## Advances in Drug Abuse and Addiction from NIDA: Implications for Treatment

Timothy P. Condon, Ph.D. Deputy Director National Institute on Drug Abuse National Institutes of Health Department of Health and Human Services

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## NIDA Research

#### From Molecules...







...To Managed Care ...Drug Courts ...Community Coalitions





DRUGS

NEUROTOXICITY OBESITY AIDS CANCER MENTAL ILLNESS

Medical

Economic health care costs productivity loss accidents

HOMELESSNESS CRIME VIOLENCE

CIA

### Advances in Science Are Bringing Us New Understanding of Drug Abuse & Addiction



This Knowledge Is Allowing Us To Develop More *Targeted Strategies* for Its Prevention and Treatment



#### Your Brain on Drugs - Then

#### this is your brain on drugs.



#### Your Brain on Drugs – Now



#### Source: Breiter & Rosen, Ann N Y Acad Sci 1999

## What have we learned?

## Drug Abuse is a Preventable Behavior Drug Addiction is a Treatable Disease

**Partnership for a Drug Free America** 

In 2008, an estimated 20.1 million Americans, or 8.0 percent of the population aged 12 or older, were current illicit drug users.

Source: 2008 National Survey on Drug Use and Health (NSDUH), SAMHSA

#### Percent of Students Reporting Past Month Use of Any Illicit Drug Has Decreased

25% Decline 2001 to 2008\*



**P**<.001

\*

SOURCE: University of Michigan, 2008 Monitoring the Future Study NIDA

#### Percent of Students Reporting Any Illicit Drug Use in Past Year, by Grade



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#### Issues of Concern Percent of 12th Graders Reporting Nonmedical Use of OxyContin and Vicodin in the Past Year Remained High



No year-to-year differences are statistically significant.

SOURCE: University of Michigan, 2008 Monitoring the Future Study

#### Prescription/Over-the-Counter Drugs Account for 7 Out of 11 of the Most Frequently Abused Drugs

Prevalence of Past Year Drug Use Among 12th Graders



In 2008, 15.4% of 12<sup>th</sup> graders reported abusing prescription drugs within the past year.

# Source of Prescription Narcotics among those who used in the Past Year, 12<sup>th</sup> grade





Projected Prescriptions for Hydrocodone and Oxycodone Products Dispensed by US Retail Pharmacies, Years 1991–2008



#### National Estimated Prevalence (Rate per 1,000 Population, aged 0 to 85+) of Persons with a Dispensed Opioid Prescription, by Specialty, 2007



Opioids Include Codeine & Comb NON-INJ (USC 02232), Morphine & Opium NON-INJ (USC 0222), Morphine & Opium INJ (USC 0221), Codeine & Comb INJ (USC 02231).

Source: SDI Health, TPT 2008 09-29-08 Opiates and US Census

# Why ? Why do people take drugs?

## Why do people take drugs?



To feel better To lessen: Anxiety Worries Fears Depression Hopelessness Withdrawal

Drawings courtesy of Vivian Felsen

## **Drug Abuse Risk Factors**

Community

#### **Peer Cluster**

Family



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# A Major Reason People Take a Drug is they Like What It Does to Their Brains

**Initial Drug Use Is A** *Voluntary* **Behavior...** 

A Person *Chooses* to Take a Drug for the First Time

## Initially, A Person Takes A Drug Hoping to Change their Mood, Perception, or Emotional State

Translation---

...Hoping to Change their Brain

# What have we learned about Vulnerability?

# Why do some people become addicted while others do not?

### We Know There's A Big Genetic Contribution To Drug Abuse and Addiction...

And the Nature of this Contribution Is Extremely Complex

## Genetic component of common traits

Trait	Heritability
Type II (adult-onset) diabetes	0.31
Type I (insulin-dependent) diabetes	$0.7^{2}$
Hypertension	0.3 - 0.5 <sup>3</sup>
Peanut allergy	0.84
Cataract (age-related)	0.55
Alcoholism	0.66
Nicotine	$0.5 - 0.6^{7}$
Cocaine and stimulants	$0.4 - 0.8^{8}$
Heroin and opiates	0.59
Marijuana	$0.3 - 0.8^{10}$

