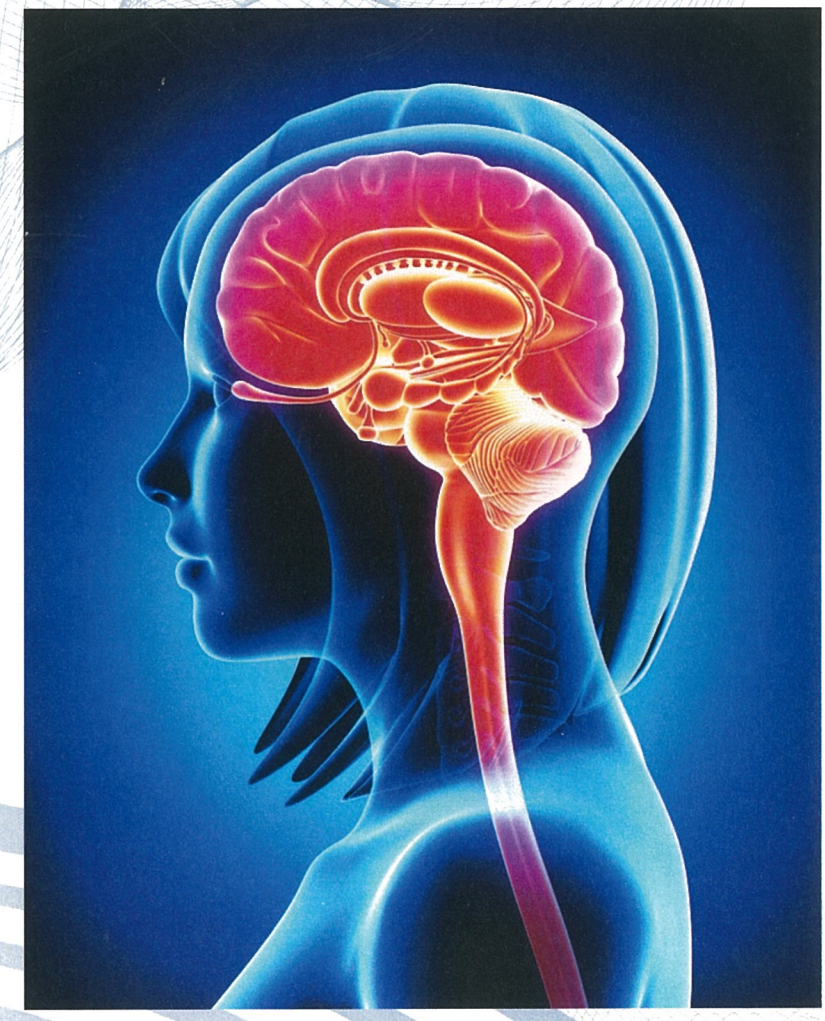
104年台灣成癮科學學會

年會暨學術活動

Brain Science and Addiction



日期 104年11月21日（星期六）

地點 台北國際會議中心一樓102廳

2015 年台灣成癮科學學會 年會暨學術活動

主　　題： Brain Science and Addiction

日　　期：104 年 11 月 21 日(星期六) 、PM 14:15~18:30

地　　點：台北國際會議中心一樓 102 廳

主 辦 單 位：台灣成癮科學學會、國家衛生研究院、WPAIC

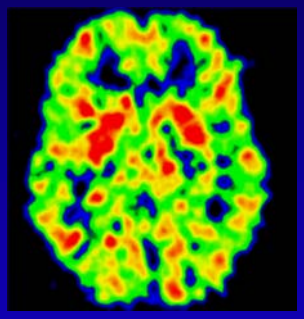
Time	Topic	Speaker	Moderator
14:15-14:25	Registration		
14:25-14:30	Opening	成大醫學院 陸汝斌 教授	
14:30-15:10	Neurobiology of Addiction	Barry Hoffer NIH,USA	王 昀 教授 國家衛生研究院
14:10-15:15	Question and Discussion		
15:15-15:55	Altered Resting-State Functional Brain Connectivity during Early Recovery from Alcohol Use Disorder	Andrew Greenshaw Alberta, Canada	萬芳榮 教授 國防醫學院
15:55-16:00	Question and Discussion	Kent,USA 周文海 教授	
16:00-16:10	Tea/Break		
16:10-16:15	Opening	衛生福利部 謝立中 司長	
16:15-16:55	GABAergic Genetic Investigations into Impaired Inhibitory Control in Cocaine Dependence	Bao-Zhu Yang Yale, USA	宋維村首席顧問 天主教若瑟醫院
16:55-17:00	Question and Discussion		
17:00-17:20	The Role of Brain Dopamine Transporter in the Development of Alcohol Dependence	San-Yuan Huang 黃三原 教授 NDMC, Taiwan	陳志根 教授 長庚醫學院
17:20-17:40	The Molecular Neuroimaging Studies in Opioid Users – a Study Combined with Economic Eevaluation	Yen-Kuang Yang 楊延光 教授 NCKU, Taiwan	朿連文 主任 北市聯合醫院
17:40-17:50	Discussion and Comment	All audience and speakers	陸汝斌 教授 謝立中 司長
17:50-18:30	2015 台灣成癮科學學會 會員大會		

＊台灣成癮科學學會:全程參加 5 學分、擇一參加者 2 學分(須簽到及簽退)。

＊僅台灣成癮學會會員(含新進會員)才需簽學分。

＊衛福部藥癮治療繼續教育時數 2.5 小時。

Neurobiology of Addiction



Barry J. Hoffer, MD, PhD
Scientist Emeritus, NIH
Adjunct Professor of Neurosurgery and Genetics
Case Western Reserve University School of Medicine

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In 2005, an estimated 19.7 million Americans, or 8.1 percent of the population aged 12 or older, were current illicit drug users.

Sources: 2005 National Survey on Drug Use and Health (NSDUH), SAMHSA

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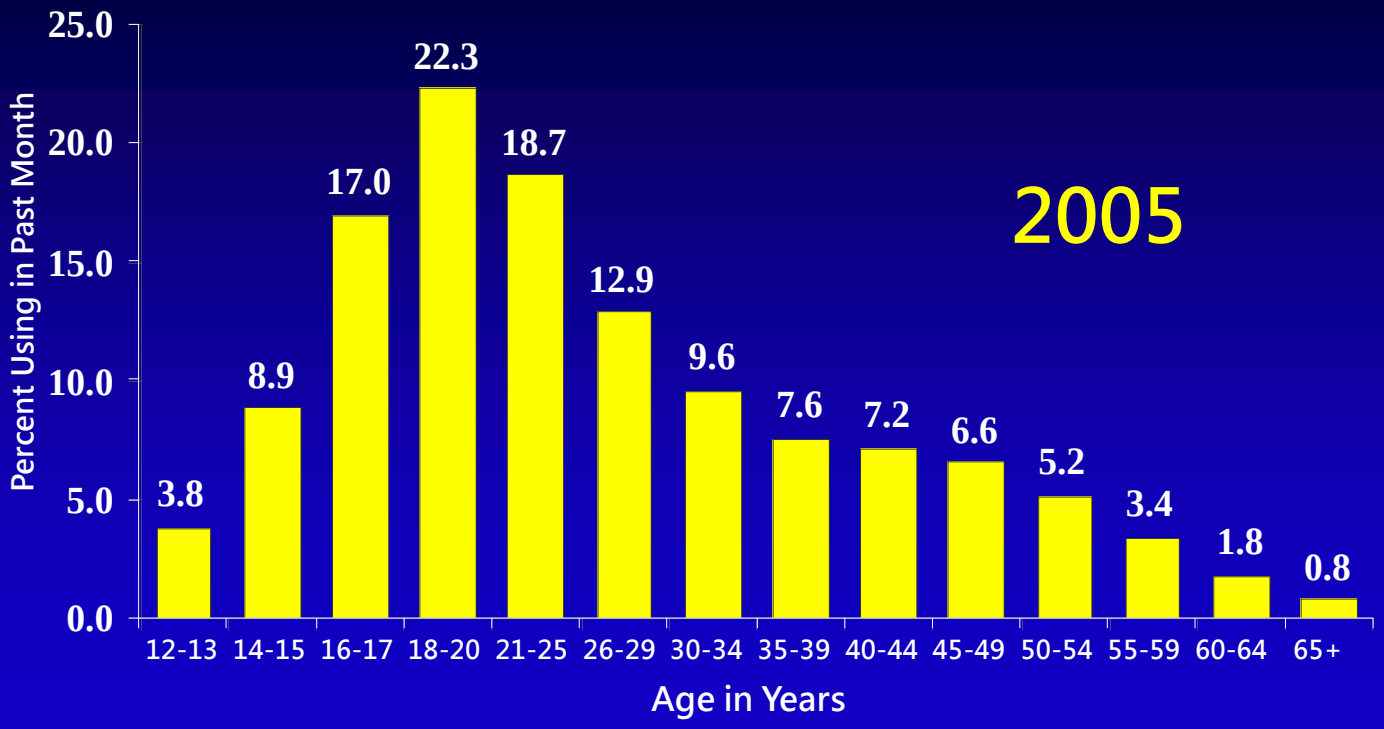
Past Month Illicit Drug Use, by Age



National Survey on Drug Use & Health (SAMHSA)

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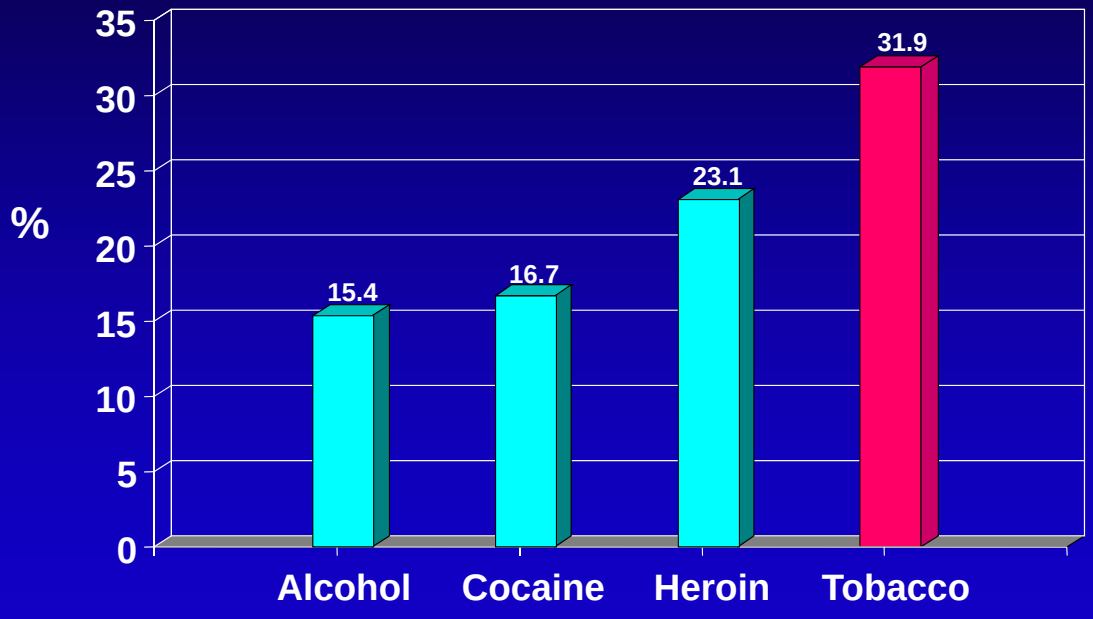
Percent of those *ever* using a drug who become addicted



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Estimated Economic Cost to Society from Substance Abuse and Addiction

Illegal Drugs: $161 Billion/Year

Alcohol: $185 Billion/Year

Tobacco: $138 Billion/Year

Total: $484 Billion/Year

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Important Drug Abuse Terms

Addiction

State in which individual engages in COMPULSIVE behavior and loss of control

Dependence

State in which an individual functions normally only in the presence of the drug. When drug is removed (withdrawal), manifest as physical and/or psychological disturbance

Tolerance

State of requiring increased drug to yield a constant effect (or given a constant dose, the effect size decreases)

Sensitization

Opposite of Tolerance; drug now causes an INCREASED response

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Why Do People Take Drugs In The First Place?

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How do drugs work in the brain?

We know that despite their many differences, most abused substances ENHANCE the Dopamine (reward/motivation) and Serotonin (affect/emotion) Synapses And 'Downstream' Pathways

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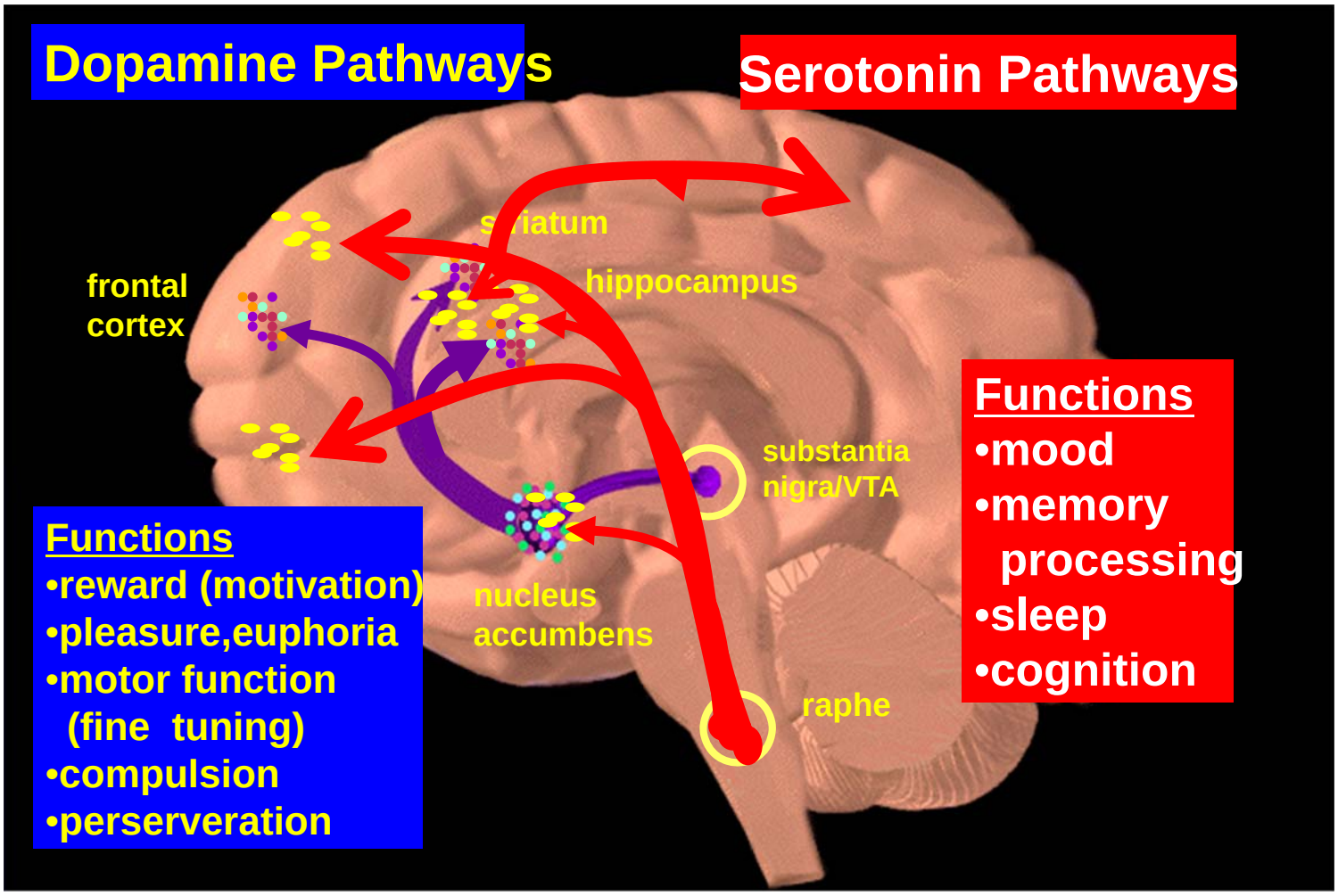
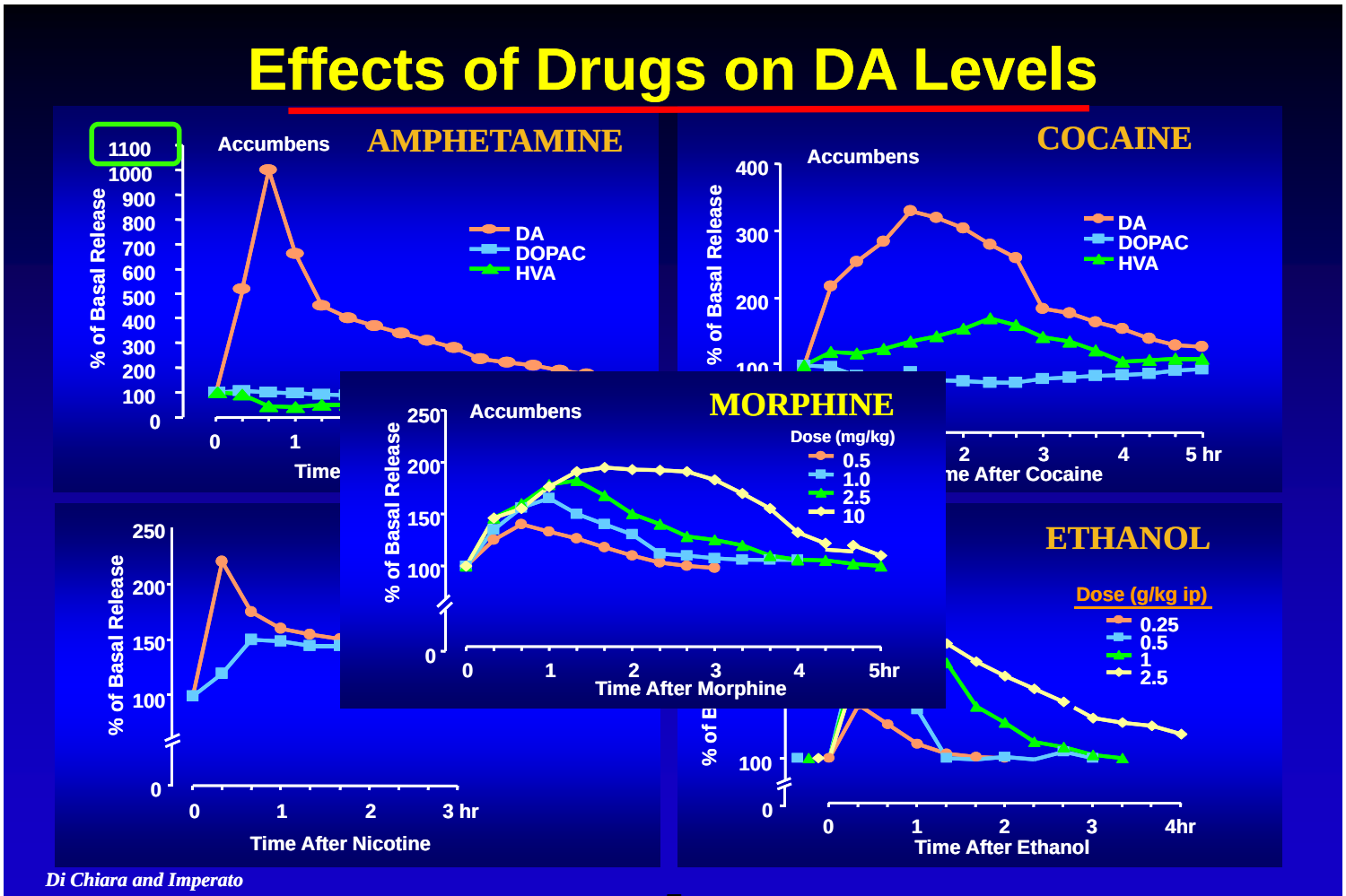
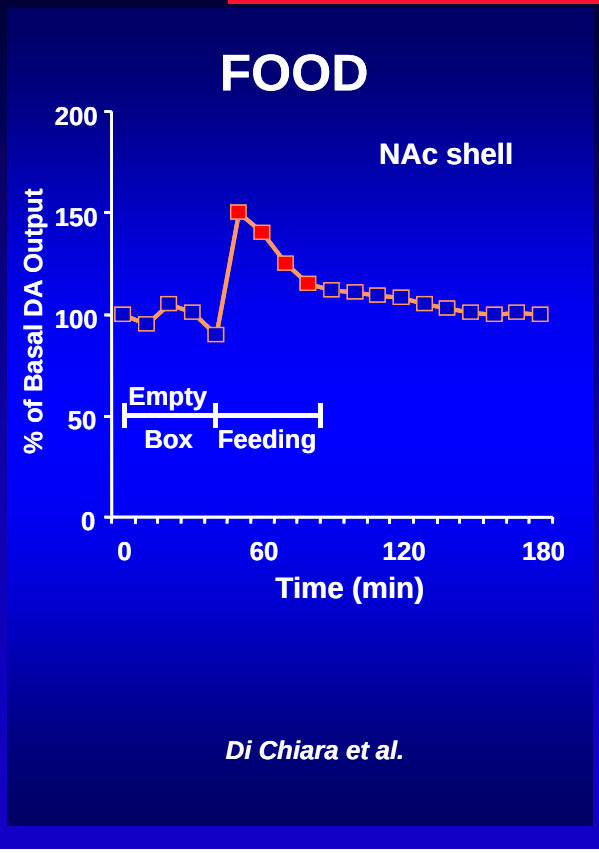
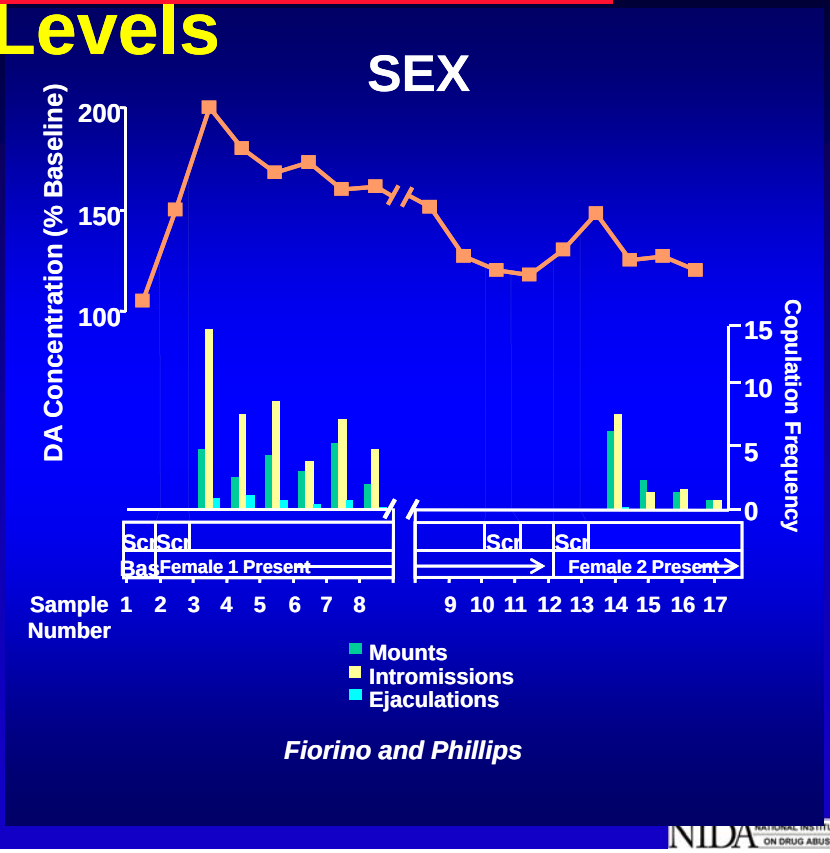

Dopamine Pathways
Serotonin Pathways
striatum
hippocampus
frontal cortex
substantia nigra/VTA
nucleus accumbens
raphe
Functions
•reward (motivation)
•pleasure,euphoria
•motor function (fine tuning)
•compulsion
•perserveration
Functions
•mood
•memory processing
•sleep
•cognition


Effects of Drugs on DA Levels
AMPHETAMINE
Accumbens
% of Basal Release
DA
DOPAC
HVA
Time
COCAINE
Accumbens
% of Basal Release
DA
DOPAC
HVA
Time After Cocaine
MORPHINE
Accumbens
% of Basal Release
Dose (mg/kg)
0.5
1.0
2.5
10
Time After Morphine
Time After Nicotine
ETHANOL
Dose (g/kg ip)
0.25
0.5
1
2.5
Time After Ethanol
Di Chiara and Imperato

Natural Rewards Also Elevate DA Levels





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Advances in Science Have Revolutionized Our Fundamental Views of Drug Abuse and Addiction

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Science Has Generated A Lot of Evidence Showing That…

Prolonged Drug Use Changes the Brain In Fundamental and Long-Lasting Ways

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CS → **CR**

Environmental Cues

CRAVING

UCS → **UCR**

Drug

"High"

-Stress -Places where drugs were used -Viet Nam example

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The Brains of Addicts Are Different From the Brains of Non-Addicts

…And Those Differences Are An Essential Element of Addiction

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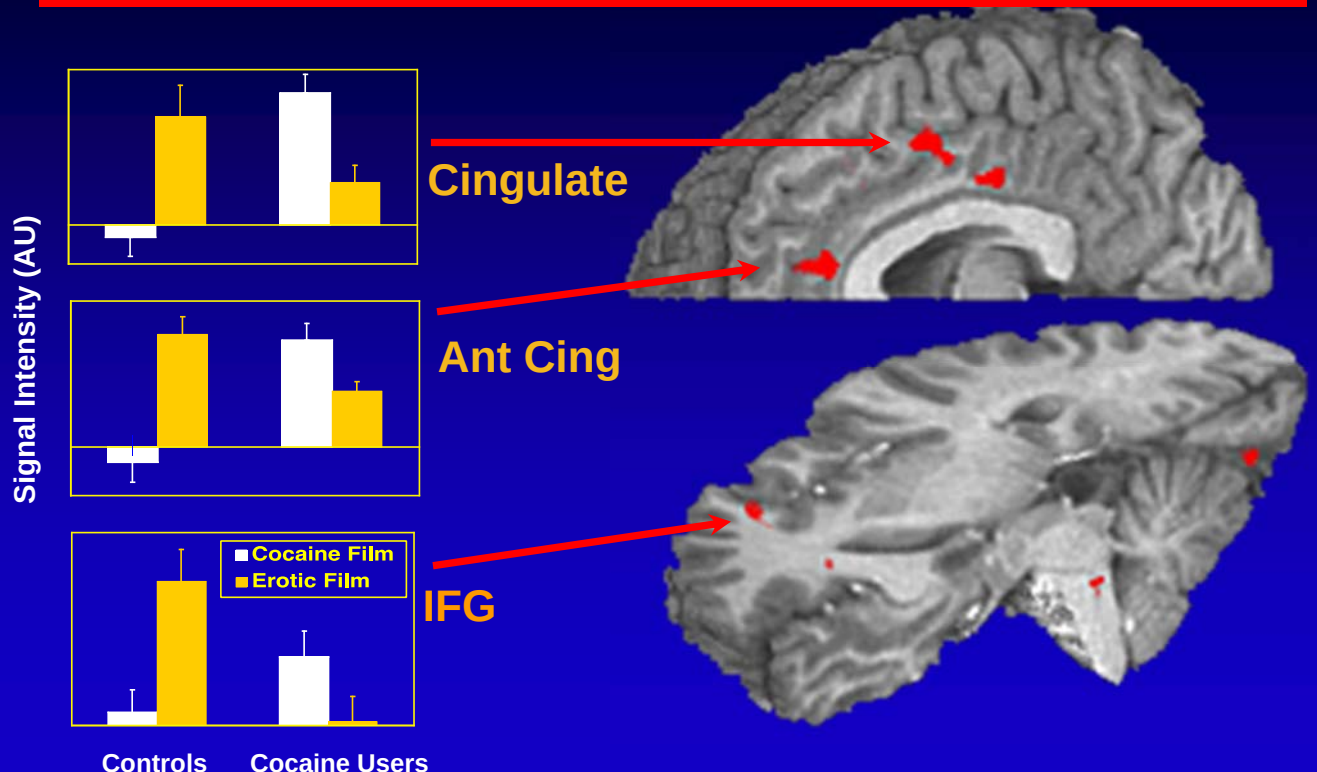
Cocaine Craving

Population (Controls, Cocaine Users) x Film (Cocaine, Erotic)



Garavan et al Am.J. Psych 2000

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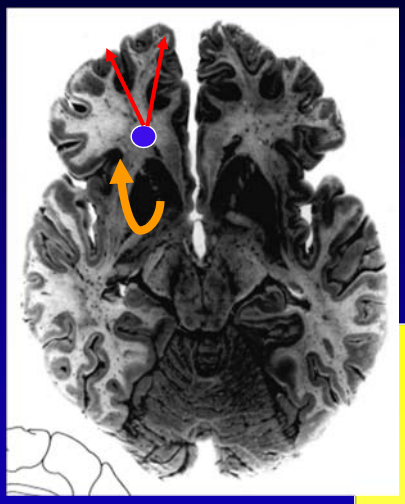
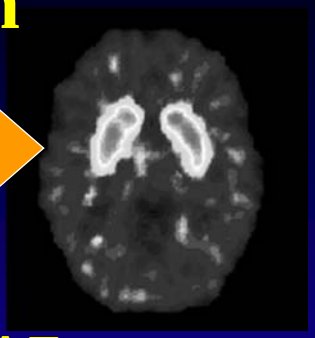
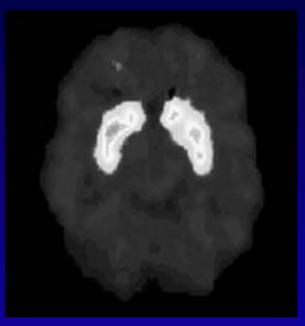
Brain Dopamine System



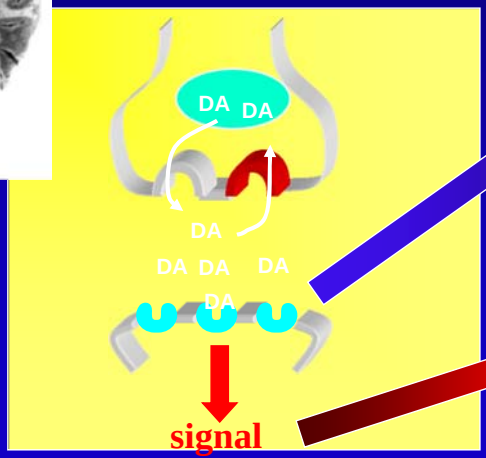
Anatomy



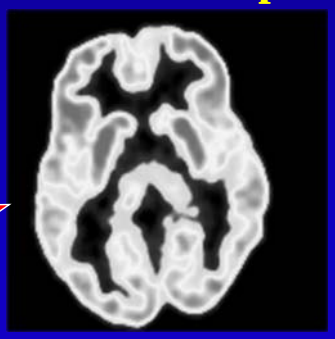
DA Transporters



DA Receptors



Dopamine Cell



Metabolism

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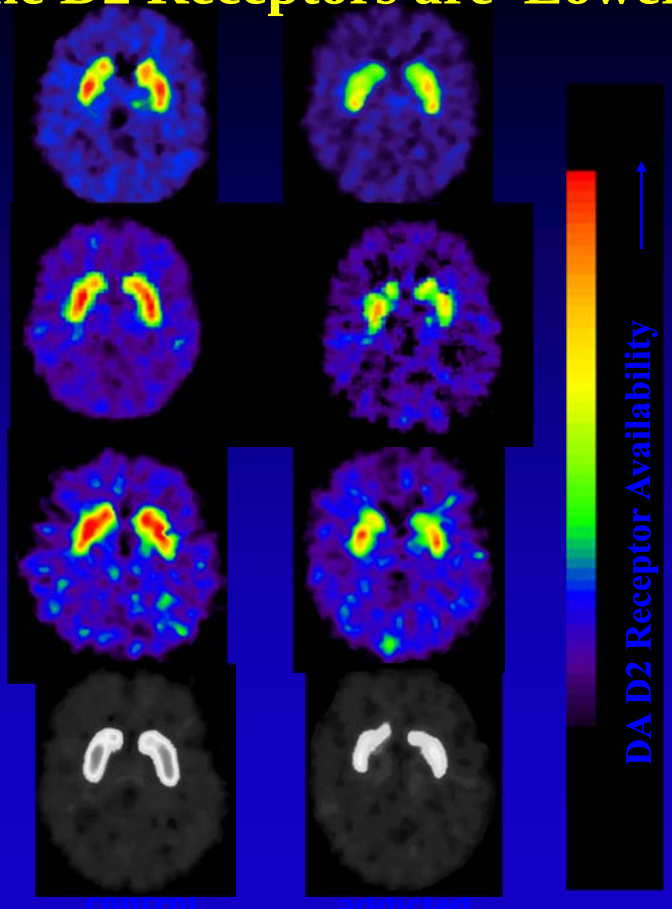
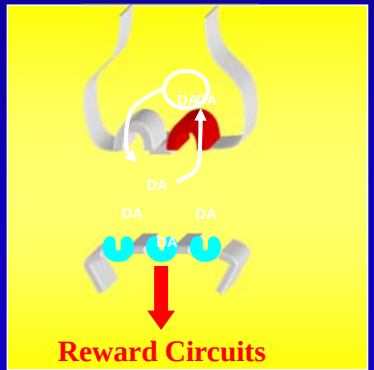
Dopamine D2 Receptors are Lower in Addiction



Non-Drug Abuser



Drug Abuser

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Genetic determinants for addiction vulnerability

Family studies — **Abuser's sibs have 5-8 fold greater risk than members of the general population**

Adoption studies — **Adoptees with abuser biological parents are more likely to become abusers**

Twin studies — **Genetic contributions:** *alcoholism: 0.5-0.6*
polysubstance abuse: 0.4-0.8
Much of the genetic vulnerability to alcohol, nicotine, illegal drugs overlaps

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Addiction is a Heritable Disorder: Twin Studies

DRUG	Males		Females	
Heroin (opiates)	54%	(Tsuang et al., 1996)		
Sedatives	87%	(Kendler, et al., 2000)		
Marijuana	33% 58%	(Tsuang et al., 1996) (Kendler, et al., 2000)	79%	(Kendler & Prescott, 1998)
Cocaine	44% 79%	(Tsuang et al., 1996) (Kendler et al., 2000)	81%	(Kendler et al., 1999)
Hallucinogens	79%	(Kendler, et al., 2000)		
Nicotine	53%	(Carmelli et al., 1990)	72%	(Kendler et al., 1999)

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Defining molecular bases of complex genetic components of brain disorders

"Top down": **Genome scanning/positional cloning:**
Linkage- and association approaches to substance abuse molecular genetics:
a) Define chromosomal regions that contain vulnerability alleles/haplotypes
b) Search for the vulnerability genes, alleles and haplotypes in the chromosomal regions

2) ***"Bottom up":*** **Candidate gene**

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Identifying chromosomal regions harboring substance abuse vulnerability alleles: Positional cloning approaches

Linkage: Studies how DNA markers and disease move together through families. Thus, collect families

Association: Studies how DNA markers and disease move together through a population. Thus, collect unrelated individuals with disease or without disease

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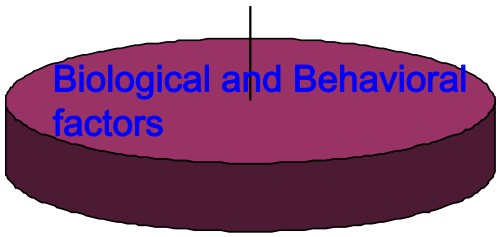
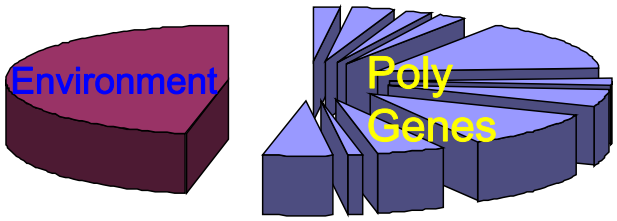
Drug Abuse Vulnerability Models: 1988 - 2003

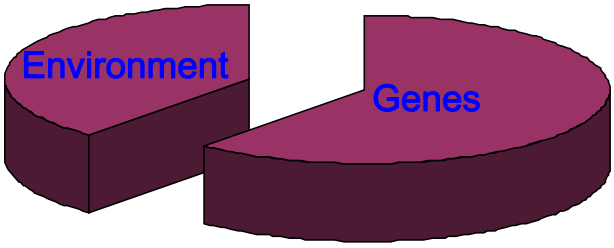
Late 1980's



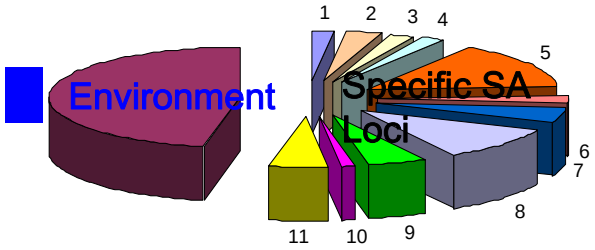
2000



Mid 1990's



2001



PRECLINICAL ANIMAL MODELS USEFUL FOR DRUG DEVELOPMENT IN ANTI-ADDICTION PHARMACOTHERAPY:

- DRUG SELF-ADMINISTRATION
  - SYSTEMIC
  - INTRACEREBRAL
  - PROGRESSIVE-RATIO BREAK-POINT
  - SECOND-ORDER REINFORCEMENT SCHEDULES
- CONDITIONED PLACE PREFERENCE/AVERSION
- REINSTATEMENT (RELAPSE)
- DRUG DISCRIMINATION
- BRAIN-STIMULATION REWARD
- IN VIVO BRAIN MICRODIALYSIS

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Requirements of a relapse model

At time of testing

- **Animal SHOULD be:**

  An experienced drug user

  Drug-free

  Free to engage in drug-taking behavior

- **Prior to testing**

  Animal SHOULD NOT be engaging in drug-taking behavior

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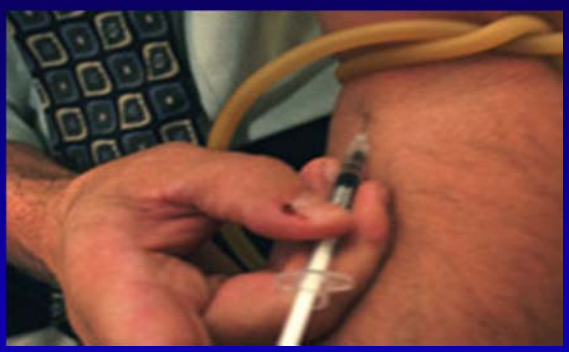
Factor contributing to relapse in humans

Drug-related cues **Drug reexposure** **Drug withdrawal** **Stress**



Can we study drug relapse by these factors in laboratory rats?

