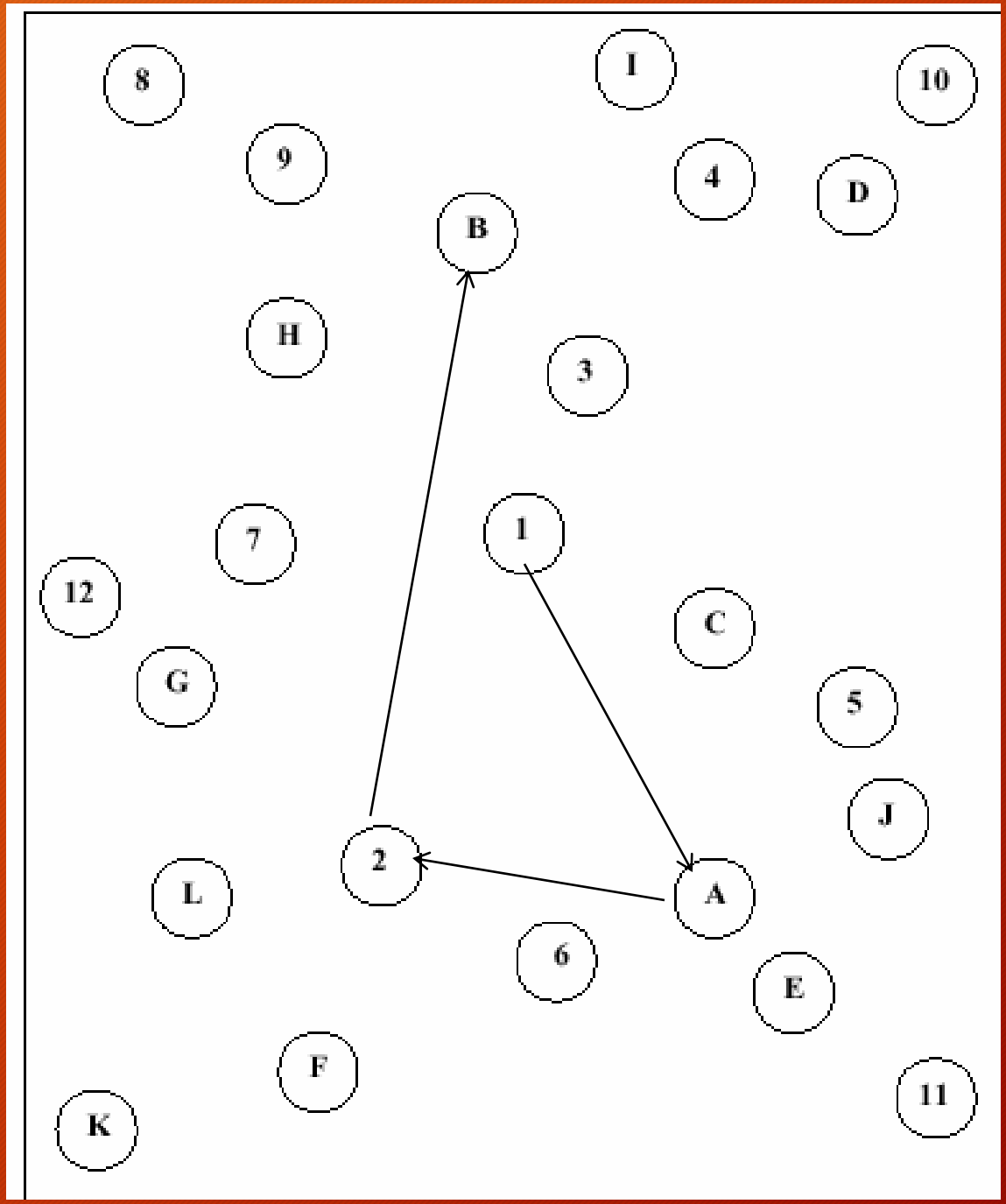
Alcoholics
>78 seconds
Most in 90 seconds



Trails: Part B

Trail B
Controls 66.1 ± 23.0
Average:75 seconds

Alcoholics
84.4 ± 42.9
Most in 3 minutes



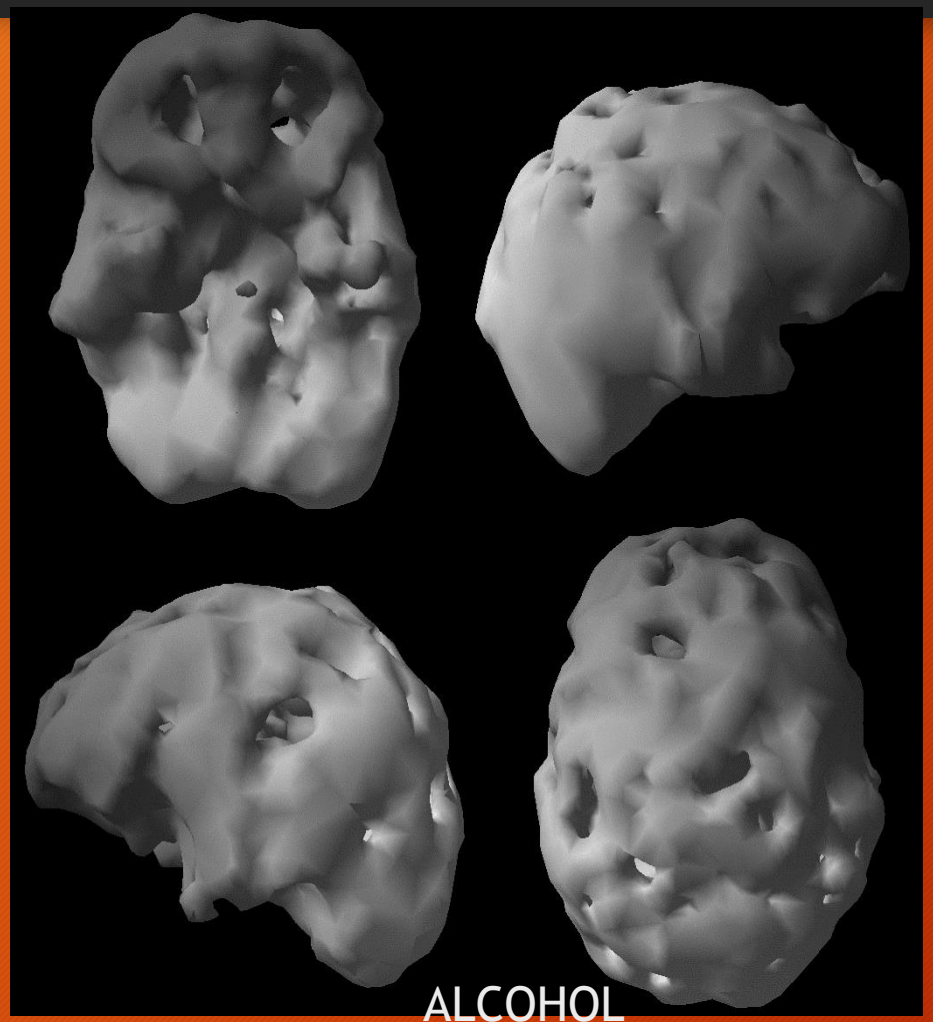
DIGIT SPAN TEST

- A common test of short term memory
- Say the digits slowly in a monotone at one second intervals
- Patient must say the digit back 75% correct on the first try to be considered as having a digit span of _X__
- A 2 year old will have a digit span of 2, a 3 year old-3, 4year old-4
- Average for 7 year old-7 thru adult

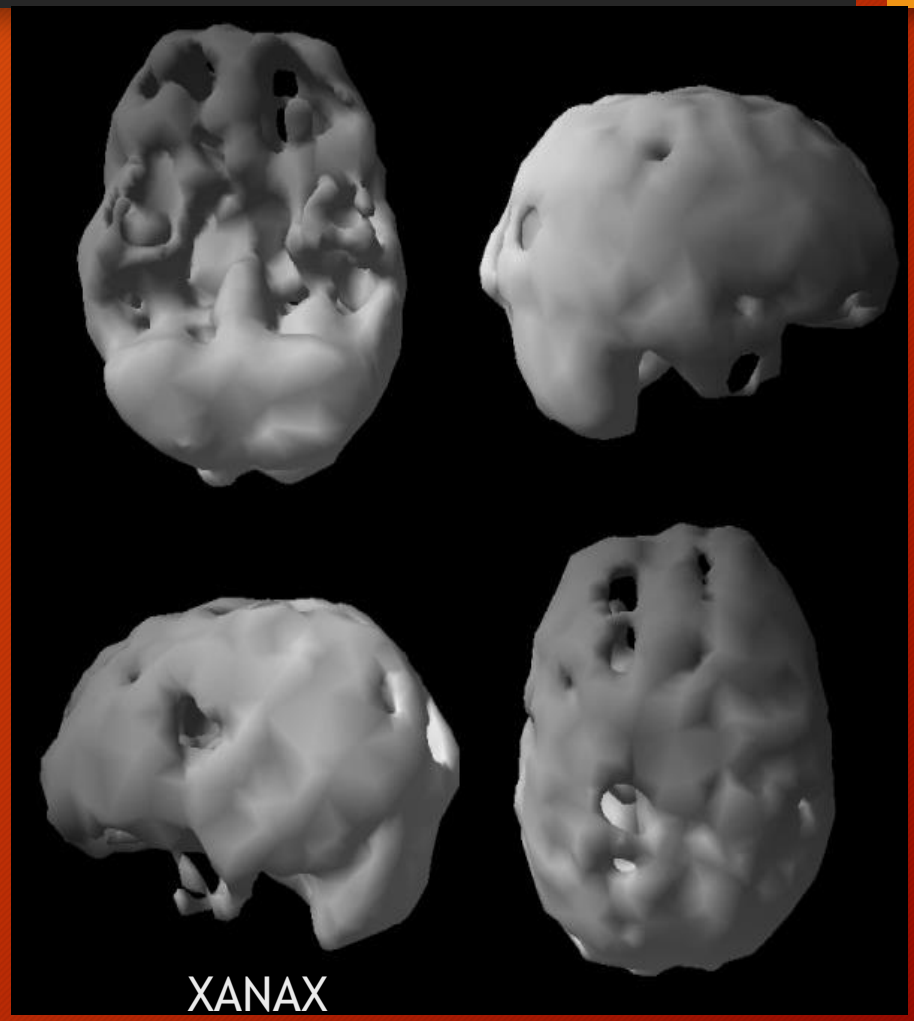
Controls
11 ± 2.5

Alcoholics
9.2 ± 2.7

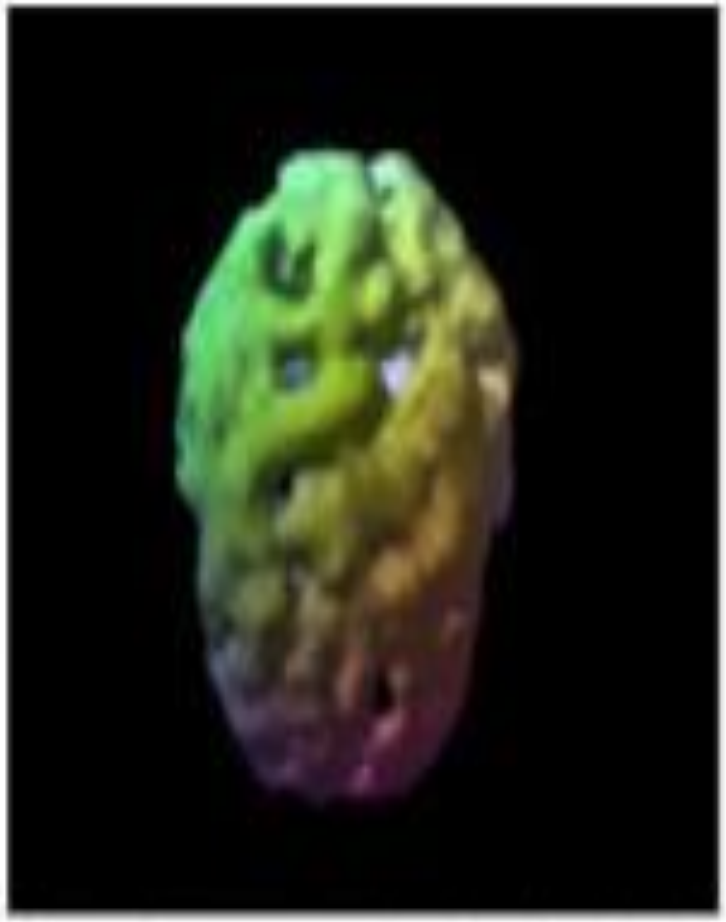
XANAX and Alcohol



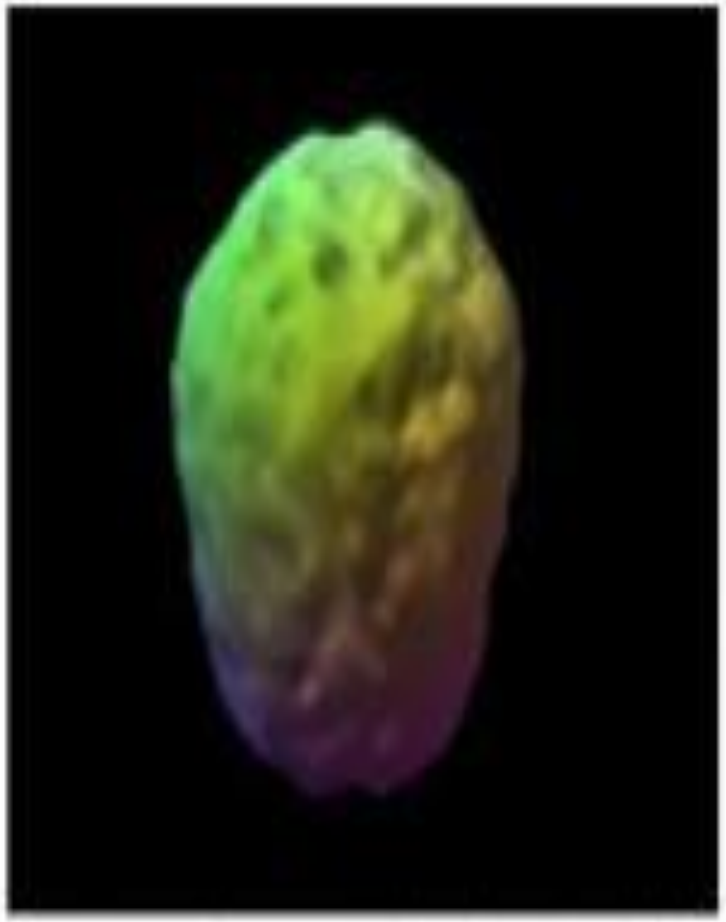
ALCOHOL



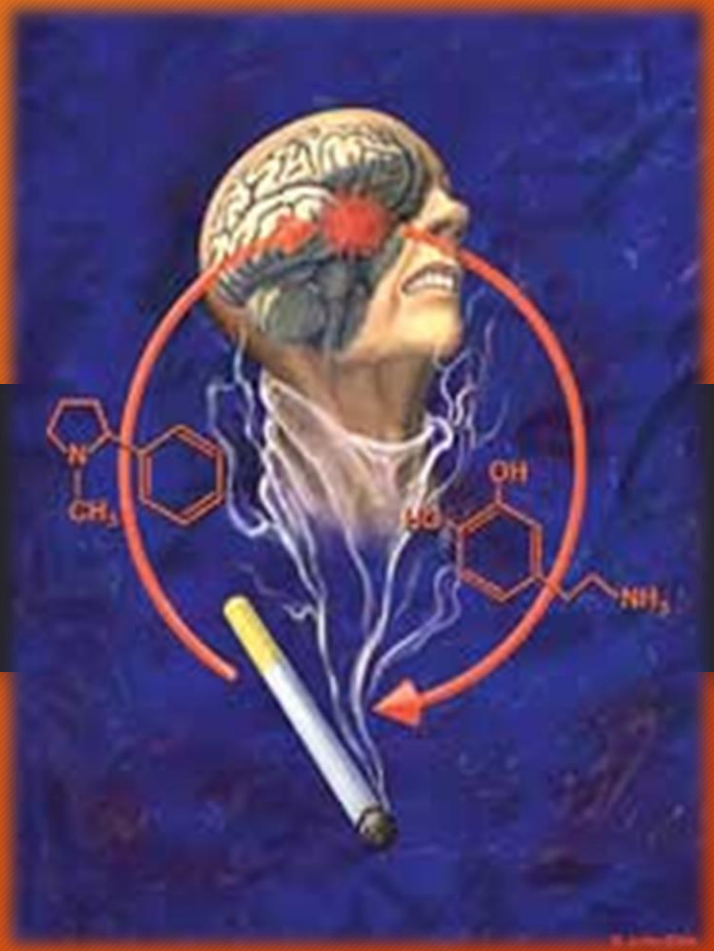
XANAX



Active drug and alcohol abuse



A year drug and alcohol free



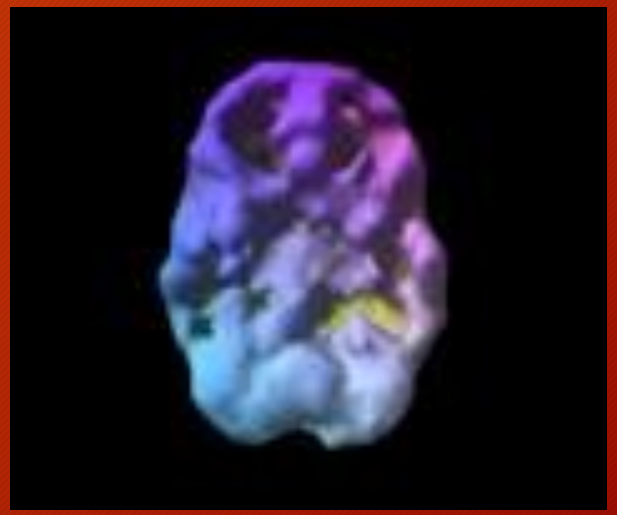
Smoking

The worst addiction

Cognitive Effects of Chronic Smoking

- The effect of smoking on measures relying on response speed were independent of IQ
- Suggesting a more specific processing speed deficit associated with chronic smoking

45 y/o – 27 year history of Smoking 3 packs of cigarettes and drinking 3 pots of coffee daily



Glass, J, et al. Addiction. 2009 Jan;104(1):38-48.***Effects of alcoholism severity and smoking on executive neurocognitive function***.

The Whitehall II study is based on employees of the British Civil Service

- Analysis of data of over 7,000 using 6 assessments of smoking status over 25 years and 3 cognitive assessments over 10 years.
- 1. Men: smoking was associated with faster cognitive decline; analyses using pack-years of smoking suggested a dose-response relation.
- 2. Men: who continued smoking over the follow-up experienced greater decline in all cognitive tests.

Séverine S, et al, **Impact of Smoking on Cognitive Decline in Early Old Age: The Whitehall II Cohort Study**; *Arch Gen Psychiatry.* 2012;69(6):627-635.

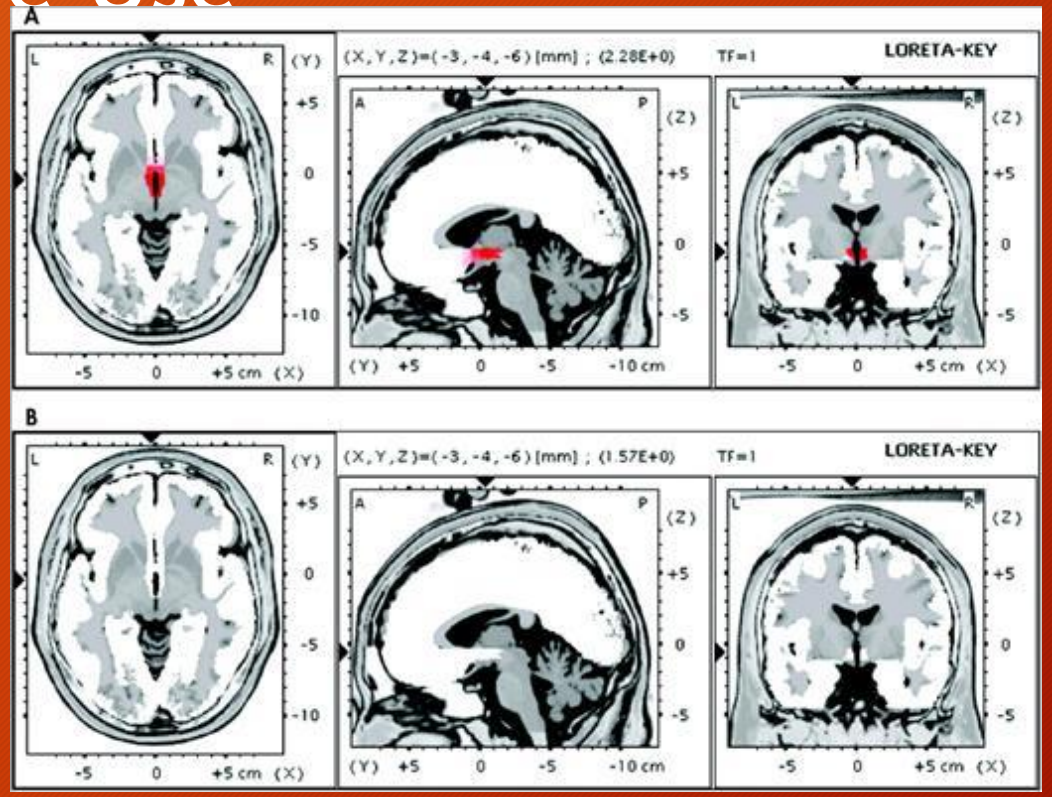
The Whitehall II study is based on employees of the British Civil Service

- 3. Men who quit smoking in the 10 years preceding the first cognitive measure were still at risk of greater cognitive decline, particularly in executive function. However, long-term ex-smokers did not show faster cognitive decline.
- 4. Association between smoking and cognition, particularly at older ages, is likely to be underestimated owing to higher risk of death and dropout among smokers.

Séverine S, et al, **Impact of Smoking on Cognitive Decline in Early Old Age: The Whitehall II Cohort Study**; *Arch Gen Psychiatry.* 2012;69(6):627-635

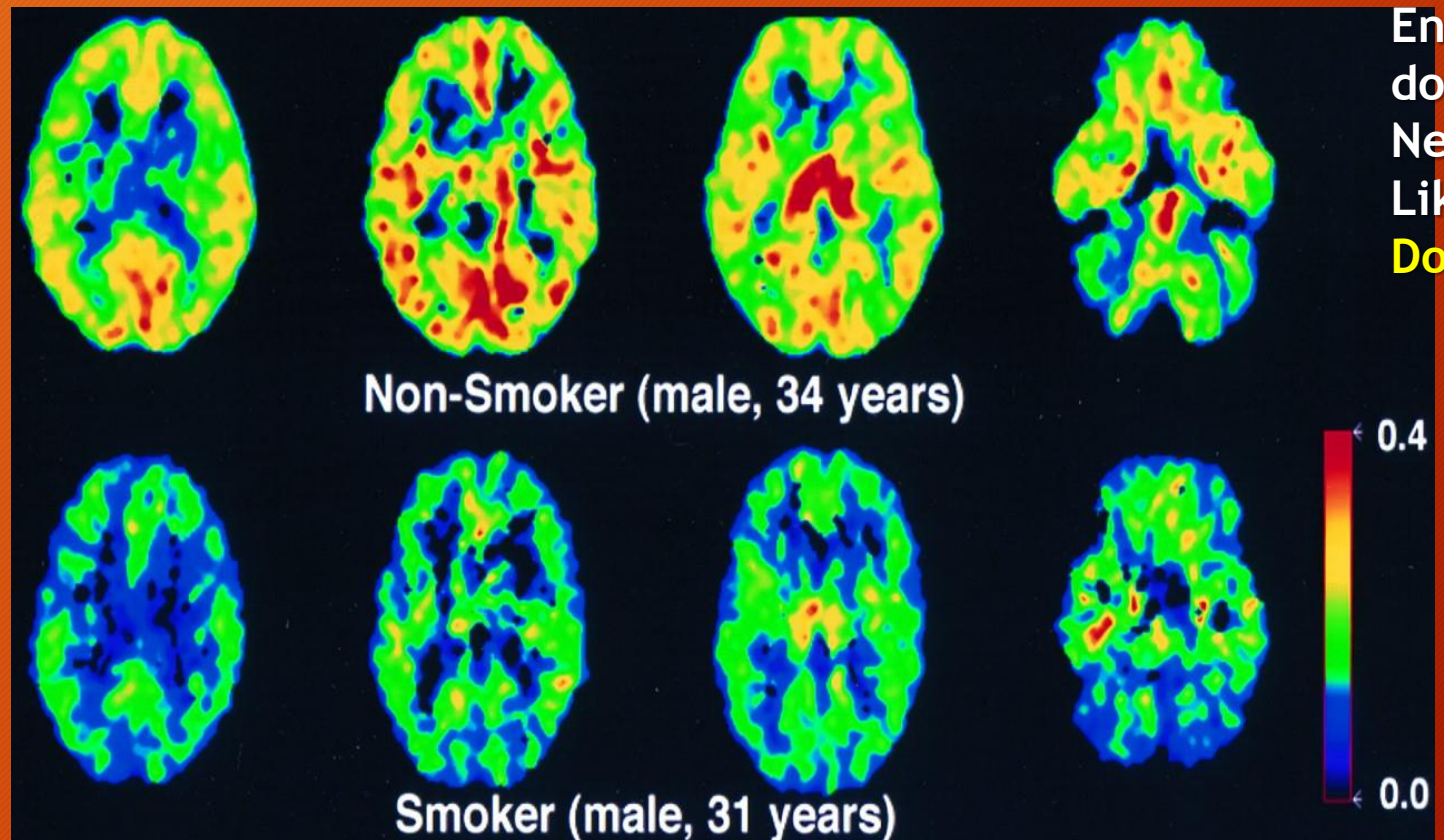
QEEG and Nicotine Use

- Neuroelectric source analysis [LORETA] revealed hypoactivation of
- anterior cingulate,
- orbitofrontal cortex
- prefrontal cortex
- of smokers and former smokers, as compared to never-smokers.



Neuhaus A, et al; Persistent dysfunctional frontal lobe activation in former smokers. Psychopharmacology. 2006;186:191–200

Loss of MAO in brains Of smokers,

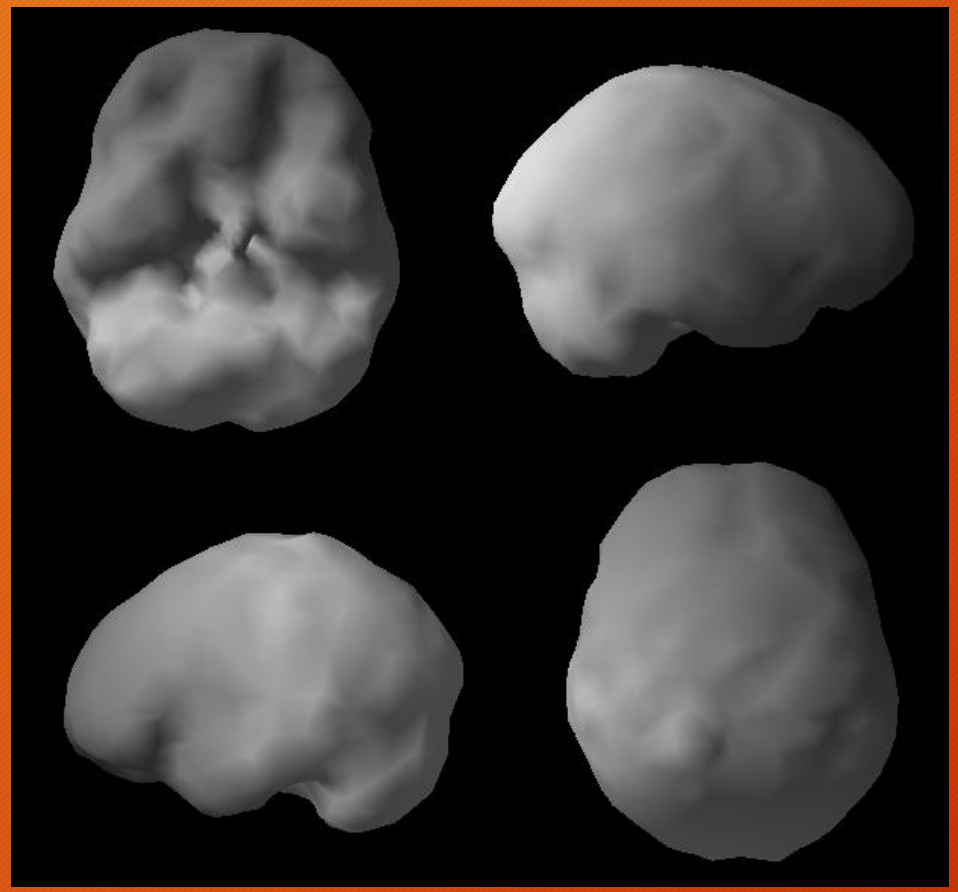


MAO"s are important Enzymes in the break down of Neurotransmitters Like Serotonin and Dopamine

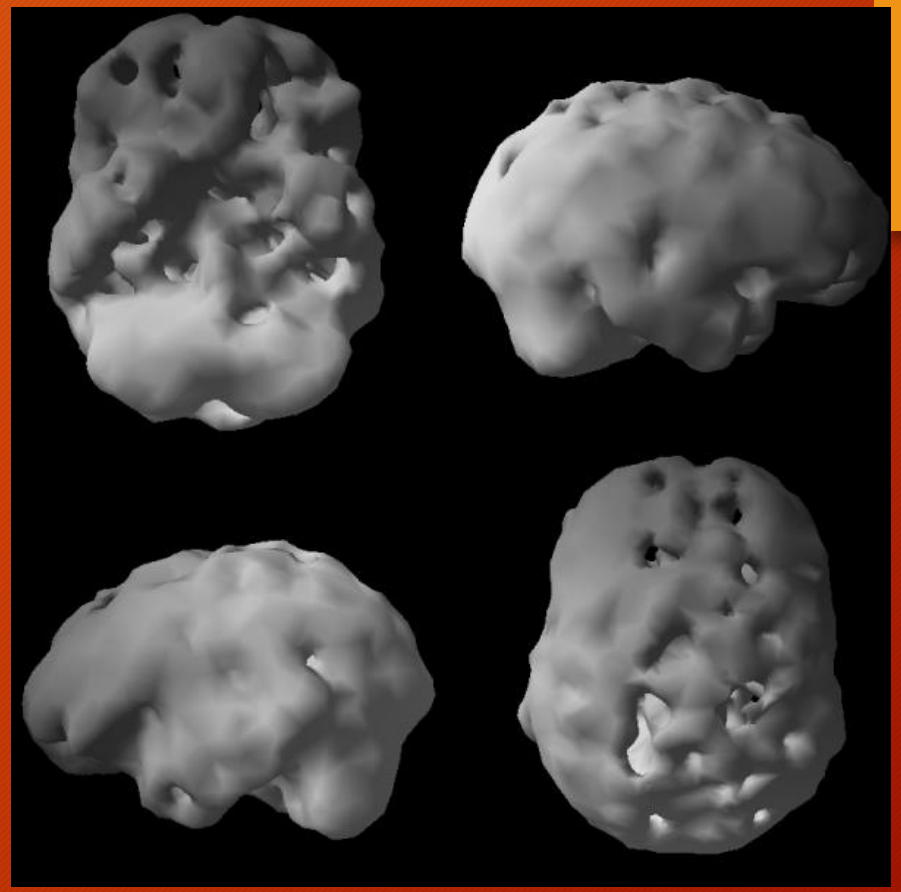
COCAINE

? Our next epidemic?

Healthy Brain



Cocaine Damaged Brain



Unchain your brain, Amen, D and Smith D; 2010, Mindworks Press.