#### **DA Receptor Levels and Response to MP**



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Subjects with low receptor levels found MP pleasant while those with high levels found MP unpleasant

#### **Some Gene Variants Implicated in Addiction**

- FAAH associated with drug dependence
- **OPRM1** associated with opiates and alcoholism
- CYP2A6, CYP2B6 associated with smoking and smoking cessation
- ALDH2 associated with protection against alcoholism
- **DBH** (Dopamine beta-hydroxylase) cocaine-induced paranoia
- DRD2, DRD4 (Dopamine receptors) reward, craving
- NrCAM, neurexins (Cell adhesions genes) assoc with drug abuse and addiction
- **Prodynorphin gene -** associated with protection against cocaine dependence
- Nicotinic alpha 7 promoter assoc. with decreased expression of its message in different brains regions and with sensory gating defects in schizophrenics
- -- Alpha 5 and beta 3 (nicotinic receptors) assoc. with nicotine dependence
- -- **5HT1B** (serotonin receptor) associated with conduct disorder and alcoholism

## Initial p values of Top 40 K SNPs



#### Epigenetic Mechanisms Regulate How Genetic Information Is Expressed Across Development, Tissue, Environment and Disease States



**Epigenetics** 

DNA Methylation – silences gene

- Histone Modification methylation, acetylation, or phosphorylation
- Non coding RNA

**Epigenetics + Disease** 

#### Epigenetic Mechanisms Regulate How Genetic Information Is Expressed Across Development, Tissue, Environment and Disease States

#### EPIGENETIC REGULATION IN DRUG ADDICTION



Cocaine, by inducing the transcription factor △FosB, and △FosB's recruitment of numerous co-activators (e.g., HAT's, SWI-SNF), causes sustained acetylation and activation of susceptible genes (e.g., Cok), which helps drive the addicted state.



DNA Methylation – silences gene Histone Modification – methylation, acetylation, or phosphorylation Non coding RNA





#### **Risk Factors**

Poor Family Support
Drug availability
Poverty
Crime



## What have we learned about

## other aspects of vulnerability?

#### **Addiction Is a Developmental Disease** starts in childhood and adolescence 1.8 ΓΟΒΑϹϹΟ THC 1.6 % in each age group to develop ALCOHOL 1.4 first-time dependence 1.2 1.0 0.8 0.6 0.4 0.2 0.0 15 45 **50** 55 65 5 10 20 25 30 35 **40 60** 70 75 Age

Age at tobacco, at alcohol and at cannabis dependence, as per DSM IV

National Epidemiologic Survey on Alcohol and Related Conditions, 2003

**Right Lateral and Top Views of the Dynamic Sequence of GM Maturation Over the Cortical Surface** 



Source: Gogtay, Nitin et al. (2004) Proc. Natl. Acad. Sci. USA 101, 8174-8179 Copyright ©2004 by the National Academy of Sciences
Exposure to drugs of abuse during adolescence could have profound effects on *Brain Development & Brain Plasticity*



 Understanding drug abuse and addiction from a *Development Perspective* has important implications for their Prevention & Treatment



Notice: Judgment is last to develop!

#### **K. Winters**

# What Else Have We Learned?

#### Substance Abuse Is Commonly Linked To A Variety of Other Medical & Mental Health Conditions



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Source: Mertens JR et al. Arch Intern Med, 163, November 10, 2003.

