Substance Use Disorders Treatment: Pharmacopsychosocial Perspectives

Causality and Treatment of Substance Use Disorders (SUD)

- Treatment mostly influenced by widely-held attributions within society of responsibility for causation of the problem and for its solution
- View the addict as *either*:
  - Patient (moral, innocent, and victim), or
  - Criminal (immoral, guilty, and perpetrator)
- Accordingly, rehabilitation is in the realm of either medicine or the criminal justice system

Clearly, we view SUD as biopsychosocial disorders in the realm of medicine complemented by the law!

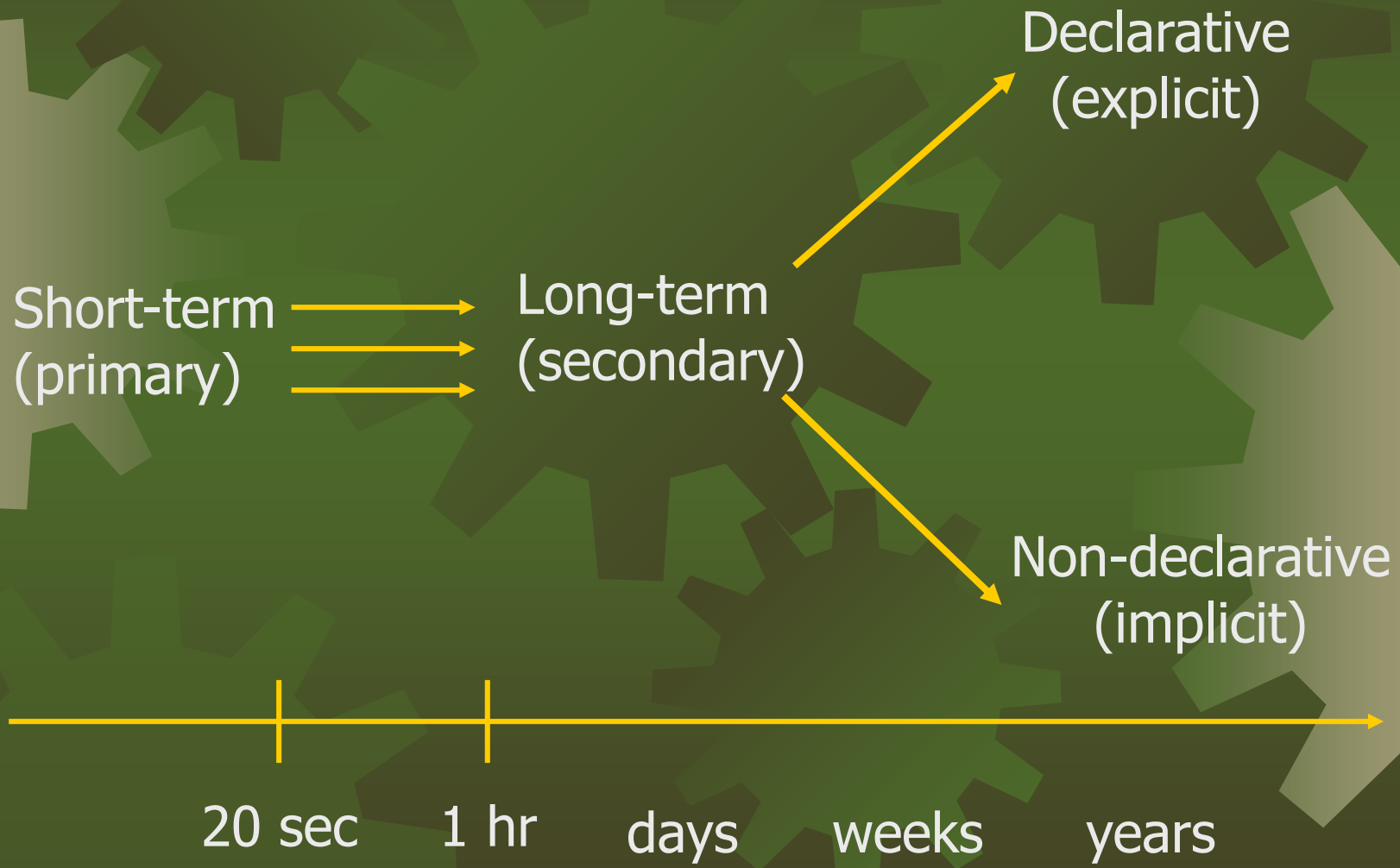
What is *Pharmacopsychosocial* Treatment?

- Clinical evaluation with emphasis on medical and psychiatric precursors & complications including treatment of withdrawal syndrome(s)
- Inpatient, outpatient, residential, aftercare
- Psychotherapies (social or milieu, insight-oriented, behavioral, individual, and group)
  - ± pharmacotherapy of drug use disorders
  - ± compatible treatment of co-occurring disorders
- Introduce/encourage participation in 12-step self-support groups, e.g. AA

Addiction, Learning, and Treatment of Addiction

- Addiction relies on some of the same neurobiological mechanisms as learning
- Cravings are triggered by memories, affective states, and situations associated with drug use
- Treatment must involve avoiding triggers, but preferably, learning new behaviors/responses to the environment despite presence of triggers
- Both declarative and non-declarative (more recalcitrant) learning are involved in relapse and must be modified in treatment

Learning is the "Currency" of Addiction: Stages of Memory Processes



Molecular Mechanisms of Learning/Memory

- Long-term potentiation (LTP) is one of the best studied models of memory at the cellular level
- Electrical hyperstimulation of the pre-synaptic cell makes the synapse more responsive to future stimulation, specifically, this changes signal transduction between cells through both pre- and post-synaptic mechanisms

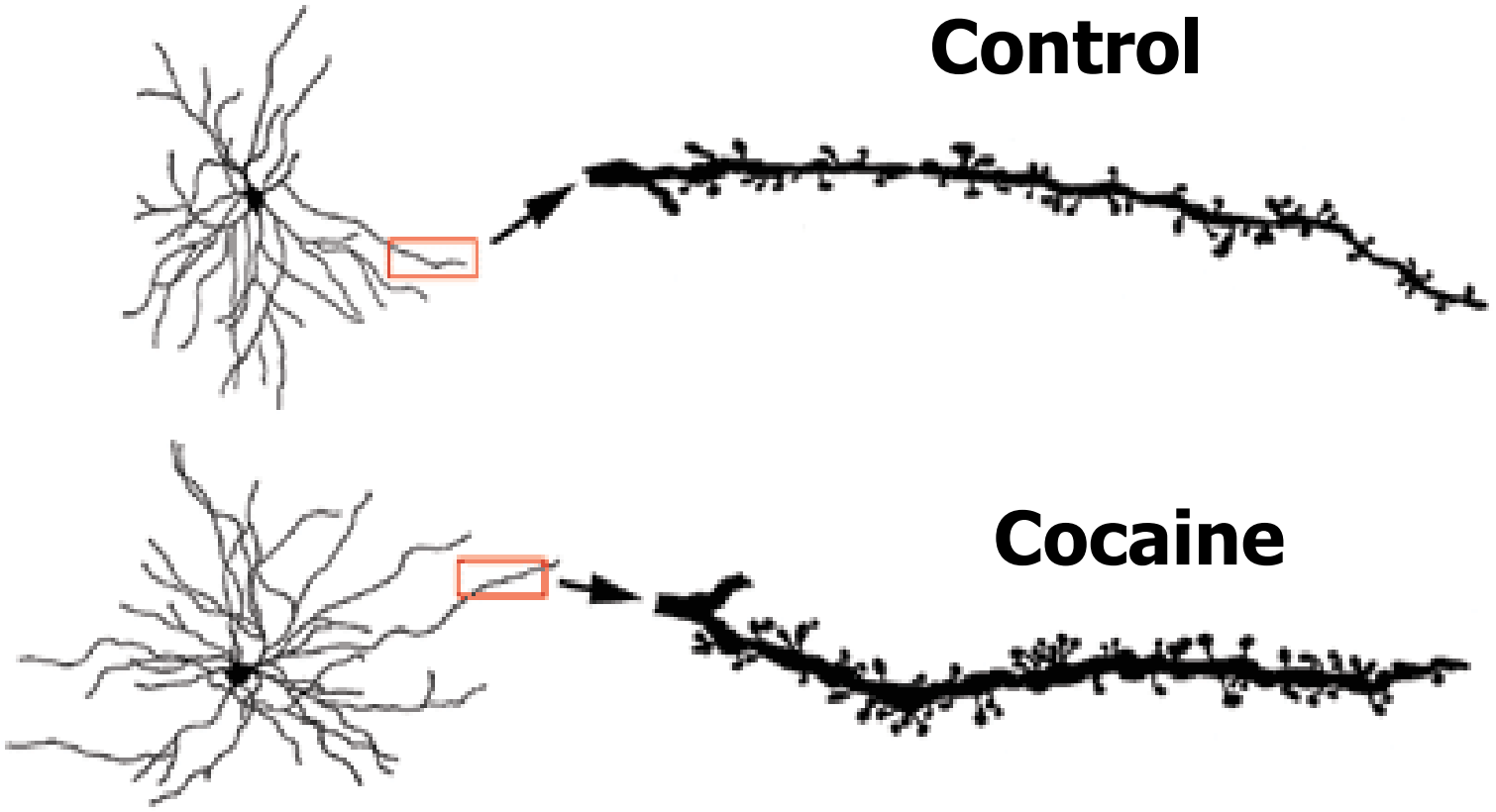
Long-Term Potentiation (LTP)

- LTP initiates a cascade of molecular signals within neurons
- Changes the expression of genes in neurons within brain networks that mediate drug reward and other effects
- Even a single dose of cocaine induces LTP in dopamine cells in the ventral tegmental area (Ungless et al., 2001)

Lasting Structural Changes in Neurons Ensue

- Animals sensitized to stimulants have more dendritic branches and a greater density of neurons in the nucleus accumbens and the prefrontal cortex (can last a month, or more)
- Subsequent stimulation of the hippocampus makes formerly exposed (now drug-free) rats seek out cocaine