Cognitive Impairment: Cocaine

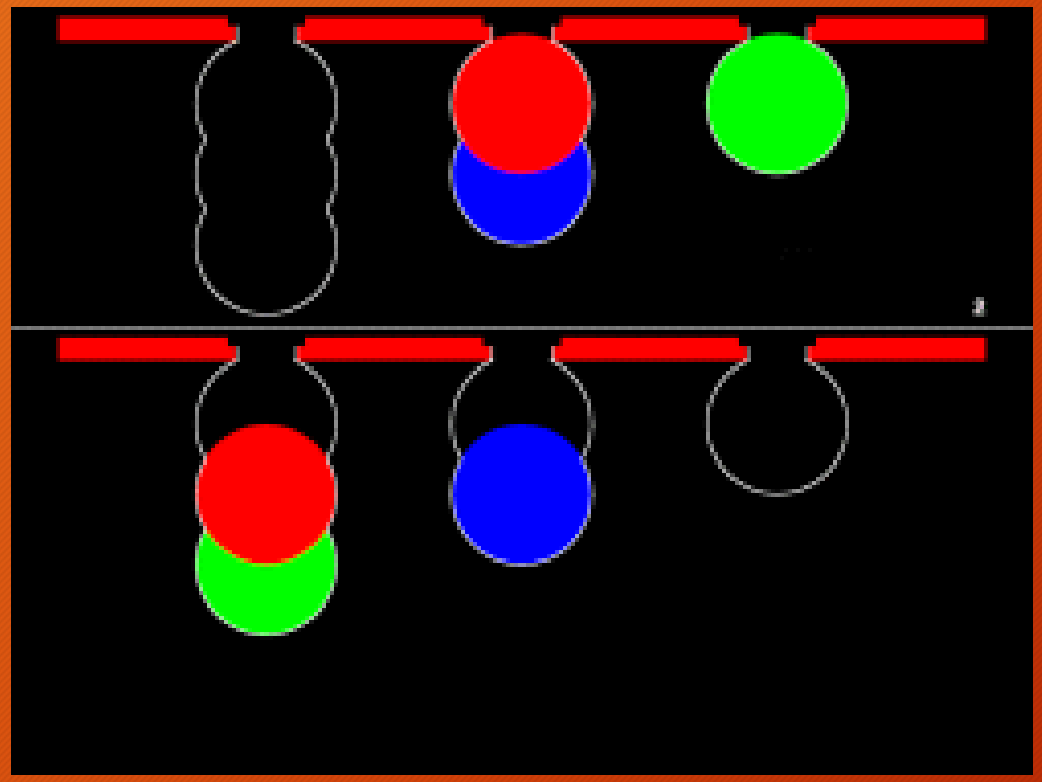
- Compared with healthy subjects, cocaine abusers had deficits on tasks that tested attention, executive function, and verbal memory.
- The deficits were most obvious in the cocaine-addicted individuals who had been abstinent from cocaine longer than 72 hours. “and this effect was not due to withdrawal-related depressive symptoms.”
- Surprisingly, the subjects with the most cognitive impairment reported the least depression and vice versa.

Neuropsychological Testing in COCAINE USE

- **Chronic cocaine users show performance declines over time in:**
- **Vigilance**
- **Reaction time**
- **Recognition memory**
- **From binge to abstinence days and during abstinence itself.**

Cognitive performance by humans during a smoked cocaine binge-abstinence cycle. *American Journal of Drug and Alcohol Abuse*, Nov, 2005 by Edward F. Pace-Schott,

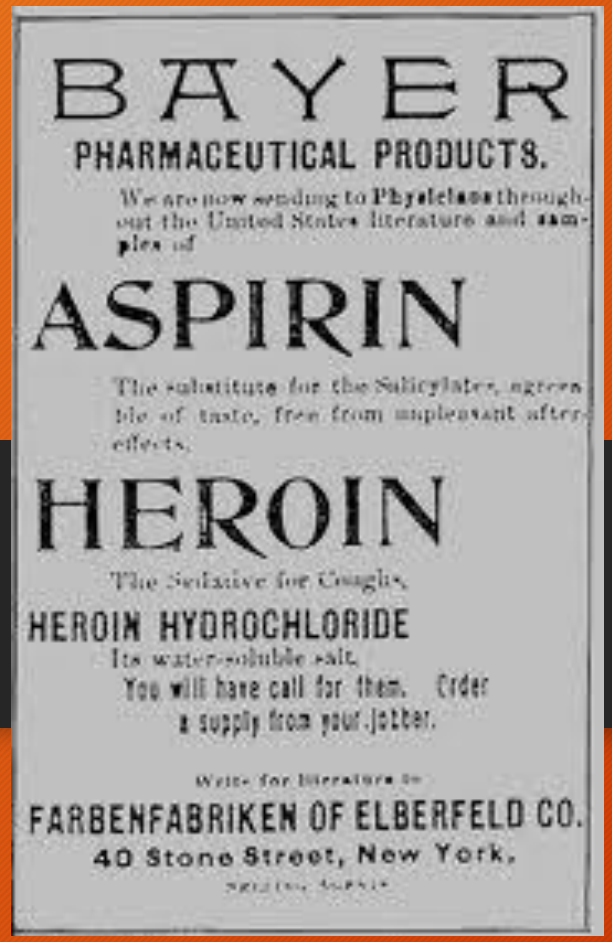
SOC is a spatial planning test which gives a measure of frontal lobe function.



The subject must use the balls in the lower display to copy the pattern shown in the upper display.

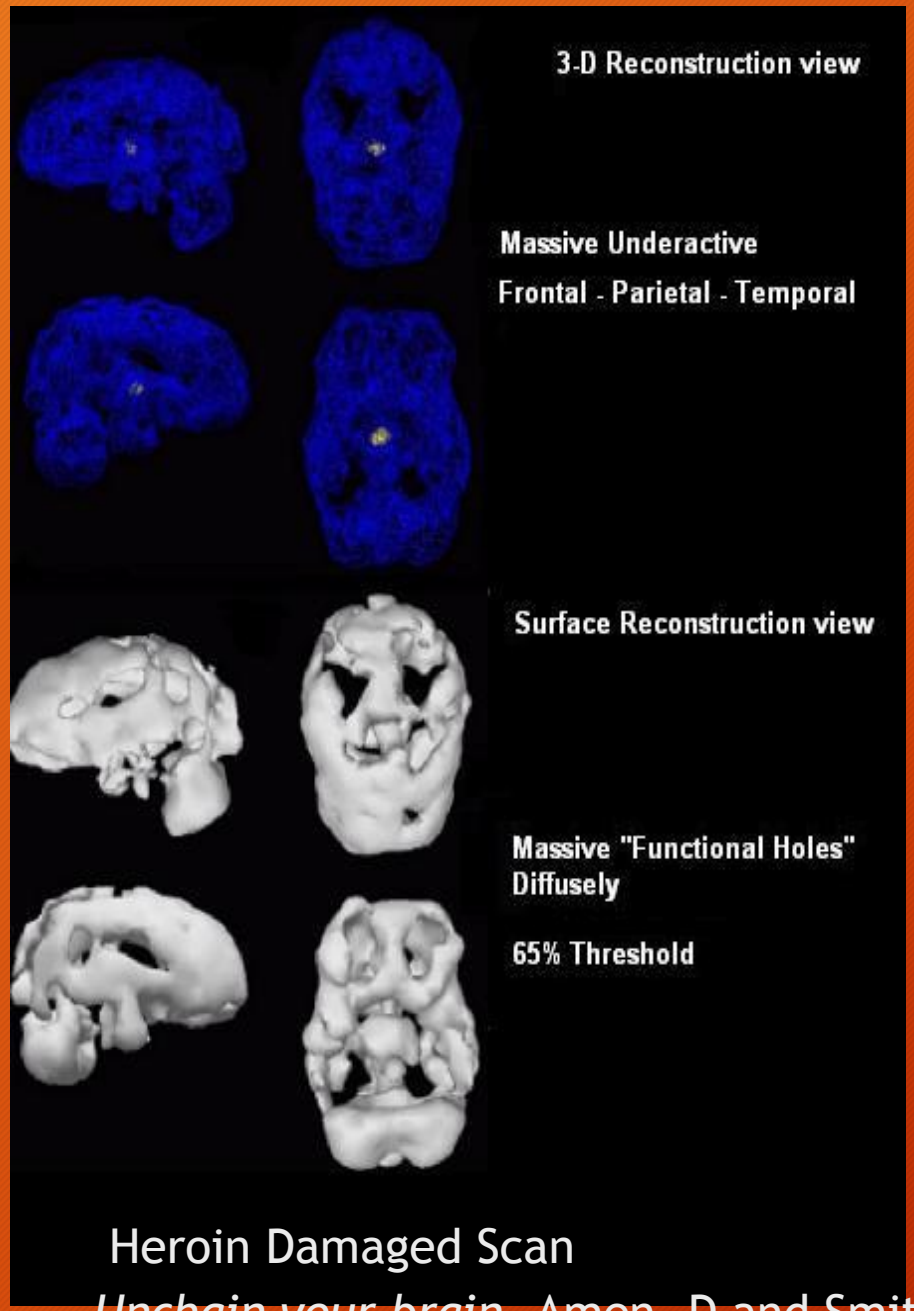
The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved.

The time taken to complete the pattern and the number of moves required are taken as measures of the subject's planning ability.



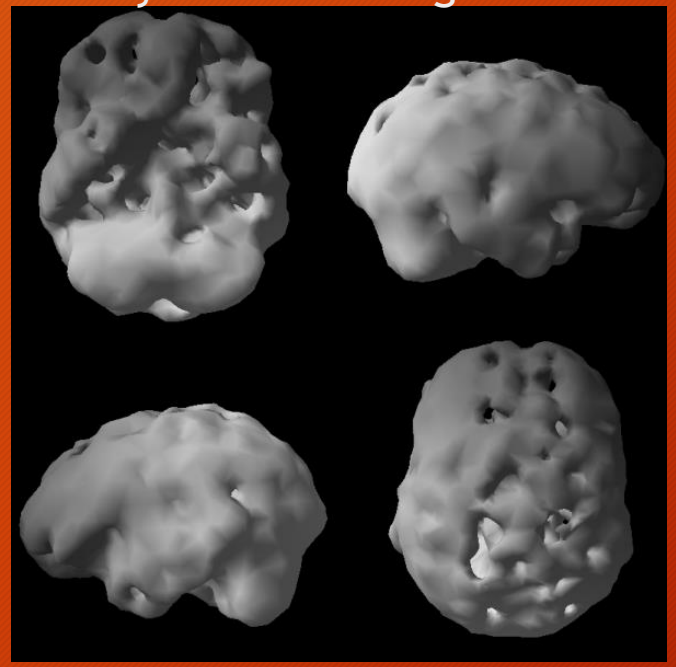
OPIATES

Brain Effects with:

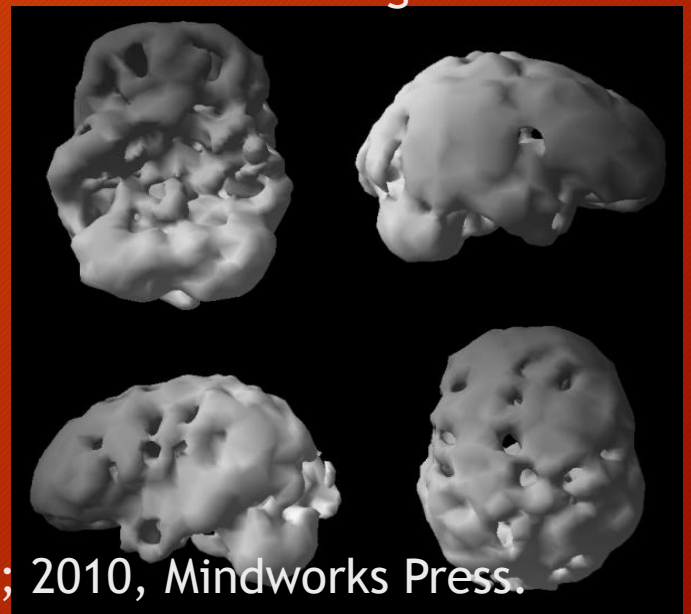


Heroin Damaged Scan

OxyContin Damaged Scan



Vicodin Damaged Brain



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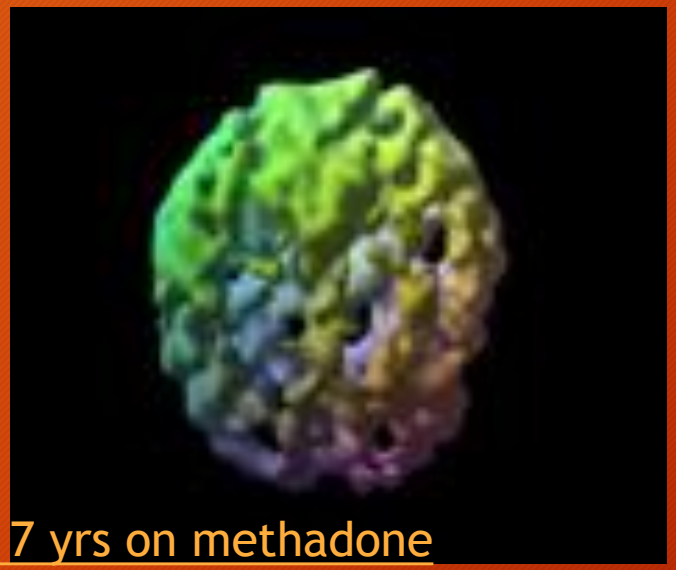
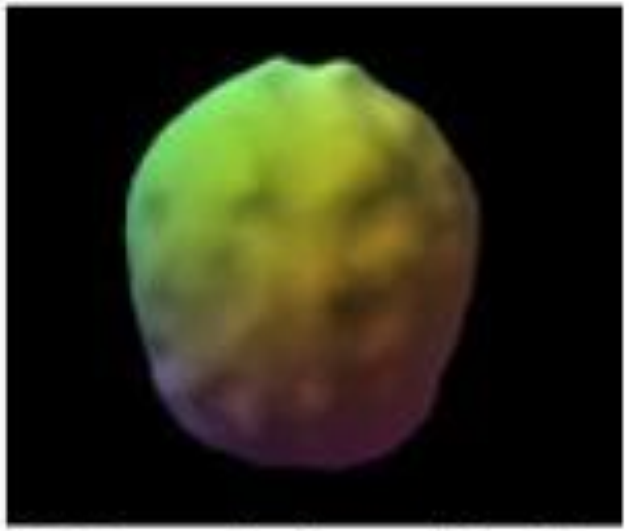
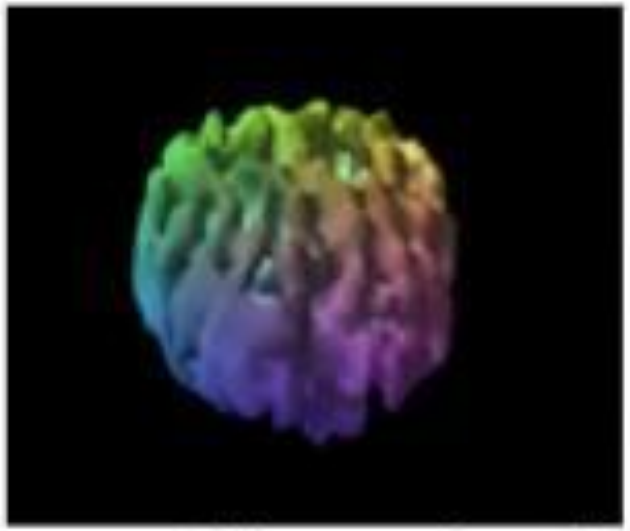


40 y/o, 7 yrs on methadone
heroin 10 yrs prior



Normal view of brain



25 years of frequent heroin use

Stroop Effect

YELLOW BLUE ORANGE

BLACK RED GREEN

PURPLE YELLOW RED

ORANGE GREEN BLUE

BLUE RED PURPLE

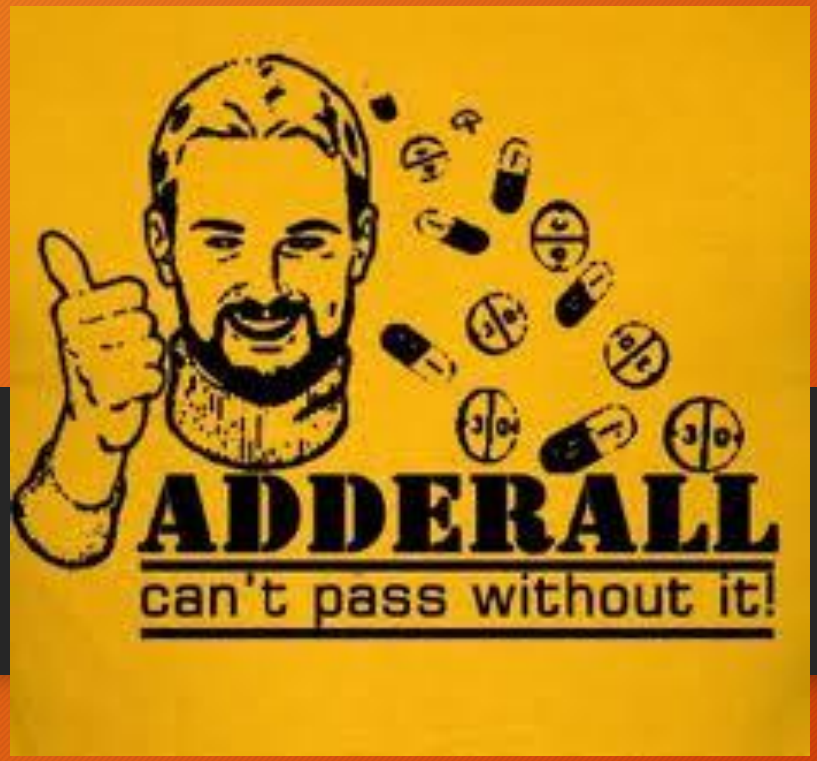
YELLOW RED GREEN

Long Term Opiate User's Cognitive Impairment

- The results of this study have important clinical implications.
- It seems likely that participants in opiate abuse treatment programs will have difficulty with attention and memory, and these deficits may persist for months and years past detoxification.
- Recent studies have suggested that cognitive status may play a role in treatment efficacy

•

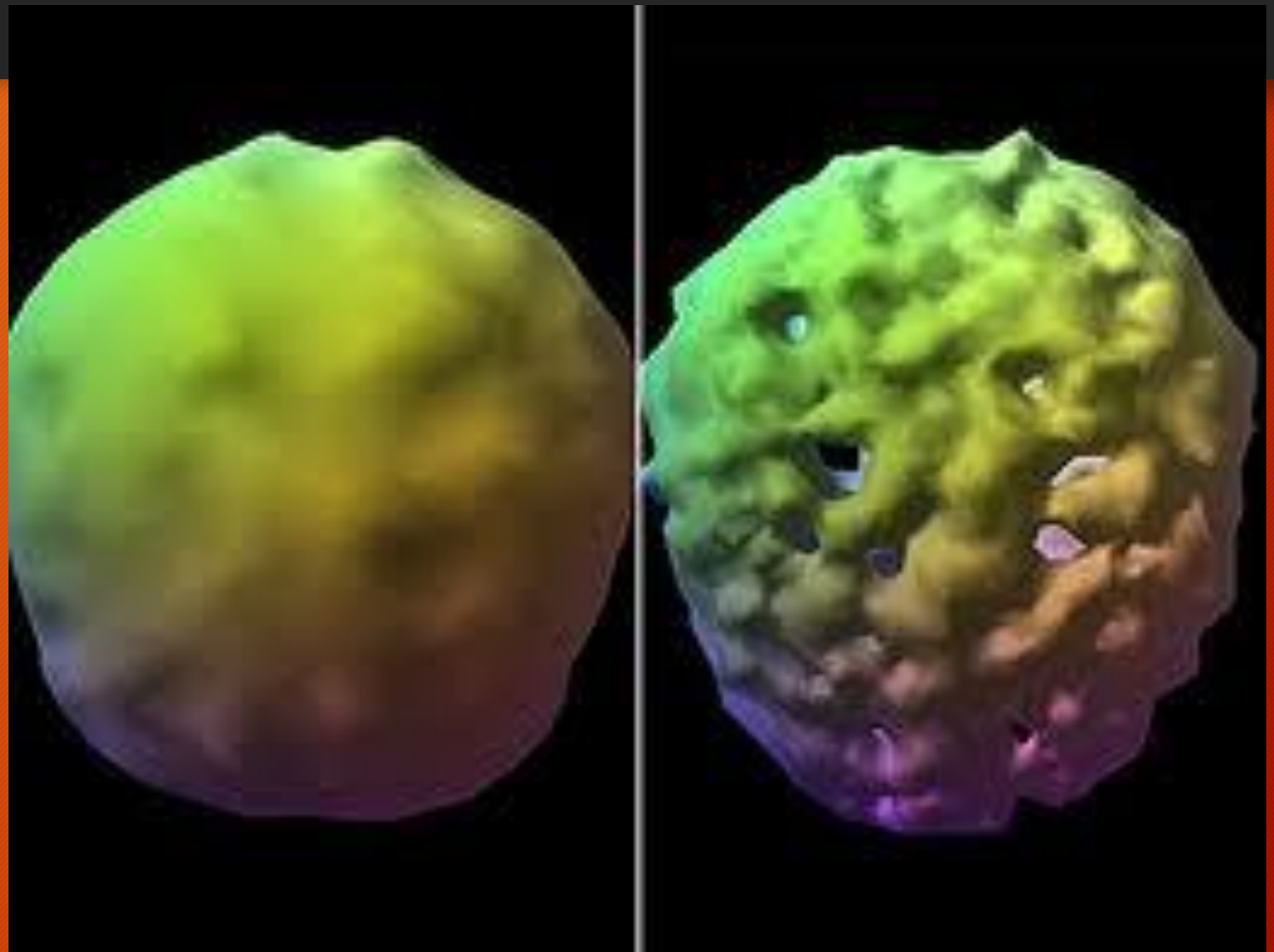
Prossor, et al, Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment Drug Alcohol Depend. 2006 October 1; 84(3): 240-247



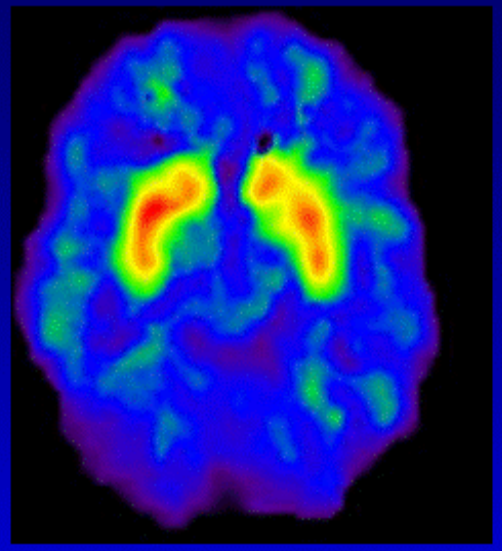
Brain Effects with:

AMPHETAMINES

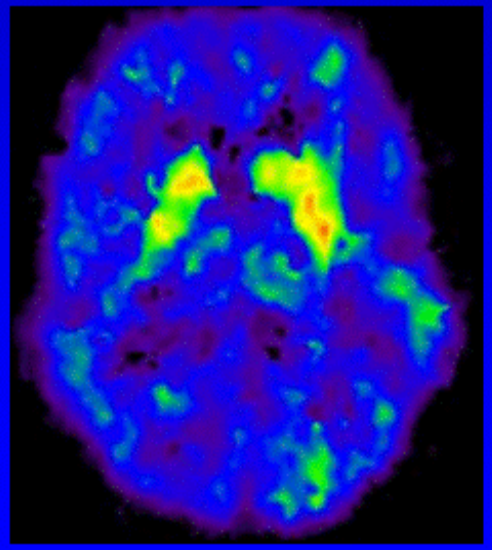
NORMAL Methamphetamine



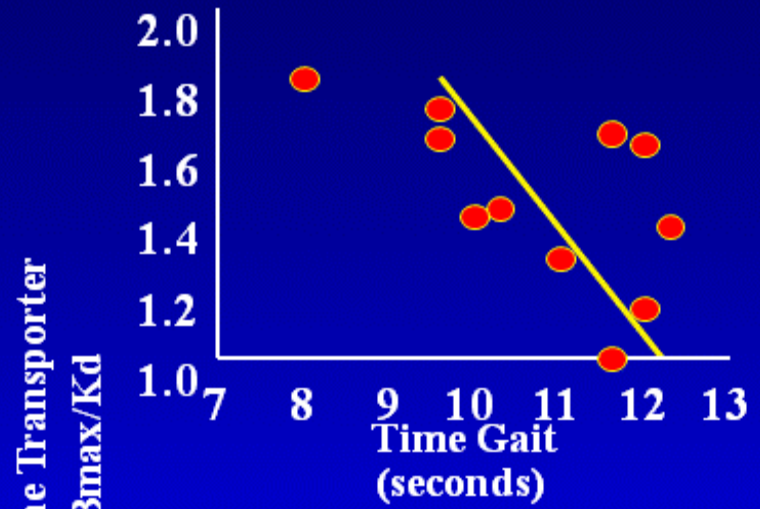
Dopamine Transporters in Methamphetamine Abusers



Normal Control

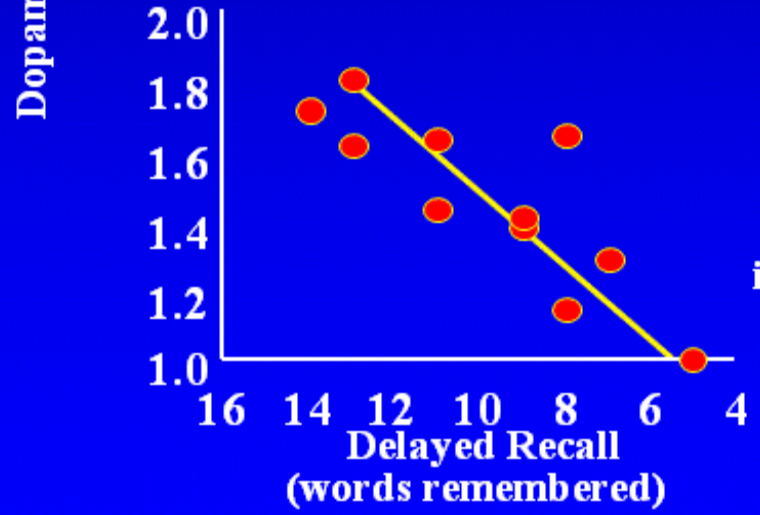


Methamphetamine Abuser



Motor Task

Loss of dopamine transporters in methamphetamine abusers may result in slowing of motor reactions.



Memory Task

Loss of dopamine transporters in methamphetamine abusers may result in memory impairment.

NIDA

Volkow et al., Am. J. Psychiatry, 2001.

STOP SIGNAL TASK


Wow, you ever just like, stare at your foot?
Then you're all, like, "whoa that's my foot"


MARIJUANA
PROUD SPONSORS OF
...UMM...WE FORGET!

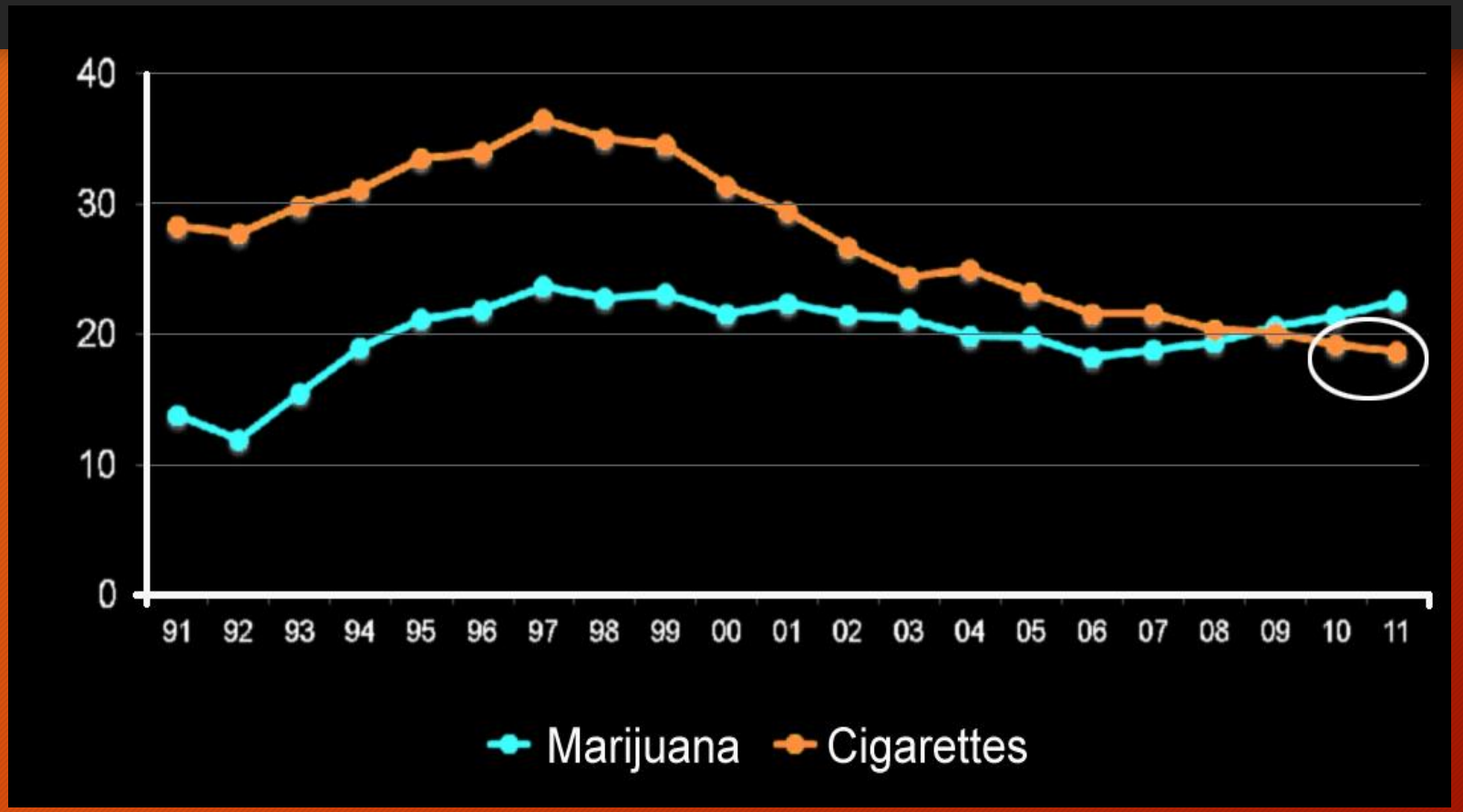
Marijuana Effects

Brain Activity:
Normal, Healthy Brain
(Underside surface)

Brain Activity:
18 year old
3 years of
4x week
marijuana use
(underside surface)

Brain Activity:
16 year old
2 years of
daily marijuana use
(underside surface)

In 2009, Reports of Past Month Use of Marijuana Among 12th Graders Exceeded that of Cigarette for the First Time in the Survey's History



SOURCE: University of Michigan, 2011 Monitoring the Future Study

Cognitive Impairment: Marijuana

- NIDA study at McLean Hospital revealed that college students who used THC had impaired skills related to
- Attention
- Memory
- Learning
- 24 hours after they last used the drug

Pope, H G, Yurelun-Todd, D. The residual cognitive effects of heavy marijuana Use in college students. *Journal of American Medical Association*, 275 (7): 521-527, 1996

Cognitive Impairment: Marijuana

- Study at University of Iowa College of Medicine
- Frequent Marijuana users (7 or more times weekly)
- Deficits in Mathematical skills
- Verbal expressions
- Memory -retrieval processes
- Youths with a GPA of D or below were 4 times more likely to have used THC than those with a GPA of A

Block, RI and Ghoneim, MM. Effects of chronic marijuana use on human cognition. *Psychopharmacology*. 1100(1-2):219-228. 1993.

Cognitive Impairment: Marijuana

- Other Impairments:
- Sensory and time perception
- Problems with driving
- Difficulty with sports performance
- Effects may be especially problematic during teen's peak learning years when brain is still developing.

The NHSDA Reports, *Marijuana use among youth*. July 19, 2002

September 2012 NIH Study Results

- NIH-funded research shows that long-term marijuana is associated with impaired intellectual functioning, especially if usage starts during the teen years.
- Over 1,000 study participants were given neuropsychological tests in early adolescence, prior to initiation of marijuana use, and then re-tested in mid adulthood after 20 + Years.