#### ADDICTIVE DISORDERS OFTEN CO-EXIST WITH MENTAL DISORDERS



### Drug Users have a Higher Risk of Developing Mental Disorders

Psychosis

Depression

AnxietyPanic attacks

Co-Occurrence of Serious Psychological Distress and Substance Use Disorder in the Past Year among Adults Aged 18 or Older: 2006



**Co-Occurring SUD and SPD** 

National Survey on Drug Use and Health, SAMHSA

### Many Common Factors Are Involved in Addiction and Mental Illness

#### **Addiction:**

•Early Physical or Sexual Abuse

•Stress

•Family History

•Mental Illness

•Peers who use Drugs



**STRESS & DRUG ABUSE** 

**Mental Illness:** 

•Early Physical or Sexual Abuse

•Stress

•Family History

•Drug and Alcohol Abuse

### Why do Mental Illnesses and Substance Abuse Co-occur?



- Self-medication hypothesis
  - substance abuse begins as a means to alleviate symptoms of mental illness
- Causal effects of substance abuse
  - Substance abuse may increase vulnerability to mental illness
- Common or correlated causes
  - the life processes and risk factors that give rise to mental illness and substance abuse may be related or overlap

# **Comorbidity is a Reality**



# What have learned about

how drugs work?



We Now Know That... Despite Their Many Differences, Most Abused Substances Enhance the Brain's Reward Pathway

# A Major Reason People Take a Drug is they Like What It Does to Their Brains

# Activation of the reward pathway by addictive drugs

alcohol

cocaine heroin nicotine



#### **Dopamine Pathways**

matum

ucleus

ccumbens

hippocampus

frontal cortex

<u>Functions</u>
reward (motivation)
pleasure, euphoria
motor function (fine tuning)
compulsion
perseveration substantia nigra/VTA We Know That... In Combination with Many Other Transmitter Systems, and Despite Their Many Differences, Most Abused Substances Enhance Dopamine Activities

#### Nuclear Circuitry Mediating the Activation of Goal-Directed Behavior



### **Circuits Involved In Drug Abuse and Addiction**



Science Has Generated A Lot of Evidence Showing That...

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

### AND...

# We Have Evidence That These Changes Can Be Both Structural and Functional





#### **Dopamine D2 Receptors are Lower in Addiction**

addicted



















#### **Effect of Cocaine Abuse on Dopamine D2 Receptors**



normal subject



#### cocaine abuser (1 month post)



cocaine abuser (4 months post)

#### Chronic cocaine increases density of dendritic spines and neuronal branching in the nucleus accumbens



Robinson, T.E. & Kolb, B. Eur. J. of Neuro. 1999. Ferrario, C.R. et al. Biol. Psychiatry, 2005.



Normal responses to drugs

Use-dependent plasticity leading to sensitized responses to drug and environmental cues

> Nature Reviews | Neuroscience Nestler, 2001

#### Repeated Drug Abuse Increases Genetic Transcription Resulting in Long-term Structural Changes



### **Circuits Involved In Drug Abuse and Addiction**



### AND...

# We Have Evidence That These Changes Can Be Both Structural and Functional

#### **Dopamine Transporters in Methamphetamine Abusers**



**Normal Control** 



2.4 2.2 ansporters 2.0 1.8 1.6 Bm Dopamine 1.4 1.2 1.0 Normal Meth Controls **Abusers** p < 0.0002

**Methamphetamine Abuser** 

Methamphetamine abusers have significant reductions in dopamine transporters.

BNL - UCLA - SUNY NIDA - ONDCP - DOE



#### **Dopamine Transporters in Methamphetamine Abusers**



#### **Motor Task**

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

Memory Task Loss of dopamine transporters in the meth abusers may result in memory impairment.

> BNL/UCLA/SUNY NIDA, ONDCP, DOE



### **Implication:**

### Brain changes resulting from prolonged use of drugs may be reflected in compromised cognitive functioning

Is there recovery?

#### [C-11]d-threo-methylphenidate



**Methamphetamine Abuser** (14 month abstinent)

Source: Volkow, N.D. et al., Journal of Neuroscience, 21(23), pp. 9414-9418, December 1, 2001.