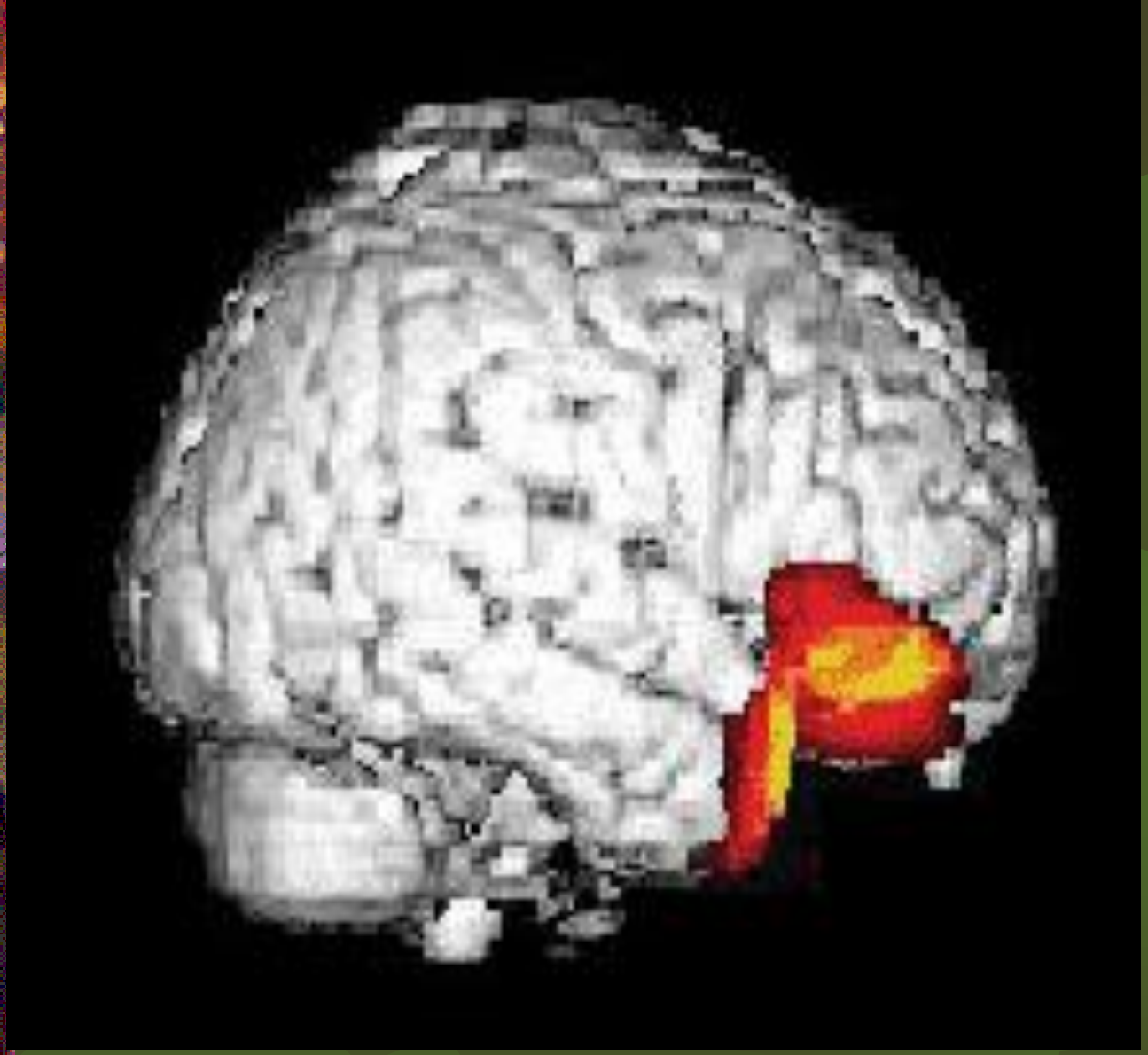
Lasting structural changes in neurons from cocaine



ROBINSON and KOLB, *EUR. J. NEUROSCI.* 11, 1598 (1999)

Brain Response Changes with Learning

- A neuron's dendrites develop more branching projections and have more synaptic connections to neurons with which it communicates regularly
- Creates deeply ingrained and persistent behavioral (conditioned) responses to specific stimuli (so-called, cues)
- Exposure to drug cues causes signs of stress and increased craving, associated with increased activation of the parts of the brain involved in reward, particularly the orbito-frontal cortex and temporal lobe



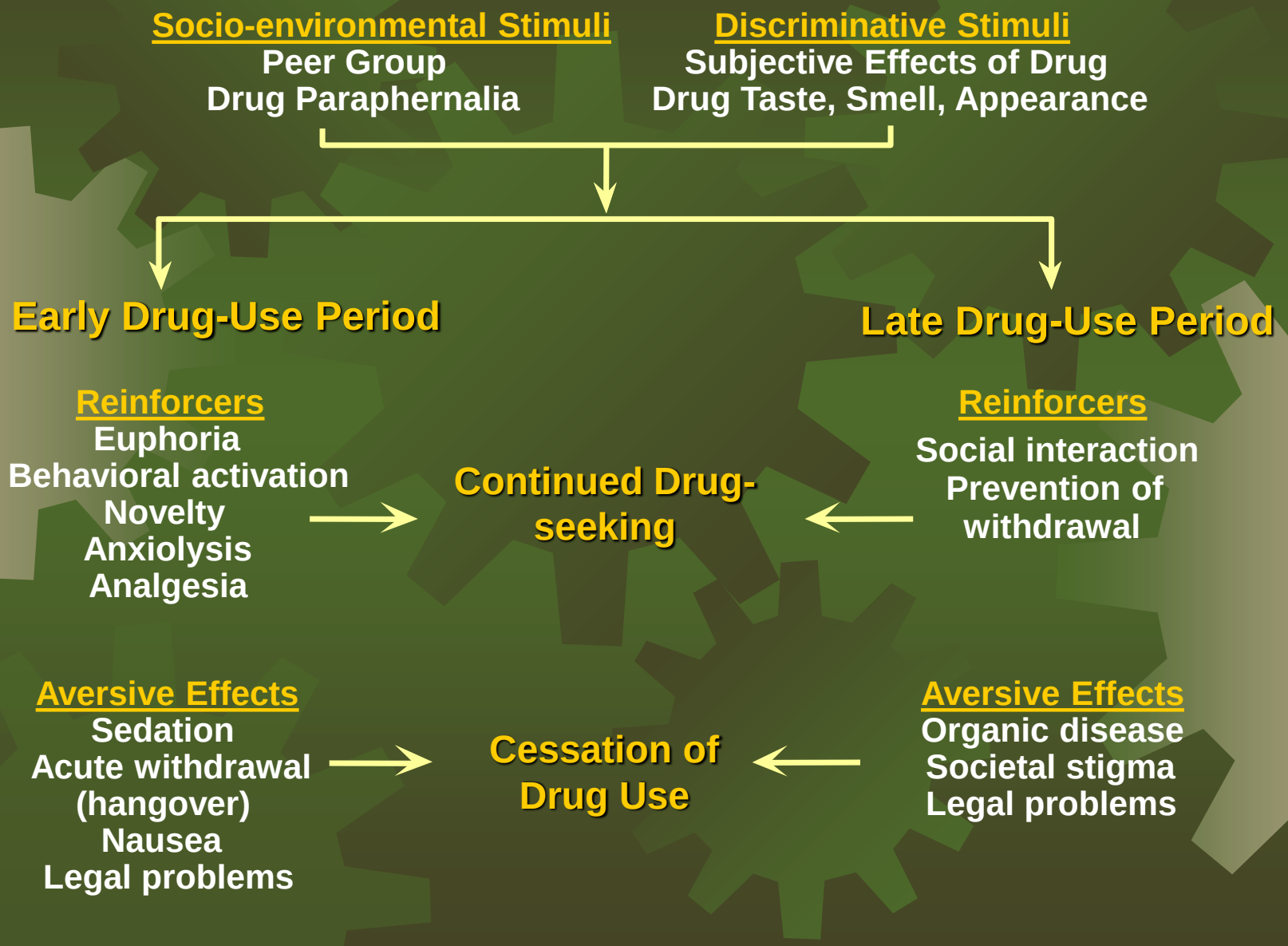
PET Scan of Addict during Exposure to Videos with Drug Cues

CHILDRESS *ET AL.*, *AM. J. PSYCHIATRY* **156(1)**, 11 (1999)

