Neurobiology of Reward and Addiction in the Vulnerable Brain

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DSM-IV Substance Abuse

• Maladaptive pattern of substance use leading to significant impairment distress, as indicated by one or more of the following within a 12-month period:
  – Recurring substance use resulting in failure to fulfill major life roles
  – Recurrent substance use in physically hazardous situations
  – Recurrent substance-related legal problems
  – Continued substance use despite its causing persistent personal/social problems
DSM-IV Substance Dependence

• Maladaptive pattern of substance use leading to significant impairment or distress, as indicated by three or more of the following within a 12-month period:
  – Tolerance
  – Withdrawal syndrome or use of substance to avoid withdrawal
  – Use in larger amounts or for longer periods than intended
  – Persistent desire/effort to decrease use
  – Extensive time obtaining/using substance or recovering from effects
  – Giving up social, leisure, or occupational activities
  – Continued use despite awareness of problems
Overview Questions

• Why are some people more likely to develop a substance use disorder than others?

• What is the role of neurobiologic vulnerability?
Two Groups with High Rates of Substance Use Disorder

- Adolescents
- Patients with schizophrenia
Adolescent Substance Use

• Adolescents/young adults have higher rates of use and use disorders than older adults

• Addictive disorders in adults most often have onset in adolescence/young adulthood

• Earlier onset of substance use predicts greater addiction severity and morbidity

Volkow and Li, Nature Neuroscience, 2005
Adolescent Substance Use

• By 12th grade in the US, adolescents have used substances as follows:
  80% -- alcohol
  63% -- tobacco
  49% -- marijuana
  16% -- amphetamines
  9% -- cocaine

Source: NIDA, NIAAA -- 2004
Adolescent Substance Use

• Five or more drinks in a row during the past 2 weeks:
  • 14% of 8th graders
  • 26% of 10th graders
  • 30% of 12th graders

• Inhalant use: 17.3% of 8th graders

• Marijuana use: 6.4% of 8th graders

Source: NIDA, NIAAA -- 2004
Variables in Genesis of Addictive Disorders

• Degree/amount of drug intake; nature of drug itself

• Environmental influences

• Inherent vulnerability to regular use and/or to addiction given a fixed amount of drug intake
Course of Schizophrenia

Functioning

Course
Premorbid
Prodrome
First episode

Intervention
Selective
Indicated
Early Intervention

Onset psychosis
Illness begins
Lifetime Prevalence of Substance Use Disorder in Patients With Schizophrenia

Regier et al. JAMA 1990; 264-2511.
Biologic Predisposition to Substance Abuse in Patients with Schizophrenia?

- Patients with schizophrenia have mesocorticolimbic dopamine system dysfunction
- Do patients with schizophrenia have a reward system deficit?
- Substances of abuse potentiate dopamine functions
- However, substances of abuse also have detrimental effects in patients with schizophrenia
Mesocorticolimbic Dopamine System

Normal

Mesolimbic

Mesocortical

NAc: Nucleus Accumbens
PFC: Prefrontal Cortex
DA: Dopamine

Schizophrenia

Mesolimbic

Mesocortical

NAc: Nucleus Accumbens
VTA: Ventral Tegmental Area
DA: Dopamine
Brainstem

Nuclei

Extrapyramidal motor circuits

MPFC

/AC

OpFC

MD Thalamus

DLPFC

VP

LH

VTA

SN

PPT

Mesolimbic pathway

Mesocortical pathway

Hippocampus: ventral subiculum, CA1

BNST, SLEA

CeA

BLA

Amygdala

LA

PFC

DA

VTA

SN

Extrapyramidal motor circuits

Brainstem Nuclei

Nucleus Accumbens

core

shell

PFC

BNST, SLEA

Hippocampus: ventral subiculum, CA1

LA
Do Patients with Schizophrenia Have a Brain Reward Deficiency?

- Some Probes of Brain Reward Circuitry:
  - Beautiful faces
  - Pain
  - Olfaction
  - Monetary paradigms
  - Substances of abuse
Aharon et al. (2001)
Substances of Abuse

- Cocaine infusion in patients with cocaine dependence:

Breiter et al., 1997
Brain reward circuitry fMRI activation to anticipation and consumption of reward

Knutson et al. (2001)
Brain activation to anticipation of reward in healthy controls and patients with schizophrenia and co-occurring cannabis use disorder (SCZ+CUD) \[p < .001, k = 3\]

**Healthy Control**  
(n=10)

**SCZ+CUD**  
(n=6)

**HC > SCZ+CUD**

Green et al, Brain Imaging Lab at Dartmouth
Mesocorticolimbic Dopamine System

Normal

Mesolimbic  Mesocortical

Mesolimbic  Mesocortical

Schizophrenia

NAc: Nucleus Accumbens
PFC: Prefrontal Cortex
VTA: Ventral Tegmental Area
DA: Dopamine
Normal Brain Development