**DAT Recovery** 

## As We've Seen, Drug Use Can Lead to Structural and Functional Changes in the Brain...

# Addiction is, Fundamentally, a Brain Disease

# Addiction is Not Just a Brain Disease

# **Addiction Is A Brain Disease Expressed As Compulsive Behavior**

Both Developing and Recovering From It Depend on Behavior and Social Context
### **CRAVING INDUCTION IN PET SETTING**



#### Amygdala



#### **Anterior Cingulate**



### **Conditioned Association**



2.5

#### **Nature Video**

**Cocaine Video** 

#### Source: Childress, et al., AJP, 1999

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# Memories Appear to Be A Critical Part of Addiction

# "People, places and things..."

# **But Not Just Memories...**

**CRIT 2010** 



# We Don't Know the Exact Switch

# **BUT...**

We Do Know that the Brain Circuitry Involved in Addiction Has Similarities to that of Other Motivational Systems

### **Cocaine Craving:** Population (Cocaine Users, Controls) x Film (cocaine )



### **Cocaine Craving:** Population (Cocaine Users, Controls) x Film (cocaine, erotic)



This Results in "Motivational Toxicity" and Compulsive Drug Use (Addiction)



Addiction is the Quintessential Biobehavioral Disorder

## **So....**

# ....What Does This Mean For Treatment?

The Most Effective Intervention Strategies Will Attend to All Aspects of Addiction:

Biology

Behavior

Social Context

# **Circuits Involved In Drug Abuse and Addiction**



### **Non Addicted Brain**

### **Addicted Brain**



### **Brain Glucose Metabolism** in Cocaine Abusers (n = 20) and Controls (n = 23)



# **Treating the ADDICTED Brain**









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### **Outpatient Study: Percent of Negative Urines After Depot Naltrexone Administration**



Visits (2 per week)

Comer, S. D., Sullivan, M. A., Yu, E., Rothenberg, J. L., Kleber, H. D., Kampman, K. et al. Arch Gen Psychiatry, 63, 210-218, 2006.

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### **Disulfiram and Naltrexone for the Treatment of Co-occurring Cocaine and Alcohol Dependence**

Percent of Cocaine-Alcohol Dependent Patients that Achieved at Least 3 Consecutive Weeks of Abstinence from both Cocaine and Alcohol in an 11 Week Trial



Source: Pettinati, HM et al., Addictive Behaviors, 33, pp. 651-667, 2008.

#### Antibodies can reduce brain concentrations

#### Capillary Blood Flow



#### Antibody holds drmcg in blood stream





# **Fewer cocaine urines at higher Vaccine Dose**

Vaccination makes antibodies by Week 4 (n=11)



# **Treating the ADDICTED Brain**







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### **Contingency Management for the Treatment of Methamphetamine Use Disorders**



Roll, J.M. et al., AJP 163(11) pp. 1993-1999, November 2006.

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# **Treating the ADDICTED Brain**



**Medications Biofeedback Coping Skills** Desensitization **Other behavioral strategies** 

#### Time-dependent increases in cue-induced cocaine seeking after withdrawal from drug self-administration



Grimm et al. Incubation of cocaine craving after withdrawal. <u>Nature</u>, 2001 Lu et al. <u>Psychopharmacology</u>, 2004

#### Summary of neuropharmacological findings

#### Incubation of cocaine craving:

Associated with increases in peptide levels of BDNF in VTA, accumbens and amygdala (Grimm et al. J Neurosci 2003; Lu et al. J Neurosci 2004)

Mediated by time-dependent increases in responsiveness of central amygdala ERK and glutamate to cocaine cues (Lu et al. Nat Neurosci 2005; Lu et al. Biol Psychiatry 2007)



ERK=extracellular signal-regulated kinase

#### AMYGDALAR CONNECTIVITY during brief .5 sec Cocaine Cues

Placebo



Drug 2 amyg conx (n=7)