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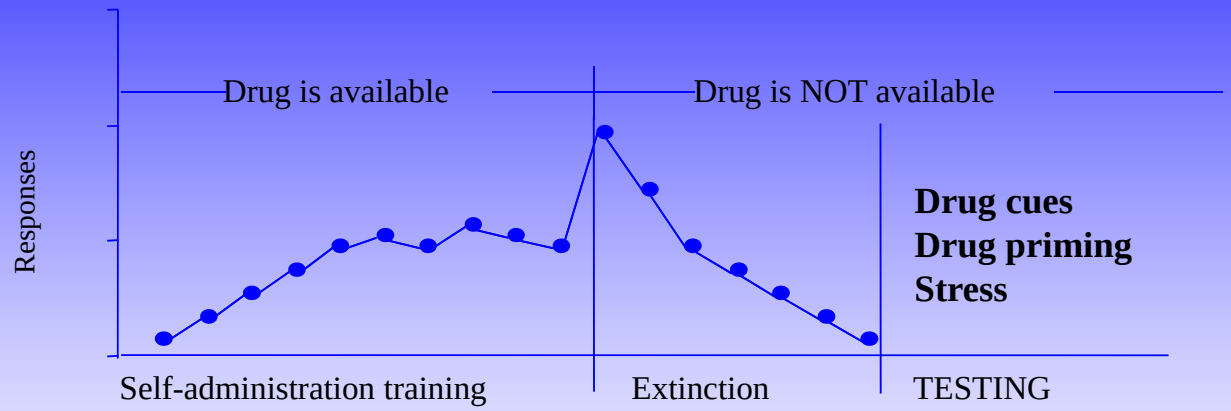
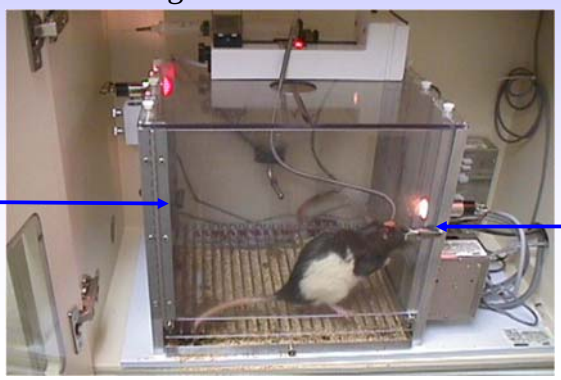
The reinstatement procedure





Inactive lever

Active lever

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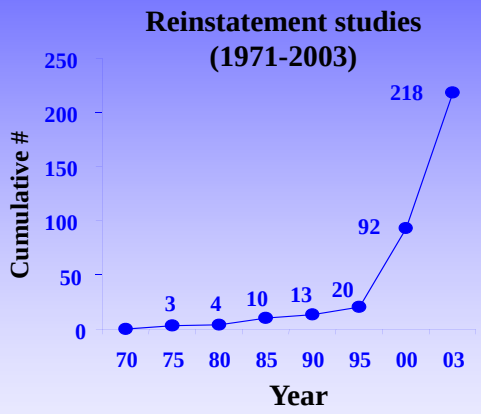
The reinstatement model: predictive validity

Relapse in human drug users	Reinstatement in laboratory animals
Drug reexposure	Reliable effect
Stress	Reliable effect
Drug-related stimuli	Reliable effect



Modified from
Shaham & Miczek.
Psychopharmacology 2003

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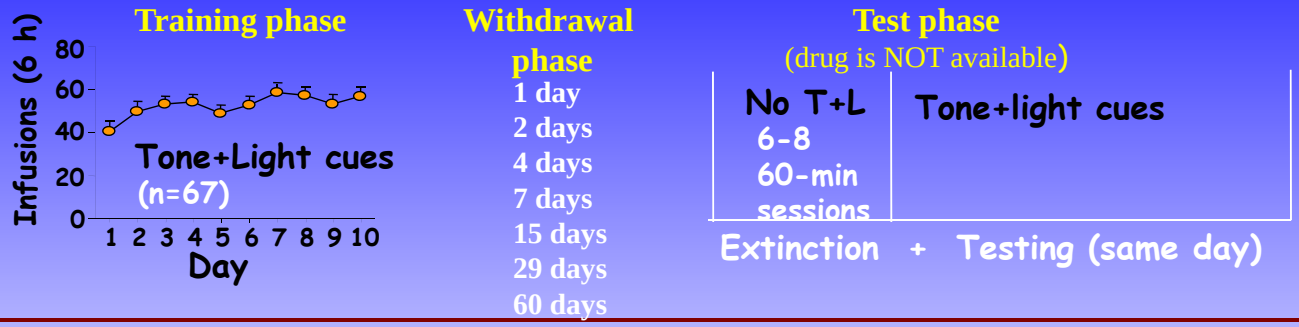
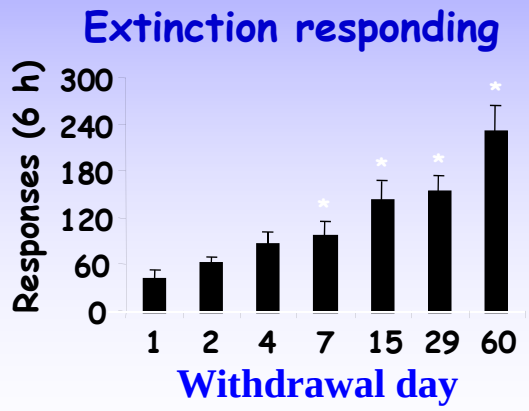
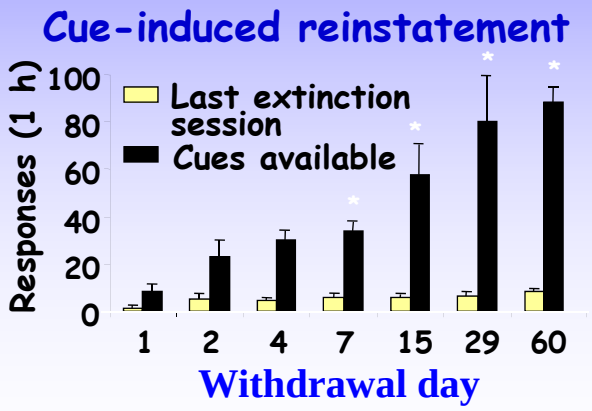
Extinction responding and cue-induced reinstatement of cocaine seeking at different withdrawal periods







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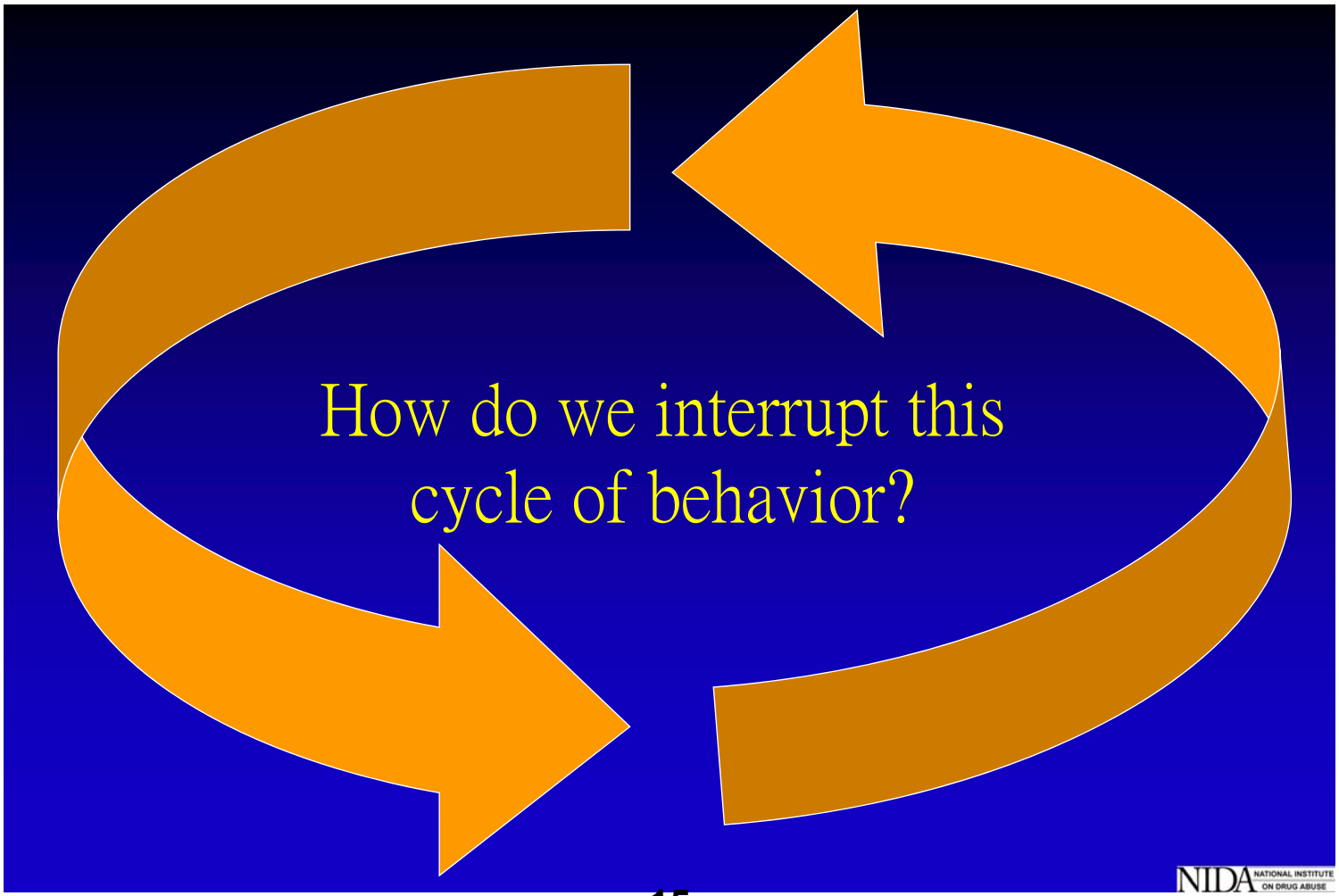

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A Major Task for Drug Treatment is Changing Brains Back!

- **Pharmacologically**
- **Behaviorally**

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Treating A Brain Disease Must Go Beyond Just Fixing The Chemistry

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Drug Addiction is a chronic illness that can be treated in the same fashion as hypertension, diabetes and asthma

Findings from a study sponsored by:
Physician Leadership on
National Drug Policy, March 1998

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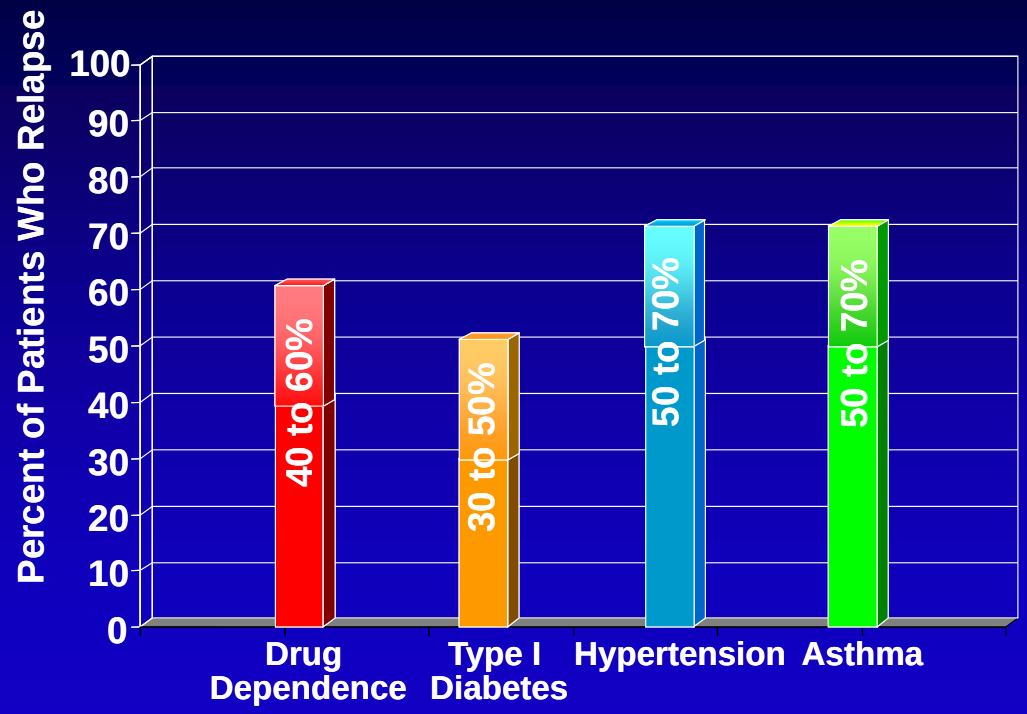
Relapse Rates Are Similar for Drug Dependence and Other Chronic Illnesses



McLellan, A.T. et al., JAMA, Vol 284(13), October 4, 2000.

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If we treat a diabetic and symptoms don't subside….what do we do?

Would we increase the dose?
Would we change medications?
Would we change treatment approaches?

Would we fail to provide ongoing treatment for a diabetic?

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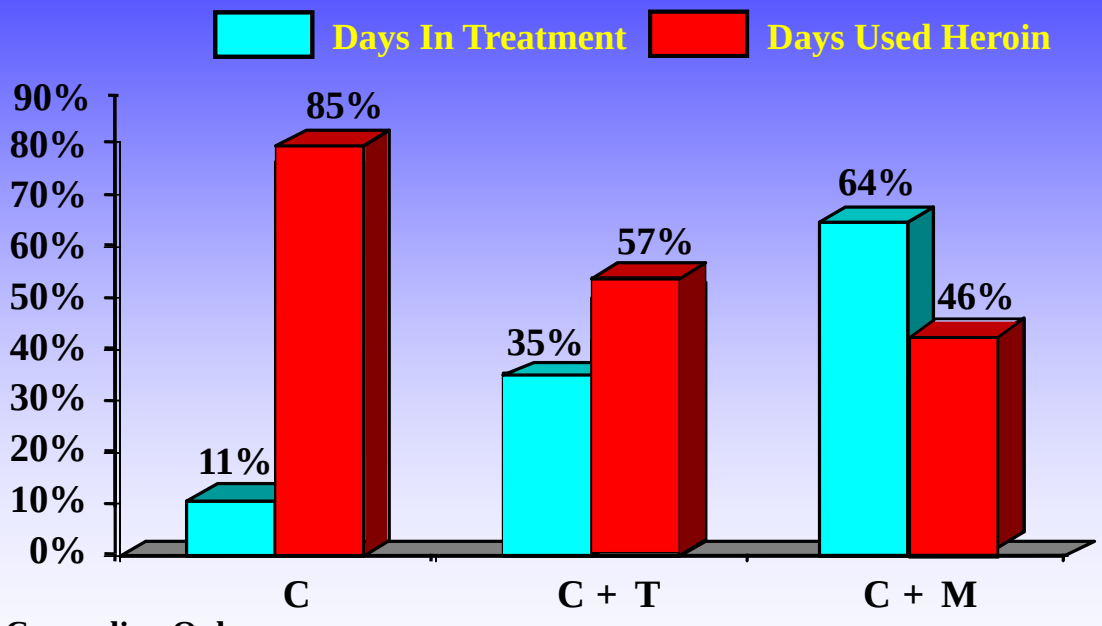
Treatment Linkage & Days Used Heroin 6 Months Post-release



C = Counseling Only
C+T = Counseling & Treatment Referral
C+M = Counseling & Methadone Started in Prison

Source: Gordon, MS et al., Addiction 103:1333-1342, 2008.

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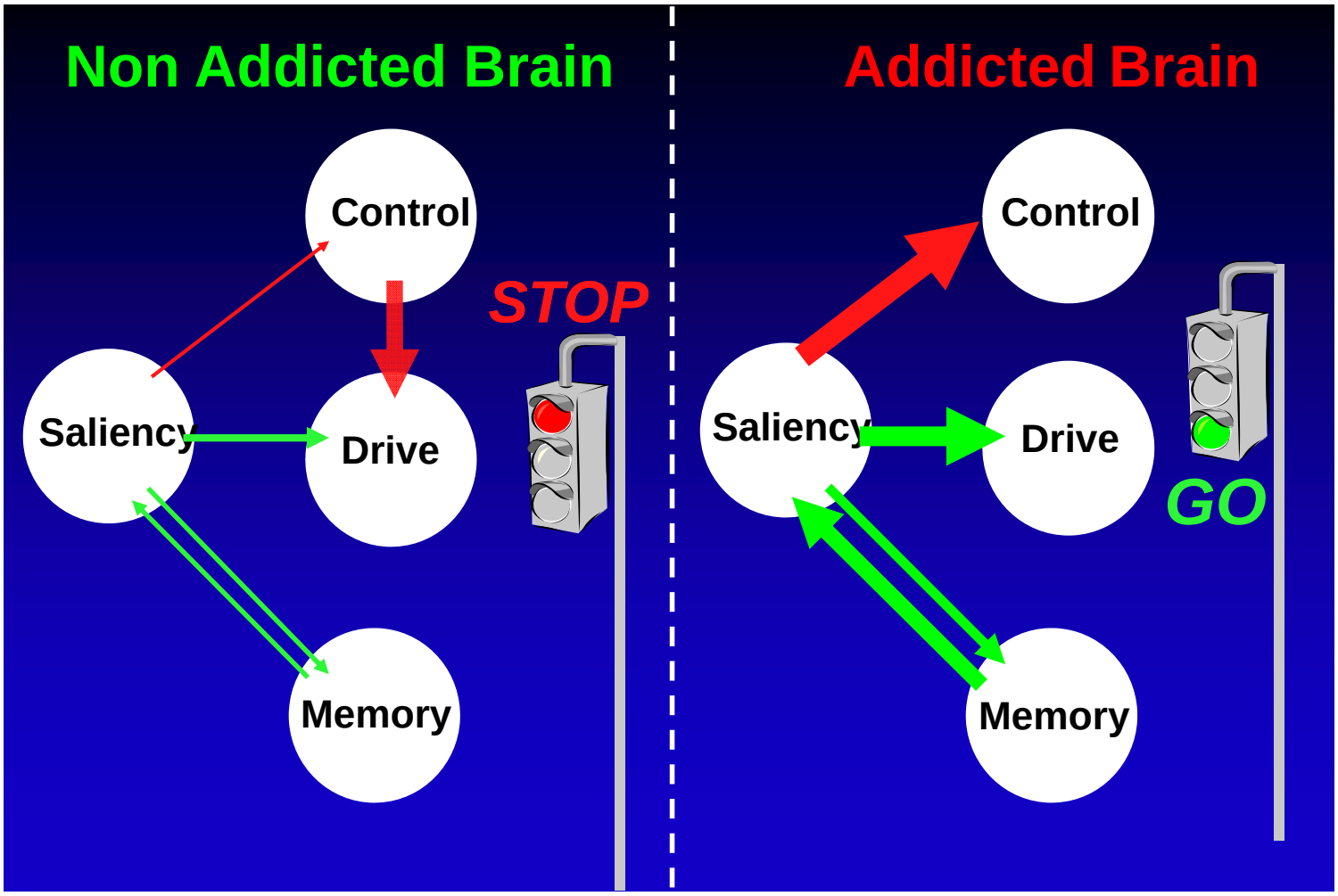

Effectiveness of Treatment

- Goal of treatment is to return to productive functioning
- Treatment reduced drug use by 40-60%
- Treatment reduces crime by 40-60%
- Treatment increases employment prospects by 40%
- Drug treatment is as successful as treatment of diabetes, asthma, and hypertension

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Cost-Effectiveness of Drug Treatment

- Treatment is less expensive than not treating or incarceration (1 yr methadone maintenance = $4,700 vs. $18,400 for imprisonment)
- Every $1 invested in treatment yields up to $7 in reduced crime-related costs
- Savings can exceed costs by 12:1 when health care costs are included
- Reduced interpersonal conflicts
- Improved workplace productivity
- Fewer drug-related accidents

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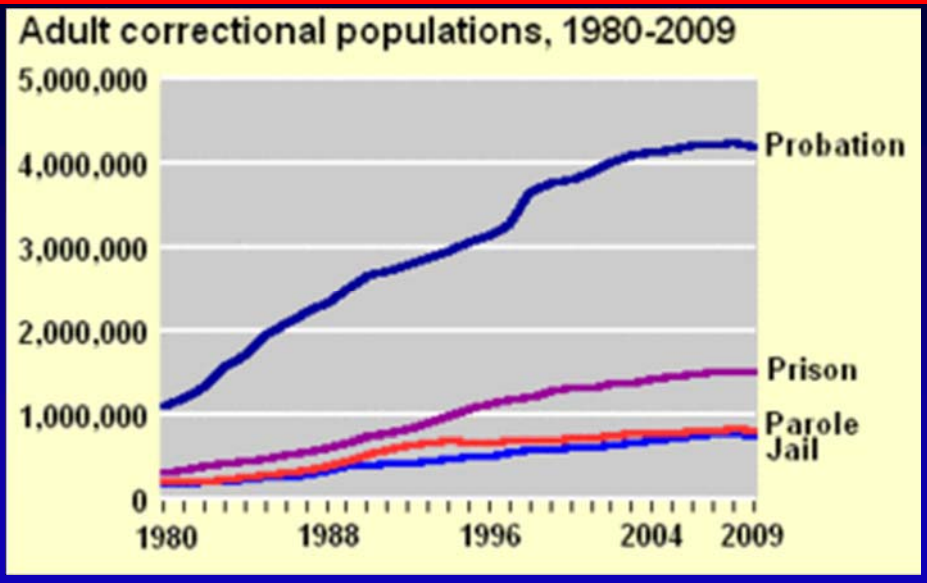
Although We Do Have Treatments That Work We Face Some Major *Challenges* in Using Them

- Stigma-related issues
- Criminal Justice System's Reluctance to Use
- Many Countries' Reluctance to Use

U.S. Adult Offender Population



The number of incarcerated *drug offenders* has increased twelvefold since 1980.

In 2008, approximately one in every 31 adults (7.3 million) in the US was behind bars, or being monitored (probation and parole).

US Bureau of Justice Statistics; US Crime Rates 1960-2011.

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Substance Abuse Has Many ADVERSE CONSEQUENCES

- **Addiction**
- **Impaired Performance/Judgement/ Decision Making**
- **Accidents/Injuries DUI - Drugs**

  Every day, almost 30 people in the U.S. die in motor vehicle crashes that involve an alcohol impaired driver – one death every 48 minutes*
- **HIV/AIDS**
- **Other Medical Consequences**

**Source: Department of Transportation, National Highway Traffic Safety Administration (NHTSA). Traffic Safety Facts 2009.*

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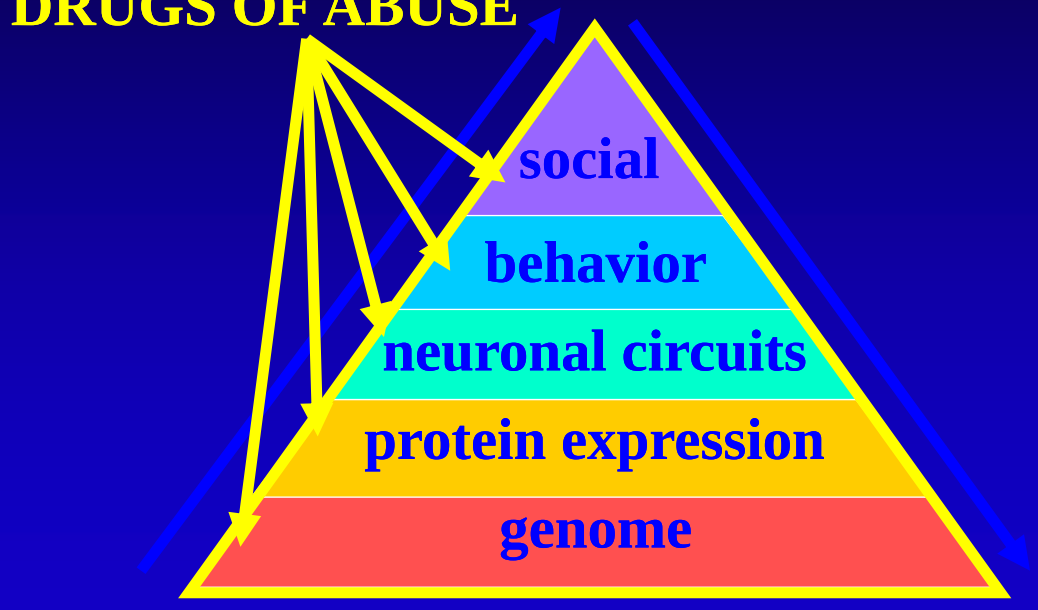
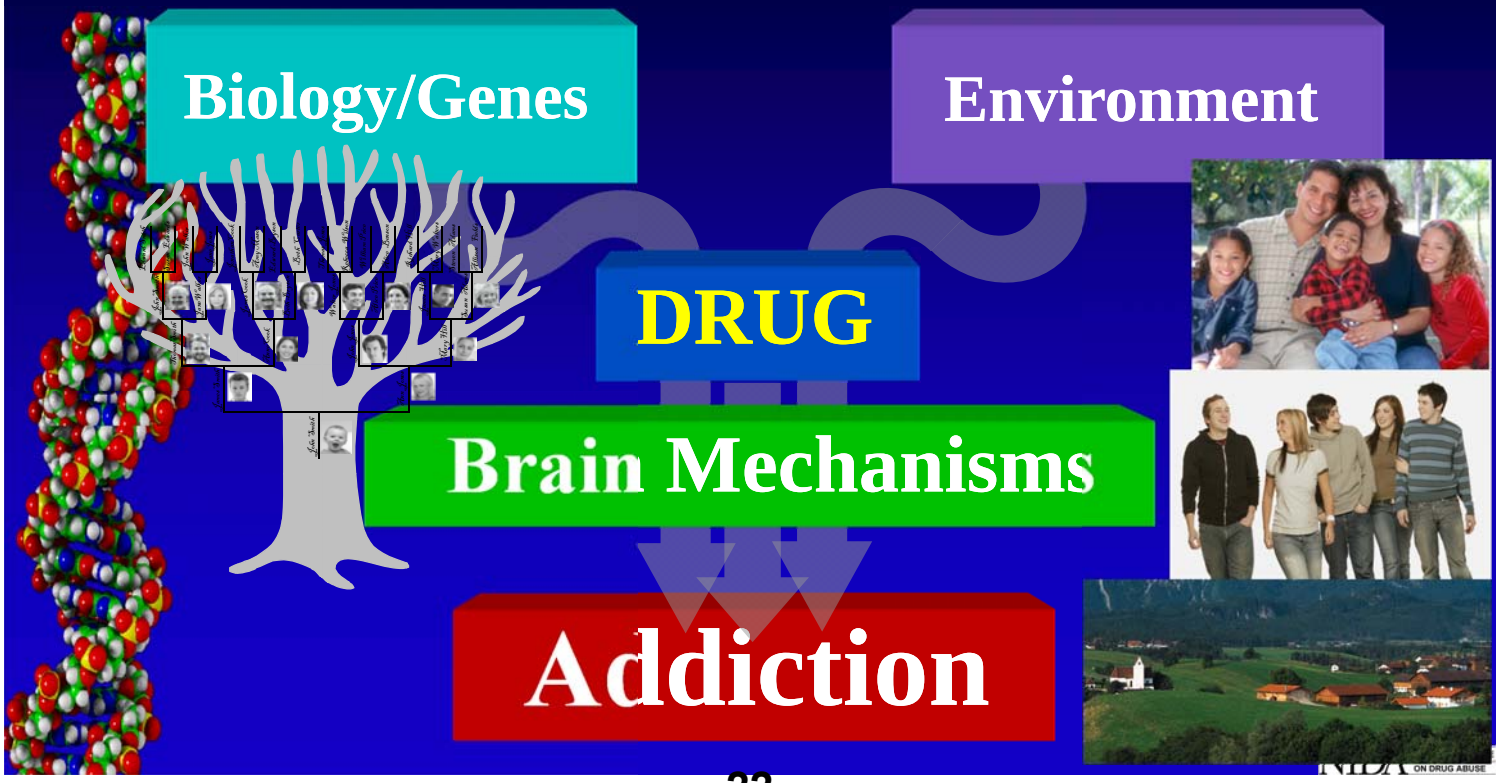
Research in ADDICTION Requires a Systems Approach



NIDA NATIONAL INSTITUTE ON DRUG ABUSE

ADDICTION INVOLVES MULTIPLE FACTORS



BIOSKETCH **GREENSHAW, Andrew James**

Professor of Psychiatry and Neuroscience, University of Alberta

- Dr. Andy Greenshaw is a Professor of Psychiatry and Neuroscience at the University of Alberta. He Trained in Europe and Canada and moved to a faculty position at the University of Alberta in 1986. He began as an Assistant Professor and Heritage Medical Research Scholar and became a Full Professor in 1996.
- Andy is a Fellow of the Canadian College of Neuropsychopharmacology (CCNP), for which he served as President from 2000-2002, and a Fellow of the Collegium Internationale Neuropsychopharmacologicum (CINP). He served as Associate Vice President (Research) for the University of Alberta from 2003-2010 and has served on a number of national boards including the Canadian Psychiatric Research Foundation, the Institute of Health Economics, the Saskatchewan Health Research Foundation and The University of the Arctic. Since 2006 he has served as Co-Chair of the Alberta Addictions and Mental Health Research Partnership Committee.
- Andy has served on numerous Canadian Medical Research Council and Canadian Institutes of Health Research (CIHR) grant panels since 1989 and is currently a member of the Scientific Advisory Board of the CIHR Institute of Neuroscience Mental Health & Addiction. He is a director of the Alberta-based node of the national Canadian Depression & Research Intervention Network (CDRIN), which focusses on engagement of people with lived experience of mental disorders as partners in patient-oriented research, he is also interim-Chair of the CDRIN Depression Hubs National Advisory Panel.
- Andy's scientific interests include a broad range of biological and psychosocial areas in biological psychiatry and behavioural neuroscience and his research continues to focus on research questions related to the regulation of motivation and reward.
- He is studying the basis of risk behaviour in high risk youth and investigating bioclinical aspects of alcohol use disorder in adults, including pregnant women. He is also collaborating with an inter-professional research team on research into the impact of prenatal mental health and adverse environmental influences on brain development. His work includes health economic analysis in collaboration with the Institute of Health Economics.

UNIVERSITY OF ALBERTA
NEUROSCIENCE AND
MENTAL HEALTH INSTITUTE

TRANSLATIONAL SCIENCE INSTITUTES

Great Science = Better Health

Professor Andrew Greenshaw,
Department of Psychiatry
Faculty of Medicine & Dentistry

COLLABORATE, ACCELERATE, TRANSLATE

ccnp
Canadian College of
Neuropsychopharmacology

CCNP President 2000-2002

Disclosure

The presenter, co-investigators and trainees directly involved in the studies presented, have no financial conflicts of interest or commitment in relation to the work described.

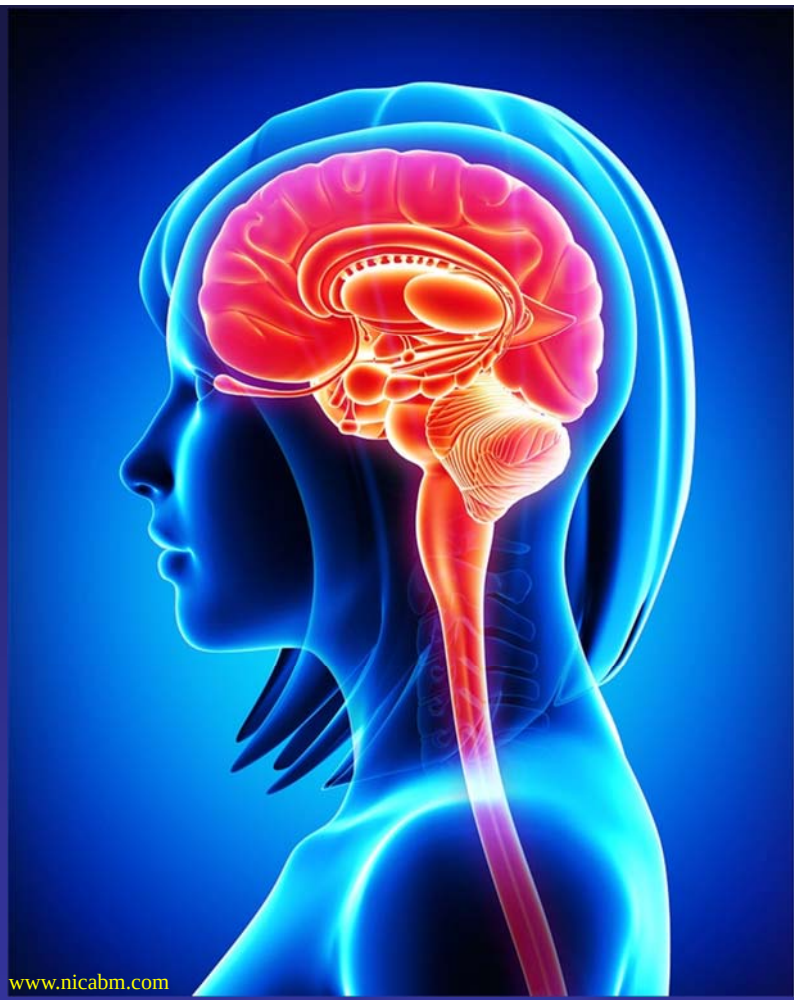
All the work presented from this group has received prior ethics approval from the Health Research Ethics Board of the University of Alberta and clinical approval from Alberta Health Services.

Alcohol Use Disorder:

Brain changes in abstinence and effects of naltrexone

Dr Andy Greenshaw
Department of Psychiatry & Neuroscience & Mental Health Institute
University of Alberta

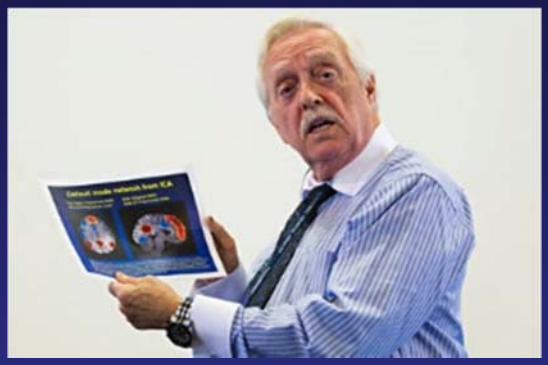
TAP, Antalya,
April 17th, 2015



What does a healthy brain look like?

What happens to the brain in addiction?

RESEARCH TEAM



Dr. Tim Gillese

Clinical leads – Edmonton Node of TRANSALC

Professor Serdar Dursun

RESEARCH TEAM

Marnie Mackay R.N.

Dr. Matt Brown

Thanks to key people and funders -

TRANSALC Edmonton clinical node & AHS*

Serdar Dursun, Matthew Brown, Tim Gillese*, Michal Juhas, Marnie Mackay, James Benoit, J., Allan Aubry*, Glenn Walmsley*, Blayne Blackburn*, Cindy King*, Liana Urichuk*, Mark Loowell*, Ericson Dametto, Manoj Malik, Tiffany Tse

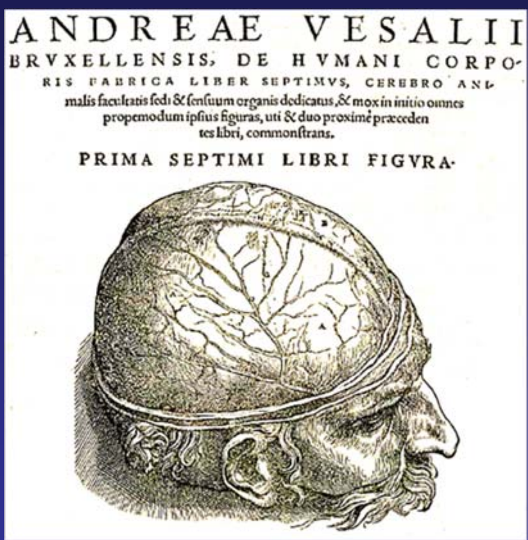
TRANSALC Mannheim Lead Clinical Node

Wolgang Sommer, Derik Hermann, Sabine Vollstädt-Klein, Karl Mann, Wolfgang Weber-Fahr, Gabi Ende

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada — neuron Network of European Funding for Neuroscience Research — Norlien Foundation — University of Alberta — Alberta Health Services

The Human Brain - Vesalius 1543

De humani corporis fabrica libri septem


ANDREAE VESALII BRVXELLENSIS, DE HVMANI CORPORIS FABRICA LIBER SEPTIMVS, CEREBRO ANImalis facultatis sedi & sensuum organis dedicatus, & mox in initio omnes propemodum ipsius figuras, uti & duo proxime præcedentes libri, commonstrans.