Meter, et al Long-term effects of adolescent-onset and persistent use of cannabis. [Proc Natl Acad Sci U S A. 2012]

September 2012 NIH Study Results

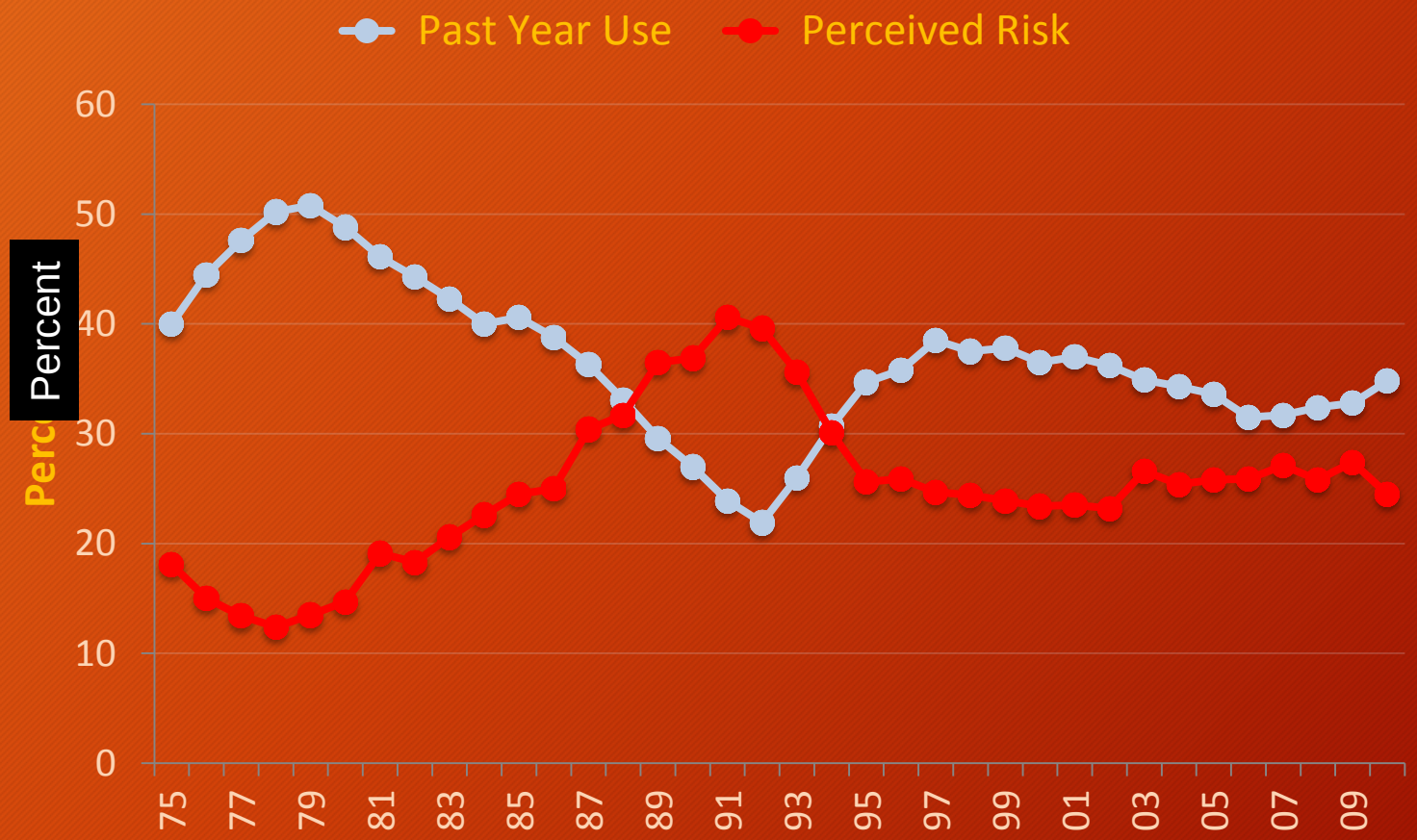
- Study members with more persistent marijuana dependence showed greater IQ decline and greater impairment across five different cognitive domains, especially executive function and processing speed.
- The study was thus able to rule out pre-existing differences in IQ between heavy marijuana users and others; it is also significant for including degree of cannabis exposure and age of onset as factors.

September 2012 NIH Study Results

- Those who started use during the teen years showed greater IQ decline than those who began use as adults.
- These latter results are especially troubling, given recent date showing increased marijuana use among teens over the last five years, along with declines in perceived risk of harm associated with use.

Meter, et al Long-term effects of adolescent-onset and persistent use of cannabis. [Proc Natl Acad Sci U S A. 2012]

Changes in Attitude Lead to Changes in Use: Marijuana Use and Perceived Risk in 12th Graders, (1975 to 2010)



Source: The Monitoring the Future study, the University of Michigan


HIGH QUALITY BATH SALT
WHITE CHINA
氣 康
Bath Salt 250 mg
COTTON
DYNAMITE
BATH SALT
½ gram

Bath Salts

Overview

- Not the bath salts you use in your tub!
- Designer drug that contains substituted cathinones
- Methylenedioxypyrovalerone (MDPV), mephedrone & methylone most commonly used
- Classified as Schedule **I substance in October 2011**

History

- Cathinone: found naturally in the plant *Catha edulis* (khat)
  - Beta-keto analog of amphetamine
- 1st synthetic cathinones synthesized in late 1920s
- Limited therapeutic use due to serious side effects
- Emerged as popular designer drugs of abuse in 2000's

Photo From: http://www.botanypictures.com/plantimages/catha%20edulis%2004%20NL%20uithof%20greenhouse.jpg

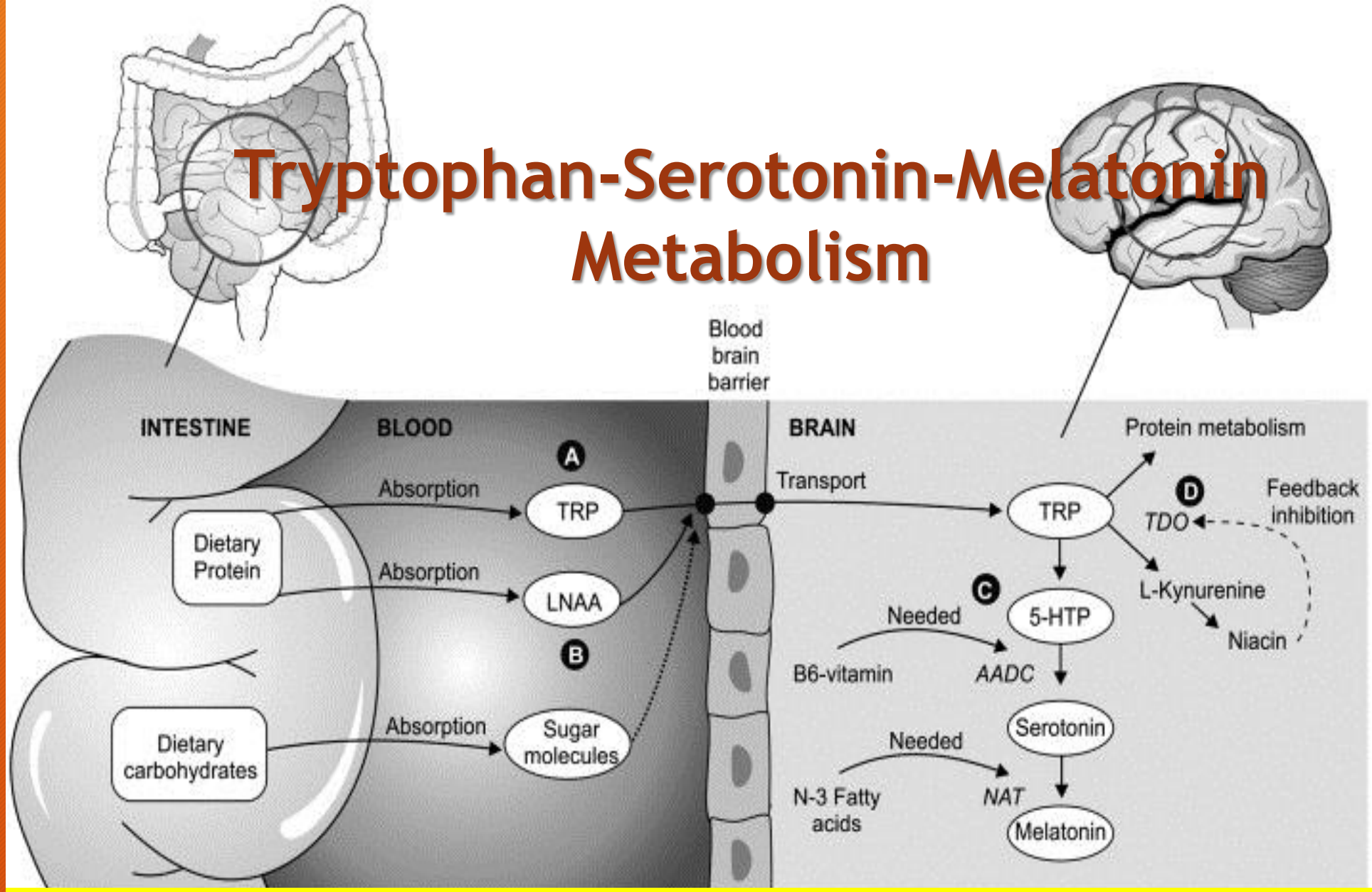
Snorted, Smoked or Injected

- Extreme Agitation
- Hallucinations & Delusions
- Chest Pain
- Suicidal Thoughts
- High Blood Pressure
- Acute Toxicity
- Hyperthermia
- Delirium
- Violent Behavior
- Foaming at the Mouth
- Extreme Paranoia
- Delusional Paracitosis
- Parkinson-Type Limb Twitching
- Paranoia
- Severe Insomnia

Common Names[3,4]

- Ivory Wave
- Purple Wave
- Red Dove
- Blue Silk
- Zoom
- Bloom
- Cloud Nine
- Drone
- Meow Meow
- Plant Fertilizer
- Ocean Snow
- Lunar Wave
- Vanilla Sky
- White Lightning
- Scarface
- Hurricane Charlie
- Bliss
- Energy-1
- Stardust
- Insect Repellent

Tryptophan-Serotonin-Melatonin Metabolism



5-HTP, 5-hydroxytryptophan, AADC, aromatic l-amino acid decarboxylase, LNAA, large neutral amino acid, TDO, tryptophan 2,3-dioxygenase, TRP, tryptophan

Hallucinogens

Hallucinogenic Drug effects related to neurotransmitters:

- **Serotonin**:
  LSD, psilocybin, DMT
- **Norepinephrine**:
  amphetamine related, mescaline, MDMA
- **Acetylcholine**:
  atropine, scopolamine
- **Dissociative anesthetics**:
  PCP, ketamine

Impairment related to Hallucinogens

- **Persistent palinopsia:**
  Visual changes,
  afterimages
- **Visual Snow**
- **Can last for months to years, causing significant depression**

- Flash backs
- Psychosis- which may be permanent

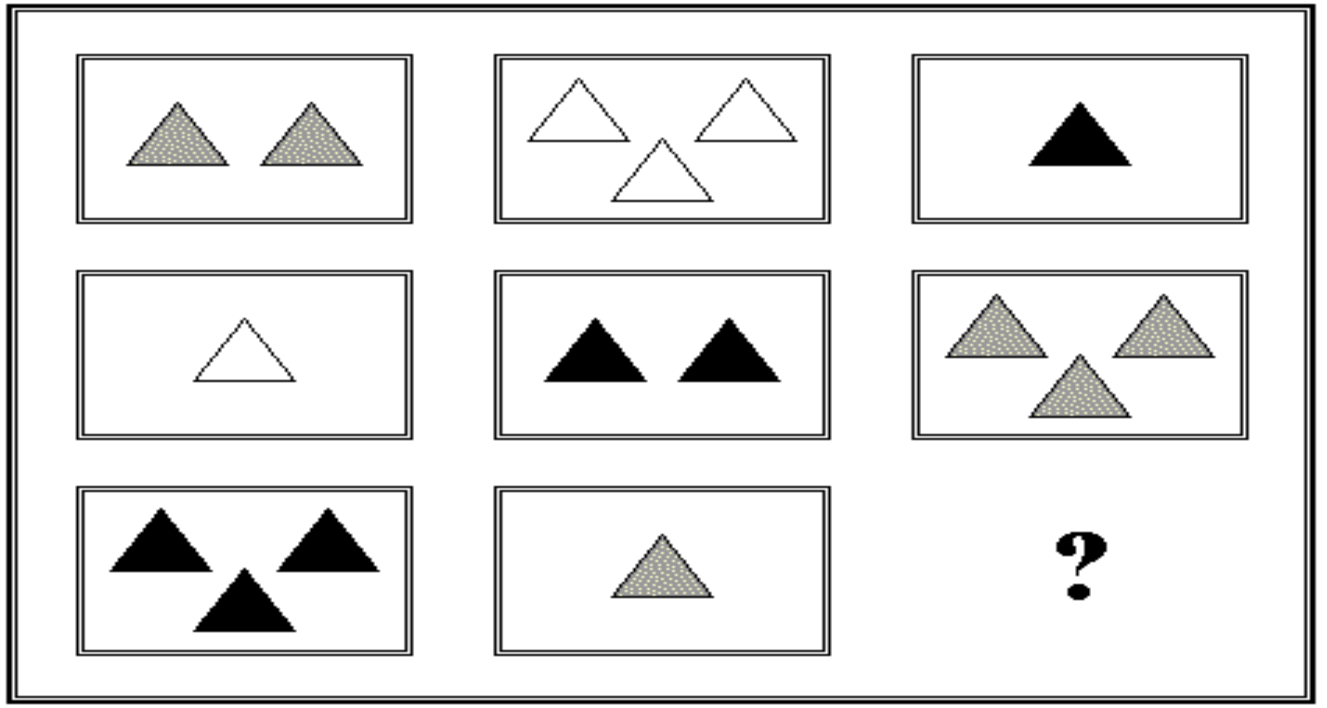
Neuropsych Testing

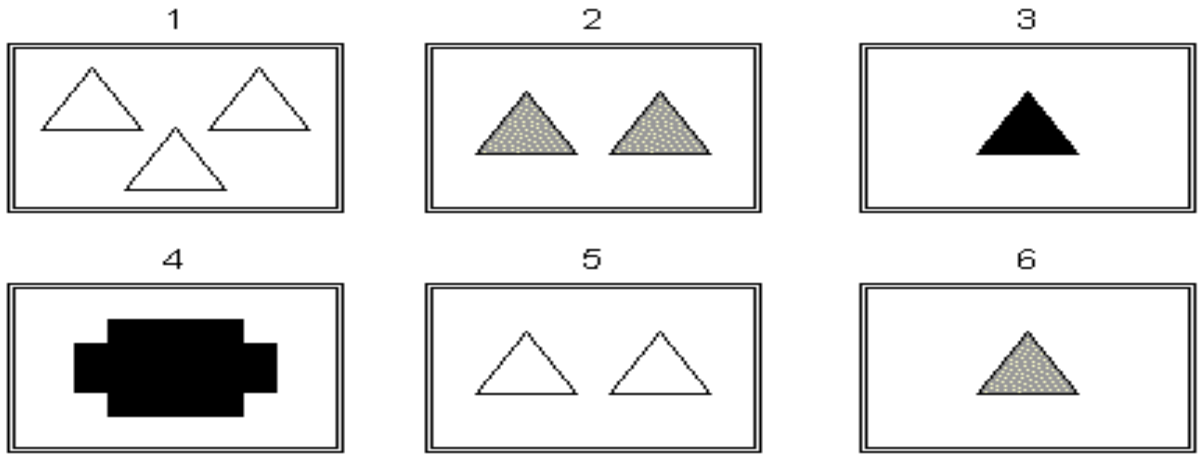
- Cohen and Edwards reported impaired visuospatial orientation among 30 LSD users in contrast to 30 controls
- The authors also found that performance on the Reitan Trail MakingTest A and B and the Ravens Matrices correlated negatively with extent of LSD use.

Halpern, JH, et al. Review Do hallucinogens cause residual neuropsychological toxicity? Drug and Alcohol Dependence 53 (1999) 247–256

Ravens Matrices

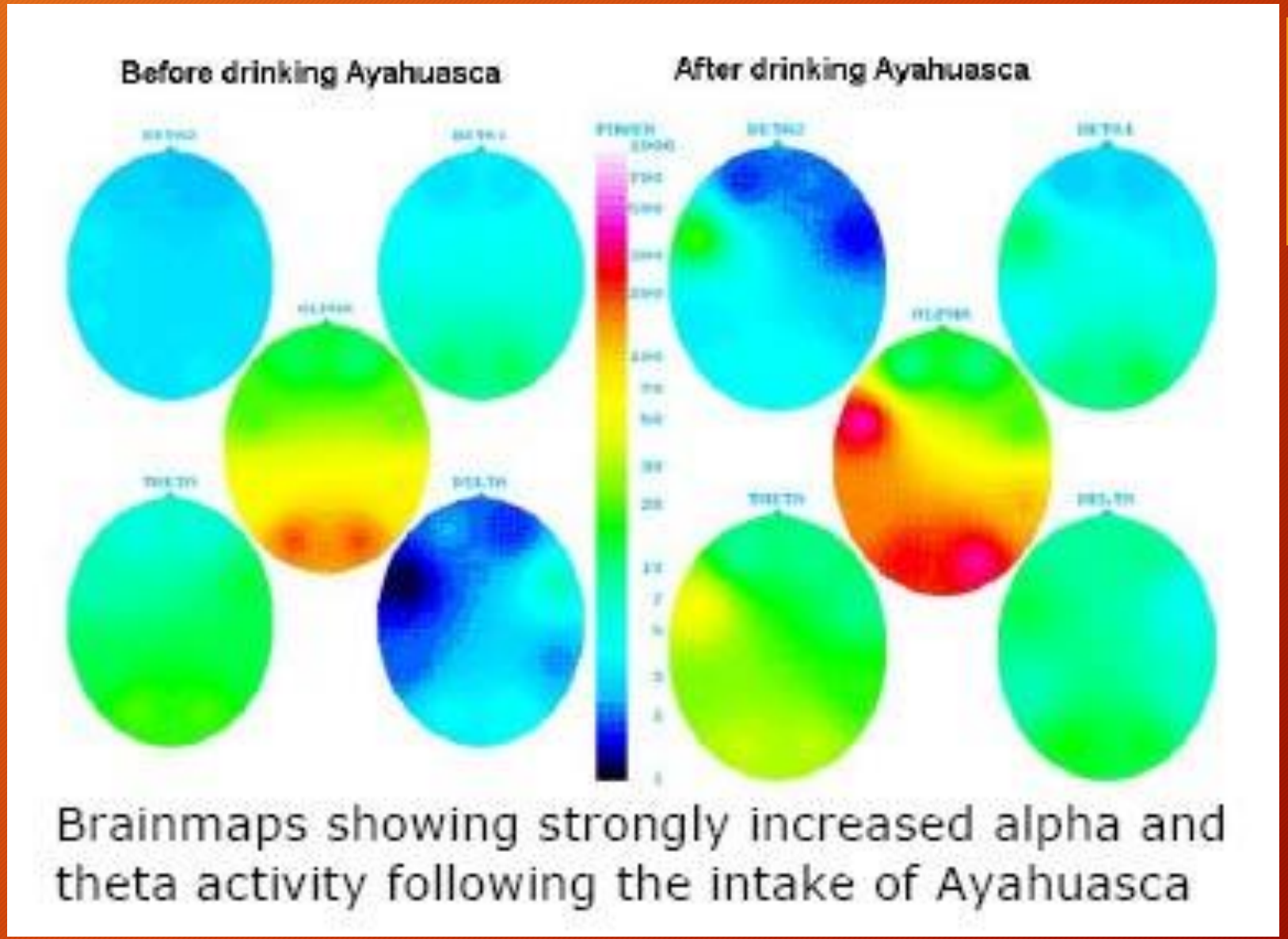
Which answer fits in the missing space to complete the pattern?





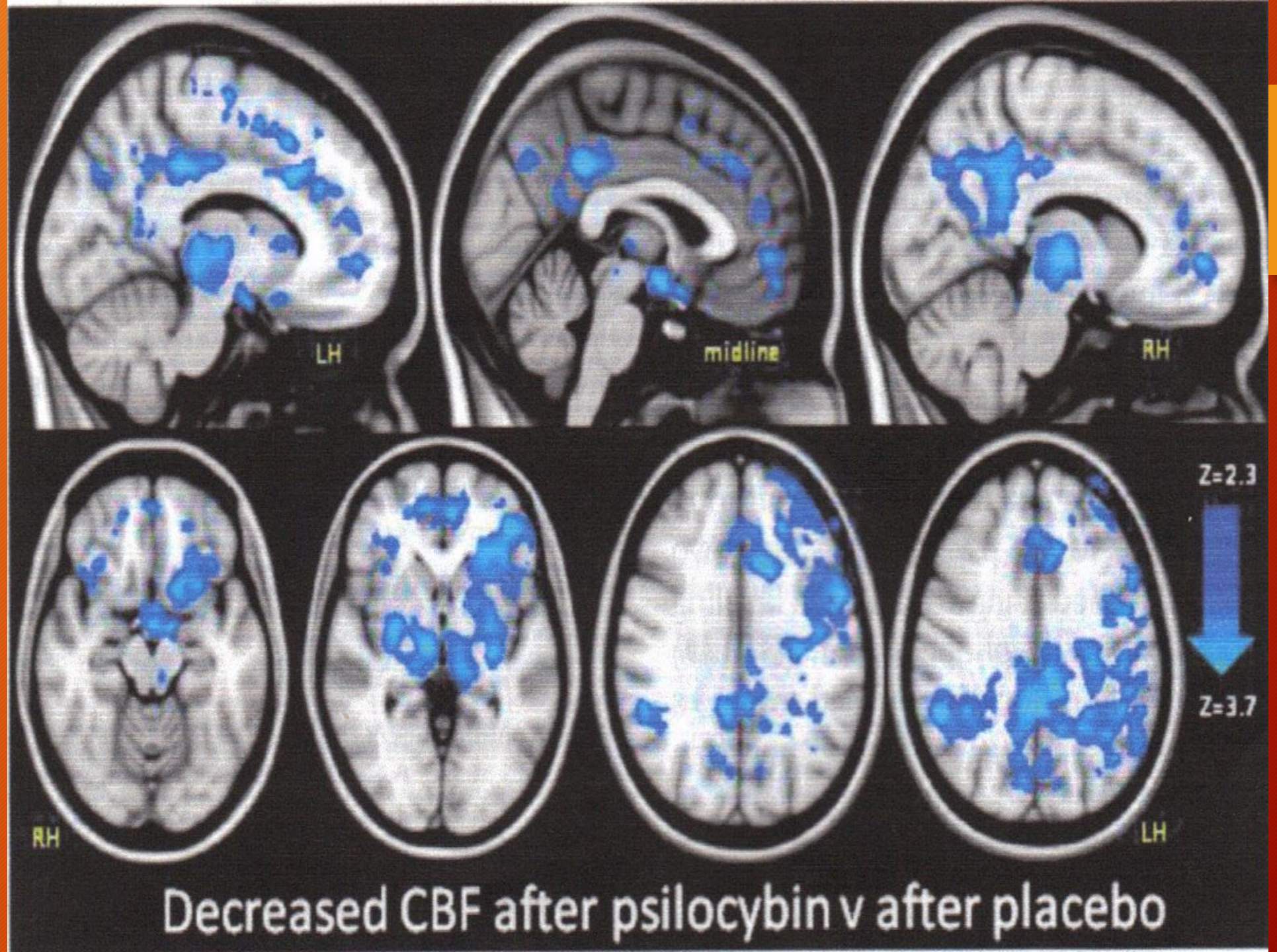
EEG and LSD

- Blacker et al. (1968) compared 21 LSD users (whom the authors referred to as ‘acidheads’) with unmatched controls
- The investigators found subtle electroencephalographic (EEG) changes in the LSD group in comparison to controls, with increased alpha, beta, delta, and theta activity and increased visual evoked response amplitudesat the dimmer intensities.



Brainmaps showing strongly increased alpha and theta activity following the intake of Ayahuasca

A current paper in the prestigious Proceedings of the National Academy of Science, "Neural Correlates of the Psychedelic State As Determined By fMRI Studies with Psilocybin" by Carhart-Harris, et.al from Oxford, Imperial College London, University of Bristol, Cardiff University and University of Copenhagen, is the first to examine how the active material in mushrooms, psilocybin, works in the brain.


LH
midline
RH
Z=2.3
Z=3.7
RH
LH
Decreased CBF after psilocybin v after placebo

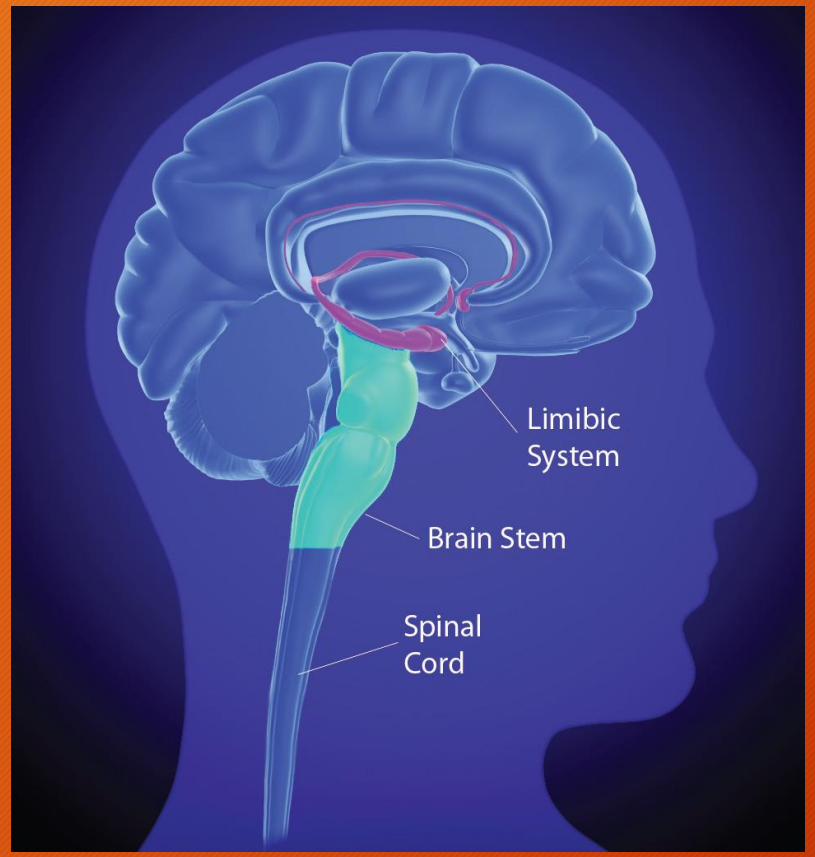
Adverse Effects

- Prolonged Panic Attack
- Tremor
- Agitation
- Insomnia
- Nausea
- Headache
- Tinnitus
- Vertigo
- Muscle Twitching
- Dizziness
- Elevated Heart Rate
- Altered Vision
- Confusion
- Short-term Memory Loss
- Anhedonia
- Depression
- Suicidal Thoughts
- **Psychosis**

Neuroendocrine Dysfunction

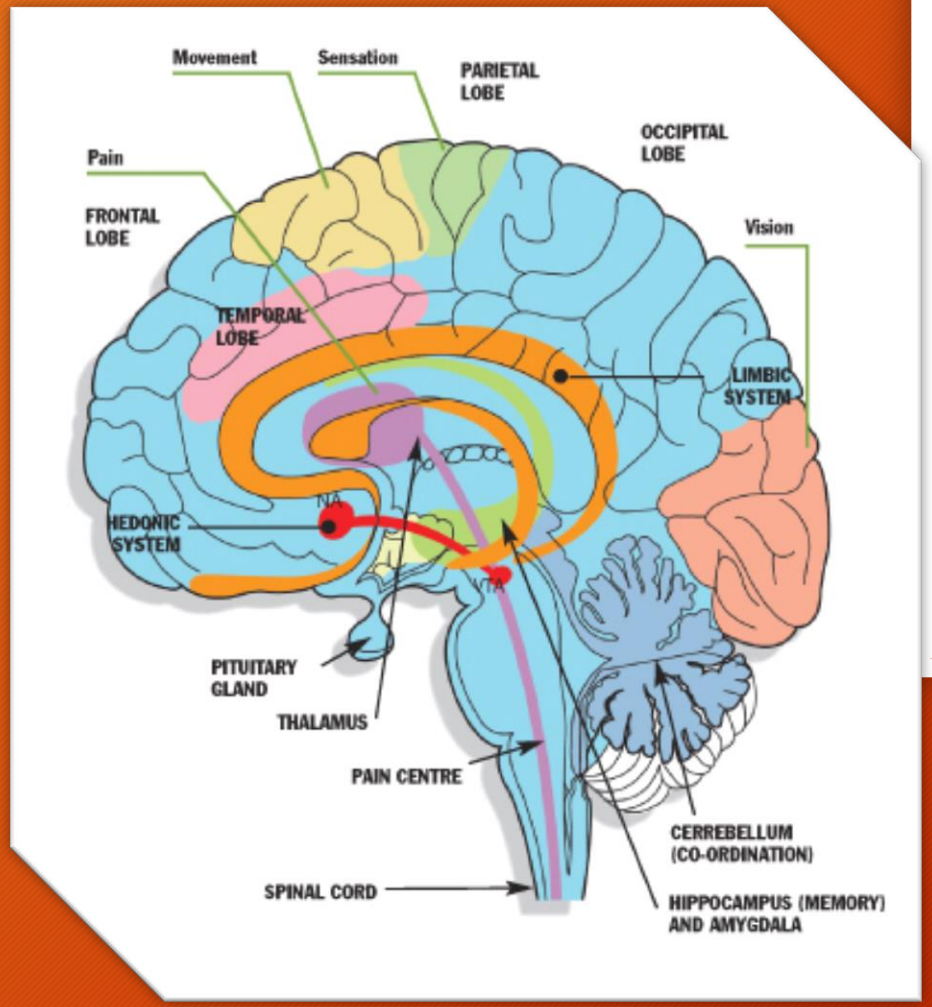
Hormonal Issues in patients with Substance Use Disorder

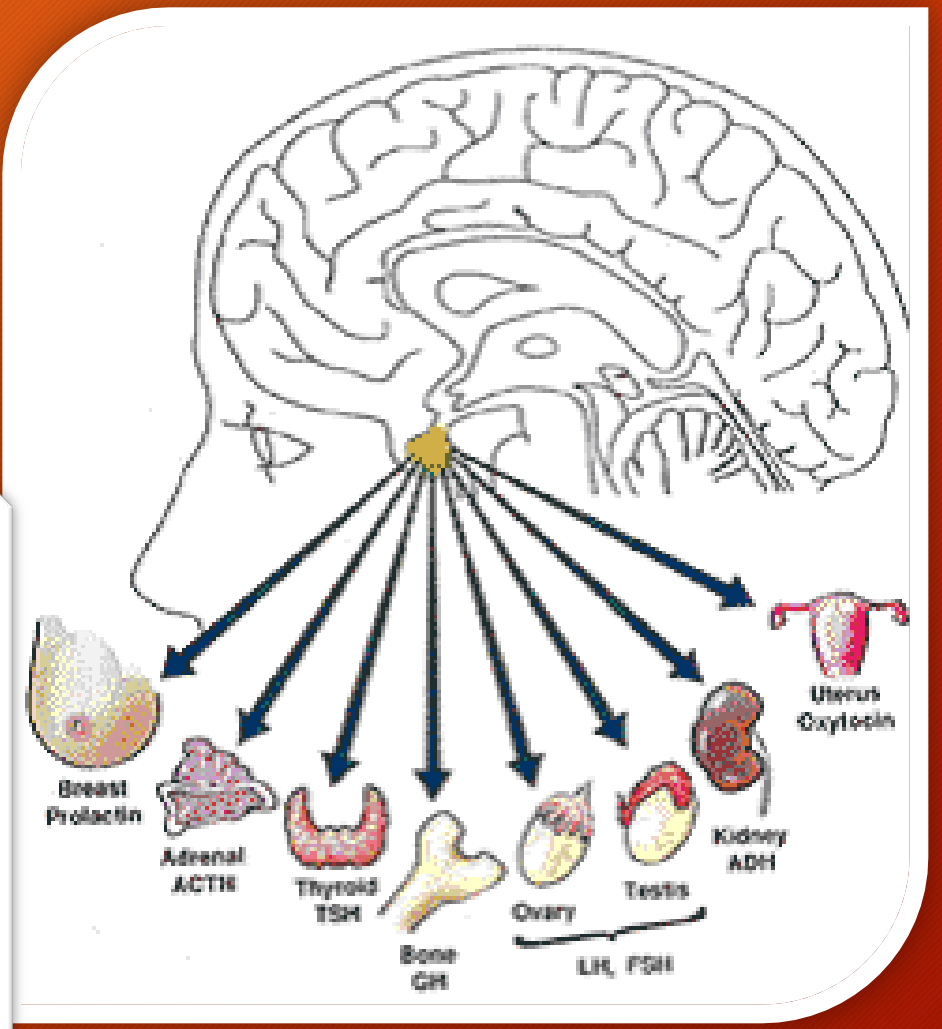
The problem with Heroin



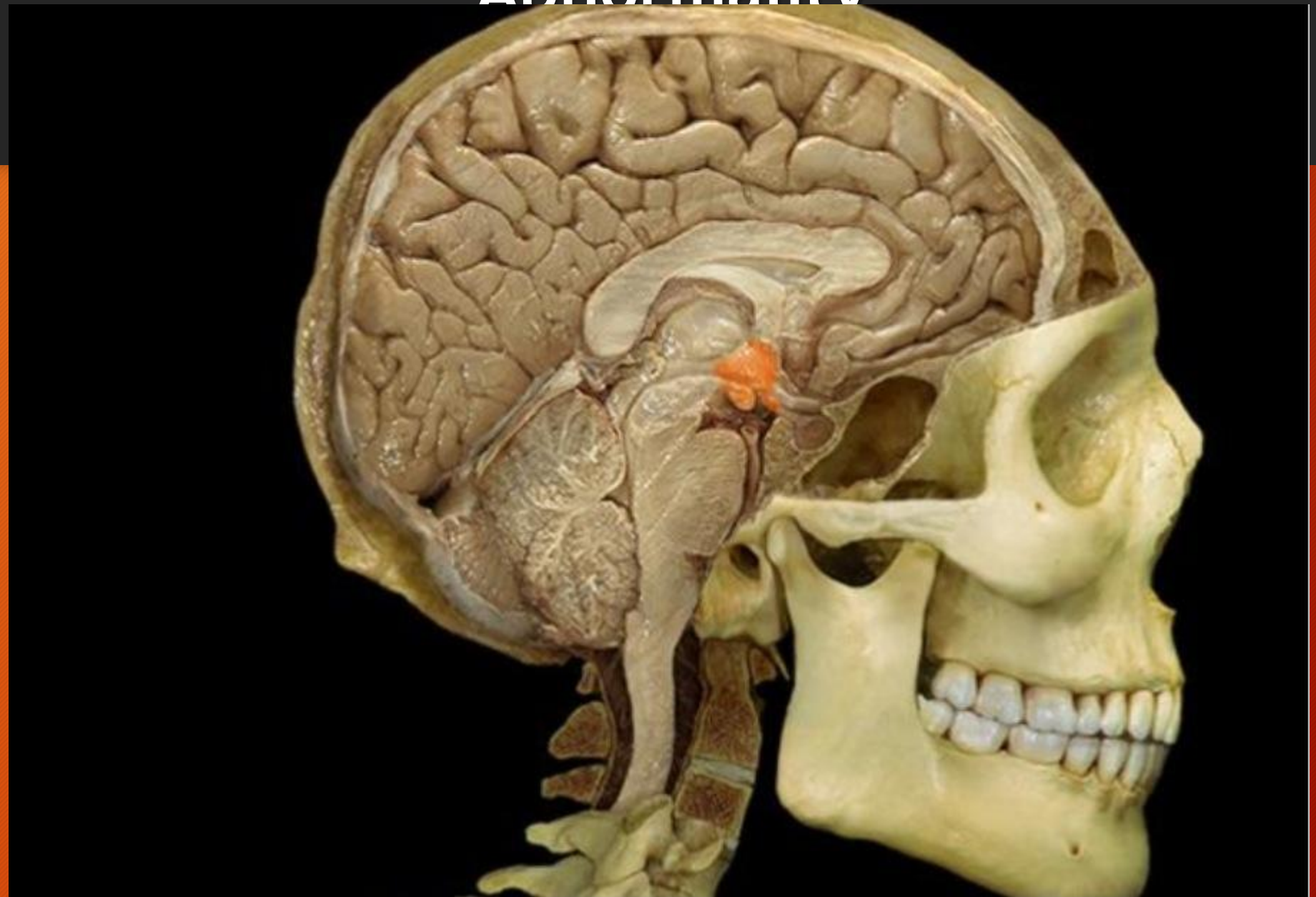
- **Repeated heroin use changes the physical structure and physiology of the brain, creating long-term imbalances in neuronal and hormonal systems that are not easily reversed.**

- Ignar, D.M.; and Kuhn, C.M. Effects of specific mu and kappa opiate tolerance and abstinence on hypothalamo-pituitary-adrenal axis secretion in the rat. *J Pharmacol Exp Ther* 255(3):1287–1295, 1990.
- 14. Kreek, M.J.; Ragunath, J.; Plevy, S.; Hamer, D.; Schneider, B.; and Hartman, N. ACTH, cortisol and beta-endorphin response to metyrapone testing during chronic methadone maintenance treatment in humans. *Neuropeptides* 5(1-3):277–278, 1984.