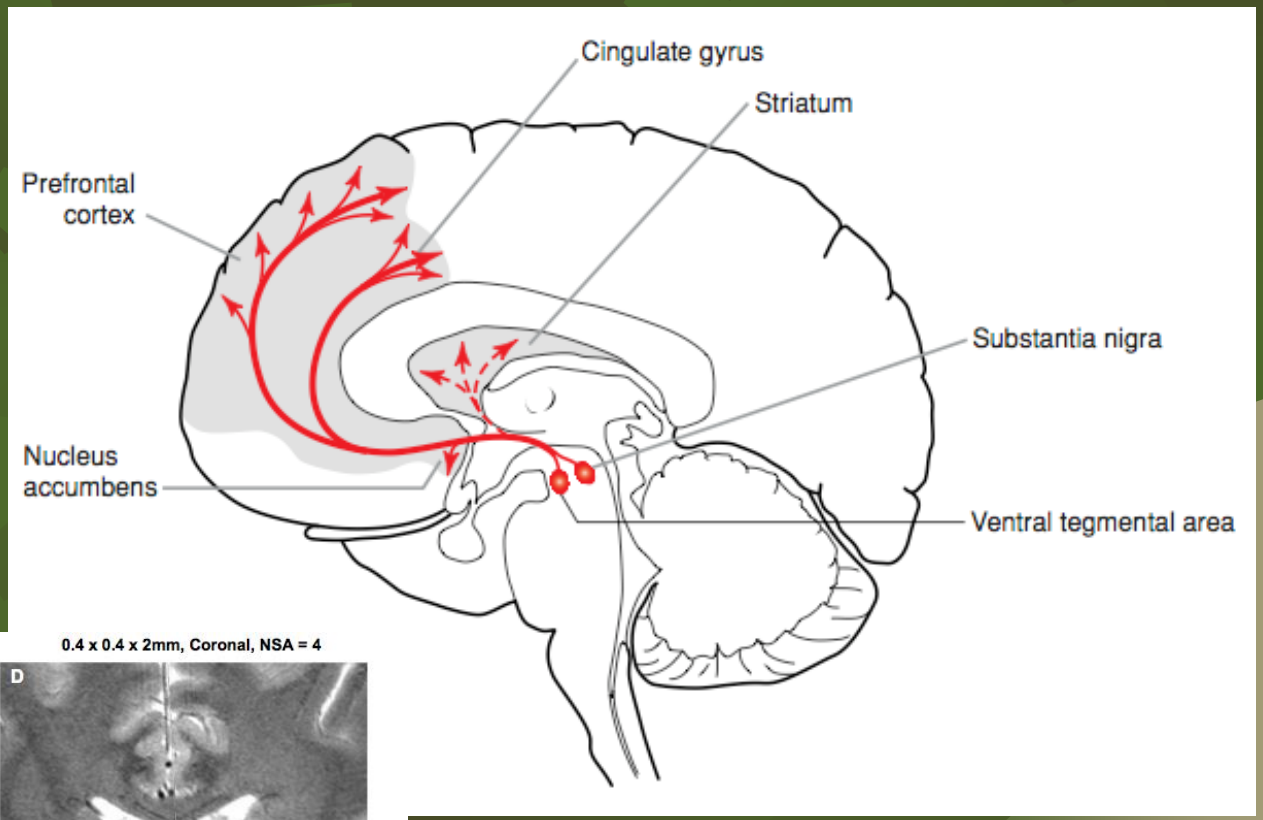
Long-term Effects of Drug Use

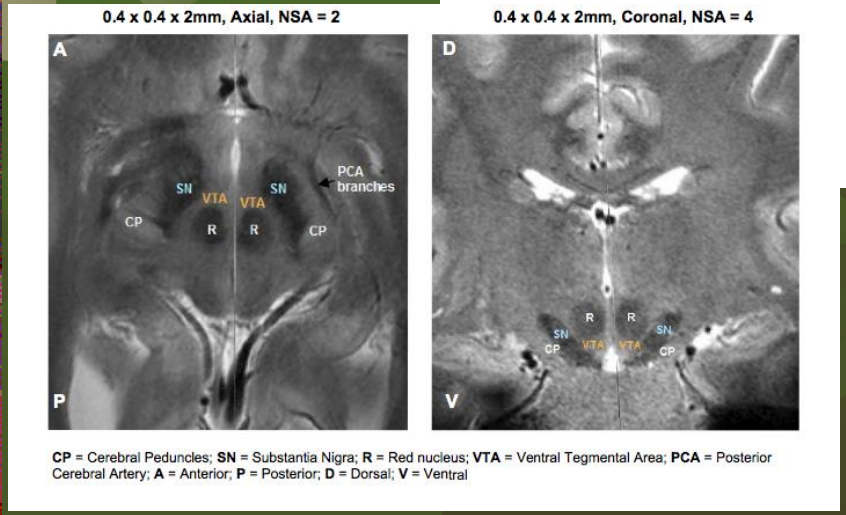
- Anhedonia results from ‘burnt out’ neural pathways (reduced numbers of dopamine receptors demonstrable by PET) that subserve reinforcement or pleasure
- Less sensitivity to dopamine results in less pleasure from natural stimuli and eventually only unnatural stimuli (drugs) can ‘tweak’ the brain’s pleasure systems
- Drug/alcohol-induced brain injury can indirectly affect memory and motivation systems and thereby alter reinforcement, e.g., alcohol amnestic disorder

