



Neuroscience of Substance Dependence

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**Principal Editor, WHO Report on
Neuroscience of Psychoactive Substance Use and Dependence**

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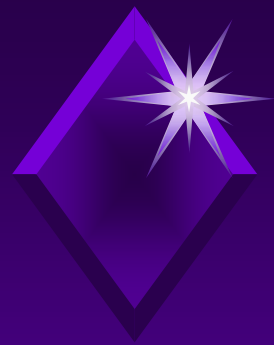
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WHO Report

- ◆ Launched March 2004—first report of its kind
- ◆ GLOBAL EMPHASIS
- ◆ Authoritative report summarizing latest scientific knowledge on the role of the brain in substance dependence
- ◆ Concludes that substance dependence is as much a disorder of the brain as any other neurological or psychiatric disorder
- ◆ Emphasizes that substance dependence is multifactorial with biological, genetic, cultural, environmental and psychosocial factors all playing strong roles
- ◆ Discusses neurobiological commonalities across different drug classes and new developments in neuroscience research with implications for our understanding and treatment of substance dependence



Topics Covered by the Report

- ◆ Introduction--Global Burden of Disease/ Rationale
- ◆ Brain Mechanisms
- ◆ Biobehavioral Processes Underlying Dependence
- ◆ Psychopharmacology of Dependence for Different Drug Classes
- ◆ Genetic Basis of Dependence
- ◆ Concurrent Disorders
- ◆ Ethical Issues
- ◆ Conclusions and Implications for Policy Development



Global Burden of Disease

- ◆ About 205M people use illicit substances
- ◆ More than 5500 billion cigarettes are manufactured annually for the 1.2 billion smokers in the world.
- ◆ Substance abuse and dependence exacerbate the challenges of mental illness (ie concurrent disorders)
- ◆ Substance dependence among the top 10 causes of disability worldwide
- ◆ Global Burden of disease as measured by DALYs for substance dependence is 8.9%
- ◆ Alcohol itself contributes 4%

Global use of psychoactive substances: Tobacco

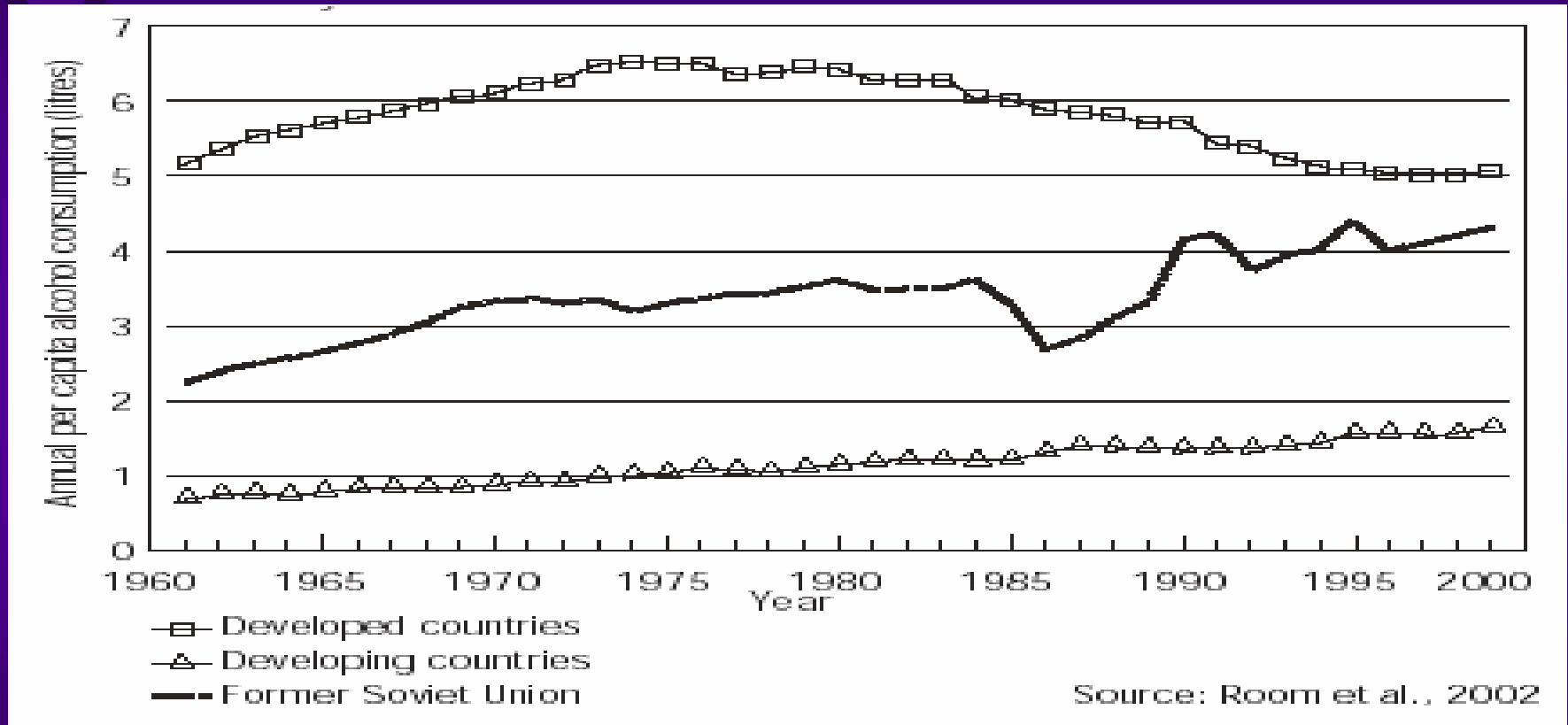
Table 1.1 Prevalence of smoking among adults and youths in selected countries