Source: Childress, et al, unpublished

#### AMYGDALAR CONNECTIVITY during brief .5 sec Cocaine Cues



Drug 2 amyg conx (n=7)

#### **Baclofen blunts AMYGDALAR CONNECTIVITY**



Baclofen



Source: Childress, et al, unpublished

# **Treating the ADDICTED Brain**



Behavioral Interventions Medications Biofeedback

### Abstinence Rates Following Behavioral Treatments for Marijuana Dependence



### **Brief Motivational Intervention at a Clinic Visit Reduces Cocaine and Heroin Use**

Abstinence Among Those Screening Positive At Baseline



Bernstein et al. Drug and Alcohol Dependence 2005;77:49-59

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# Can We Predict Whether or Not a Treatment Will Work?

# **Brain Network For Recovery ?**

#### • Insula

- Monitor internal body state (Visceral sensory)
- Register and Predict Adverse Events

#### • Anterior Cingulate

- Drives body states (Viscero-motor)
- Error Detection
- Monitor (resolve) Conflicts
  - Stroop Task (Blue Blue)
- Cognitive Dissonance

#### • Predicts

- Treatment Adherence
- Slips, Relapse, Abstinence
### **Predictors of Nonresponse to Cognitive Behavioral Therapy or Venlafaxine in MDD**



Ventral anterior cingulate cortex hypermetabolism in non-responders to either treatment

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Konarski et al, J Psychiatry Neurosci. 2009 May; 34(3): 175–180

### **Brain Regions Predictive of Smoking Relapse**

**Relapses > Non-Relapsers during Emotional Stroop with Smoking Words** 



**Relapsers < Non-Relapsers Functional Connectivity** 



Janes et al., 2010 NIDA

## **Brain Predictor of Relapse**



Paulus, 2005



### Drug Addiction: A Complex Behavioral and Neurobiological Disorder



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

...And Those Differences Are An Essential Element of Addiction

# That's Why Addicts Can't Just Quit That's Why Treatment Is Essential!



Treating A Biobehavioral Disorder Must Go Beyond Just Fixing The Chemistry The Most Effective Treatment Strategies Will Attend to All Aspects of Addiction:

Biology

- Behavior
- Social Context

### Drug Abuse Treatment <u>Core</u> Components and <u>Comprehensive</u> Services



Etheridge, Hubbard, Anderson, Craddock, & Flynn, 1997 (PAB)

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# In Treating Addiction... We Need to Keep Our Eye on the Real Target





# We Need to View and Treat Addiction As A Chronic, Relapsing Illness

### Longitudinal Trends in Recovery (Pathways *N*=1326)



Dennis, ML Foss MA & Scott CK (2007). An eight-year perspective on the relationship between the duration of abstinence and other aspects of recovery. Eval. Rev.

athways

### **Relapse Rates Are Similar for Drug Dependence and Other Chronic Illnesses**



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



#### **Treatment Research Institute**



#### **Treatment Research Institute**

NIDA



#### **Treatment Research Institute**

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?

## NIDA Physician Outreach

### Research



# NIDAMED 🗾

#### Introducing NIDAMED!

NIDAMED is NIDA's new initiative to provide the medical community with drug abuse resources to enhance patient care.

At the heart of NIDAMED are research-based drug use screening tools and resources. Designed with the demands of modern clinical practice in mind, these products help clinicians to efficiently screen at-risk patients and conduct the follow-up steps necessary to provide the very best in medical care.

Visit www.drugabuse.gov/NIDAMED for more information.

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And in American States of Features

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### HELP YOUR DOCTOR READ BETWEEN THE LINES.

## Where Do We Need to Go From Here?

We Need to...

# Advance the SCIENCE and to... End the STIGMA and Discrimination

# NATIONAL INSTITUTE ON DRUG ABUSE



www.drugabuse.gov

www.drugabuse.gov/blending

www.nnp.drugabuse.gov



65 min Keynote