Drug-Seeking: Basis of Addiction



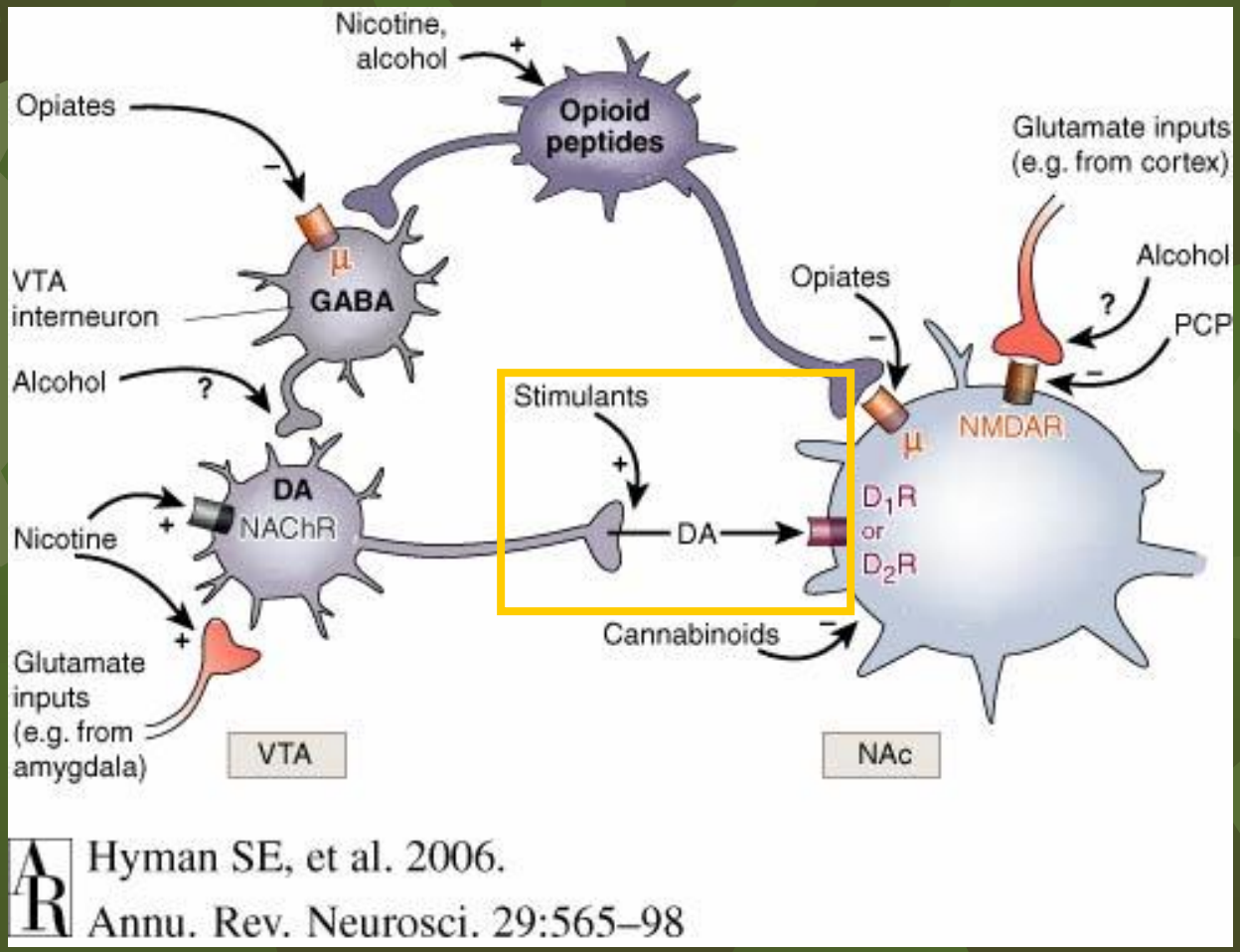
Central Role of Dopamine in Addiction





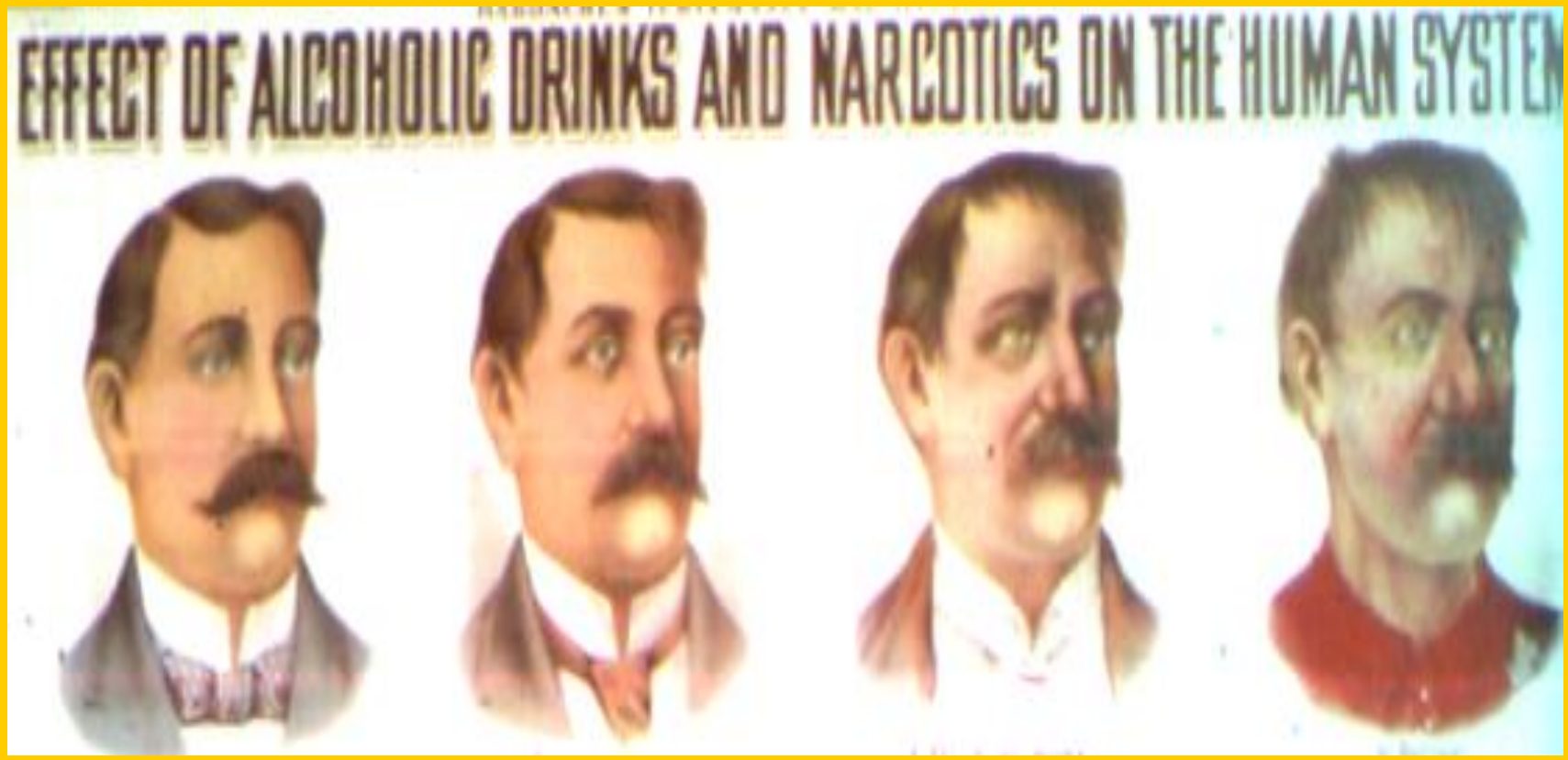
Hyman et al., Ann Rev Neurosci 2006

The Common Denominator of Reward: Dopamine in Nucleus Accumbens and VTA

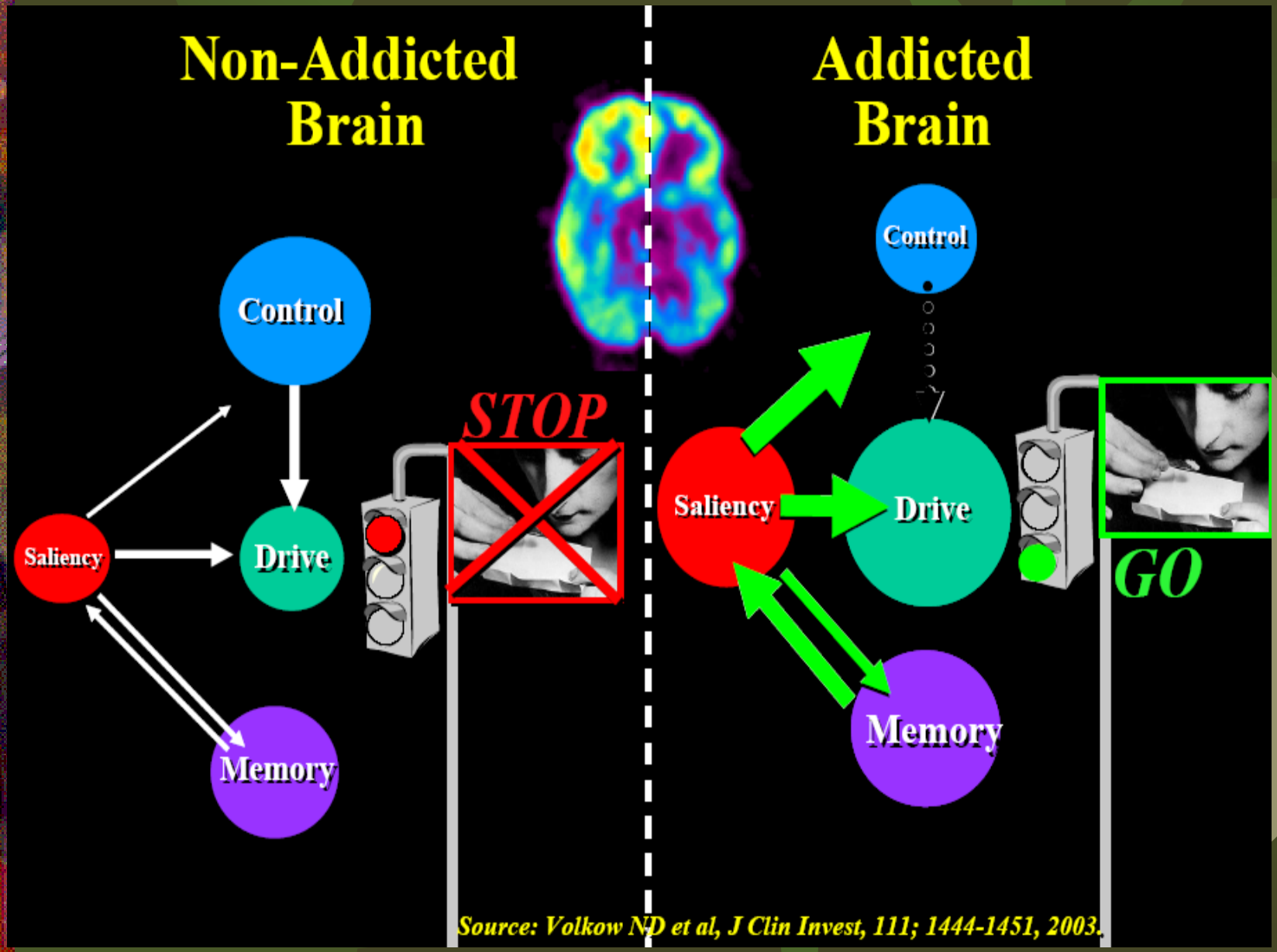


Hyman SE, et al. 2006.
Annu. Rev. Neurosci. 29:565–98

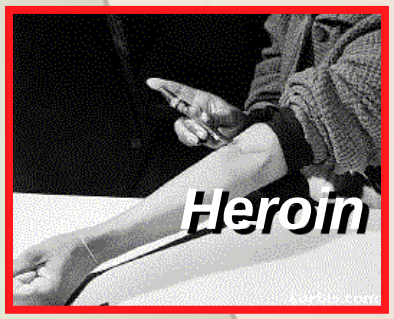
Intoxication/Drug-Seeking Change with Lifetime of Out-of-Control Use

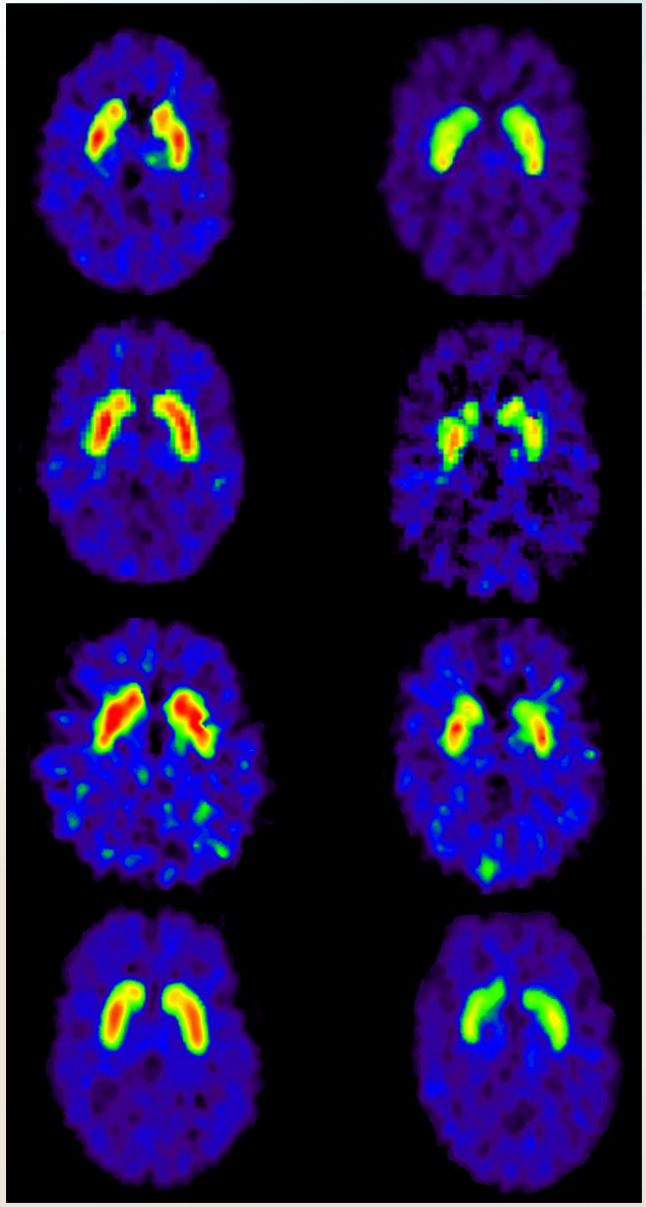


Addiction Changes Brain Circuits



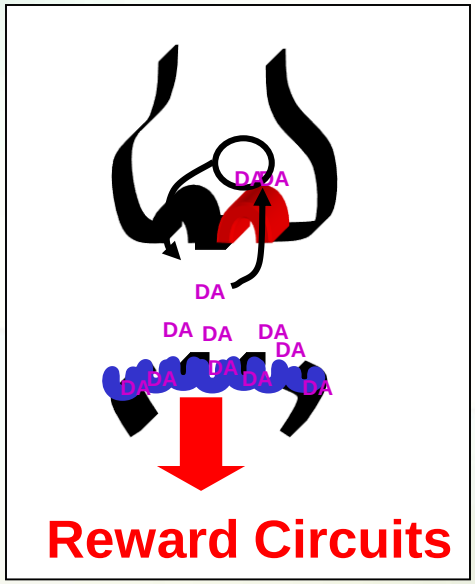
Dopamine D2 Receptors are Lower in Addiction