Country	Annual per capita consumption of cigarettes	Prevalence of smoking (%)			
		Adults		Youths	
		Males	Females	Males	Females
Argentina	1495	46.8	34.4	25.7	30.0
Bolivia	274	42.7	18.1	31.0	22.0
Chile	1202	26.0	18.3	34.0	43.4
China	1791	66.9	4.2	14.0	7.0
Ghana	161	28.4	3.5	16.2	17.3
Indonesia	1742	59.0	3.7	38.0	5.3
Jordan	1832	48.0	10.0	27.0	13.4
Kenya	200	66.8	31.9	16.0	10.0
Malawi	123	20.0	9.0	18.0	15.0
Mexico	754	51.2	18.4	27.9	16.0
Nepal	619	48.0	29.0	12.0	6.0
Peru	1849	41.5	15.7	22.0	15.0
Poland	2061	44.0	25.0	29.0	20.0
Singapore	1230	26.9	3.1	10.5	7.5
Sri Lanka	374	25.7	1.7	13.7	5.8
USA	2255	25.7	21.5	27.5	24.2

Source: Mackay & Eriksen, 2002.

Global use of Psychoactive Substances- Alcohol

Figure 1.1 Annual per capita alcohol consumption among adults aged 15 years or more.



Neuroscience of Substance Dependence

Report: Why and Why now?

- ◆ Timing—recognition that neurobiological alterations caused by drugs of abuse, represent major causal and perpetuating factors to dependence
- ◆ Timing—Scientific advances in the last 30 years and philosophical changes over the last 100 years (e.g., biological determinism), have permitted a neuroscience-based understanding of dependence to emerge
- ◆ Critical mass of scientific literature now exists to support a broad based report on the neuroscience of Drug Dependence

Neuroscience of Substance Dependence

Report: Why and Why now?

- ◆ The “biologizing” of drug dependence helps bring dependence into the realm of health
- ◆ *Stigma still a major problem and neuroscience knowledge can help (as in the case of mental health) lift stigma*
- ◆ Still, there are many places in the world that continue to view drug dependence in non-health terms
- ◆ The present WHO report: a catalyst internationally for the development of health-based policies for dealing with drug dependence



Challenges for the Report

- ◆ Although considerable preclinical literature exists concerning the neurobiology of dependence, there is limited literature that pertains directly to human substance dependence.
- ◆ As such, relative to other areas of health, biologically-based treatment-relevant frameworks for dependence are at an early stage of development
- ◆ As a global report, the report focused on well developed literature, and arrived at a framework that reflects broadly supported views of well developed literature
- ◆ At the same time, this needed to be balanced with the need for including important new developments with future implications— e.g., PET studies



Process for the Report

- ◆ Product of 3 years of work involving contributions from experts around the world (truly global)
- ◆ Project began in 2000 with a consultation in New Orleans at the Congress on Neuroscience
- ◆ Meetings convened by WHO attended by societies and selected experts from around the world
- ◆ 25 reviews commissioned, completed and submitted formed the basis for the report
- ◆ Meetings held in Geneva and Mexico to discuss report structure, content and background papers

What Makes Substance Dependence a Public Health Concern?

- ◆ Broad-based health consequences
- ◆ Drug dependence as a CNS motivational disorder
- ◆ Can be understood in terms of public health principles of etiology, course, epidemiology and population-based responses

Substance Dependence: A Broad Based Health Problem

- ◆ The health burden that results from chronic use of addictive substances is enormous (i.e., cancer, cardiac, respiratory, HIV etc).
- ◆ The consequences of life style changes and market factors associated with substance dependence, further contribute to this burden