PRIMA SEPTIMI LIBRI FIGVRA.


QVINTA SEPTIMI LIBRI FIGVRA.

PRÆSENS figura quod ad relictam in caluaria cerebri portionẽ attinet, nulla ex parte uariat: atq; id solũ habet proprium, quod callosum corpus hic anteriori sua sede à cerebro primùm liberauimus, ac dein eleuatum in posteriora reflexímus, septum dextri ac sinistri uentriculorum discellentes, & corporis instar testudinis extructi superiorem superficiem ob oculos ponẽtes.

Ab A ad Q A, A, A itaq; & B, B, B, ac dein D, D, D, & E & F, & G & H eadem hic indicant, quæ in quarta figura. Sic quoque & L, L, & M, M, & O & P & Q eadem insinuant.

R, R, R Notatur inferior callosi corporis superficies. est enim id à sua sede motum, atque in posteriora reflexum.

S,T,V Supe-

The promise of neuroimaging

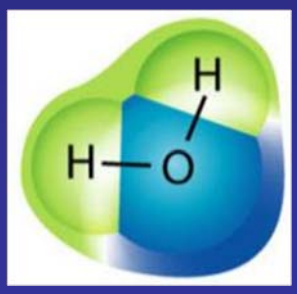
Outline of Presentation

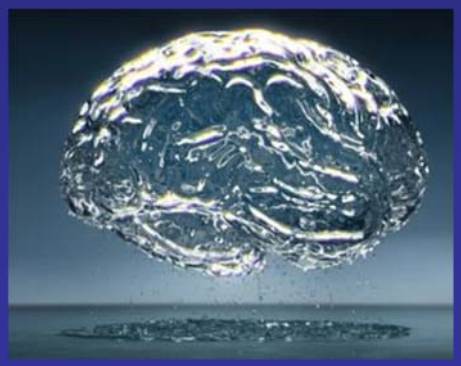
- Behavioural constructs relevant to addiction
  - Brain regions associated with risk and impulsivity – fMRI analysis
- TRANSALC study Edmonton clinical node
  - Study design
  - Naltrexone and relapse
  - Resting state fMRI analysis and DTI
  - Preliminary data will be reported
- Summary and implications

MAGNETIC RESONANCE IMAGING

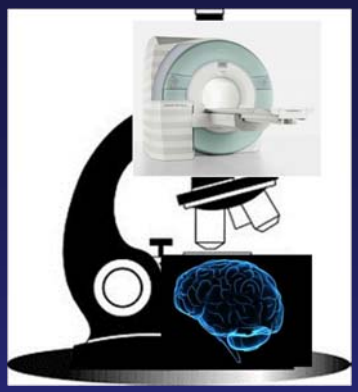
Non-invasive diagnosis, prognosis, understanding of disease

MRI Measures WATER in Tissue

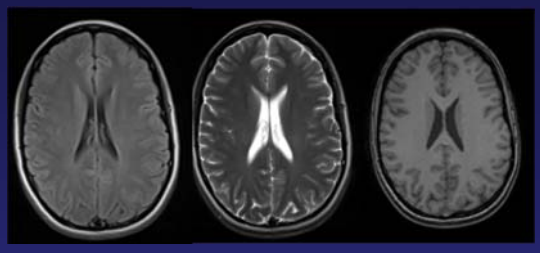




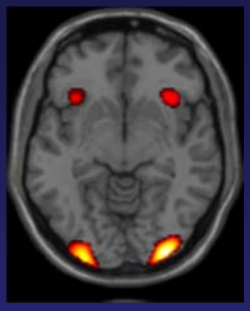
MRI of the BRAIN



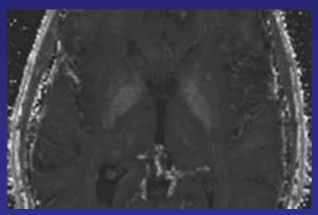
Anatomy



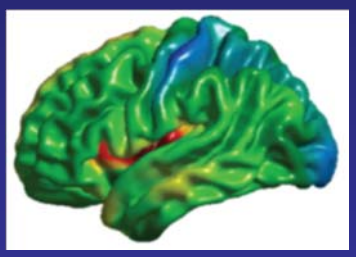
Function



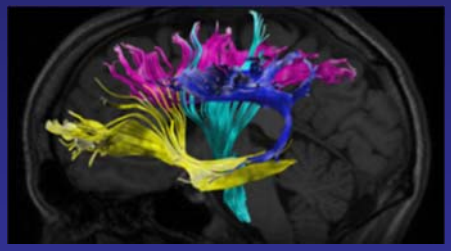
Iron

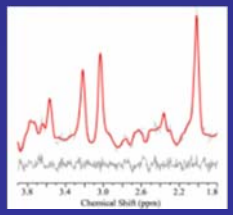


Cortex

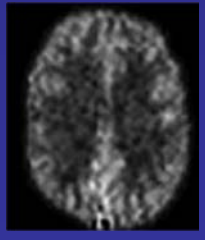


Wiring

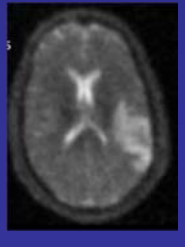




Metabolites

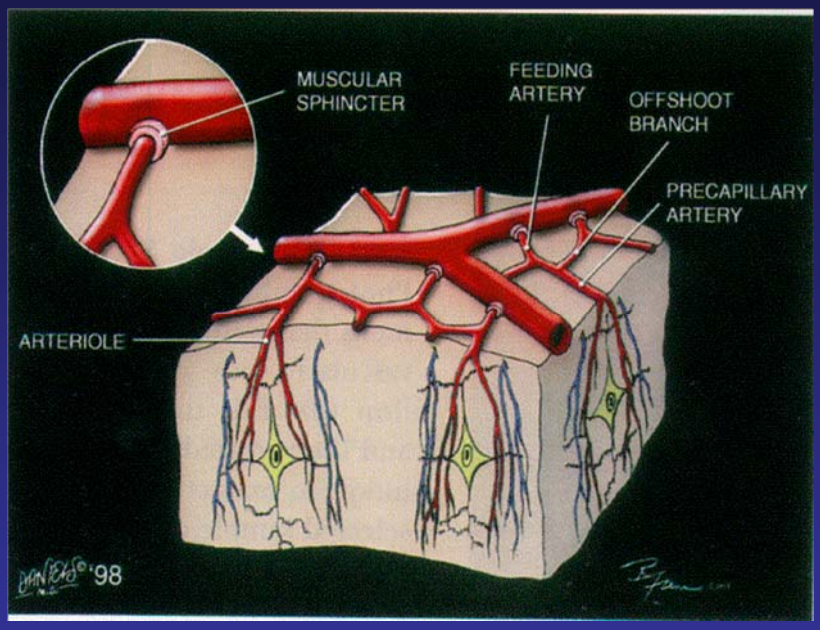


Perfusion



Sodium

fMRI Blood oxygen level dependent (BOLD)

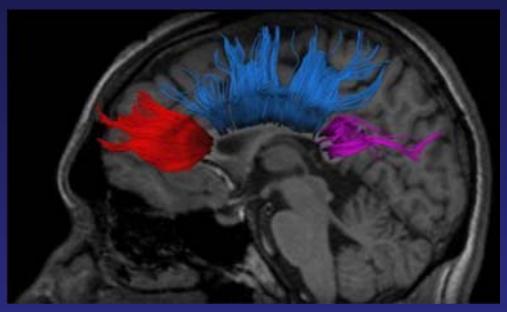


Increased neuronal firing – increased brain oxygen uptake
Local increase in blood flow leads to increased oxy-haemoglobin

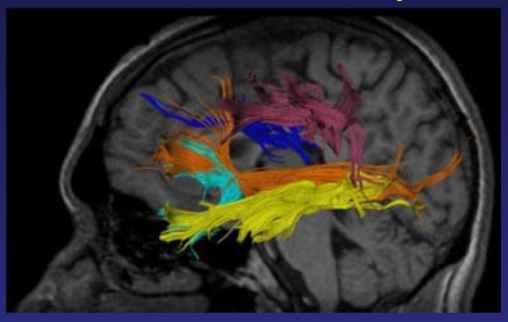
Yields altered local magnetizability - BOLD imaging

DTI Tractography – Virtual Brain Wiring

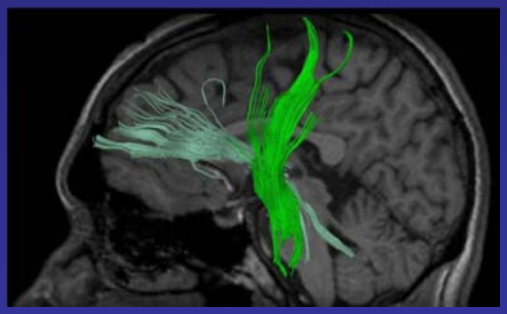
Commissural Pathways



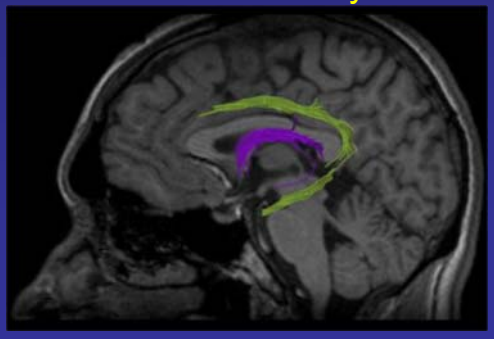
Association Pathways



Projection Pathways



Limbic Pathways



Peter S Allen Neuroimaging Centre
University of Alberta

1.5T, 3.0T, 4.7T Scanners:

Structural MRI
Resting state analysis
DTI
MRS
(*new PET-MRI 2016*)

Risk, Impulsivity and Addiction

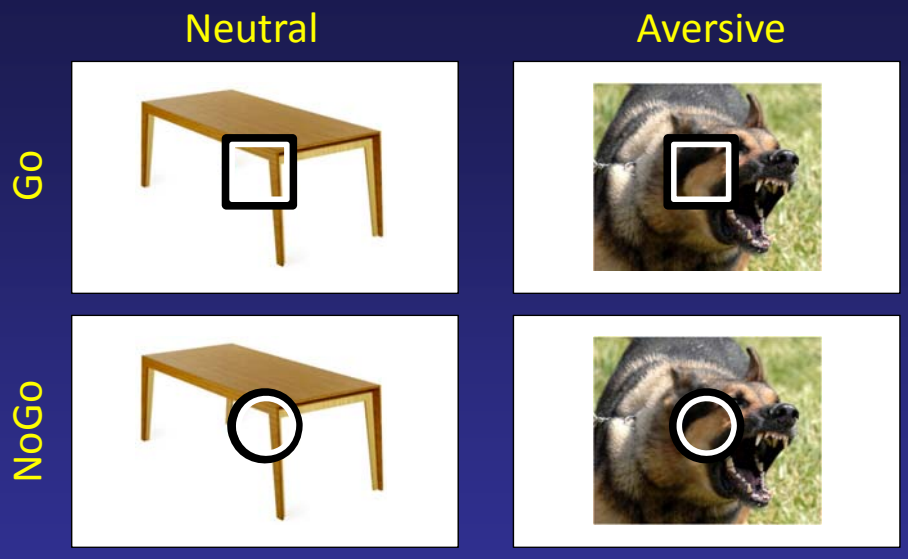
Behavioural constructs generally relevant to addiction:

- Decision making and risk taking
- Impulsivity and response inhibition
- Reward and craving

Emotional Go/NoGo Task

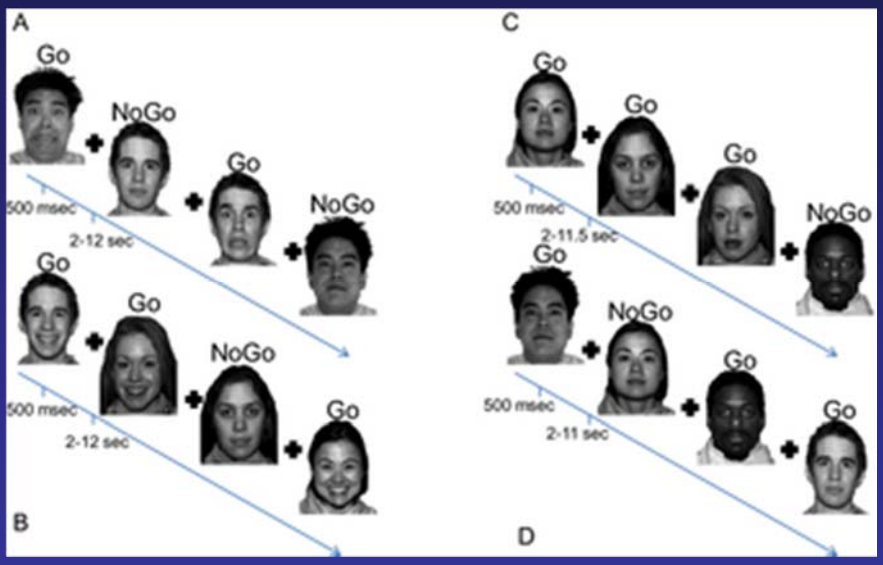
- Prior work demonstrated the value of a novel Go/NoGo task with a decision-independent emotional distractor stimulus embedded in the Go/NoGo stimulus
- Brown et al. 2012 NeuroImage 63: 434-446

Emotional Go/NoGo



Brown et al. 2012 NeuroImage 63: 434-446

Go/NoGo task with single 'emotional + decision' stimulus



From Cservenka et al 2014 Alcoholism: Clinical and Experimental Research DOI: 10.1111/acer.12435

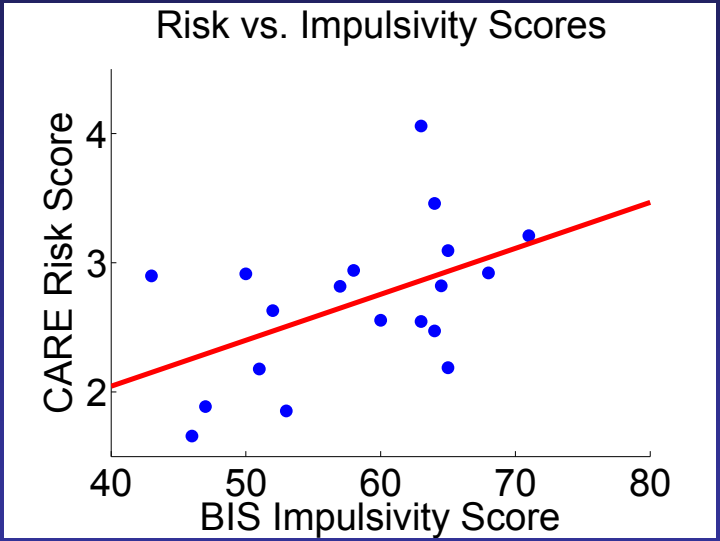
Emotional Go/NoGo Task

Using the independent stimulus task of Brown et al (2012) with fMRI–

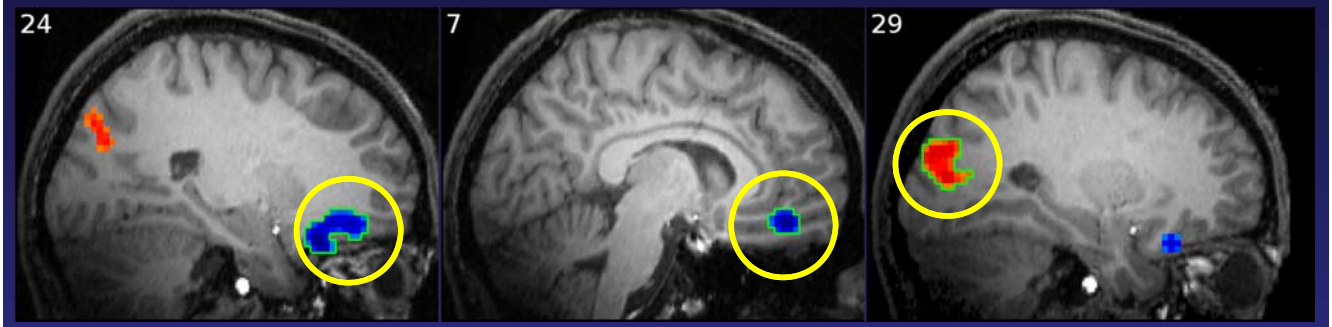
We examined the relationship of brain activity reflecting Emotional Context and Go/NoGo performance respectively, to measures of:

- RISK CARE (Cognitive Appraisal of Risky Events scale)
- IMPULSIVITY (BIS)

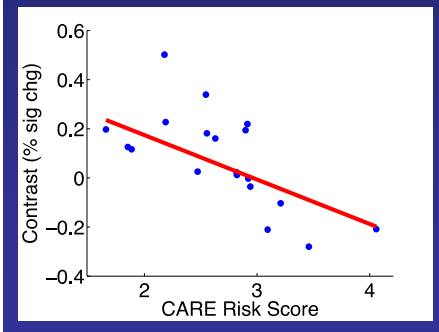
CARE Risk Scores vs. BIS Impulsivity

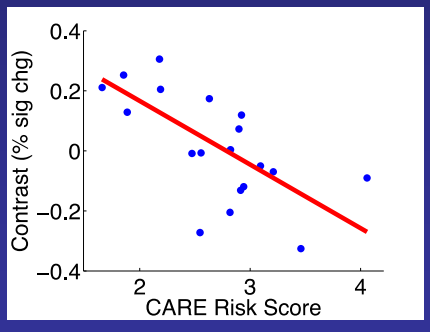


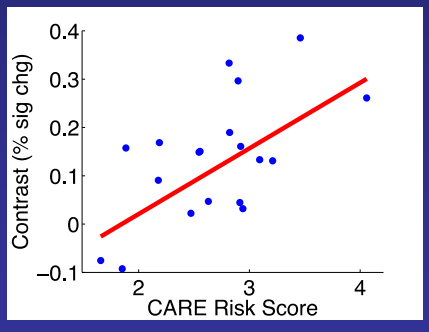
Inhibition fMRI vs. RISK



R Orbitofrontal Cortex Ventromedial PFC R Occipital Cortex

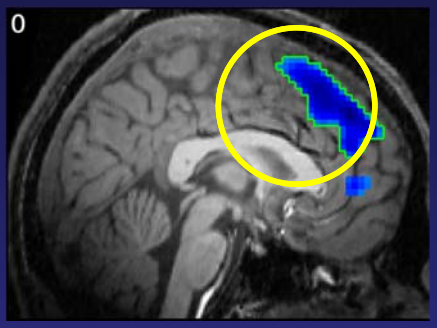




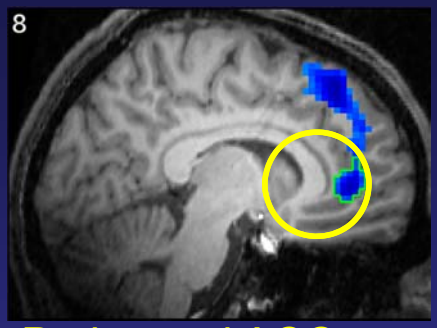


No relationship to impulsivity scores in these regions

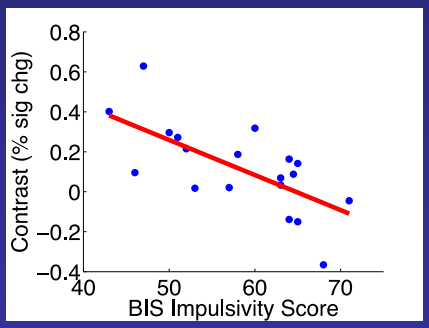
Emotion fMRI vs. IMPULSIVITY

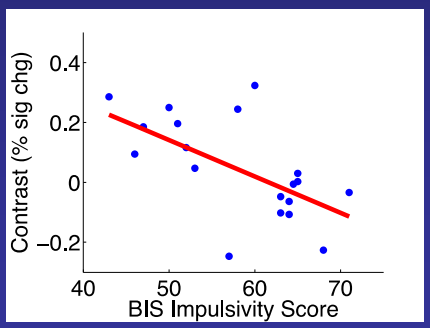


Dorsomedial PFC



Perigenual ACC





No relationship to risk scores in these regions

Emotional Go/NoGo: Risk and Impulsivity

		ROI fMRI CORRELATION WITH:	
fMRI change		**RISK**	**IMPULSIVITY**
Overall Go/NoGo (Response Inhibition)			
Right OFC	↓	-VE	NS
vmPFC	↓	-VE	NS
Right OCC	↑	+VE	NS
Overall Distractor (Emotion)			
dmPFC	↓	NS	-VE
pgACC	↓	NS	-VE

Impulsivity and risk-taking - separable traits with distinguishable associations in addiction?

Ryan et al (2013) Addictive Behaviours 38: 431–1434

Barratt Impulsiveness Scale-11 (BIS-11), the Balloon Analogue Risk Task (BART), and self-report measures of smoking behavior and nicotine dependence

- +ve relationship between dependence and the BIS-11 (attention subscale and the non-planning subscale)
- -ve relationship between dependence and the BART.

Emotional Go/NoGo summary

- Differential correlations of 'emotional distractor-' and 'inhibition-related' fMRI patterns in relation to CARE risk scores and BIS impulsivity scores, respectively
- Impulsivity and risk tendency are dissociable constructs?

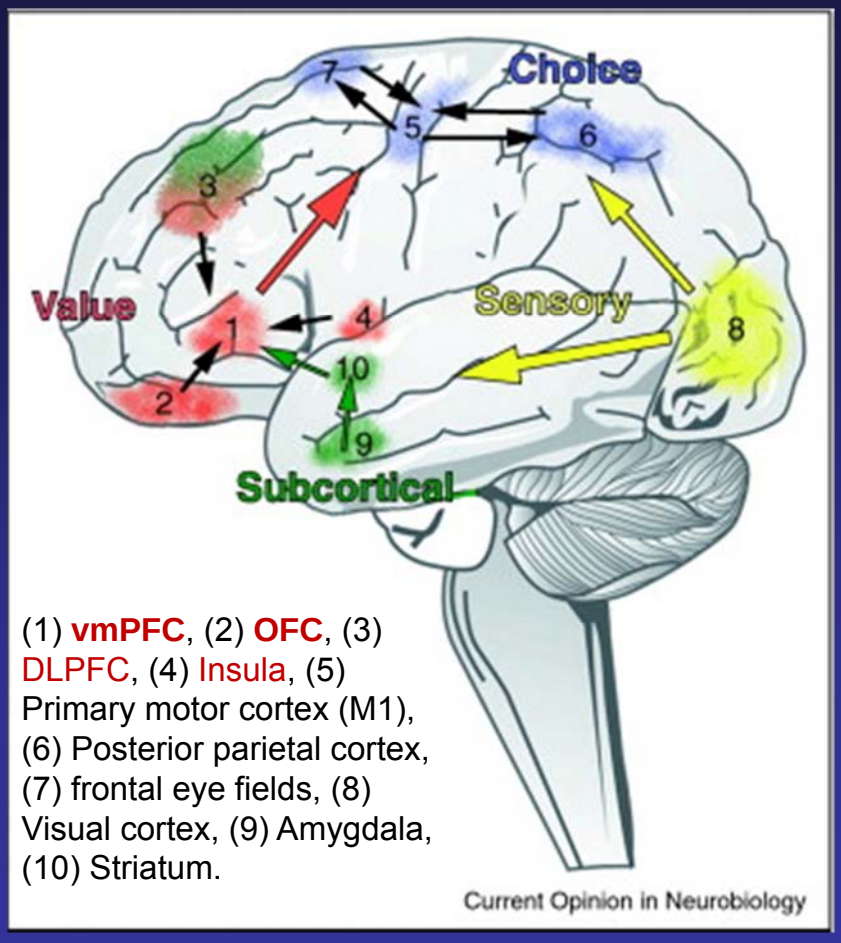
Brain pathways and decisions related to "reward value"

"a small group of specific brain sites…encode the subjective values of…rewards on a neural common scale…associated with this common representation is a subregion of vmPFC / OFC

Levi & Glimcher (2012) Curr Opin Neurobiol. 22:1027-38

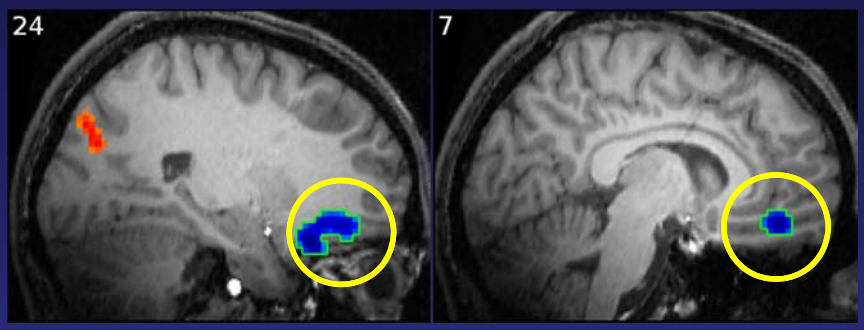
"Schema…decision-making networks of the human brain….information from cortical and subcortical structures converges toward a single common value representation before passing on to the choice-related motor control circuitry…"

From: Levy & Glimcher (2012) Current Opinion in Neurobiology, 22: 1027 - 1038

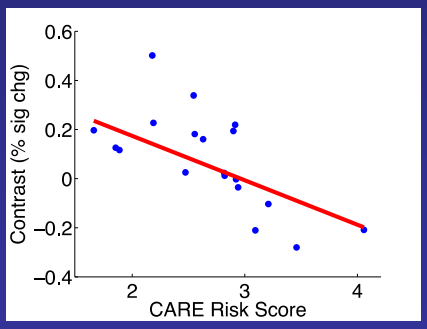


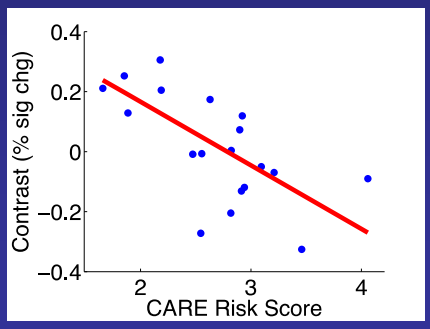
(1) **vmPFC**, (2) **OFC**, (3) DLPFC, (4) Insula, (5) Primary motor cortex (M1), (6) Posterior parietal cortex, (7) frontal eye fields, (8) Visual cortex, (9) Amygdala, (10) Striatum.

Inhibition fMRI vs. Risk



R Orbitofrontal Cortex Ventromedial PFC



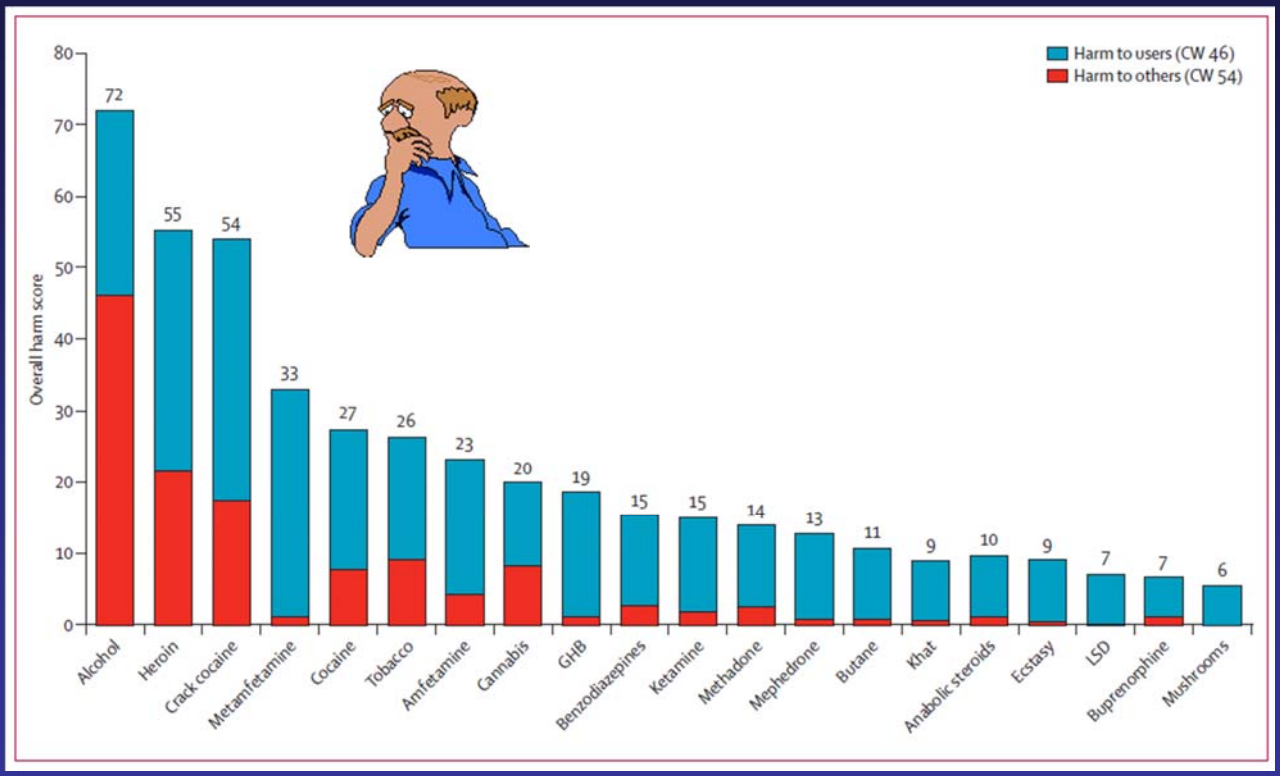


Regional specificity for risk and impulsivity changes during withdrawal?

- Are brain regions that exhibit differential correlation to risk and impulsivity relevant to decision making in addiction and during abstinence?

- In relation to brain changes during abstinence from alcohol – we are interested in regional dissociation effects, for risk and impulsivity.

Alcohol: most harmful drug of abuse?



Nutt et al, fig 2, Lancet 2010)

Substance abuse – prevalence in Edmonton

Royal Alexandra Hospital in Edmonton:

Convenience sample of patients presenting to Emergency completing a computerized health promotion survey

43% reported active substance abuse
(58% alcohol, 14% street drugs and 28% both).

Sixty-three percent of patients accepted a referral for counseling .

(Dong, et al., 2012).

Alcohol Abstinent Brains

We are learning that the "Abstinent Brain" is a brain in recovery

- Emotional circuits appear to be inhibited
- Executive "decision making" circuits appear to be enhanced

TRANSALC: some preliminary results

- How does the brain change in abstinence from alcohol misuse?
- TRANSALC study Edmonton clinical node
  - Study design
  - Naltrexone and relapse
  - Resting state fMRI analysis
  - Preliminary data related to Default Mode Network
  - DTI analysis in progress

TRANSALC

- ERA-NET and CIHR funded multidisciplinary project.
  - Basic neuroscience arm (Finland, Germany, Spain)
  - Clinical research arm (Germany, Canada)
  - University of Alberta-based Edmonton node is the second clinical site

TRANSALC

- Edmonton study design focusses on recruitment of people with DSM IV-TR Alcohol Use Disorder who have just completed detox and are entering a residential treatment program
- First MRI scan on completion of detox
- Second MRI scan on completion of residential treatment
- Open label effects of Naltrexone to be assessed

TRANSALC

Goals for Edmonton node:

Recruitment target of 45 alcohol addicted patients and 45 healthy controls under the same criteria.

Male subjects selected due to OPRM1 genotyping

Screening

Alcohol Use Disorders Identification Test (AUDIT)

Alcohol withdrawal symptoms (CIWA-R)

Craving (obsessive compulsive drinking scale = OCDS)

Amount of alcohol consumption of the last 90 days (Form 90),

Beck depression inventory (BDI)

State trait anxiety scale (STAIT).

Inclusion criteria:

- Male, 18-65 years old
- Alcohol use disorder DSM IV TR confirmed by Structured Clinical Interview (SCID-I Version 2.0 DSM-IV)]
- Drinking habits: chronic steady/daily drinker

Exclusion criteria:

- Prolonged abstinence
  (> 12 days prior to scan 1, or extended abstinence in the recent past)
- Only binge drinking / irregular drinking pattern
- Significant history of abuse of non-consumption alcohol
  (e.g. hair products, sanitizers, mouthwash)

- Comorbid substance abuse / dependence
  (other than nicotine and non-recent, limited THC abuse)

- History of neurological or psychiatric disorders
  (other than alcohol-use-disorder-related depression / anxiety)
- History of severe head injury
  (requiring multiple stitches or causing concussion)
- History of chronic or major medical disorders

- Magnetic resonance safety criteria*

TRANSALC: 4.7T Scanner

3 week in-patient treatment program

Session 1
(6 - 12 days abstinent)

Measures:
Resting state fMRI
DTI
Structural scan

Session 2
(27-33 days abstinent)

Male patients with alcohol use disorder +/- naltrexone
Healthy male controls

TRANSALC 3 year Recruitment Summary March 8th, 2015

Demanding protocol – stringent inclusion/exclusion criteria

Total >1,123 patients screened

29 patients enrolled
19 patients with one acceptable scan
10 patients with two acceptable scans

Total >668 controls screened (over 22k online advertisement views)

18 controls enrolled
13 controls with one acceptable scan
10 controls with two acceptable scans

Naltrexone

- Selection of naltrexone patients after admission to study - open random basis - patients receiving naltrexone had prescription for up to 90 days. Start dose at 50 mg x 3 days then increased 100 mg per day.
- Naltrexone was well-tolerated at 100mg, reported side-effects: some tiredness (encouraged to take at night instead of am) and muscle stiffness, no adverse events related to naltrexone.

Preliminary results

- Naltrexone patients:
  - 13 subjects recruited; 10/12 (83%) remained abstinent at 1 month; 10/12 (83%) also remained abstinent at the 4 month mark.

  (**current Naltrexone publications***)

- Non-medicated patients:
  - 12 subjects recruited; 5/9 (56%) remained abstinent at 1 month

Major issue for recruitment –

MRI safety criteria for high field MRI scanning – tattoos and metal

Brain imaging –

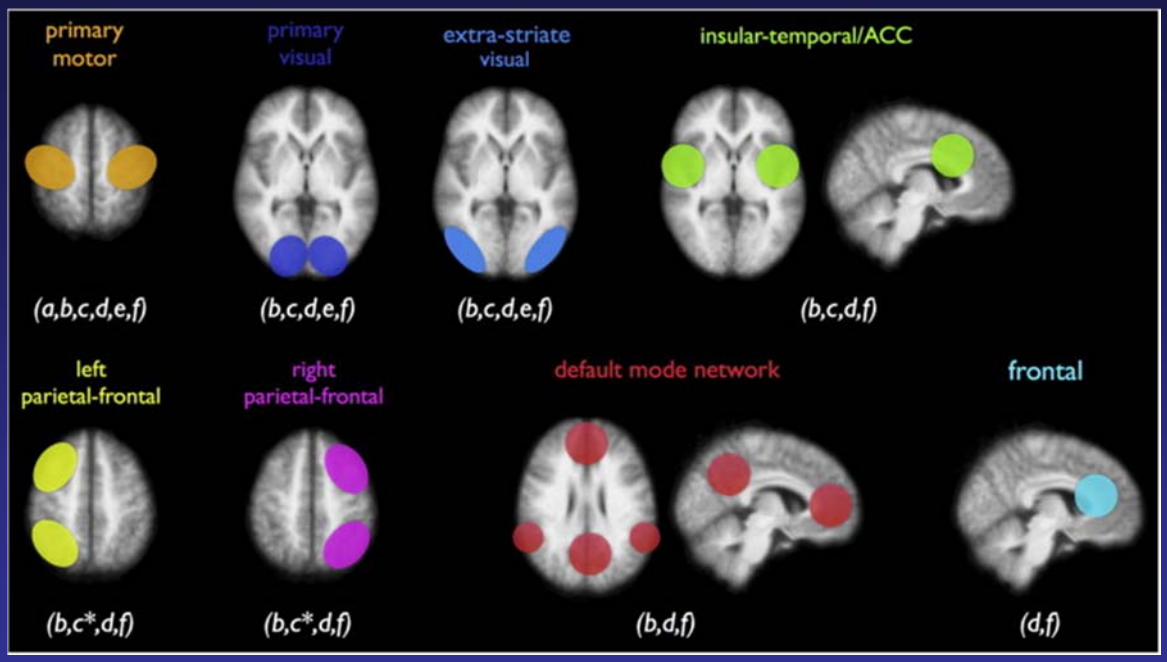
preliminary results

Brain RESTING STATE and DMN

- RESTING STATE (Raichle et al, 2001: recent review Northoff et al, 2010)
- Brain's high intrinsic resting state activity apparently independent of any kind of extrinsic stimuli or tasks – current operational definition approach (eyes open/ eyes closed)
- Recent fMRI and PET studies have revealed high resting state and metabolic activity in a default-mode network (DMN)
- DMN includes predominantly subcortical and cortical midline regions in humans and monkeys and DMN shows strong activity, especially in the resting state

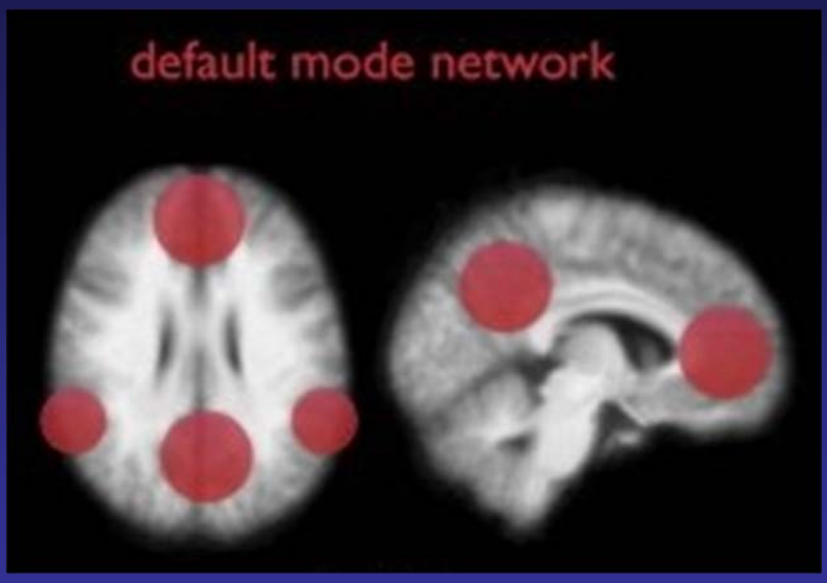
TRANSALC: Edmonton Node Resting State Networks and Abstinence

- Our analyses revealed changes in several resting state networks including:
- Default mode network,
- Frontal network,
- Fronto-parietal network
- In comparison to controls, patients had significant differences in functional connectivity between anterior cingulate cortex and an array of somatosensory, motor, visual, and association regions.