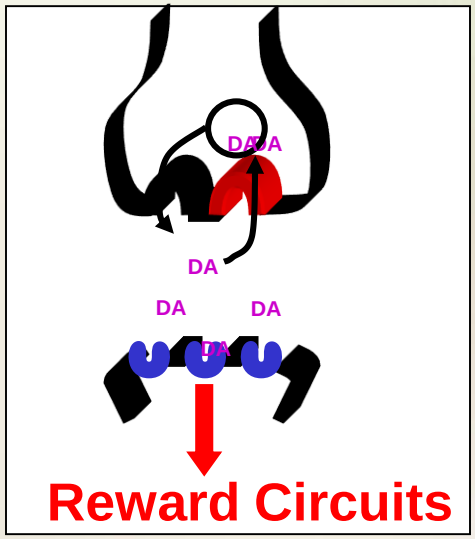


Control Addicted

DA D2 Receptor Availability

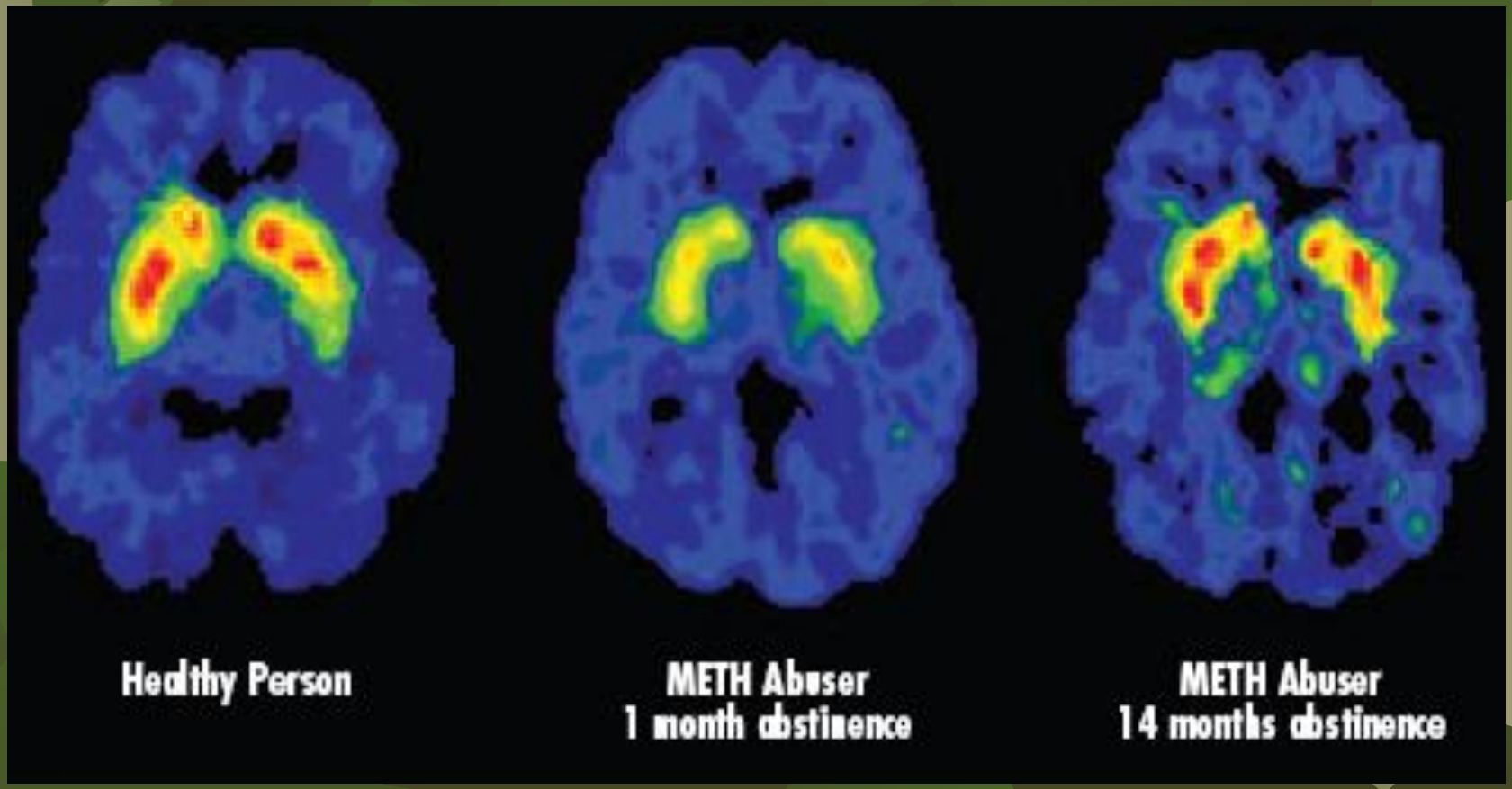


Non-Drug Abuser



Drug Abuser

Recovery of Brain Function with Prolonged Abstinence from METH



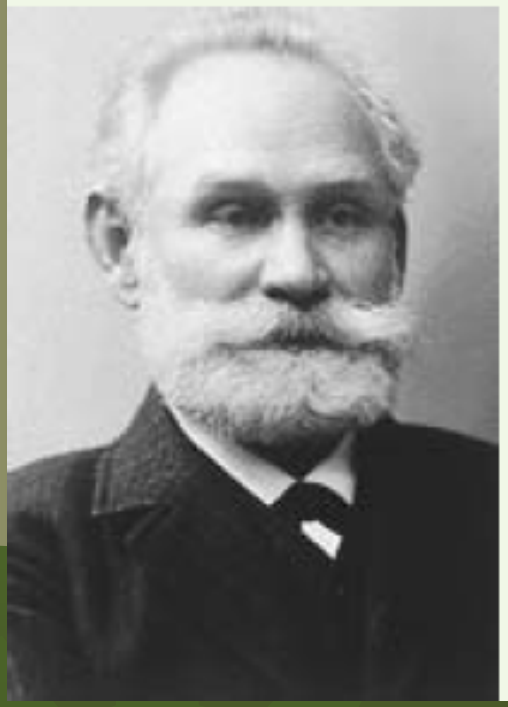
After Volkow et al.

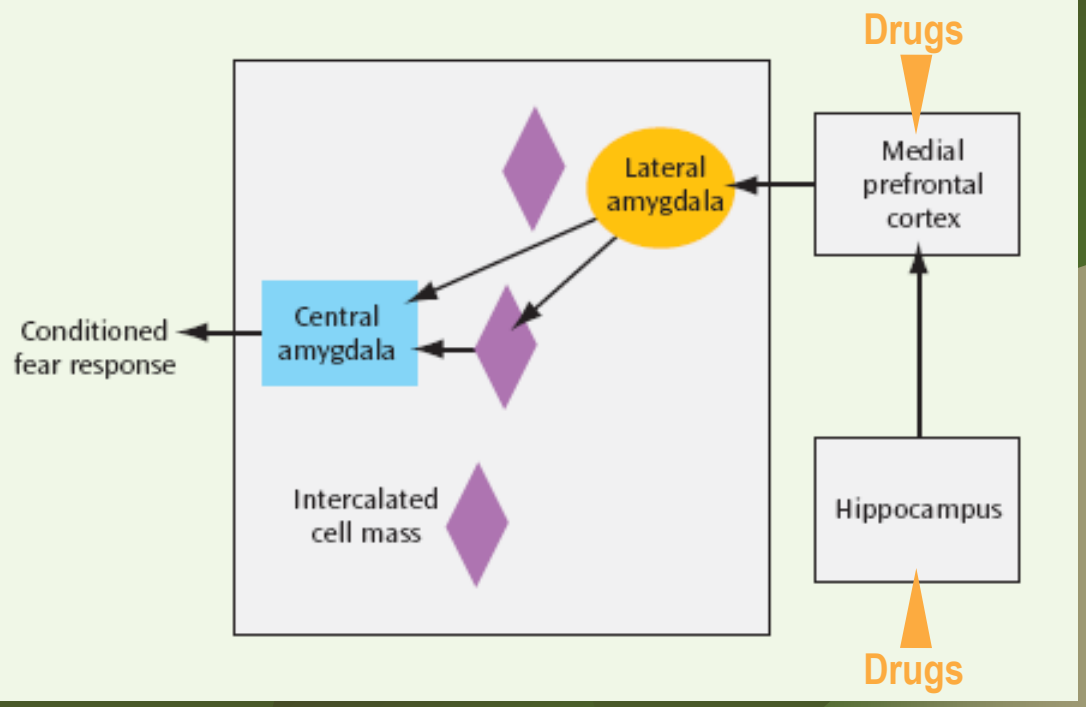
Adjusted Relative Risk of Drug Problems with Exposure to Trauma and PTSD

Exposure	Drug Abuse or Dependence		Drug Abuse Without Dependence		Drug Dependence		Emerging Drug Dependence Problems	
	Adjusted RR (95% CI)	*P* Value	Adjusted RR (95% CI)	*P* Value	Adjusted RR (95% CI)	*P* Value	Adjusted RR (95% CI)	*P* Value
No trauma as reference								
No trauma	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Trauma only	2.4 (0.9-6.3)	.06	1.2 (0.6-5.8)	.27	4.6 (0.6-31.3)	.12	4.2 (1.0-18.1)	.06
PTSD	4.9 (1.6-15.2)	.006	4.3 (1.2-15.0)	.02	9.1 (1.0-82.8)	.049	4.9 (1.2-20.1)	.03
Trauma only as reference								
Trauma only	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
PTSD	2.0 (1.1-3.8)	.03	2.3 (1.0-5.2)	.046	2.0 (0.8-5.0)	.12	1.2 (0.4-3.5)	.76

Reed, Anthony, Breslau, *Arch Gen Psychiatry* 2007;64(12):1435-1442

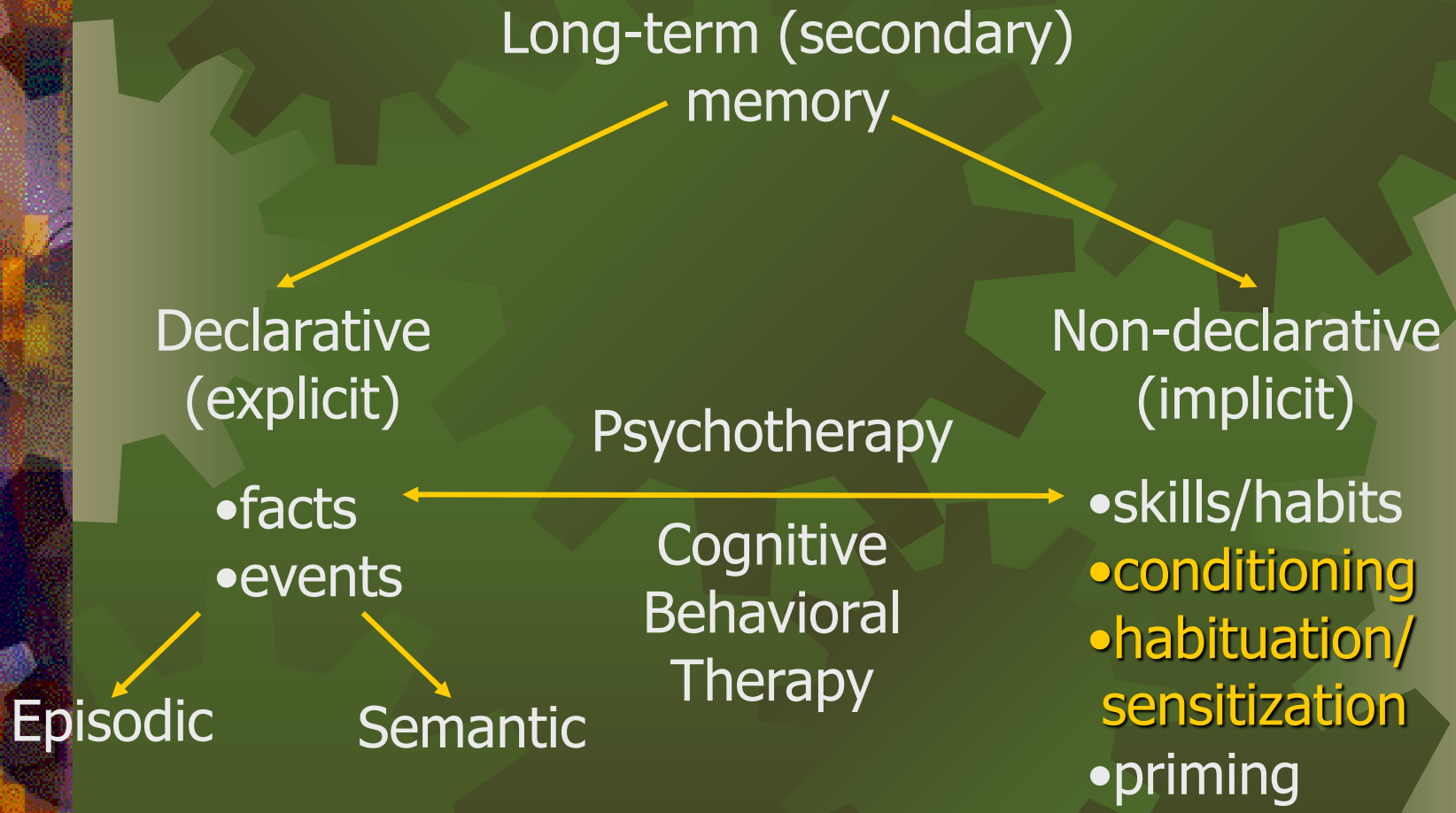
Classical Conditioning/Extinction Model of Pavlov and PTSD/SUD





Tamminga, *Am. J. Psychiatry* 163:961 (2006)

Addiction Treatment: Modification of Long-term Memory by Therapy



Diminish and Manage Relapse(s) in a Life-long Chronic Disorder

- Reduce states and stimuli which might reinstate active addiction:
  - Stress and related internal cues
  - Environmental cues
  - Re-exposure to drugs

“Doctor, I do not think I have a problem!” “I’m not sure I want to (or can) change.”