Substance Dependence: A CNS Motivational Disorder

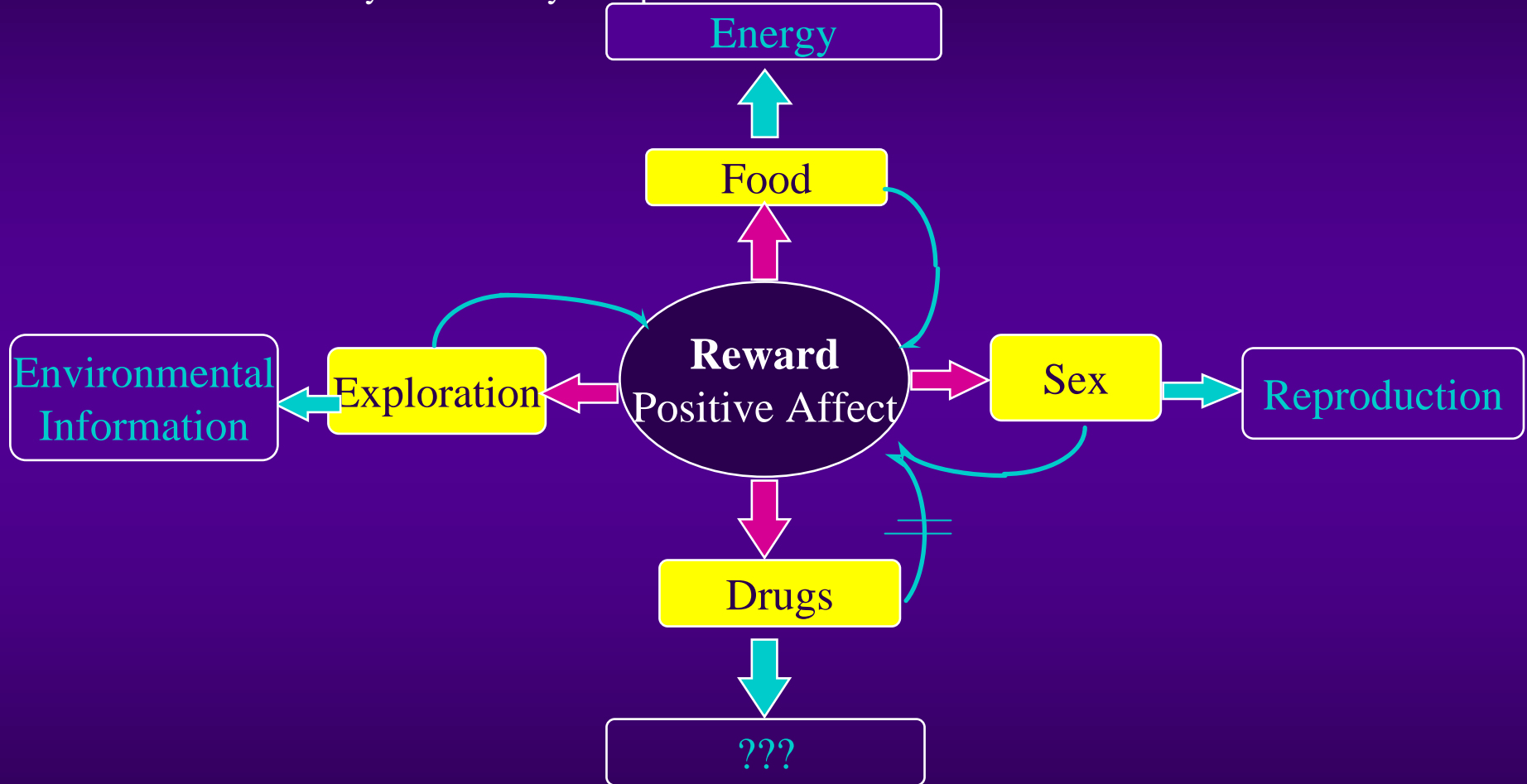
- ◆ apart from the negative health “side-effects”, substance dependence itself represents a behavioural (motivational) disorder
- ◆ Substance dependence is characterized by dysregulation of motivational processes
- ◆ motivational systems in the brain are disrupted following short and long term exposure to drugs of abuse.

Substance Dependence: A CNS Motivational Disorder (cont'd)

- ◆ Alterations in the brain's motivational systems responsible for initiating and/or perpetuating substance dependence, are associated with:
 - ◆ *drug use (reward, conditioning, sensitization, tolerance)*
 - ◆ *psychosocial and environmental factors (e.g. stress, stigma, social context, drug controls, availability, poverty, globalization)*
 - ◆ *neurobiological conditions inherent to the individual (e.g., mental illness)*

Drugs as Surrogates of Conventional Reinforcers

- ◆ Stimuli with positive affective valence increase reward system activity.
- ◆ Increased reward system activity is expressed as increased behavior directed at the relevant stimuli.