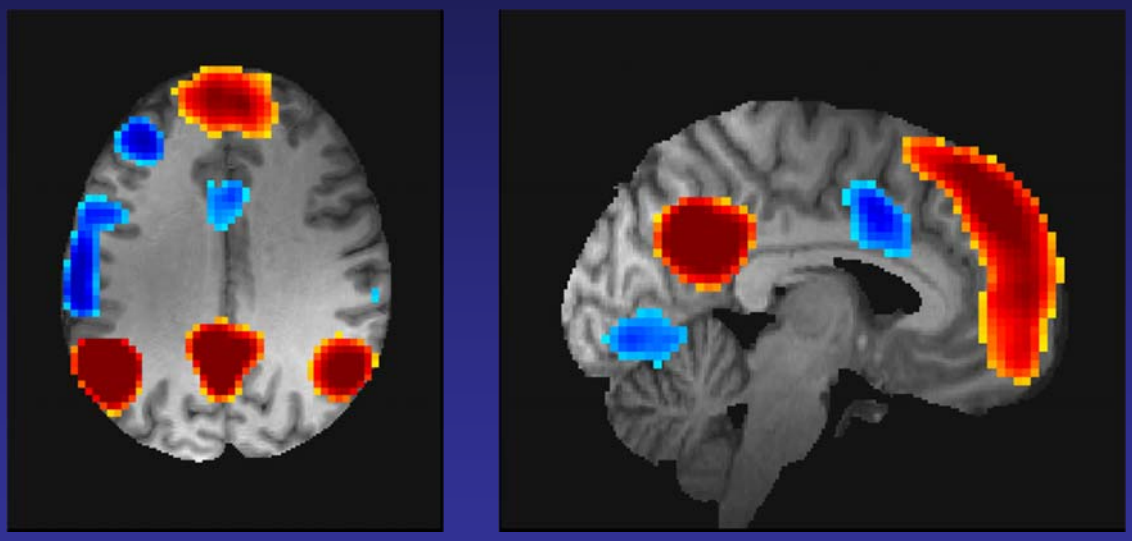
Resting state networks based on results from multiple studies – adapted from Martijn et al (2010) European Neuropsychopharmacology 20: 519 - 534

Default mode network



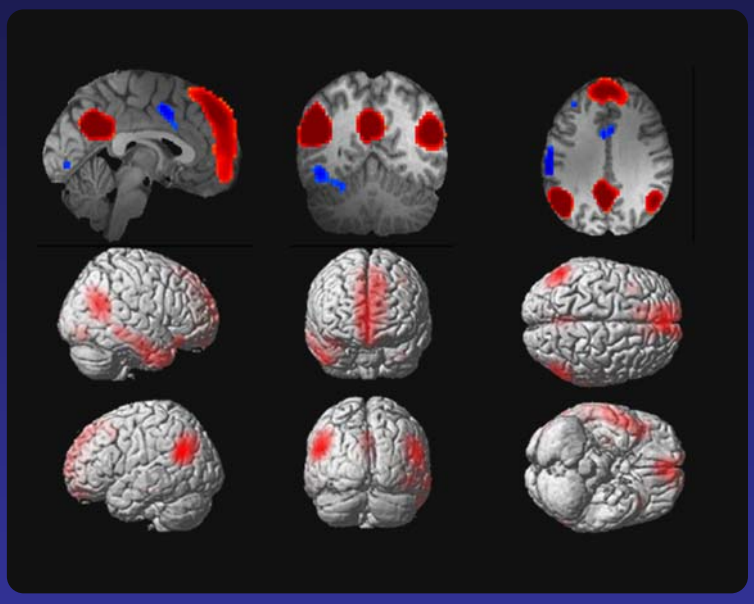
Adapted from Martijn et al (2010) European Neuropsychopharmacology 20: 519 - 534

TRANSALC: Default mode network from ICA



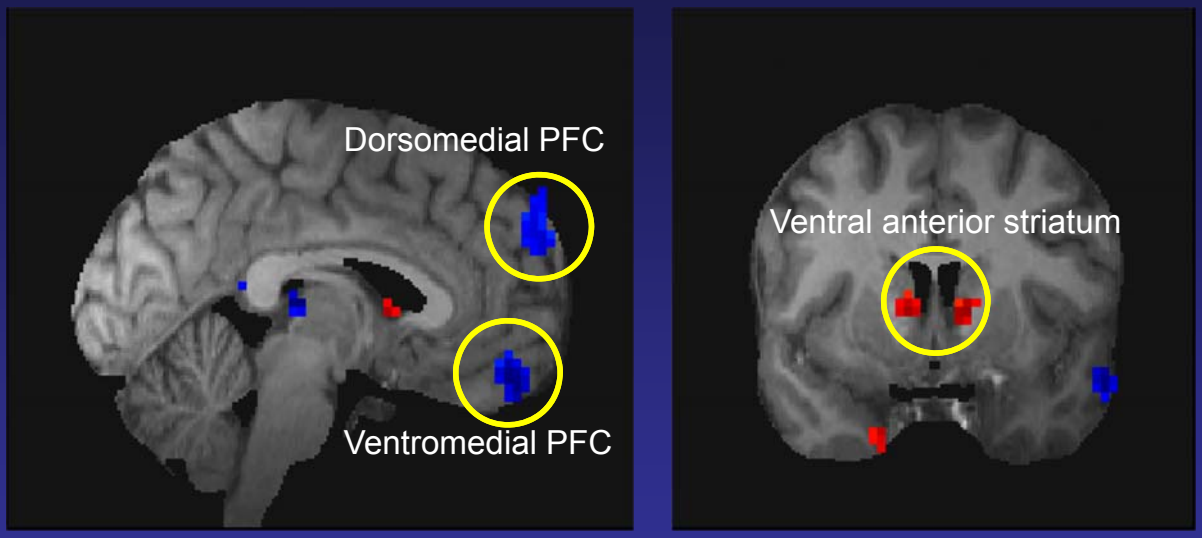
P<0.05 corrected

Default mode network



TRANSALC Edmonton Clinical Node

TRANSALC: Patients vs Controls Scan 1 (6-12 d)

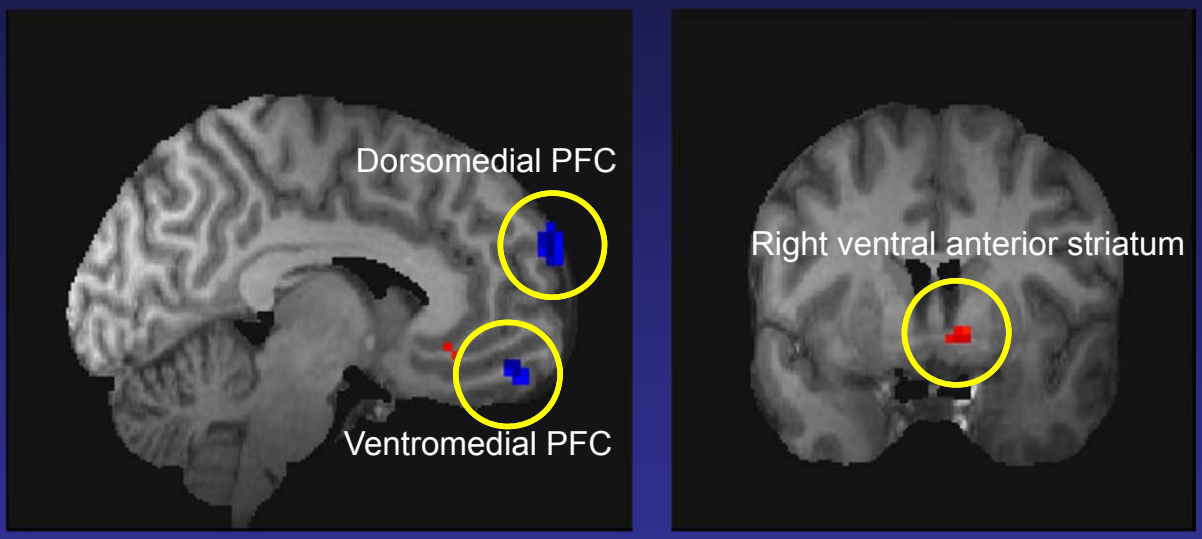


Patients < Controls in blue regions

Patients > Controls in red regions

p<0.05 corrected (10 patients, 12 controls)

TRANSALC: Patients vs Controls Scan 2 (27-33d)

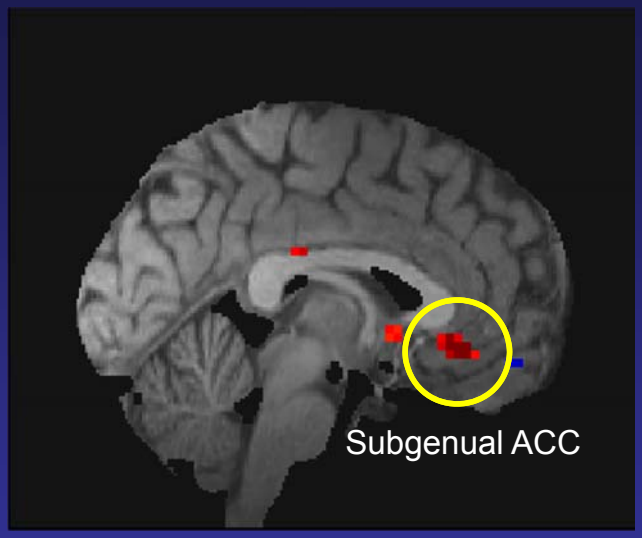


Patients < Controls in blue regions

Patients > Controls in red regions

p<0.05 corrected (10 patients, 12 controls)

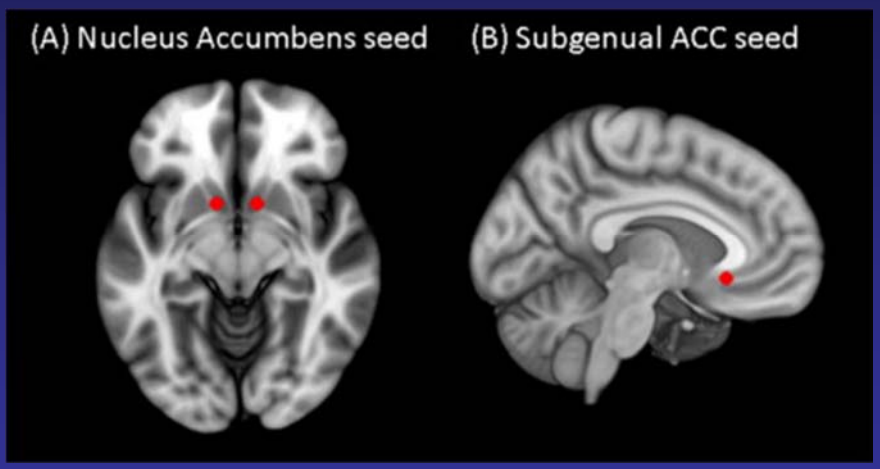
TRANSALC: Patients vs Controls Scan 2 (27-33d)



Patients > Controls in red regions

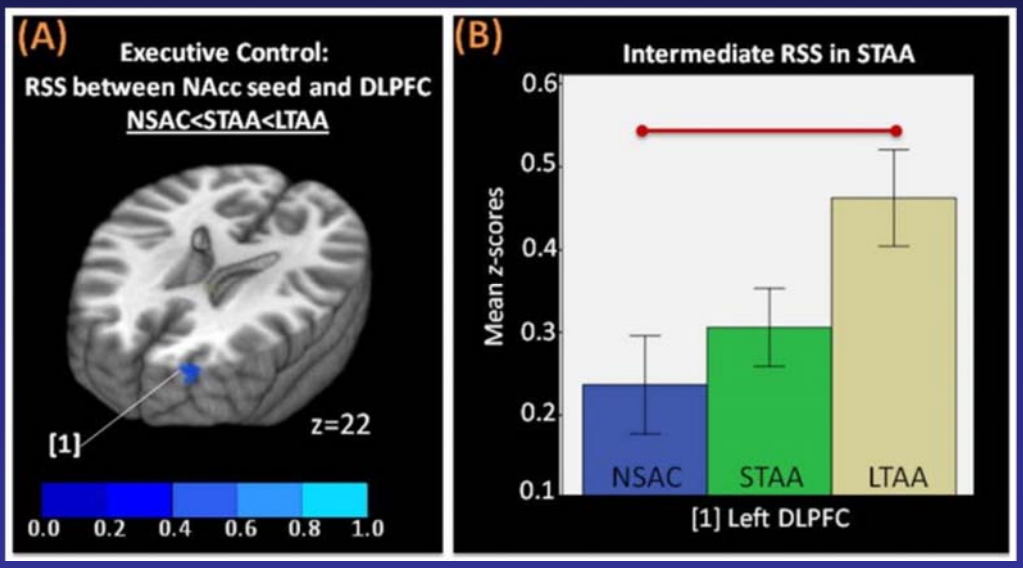
p<0.05 corrected (10 patients, 12 controls)

Nucleus accumbens and subgenual anterior cingulate cortex (ACC) seeds used to examine strength of functional connectivity overlaid on Montreal Neurological Institute (MNI) templates.



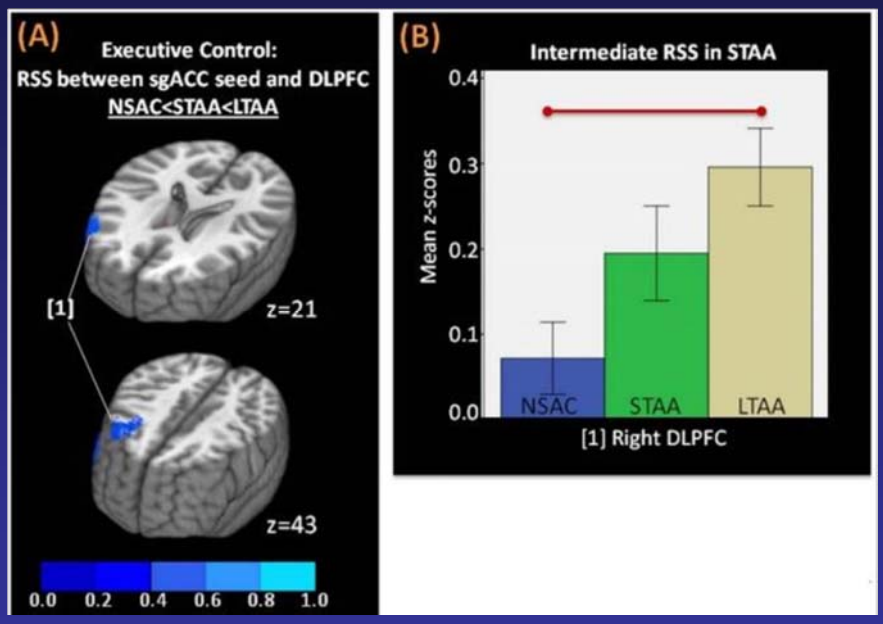
From Camchong et al (2014) Drug and Alcohol Dependence, Volume 139, 2014, 145 - 151

Comparisons of short vs long-term abstinence in alcohol use disorder



From Camchong et al (2013) Alcoholism: Clinical and Experimental Research 37:794-803

Comparisons of short vs long-term abstinence in alcohol use disorder



From Camchong et al (2013) Alcoholism: Clinical and Experimental Research 37:794-803

Comparing network connections may be a useful new approach to analysis (Lehman et al, 2014)

- Resource allocation index (RAI: a measure of coupling between brain networks) is lower in abstinence compared with satiety states in nicotine addiction.
- Weaker inter-network connectivity (reduced RAI) predicted abstinence-induced cravings to smoke.
- Alterations in coupling of the salience and default mode networks and the inability to disengage from the default mode network may be critical in cognitive/affective alterations that underlie substance dependence

SUMMARY & Key Points

Alcohol Withdrawal and "The Abstinent Brain"

- Recovery from addiction is of extreme interest
- Using fMRI we are measuring changes in Resting State and Brain Circuit connections in withdrawal
- Evidence suggests that the "Abstinent Brain" is a brain in recovery
- It may be useful to focus on brain correlates of RISK and IMPULSIVITY to determine the relationship of these constructs to recovery and sustained abstinence.

THANK YOU 謝謝

Lake Louise, Alberta, Canada

Dr. Yang is Assistant Professor of Psychiatry at Yale University School of Medicine. She was born in Taipei, and growing up in the central part of Taiwan. After finishing her college degree on psychology at Chung-Yuan University in Taiwan, she pursued her graduate study on Biometry and Statistics at University of Albany, State University of New York. Upon obtaining her doctoral degree, she took a postdoctoral fellowship at Yale University, Department of Psychiatry, Division of Human Genetics, for research training on psychiatric genetics under Professor Joel Gelernter. She is a five-year NIDA K01 mentored career award recipient on investigation of genetic basis of substance use disorders comorbid with depression and training on human molecular genetics. She also won the Young Investigator Award from the Brain and Behavior Research Foundation for investigating the genetic basis of cocaine dependence comorbid with depression. Her research focus has been on the genetic basis of complex traits, endophenotypes and epigenetics in response to environmental factors, particularly, for addictive diseases and their co-occurring affective disorders. In the last two years, she also has been learning to conduct brain image study and extended her research to image genetics in hope to map genetic basis of addiction and its related psychiatric disorders to discover brain mechanisms in these disorders.#

GABAergic Genetic Investigations into Impaired Inhibitory Control in Cocaine Dependence

World Psychiatric Association International Congress
November 18-22, 2015 Taipei

Bao-Zhu Yang
Division of Human Genetics
Department of Human Genetics

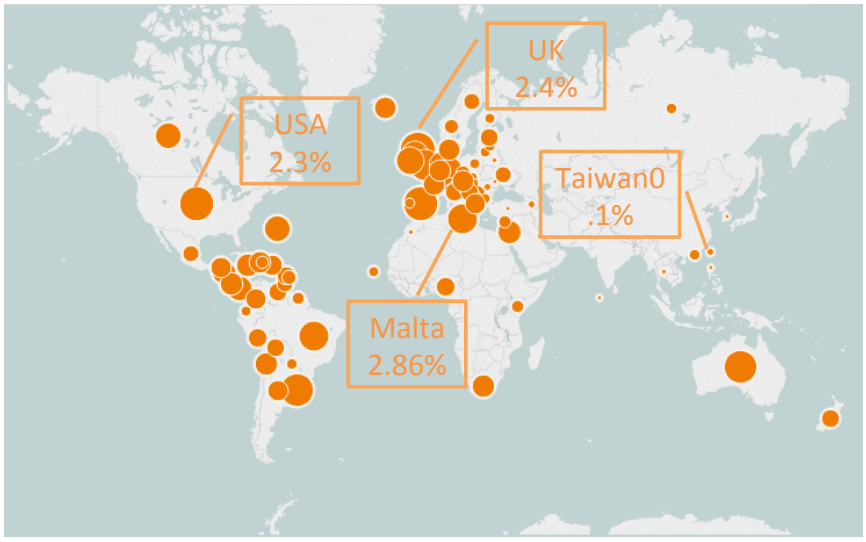
U.S. is one of the world's largest consumers of cocaine

Cocaine is the 2nd most common illicit drug in the US.

In 2013, the number of current users aged 12 or older was 1.5 million (Drug Fact, NIDA).

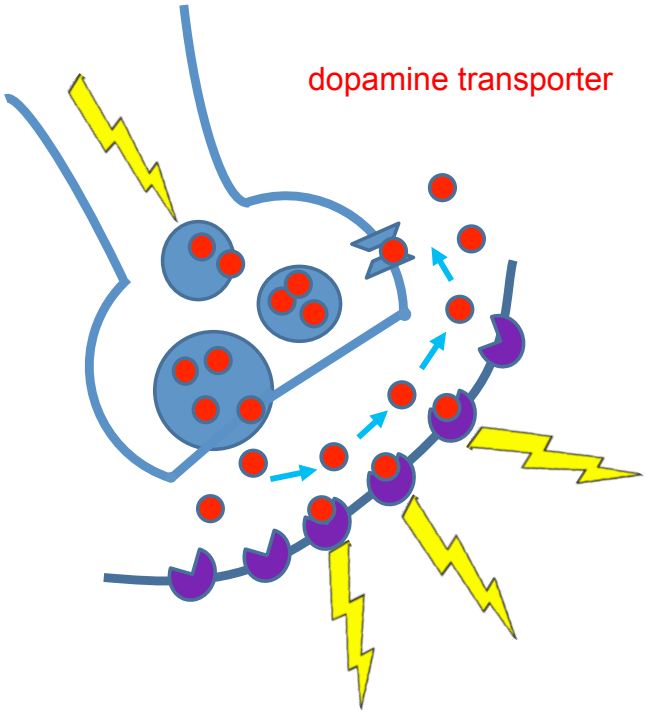
World Drug Report 2014
Cocaine

Population prevalence of cocaine use



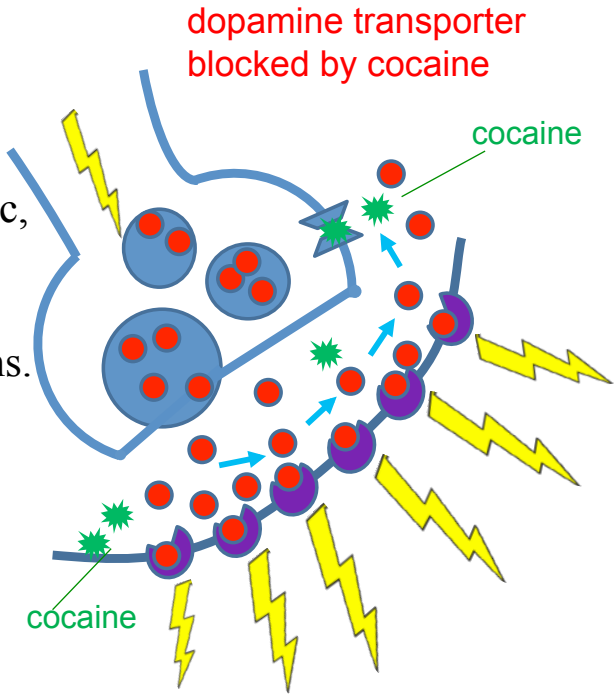
http://www.unodc.org/wdr2014/en/interactive-map.html

Synaptic Transmission



Cocaine Action on the Synaptic Transmission

Major effects: Euphoric, energetic, deep and unusual thoughts, perceived inspiration and novelty, enhances sex, dancing, music, art, touch & senses. Contentment. Connection to other people, strong emotions.

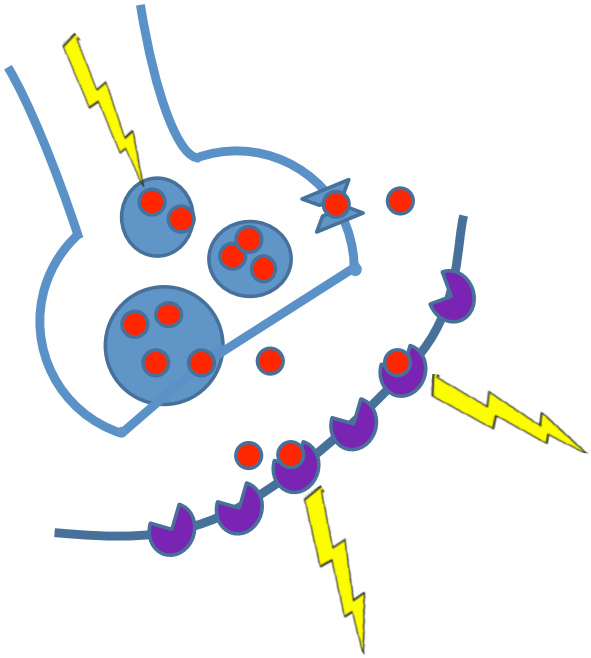


Cocaine blocks

- **DAT**
- **SERT**
- **NET**

Cocaine Action on the Synaptic Transmission

Sides effects: Anxiety, paranoia, psychosis, high blood pressure, acute myocardial infarction, stroke etc.



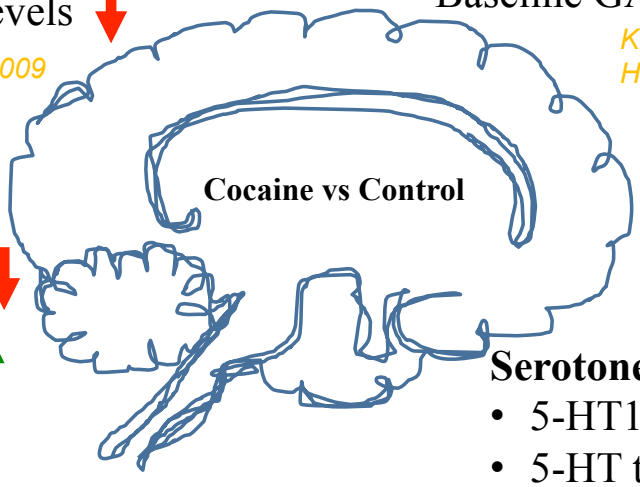
Neurochemical differences in the brain of cocaine dependence subject

Glutamatergic System
- Glutamate levels ↓

Yang S et al. 2009

GABAergic System
- Baseline GABA levels ↓

Ke et al. 2004
Hetherington et al. 2000



Dopaminergic System
- D2 receptor ↓
- Dopamine transporter ↑
- VMAT2 ↓

Volkow et al. 1990, 1993, 1997
Malison et al. 1998
Narendran et al. 2012

Serotonergic System
- 5-HT1B receptor ↓
- 5-HT transporter ↑
- Extracellular 5-HT ↑

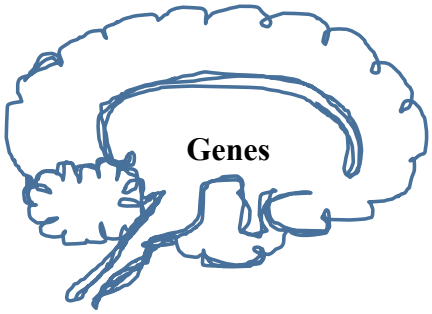
Matuskey et al. 2014
Jacobsen et al. 2000; Little et al. 1996;

GABAERGIC GENETIC INVESTIGATIONS INTO IMPAIRED INHIBITORY CONTROL IN COCAINE DEPENDENCE

Why GABA?

- Why GABA?

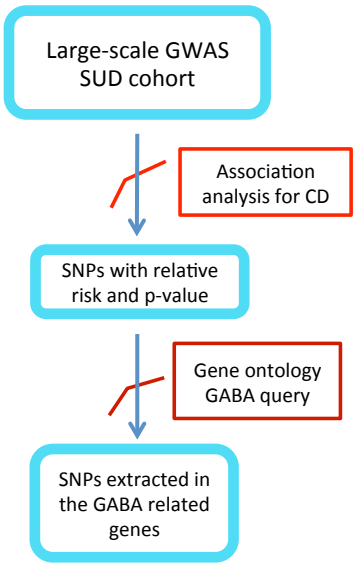
Roles of Genes in Neurotransmitter Systems in the Brain of Cocaine Dependence Subject



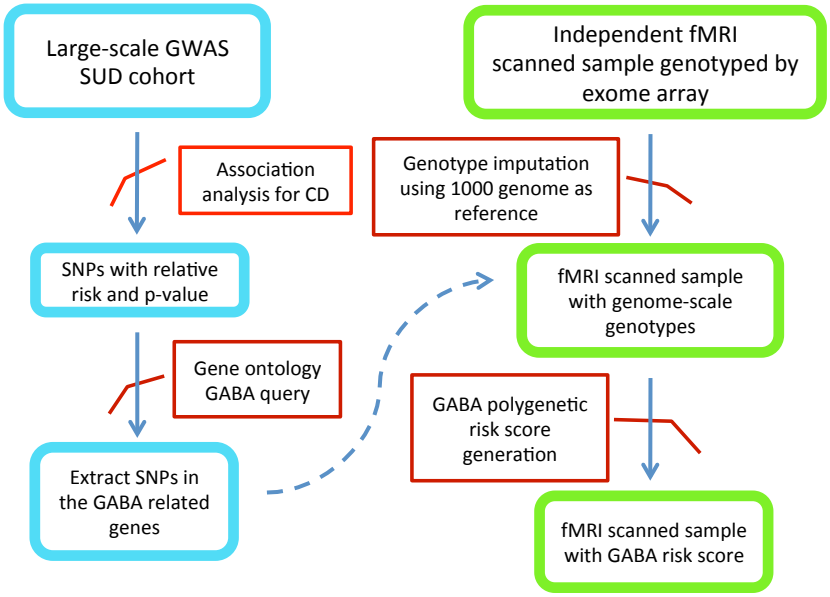
GABAergic System
Glutamatergic System
Dopaminergic System
Norepinephrinergic System
Serotonergic System

- Genes encode all these Neurotransmitter systems.
- What brain regions do the genetic risk of CD impact on?

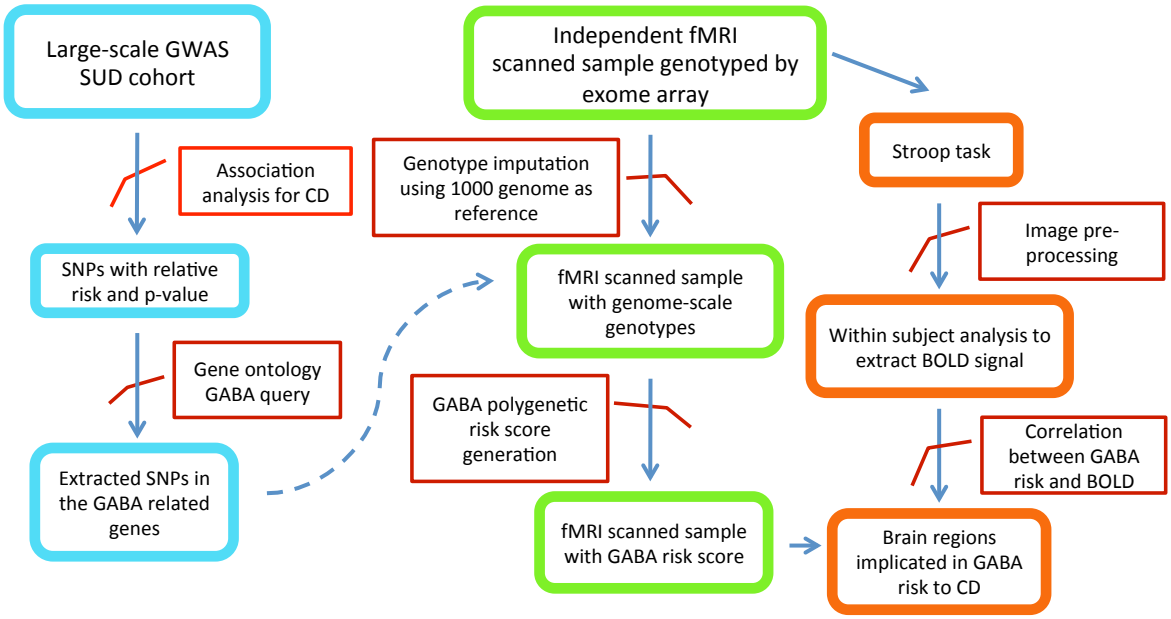
Study Design and Analytical Approaches



Study Design and Analytical Approaches



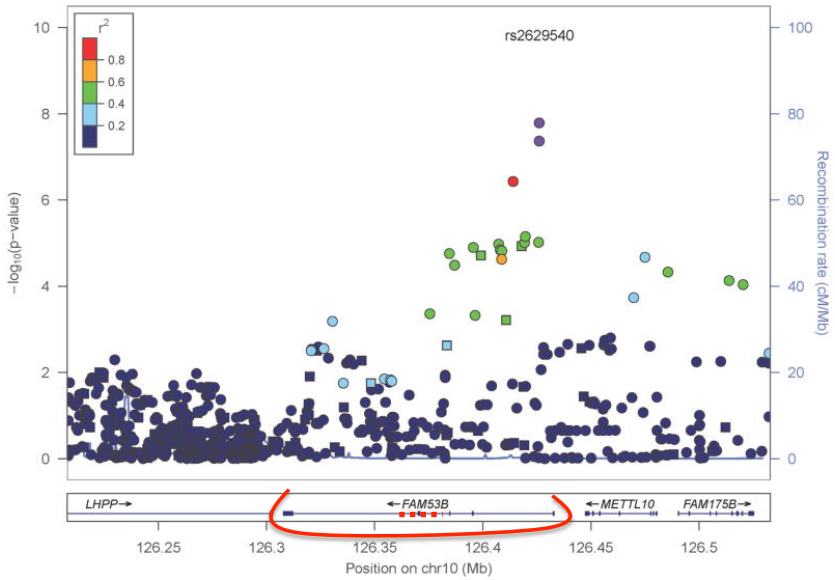
Study Design and Analytical Approaches



Heritability, the first check!

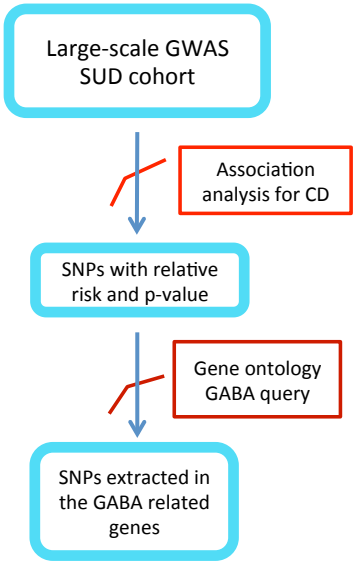
- Heritability estimates for **cocaine** use disorders range from 42 to 79%, with the lower estimates reported for females. (Kendler et al. 2000; Tsuang et al. 2001; van den Bree et al. 1998)

GWAS on Cocaine Dependence



Gelernter et al. Mol. Psychiatry 2014

LARGE-SCALE GWAS SUBSTANCE DEPENDENCE COHORT



Genetics of Cocaine & Opioid Dependence

- *NIDA-funded studies starting with affected sibling pair linkage, and continuing with case-control association*
- Yale – Gelernter (PI), Zhao
- Univ. Pennsylvania – Kranzler (co-PI)
- Boston University – Farrer
- Univ. PA – Oslin
- Southwest Foundation -- Almasy
- McLean Hospital – Weiss
- Medical Univ. South Carolina – Brady

> 12,000 SSADDA-assessed subjects ascertained

- What is SSADDA?
- Semi-Structure Assessment for Drug Dependence and Alcoholism

-Very detailed assessment
-3500 items (most people skip out of a majority of them)
-Strong coverage of major psychiatric diagnoses plus environmental factors

SSADDA assessment reliability (κ coefficients)

Diagnosis	Total Sample (n= 294)	Test-Retest Reliability (n=120)	Inter-Rater Reliability (n=174)
Nicotine Dependence	.843	.950	.769
Alcohol Dependence	.744	.870	.662
Cocaine Dependence	.864	.916	.828
Opioid Dependence	.920	.935	.910

SSADDA Training in Taipei

Dates: 12/04 (Friday) to 12/06 (Sunday), 2015

Location: 台北市立聯合醫院仁愛院區8F
臨床訓練與研究中心

Contact:

– 基隆長庚 精神科 陳怡婷小姐
– **02-2432-9292 ext.2725**
– **joycechen1018@gmail.com**

Substance Dependence GWAS

Illumina Omni-Quad microarray
Genotyping split between CIDR
and the Yale Keck center

GWASed Sample
Total n ~5600

Substance	AA	EA
CD cases controls (exposed, unexposed)	2474 799 (186, 613)	1813 486 (291, 195)

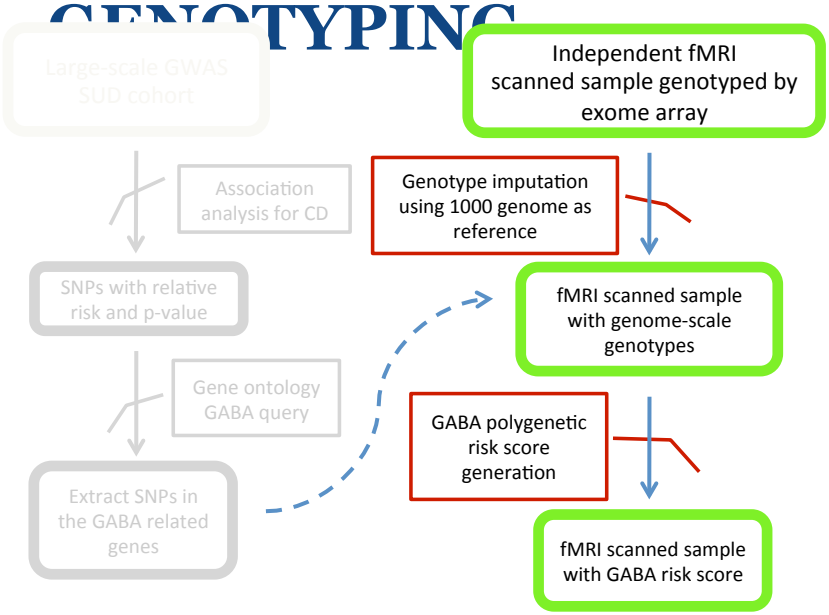
Genes in GABAergic Pathways

- GABA related genes involved in coding GABA receptors, GABA neurotransmitters and the GABAergic pathways were retrieved from AmiGO2.
- A total of 101 entities were retrieved from search of Gene and Gene Product for the taxon of Homo Sapiens.
- 43 unique genes were identified and encode 155 regions of isoforms.