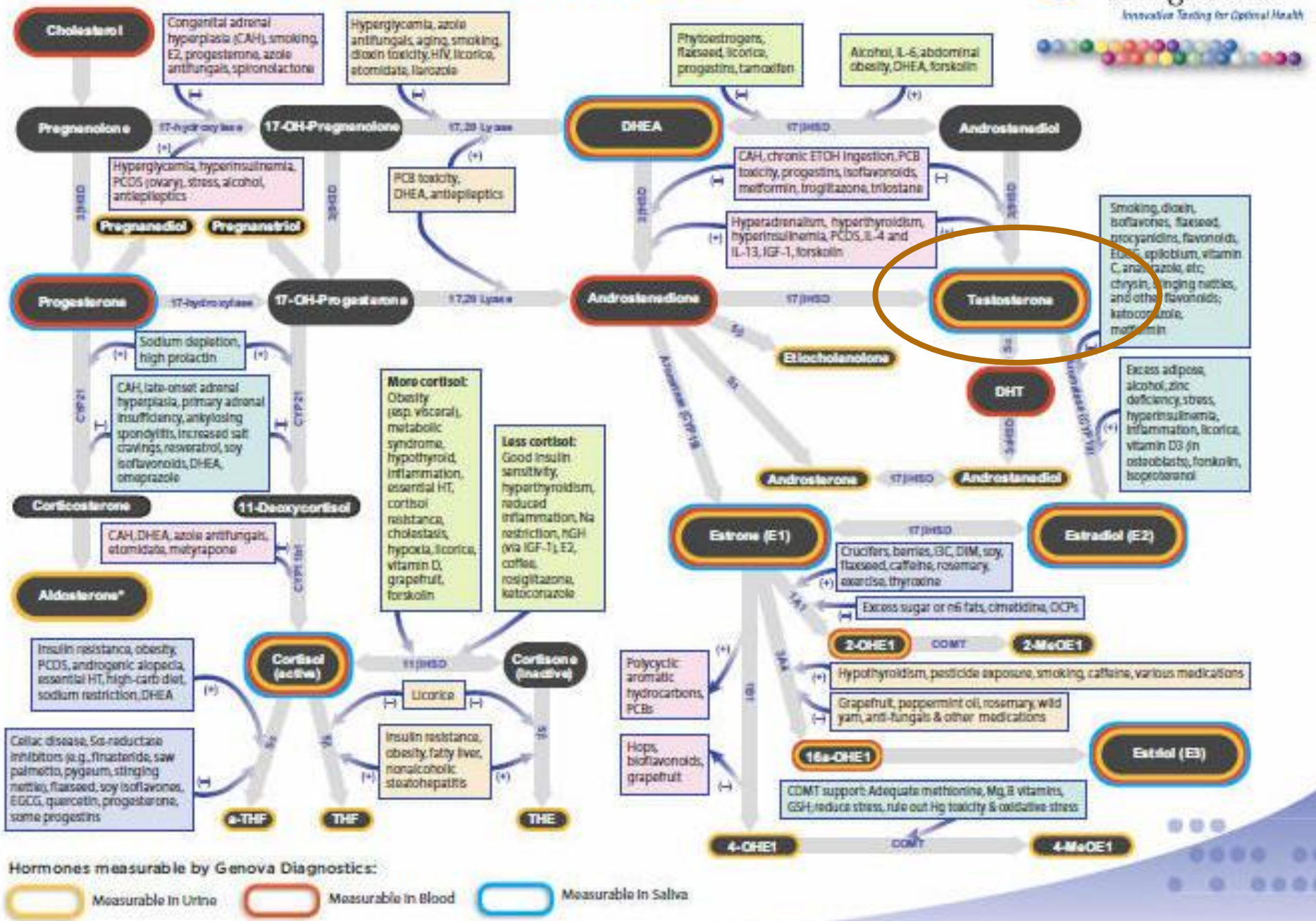

Movement
Sensation
PARIETAL LOBE
Pain
OCCIPITAL LOBE
FRONTAL LOBE
Vision
TEMPORAL LOBE
LIMBIC SYSTEM
HEDONIC SYSTEM
NA
VTA
PITUITARY GLAND
THALAMUS
PAIN CENTRE
CERREBELLUM (CO-ORDINATION)
SPINAL CORD
HIPPOCAMPUS (MEMORY) AND AMYGDALA


Breast
Prolactin
Adrenal
ACTH
Thyroid
TSH
Bone
GH
Ovary
Testis
LH, FSH
Kidney
ADH
Uterus
Oxytocin

Head Trauma risk of pituitary Abnormality

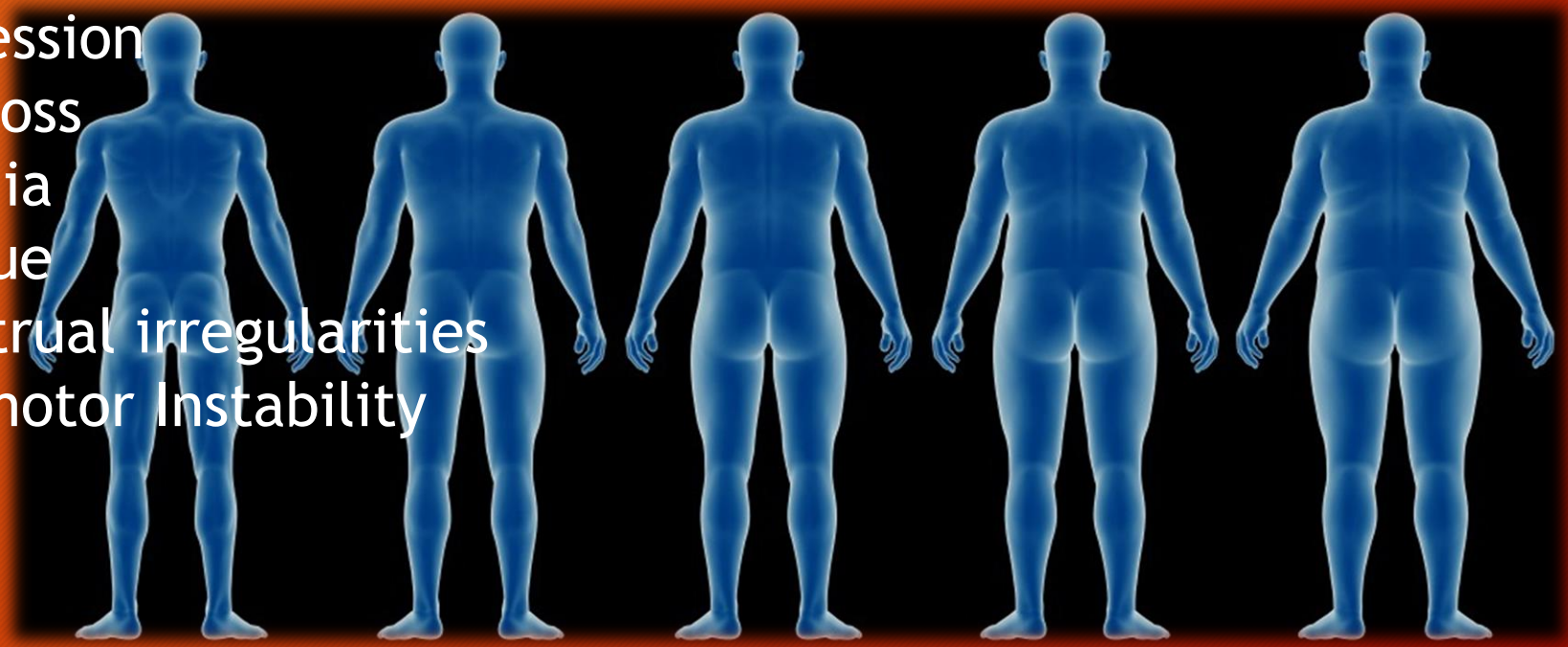


Steroidogenic Pathways



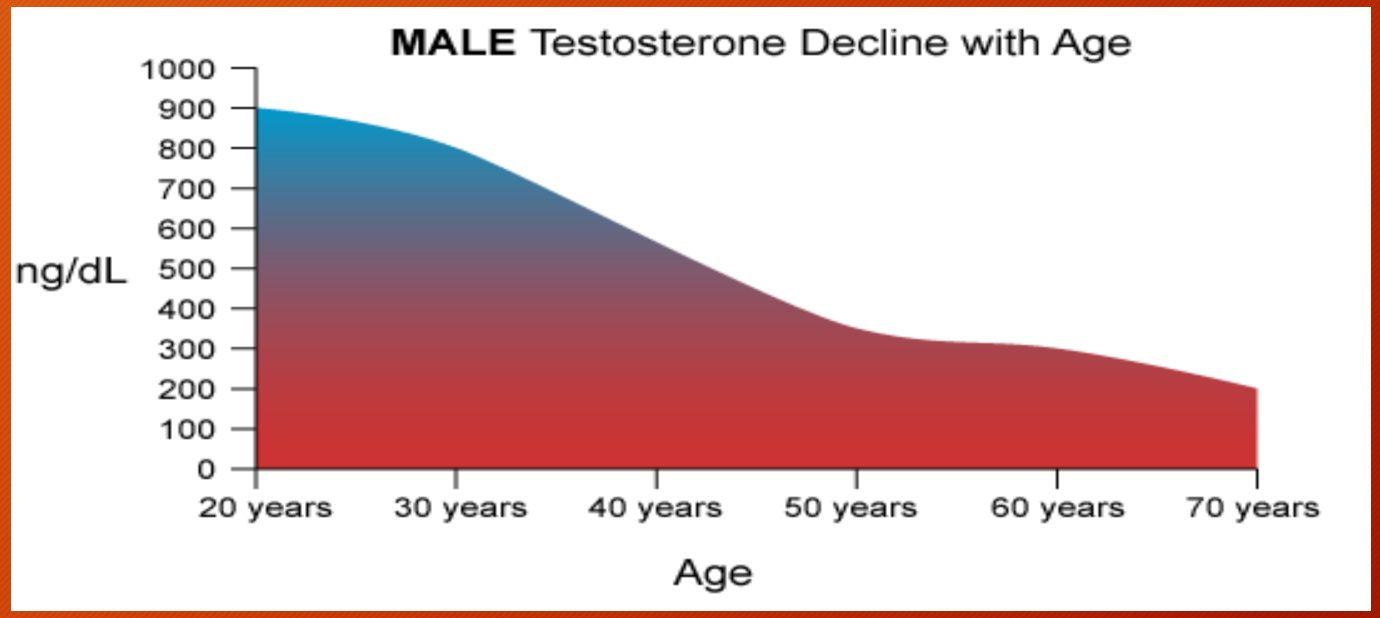
Hypogonadism is a relatively common endocrine disorder, in both men and women

- Increased body fat
- Decreased lean muscle mass
- Decreased bone density
- Increased Cholesterol levels
- Decreased insulin sensitivity
- Sexual dysfunction
- Depression
- Hair loss
- Anemia
- Fatigue
- Menstrual irregularities
- Vasomotor Instability



2013 Kaiser Permanente Study

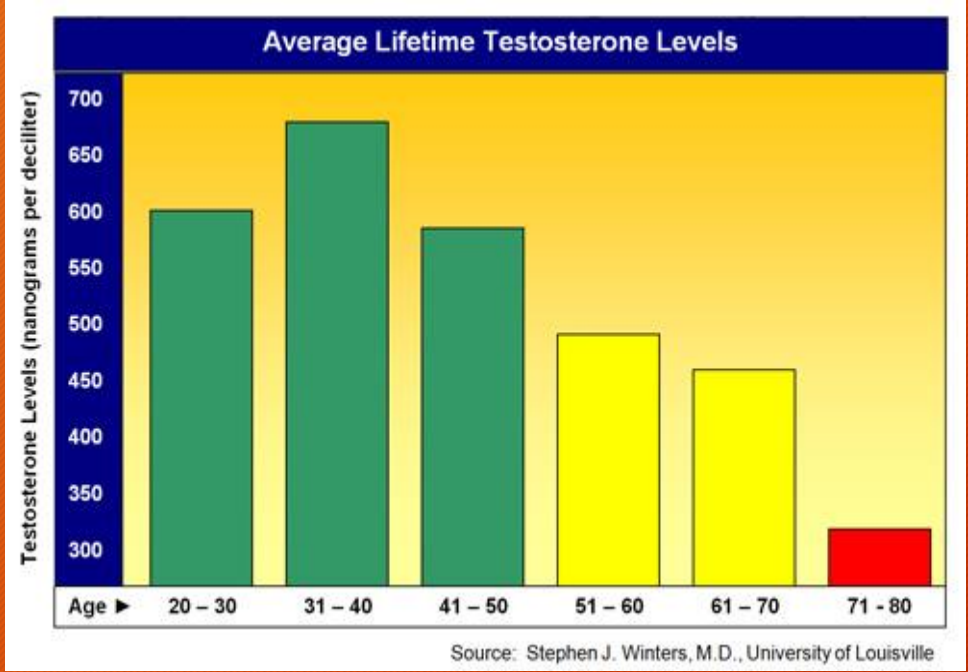
- Men taking long-acting chronic pain medications are 5 times more likely to have low testosterone levels
- 74% of men 26-79 years of age had levels of 250 or less. (300-1100 ng/dl)

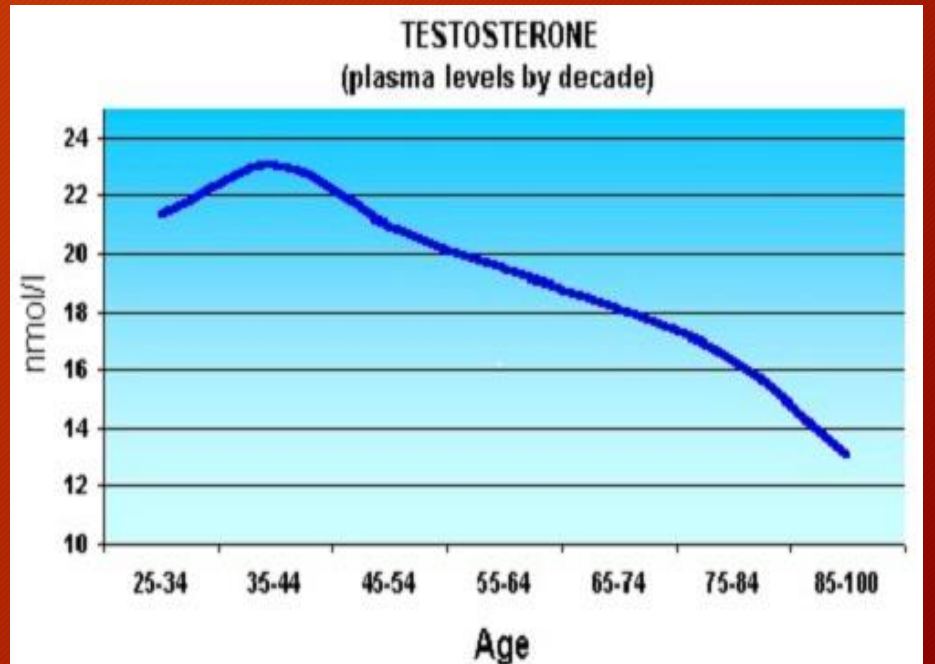


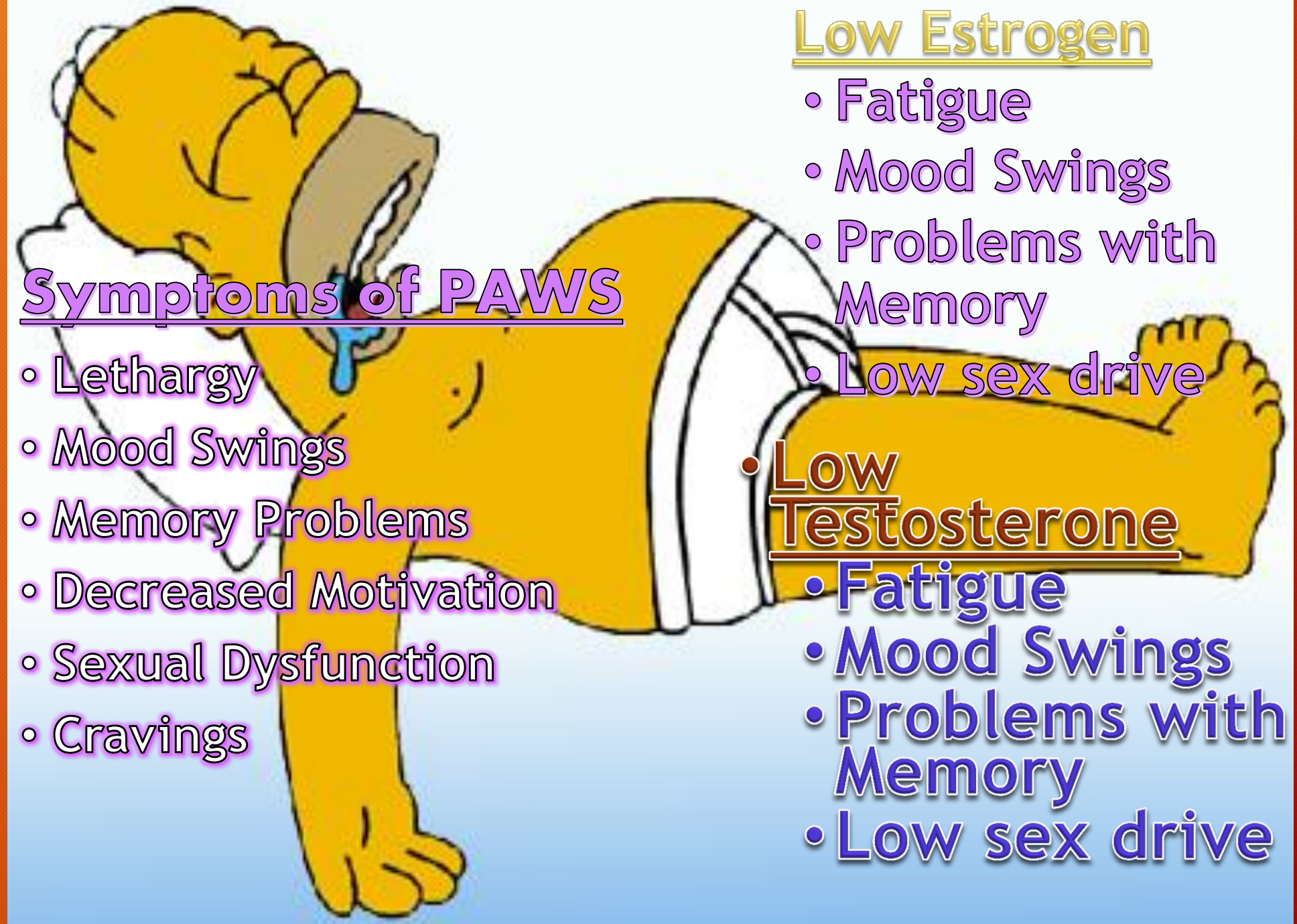
Carpenter and Minkofff, Kaiser Permanente Department of Endocrinology Jan 2013

Testosterone and Opiate Use

- Patient is 23 yrs old, 6’ 3”, 186 lbs
- College Student, long distance cyclist
- Testosterone Total 122 ng/dl (348-1197)
- Free Testosterone 4.2 ng/dl (9.3-26.5)







Symptoms of PAWS

- Lethargy
- Mood Swings
- Memory Problems
- Decreased Motivation
- Sexual Dysfunction
- Cravings

Low Estrogen

- Fatigue
- Mood Swings
- Problems with Memory
- Low sex drive

Low Testosterone

- Fatigue
- Mood Swings
- Problems with Memory
- Low sex drive

Heroin and Hypogonadism

- The association of intravenous heroin use with decreased libido, erectile dysfunction and menstrual cycle abnormalities in women has been recognized for DECADES
- Heroin and methadone are also associated with depression, fatigue, hot flashes, sweating weight gain.
- 5 million men treated with sustained action opiates are TESTOSTERONE Deficient.

Azizi, F, et al Decreased serum testosterone concentrations in male heroin and methadone addicts. *STERIODS*, 1973, 195:296-302

Methadone and Hypogonadism

- Despite the fact that this condition was well established as an adverse effect of methadone therapy in the 1970 and 1980, screening for hypogonadism was not common!
- Reason: Clinics do not diagnose of treat conditions other than opiate dependence!!!!
- Treatment providers are unaware of the adverse endocrine effects!!!
- FOR WHATEVER REASON: countless individuals receiving methadone for addiction have not been diagnosed or treated for symptomatic endocrine deficiencies.

Colameco & Coren Opioid-Induced Endocrinopathy JAOA Vol 109, #1, Jan 2009

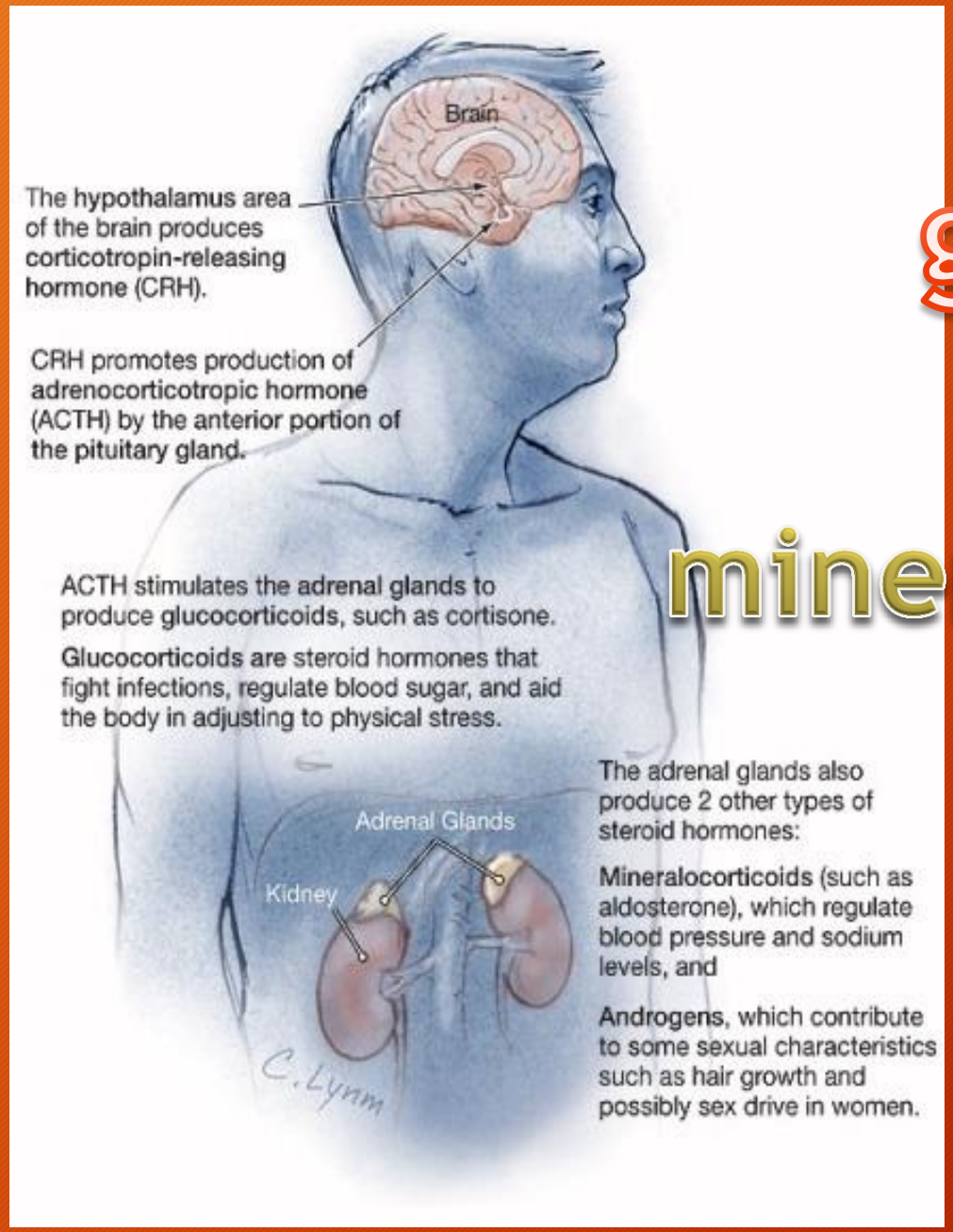
Treatment for Hypogonadism

- Opiates decrease LH and FSH
- Naloxone increases these hormones *
- Opiates decrease LH and FSH
- *B HCG will increased production***

•*Woodall, W.S “Opiods and the Endocrine System”, Advance Healthcare Network, 2013

•**Mendelson, JH et al, Heroin and naltrexone effects on pituitary-gonadal hormones in man: interaction of steroid feedback effects, tolerance and supersensitiviey. J Pharmacol Exp Ther.1980:214-503-506

Hormones



glucorticoids

Cortisol

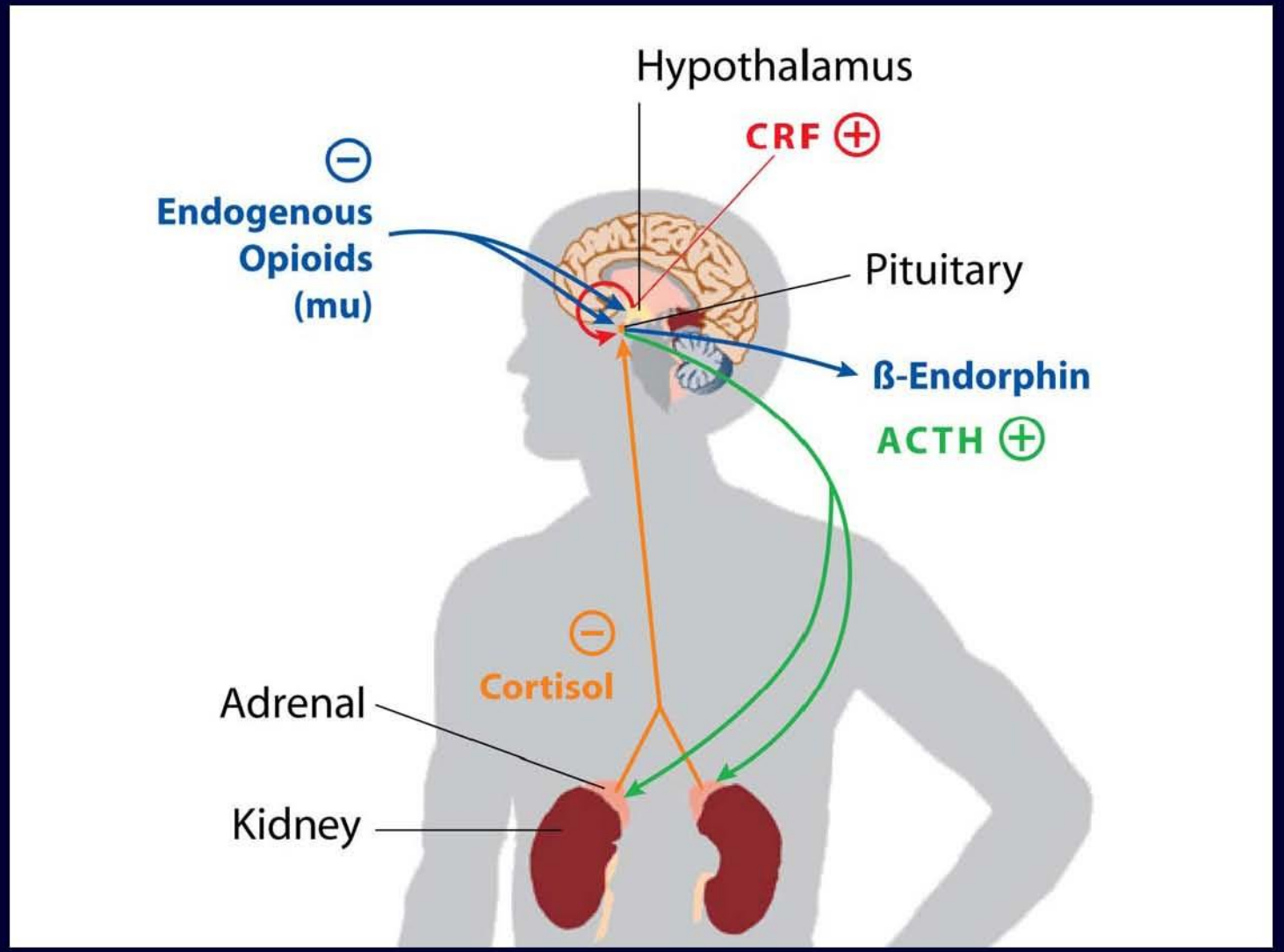
mineralocorticoids

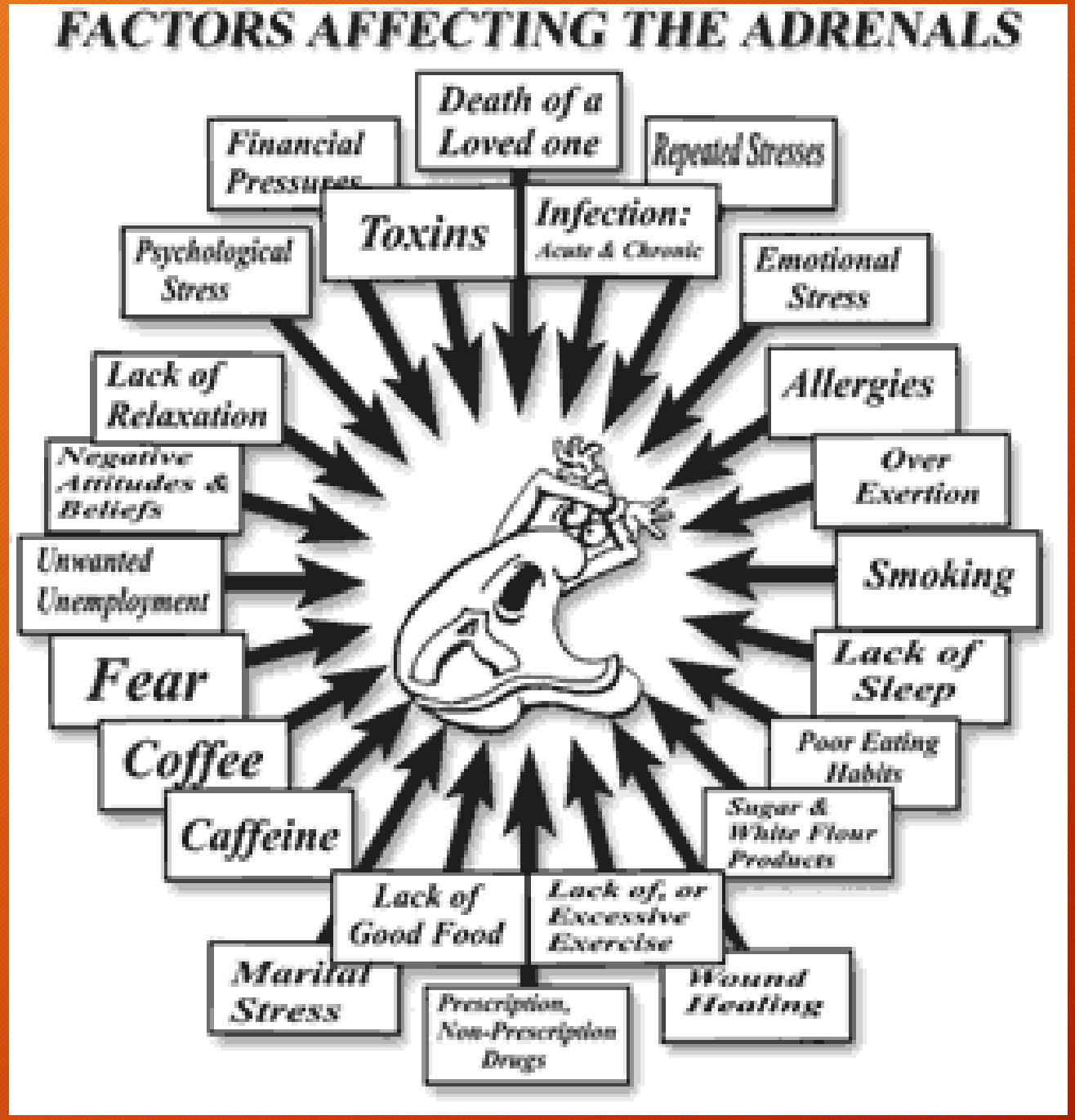
Aldosterone

androgens

DHEA
Estrogens
Testosterone

Hypothalamic Pituitary Adrenal (HPA) Axis





Cortisol is the only hormone that **Increases** with age!