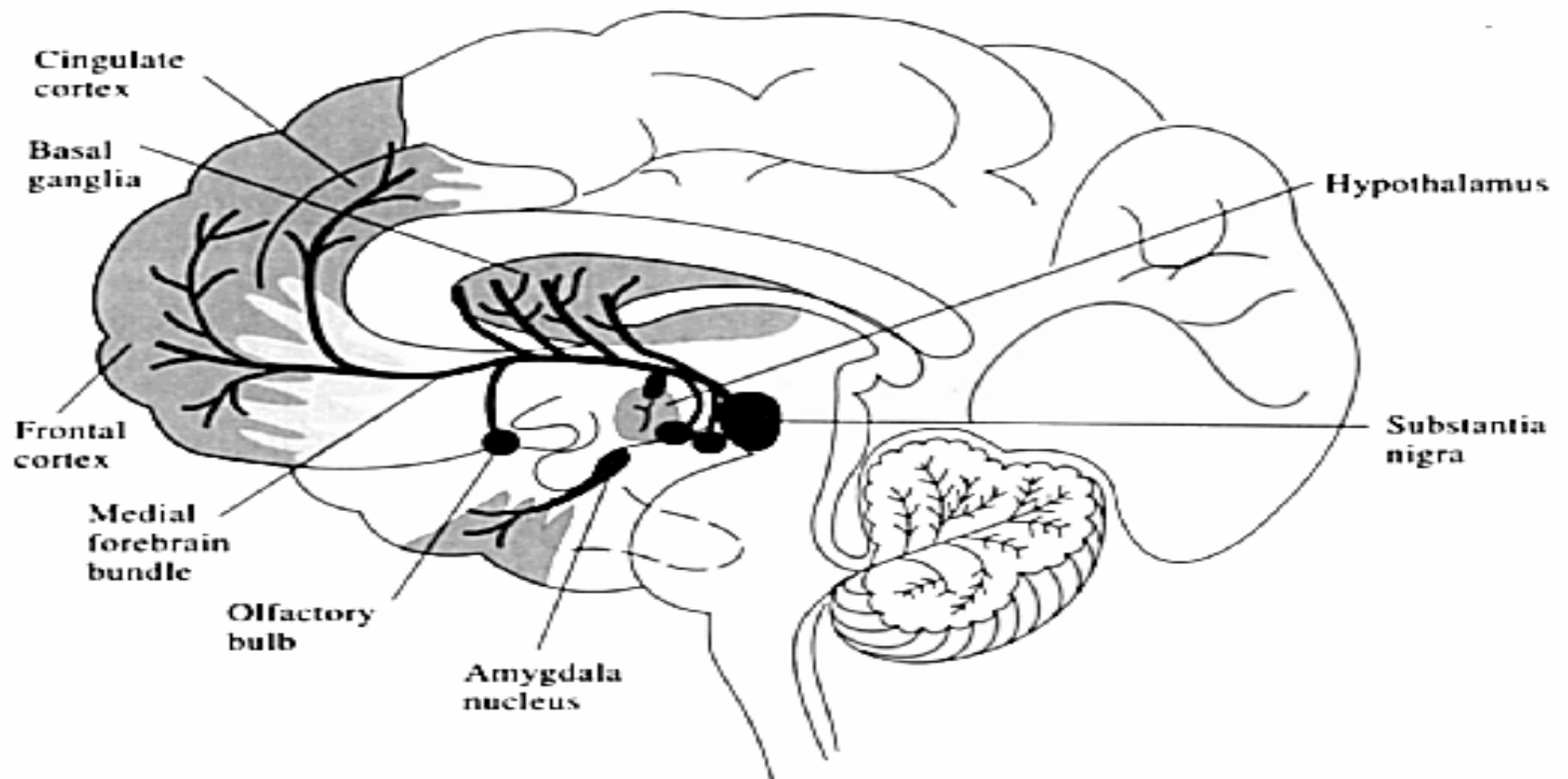




The role of dopamine

- ◆ Dopamine is important to the development of dependence for all classes of psychoactive substances because of its critical role in response-reinforcement learning.
- ◆ Almost all psychoactive substances with reinforcing properties activate mesolimbic dopamine, either directly or indirectly.
- ◆ Dopamine is released in response to rewards, thus reinforcing the behaviours that led to the occurrence of that reward.

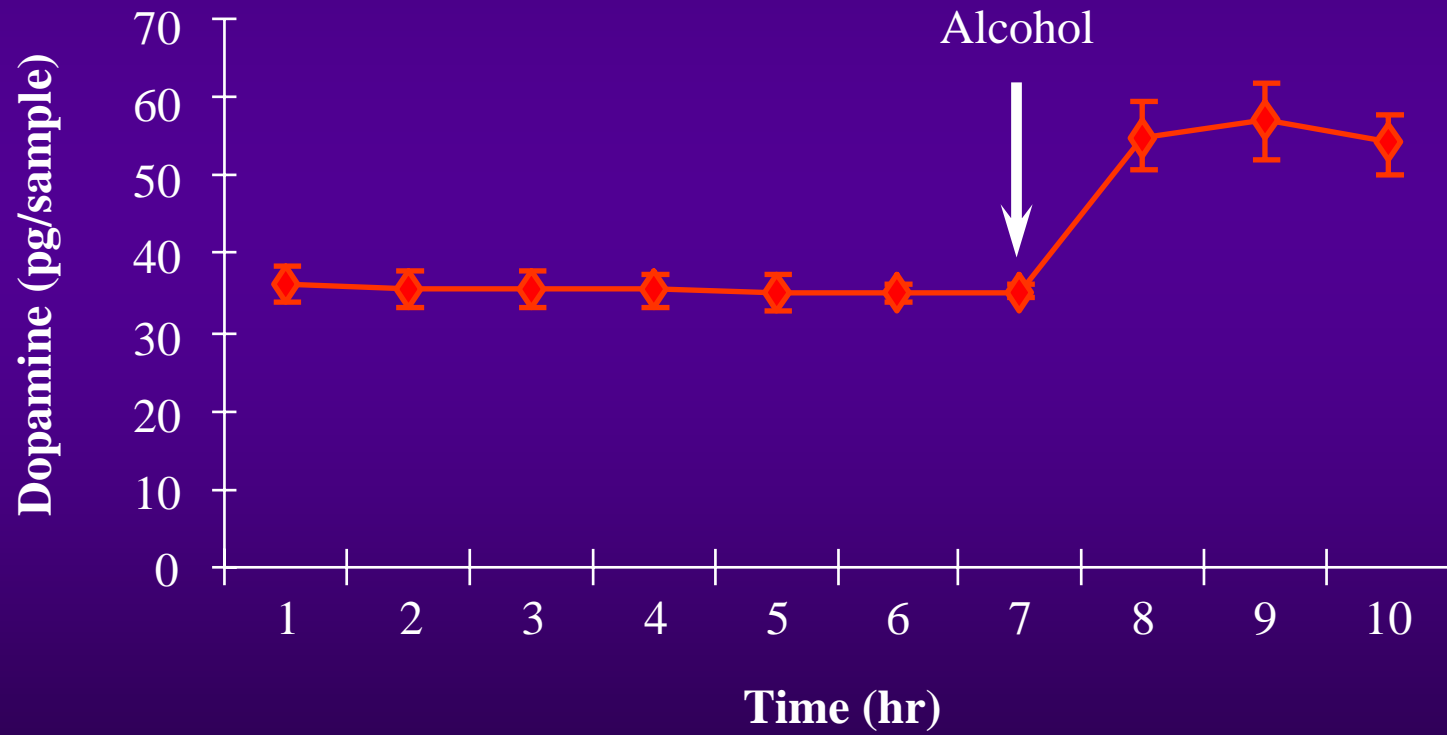
Dopamine Pathways



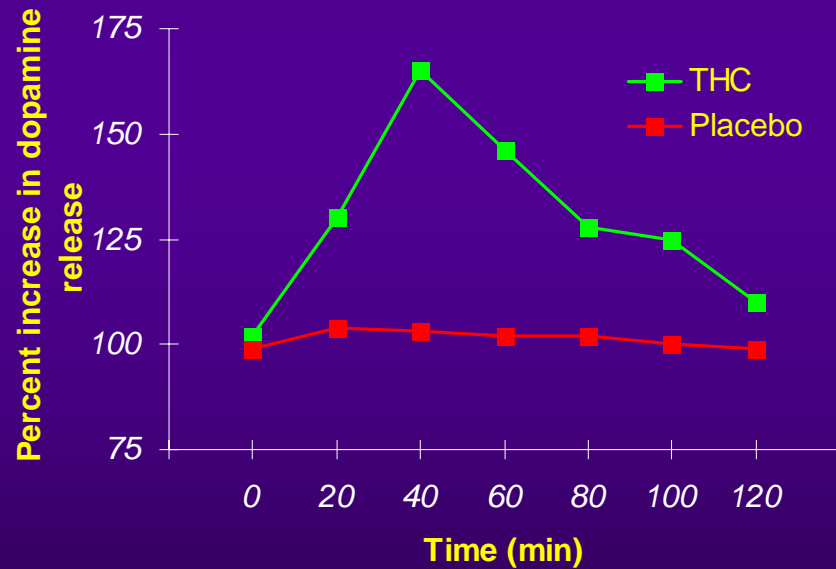
Neurobiological Mechanisms of Substance Dependence