- Motivating an individual to seek recovery is by far the most important and difficult challenge of addiction treatment
- Substance use disorders are correctly viewed as chronic, relapsing conditions that cannot be “cured”, but must be managed continuously over a lifetime
- Accordingly, slips and relapses should be considered as an opportunity to learn about the illness and oneself, rather than as a failure

Molecules to Man to Society

Motivational Interviewing is Often the Beginning…

- Direct, patient-centered counseling style
- Elicits behavior change by helping patients to explore and resolve ambivalence about discontinuing alcohol/drugs
- Motivational Enhancement Therapy (MET) is a formalized version of this technique that has been demonstrated to be effective
- First step is to determine how ready the individual is to change and then adapt intervention appropriately

Is the Patient Ready to Change?

(Prochaska, DiClemente, Psychother Theory Res Pract, 1982)

Motivational Enhancement

- Direct, client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence
- Demonstrated to be effective especially with alcohol use disorder (Miller et al., 1993)
- Motivational Enhancement Therapy
  - 4 session version of MI
  - Favorable outcomes in the NIAAA Project MATCH Study (Project MATCH Research Group, 1998; McGovern et al., 2003)

Brief Intervention

- Can typically be delivered by PCP
- 10 to 15 minute sessions include advice, education, and contracting information (Fleming et al., 1997)
- Low-cost, effective preventive measure for heavy drinkers in outpatient settings (Wilk et al., 1997)
- Powerful effects demonstrated in patients with alcohol use disorder (Friedman et al., 2001; McGovern et al., 2003)

Drug Counseling

- Emphasis on abstinence, problem solving, involvement in 12-step program for extended periods (Woody, 2003)
- Widely used, shown to be associated with positive change, standard against which psychotherapies have been evaluated
- Demonstrated effective in alcoholics and heroin or cocaine addicts in outpatient treatment

  (McLellan et al., 1993; Crits-Christoph et al., 1999; National Institute on Drug Abuse, 1999)

Alcoholics Anonymous (AA)

- A fellowship of men and women (established in 1935 in Akron, Ohio)
- Who share their experience, strength, and hope with each other and help others to recover from alcoholism
- Who developed “Twelve Steps for recovery from alcoholism” (Emrick, 1987; Bean, 1975)
- Frequency and duration of AA attendance associated with positive outcomes (Galanter et al., 1990; Cross et al., 1990; Humphreys et al., 1997; Brown et al., 2001)

Psychotherapy (1)

- APA, 2006
  - psychotherapy is superior to control conditions as a treatment
- Cognitive Behavioral Therapy (CBT)
  - based on principles of cognitive psychology and social learning theory
  - teaches patient to develop new cognitive and coping skills to replace substance use behaviors
  - relapse prevention based on triggers
- Project MATCH
  - effective in reducing alcohol use and in improvement in other life domains

(McGovern et al., 2003)

Psychotherapy (2)

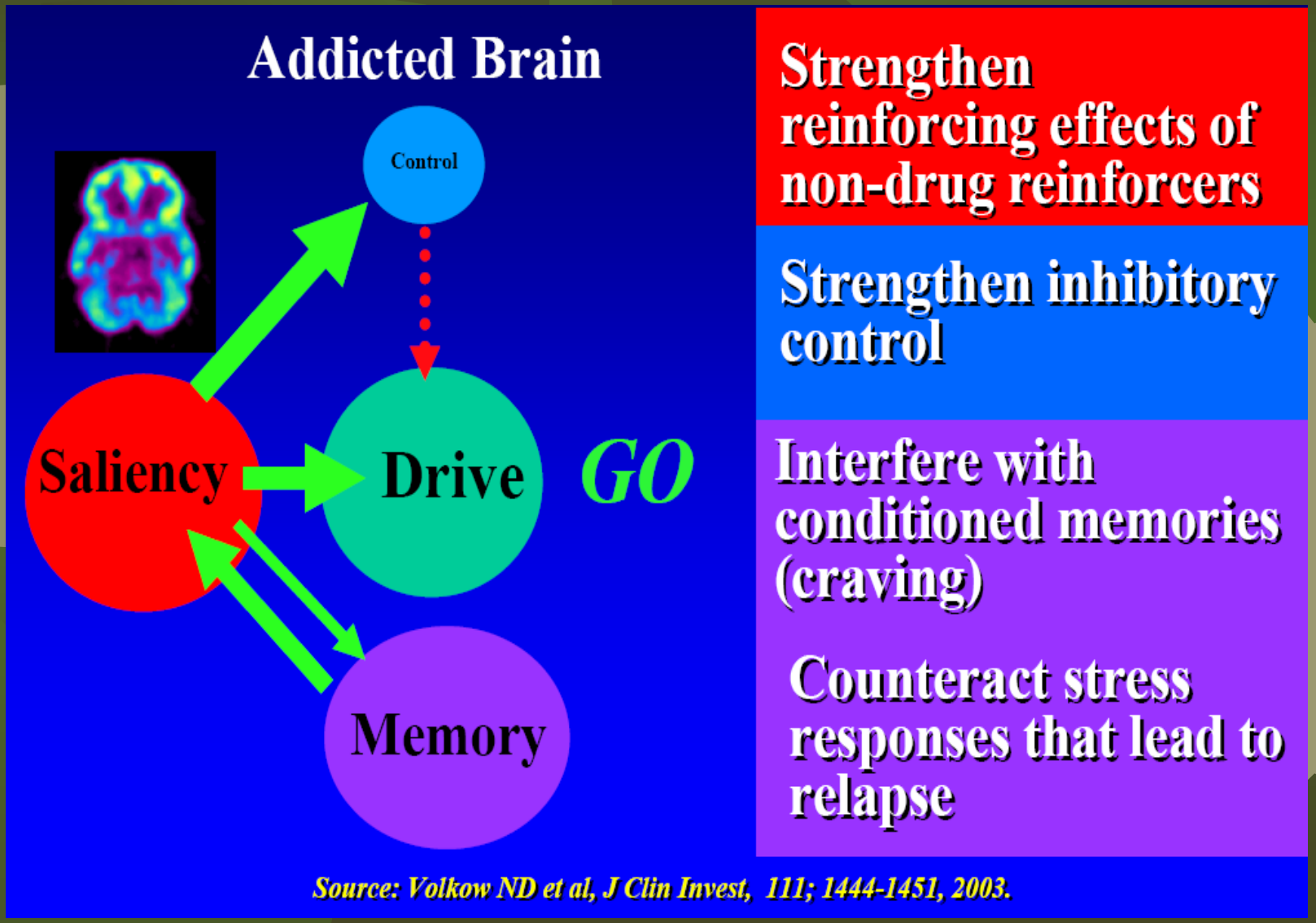
- Supportive-Expressive Psychotherapy
  - analytic oriented psychotherapy
  - focuses on substance use within the context of the person and interpersonal relationship difficulties

  (Woody et al., 1983; Amato et al., 2004; McGovern et al., 2003)
- Twelve-Step Facilitation Therapy
  - content is consistent with the 12-steps of AA, with primary emphasis given to step 1 through 5
  - major goals are abstinence from alcohol/fostering the patient's commitment to participation in AA

  (Nowinski et al., 1999)
  - TSF produced favorable outcomes on abstinence from alcohol, treatment retention, and other life dimensions

  (NIAAA's Project MATCH)

Pharmacopsychosocial Approaches for Relapse Prevention



Treatment

- Careful clinical evaluation with emphasis on medical and psychiatric complications
- Treatment of withdrawal syndrome
- Inpatient, outpatient, residential, aftercare
- Psychotherapies (social or milieu, insight-oriented, behavioral, individual, and group)
- Introduce/encourage participation in 12-step self-support groups, e.g. AA, NA, CA
- Chronic (life-long) illness with expected relapses

Signs and Symptoms of CNS Depressant Intoxication and Withdrawal

Intoxication

- Disinhibition (inappropriate sexual or aggressive behavior, impaired judgment, mood lability)
- Somnolence, stupor, or coma
- Impaired attention or memory
- Slurred speech
- Incoordination
- Ataxic gait
- Nystagmus

Withdrawal

- Anxiety or psychomotor agitation
- Tremor, hyperreflexia
- Craving
- Autonomic hyperactivity (pulse, BP, T, sweating, arrhythmia)
- Insomnia
- Sensory distortions or transient hallucinations
- Nausea or vomiting
- Seizures
- Delirium

Signs and Symptoms of Psycho-stimulant Intoxication and Withdrawal

Intoxication

- Stimulation (euphoria, hypervigilance, anxiety, tension, anger, impaired judgment, psychosis)
- Psychomotor agitation (stereotyped behaviors, dyskinesias, dystonias)
- Energy (decreased need for sleep)
- Anorexia (nausea, vomiting, weight loss)
- Autonomic arousal (P, BP, T, pupillary dilation)
- Chest pain, arrhythmias, respiratory depression
- Confusion
- Seizures

Withdrawal

- Depression (dysphoria)
- Psychomotor retardation
- Fatigue (increased need for sleep)
- Increased appetite
- Craving

Signs and Symptoms of Opioid Intoxication and Withdrawal

Intoxication

- Activation/"rush" (early/low doses) and sedation /apathy/ "nod" (late/high doses)
- Euphoria or dysphoria
- Feelings of warmth, facial flushing, or itching
- Impaired judgment, attention, or memory
- Analgesia
- Constipation
- Pupillary constriction
- Drowsiness
- Respiratory depression, areflexia, hypotension, tachycardia
- Apnea, cyanosis, coma

Withdrawal

- Depressed mood, anxiety, dysphoria
- Craving
- Piloerection ("goose flesh"), lacrimation, rhinorrhea
- Hyperalgia, joint/muscle aches
- Diarrhea and gastrointestinal cramping, nausea, or vomiting
- Pupillary dilation and photophobia
- Insomnia
- Autonomic hyperactivity (P, BP, T , sweating), hyperreflexia
- Yawning