Hypothesis — Atypical Responsivity to Stressors: A Possible Etiology of Addictions

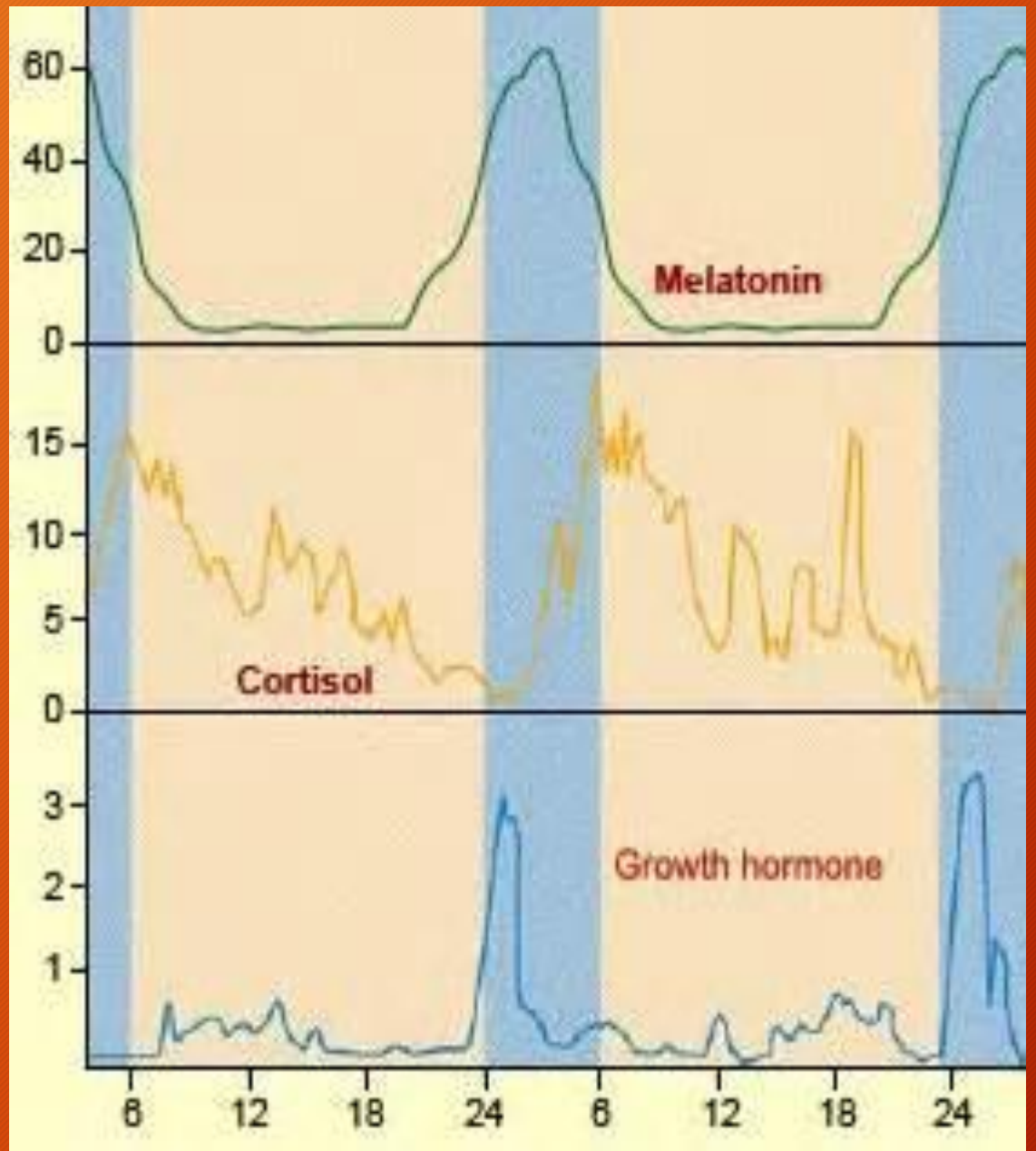
Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to, self-administration of drugs of abuse and addictions.

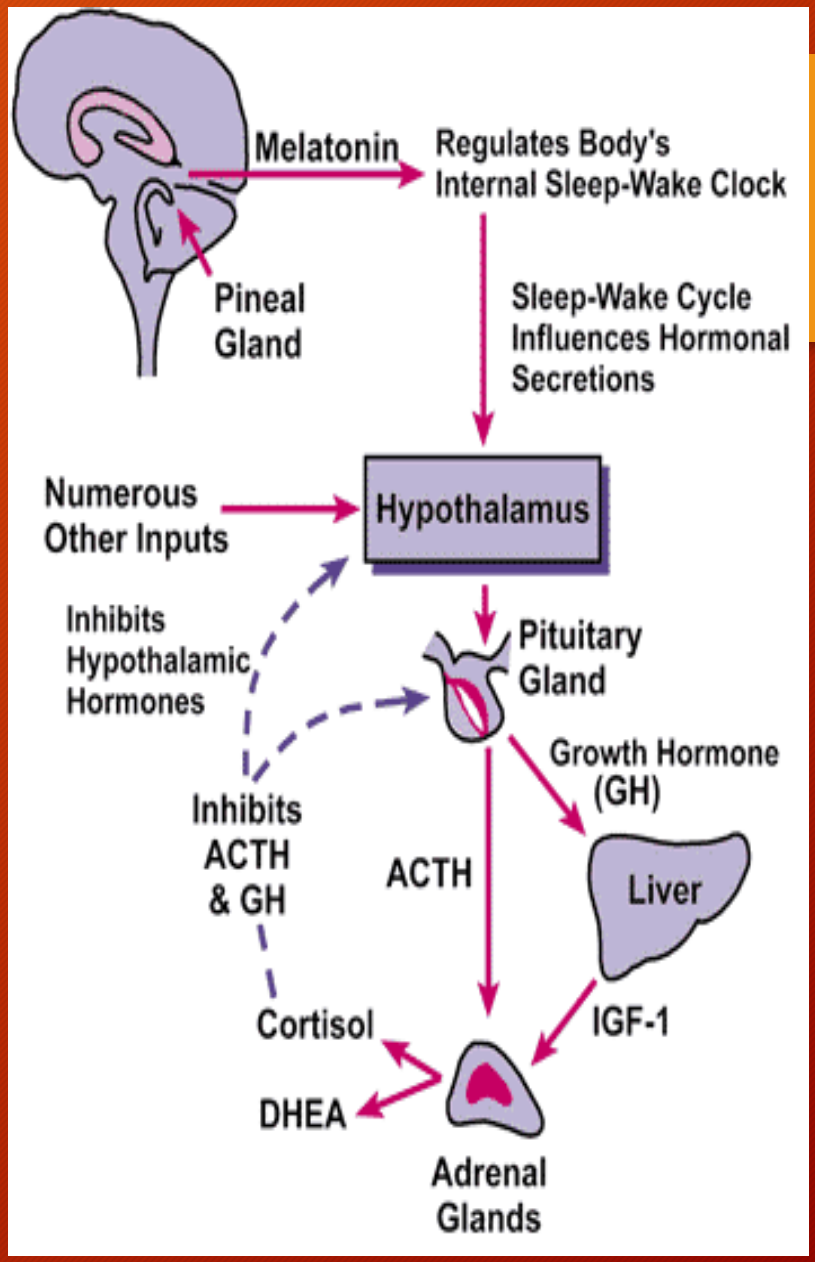
Such atypical stress responsivity in some individuals may exist prior to use of addictive drugs on a genetic or acquired basis, and lead to the acquisition of drug addiction.

Kreek, 1972; 1981; 1984; 1987; 1992; 2001; 2008

Functions of Cortisol

- Balances Blood Sugar
- Weight Control
- Immune system response
- Bone turnover rate
- Stress reaction
- Sleep/wake cycle
- Protein Synthesis
- Mood and thoughts
- Testosterone & estrogen ratio
- DHEA/insulin ration
- Effects pituitary/thyroid/ adrenal system
- Is anti-inflammatory

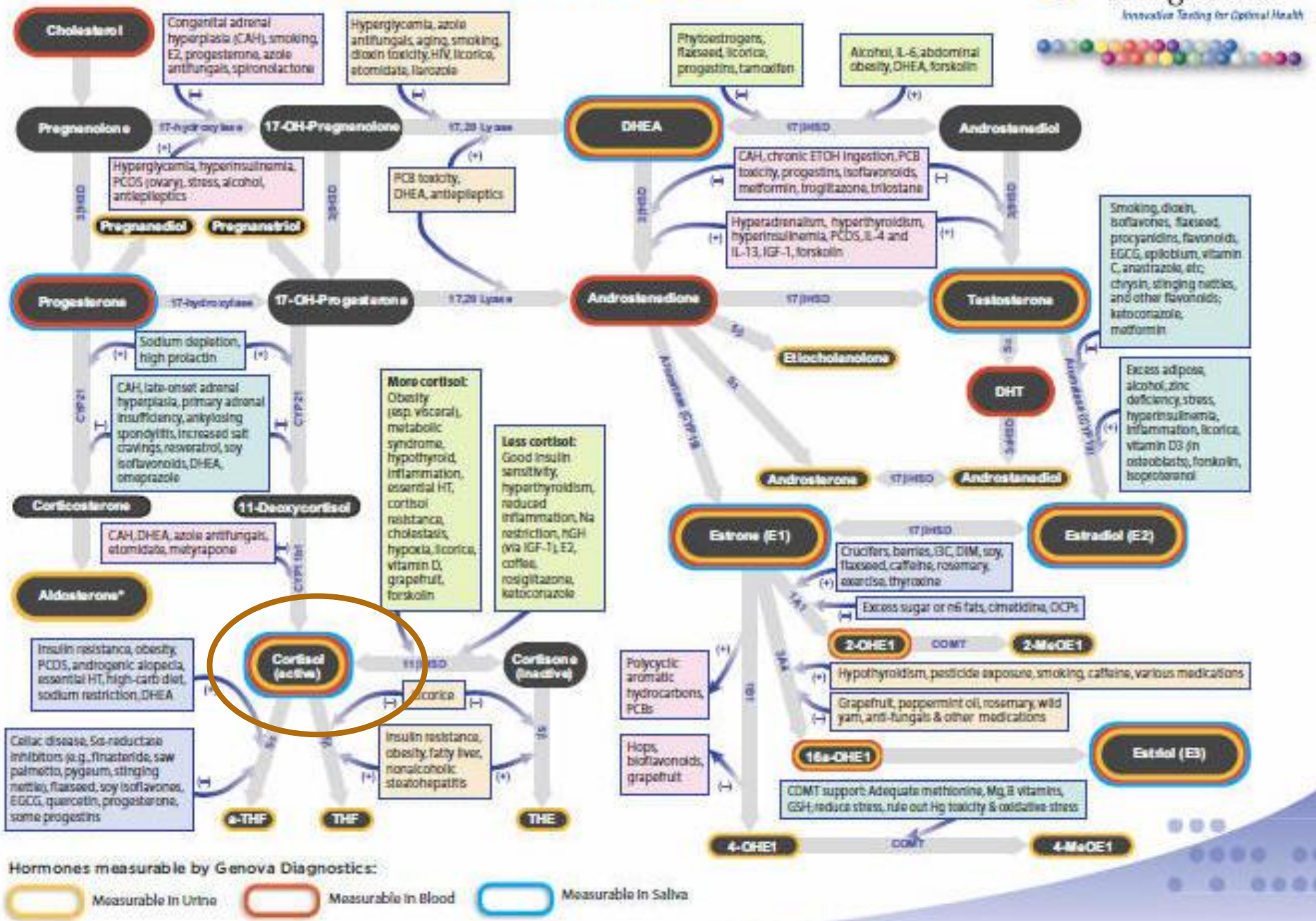

60
40
20
0
Melatonin
15
10
5
0
Cortisol
3
2
1
Growth hormone
6
12
18
24
6
12
18
24


Melatonin
Regulates Body's Internal Sleep-Wake Clock
Pineal Gland
Sleep-Wake Cycle Influences Hormonal Secretions
Numerous Other Inputs
Hypothalamus
Inhibits Hypothalamic Hormones
Pituitary Gland
Growth Hormone (GH)
Inhibits ACTH & GH
ACTH
Liver
IGF-1
Cortisol
DHEA
Adrenal Glands

Cortisol and An Emergency:

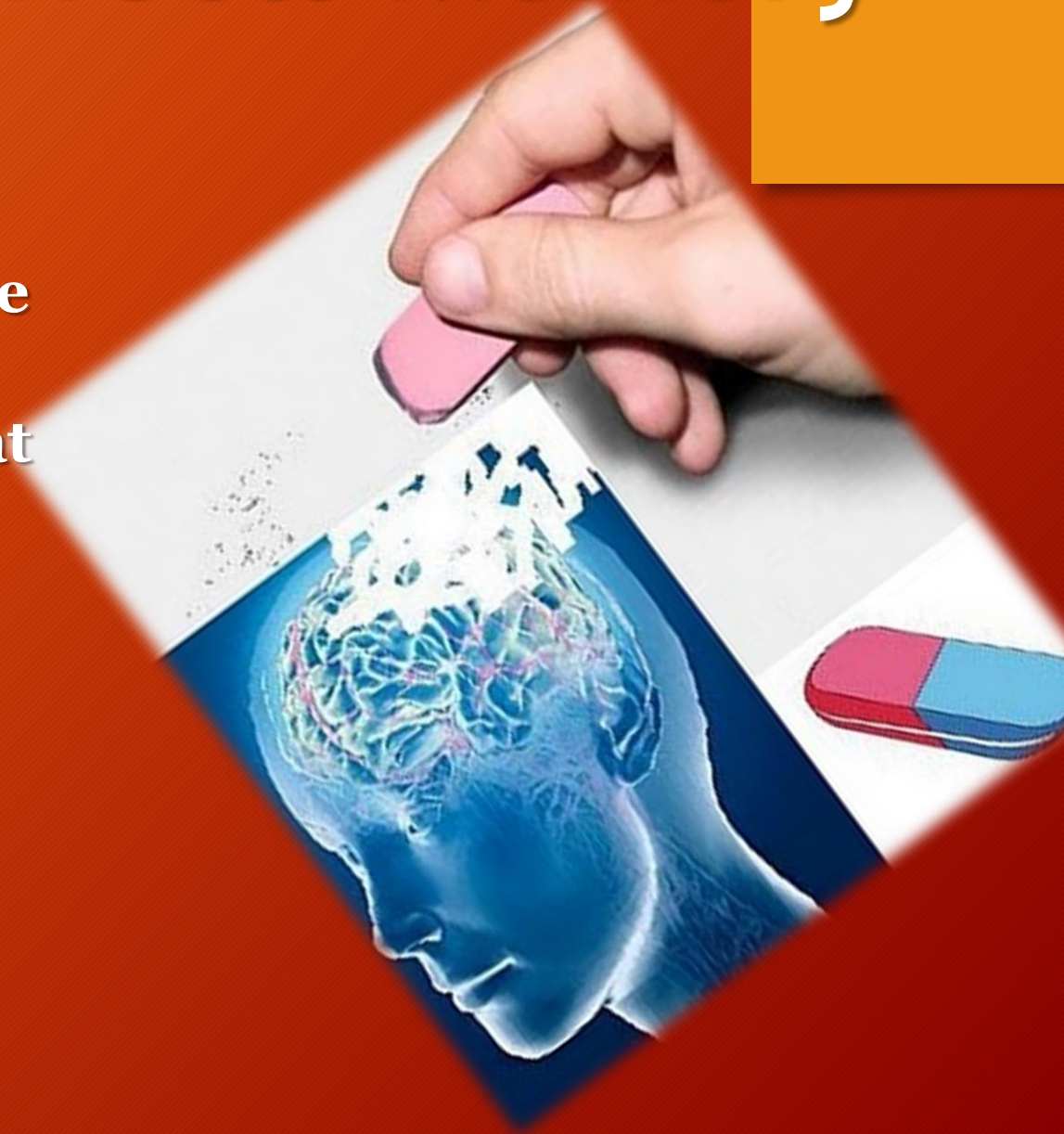
- Cortisol is released in response to stress
- Sparing available glucose for the brain
- Generating new energy from stored reserves
- Diverting energy from low-priority activities (such as the immune system) in order to survive immediate threats or prepare for the exertion of rising to a new day.

Steroidogenic Pathways



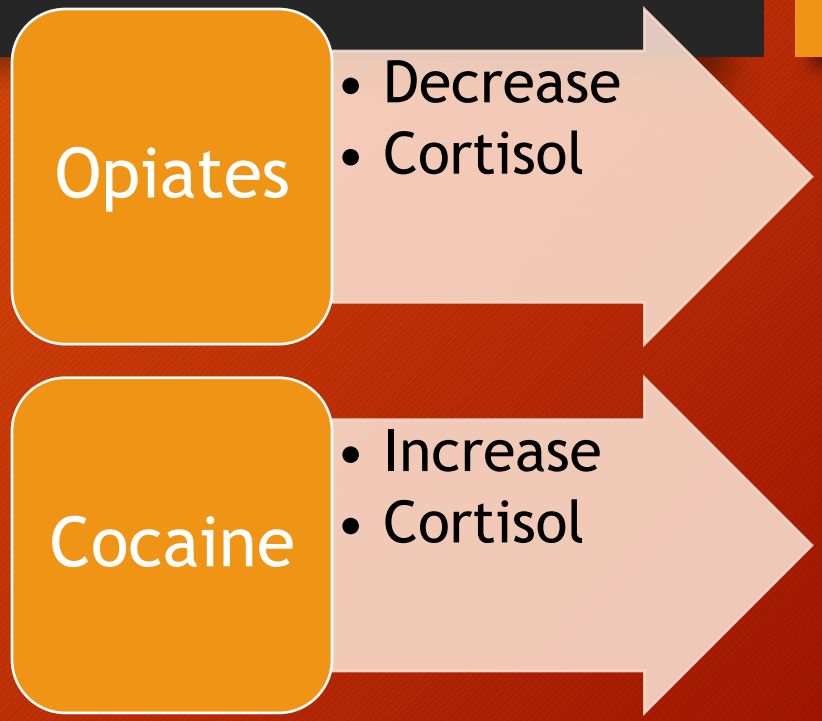
Cortisol effects Memory

- Cortisol works with epinephrine (adrenaline) to create memories of short-term emotional events; this is the proposed mechanism for storage of flash bulb memories, and may originate as a means to remember what to avoid in the future.
- However, long-term exposure to cortisol damages cells in the hippocampus;
- This damage results in impaired learning.
- Furthermore, it has been shown that cortisol inhibits memory retrieval of already stored information



Adrenal Dysfunction in Drug Use

- Opiates inhibit CRH release leading to decreased Cortisol production resulting in adrenal insufficiency.
- Conversely, Cocaine administration results in enhanced HPA activity with elevated levels of Cortisol
- Both result in atypical circadian rhythm.



Brown, TT et al, Gonadal and Adrenal abnormalities in drug users; Cause or consequence of drug use behavior and poor health outcomes. Am J Infect Dis March 2007

Consequences of Elevated Cortisol

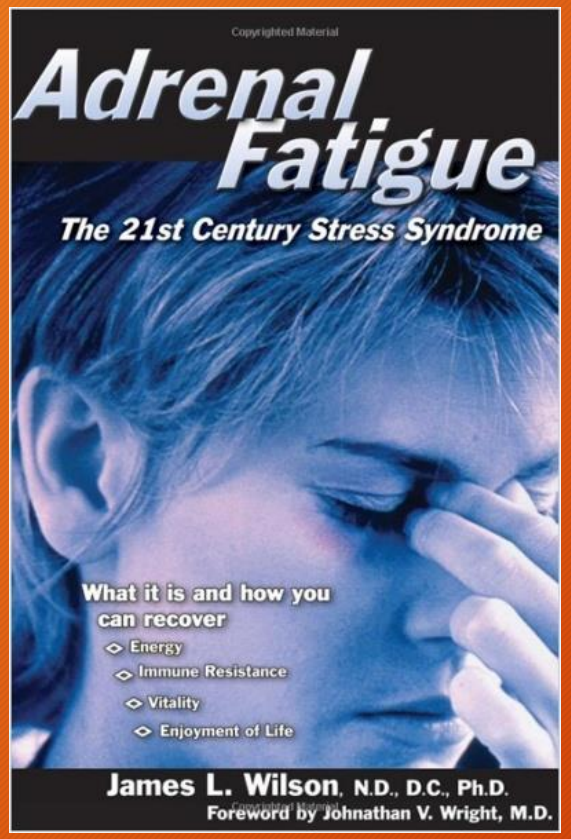
- Decreased immune system
- Increased osteoporosis risk
- Fatigue
- Irritability
- Sugar cravings
- Shakiness between meals
- Confusion
- Low Energy
- Night Sweats
- Binge eating
- Increased Blood Pressure, cholesterol, triglycerides, blood sugar
- Weight gain around the middle
- Impaired conversion of T4 to T3

Symptoms of Adrenal Fatigue

- Difficulty getting up in the morning
- Continuing Fatigue not relieved by sleep
- Craving for salt or salty food
- Lethargy
- Increased effort to do every day tasks
- Thoughts less focused/fuzzy
- Memory less accurate
- Decreased sex drive
- Decreased ability to handle stress
- Increased time to recover from illness, injury or trauma
- Light-headed when standing up quickly
- Increased PMS
- Sx increase if meals are skipped or inadequate

*3 or more symptoms suggest adrenal problems

Wilson, J L: *Adrenal Fatigue: The 21st Century Stress Syndrome.* Smart Publications 2001. Pp 27-45.



Chocolate cravings:
may be caused in part by low levels of Magnesium
So consider adding magnesium to
Tame cravings and to help calm
Frayed nerves and assist in restful sleep.

Consequences of adrenal and gonadal abnormalities

Cravings

- When drugs are withdrawn, the brain releases CRH with stress which causes cravings and the desire to use.
- HPA de-activation during drug use reinforces cravings and drug seeking behavior

Relapse

- Increased CRH creates anxiety and increased the adverse effects of drug withdrawal.
- Low Estrogen and Testosterone levels decrease endogenous opiate levels and contribute to cravings and relapse

Brown, TT et al, Gonadal and Adrenal abnormalities in drug users; Cause or consequence of drug use behavior and poor health outcomes. Am J Infect Dis March 2007

Consequences of adrenal and gonadal abnormalities

Depression and Gonads

- Estrogen and Testosterone have a direct effect on Serotonin synthesis.
- If there are low levels due to gonadal dysfunction with addiction, the patients can suffer from depression, sadness and anger that does NOT respond to antidepressants

Depression and Adrenals

- Reduced Cortisol has been linked to depressive symptoms, apathy, profound fatigues and even delusional behavior
- Moderate to severe depression has been identified in more than 50% of people with addiction

Brown, TT et al, Gonadal and Adrenal abnormalities in drug users; Cause or consequence of drug use behavior and poor health outcomes. Am J Infect Dis March 2007

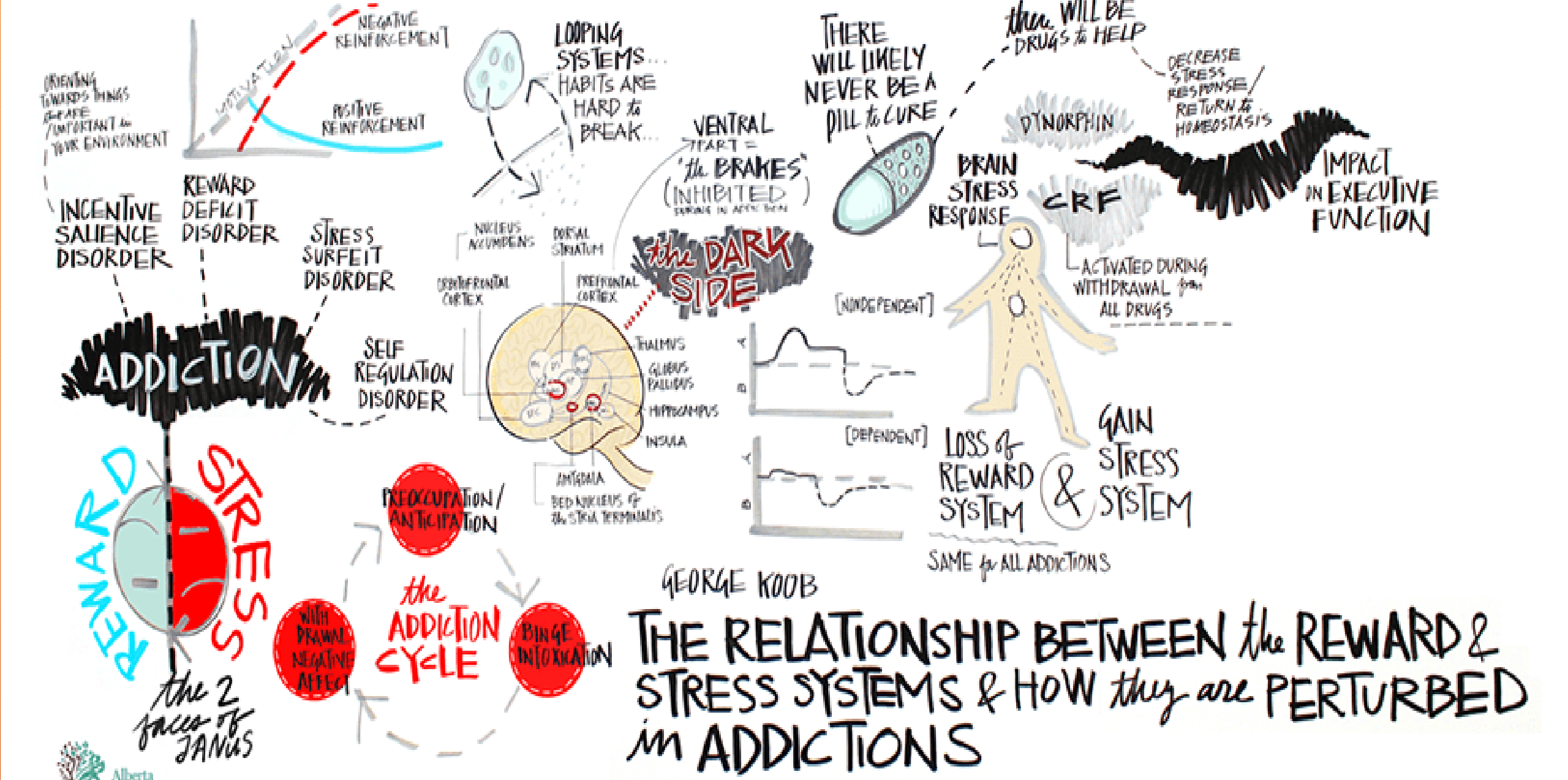
Our Autonomic Nervous system

Sympathetic: Flight or Flight

- Increased cortisol and adrenaline cause a number of physical and hormonal changes
- Increase a person's risk of relapse by creating an emotional and physiological state of over- stimulation
- Impair healing, interfere with memory production, increase risk of disease, including cancer
- Negatively impacts sleep cycle.

Parasympathetic: Rest and Digest

- Yoga: Breathing and poses help to engage the parasympathetic nervous system, allowing our bodies to counter balance the stress response
- Meditation: Breathing and mindfulness allow us to remain in the present, not in the past (depression) or in the future (anxiety)
- Exercise (moderate) especially upper body work to release energy created by anger
- Adaptogens
- Tapping



Alberta family wellness initiative

Norlien Foundation

27 October - 1 November 2013 | Edmonton, Alberta

Symposium 2013 | **ACCELERATING INNOVATION: Telling the Brain Story to Inspire Action**

graphic facilitation by depict. in affiliation with THE VALUE WEB

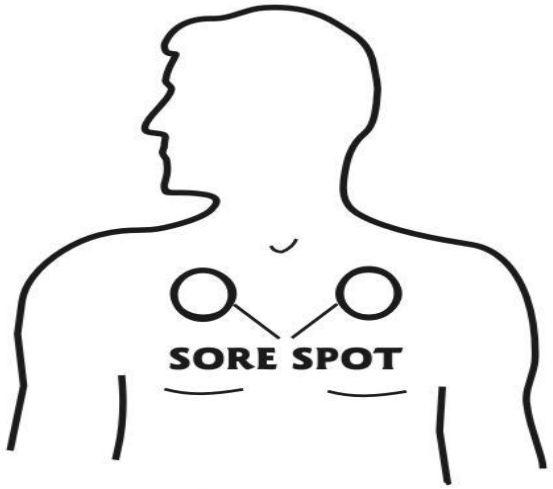
#1...The Setup

1) Repeat 3X

*Even though I have this _____(problem)_*
I deeply & completely accept myself.

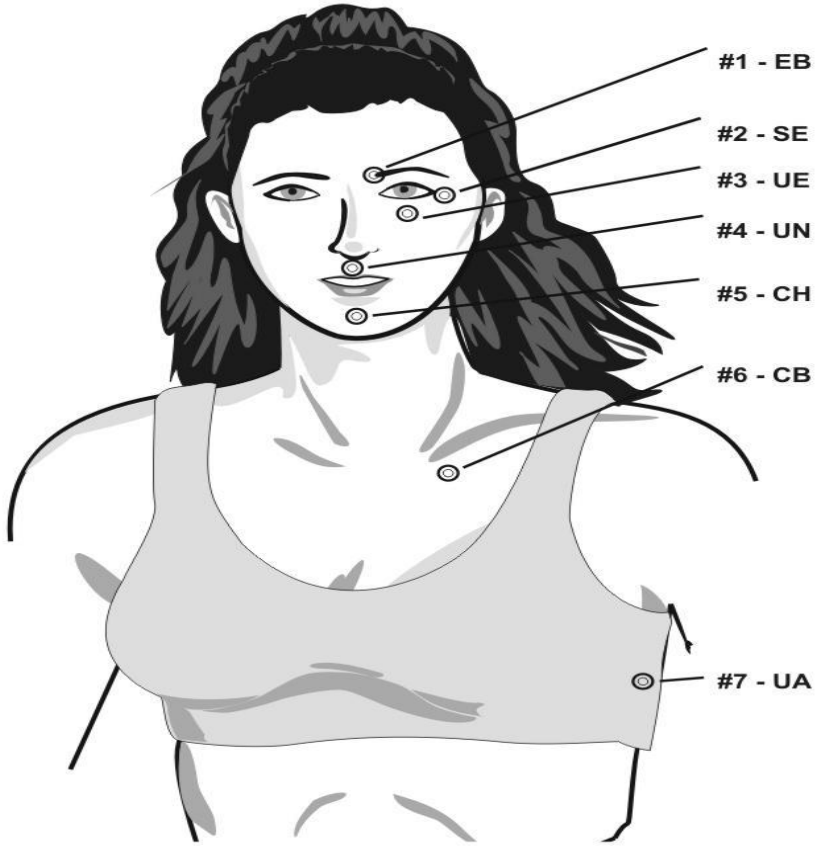
2) While continuously rubbing the "Sore Spot" or tapping the "Karate Chop" point.