- ◆ *A common path or not?*
- ◆ neurotransmitters, intracellular mechanisms
- ◆ neuroimaging and neurochemical anatomy

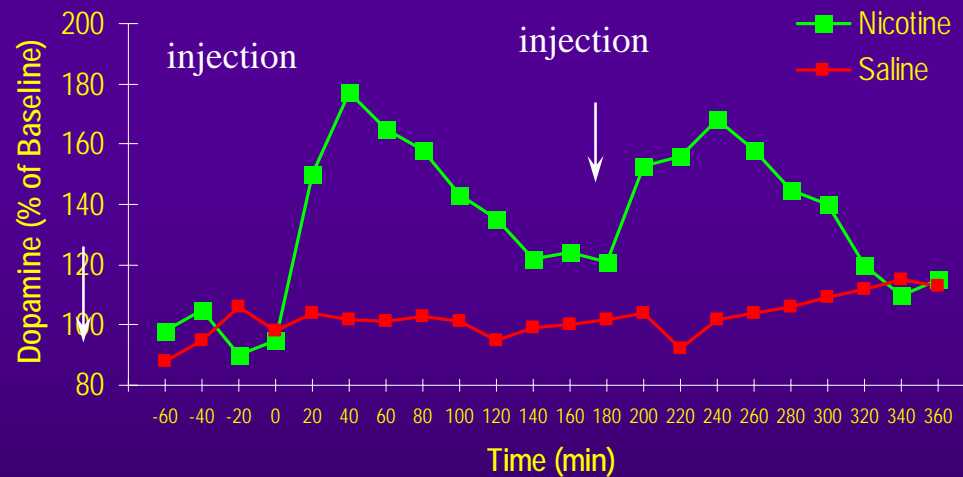
Other Self-Administered Drugs and Dopamine: Alcohol



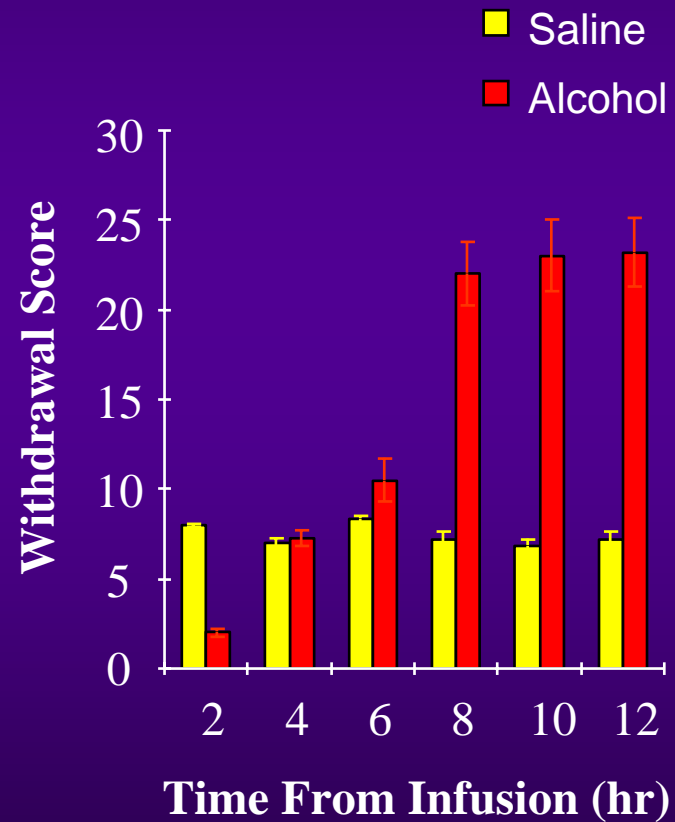
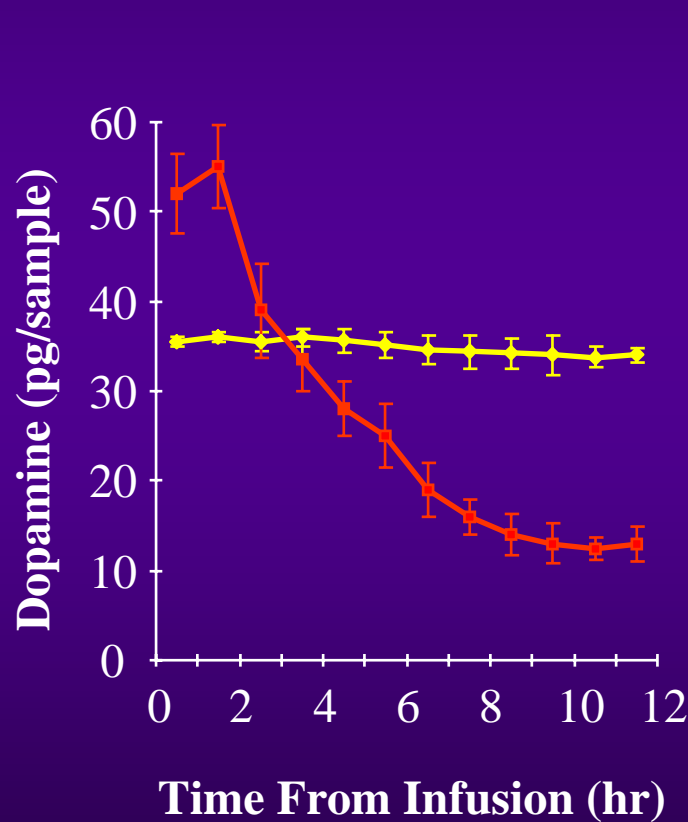
Release of dopamine in the Nacc caused by injections of THC