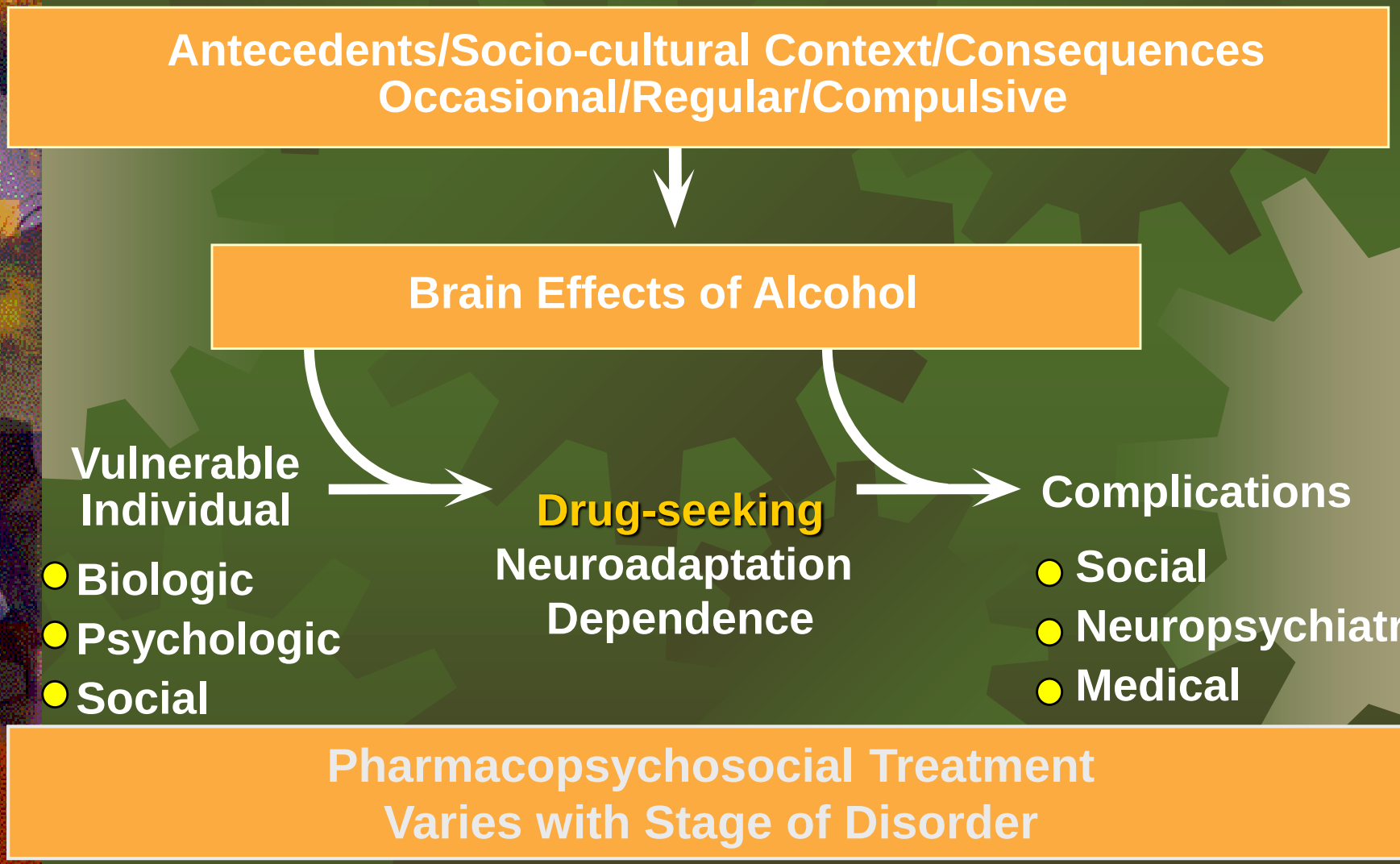
Signs and Symptoms of Marijuana (Cannabis) Intoxication

- Euphoria, drowsiness, or sedation
- Anxiety, acute (subsequently chronic) panic reactions, paranoia, illusions, or agitation
- Sensation of slowed time
- Auditory or visual distortions, dissociation
- Impaired judgment, motor coordination, attention, or memory
- Slowed reaction time
- Conjuctival injection
- Tachycardia
- Increased appetite

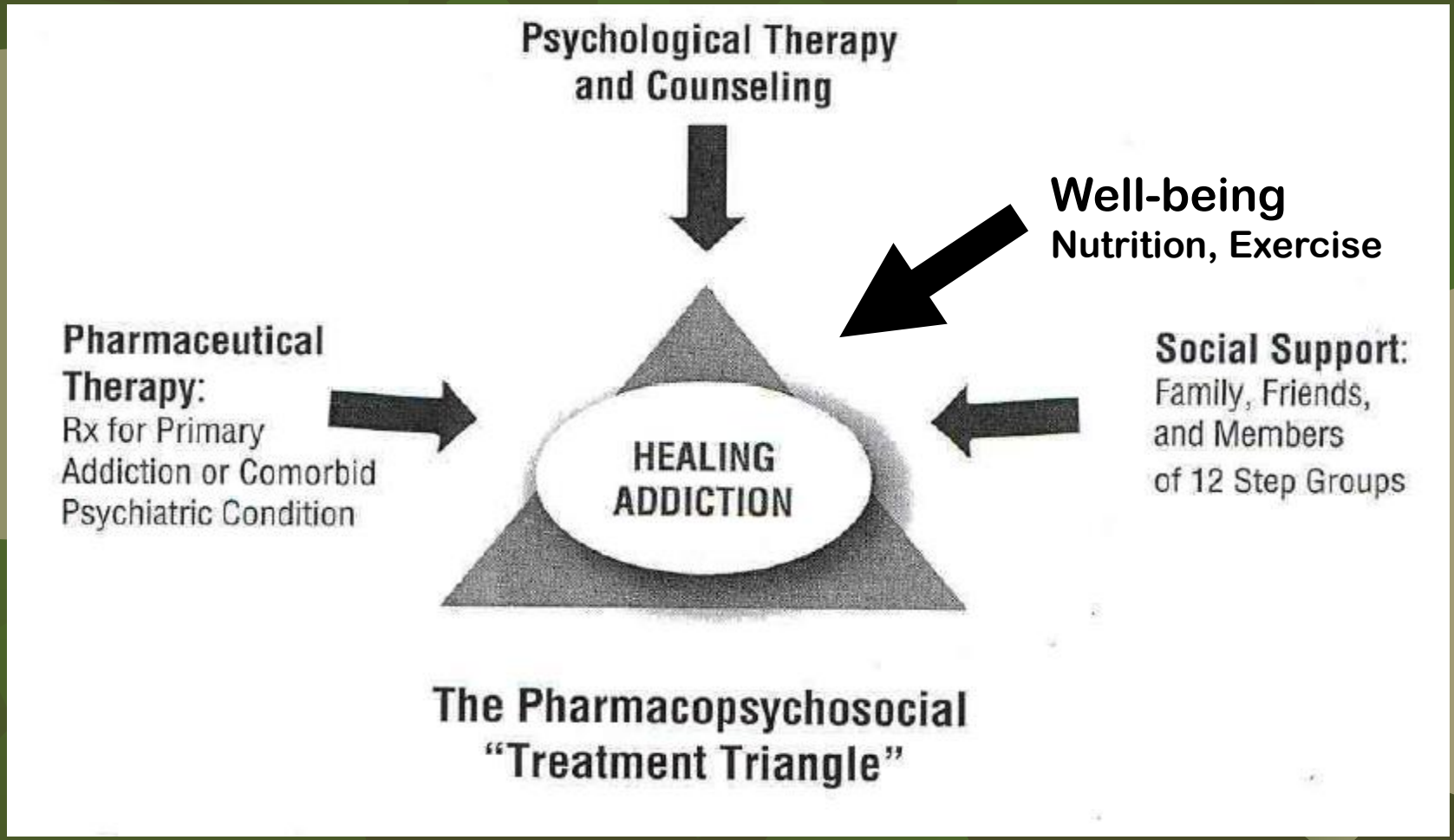
Signs and Symptoms of Hallucinogen Intoxication

- Marked anxiety or depression
- Perceptual changes (eg, intense perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias)
- Thought disorders (eg, ideas of reference, paranoia, impaired reality testing)
- Impaired judgment
- Autonomic arousal (eg, pupillary dilation, tachycardia, sweating, palpitations, blurred vision, tremors, incoordination)

Longitudinal Perspective on Treatment of Alcohol Abuse/Dependence



Pharmacopsychosocial Treatment of Alcoholism



Martin et al., 2006

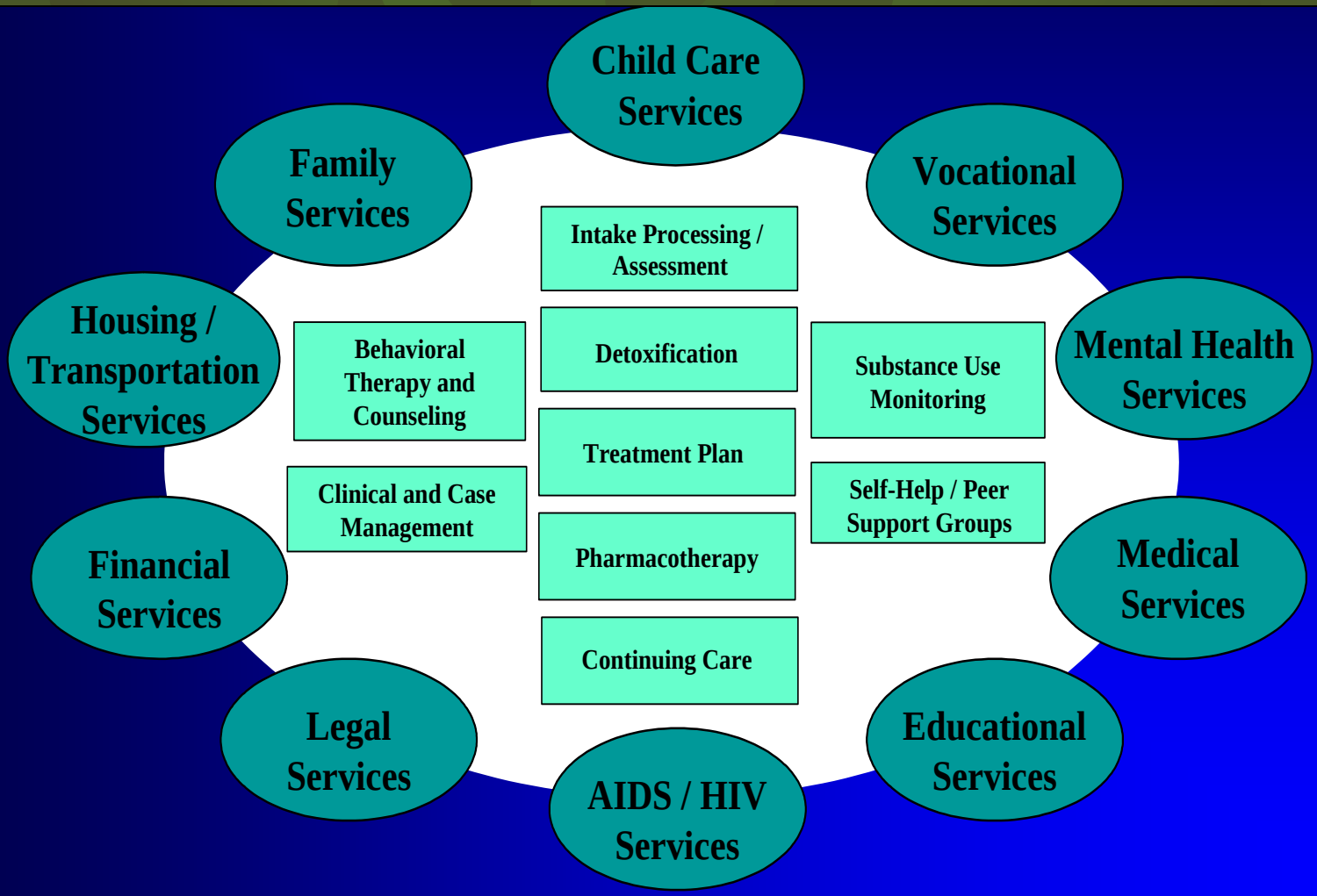
Medications Used in Treatment of Addiction