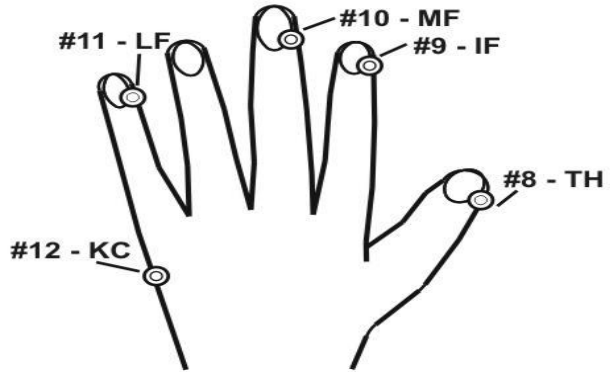
The Sore Spot/ Karate Chop Point



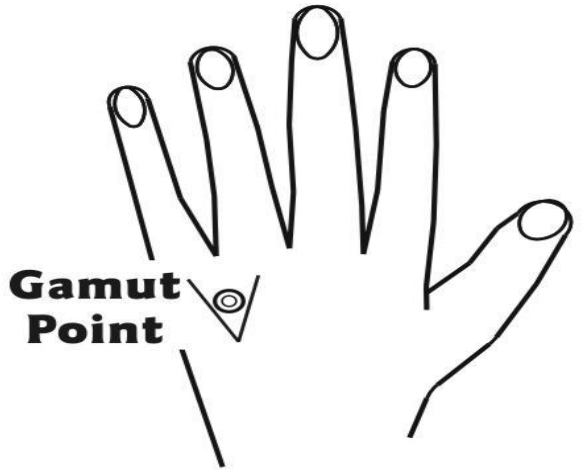
#2...The Sequence

Tap about 5X on each point





#3...The 9 Gamut



Perform 9 actions while tapping the GAMUT POINT continuously:

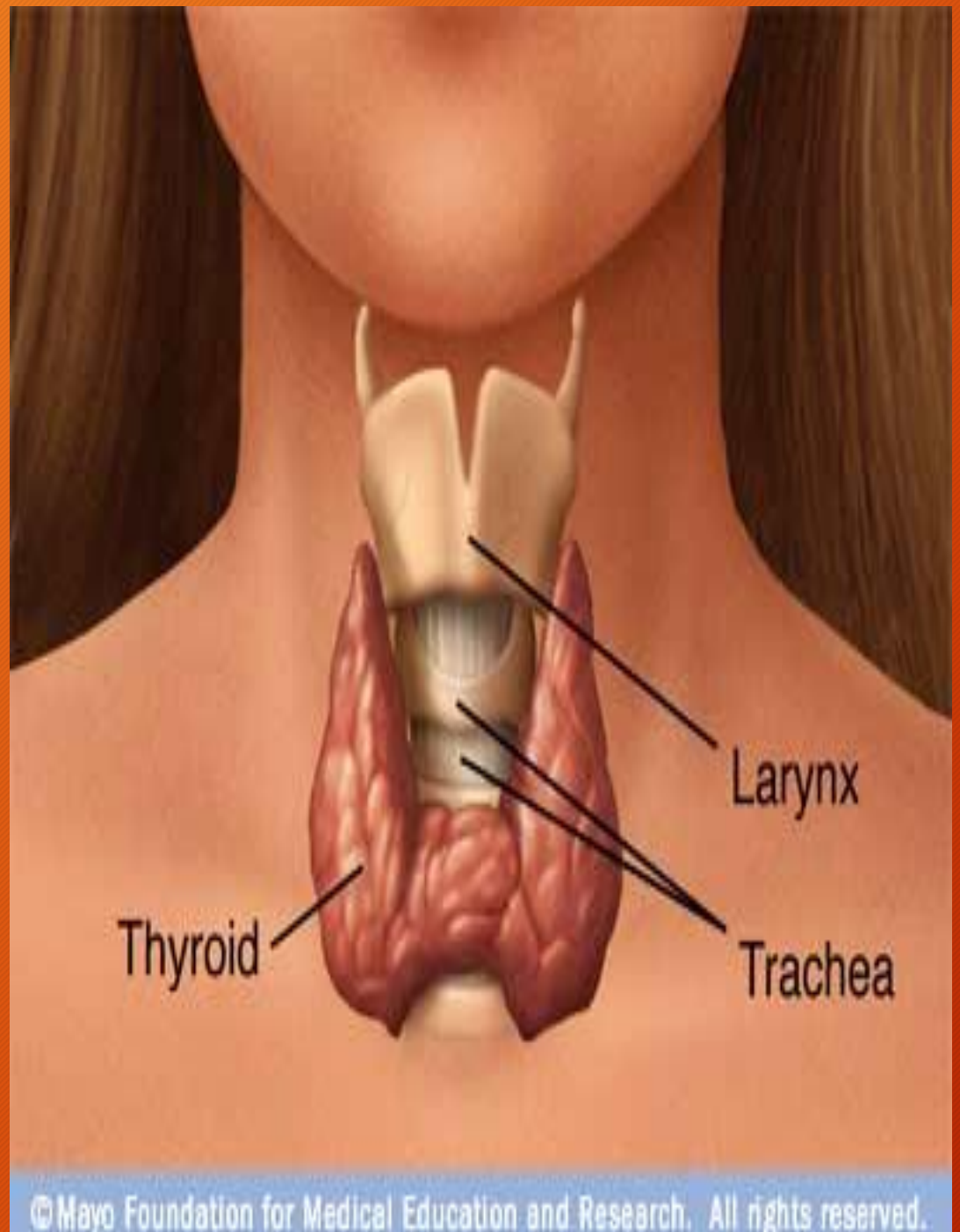
1) Eyes closed
2) Eyes open
3) Eyes hard down right (head steady)
4) Eyes hard down left (head steady)
5) Roll eyes in a circle
6) Roll eyes in opposite direction
7) Hum 5 seconds of song (Happy Birthday)
8) Count from 1 to 5
9) Hum 5 seconds of a song again.

#4...Repeat (#2) The Sequence

NOTE: In subsequent rounds of tapping, change the setup language to *"Even though I STILL have SOME OF this problem..."* and use *"REMAINING problem"* as a reminder phrase.

Stressed spelled backwards

DESSERTS



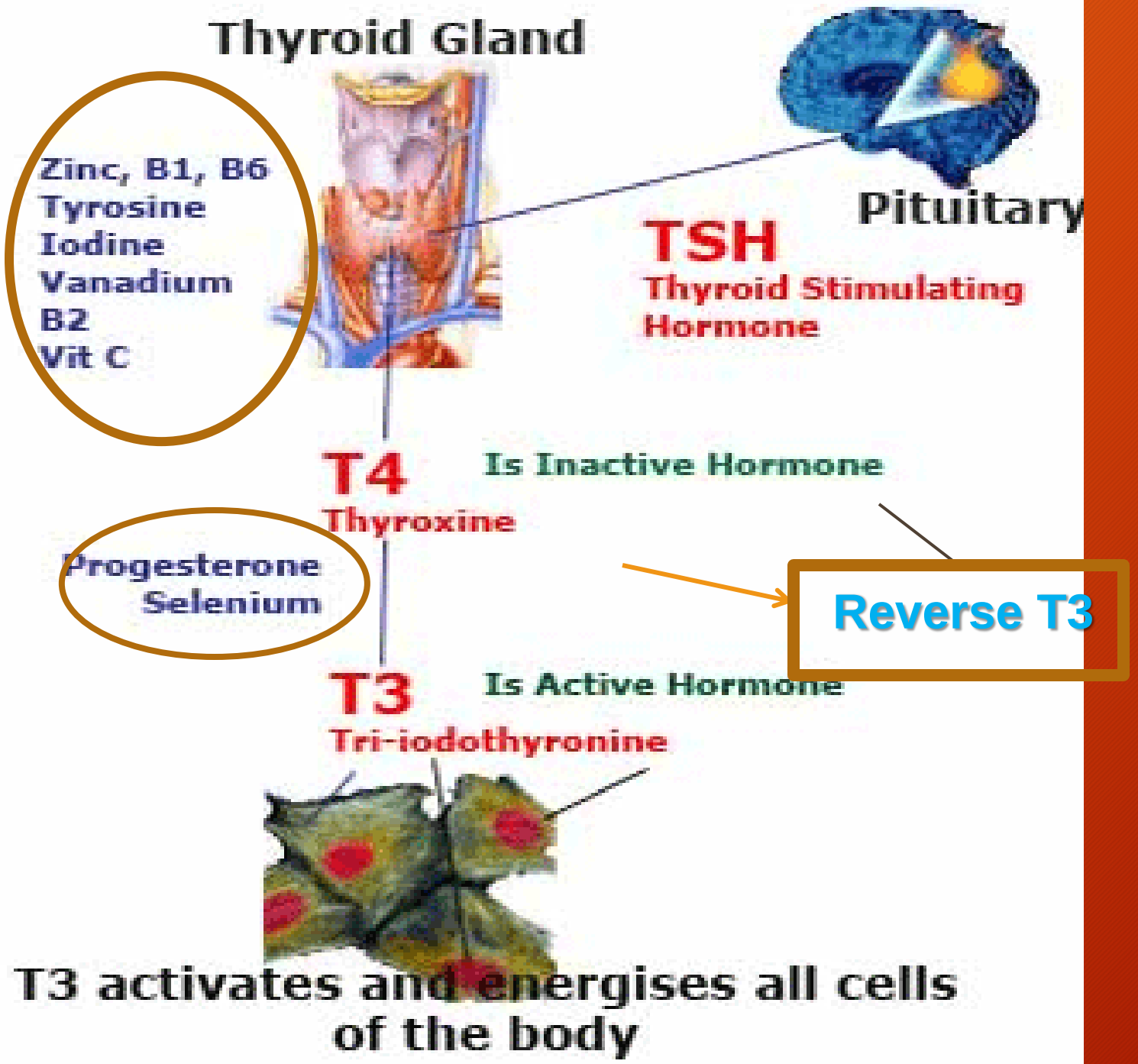
Some Common Thyroid Symptoms*

*That Your Doctor Probably Ignores or Explains Away

-- Fatigue
-- Weight gain
-- Inability to lose weight
-- Hair loss/thinning
-- Eyebrow loss/thinning
-- Fertility problems
-- Low sex drive
-- Muscle aches/pains
-- Depression
-- Brain fog

GET TESTED! TSH, FT4, FT3, TPO!

www.facebook.com/ThyroidSupport



Tests to Run

TSH

Free T3

Free T4

Reverse T3

TPO

Thyroid Pathology

Physiologic state	Serum TSH	Serum Free T4	Serum T3	24-h radioiodine uptake
Hyperthyroidism, untreated	Low	High	High	High
Hyperthyroidism, T3 toxicosis	Low	Normal	High	Normal or High
Primary Hypothyroidism, untreated	High	Low	Low or Normal	Low or Normal
Hypothyroidism secondary to pituitary disease	Low or Normal	Low	Low or Normal	Low or Normal
Euthyroid, on exogenous thyroid hormone	Normal	Normal on T4, Low on T3	High on T3, Normal on T4	Low

What can we do when anti-depressants don’t work?

“Depression is often anger, without enthusiasm”

Patrick Holford,

New Optimum Nutrition for the Mind

Sex and Serotonin

- A man's average production of Serotonin is about 52% greater than a woman's
- In women, low serotonin is associated with depression and anxiety
- In men, low serotonin is related to aggression and alcoholism
- Men *act out* their mood
- Women *act in* their moods

Depression in Addiction

- Male addicts have a rate of depression three times higher than the general public
- Female addicts have a rate that's four times higher [source: Albrecht, Herrick].

Depression in Addiction

The link between depression and addiction holds true for more traditional substance addictions like nicotine and alcohol as well as more recently recognized impulse-control addictions, such compulsive gambling.

Is it any wonder then that Nevada, with the smoky, cocktail-fueled casinos of Las Vegas, ranked as one of the 10 most depressed states in 2007


CURRENTLY ON
EXIT 58A-B
95
1
Zoloft
9
Prozac
Paxil
Buspar
Wellbutrin
Celexa

Truth about Antidepressants

The Truth……

A word about Mania and Antidepressants

- Review of 173 studies to assess the quality of the evidence for antidepressant use in bipolar patients
- "The take-home message is that antidepressants have a questionable benefit-risk and should only be used in certain cases in bipolar disorder,"

Vieta, *Nolen* 10th International Conference on Bipolar Disorders (ICBD). Abstract 13. Presented June 14, 2013.

A word about Mania and Antidepressants

- "First, they shouldn't be used in mania or in mixed episodes
- They should only be used in bipolar depression in patients with a history of a good response in the past to antidepressants and no history of rapid cycling or switches into mania right away," he said

Vieta, *Nolen* 10th International Conference on Bipolar Disorders (ICBD). Abstract 13. Presented June 14, 2013.

CDC Report on Antidepressants

- 1 in 9 Americans over age 12 takes antidepressants
- 1 in 4 women between 40 and 59
- Since the early 1990s antidepressant use has increased 400% across all age groups
- 1 in 12 takes antidepressants despite having no depressive symptoms whatsoever.
- Less than 1/3 of those taking antidepressants have had a checkup with a mental health professional in the last year
- 1 in 7 has been on antidepressants for more than a decade.

Centers for Disease Control: NCHS Data Brief Number 76, October 2011.
"Antidepressant Use in Persons Aged 12 and Over: United States, 2005-2008"

Antidepressants without a DX

- Nearly 3/4of all antidepressant prescriptions are written without any diagnosis of a psychiatric problem.
- Primary-care physicians are much more likely to prescribe these drugs than specialists
- 1 in 11 visits to a primary-care physician results in a new antidepressant prescription or refill.
- In nearly 80% of these office visits where there's no psychiatric diagnosis, there's also no specific psychiatric complaint from the patient.

Mojtabai, Ramin and Olfson, Mark. "Proportion of Antidepressants Prescribed without a Psychiatric Diagnosis is Growing" *Health Affairs* 30.8 (2011): 1434-1442

Antidepressants and Placebo Response

- A review of 96 studies published from 1980 to 2005 concluded the placebo effect was likely responsible for 68% of the improvement seen in patients taking antidepressants.
- Another review pegged it at 84%.
- What's more, the placebo effect appears to be growing over time.

Khan, Arif et al. "Why Has the Antidepressant-Placebo Difference in Antidepressant Clinical Trials Diminished over the Past Three Decades?" *CNS Neuroscience & Therapeutics* 16 (2010): 217-226.

Kirsch, Irving "Antidepressants and the placebo response" *Epidemiologia e Psichiatria Sociale* 18.4 (2009): 318-322.

Placebo v. Antidepressants v. Therapy

- A review of 177 studies involving more than 24,000 depressed patients found placebos alleviated symptoms in 38%, while antidepressants reduced them in 46%.
- Psychotherapy alone reduced symptoms in 47 percent, about the same as antidepressants but usually at higher cost.
- Best of all was combining antidepressants and psychotherapy, with a 52% success rate.

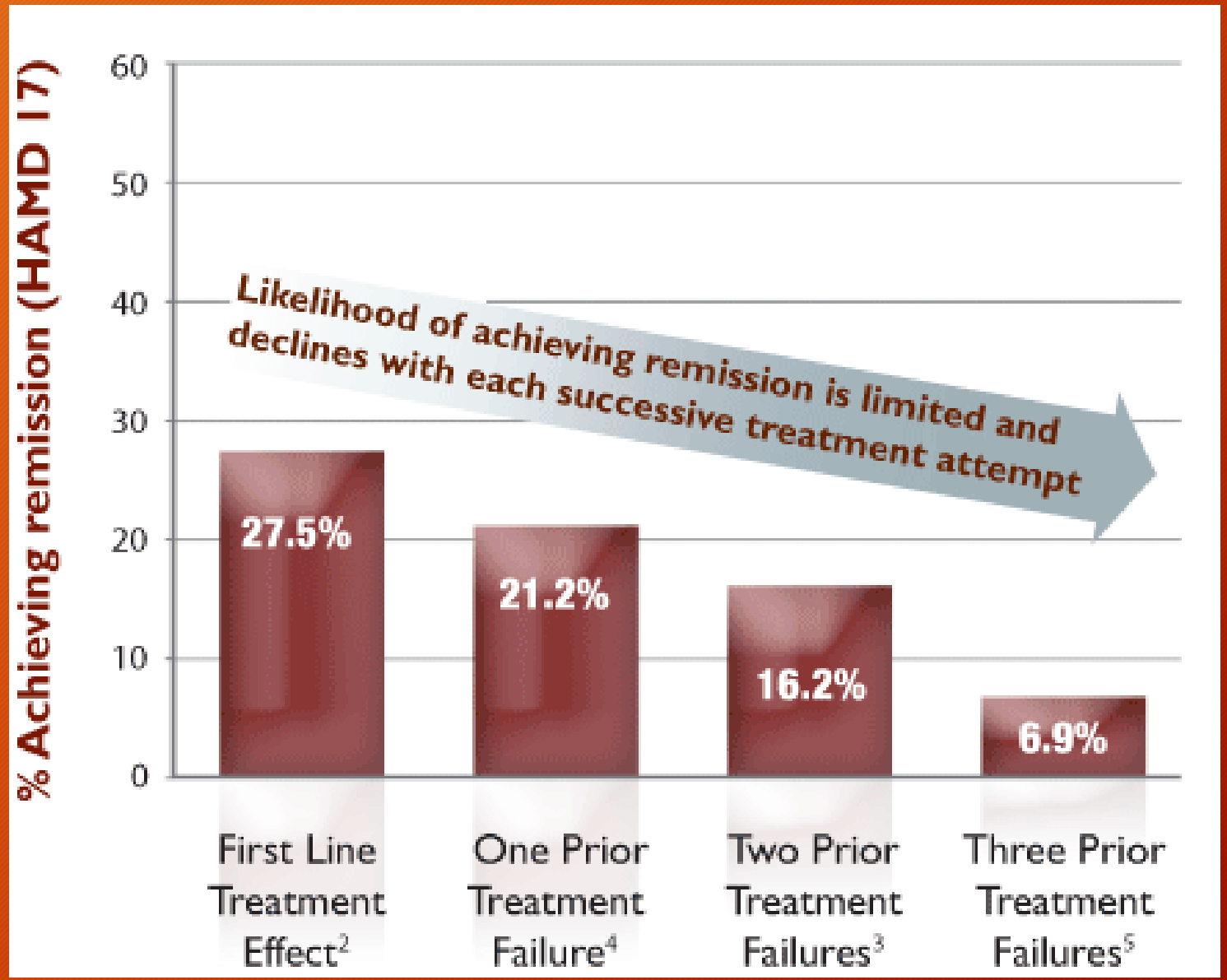
Khan, Arif et al. "A Systematic Review of Comparative Efficacy of Treatments and Controls for Depression" *PLOS One* 7.7 (2012): e41778

Antidepressants and the placebo response

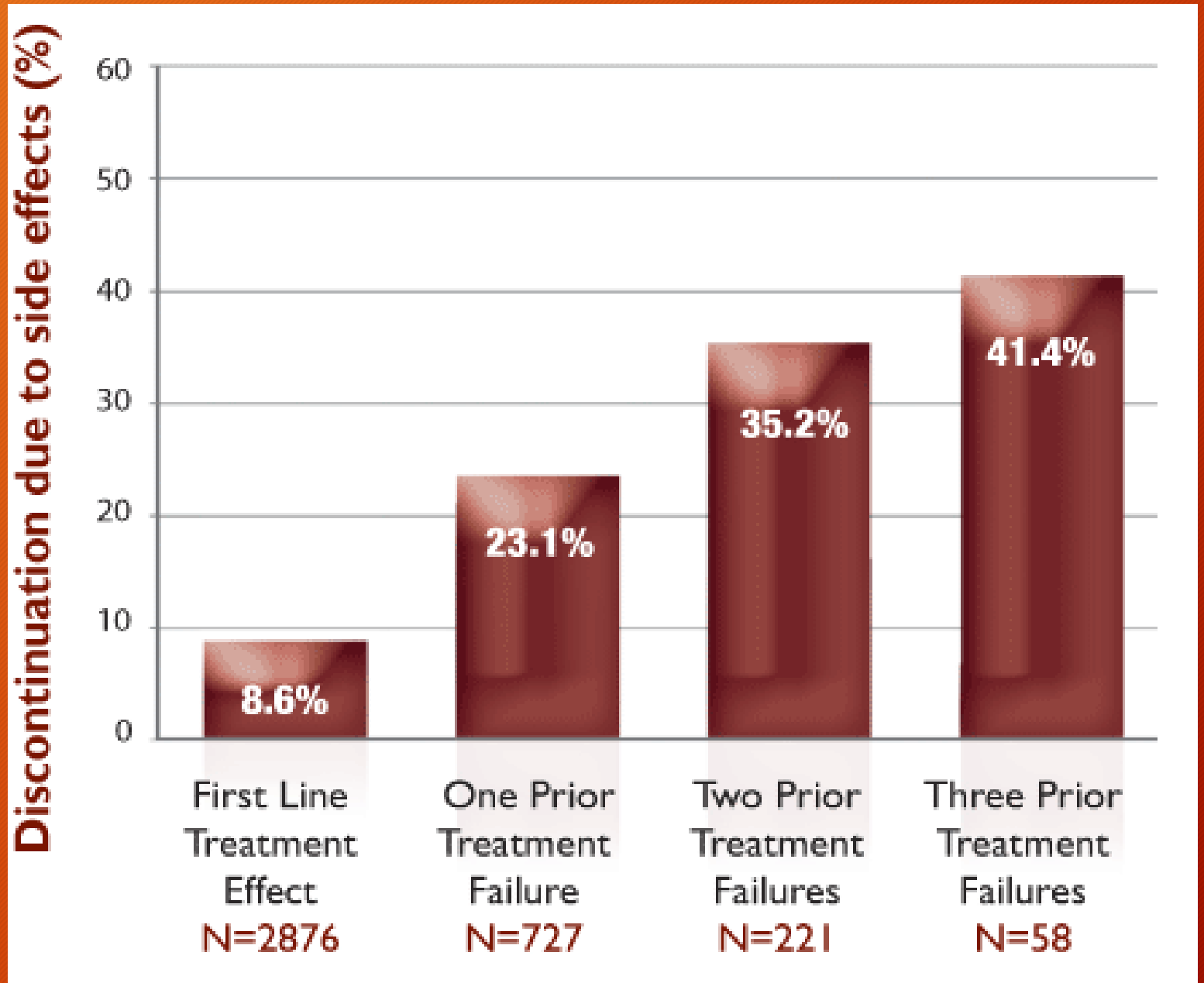
- Some research says there's *no* medicinal benefit.
- A European study of "active placebos" (where the placebo mimicked the drug's side effects) found no significant difference between placebos and antidepressants.

Kirsch, Irving "Antidepressants and the placebo response" *Epidemiologia e Psichiatria Sociale* 18.4 (2009): 318-322.

The STAR*D study is the largest and longest study ever conducted to evaluate depression medication[2,3]



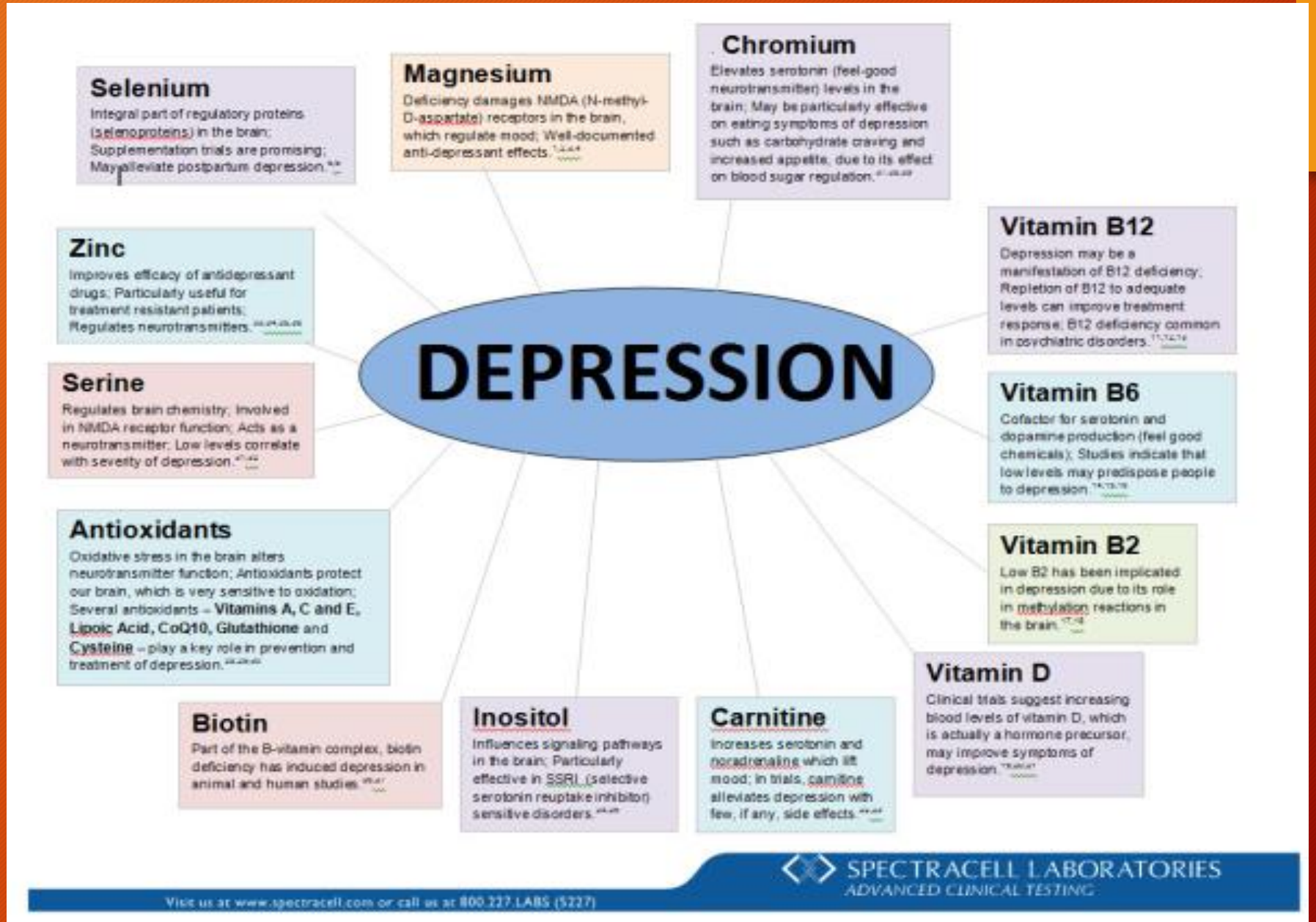
Likelihood of discontinuing treatment increases with each new medication attempt[2,]



Antidepressants and Nutrients

- Antidepressants DEPLETE melatonin which is important for sleep as well as one of the most powerful antioxidants in the body
- Deficiency of B Vitamins

Potential Nutritional Causes of Depression



Magnesium Rich Foods

Serum Levels of Magnesium

After a 150 mg elemental dose from four different magnesium sources

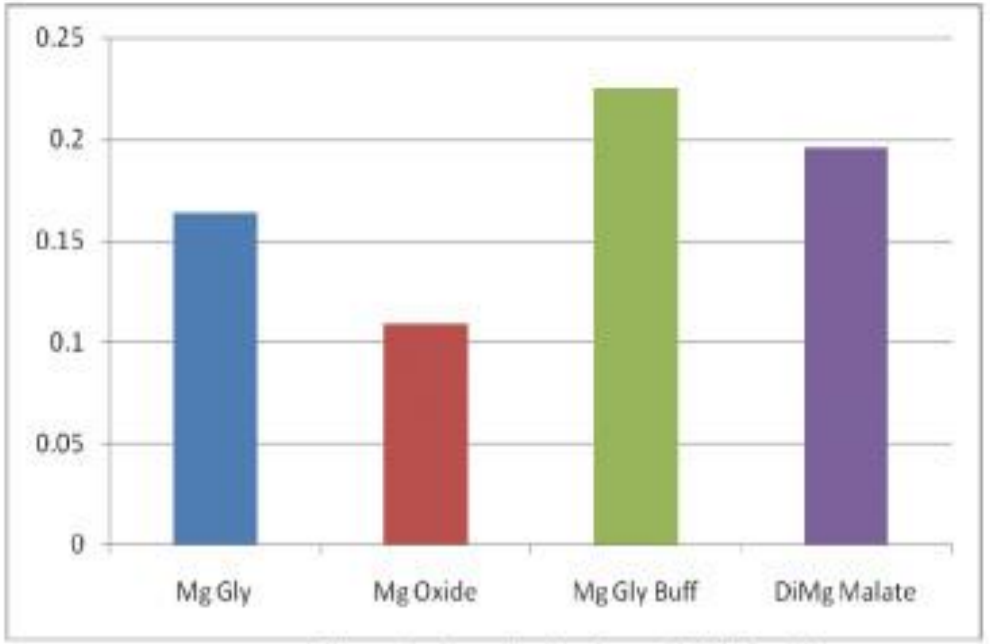


Figure 2. Area Under Curve (AUC) for 8 hours.

Magnesium Glycinate Chelate Buffered (Mg Gly Buff)	0.225
DiMagnesium Malate (DiMag Malate)	0.196
Magnesium Glycinate Chelate (MgGly)	0.164
Magnesium Oxide (Mg Oxide)	0.109

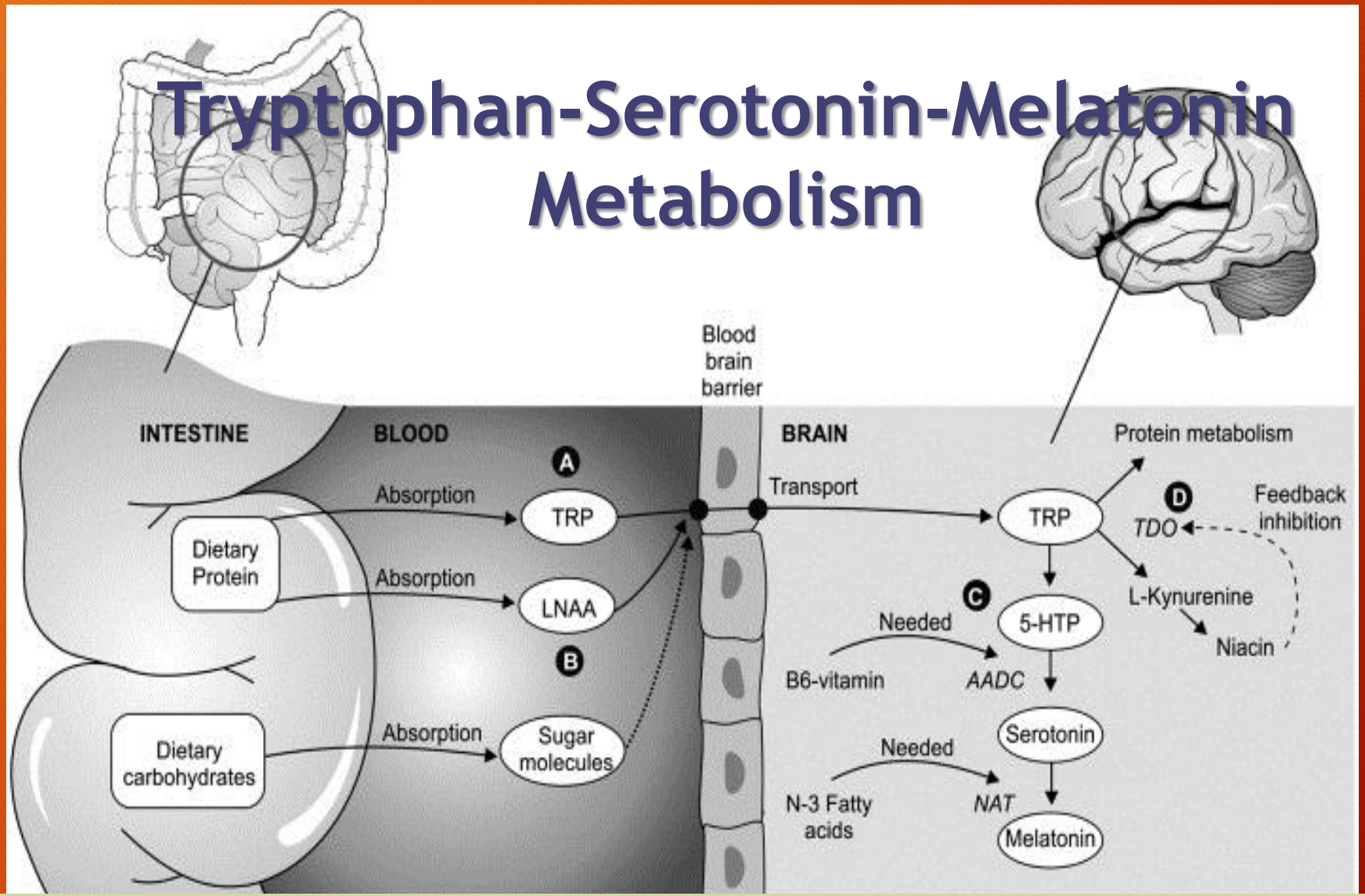
Source: Bioavailability and tolerability of various Albion manufactured organic magnesium sources compared to magnesium oxide.