Release of Dopamine in the NAcc Caused by Injections of Nicotine



Withdrawal and Dopamine



Dependence is much more than Reward

Reward

- ◆ Approach Behavior
- ◆ Hedonic Reactivity
- ◆ Assignment of Positive Valence to Stimuli
- ◆ Conditioning and sensitization

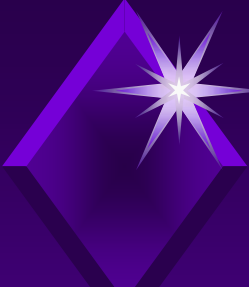
Drug Dependence

- ◆ Maladaptive Reward Functioning
- ◆ Anticipatory Arousal
- ◆ Relapse/Craving
- ◆ Sensitivity to Drug-Related Cues
- ◆ Generalization of Drug-Related Cues
- ◆ Exaggerated Mental Preoccupation
- ◆ Tolerance
- ◆ Withdrawal



Drug dependence as a response to incentive-motivation

- ◆ The rewarding properties of drugs are necessary for their dependence-producing effects for at least 2 reasons:
 - ◆ Drug reward, by promoting drug self-administration, is necessary for repeated drug exposure
 - ◆ The rewarding properties of drugs are necessary for attributing- by an associative learning mechanism- positive motivational value to stimuli that predict drug availability and act as powerful incentives of drug – seeking behaviour.

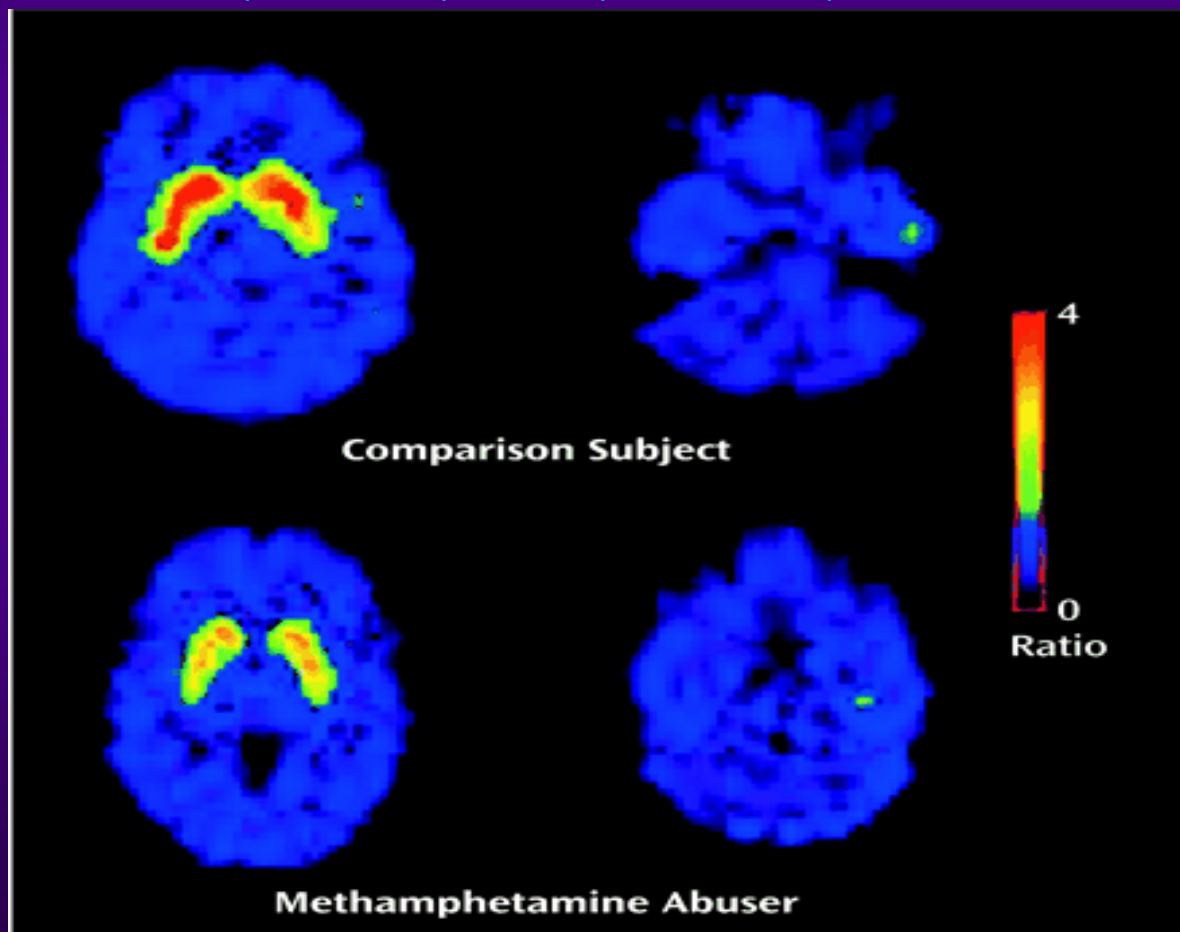


Drug dependence as a response to drug withdrawal

- ◆ Early theories of drug dependence placed major emphasis on the physical effects of withdrawal as a factor of drug dependence (Himmelsbach, 1943). In this regard, the adverse physical consequences of withdrawing from a drug's effects are viewed as a key motivational determinant of sustained drug taking through negative reinforcement mechanisms.