- Withdrawal
  - diazepam, phenobarbital, clonidine/buprenorphine
- Craving/Relapse
  - disulfiram, naltrexone, acamprosate, topiramate, oxcarbazepine
  - methadone, buprenorphine, LAAM
  - bupropion, nicotine replacement, varenicline
- Depression/Anxiety
  - fluoxetine, sertraline, paroxetine, etc
- Mood instability
  - valproate, carbamazepine, oxcarbazepine, lithium, etc
- Psychosis
  - haloperidol, risperidone, olanzapine, etc

Differential Diagnosis of SUD: Implications for Pharmacotherapy

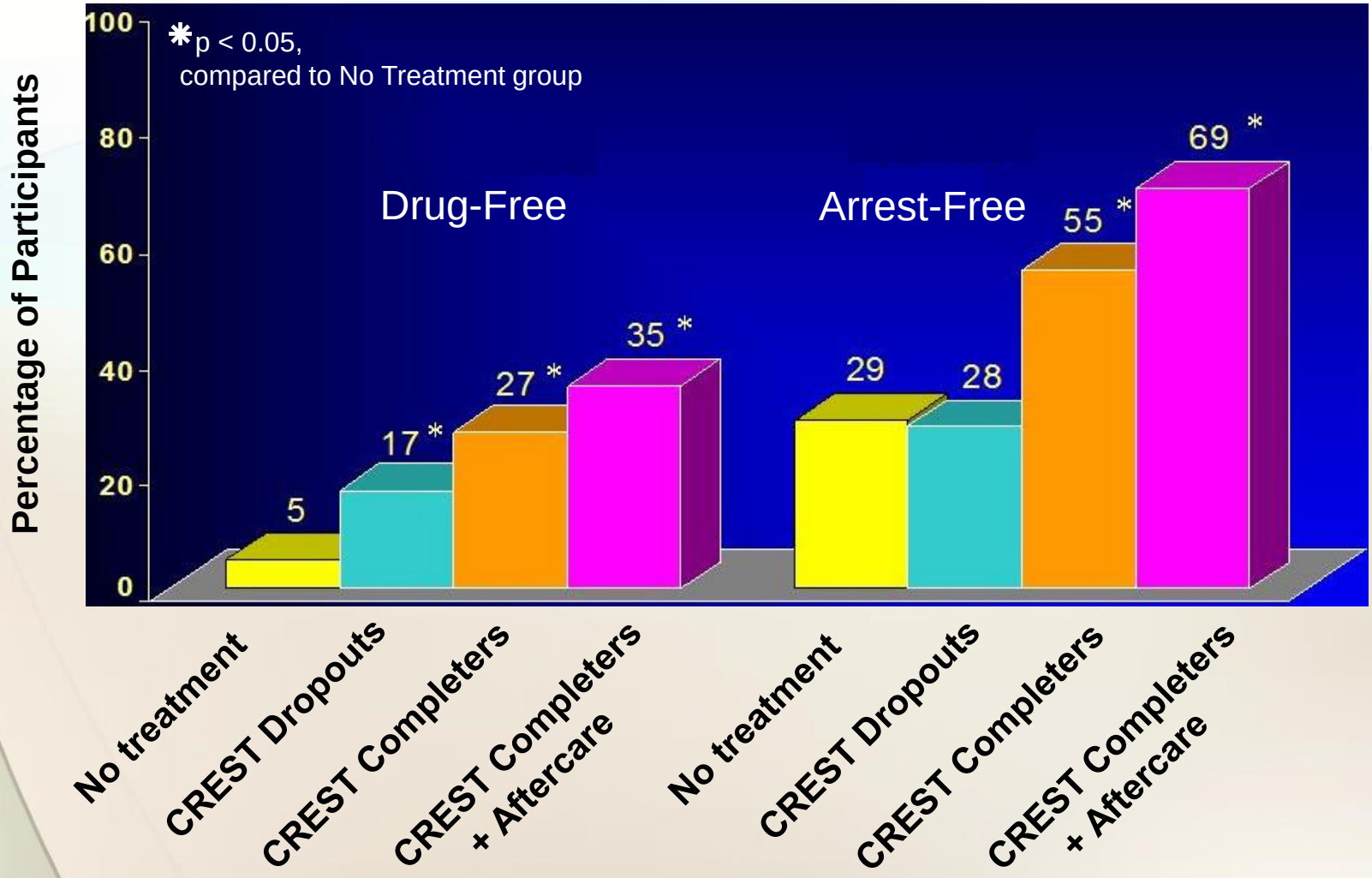
- Pharmacotherapy of a complicating psychiatric disorder is appropriate only if it is independent (primary), but not if it is a consequence of a alcoholism (secondary)
- Treating a co-existing psychiatric disorder using medications with dependence liability (e.g. benzodiazepines, methylphenidate, barbiturates, anticholinergics) or failing to address the primary disorder (SUD) may be detrimental
- Some medications may do more harm than good (e.g., SSRIs in patients with externalizing disorders); others may have beneficial effects on SUD and also on other psychopathology (e.g., anticonvulsants in mood instability)

Matching Treatment to Need is Critical for Success

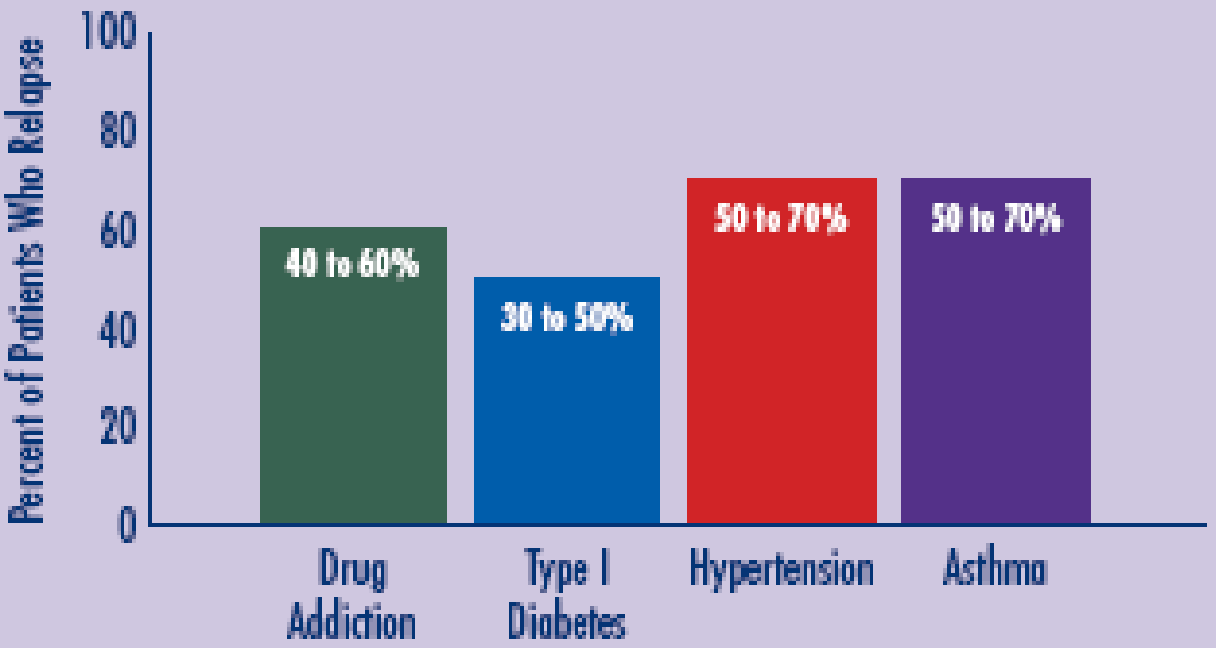


Treatment Reduces Drug Use and Recidivism

Delaware Work Release Therapeutic Community (CREST) + Aftercare
3 Years After Release (N=448)



Relapse Rates of Addiction & Common Chronic Illnesses are Comparable



Relapse rates for drug-addicted patients are compared with those suffering from diabetes, hypertension, and asthma. Relapse is common and similar across these illnesses (as is adherence to medication). Thus, drug addiction should be treated like any other chronic illness, with relapse serving as a trigger for renewed intervention.

Source: McLellan et al., JAMA 284:1689–1695. 2000.

Slip (Lapse)/Relapse

- Lapse
  - initial episode of alcohol or other drug use following a period of abstinence
  - may end quickly or lead to a relapse of varying proportions

  (Daley et al., 2005)
- Relapse
  - failure to maintain behavior change over time

  (Daley et al., 2005)
- Viewpoint
  - lapse can be viewed more optimistically as a challenging mistake or error, an opportunity for new learning to occur

  (Marlatt et al., 1999)

“Did you once have a problem with drugs or alcohol, but no longer do?”

- 10% (est. 23.5 M American) adults answered “yes” to the question in a nationally representative survey of 2,526 adults*
- 12% of males *vs.* 7% of females
- Adults aged 35-44 most commonly reported being in recovery
- Midwest prevalence (14 percent) *vs.* the South (7 percent)

* Opinion Research Corporation, 2011