Association Analysis of CD for AA

- Model: logit (CD/non-CD)=age+sex+3PCs +SNP+4SDs
- 89 SNPs out of 3009 SNPs (43 genes) involved in the GABAergic pathways past p-value cut-off of 0.005 and allocated in 16 genes:
  - PRKCE PLCL1 NLGN1 USP46 LHX6 SLC6A13 CNTNAP4 NLGN2 NF1 ADORA2A GABRG1 GABRB1 GABRA1 GABRP GABARAPL1 GABRB3

INDEPENDENT FMRIED SAMPLE WITH EXOME ARRAY GENOTYPING



fMRIed Study Subjects

- **fMRI scanned African American subjects genotyped using the Illumina Exome array**

	N	Mean Age (yrs)	Sex (M/F)	% Male
Cocaine Dependence (CD)	44	43.5	29M/15F	65.9
Healthy Comparison (HC)	23	31.9	9M/14F	39.1
Total	67	39.5	38M/29F	56.7

Genotype Imputation for the fMRIed subjects

- The GWASed AA sample was combined with the fMRI scanned subjects for imputation.
- 1000 Genomes (released in June 2014) was used as reference.
- Post imputation filtering criteria includes MAF>1% and certainty score >= 0.9.

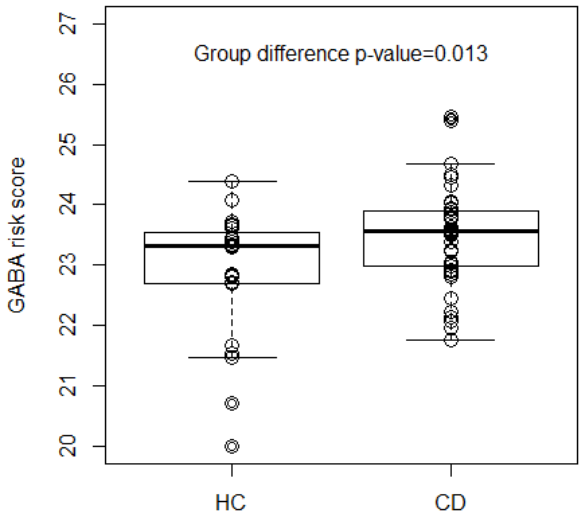
SNP Identification

- A total of 61,114 SNPs were detected in the imputed sample among the 155 regions.
  - *MAF > 1%*
  - *Imputation certainty >= 0.9*
  - *Linkage equilibrium-based SNP pruning*
  - *3,309 SNPs passed the pruning for further analysis.*

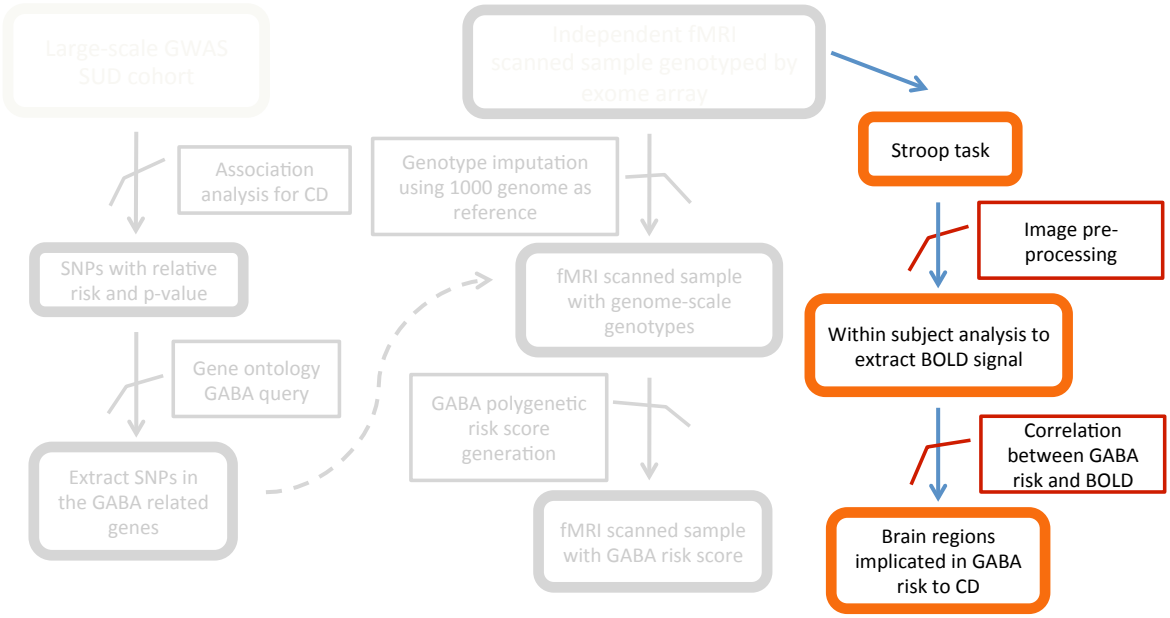
Polygenic Risk Score Calculation

- Use PLINK to calculate the risk score
- Input files
  - The relative risk of each SNP was from the AA GWASed analysis.
  - The genotypes of the 67 fMRI scanned subjects
- The risk score was multiplied by 100.

GABA Polygenic Risk Score differs between CD versus HC



INDEPENDENT FMRI SCANNED SAMPLE IMAGE ANALYSIS



Stroop Task Implementation

- Frequently used word-color interference test.
- Involves frequent presentation of matched color-word pairs and infrequent mismatched color-word pairs during fMRI.
- Subjects are instructed in all cases to name silently the color rather than read the word.

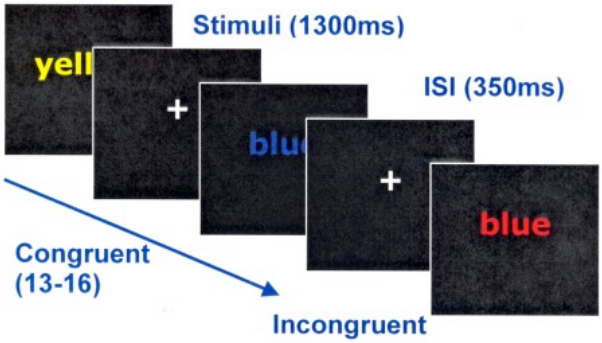


Image Acquisition

- Images were obtained using a 3-T Siemens Trio MRI system.
- Anatomical images of the functional slice locations were obtained with spin-echo imaging in the axial plane parallel to the AC -PC line.
- Functional, blood-oxygen-level-dependent (BOLD) signals were then acquired with a single-shot gradient echo-planar-imaging (EPI) sequence.

Image Pre-processing

- Images pre-processing included:
  - *Motion correction*
  - *Slice timing correction*
  - *Spatial and temporal filtering*
  - *Intensity normalization*
- Five subjects failed to pass the the preprocessing, and were excluded from further analysis.

Image Data Analysis

- Incongruent > congruent was acquired

- "Incongruent > congruent" was used to correlate with the polygenic GABA risk score of CD.

- Age was controlled as a covariate.

RESULTS

Iris Balodis, PhD

Hedy Kober, PhD

Marc Potenza, MD, PhD

Joel Gelernter, MD

- *Funding was provided by NIDA grant K01 DA24758 (Yang) , and NARSAD Young Investigator award (Yang).*

- R01 DA019039, R01 DA12849, R01 DA012690, P20 DA027844, R01 DA020908, R01 DA035058, P50 DA09241, the CT State Department of Mental Health and Addictions Services/CMHC, an unrestricted research gift from the Mohegan Sun casino.

Prof. San-Yuan Huang

Prof. **San-Yuan Huang** graduated in medicine at the National Defense Medical Center, Taipei, Taiwan, ROC. He completed his psychiatry residency at Tri-Service General Hospital, Taipei, Taiwan. After psychiatry resident training, Dr. Huang received his Ph.D. degree also from the National Defense Medical Center. His academic research focuses on gene-gene, and gene-behavior-environment interaction in substance use disorders such as alcohol dependence, depressive alcoholism and other illegal drug abuse. After Ph.D. degree, he main academic interests/ research are in gene, brain image with SPECT and PET, psycho-immunology in addiction and mental related disorder.

Currently Dr. Huang is the president of Taiwanese society of addiction science (TSAS). He is also a professor in Psychiatry at National Defense Medical Center, and the Director of the Department of Psychiatry at the Tri-Service General Hospital. He is active in addiction services, particularly in the rehabilitation of addictive patients and promotion of mental health in the addiction.

Prof. Huang has published more than one hundred and ten original paper, and he serves on various journal/ and grant review committees including NSC/ MOD, NHRI and NRPB….. research study sections.

黃三原 近一年代表著作

SCI (Original article, First or corespondance, SCI only)

1. Chang CC, Chang HA,.. ***Huang SY (correspondence)** Functional Ser205Leu polymorphism of the nerve growth factor receptor (NGFR) gene is associated with vagal autonomic dysregulation in humans Sci Aug. 2015 Sep.
2. Yen CH, Yeh YW, Liang CS, Ho PS, …..Lu RB, ***Huang SY (correspondence)** Reduced dopamine transporter availability and neurocognitive deficits in male patients with alcohol dependence. PLoS One. 2015 Jun 29;10(6):e0131017
3. Yeh YW, Ho PS, Chen CY,…..Lu RB, ***Huang SY (correspondence)** Suicidal ideation modulates the reduction in serotonin transporter availability in male military conscripts with major depression: a 4-[18F]-ADAM PET study. World J Biol Psychiatry. 2015 Jun 12:1-11. (**2013 Impact factor: 4.225; 26/134 on psychiatry)**

4. Yeh YW, Kuo SC, Chen CY,…..Lu RB, ***Huang SY (correspondence)** Harm avoidance involved in mediating the association between nerve growth factor (NGF) gene polymorphisms and antidepressant efficacy in patients with major depressive disorder J Affect Disord. J Affect Disord. 2015 May 15;183:187-194
5. Chang HA, Chang CC, Kuo TB, ***Huang SY (correspondence)** Distinguishing bipolar II depression from unipolar major depressive disorder: Differences in heart rate variability. World J Biol Psychiatry. 2015 Mar 24:1-10. (**2013 Impact factor: 4.225; 26/134 on psychiatry)**
6. Tzeng NS, Lu RB, Yeh HW, Yeh YW, Huang CC, Yen CH**,** Kuo SC, Chen CY,, , Chang HA, Ho PS, Cheng S, Shih MC, ***Huang SY (correspondence)** The dopamine transporter gene may not contribute to susceptibility and the specific personality traits of amphetamine dependence. Drug and Alcohol Dependence 2015 Apr 1;149:100-7. (**2013 Impact factor: 3.23; 4/18 on substance abuse)**
7. Yeh YW, Ho PS, Kuo SC,….., ***Huang SY (correspondence)** Disproportional reduction of serotonin transporter may predict the response and adherence to antidepressants in patients with major depressive disorder: a positron emission tomography study with 4-[18F]-ADAM. Int J Neuropsychopharmacol. 2015 Jan 18 (7) 1-12 (2014-12 accepted) (**2013 Impact factor: 5.264; 18/134 on Psychiatry)**
8. Huang CC, Lu RB, Yen CH, ……. Shih MC, ***Huang SY (correspondence)** Dopamine transporter gene may be associated with bipolar disorder and its personality traits. Eur Arch Psychiatry Clin Neurosci. 2015 Jun;265(4):281-90 (**2013 Impact factor: 3.355; 39/134 on Psychiatry)**
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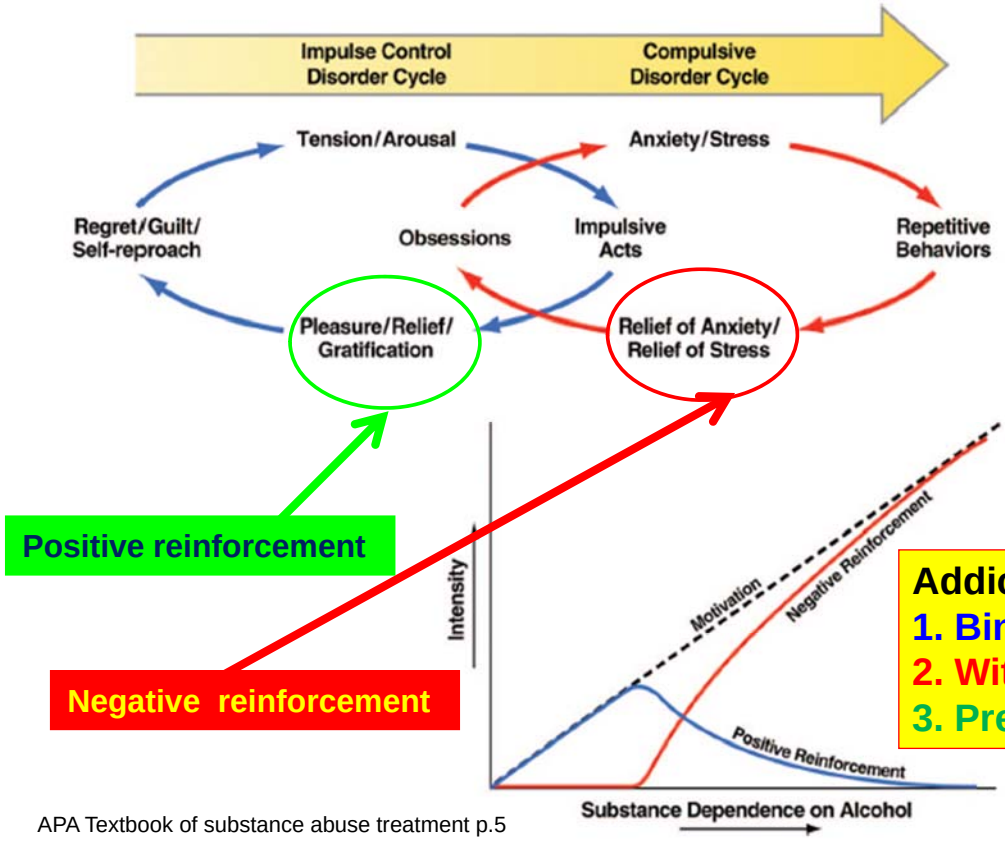
The Role of Dopamine transporter in cognitive function and alcoholism

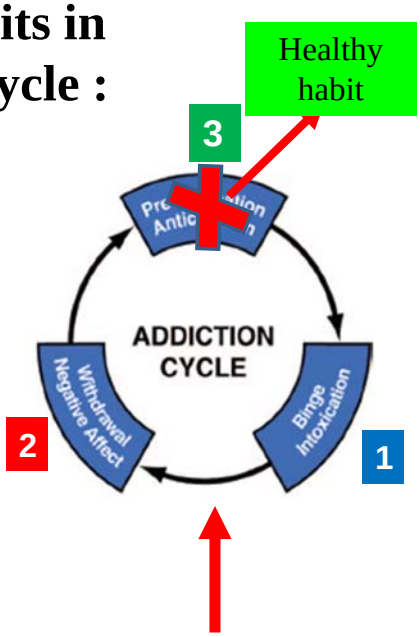
台灣成癮科學學會
TAIWANESE SOCIETY OF ADDICTION SCIENCE

Dr. San-Yuan Huang

Prof. and president of TSAS
National Defense Medical Center
Tri-Service General Hospital

Drug addiction represents a composite of deficits in impulsivity and compulsivity in a three stage cycle :





Addiction cycle :
1. Binge/ intoxication
2. Withdrawal/ negative affect
3. Preoccupation/ anticipation

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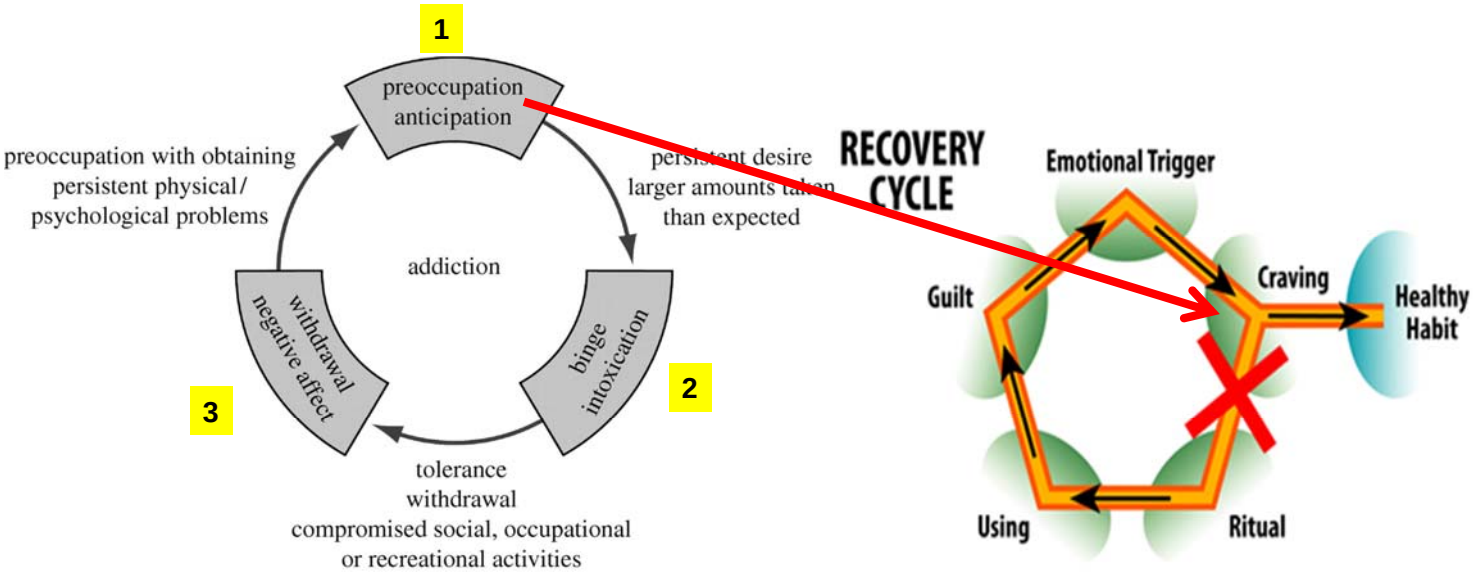
Neurobiologuy of addiction; Koob. 2011 Focus

Drug addiction represents a composite of deficits in impulsivity and compulsivity in a three stage cycle :



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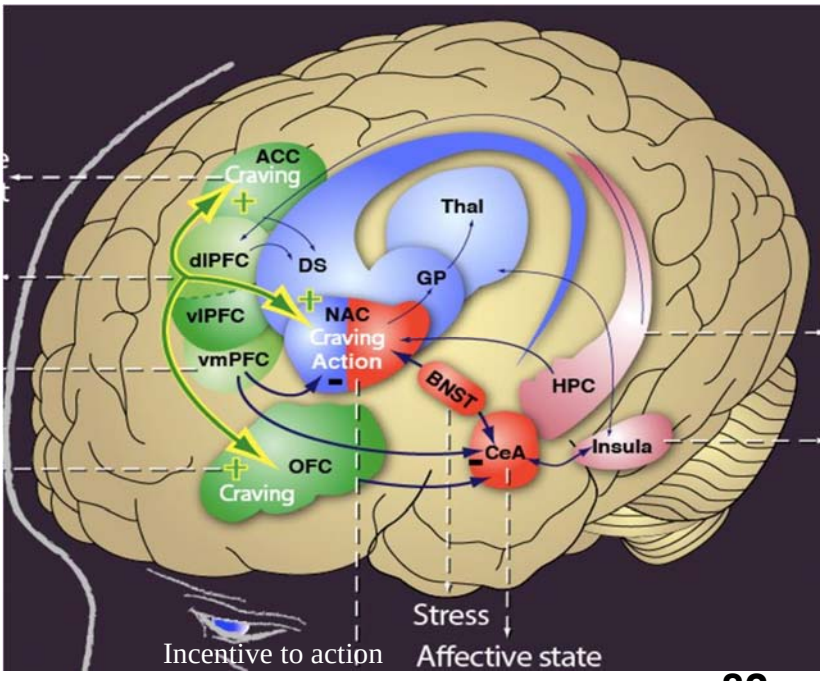
Binge/ intoxication

Acute reinforcing effect of drug

Euphoria, reward

1. ventral striatum (VS), including neucleus accumbens :
2. Dorsal striatum (DS) : habits perseveration
3. Global pallidus (GP) : habits perseveration
4. Thalamus (Thal) : habits perseveration

Habit-like drug seeking behavior : striatal-pallidal-thalamic cortical loops



Withdrawal/ negative affect

1. Amygdala (**AMG**), bed nucleus of the stria terminalis (**BNST**), together also known as extended amygdala
2. Ventral striatum (VS):

Decreased reward

Anxiety, dysphoria, negative emotional states, and malaise

Preoccupation/ anticipation

1. Anterior cingulate (**AC**)
2. Prefrontal cortex (mPFC), orbitofrontal cortex (**OFC**)
3. Balsolateral nucleus of amygdala
4. Hippocampus (**Hippo**)

Craving and executive function

Conditioned contextual cues

Basic Mechanisms of Alcohol action (1)

- Alcohol **dose not have a unique molecular target** in the nervous system (no specific neurotransmitter receptor or transporter).

- Because **no high affinity target** for alcohol, **the action of alcohol on the brain** were caused through effects on **nerve cell membranes**.

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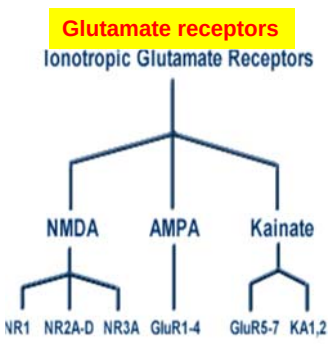
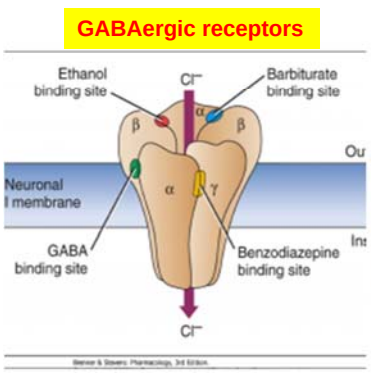
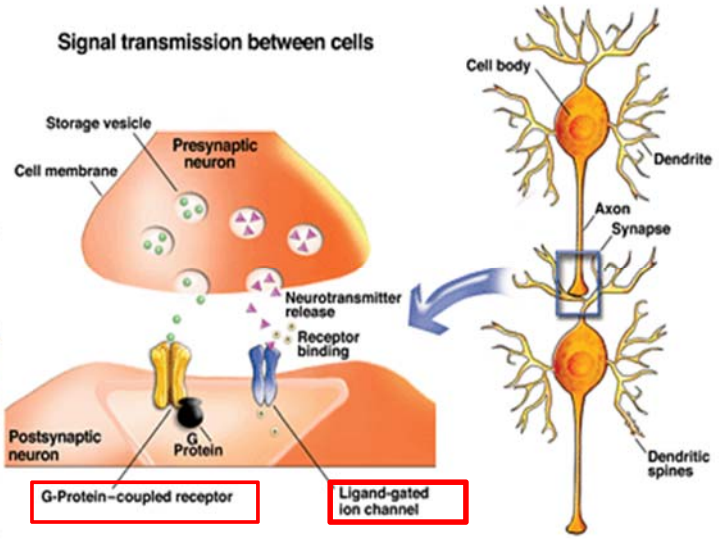
Ligand- gated ion channels

- **Three key mediators of acute alcohol effects:**
- Glutamatergic receptors
- GABAergic receptors
- Glycine receptors







Ligand- gated ion channels

- **Alcohol acutely dampens glutamatergic** transmission by **decreasing** the ion flux through the **NMDA receptor** upon its activation.
- It also potentiates **GABA** transmission, by **increasing** the **chloride flux** through **$GABA_A$ receptors** when these are activated, and probably also by **increasing** presynaptic **GABA release**.

Basic Mechanisms of Alcohol action (2)

- Reward effects of addictive drug : including the **dopamine**, **endorphin**, and **endocannabinoid systems**.
- Alcohol induced endorphins release in **VTA**, **NAc** and **prefrontal cortex**. Endorphin remove inhibitory tone from the dopamine cells $\rightarrow$ DA release in the NAc
- Alcohol induced **dopamine release** in NAc.

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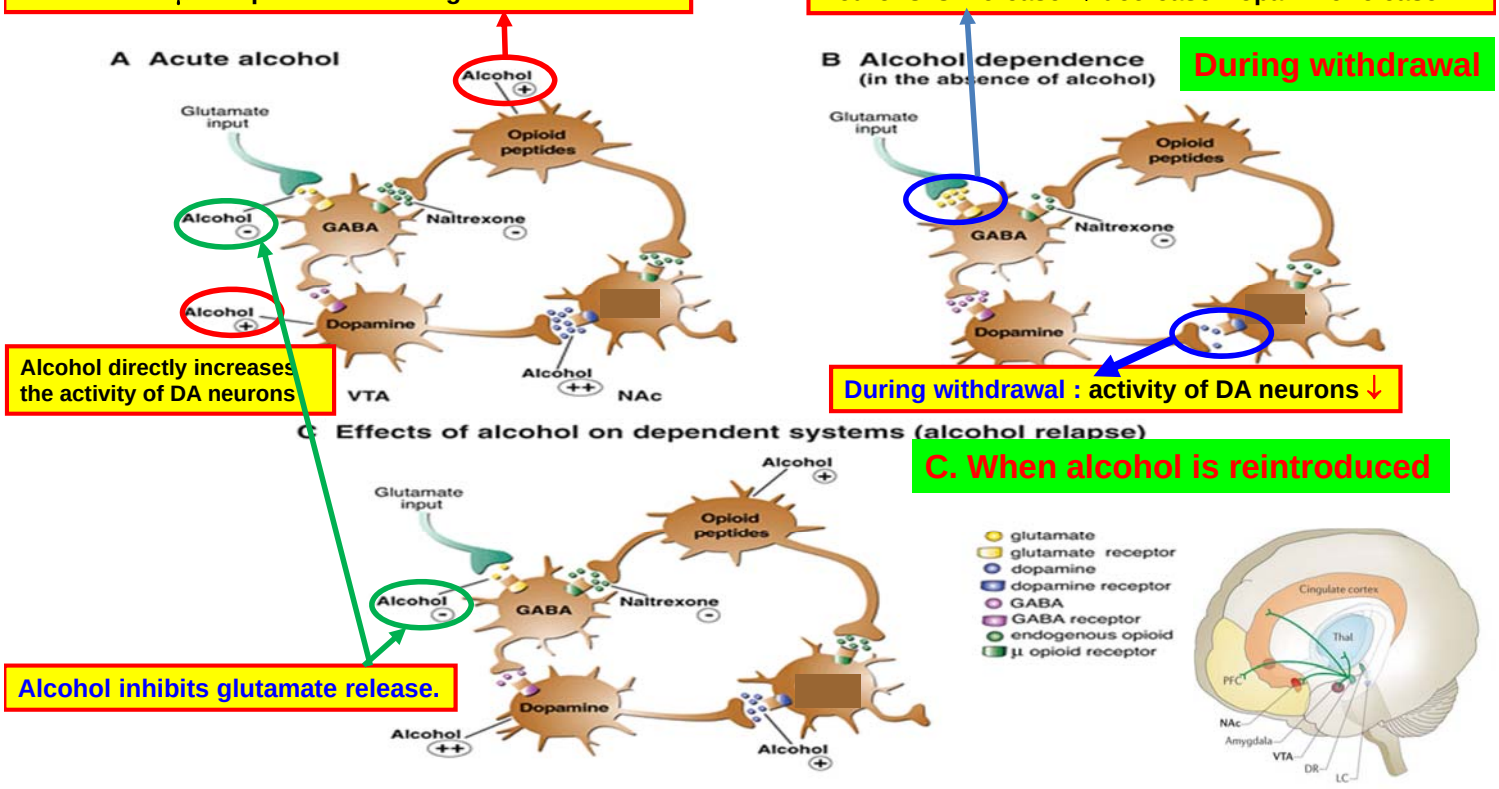
Alcohol can induced β-endorphin release, resulting in activation of μ-receptor on GABAergic neurons in VTA

During withdrawal : ↑ active glutamate input to GABA neurons is increase → decrease Dopamine release



Alcohol directly increases the activity of DA neurons

During withdrawal : activity of DA neurons ↓

Alcohol inhibits glutamate release.

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Complex action of alcohol

- Genetics of addiction: heritability of alcoholism is in the **50%-60%** range (Goldman et a. 1995)
- **Low Sedative-ataxic response to alcohol** is a phenotypic marker of genetic alcoholism risk. – blood alcohol level (BAL)
- **High sensitivity** to CNS depressant effects of alcohol :

  low risk for development of alcoholism.
- **Low sensitivity** to depressant alcohol actions are clearly able to consume large amounts of the alcohol. (**high risk**)
- **High comorbid anxiety/ depression.**

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Individual variation in alcohol reward

- Individual variation influences alcohol action e.g. sedative-ataxic, reward, psychomotor stimulant effects.

1. The **men** have a markedly more pronounced accumbal dopamine response to alcohol than do **women**. (reflected in different prevalence rate for alcohol use disorder.
2. **FH(+):** more pronounced rewarding and stimulant-like response to alcohol.
3. Individuals with FH are preferentially sensitive to rewarding and stimulant-like alcohol actions by the **μ-Opioid antagonist naltrexone**

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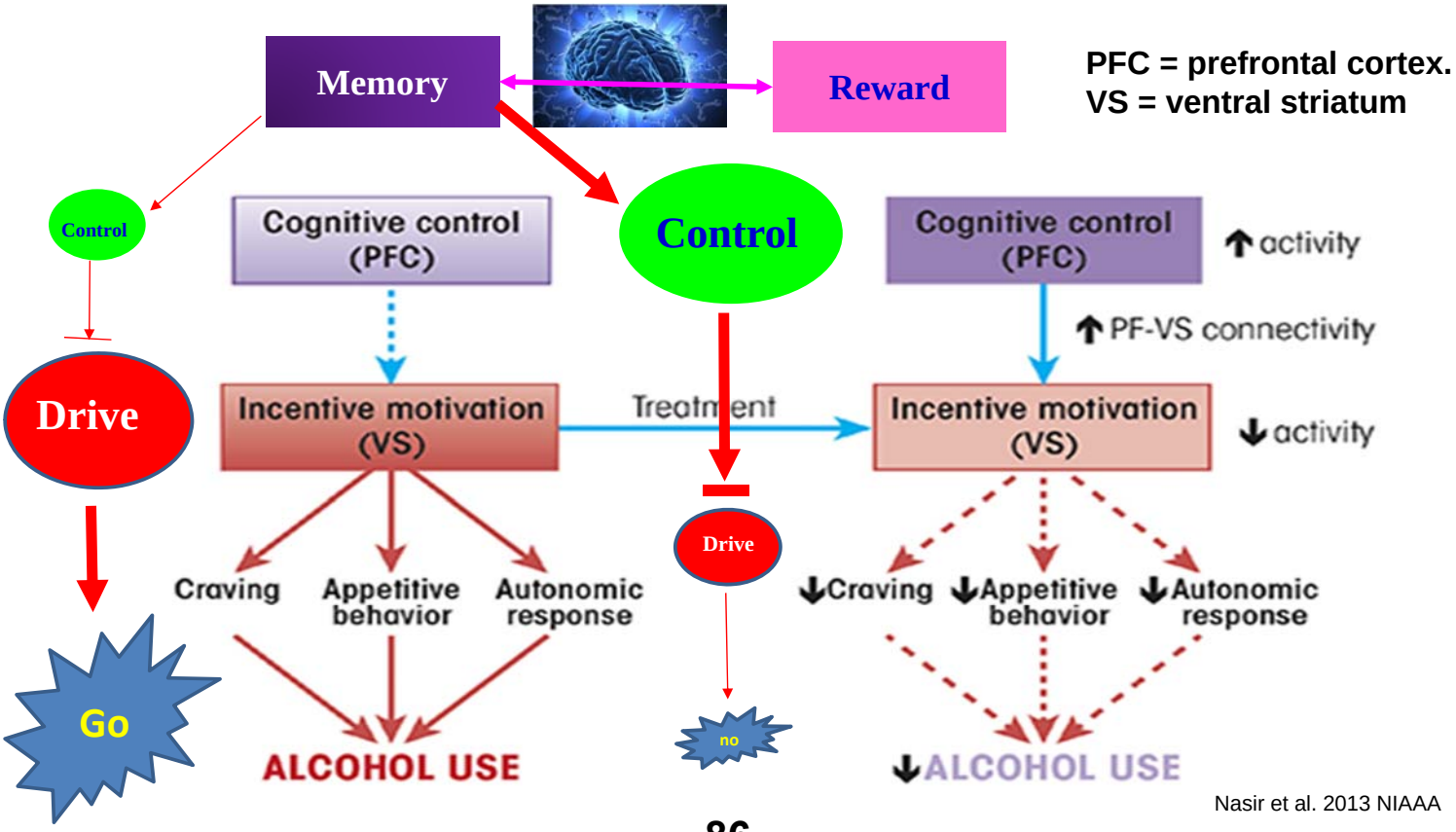
Effective treatments for AUD serve to increase prefrontal cortex function and down modulate the function of reward systems



Nasir et al. 2013 NIAAA

Study design

- **Group :**
  - Placebo group
  - Memantine 20 mg group
- **Target number** of patients: 60-90; Health controls: 30
  Placebo: Memantine =1:1
- **Study institutions**
  - Taiwan: one site - TSGH
- **Study period**
  - 1 August 2012 to 30 June 2015

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Study objective and primary endpoint

Main objective

- To evaluate the **role of DAT availability** **in the Tx. course of AD patients.**
- **Whether the memantine have neuroplasticity effect** ：Evaluate the availability of brain DAT in different treatment state (pre-treatment and post-treatment).
- **To evaluate the efficacy of Memantine** in patients with Alcohol dependence (Frequency/quantity of drinking amount)

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Study secondary endpoints:

1. **The cognitive function in AD's patients :** we used **WCST** and **TMT** for evaluate subject's cognitive function.
2. **The impulsivity in AD's patients :** we used BIS
3. **The role of pro-inflammatory factors in patient with AD (before and after follow).**

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TSGH

Healthy subject (n=30)

Alcohol subjects n=40-50 (Memantine group)

Alcohol subjects n=40 (Placebo group)

(DSM-IV criteria)

^{99m}Tc -TRODAT-1 (185MBq)

3D mode SPET scanner
Static image: 4 hours

Healthy subject (n=30)

Imaging analysis
(Target :Striatum, Caudate, Putumen, occipital lobes)

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Preliminary Results

1. Cognitive function in patient with AD.
2. **Impulsivity** in patient with AD. (Barratt Impulsiveness Scale, BIS-11)
3. DAT availability in patient with AD.
4. Pro- inflammatory factory in patient with AD.
5. The relationship between cognitive function and DAT availability

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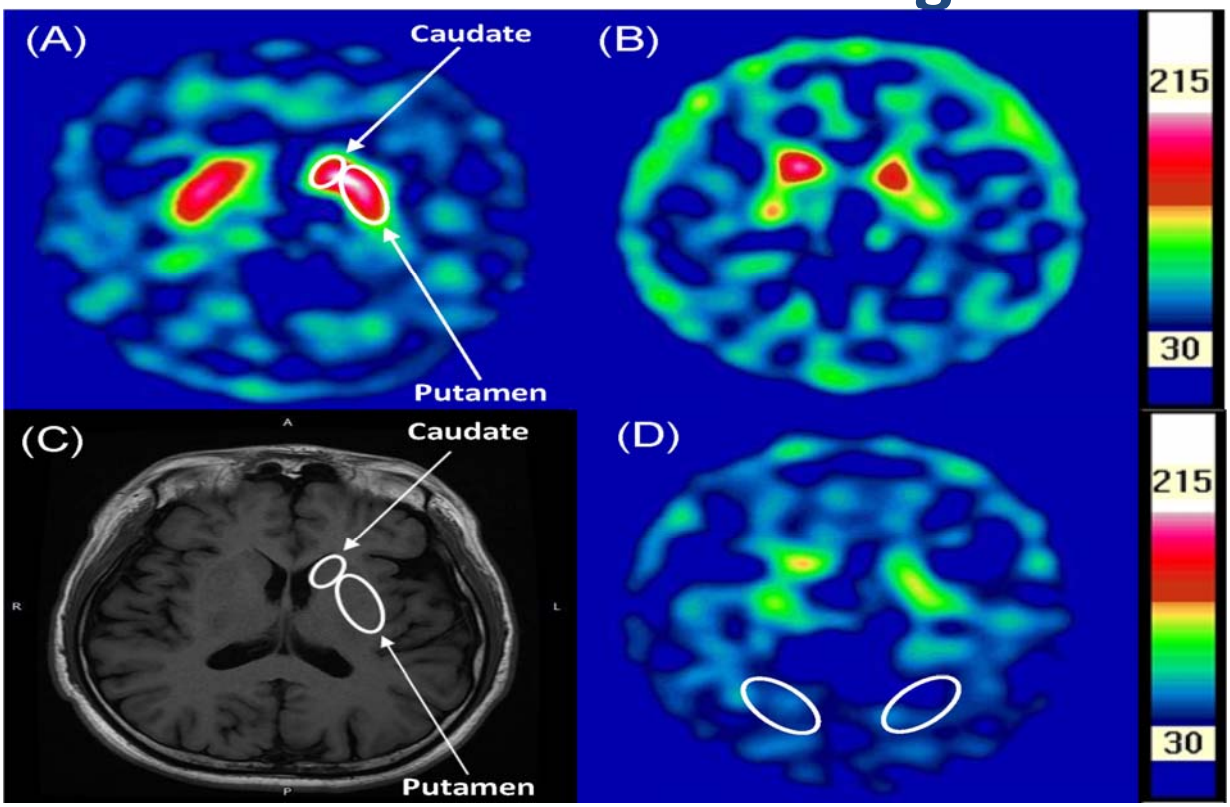
Table 1 Demographic Characteristics and Parameters of Wisconsin Card Sorting Test in People with Pure Alcohol Dependence, Alcohol Dependence comorbid Major Depression and Healthy Controls

General data	Pure AD (N = 28)		AD/MD (N = 21)		Healthy Controls (N = 24)	*p*
	Mean ± SD		Mean ± SD		Mean ± SD	
Age(years)[a]	43.29 ± 10.32		38.57 ± 6.97		39.21 ± 8.87	0.211
Education(years)[a]	13.00 ± 3.26		11.62 ± 2.36		16.50 ± 3.02	<0.001
Smoker: nonsmoker	26:2		20:1		2:22	<0.001
Smoking(cigarettes/day)[a]	22.79 ± 19.10		18.81 ± 13.78		0.83 ± 2.82	<0.001
Duration of alcohol dependence (years)[b]	12.43 ± 7.90		10.71 ± 6.77			0.663
Age of alcohol dependence onset[b]	31.07 ± 9.78		27.86 ± 6.85			0.283
Average daily alcohol intake (gram)[b]	166.07 ± 123.83		129.57 ±52.01			0.454
HDRS[b]	6.54 ± 3.42		19.38 ± 5.15			<0.001
Wisconsin Card Sorting Test		*p* [b]		*p* [b]		*p* [a]
Total corrects	66.07 ± 17.71	0.905[c]	70.29 ± 19.22	0.452[d]	68.29 ± 8.55	0.678[e]
Total errors	46.39 ± 27.59	0.001[c]	42.81 ± 22.27	0.001[d]	23.50 ± 18.28	0.001[e]
Perseverative errors	23.43 ± 19.19	0.010[c]	25.19 ± 23.57	0.031[d]	12.13 ± 9.39	0.021[e]
Non-perseverative errors	26.57 ± 21.86	0.003[c]	22.71 ± 15.32	0.002[d]	11.38 ± 9.85	0.002[e]
Categories complete	3.36 ± 2.38	0.001[c]	4.65 ± 2.83	0.058[d]	5.38 ± 1.61	0.003[e]
Failure to maintain set	1.11 ± 1.31	0.453[c]	2.64 ± 6.80	0.600[d]	0.79 ± 1.10	0.739[e]

AD: Alcohol Dependence；MD: Major Depression；SD: Standard Deviations；HDRS: 17-item Hamilton Depression Rating Scale. [a]Kruskal-Wallis test. [b]Mann-Whitney U-test. [c]Pure AD vs. healthy controls. [d]AD/MD vs. healthy controls. [e]Pure AD vs. AD/MD vs. healthy controls.