Methylfolate and Methylcobalamine

According to Dr. Lawrence Ginsberg, past studies show nearly 70% of depressed individuals will not reach remission by taking 1 antidepressant alone, "so clearly a new approach is needed."

70% of people who have depression may have a specific genetic factor that compromises their ability to convert folic acid into L-methylfolate, "the only form of folate that can cross the blood-brain barrier and regulate serotonin, norepinephrine, and dopamine.

Tryptophan-Serotonin-Melatonin Metabolism



5-HTP, 5-hydroxytryptophan, AADC, aromatic l-amino acid decarboxylase, LNAA, large neutral amino acid, TDO, tryptophan 2,3-dioxygenase, TRP, tryptophan

Tryptophan

- You need 1 gm of tryptophan for low mood
- You need 3 gm of tryptophan for treatment of depression
- You must eat tryptophan with carbohydrate for absorption across the blood brain barrier
- Promotes sleep, so best taken at night
- (If sugar gives you a lift, or if high protein diets make you depressed, you may be low in serotonin)

Tryptophan: 5 ways to eat 500 mg

- Oatmeal, with soy milk and 2 scrambled eggs
- Baked potato with cottage cheese and tuna salad
- Chicken breast potatoes au gratin and green beans
- Whole-wheat spaghetti with bean, tofu or meat sauce
- Salmon filet, quinoa and lentil pilaf and green salad with yogurt dressing

Is Apathy a Tyrosine Deficiency?

- **Phenylalanine and tyrosine are needed to make dopamine and norepinepherine**
- **150-200 mg of phenylalanine improved 31/40 depressed patients at Rush Medical Center**
- **Military has long known that tyrosine improves mental and physical performance under stress.**

- L-Phenylalanine
  - Needs B6 (pyridoxine), Mg, Mn, Fe, Cu, Zn, Vit C
- L-Tyrosine (apathy)
  - Needs B9(folate) Mg. Mn, Fe, Cu, Zn, Vit C
- L-Dopa
  - Needs B6 and Zn

Blood

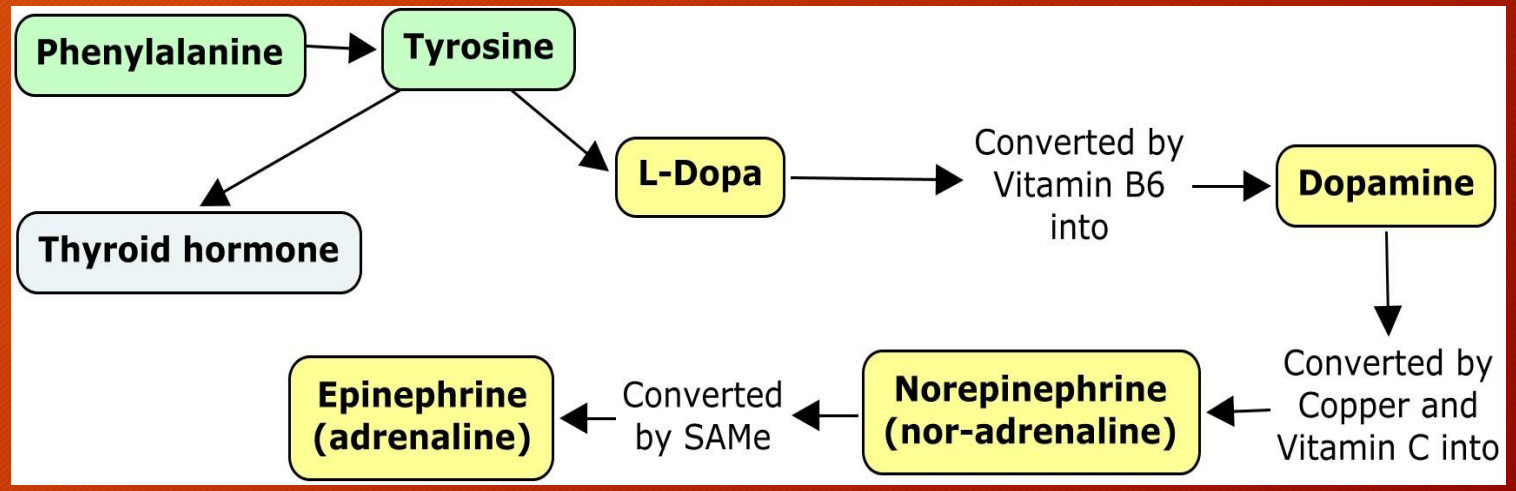
Brain Barrier

- Dopamine
  - Needs Vit C

Norepinephrine

Needs SAMe

- Epinephrine



What else looks like depression?

Another question to ask……

Alternative Causes of Depression

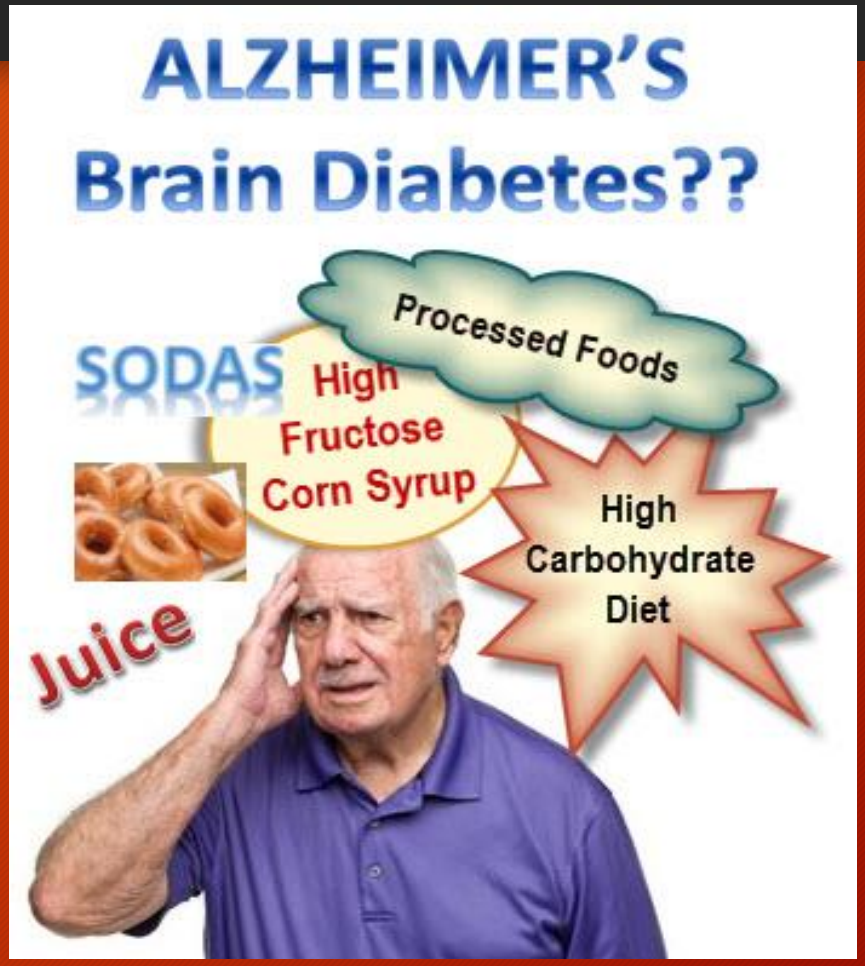
- Low estrogen in women, low testosterone in men
- Not enough full spectrum light
- Not enough exercise
- Too much stress, especially for women
- Not enough co-factor vitamins and minerals
- Blood Sugar Imbalances

Diabetes Connection

Blood Sugar and Depression

Let’s look at Diabetes

- Type I- autoimmune insulin dependent
- Type II- insulin resistance
- Gestational Diabetes
- Surgical/injury related
- Type 1.5-delayed autoimmune insulin dependent
- Type 3- Alzheimers



Depression and Diabetes

- **Studies have shown that people with diabetes are more likely to have depression than individuals who do not have diabetes. However the mechanisms linking these conditions are not entirely clear.**
- **A review of studies found that depression was associated with a 60% increase of type 2 diabetes while type 2 diabetes was only associated with a moderate (15%)** increase in risk of depression

Depression, Diabetes and VAT

- The women who showed signs of depression (assessed using the CES-D scale) had 24.5% more visceral belly fat than the women with fewer depressive symptoms.
- No association was found between depression and subcutaneous belly fat (non-visceral)

Researchers from Rush University Medical Center looked at over 400 women "who were participating in the Women in the South Side Health Project (WISH) in Chicago, a longitudinal study of the menopausal transition".

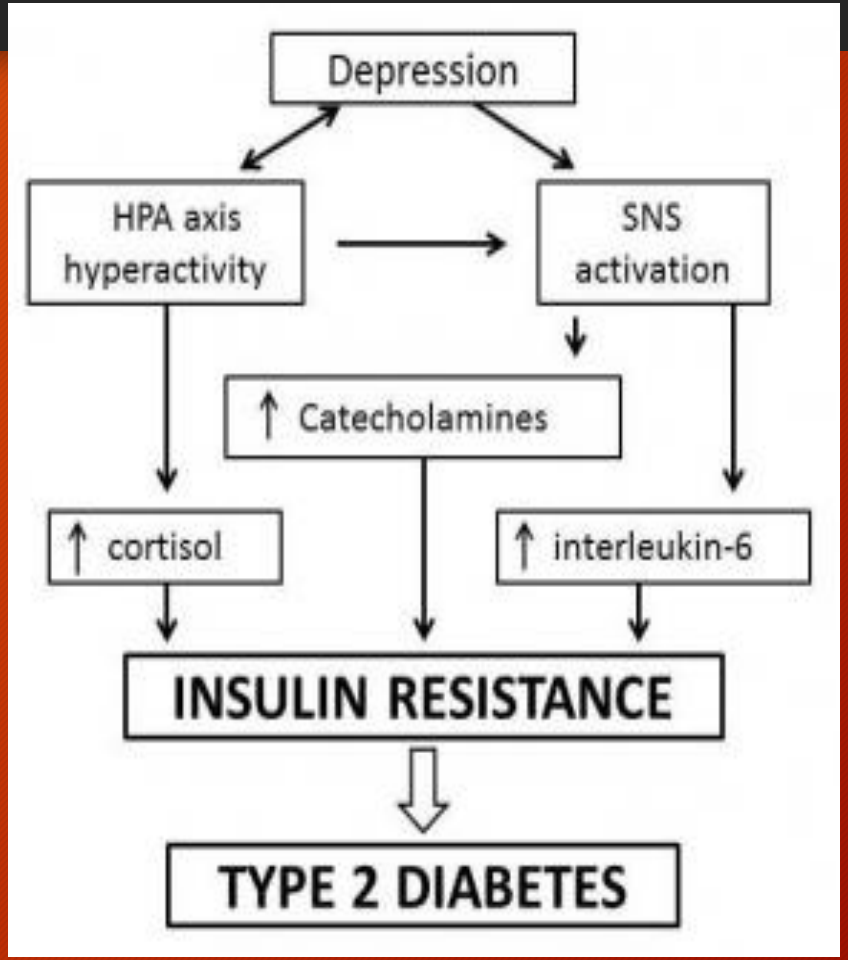
They screened the women for depression and measured their visceral fat with a CT scan

why is depression linked to increased visceral fat, diabetes and cardiovascular disease?

- Alterations of the HPA axis : resulting in excess cortisol production
- The excess cortisol could lead to increased visceral fat because glucocorticoid receptor density is higher in VAT than in other types of adipose tissue
- Depression is also associated with increased inflammation. Various markers of inflammation (C-RP, fibrinogen, interleukin-6 and tumor necrosis factor. All of these markers have been noted to be elevated in individuals suffering from obesity, diabetes and atherosclerotic vascular disease.

Why is depression linked to increased visceral fat, diabetes and cardiovascular disease?

- Adipose tissue, particularly VAT, secretes a host of inflammatory markers and is associated with increased systemic inflammation



By 2010, over one third of the kids and also adults were overweight.

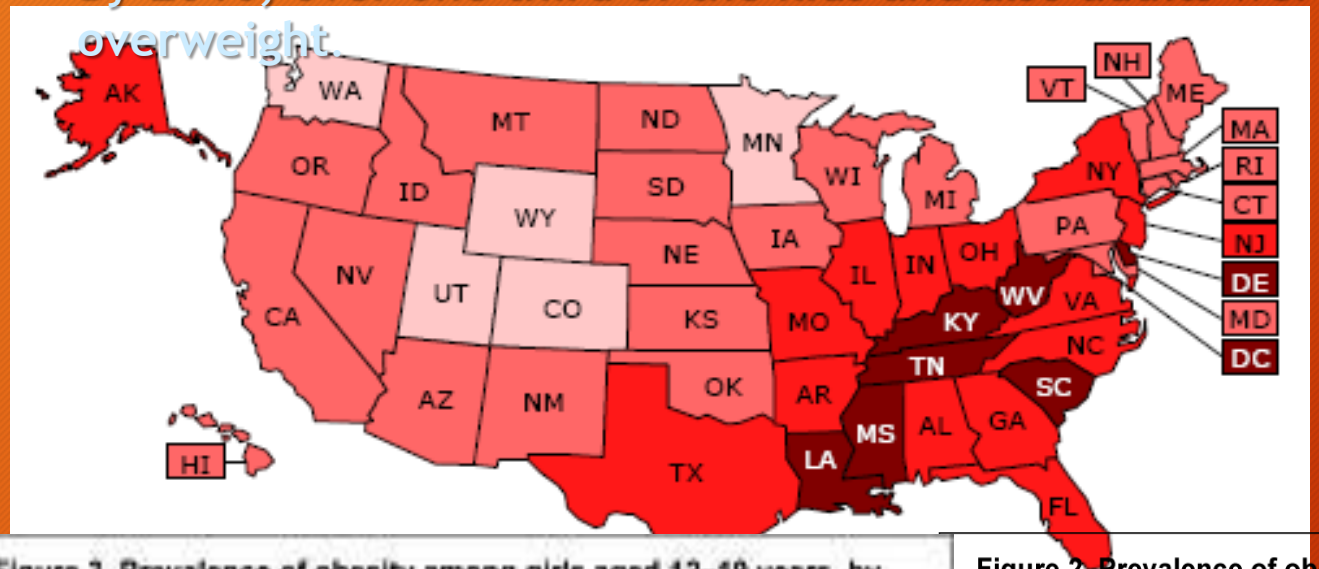
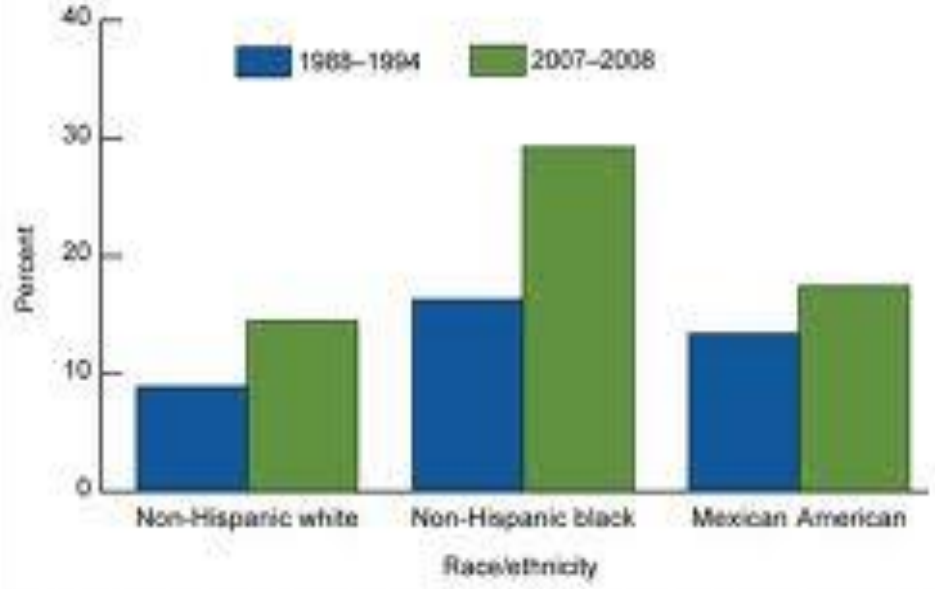
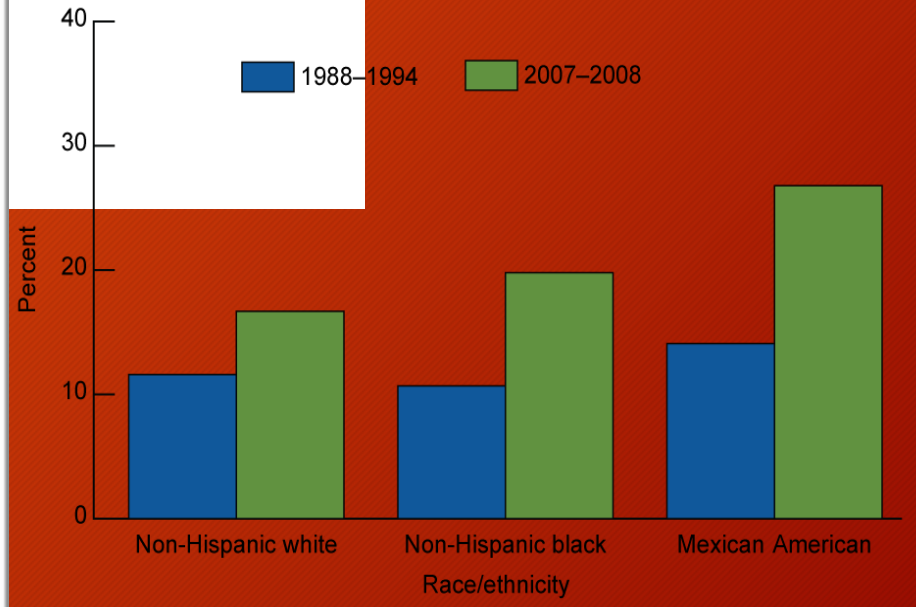


Figure 3. Prevalence of obesity among girls aged 12–19 years, by race/ethnicity: United States, 1988–1994 and 2007–2008



NOTE: Obesity is defined as body mass index (BMI) greater than or equal to sex- and age-specific 95th percentile from the 2000 CDC Growth Charts.
SOURCES: CDC/NCHS, National Health and Nutrition Examination Survey (NHANES) III 1988–1994 and NHANES 2007–2008.

Figure 2. Prevalence of obesity among boys aged 12–19 years, by race/ethnicity: United States, 1988–1994 and 2007–2008



NOTE: Obesity is defined as body mass index (BMI) greater than or equal to sex- and age-specific 95th percentile from the 2000 CDC Growth Charts.
SOURCES: CDC/NCHS, National Health and Nutrition Examination Survey (NHANES) III 1988–1994 and NHANES 2007–2008.

Vitamin D Deficiency

Lack of Sunlight

VITAMIN D LEVELS
25 HYDROXY D

DEFICIENT	OPTIMAL	THERAPEUTIC LEVEL (DISEASE TREATMENT)	EXCESS
<50 ng/mL	50-70 ng/mL	70-100 ng/mL	<100 ng/mL

Multiply ng/mL by 2.5 to convert to nmol/litre

Sunlight

Skin

7-Dehydrocholesterol

Cholecalciferol
(vitamin D_3)

dietary intake

Vitamin D_3 (fish, meat)
Vitamin D_2 (supplements)

Liver

25-hydroxyvitamin D_3

Kidney

1,25-dihydroxyvitamin D_3

Maintains calcium balance in the body

Sunlight

Skin

7-Dehydrocholesterol

Cholecalciferol
(vitamin D_3)

dietary intake

Vitamin D_3 (fish, meat)
Vitamin D_2 (supplements)

Liver

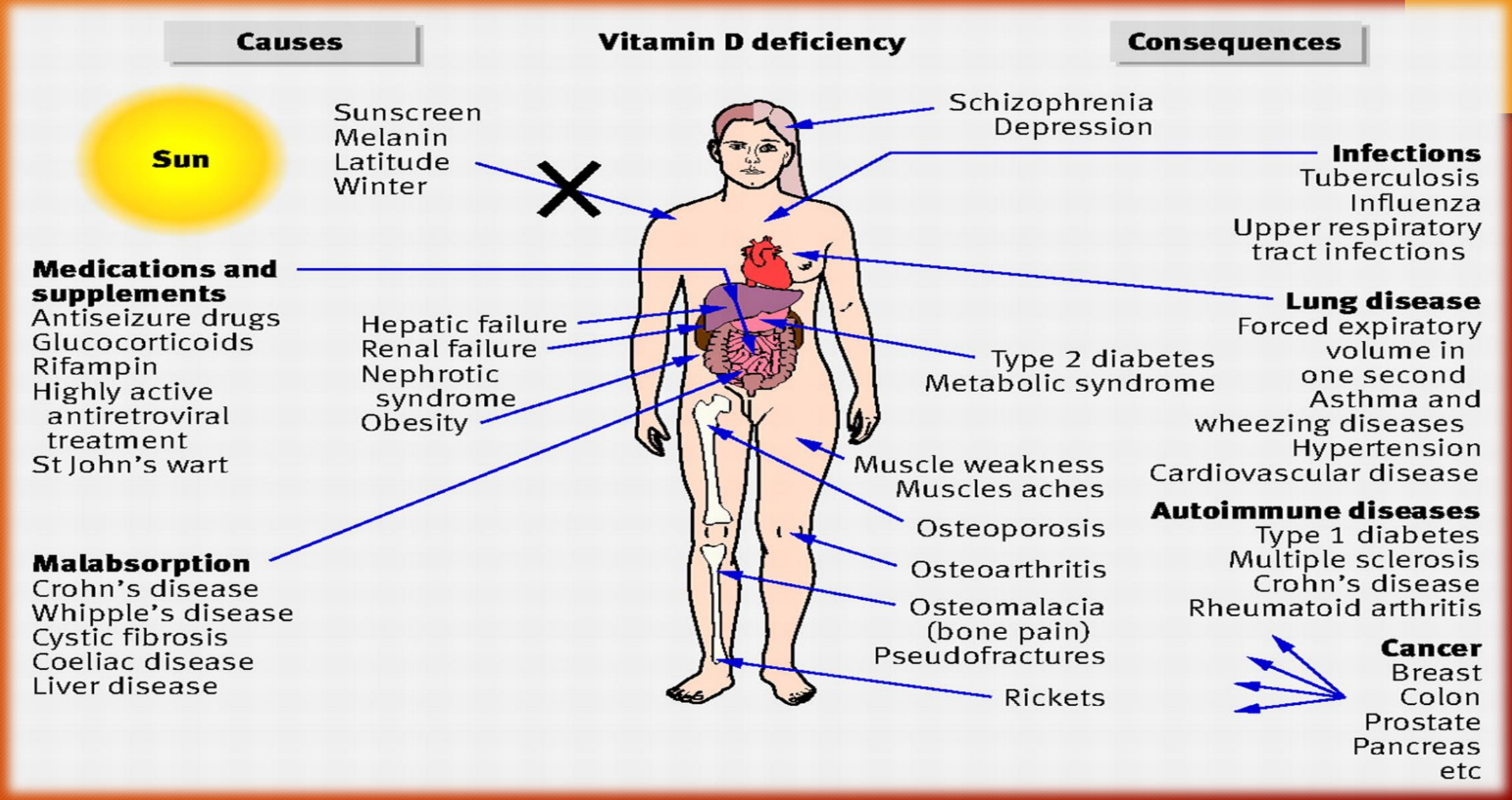
25-hydroxyvitamin D_3

Kidney

1,25-dihydroxyvitamin D_3

Maintains calcium balance in the body

Vitamin D: Depression (and about 300 other problems)



Omega III Deficiency

Chicken o the Sea

Omega 3 Fish Oil

EPA + DHA = 1-3000 mg

- **Six of 10 patients receiving EPA had a 50% reduction in Hamilton depression score compared with 1 of 10 patients receiving placebo.**
- **Mean reduction in Hamilton score was 12.4 points in the E-EPA group and 1.6 points in the placebo group.**
- **There were no significant adverse effects and no reports of fishy taste or odors.**

Supplement Facts

Serving Size: 1 Softgel
Servings Per Container: 120

Amount Per Serving		% Daily Value
Calories	10	*
Calories from Fat	10	*
Total Fat	1	2%
Saturated Fat	0.5g	3%
Polyunsaturated Fat	Less than g 0.5	*
Monounsaturated Fat	0g	*
Cholesterol	5mg	2%
Fish Oil Concentrate	1,000mg	
EPA (Eicosapentaenoic Acid)	180mg	*
DHA (Docosahexaenoic Acid)	120mg	*

* Daily Value not established.

Journal of American College of Nutrition

EPA but Not DHA Appears To Be Responsible for the Efficacy of Omega-3 Long Chain Polyunsaturated Fatty Acid Supplementation in Depression: Evidence from a Meta-Analysis of Randomized Controlled Trials

Julian G. Martins, MA, MBBS

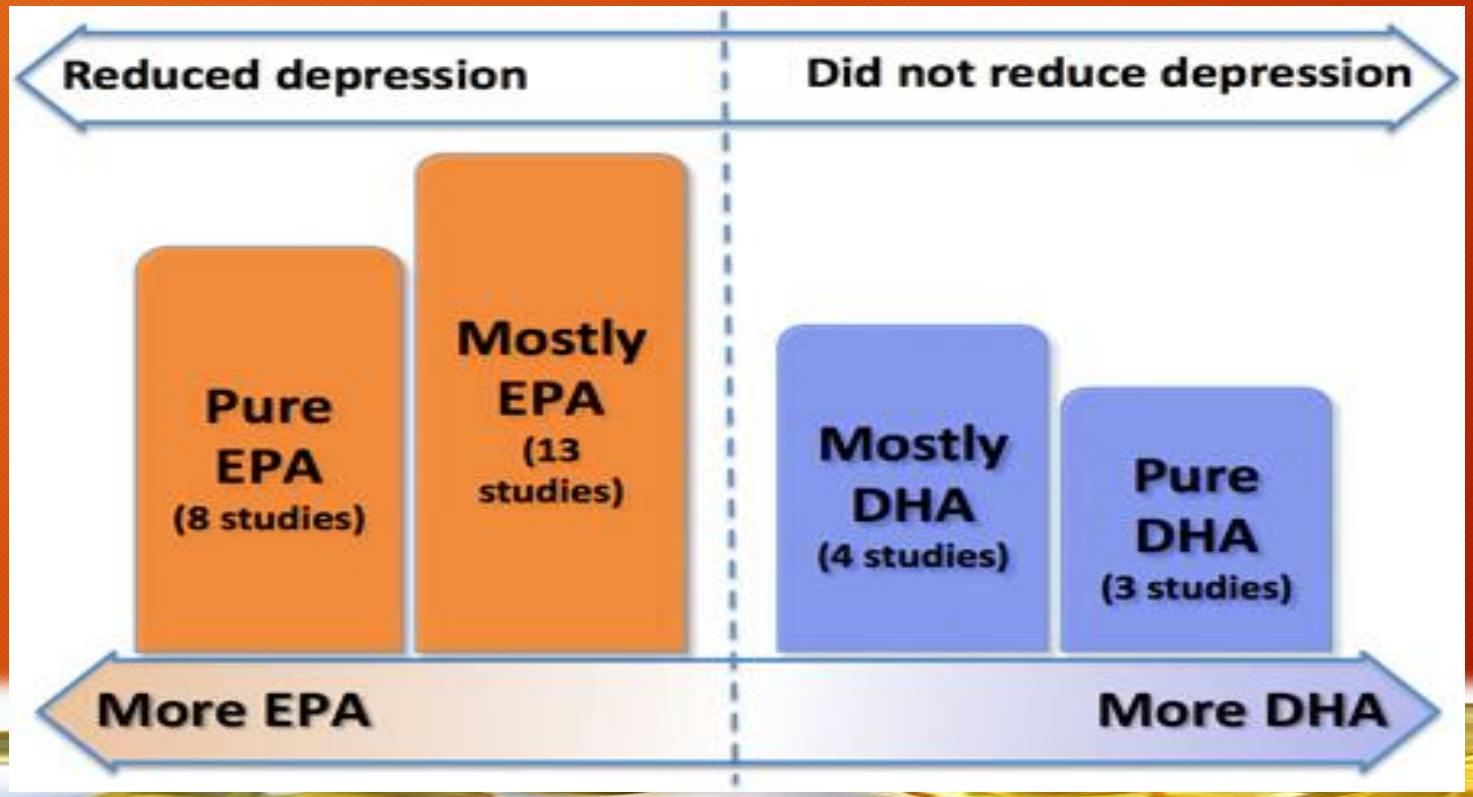
Molecular Psychiatry

EPA in major depressive disorder

Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis

JG Martins, H Bentsen and BK Puri

1000 to 2000 mg of EPA is an effective dose to help with depression.



Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain.

- CONCLUSIONS:
- Results mirror other controlled studies that compared ibuprofen and omega-3 EFAs demonstrating equivalent effect in reducing arthritic pain. omega-3 EFA fish oil supplements appear to be a safer alternative to NSAIDs for treatment of nonsurgical neck or back pain in this selective group

Maroon JC, Bost JW. Omega-3 fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain. Surg Neurol. 2006 Apr;65(4):326-31.

ADRENAL GLANDS

Multiple responsibilities

DHEA in Women and Men

- Important Adrenal Hormone
- Decreased postmenopausal bone loss
- Improves muscle strength
- Improves sexual performance
- Improves memory
- Improve weight loss efforts
- Can raise testosterone levels without some of the side effects of T replacement (acne, hirsutism, or deepening of voice)

DHEA and Opiates for Pain

- *Daniell**studied patients treated with sustained-action oxycodone, sustained released morphine, transdermal fentanyl or methadone for at least one month.
- DHEA Levels were below normal in 67% of study participants.
- Only 25% of men and 32% of women had DHEA-S levels within normal age related values

Daniell HW, DHEAS deficiency during consumption of sustained-action prescribed opiods: evidence for opiod-inducted inhibition of adrenal androgen production. J Pain 2006:7:901-907

Consequences of adrenal and gonadal abnormalities

- Depression and Gonads
- Depression and Adrenals

- **Estrogen and Testosterone have a direct effect on Serotonin synthesis.**
- **If there are low levels due to gonadal dysfunction with addiction, the patients can suffer from depression, sadness and anger that does NOT respond to antidepressants**

- **Reduced Cortisol has been linked to depressive symptoms, apathy, profound fatigue and even delusional behavior**

Brown, TT et al, Gonadal and Adrenal abnormalities in drug users; Cause or consequence of drug use behavior and poor health outcomes. Am J Infect Dis March 2007

Some CAM Therapies May Reduce Major Depression Symptoms

Here's a brief look at the effectiveness, safety, and costs of some CAM treatments that have been evaluated in major depression.