*Dependence-linked CNS Changes:
Evidence from Human
Neurobiology Studies Using PET*

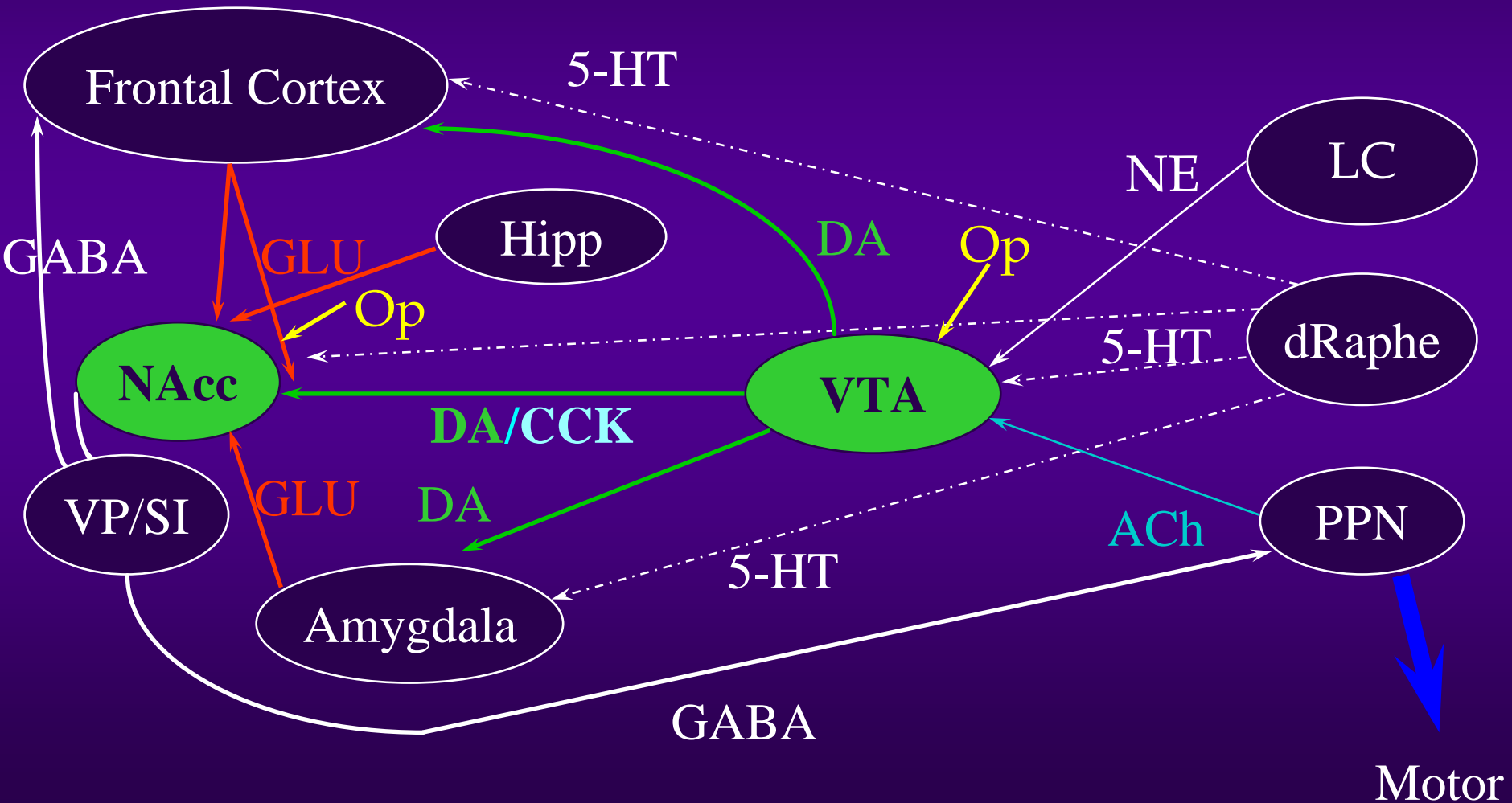
Figure 1. Ratio of the Distribution Volume of [^{11}C]Raclopride in the Striatum Normalized to the Distribution Volume in the Cerebellum in a Non-Drug-Abusing Comparison Subject and a Methamphetamine Abuser Nora D. Volkow and Joanna S. Fowler.
From Cerebral Cortex, Vol. 10, No. 3, 318-325, March 2000



BEYOND DOPAMINE

- ◆ Although DA is important for reward processes, numerous other transmitters are critical for “reward-relevant” processes such as craving, conditioning and sensitization
- ◆ Example: neuropeptides coexist with monoamines in many motivationally relevant pathways and their role is only beginning to be understood

Neurochemical Anatomy of Addiction and Reward Related Behaviours



Clinical Issues

- ◆ diagnostic issues
- ◆ concurrent disorders
- ◆ treatments

ICD Criteria for Dependence

(3 or more of these below)

1. strong desire or sense of compulsion to take the substance
2. difficulties in controlling substance-taking (i.e. onset, termination, or levels of use) \
3. a physiological withdrawal state
4. evidence of tolerance
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
6. persistent use despite clear evidence of overtly harmful consequences

ICD Criteria Parallel Neuroscience Relevant Processes

- ◆ **exaggerated preoccupation with drug**
- ◆ **sensitization followed by tolerance**
- ◆ **cravings**
- ◆ **attraction to drug related environment**
- ◆ **withdrawal symptoms**
- ◆ **liking progresses to needing (reward to dependence)**