DAT availability

^{99m}Tc -TRODAT-1 image



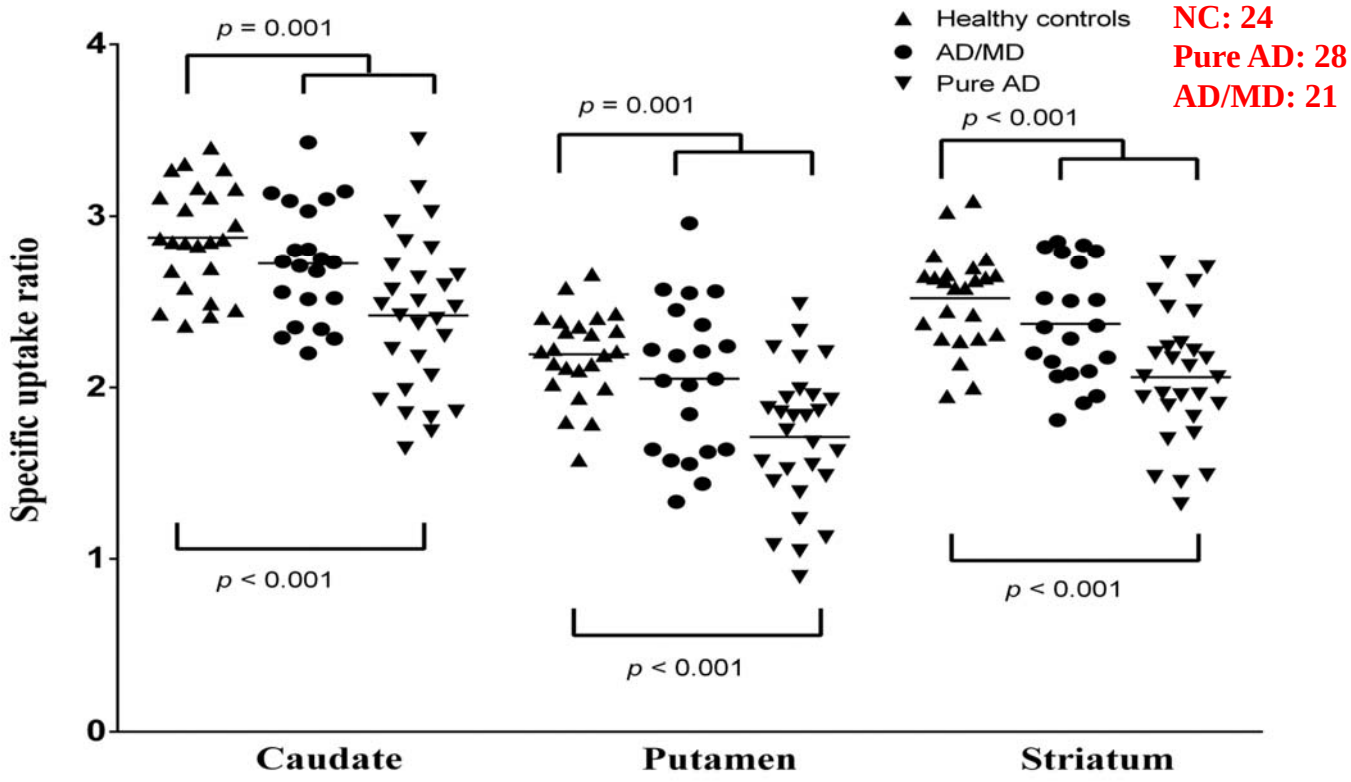
3. DAT availability

Table 2 . The brain specific uptake ratio of healthy controls, AD/MD and pure AD subgroups

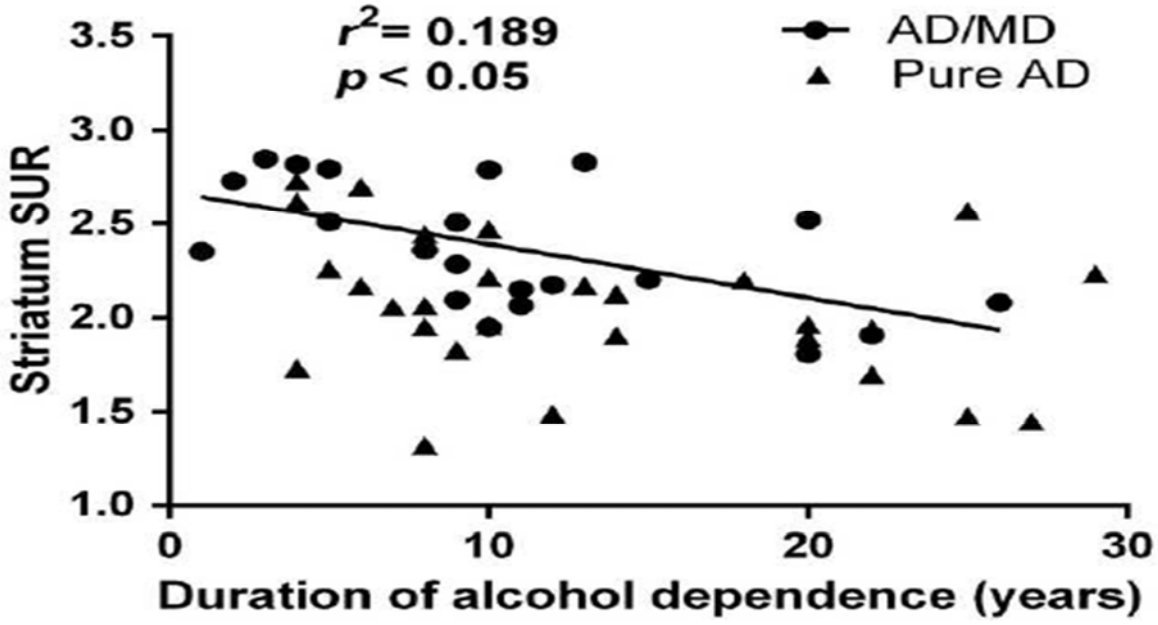
Brain area	Healthy controls n = 24	Combined AD n = 49	P value[a]	AD/MD n = 21	P value[a]	Pure AD n = 28	P value[a]
Caudate	2.87 ± 0.31	2.55 ± 0.43	0.001[b]	2.72 ± 0.34	0.086[c]	2.42 ± 0.46	<0.001[d]
Putamen	2.19 ± 0.25	1.86 ± 0.45	0.001[b]	2.05 ± 0.44	0.255[c]	1.71 ± 0.41	<0.001[d]
Striatum	2.52 ± 0.28	2.19 ± 0.39	<0.001[b]	2.37 ± 0.34	0.191[c]	2.06 ± 0.38	<0.001[d]

All entries for brain specific uptake ratio in this table are presented as mean ± SD.
[a] P value of Mann-Whitey test.
[b]Controls vs. Combined AD.
[c]AD/MD vs. healthy controls.
[d]Pure AD vs. healthy controls.

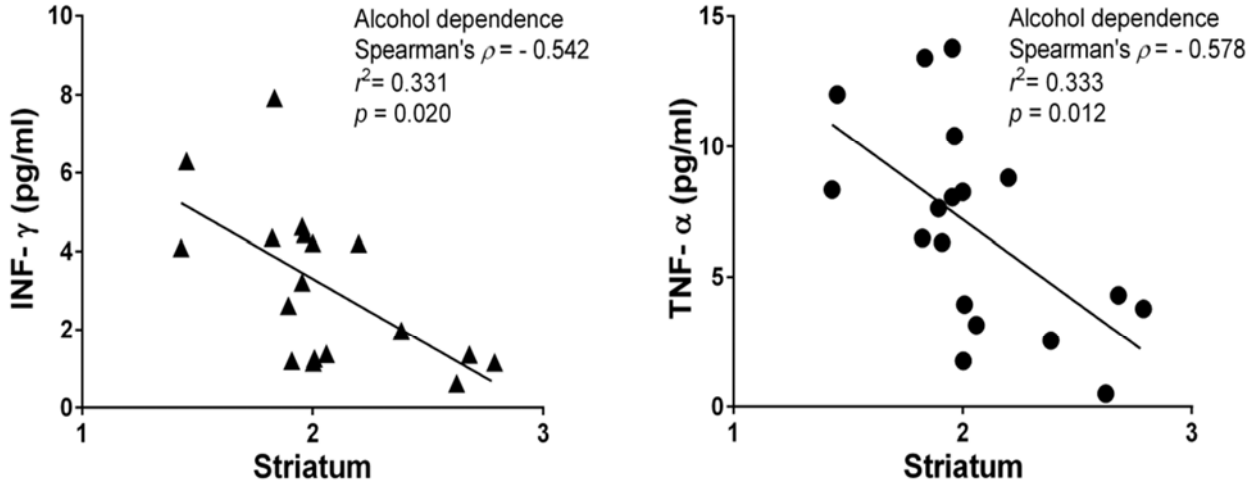
Incongruent reduction of dopamine transporter availability in different subtypes of male patients with alcohol dependence



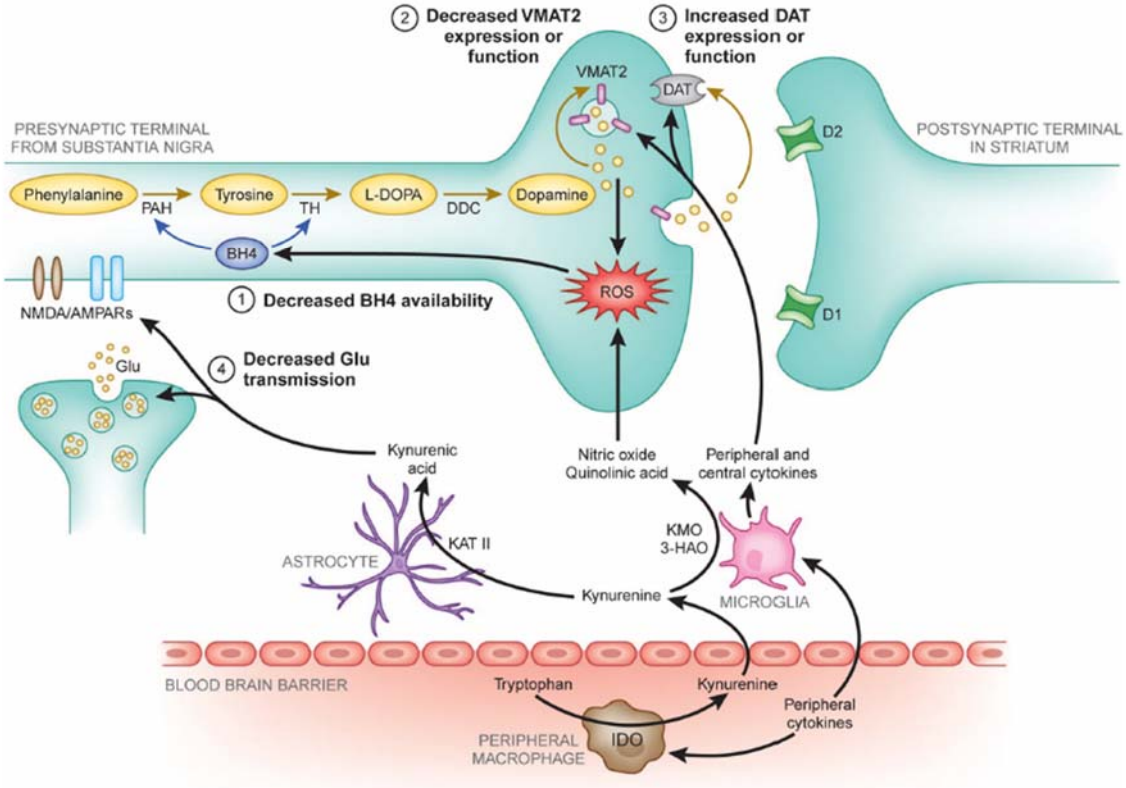
Graph showing correlation of striatal specific uptake ratio of [99mTc] TRODAT-1 with duration of alcohol dependence (years).



Correlation of striatal specific uptake ratio of [^{99m}Tc]TRODAT-1 with serum concentrations of interferon - gamma (INF-γ) and tumor necrosis factor - alpha (TNF-α)

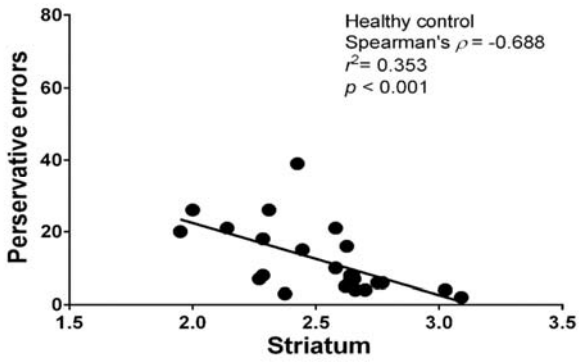


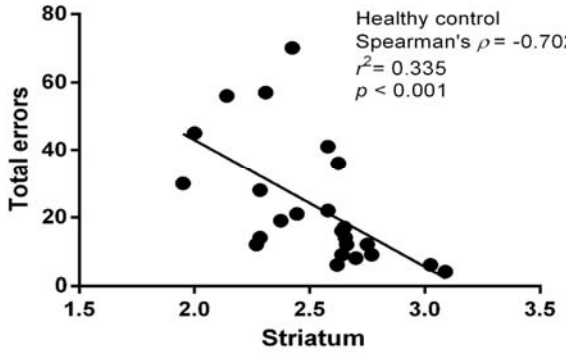
Potential mechanism of inflammatory cytokine effects on basal ganglia dopamine synthesis and release

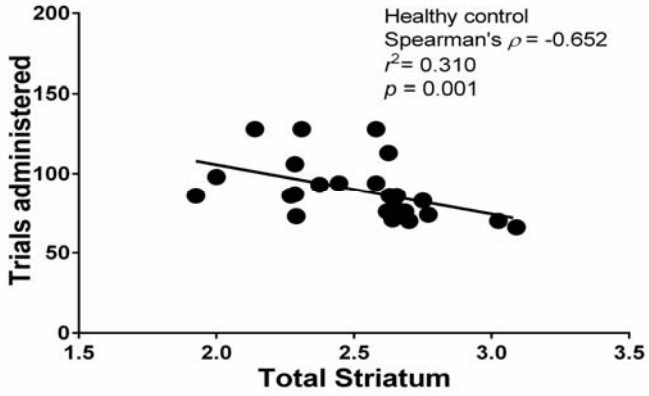


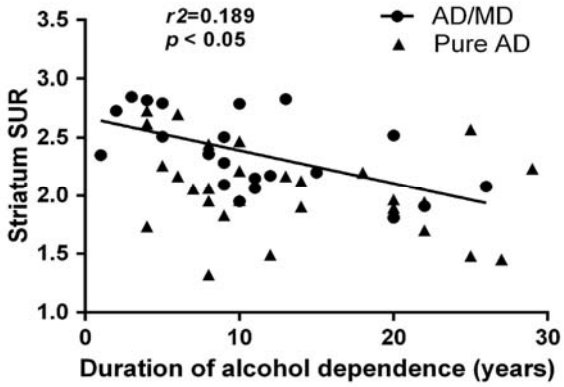
Front Neuroendocrinol. 2012 August ; 33(3): 315–327

The relationship between DAT availability and Cognitive function.









2015-7-1 published data

PLOS ONE

RESEARCH ARTICLE

Reduced Dopamine Transporter Availability and Neurocognitive Deficits in Male Patients with Alcohol Dependence

Che-Hung Yen[1,2], Yi-Wei Yeh[3], Chih-Sung Liang[1,4], Pei-Shen Ho[4], Shin-Chang Kuo[1,3], Chang-Chih Huang[1,5], Chun-Yen Chen[1,3], Mei-Chen Shih[3], Kuo-Hsing Ma[6], Gila-Sheun Peng[2], Ru-Band Lu[7], San-Yuan Huang[1,3]*

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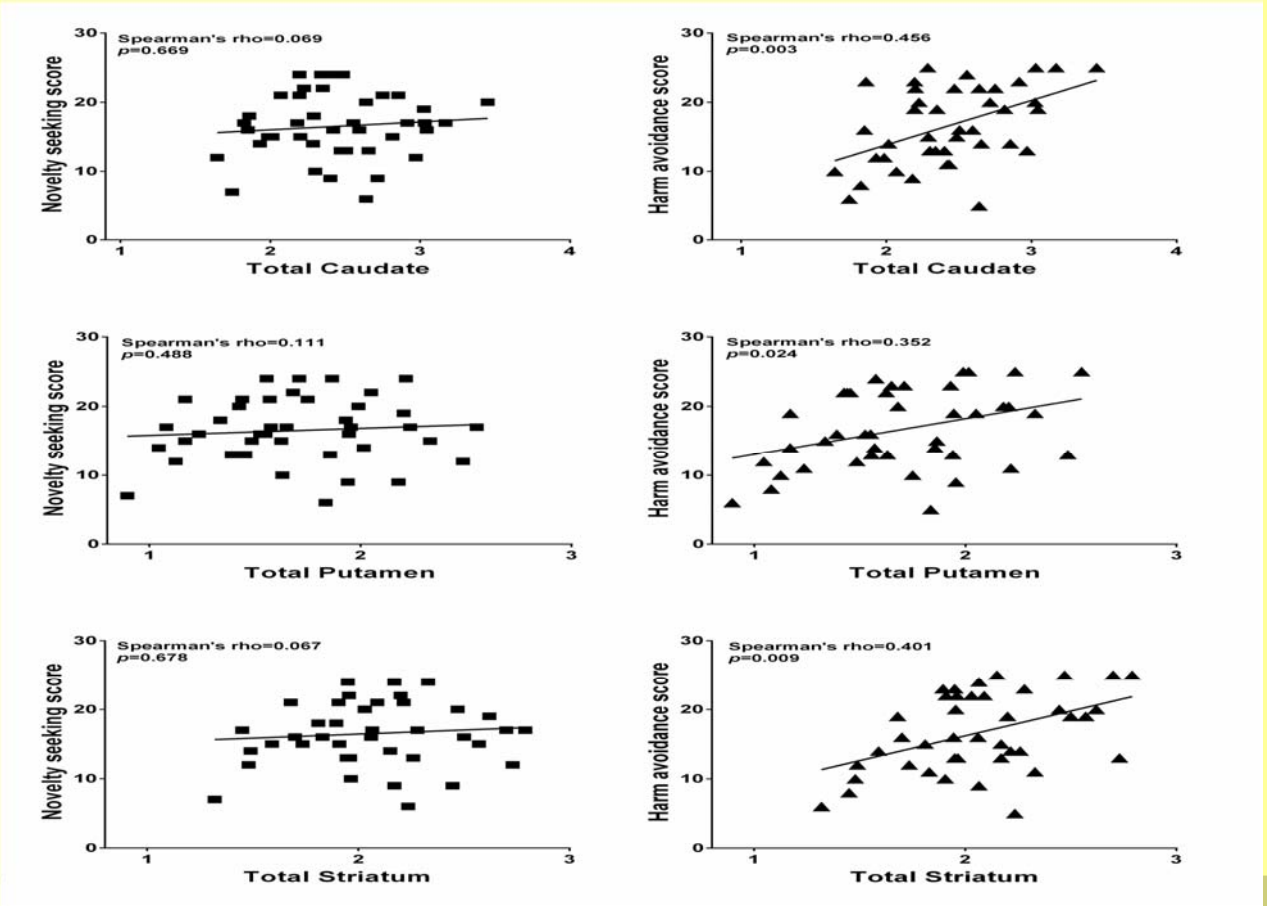
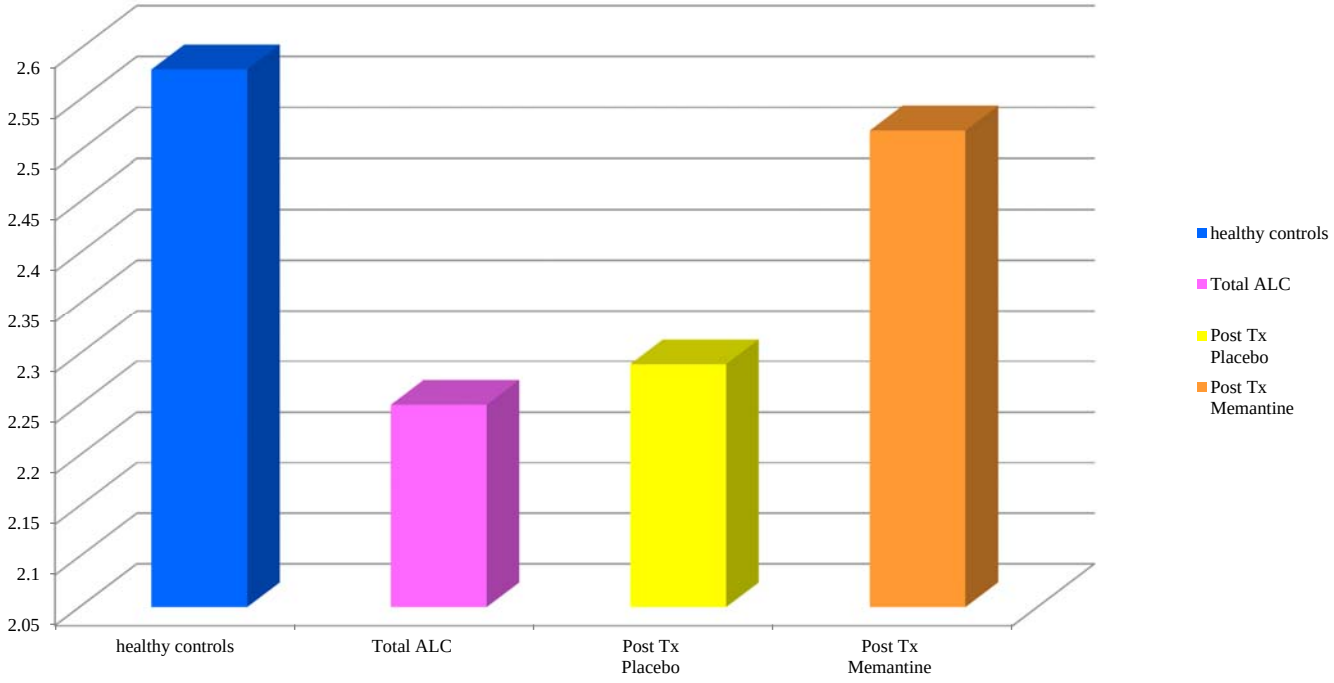
Funding: This work was supported by National Science Council NSC101-2325-B-016-003 (SYH), Tri-Service General Hospital TSGHC 101-122 (SYH),

CrossMark

The relationship between DAT availability and personality in ALC



Brain DAT availability in Striatum



Huang et al. unpublished data, 2015

Conclusion and Limitation

- **Low DAT availability** and **poor cognitive function** in patient with alcohol dependence.
- **Negative relationship** between DAT availability and Cognitive function.
- **High impulsivity and pro-inflammatory factors in patient with alcohol.**
- **Abstain from heavy drinking** may be reverse the neural damage and recovery patient's inflammatory condition.
- **Limitation:** Small sample size and multiple factors ??

謝謝大家為台灣成癮防治業務而努力

台灣成癮科學學會
TAIWANESE SOCIETY OF ADDICTION SCIENCE

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The molecular neuroimaging studies in substance users – a study combined with economic evaluation

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- Disclosure: Conflict of interest

- Honoraria:

  Astra-Zeneca, GlaxoSmithKline, Eli Lilly, Pfizer, Janssen-Cilag (J＆J), Wyeth, Otsuka, Fujsawa (Astellas), Sanofi-Aventis, Organon(Schering-Plough), Servier

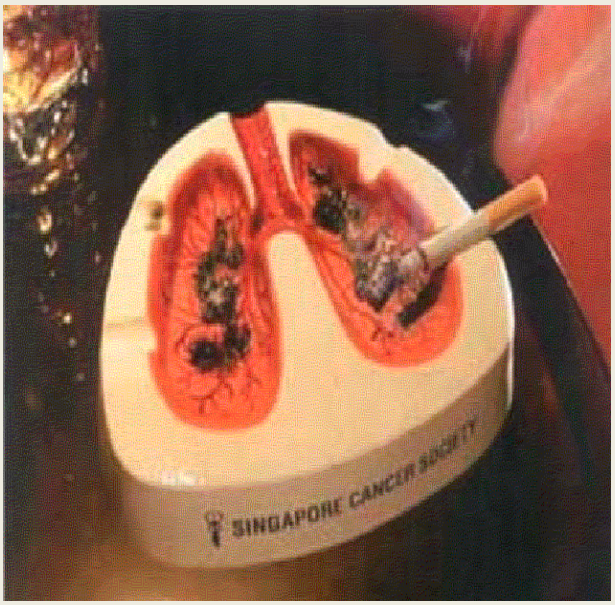
- Advisory board:

  Jassen-Cilag (J＆J), Pfizer , Eli Lilly , Lundbeck

- Research grands:

  GlaxoSmithKline, Eli Lilly, Pfizer, Janssen-Cilag (J＆J), Sanofi-Aventis, Wyeth, Otsuka, Astellas, Dai Nippon Sumitomo, Atomic Energy Council , Lundbeck, Roche, Mitsubishi Tanabe, Boehringer Ingelheim

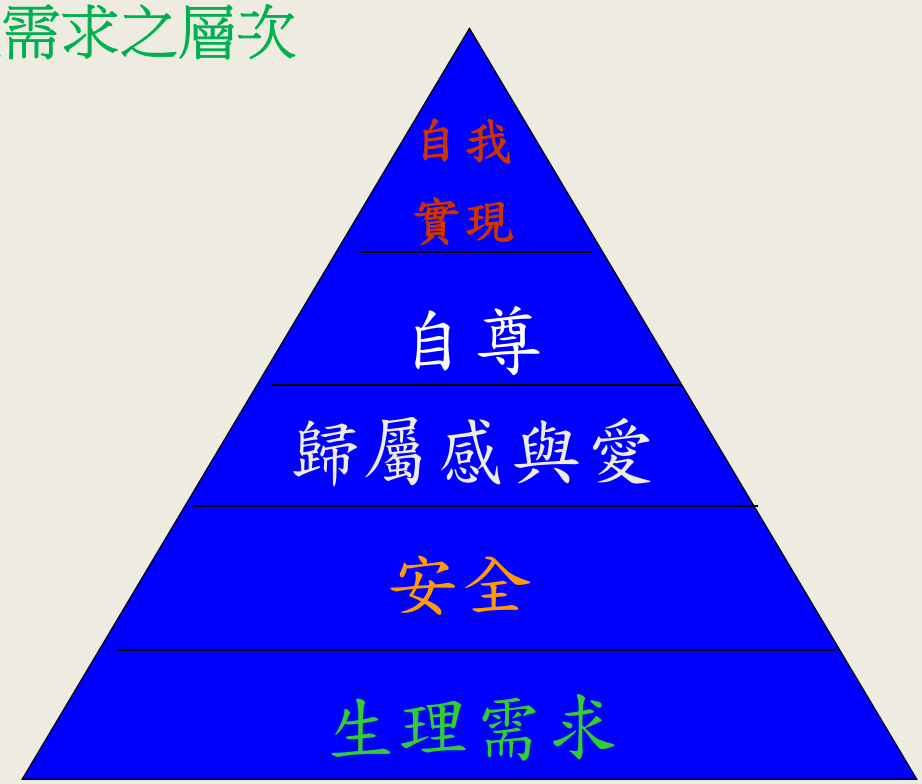
Tabacco Smoking



這個肺型煙灰缸被置於食肆及娛樂場所, 警嚇性相當高。是我見到的最最有效的戒煙廣告

Maslow's Hierarchy of Needs

人性需求之層次



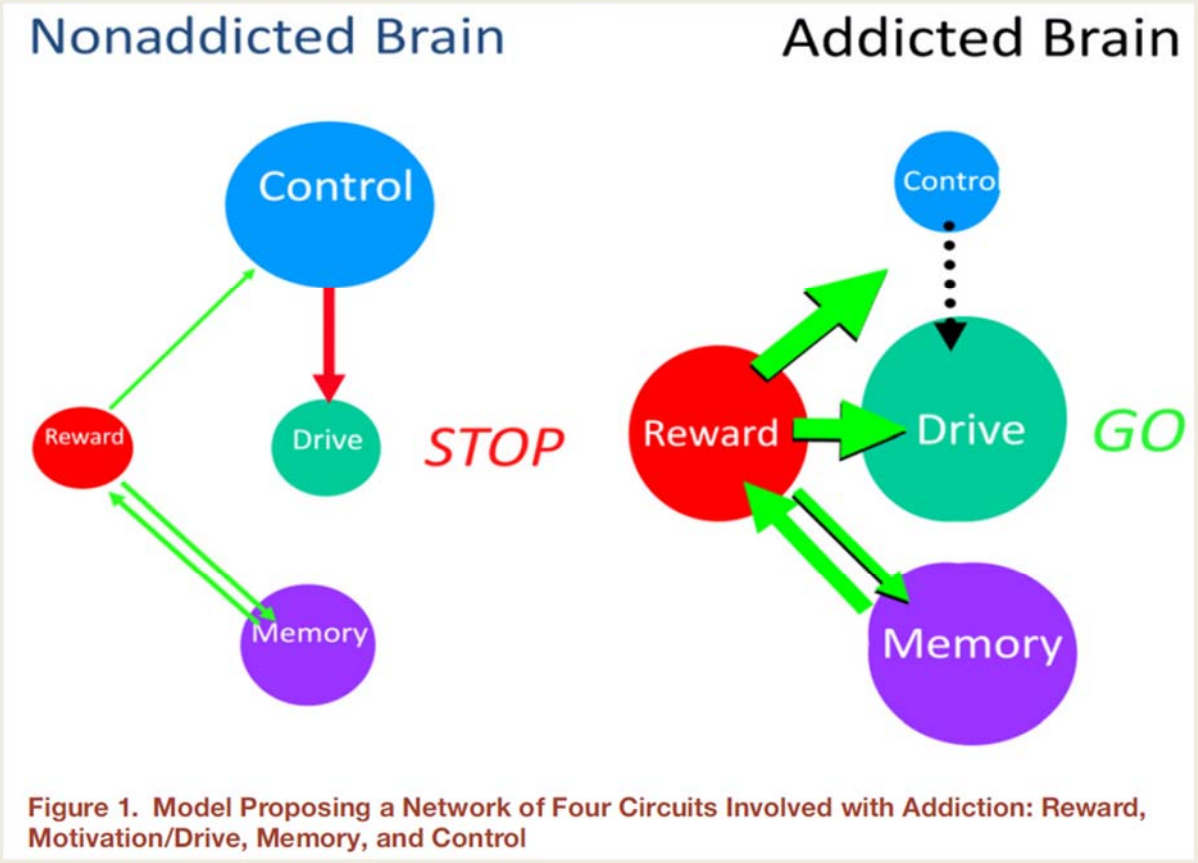
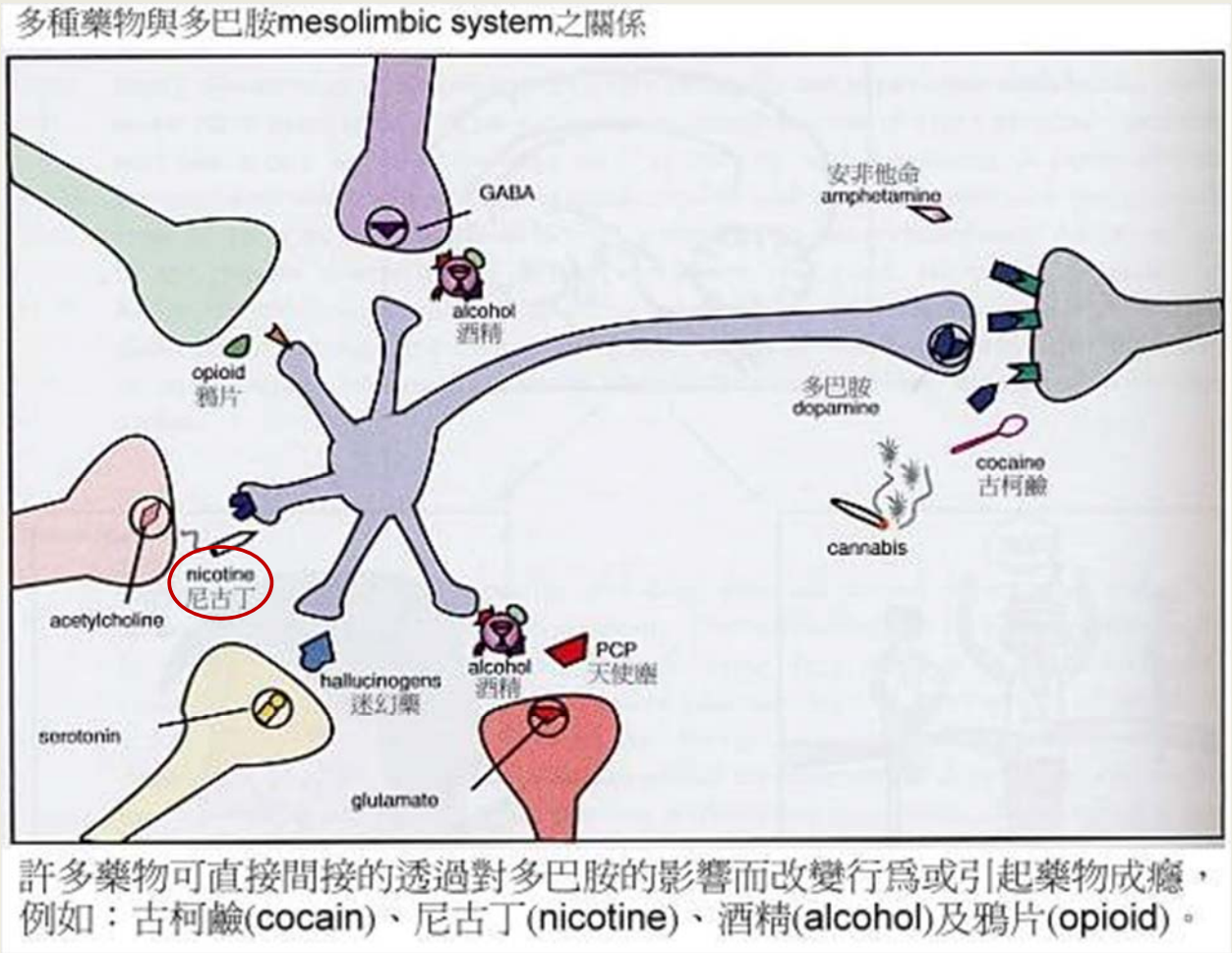