Treatment	Effectiveness	Safety	Cost
Omega-3 fatty acids	Evidence of effectiveness when used as an antidepressant supplement	Low risk	Low cost
SAMe	Evidence of effectiveness when used as a monotherapy	Relatively low risk	Expensive
Exercise	Evidence of effectiveness both as monotherapy and as antidepressant adjunct	Few medical contraindications	Low cost
Light therapy	Evidence of effectiveness when used as an adjunct to antidepressants	Low risk	Cost of light box
Folate	Possibly effective	Can mask pernicious anemia	Low cost

Source: Marlene Freeman, M.D., et al., *Journal of Clinical Psychiatry*, June 2010

Light Therapy and SAD

- Serotonin levels are lowest in the winter
- The amount of Serotonin produced is directly related to how much daylight we are exposed to
- Light therapy can improve sleep problems, lethargy, overeating, anxiety loss of libido and depression

Light Exercise: Get more winter light

- **60 watt light bulb**
- **Exercise best done at dusk, effectively extending daylight hours**
- **Choose a quite place that can be completely dark or use a blind fold**
- **Sitting position either on the floor or in a chair**

Light Exercise: Get more winter light

- **Place a table lamp with 60-watt opaque bulb without writing on it, 3 feet away, directly in line with your line of vision**
- **Make sure you can turn the light on and off without moving your head position**
- **Turn the light on and look directly at the bulb for one minute (use timer)**

Light Exercise: Get more winter light

- **After one minute, turn the light off, close your eyes (use a blind fold if you need to)**
- **Focus on the after-image without moving your head, until the after image completely vanishes (can take 3-4 minutes)**
- **Or regularly use full spectrum lights**

Long-Term Impact of Exercise vs. Medication on Depression

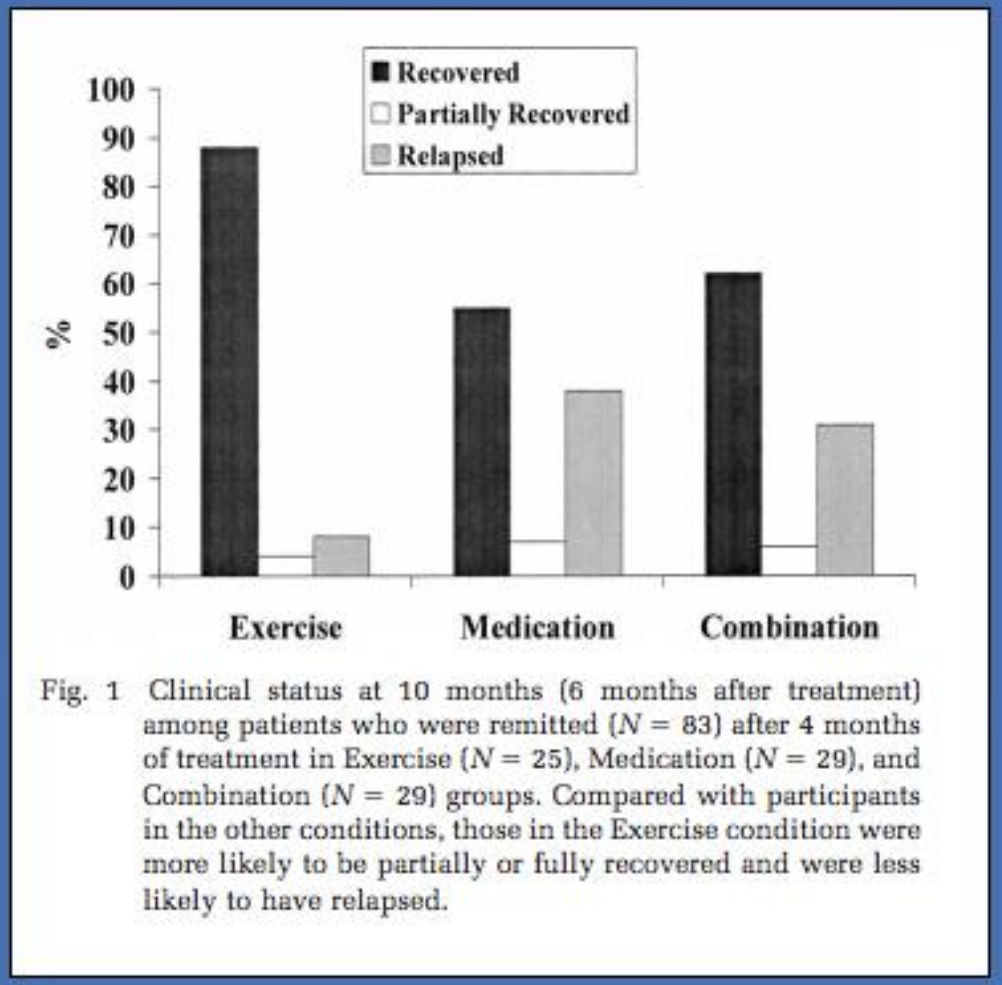
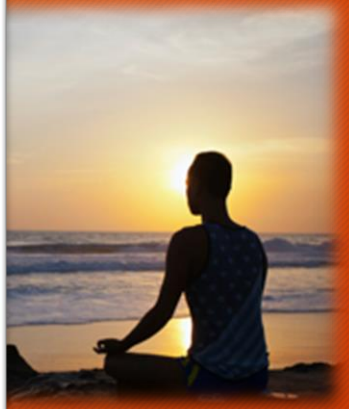


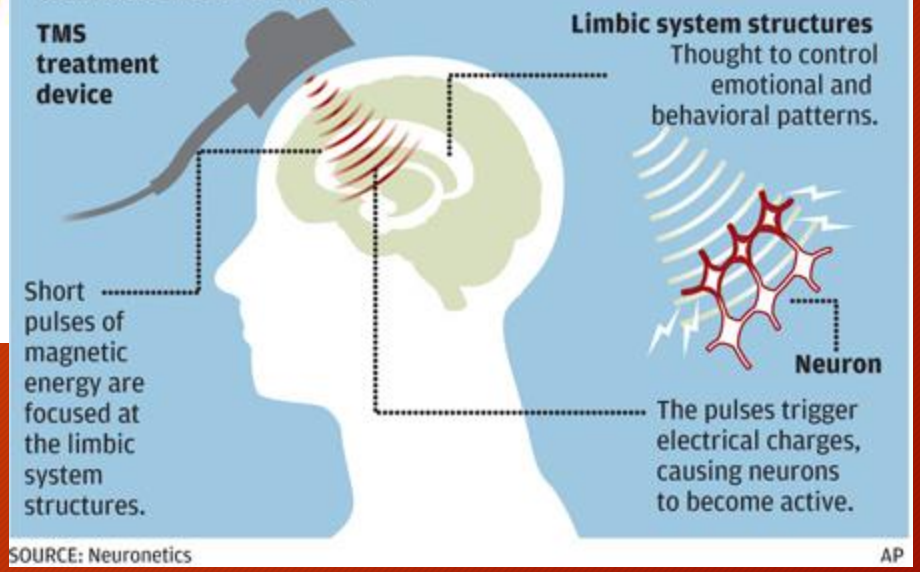
Fig. 1 Clinical status at 10 months (6 months after treatment) among patients who were remitted ($N = 83$) after 4 months of treatment in Exercise ($N = 25$), Medication ($N = 29$), and Combination ($N = 29$) groups. Compared with participants in the other conditions, those in the Exercise condition were more likely to be partially or fully recovered and were less likely to have relapsed.

Source: Psychosomatic Medicine: Journal of Biobehavioral Medicine



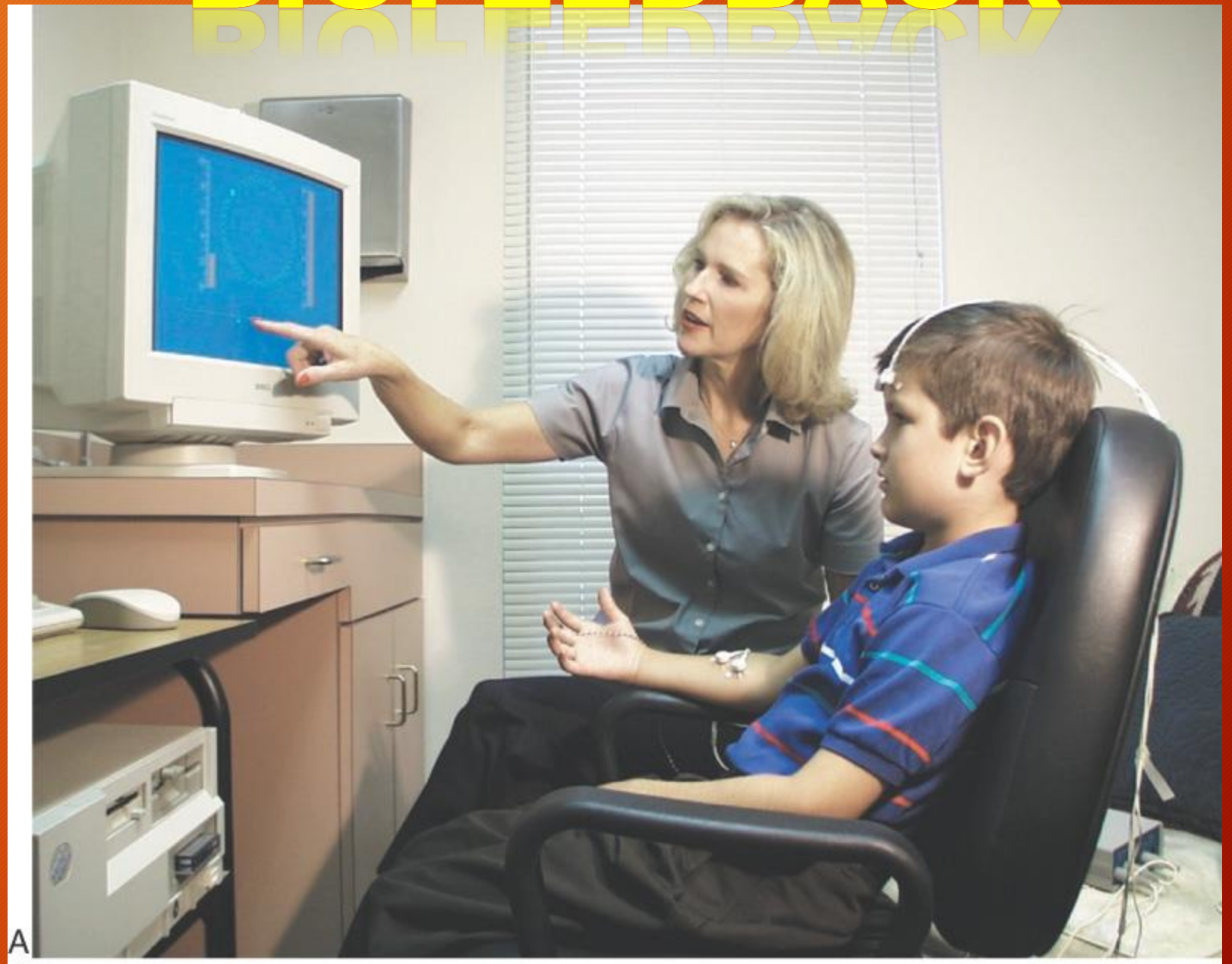
Magnetic pulse to ease depression

A non-invasive procedure to help fight depression called transcranial magnetic stimulation, or TMS, uses a magnetic pulse to stimulate brain cells that control mood.



SOURCE: Neuronetics AP

BIOFEEDBACK



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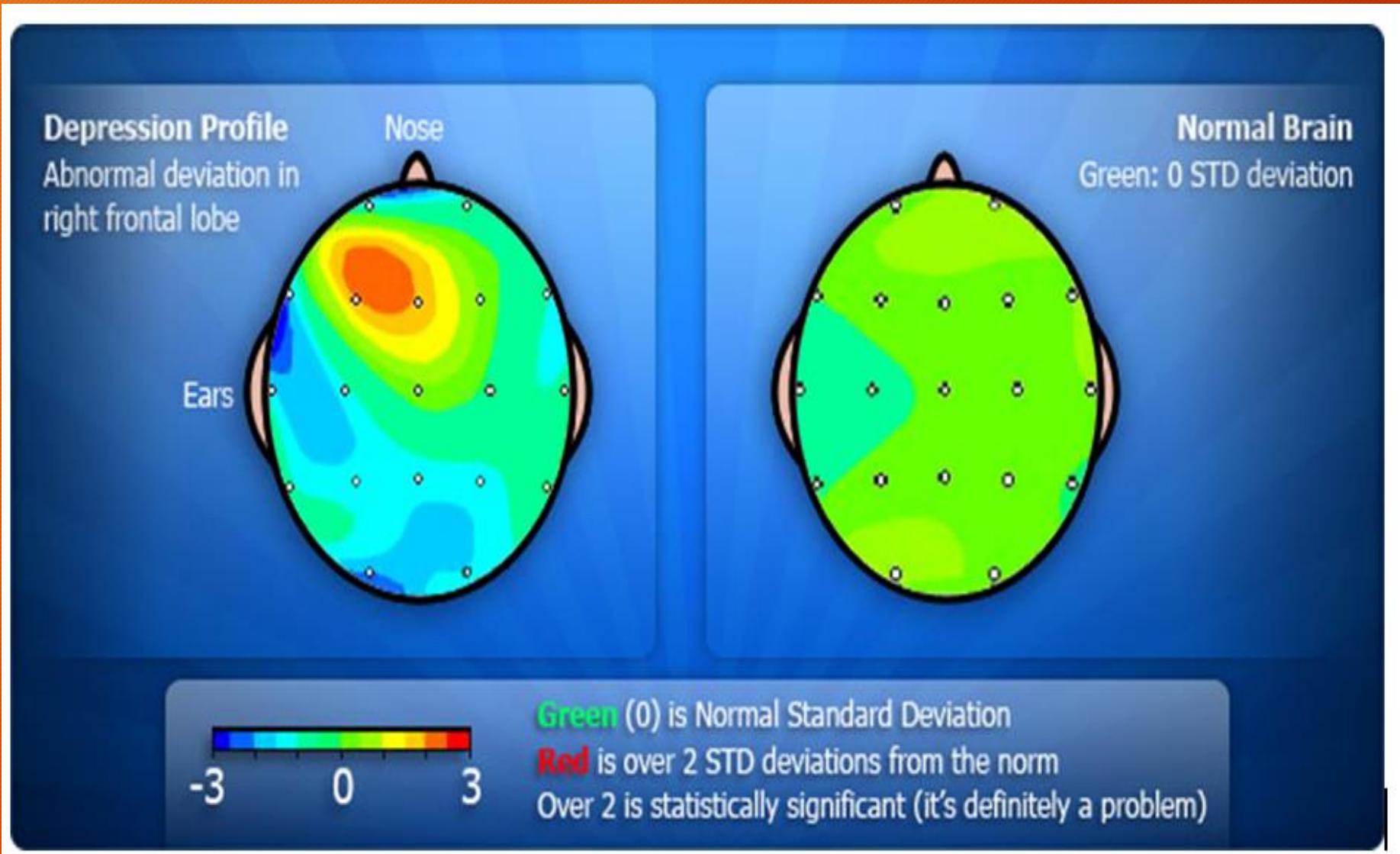
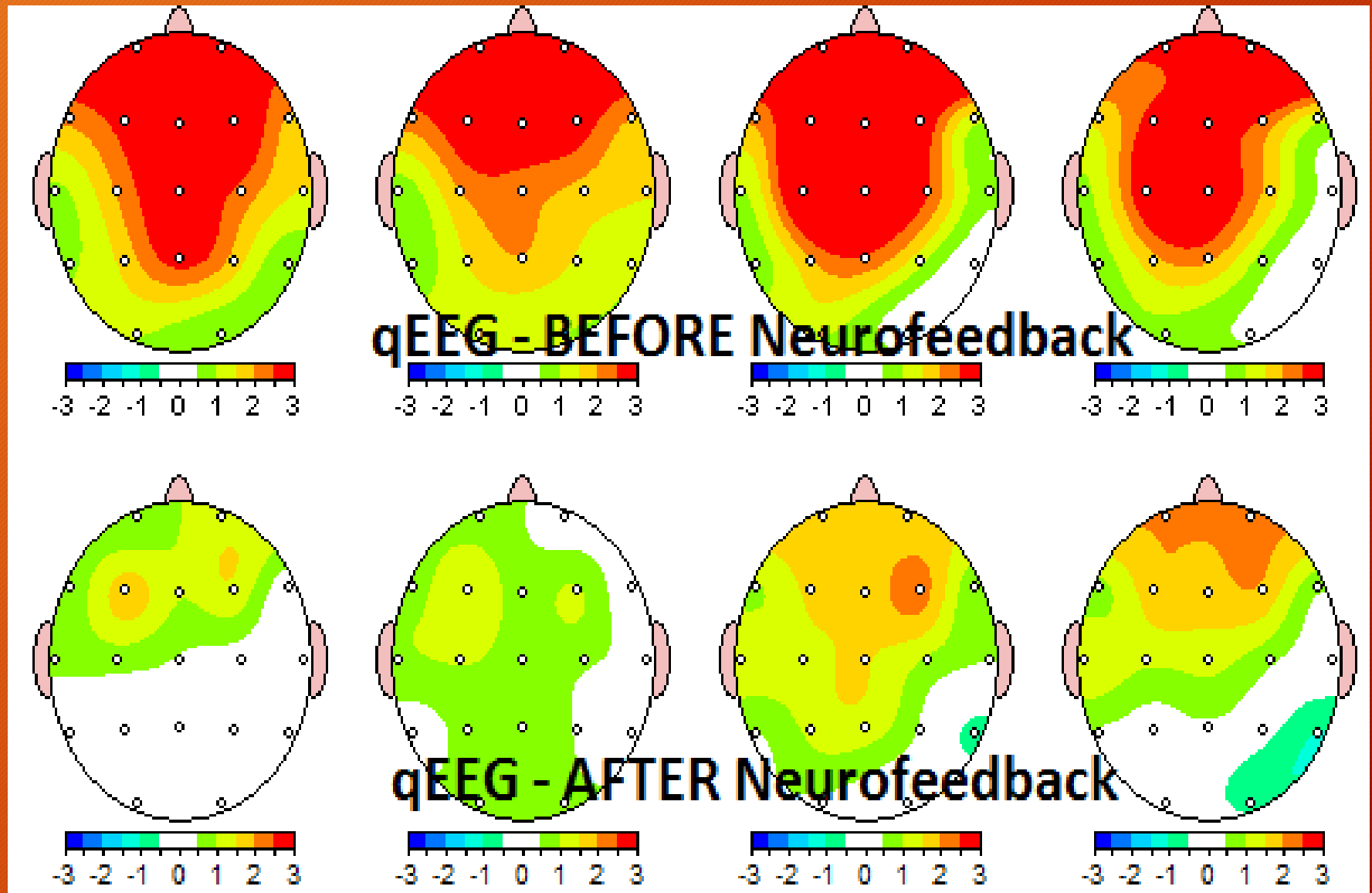

Depression Profile
Abnormal deviation in right frontal lobe
Nose
Ears
Normal Brain
Green: 0 STD deviation
-3
0
3
Green (0) is Normal Standard Deviation
Red is over 2 STD deviations from the norm
Over 2 is statistically significant (it's definitely a problem)


qEEG - BEFORE Neurofeedback
-3 -2 -1 0 1 2 3
-3 -2 -1 0 1 2 3
-3 -2 -1 0 1 2 3
-3 -2 -1 0 1 2 3
qEEG - AFTER Neurofeedback
-3 -2 -1 0 1 2 3
-3 -2 -1 0 1 2 3
-3 -2 -1 0 1 2 3
-3 -2 -1 0 1 2 3

Supplements that can Help

Supplement Facts

Serving Size 4 Capsules
Servings Per Container 15, 30

4 capsules contain	Amount Per Serving	% Daily Value
Vitamin C (as Ascorbic Acid USP)	50 mg	83%
Niacin (as Niacinamide USP)	10 mg	50%
Vitamin B6 (as Pyridoxal 5'-Phosphate)	10 mg	500%
Folate (as Quatrefolic® (6S)-5-Methyltetrahydrofolic acid glucosamine salt)	400 mcg	100%
Vitamin B12 (as Methylcobalamin)	200 mcg	3,333%
Magnesium (as DiMagnesium Malate)	75 mg	19%
Zinc (as TRAACS® Zinc Bisglycinate Chelate)	5 mg	33%
Inositol NF	1,000 mg	*
L-Tyrosine USP	400 mg	*
Mucuna Pruriens Extract (Standardized to contain 10% L-Dopa)	400 mg	*
5-HTP	150 mg	*
L-Theanine	100 mg	*
PharmaGABA™	100 mg	*

* Daily Value not established

Supplement Facts

Serving Size 3 Capsules
Servings Per Container 30

3 capsules contain	Amount Per Serving	% Daily Value
Vitamin C (as Ascorbic Acid USP)	50 mg	83%
Niacin (as Niacinamide USP)	10 mg	50%
Vitamin B6 (as Pyridoxal 5'-Phosphate)	10 mg	500%
Folate (as Quatrefolic® (6S)-5-Methyltetrahydrofolic acid glucosamine salt)	400 mcg	100%
Vitamin B12 (as Methylcobalamin)	200 mcg	3,333%
Magnesium (as DiMagnesium Malate)	75 mg	19%
Zinc (as TRAACS® Bisglycinate Chelate)	5 mg	33%
Inositol NF	1,000 mg	*
Taurine	300 mg	*
L-Theanine	100 mg	*
PharmaGABA™	100 mg	*
5-HTP	75 mg	*

* Daily Value not established

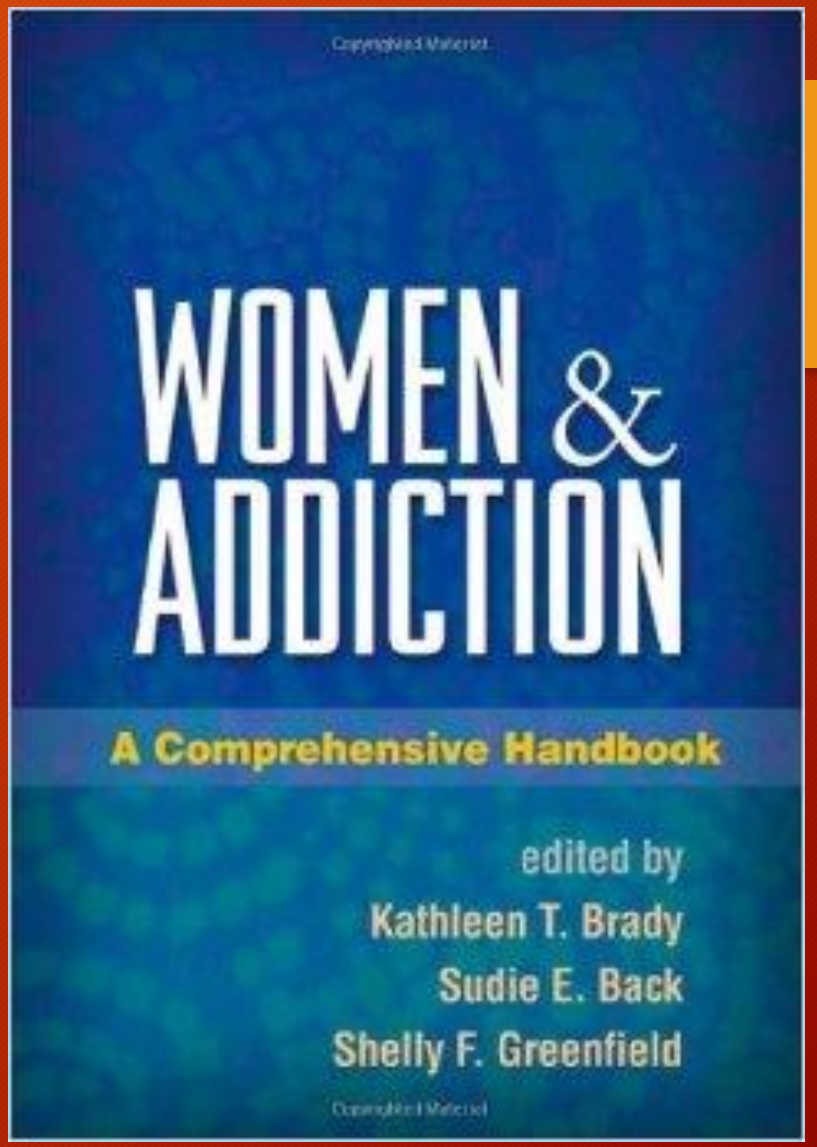
Take home message:

- 1. Good (chewable) multivitamin with minerals
- 2. B Vitamins:
  - B1-100 mg (Thiamine)
  - B6 20 mg
  - B12 10 mcg (Methylcobalamine)
  - B9 folate 200 mcg (Methyl folate)

Take home message:

- 3. *Magnesium, preferably NOT oxide (500-1500 mg per day)*
- **4.Vit D3 with Vit K2 (4000 units per day)**
- 5. *Omega 3 Fish Oil 1000-4000 units per day of DHA + EPA*

•QUESTIONS?????


WOMEN &
ADDICTION
A Comprehensive Handbook
edited by
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Women Experience Addiction in a Differently than men:

- Women do develop substance abuse problems, they tend to develop them faster than men do.

- Although women tend to be older than men, on average, when they begin a pattern of regular drunkenness, women's drinking-related problems (e.g., loss of control over drinking, negative consequences of drinking) appear to progress more quickly than those of men (Randall et al. 1999).

- This faster progression also means that women experience shorter intervals than men between onset of regular drunkenness and first encountering the negative consequences of drinking.

- Includes physical problems, interpersonal difficulties, negative intrapersonal changes (such as in personality or self-esteem), poor impulse control, and reduced ability to maintain normal social roles and responsibilities.

Women Experience Addiction in a Differently than men:

- Women also experience shorter intervals between first loss of control over drinking and onset of their most severe drinking-related consequences, and shorter intervals between onset of regular drunkenness and treatment-seeking (Randall et al. 1999).
- Women report more severe problems and experience more health-related consequences from substance use (Bradley et al. 1998), and their substance-related problems interfere with functioning in more life domains compared with men (Fillmore et al. 1997).

Women Seeking Treatment

- Women seeking treatment for alcohol or other drug problems have more severe problems (Arfken et al. 2001)
- Women are younger, have lower education levels (Wechsberg et al. 1998), and have lower incomes (Brady et al. 1993) than men seeking treatment.
- Women are more likely to have experienced emotional, physical, and sexual abuse (Wechsberg et al. 1998)
- Have more severe depressive symptoms when depressed (Pettinati et al. 1997)
- Tend to be more hostile than men upon treatment entry (Robinson et al. 2001).

Women Seeking Treatment

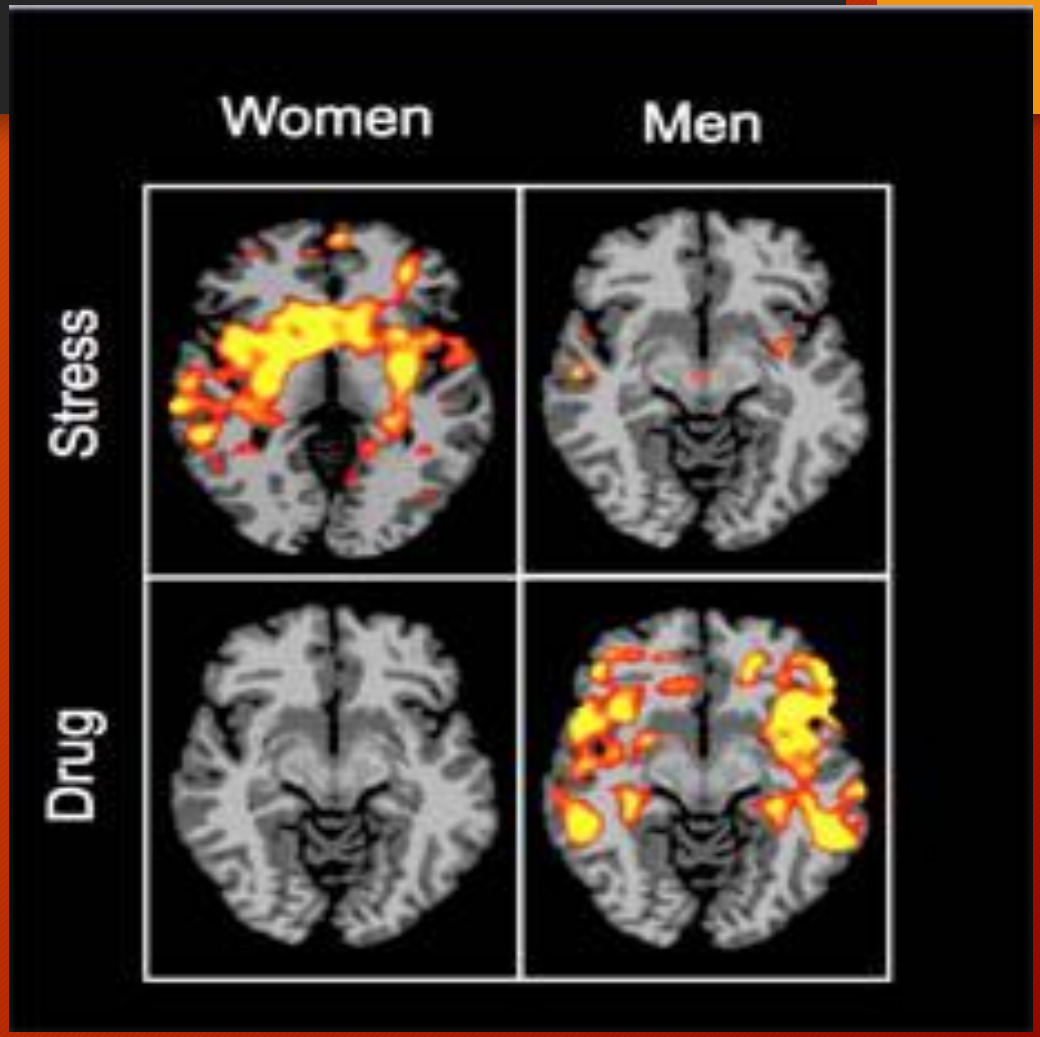
- Women also report more physical and mental health problems (Brady et al. 1993)
- Greater concerns about child-related issues (Wechsberg et al. 1998) than men do.
- In addition, women entering treatment for alcohol-related problems are more likely than men to identify factors other than drinking (e.g., stressful life events, mental health symptoms) as their primary problems
- Have been more likely to report shame and embarrassment at treatment entry (Thom 1987).

Men and women and Relapse

- Women who have stopped using substances relapse under different circumstances than men do.
- Women are more likely to relapse in the presence of a romantic partner than men are, and are less likely to relapse when they are alone (Rubin et al. 1996).
- Women also are more likely to report interpersonal problems before relapse (McKay et al. 1996).
- Women are less likely than men to relapse overall (Rubin et al. 1996)
- Women tend to have better long-term recovery outcomes (Dawson et al. 2005; Weisner et al. 2003).

Stress: Men Vs Women

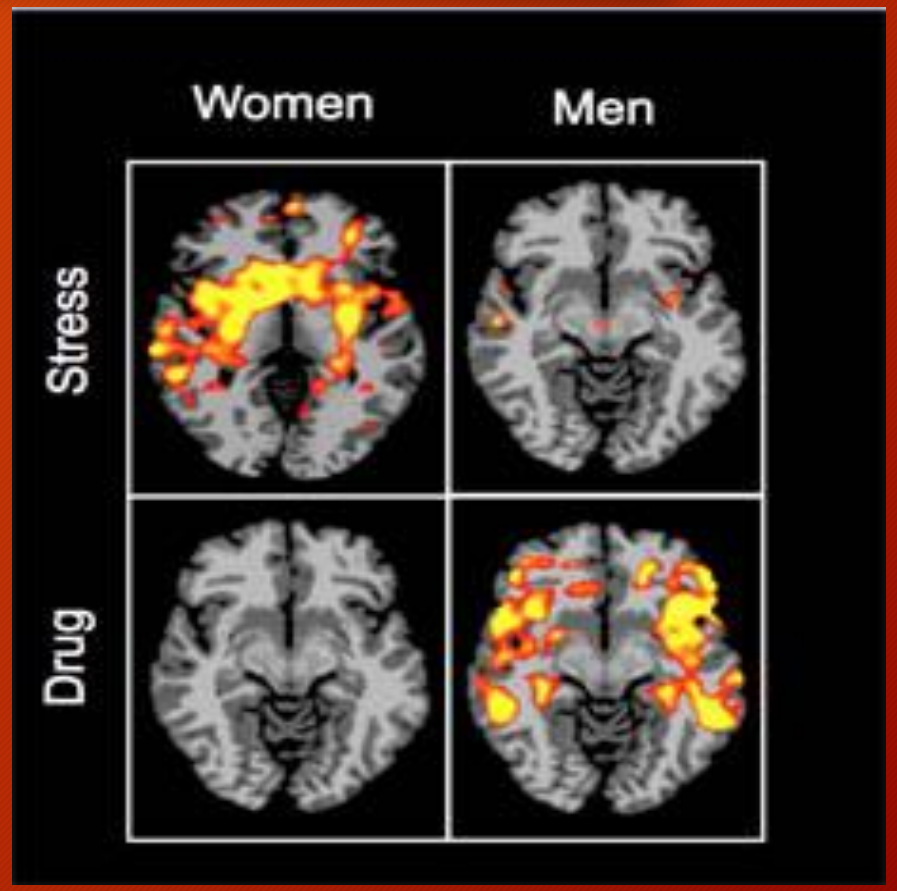
- The brain activation differences indicate a stronger response in women to stress cues
- In men, a stronger difference occurs when they are presented cues relating to substance (drug) use.



Rajita, S, et al Yale Stress Center, American Journal of Psychiatry, Jan. 2014

Stress: Men Vs Women

- The findings suggest that women with cocaine dependence might benefit from stress-reduction therapies that specifically target these cravings.
- Men, on the other hand, might derive more benefit from elements of cognitive behavioral therapy or 12-step programs based on the principles of Alcoholics Anonymous.



Rajita, S, et al Yale Stress Center, American Journal of Psychiatry, Jan. 2014

Treatment Plans: Men Vs. Women

- Men need to avoid People, Places, and Things
- AA or other 12 Step Programs can be very helpful to men (and women)
- Coping strategies are very helpful for men as well.

- Women need help with coping strategies and stress reduction
- Assistance with dealing with barriers to treatment
- The Language of AA needs to be carefully discussed with women to avoid misunderstanding

Our Autonomic Nervous system

Sympathetic: Flight or Flight

- Increased cortisol and adrenaline cause a number of physical and hormonal changes
- Increase a person's risk of relapse by creating an emotional and physiological state of over- stimulation
- Impair healing, interfere with memory production, increase risk of disease, including cancer
- Negatively impacts sleep cycle.

Parasympathetic: Rest and Digest

- Yoga: Breathing and poses help to engage the parasympathetic nervous system, allowing our bodies to counter balance the stress response
- Meditation: Breathing and mindfulness allow us to remain in the present, not in the past (depression) or in the future (anxiety)
- Exercise (moderate) especially upper body work to release energy created by anger
- Adaptogens
- Tapping

Questions?