Treatment and Prevention Approaches

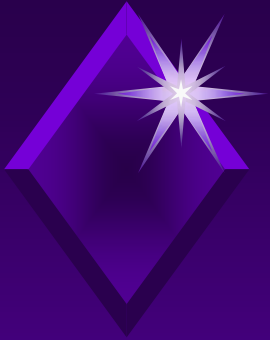
- ◆ general pharmacobiological approaches to treatment
- ◆ non-pharmacological approaches
- ◆ new developments (e.g., vaccines)
- ◆ using knowledge gained from psychobiology to inform prevention strategies (mass media/marketing, prevention in schools, peer approaches)

Biological Based Therapies


- ◆ Pharmacological approaches (e.g., buprenorphine, nicotine patch)
- ◆ Antagonists (e.g. naltrexone)
- ◆ Antidepressants
- ◆ Acamprosate (NMDA ligands)
- ◆ Future approaches
 - ◆ Immunotherapies
 - ◆ Anti-sensitization
 - ◆ Anti-memory (i.e., cue-induced relapse)



- ◆ A major realization has been that the use of psychoactive substances usurps the normal physiological mechanisms that mediate reward, learning and memory, and eventually results in remodelling of neuronal contacts and pathways, producing long-lasting, near-permanent changes.



*The Genetic Basis of
Substance Dependence*



Genetics of the combined risk of dependence on tobacco, alcohol, opioids and other psychoactive substances

- ◆ Candidate genes involved in substance dependence
 - ◆ GABAergic systems
 - ◆ Dopamine system
 - ◆ Monoamine Oxidase A
 - ◆ Catechol-O-methyltransferase
 - ◆ Tyrosine Hydroxylase
 - ◆ Serotonergic systems
 - ◆ Other systems – Cholecystokinin, Opioid receptors, Glutamate transporter



Confounding issues in linkage and candidate gene studies

- ◆ Environment
- ◆ Genetic heterogeneity
- ◆ Phenotype
- ◆ Comorbidity



Concurrent Disorders

Concurrent Disorders

Neurobiological Factors



Psychological Factors



Psychiatric Disorders



Drug Dependence



Concurrent Disorders

- ◆ Individuals with a history of one psychiatric disorder are much more likely than would be expected by chance to have a history of another psychiatric disorder (Robins & Regier, 1991; Kessler et al., 1994)
- ◆ Topics covered in report:
 - ◆ The comorbidity of schizophrenia and depression with illicit drug dependence, tobacco smoking and alcohol use.
 - ◆ Research findings over the past decade.
 - ◆ Directions for future clinical and preclinical research.
 - ◆ Treatment and prevention of substance use disorders.

Substance Dependence: Concluding Remarks

- ◆ Neuroscience evidence supports that drug dependence is a CNS-based motivational disorder
- ◆ Evidence for motivational dysregulation
- ◆ Evidence for DA dysregulation
- ◆ A variety of other systems also implicated
- ◆ Diagnostic criteria for drug dependence parallel psychological processes associated with alterations in specific neurobiological systems linked to motivational

Concluding Remarks (cont'd)

- genetic results suggest multiple candidates for genetic contributions to substance dependence
- additional data indicate that non-genetic influences also contribute to neurochemical sensitivity to drugs of abuse
- concurrent disorders suggest strong neurobiological link between dependence and affect-linked psychiatric conditions
- new treatment targets actively being pursued



Implications for Public Health Policy

- ◆ A substantial portion of the global burden of disease and disability is attributable to psychoactive substance use; and a substantial portion of the burden attributable to substance use is associated with dependence.
- ◆ Tobacco and alcohol are major contributors to the total burden and therefore measures to reduce their harm are an important part of health policy.



Implications for Public Health Policy

- ◆ Some recommendations to facilitate greater openness and assist all stakeholders in mobilizing action include:
 - ◆ Public health response to substance use should be proportional to the health related harm that psychoactive substances cause
 - ◆ Use of psychoactive substances is to be expected because of their pleasurable effects as well as peer pressure and the social context of their use
 - ◆ Societal harm is not only caused by individuals with substance dependence, but also from non-dependents, stemming from acute intoxication and overdose.



Implications for Public Health Policy

◆ Recommendations, *cont'd*

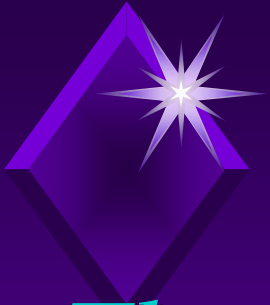
- ◆ Substance dependence is not a failure of will or strength of character, but a medical disorder that could affect anyone. Dependence is a chronic and relapsing disorder.
- ◆ There is significant comorbidity of substance dependence with various other mental illnesses; assessment, treatment and research would be most effective if an integrated approach were adopted.
- ◆ Treatment must be accessible to all in need.



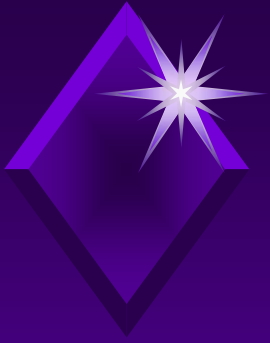
Implications for Public Health Policy

◆ Recommendations, *cont'd*

- ◆ Individuals with substance dependence have the same rights to health, education, work opportunities and integration into society as anyone else. Stigma and discrimination are often barriers to these rights.
- ◆ Investments in neuroscience research must continue and expand to include investments in social science, prevention, treatment and policy research.



*Thanks to Dr. Susan Rotzinger for
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report and editorial process*



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