Figure 1. Model Proposing a Network of Four Circuits Involved with Addiction: Reward, Motivation/Drive, Memory, and Control

(Volkow et al Neuron, 2011)



許多藥物可直接間接的透過對多巴胺的影響而改變行爲或引起藥物成癮，例如：古柯鹼(cocain)、尼古丁(nicotine)、酒精(alcohol)及鴉片(opioid)。

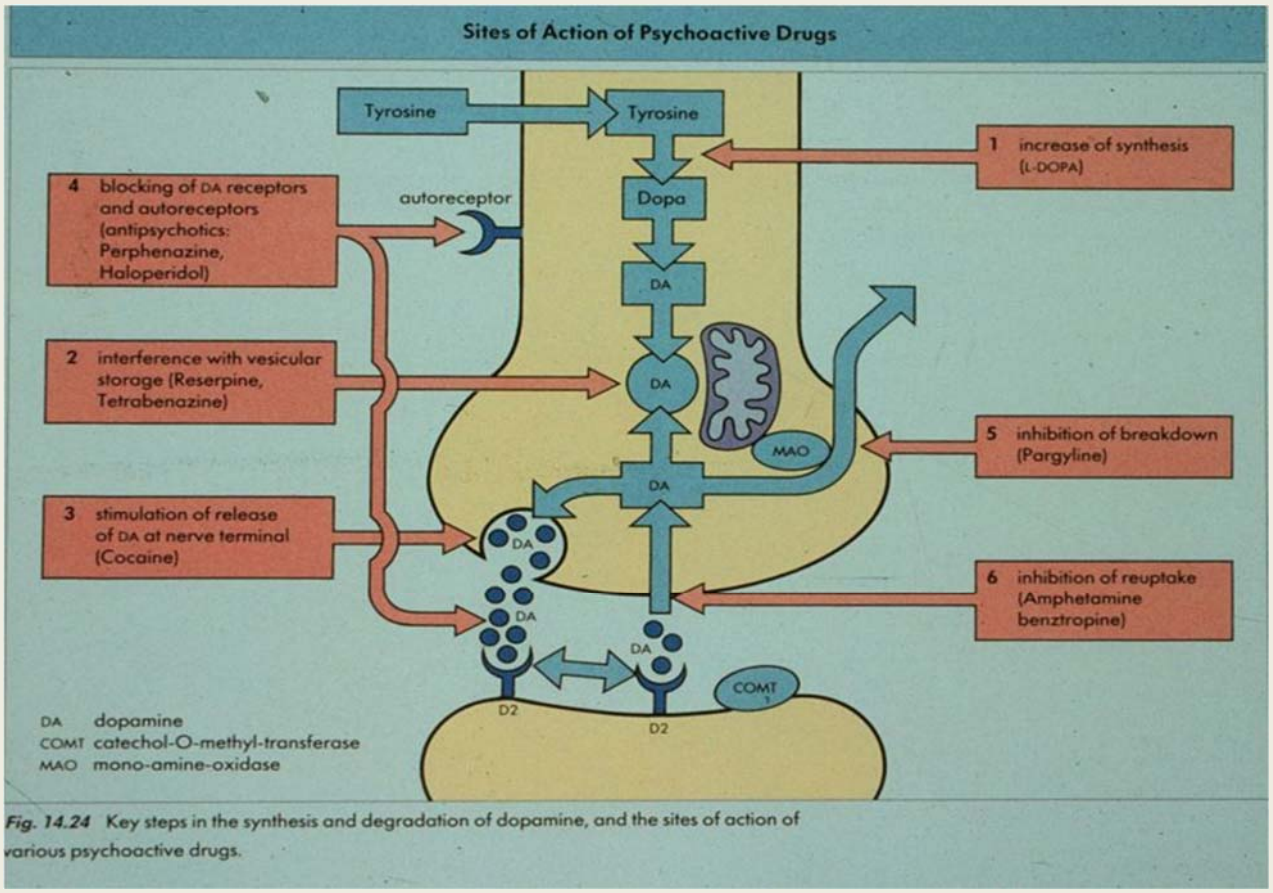
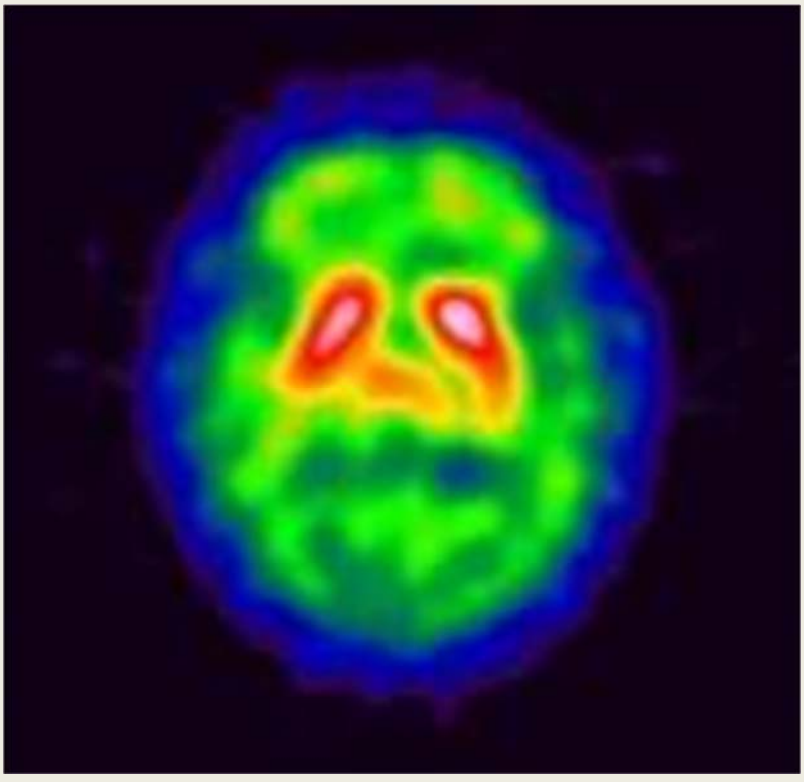


Fig. 14.24 Key steps in the synthesis and degradation of dopamine, and the sites of action of various psychoactive drugs.

[^{123}I]IBZM (for D2 receptor)



[Tc-99m]TRODAT-1 (for DAT)

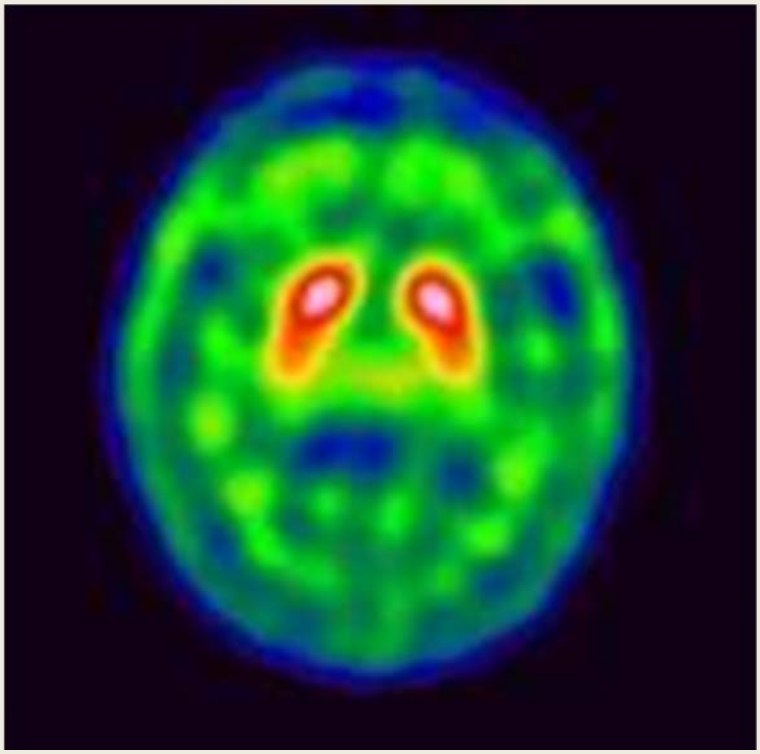
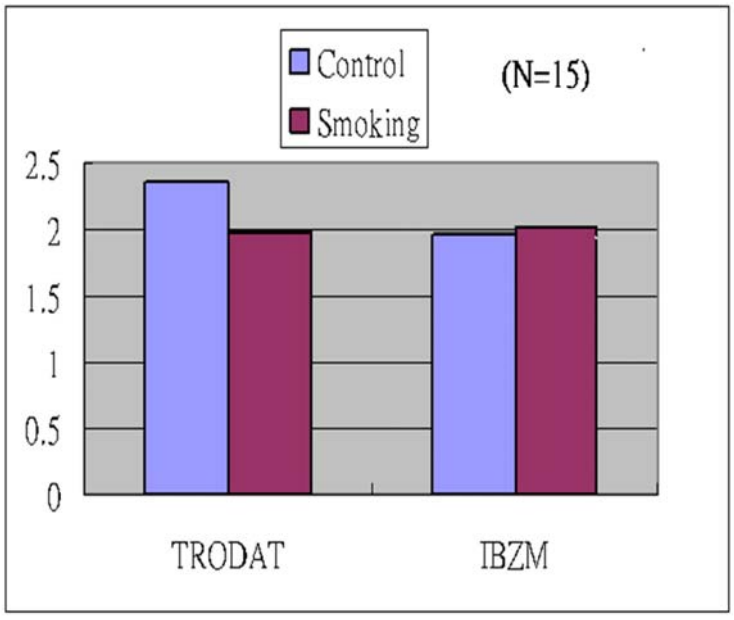


Fig 1: DAT bindings in smoker is significant higher in those of controls ($t = -3.4, p < .05$), however this is not the care in D2/D3 binding comparison.



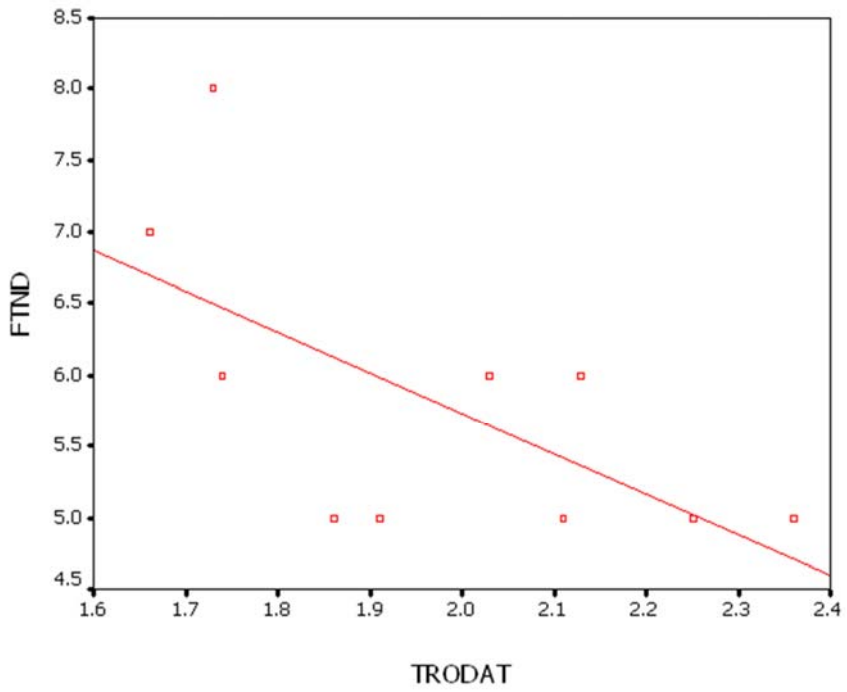
(Yang YK et al 2008)

(Rf 79)

Fagerström Test for Nicotine Dependence (FTND)

問題	答案	分數
一天平均煙量	10支以下15-25支	0
	11-20支	1
	21-30支	2
	30支以上	3
早晨醒來第一支煙	5分鐘內	3
	6-30分鐘	2
	30-60分鐘	1
	60分鐘以後	0
早上第一個小時抽的煙量是否最多	是	1
最不願意放棄的煙是什麼時候抽	早晨第一支	1
在禁菸場所是否難以忍受?	是	1
即使生病臥床還是會抽煙	是	1

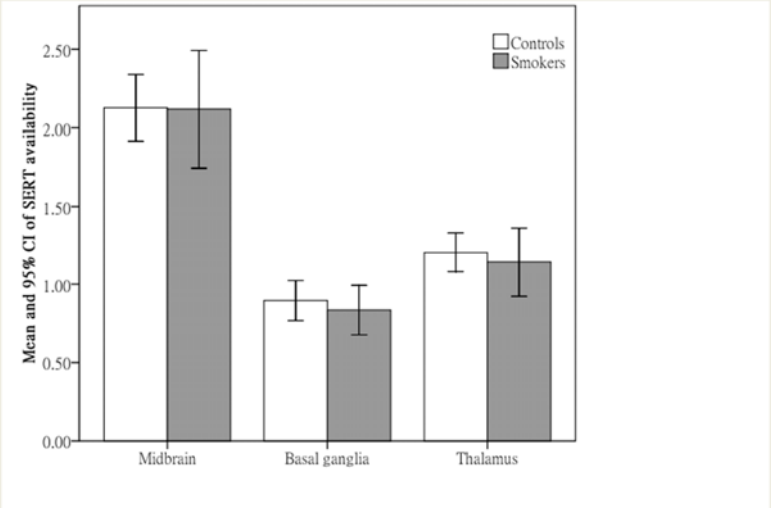
Fig 2: Total FTND Score is correlated with DAT ($r = -.77, p < .01$) binding in smoker, however, not in D2/D3 bindings.



(

(Yang et al Prog Neuro-Psycho & Bio Psychi 2008,)

SERT availability in the smokers (N = 16) and non-smokers (N = 32)



No significant difference on midbrain (P = 0.86), basal ganglia (P = 0.95), or thalamus (P = 0.88)

Zhao RJ et al, JAM revised

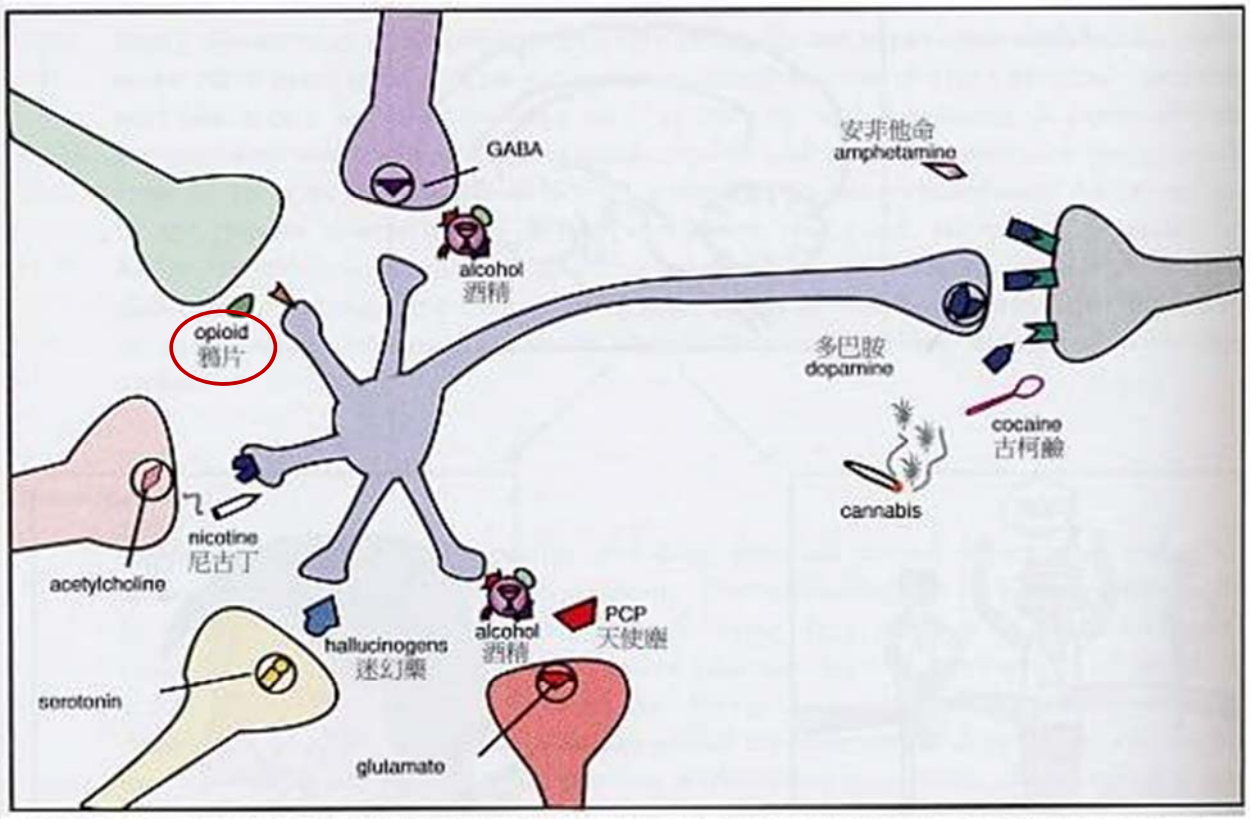
Table 2
Intercorrelations among objective measures of smoking

	Beginning CO	No. of cigarettes	End CO	Nicotine
Baseline				
No. of cigarettes	0.02			
End CO (ppm)	0.80**	0.34*		
Nicotine (ng/ml)	0.52**	0.26	0.62**	
Cotinine (ng/ml)	0.57**	−0.09	0.46*	0.76**
7 days of haloperidol treatment				
No. of cigarettes	0.05			
End CO	0.75**	0.29*		
Nicotine	0.54**	0.37*	0.72**	
Cotinine	0.68**	0.04	0.68**	0.73**

* $p < 0.05$.
** $p < 0.001$.

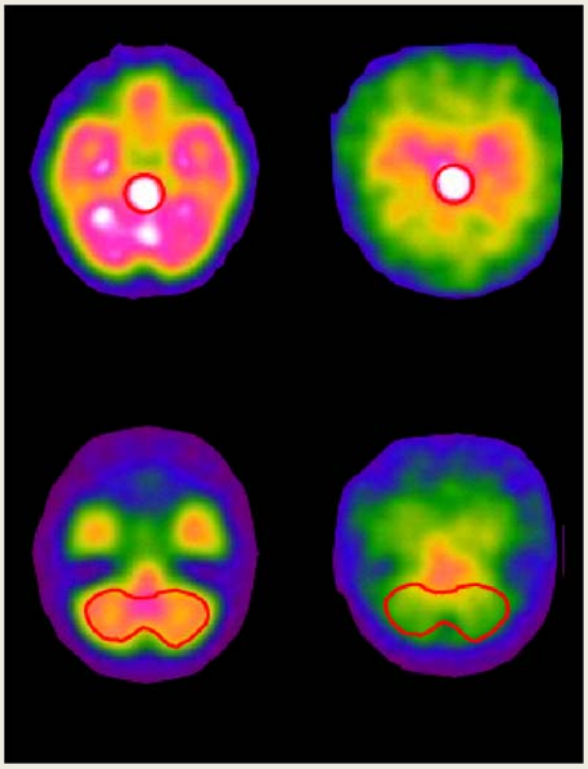
(Yang et al., Schizophrenia Research 2002)

多種藥物與多巴胺mesolimbic system之關係

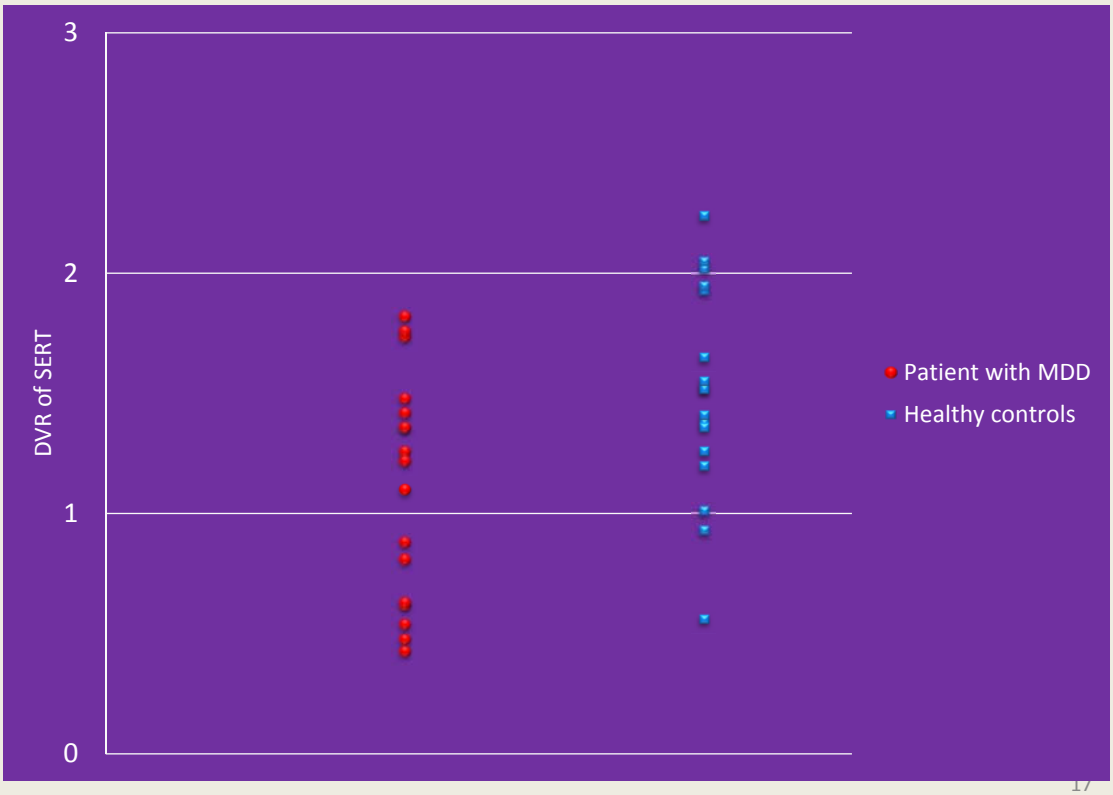


許多藥物可直接間接的透過對多巴胺的影響而改變行爲或引起藥物成癮，例如：古柯鹼(cocain)、尼古丁(nicotine)、酒精(alcohol)及鴉片(opioid)。

[^{123}I] ADAM (5HTtransports, 血清素)



Scatter plot of SERT in 17 pairs (*P* = 0.019)



Tsai SC et al Pharmacopsychiatry, 2015

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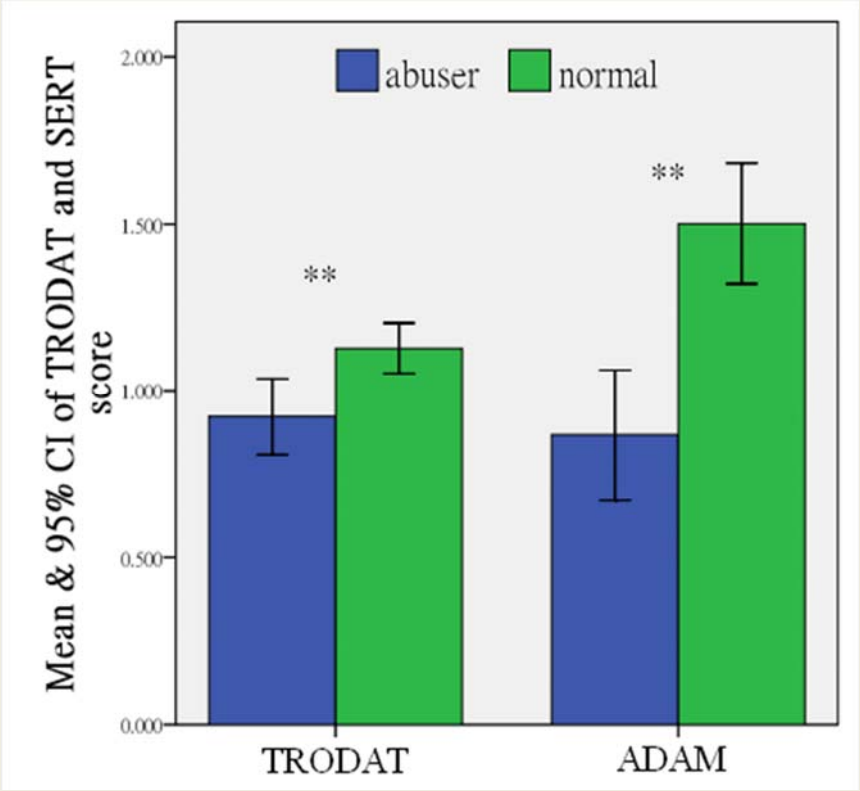
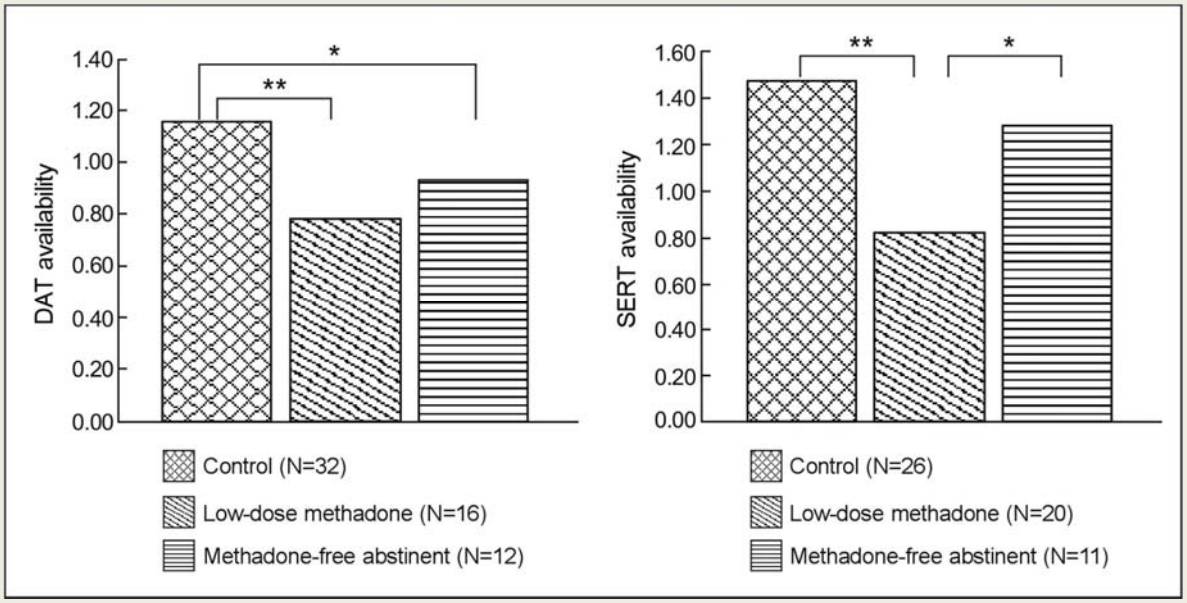
The opioid users' DATs, SERTs

(Yeh et al Psychopharmacology 2012)



18

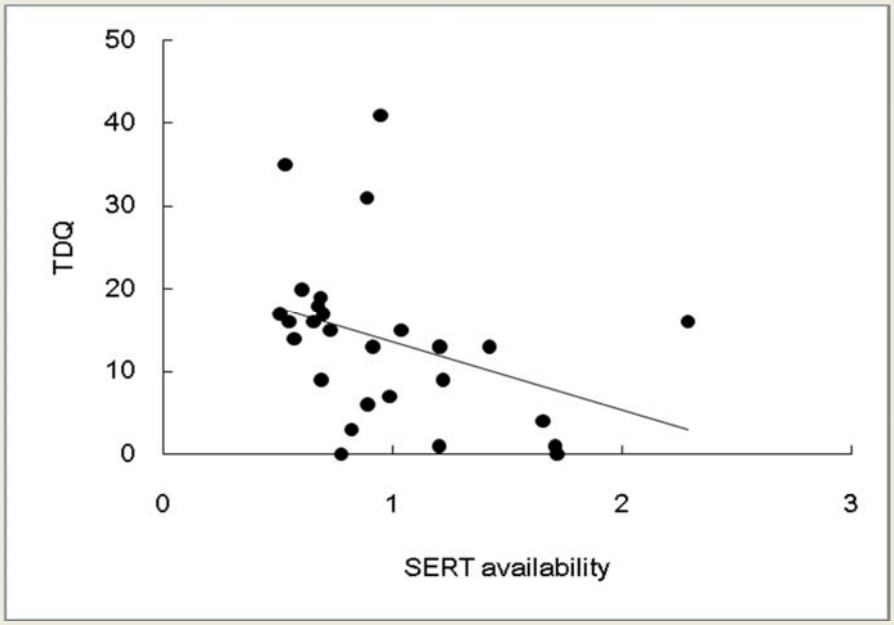
18



The difference in DAT and SERT availability between opioid users during low-dose methadone treatment, methadone-free subjects (after treatment) and controls.

*: P < 0.05. **: P < 0.01

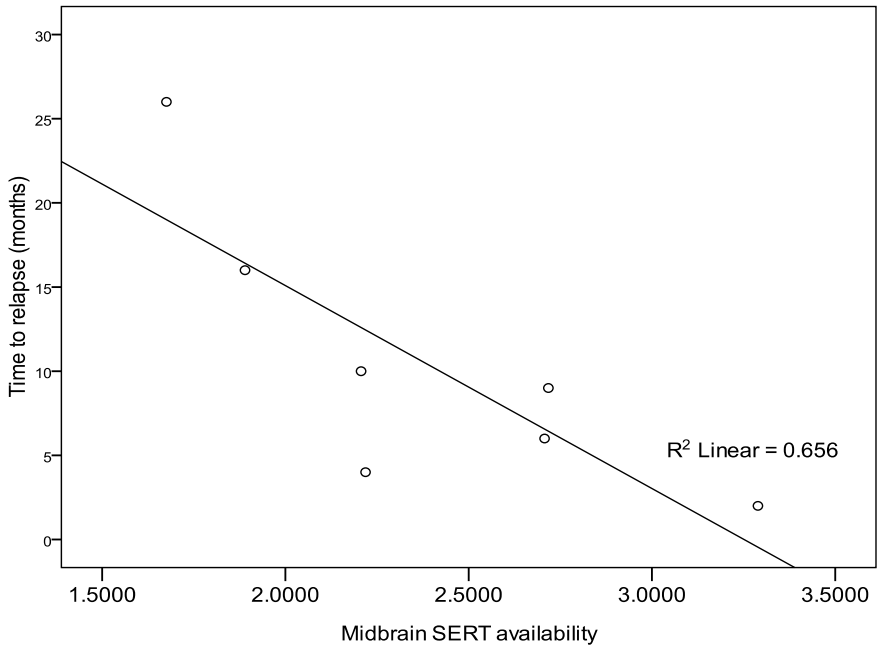
DAT: dopamine transporter; SERT: serotonin transport **(Yeh et al, Psychopharmacology, 2012)**



The association between TDQ and SERT (β= -0.50, *p* = 0.01) in opioid users

TDQ: Taiwanese Depression Questionnaire; SERT: serotonin transporter

(Yeh et al, Psychopharmacology, 2012)



The association between time to relapse and midbrain SERT availability

SERT: serotonin transport **(Lin et al ,Eur Neuropsychopharmacology, 2012)**

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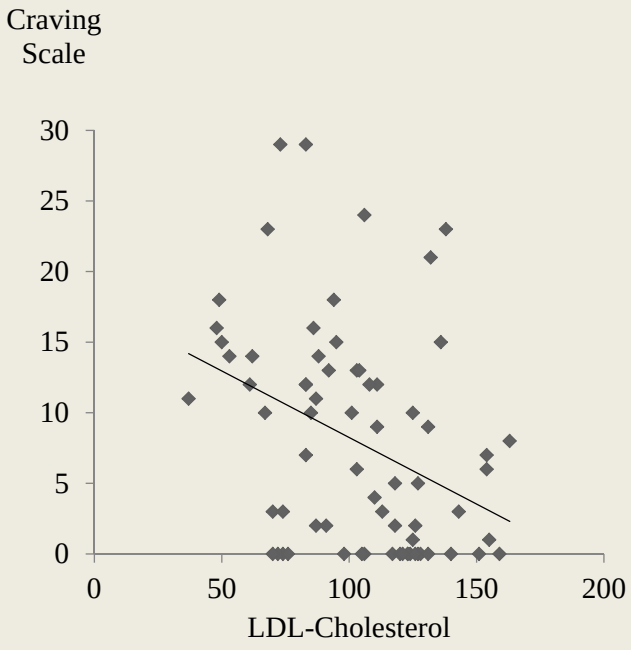
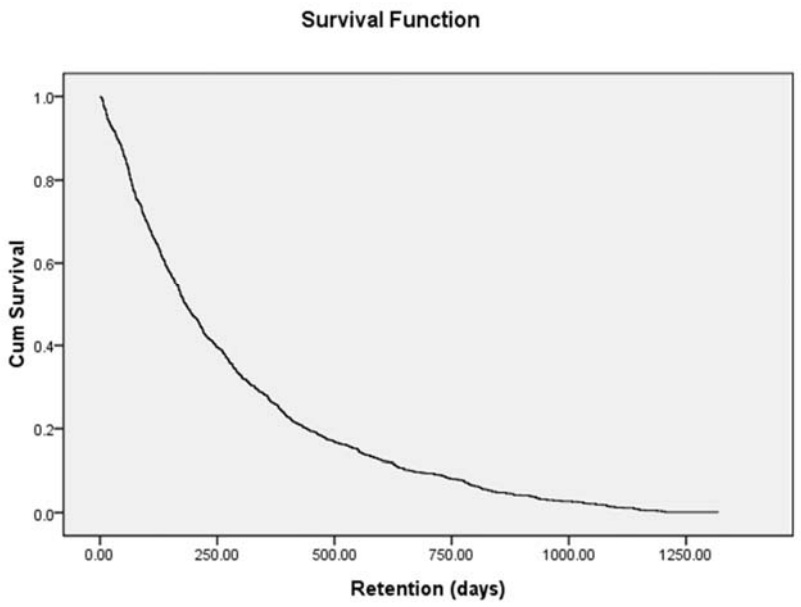
Cholesterol and Craving Tendency

Lin SH et al., J Add Medicine, 2012



- Association for total Cholesterol(p = .005) and LDL (p = .002)
- Association remains robust after controlling:
  - Group difference, demographic effect, methadone dosage, and treatment duration

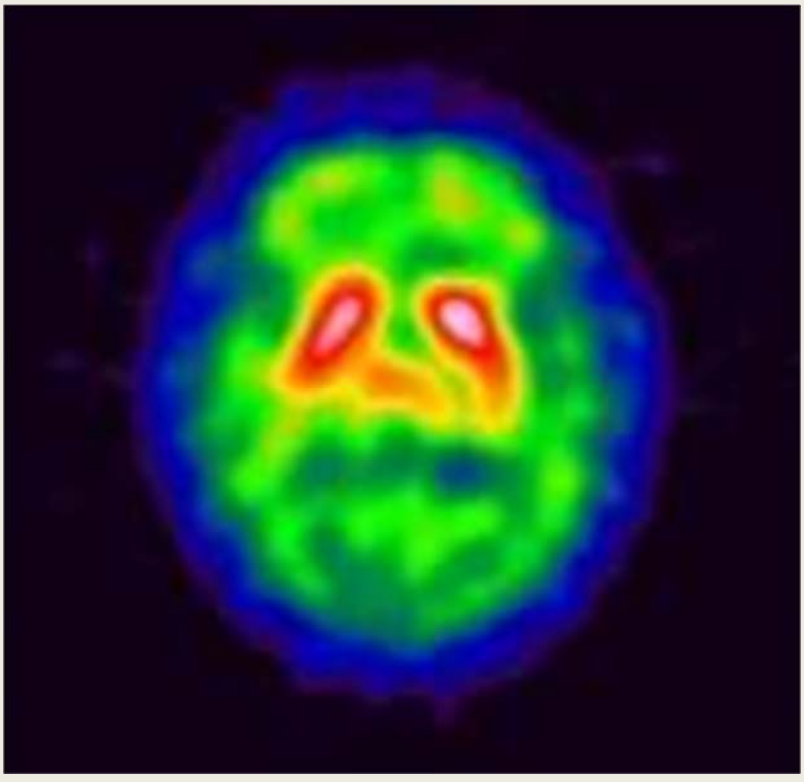
The survival function (Kaplan-Meier)



- N of drop out: 1001 (73%)
- Retention days
  - Mean = 275 (95% CI = 259-291)
  - Median = 182 (95% CI = 166-198)
- Rate of 1 year drop out: 73%
- Rate of reentry: 17%

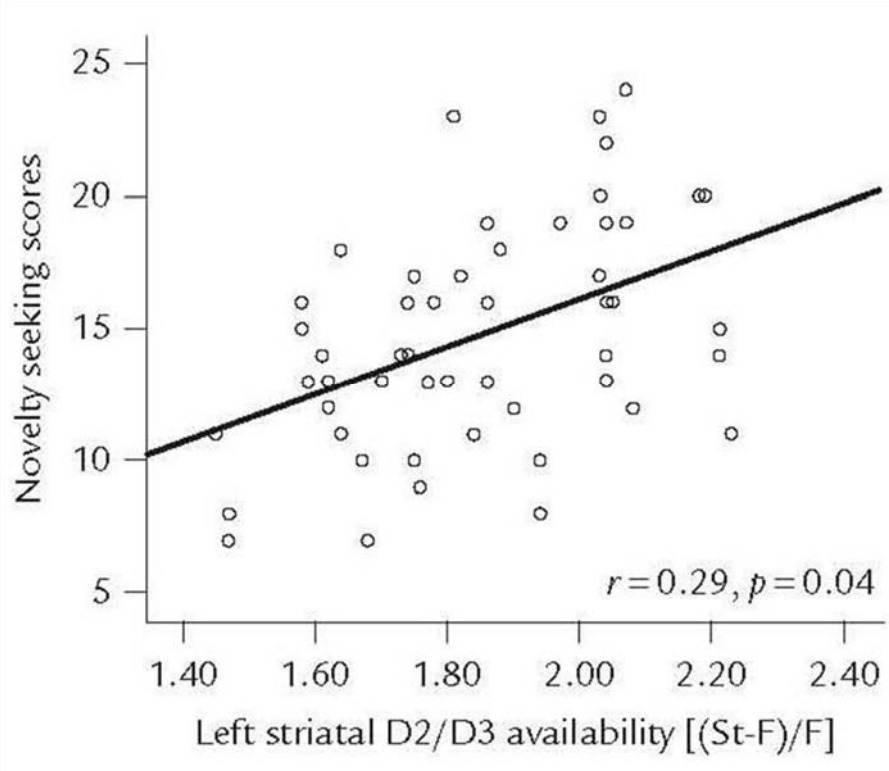
Source: **Chen and Lin (2011)**, unpublished report for NCKUH.

[^{123}I]IBZM (for D2 receptor)



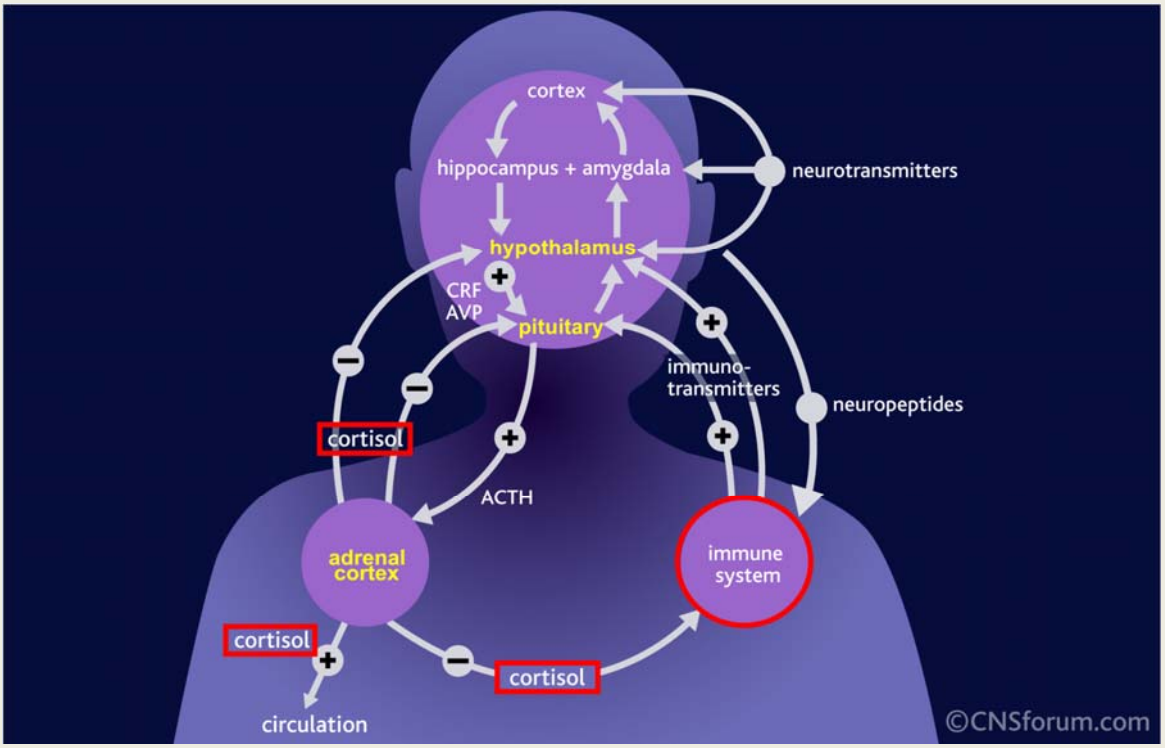
24

The correlation between NS scores and left striatal D_2/D_3 availability



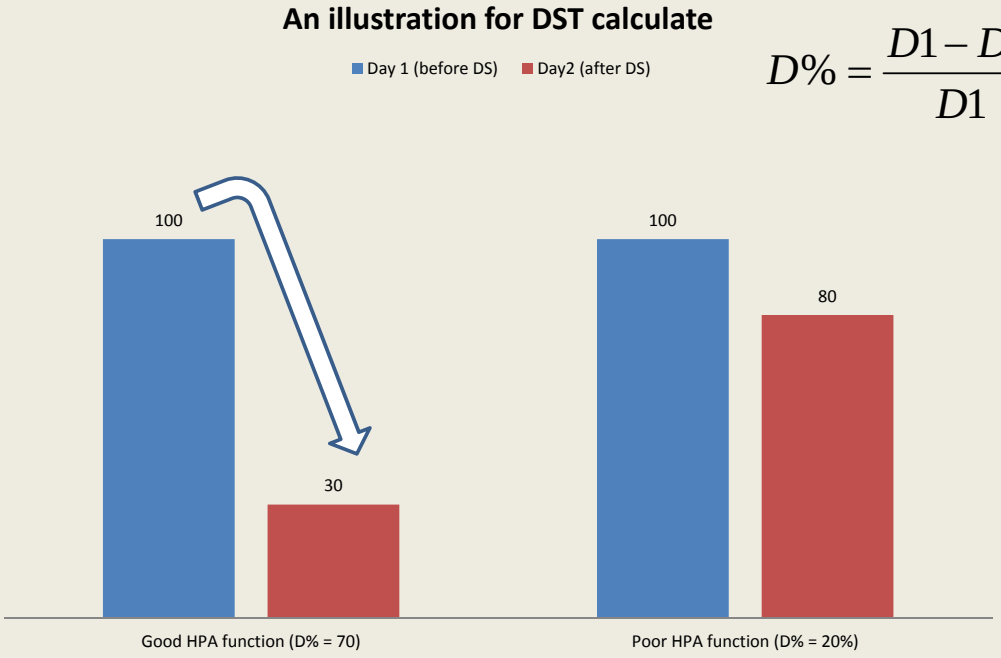
Huang HY et al., Journal of the Formosan Medical Association 2010;109:736-739

H-P-A axis and immune system



Primary Care Companion J Clin Psychiatry 2001;3:151–155. Metabolism 2002;51:5–10.

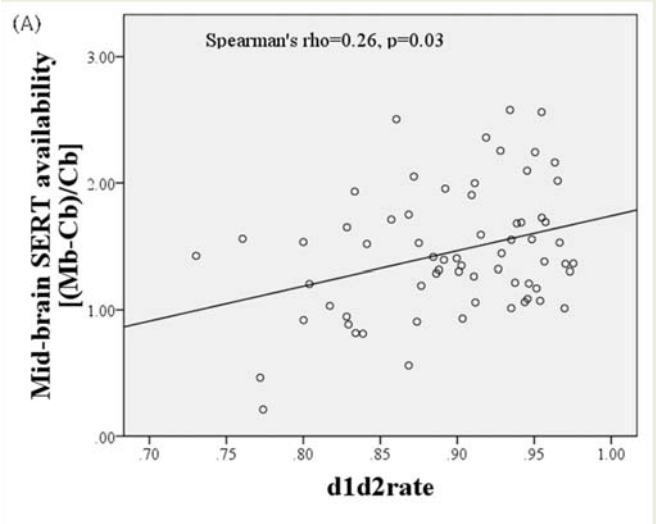
Suppression rate of DST (D%)

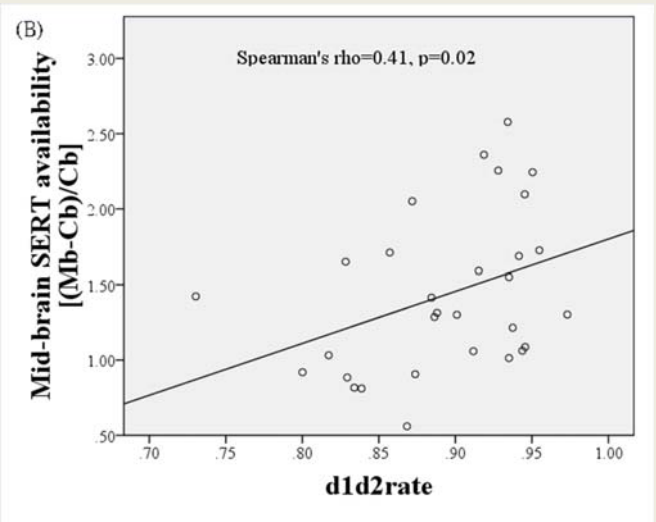


$$D\% = \frac{D1 - D2}{D1} \times 100\%$$

當壓力荷爾蒙上升時血清素下降

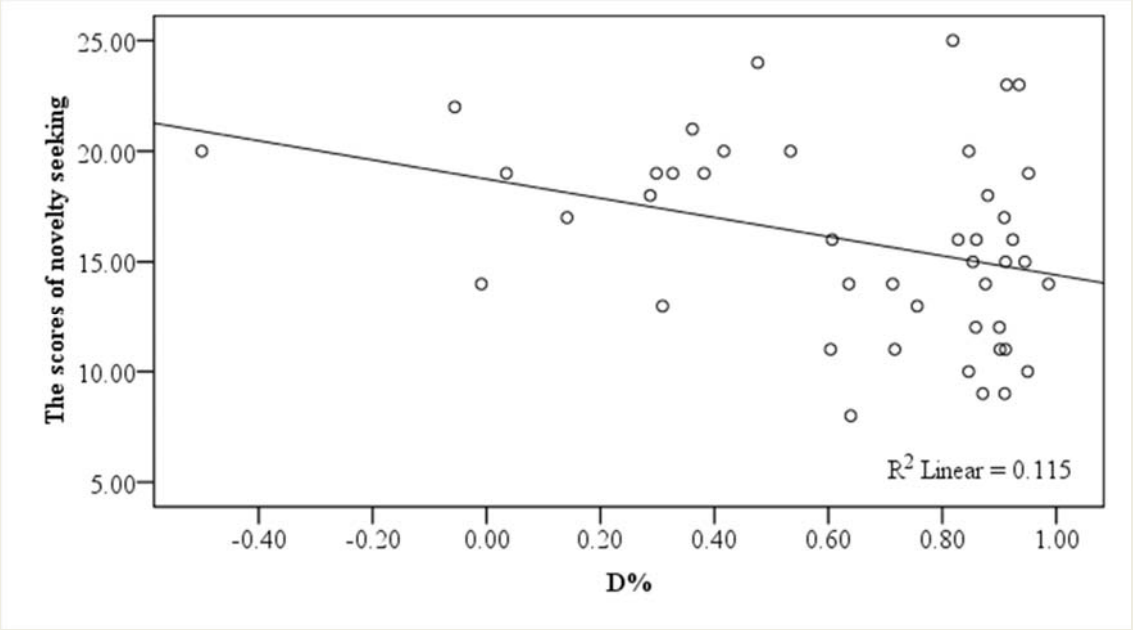
(Tsai et al Eur Neuropsychophamacology ,2012)





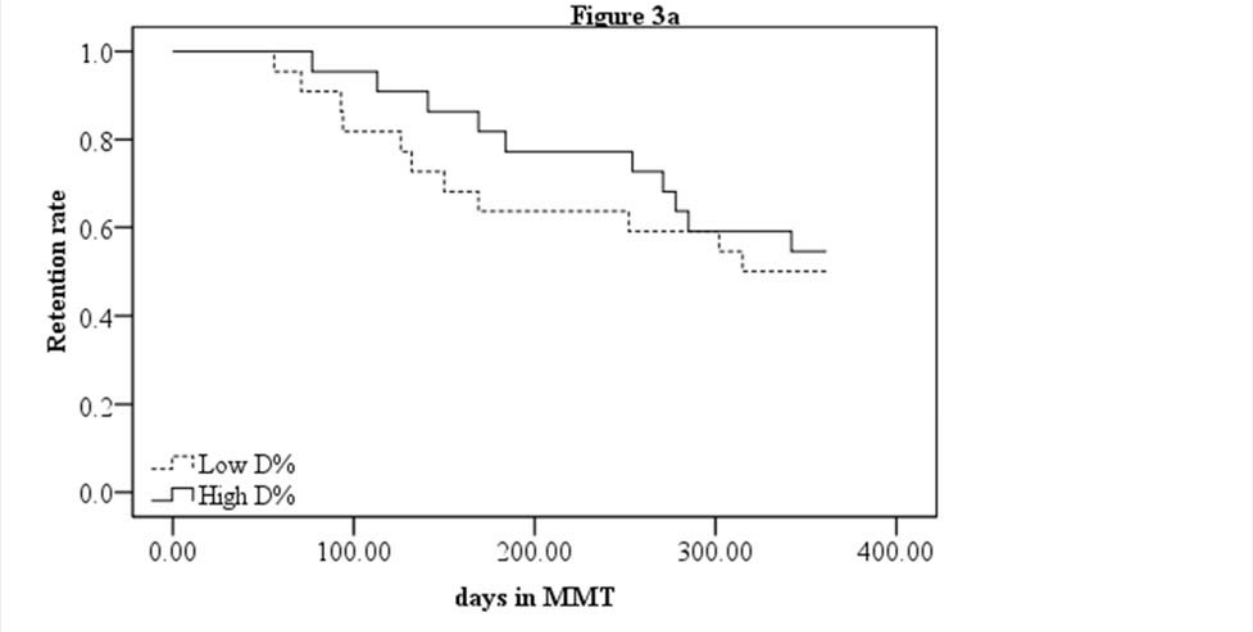
Association between D% and novelty seeking

Lin SH et al J Add Medicine 2013



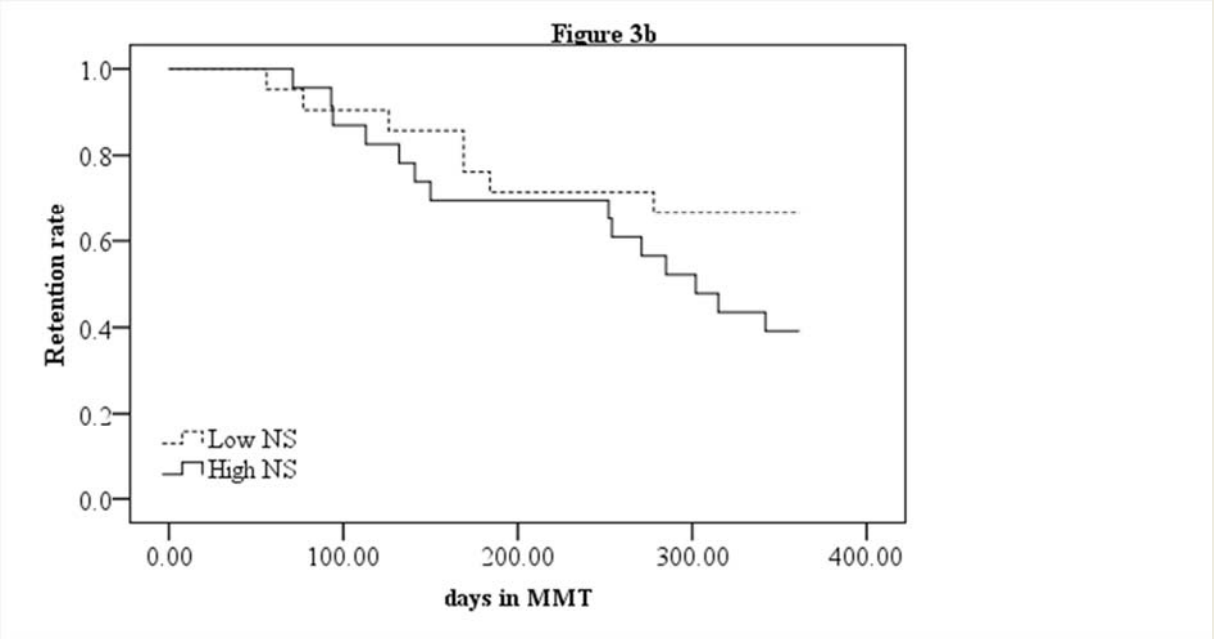
D% for predicting half-year relapse

Lin SH et al J Add Medicine 2013



NS for predicting 1-year relapse

Lin SH et al J Add medicien 2013

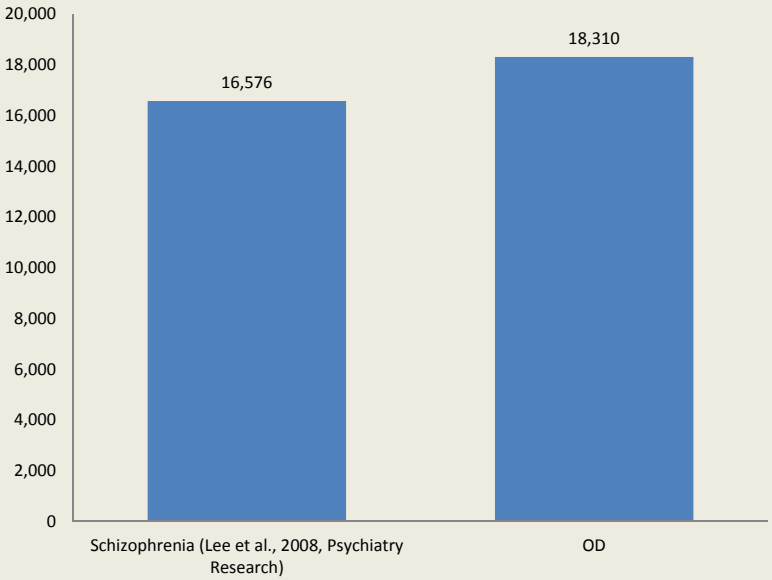


Personality trait, HPA, and retention

	Half Year			One Year		
	Yes (N = 32)	No (N = 12)	T	Yes (N = 23)	No (N = 21)	T
NS	15.78 ± 4.46	16.42 ± 4.38	0.42	14.57 ± 3.98	17.48 ± 4.41	2.30*
D%	70.94 ± 28.46	46.30 ± 42.88	2.22*	69.24 ± 28.47	58.72 ± 39.74	1.02

Lin SH et al J Add Medicine 2013

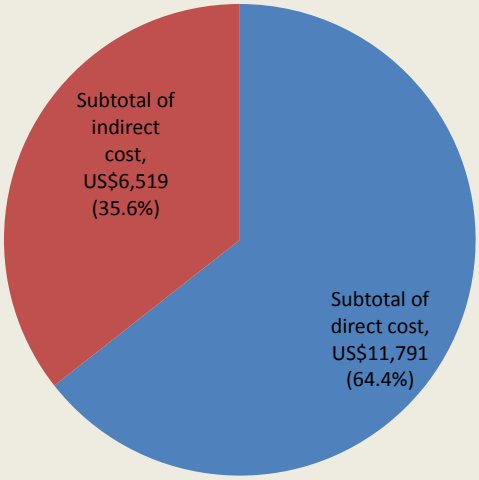
Economic cost for OD

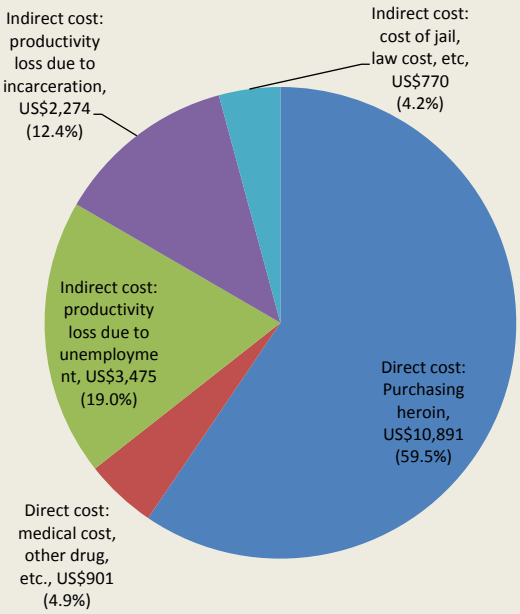


The economic cost of OD (US$/ person-year), comparing with schizophrenia (1.07 GDP)

Lee IH et al Psychiatry Research 2008

Lin SH et al Psychiatry Research 2013





Economic cost of OD

Lin SH et al (Psychiatry Research 2013)

	R(QOL, economic cost)		
	Indirect cost	Direct cost	Total cost
Overall QOL	-0.13	-0.20*	-0.23*

The association between QOL and economic cost among OD

*: P < 0.05

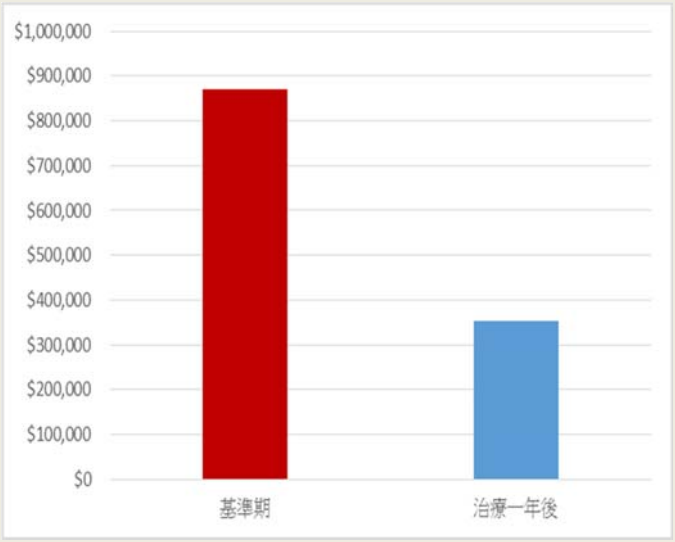
QOL: Quality of life

Lin SH et al (Psychiatry Research,2013)

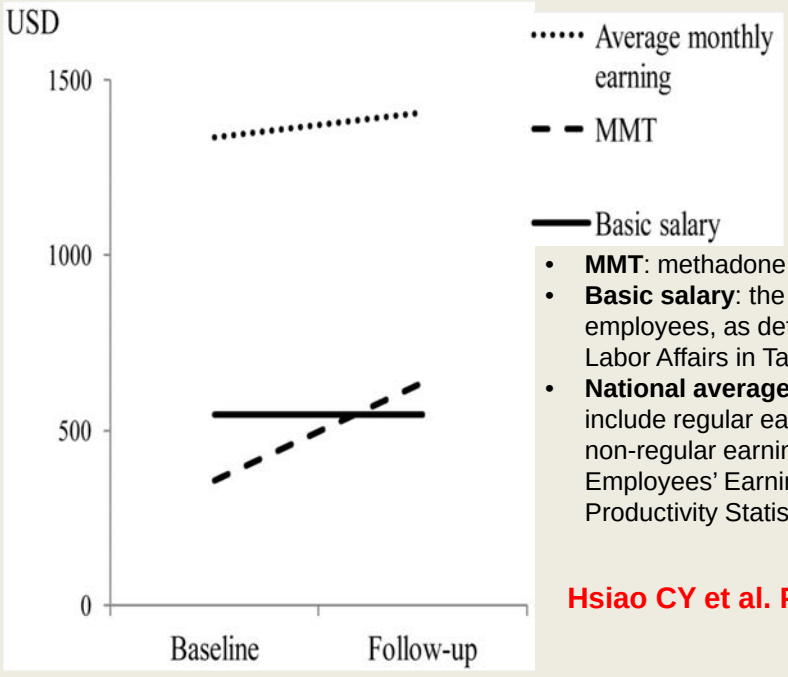
The economic gain after one-year MMT

(Hsiao et al Psychiatry Research 2014)

- 59% cost reduction in MMT program.



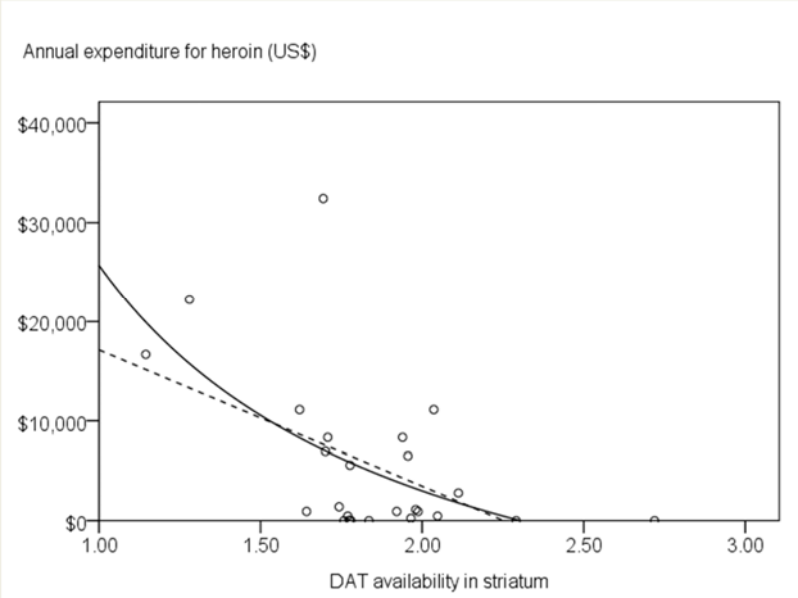
The comparison of income between patients with MMT and their controls



- **MMT**: methadone maintenance treatment.
- **Basic salary**: the lowest monthly wage for employees, as defined by the Council of Labor Affairs in Taiwan.
- **National average monthly earnings:** include regular earnings, overtime, and other non-regular earnings, as derived from the Employees' Earnings Survey and Productivity Statistics.

Hsiao CY et al. Psychiatry Research 2014

Neuroimaging and Economic cost



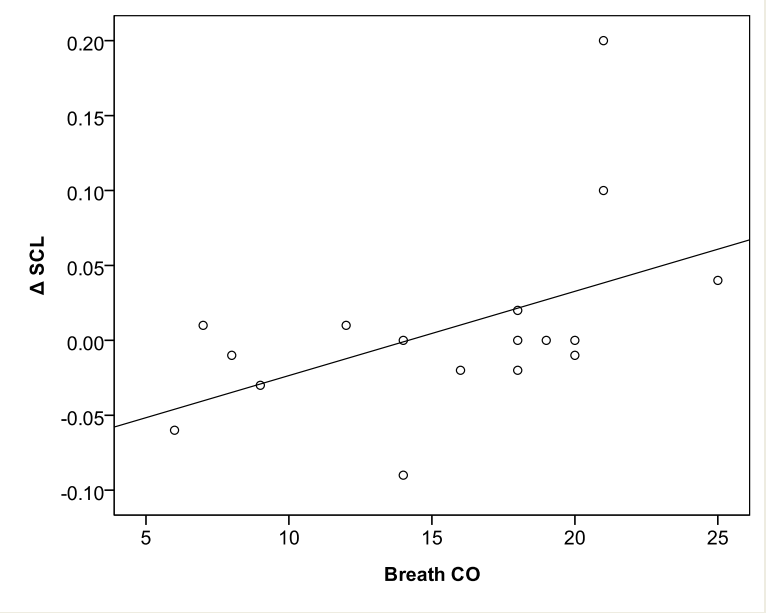
The association between dopamine function and direct economic cost

Linear model: $R^2 = 0.26$, $P < 0.01$; Inverse model: $R^2 = 0.31$, $P < 0.005$

DAT: dopamine transporter

Lin SH et al Psychiatry Research 2015

An association between high breath CO concentration and cue-induced SCL elevation



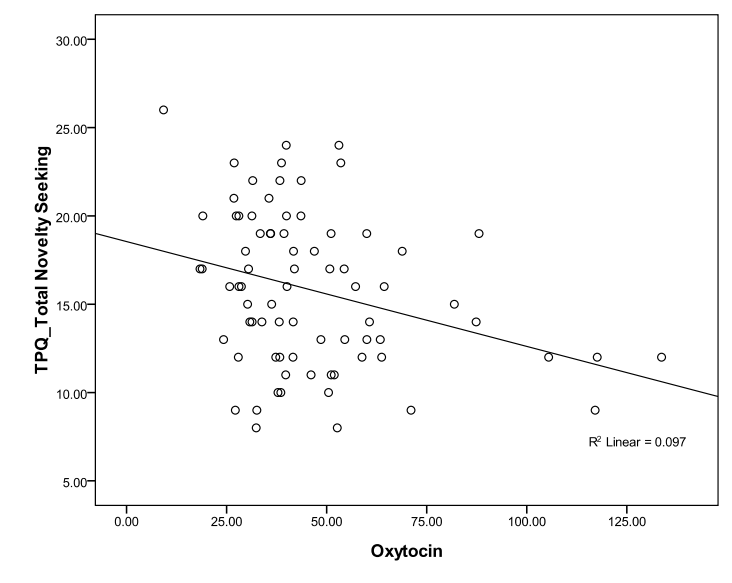
N = 17

ρ = 0.54, p = 0.02

The SCL among individuals with a higher level of CO tended to be elevated by cue of heroin

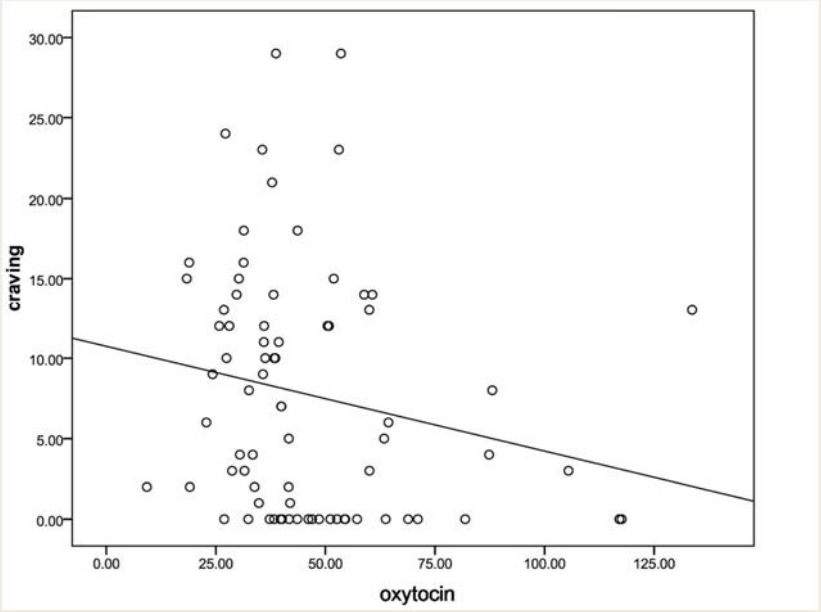
Lin SH et al., submitted

Plasma oxytocin associated with novelty seeking among heroin users



Lin SH et al Neuropsychobiology 2015

Plasma oxytocin associated with carving among heroin users

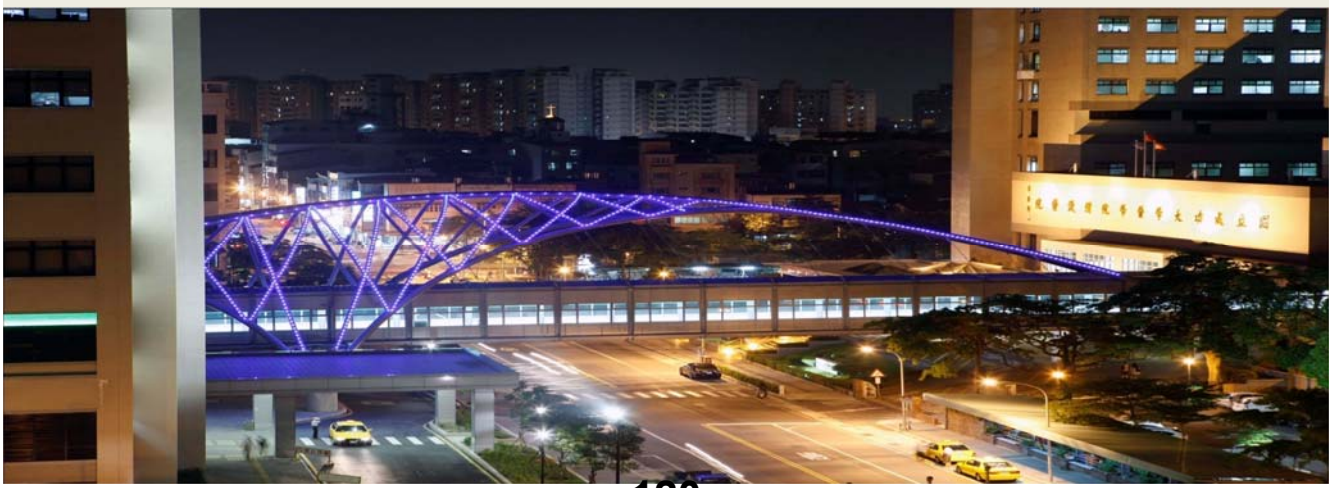


Lin SH et al, submitted

謝謝聆聽(飛躍勝利/邁向成功)

在努力將剎那化為永恆的當下,

歷史已靜悄悄的讓永恆轉為剎那般的從眼前逝去!



1. Yang YK*, Yao WJ, McEvoy JP, Chu CL, Lee IH, Chen PS, Yeh TL, Chiu NT: Striatal dopamine D2/D3 receptor availability in male smokers. Psychiatry Research-Neuroimaging 2006;146:87-90 (SCI)
2. Yang YK*, Yao WJ, Yeh TL, Lee IH, Chen KC, Ru RB: Association between serotonin transporter availability and hostility scores in healthy volunteers-A single photon emission computed tomography study with [(123)I] ADAM. Psychiatry Research-Neuroimaging 2007;154:281-4 (SCI)
3. Yang YK*, Yao WJ, Yeh TL, Lee IH, Chen PS, Lu RB: Decreased dopamine transporter availability in male smokers — A dual isotope SPECT study. Progress Neuro-Psychopharmacol and Biological Psychiatry 2008;32:274-9. (SCI)
4. Lee IH, Chen PS, Yang YK*, Liao YC, Lee YD, Yeh TL, Yeh LL, Cheng SH, Chu CL: The functionality and economic costs of outpatients with schizophrenia in Taiwan. Psychiatry Research 2008;158:306-315 (SSCI&SCI)
5. Tsai HC, Yeh TL, Hsieh MH, Lee IH, Chen KC, Chen PS, Yang YK*, Yao WJ: Association between serotonin transporter availability and overall rating scores of quality of life in healthy volunteers. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2009;33:711-4 (SCI & SSCI)
6. Yeh TL, Chen KC, Lin SH, Lee IH, Chen PS, Yao WJ, Lee SY, Yang YK*, Lu RB, Liao MS: The availability of dopamine and serotonin transporter in heroin users — a two-isotope SPECT study. Psychopharmacology 2012; 220: 54-64 (SCI)
7. Tsai HC, Lin SH, Chen PS, Lee IH, Yeh TL, Chen KC, Yang YK: Quantifying midbrain serotonin transporter in depression: a preliminary study of diagnosis and naturalistic treatment outcome. Pharmacopsychiatry 2015; 48:58-64 (SCI)
8. Lin SH, Chen KC, Lee SY, Lee IH, Yeh TL, Chen PS, Lu RB, Yang YK*: The economic cost of heroin dependency and quality of life among heroin users in Taiwan. Psychiatry Research 2013 (SCI)
9. Lin SH, Chen KC, Lee SY, Chiu NT, Lee IH, Chen PS, Yeh TL, Lu RB, Yang YK*: The association between heroin expenditure and dopamine transporter availability--a single-photon emission computed tomography study. Psychiatry Research 2015; 231: 292-297 (SCI)
10. Lin SH, Chen KC, Lee SY, Yao WJ, Chiu NT, Lee IH, Chen PS, Yeh TL, Lu RB, Yang YK*: Probing the in vivo association between dopamine and serotonin transporter availability with relapse among heroin users—a dual isotopes SPECT pilot study. European Neuropsychopharmacology 2012; 22: 647-650
11. Lin SH, Lee LT, Tsai HC, Chen KC, Chen WT, Lee IH, Lu RB, Chen PS, Yang YK*: Association between Blood Level of Plasma Oxytocin and Novelty Seeking among Methadone-Maintained Heroin Users. Neuropsychobiology 2015; 71: 65-69 (SCI)
12. Lin SH, Chen PS, Lee LT, Lee SY, Tsai HC Chen WT Chen KC, Lee IH, Lu RB, Yang YK*: The association between level of plasma oxytocin and craving among heroin users, submitted
13. Lin SH, Chen KC, Wang TY, Tsai HC, Chen WT, Lee IH Chen PS, Yang YK*: Breath carbon monoxide output and changes in cue-induced skin conductance level in heroin users: a pilot study. Submitted
14. Zhao RJ, Lin SH, Lee LT, Lee IH, Chen PS, Chen KC, Yang YK*: Probing the Serotonin Transporter Availability among Male Cigarette Smokers: A SPECT Study with [123I] ADAM. Submitted

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