• Dopamine activity in pro-motivational (e.g., VTA – accumbens) circuits peaks during adolescence

• Inhibitory (cognitive, decision making) prefrontal neural circuitry gradually develops during adolescence toward full activity in early adulthood

• Sex hormone activation of neural dopamine mediated pro-motivational circuits

Chambers et al, 2003; Steinberg, 2005
**Mesocorticolimbic Dopamine System – Adolescence**

**Adult**
- NAc (Nucleus Accumbens)
- PFC (Prefrontal Cortex)
- VTA (Ventral Tegmental Area)
- DA (Dopamine)

**Mesolimbic**
- NAc
- VTA

**Mesocortical**
- PFC
- DA

**Adolescence**
- NAc (Nucleus Accumbens)
- PFC (Prefrontal Cortex)
- VTA (Ventral Tegmental Area)
- DA (Dopamine)

**Mesolimbic**
- NAc
- VTA

**Mesocortical**
- PFC
- DA

NAc: Nucleus Accumbens
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Inherent vulnerability to drug use disorder?

• Adolescence appears to be a period of heightened vulnerability to the addictive property of substances – they show higher rates of dependence than adults at similar levels of use. Belucci et al, Psychopharmacology, 2004

• Do adolescents also demonstrate increased neurotoxicity to alcohol/substance use?
Iowa Gambling Task

- 4 card decks:
  a) High reward with frequent modest losses
  b) High reward with occasional very large losses
  c) Low reward with frequent small losses (gain)
  d) Low reward with sporadic modest losses (gain)

6-9 year olds – good or bad decks
10 – 15 year olds – 55% good decks
18 – 25 year olds – 75% good decks

Crone, 2004
Adolescence

- Is there a brain reward circuit developmental stage that serves as the basis of substance use disorder in adolescence?

- Is the BRC status in adolescence made more significant in those who are on the cusp of a psychiatric disorder or who have a family history of an addictive disorder?
Gene – Environment Interaction: Adolescent Cannabis Use and Schizophrenia

- Adolescent cannabis use and psychosis symptoms in mid-20’s assessed.
- Adolescent cannabis use not a risk factor for psychosis in mid-20’s for whole sample.
- Adolescent cannabis use was a risk associated with increased rate of psychosis in mid-20’s for subjects with active (val/val) COMT polymorphism  Caspi et al, 2005
Cannabis use and risk of psychosis

- Systematic review of evidence
- Increased risk of psychosis in those who ever used psychosis (OR = 1.41)
- Greater risk in those who used more (OR = 2.09)
- “14% of psychotic outcomes in the UK might not occur if cannabis was not used”
- “We believe there is now enough evidence to inform people that using cannabis could increase their risk of developing a psychotic illness later in life.”

Adolescence

• Use of cannabis and nicotine in periadolescent animals results in atypical effects on neurophysiologic and neurochemical functions. Dani and Harris, Nature Neuroscience, 2005

• Early adolescent (not late adolescent) rats demonstrate marked oral nicotine consumption in free choice paradigms. Adriani and Laviola, 2004

• Pretreatment of peri-adolescent rats (not adult rats) with nicotine induces increase work for nicotine self-administration in adult rats. Adriani et al, 2003

• Cannabis induces dysfunction in brain reward circuitry in rats – leading to deceased response to natural rewards, and increased use of addictive substances. Pistis et al, Biological Psychiatry, 2004
Adolescent Responsivity to Stimuli

- Decreased responsivity to stimuli with low or moderate incentive value, with increased risk taking, novelty seeking.

- In adolescent animals, less sensitive to stimulatory effects of cocaine, more sensitive to dopamine receptor antagonists.

Potential Effects of Adolescent Substance Use?

• Sensitization of DA circuitry leading to increased predisposition to addiction?

• Sensitization of DA circuitry leading to increased risk of psychiatric/addictive disorders?

• Sensitization of DA circuitry leading to development of psychiatric/addictive disorders in those without genetic risk?
Neurotoxic Effects of Substances in Adolescence?

- Adolescent rats show greater binge drinking induced neuronal damage (via argyrophilic silver stain) in forebrain than adult rats. Crews et al, 2000

- Adolescent rats more sensitive to alcohol inhibition of neurogenesis than adult rats. Mdzinarishvili et al, 2002

- Frequency of drug use (EtOH, MJ, others) during adolescence, associated with increased MDD, alcohol dependence and SUD. Brook et al, Arch. Gen. Psych., 2003
Potential Risks of Adolescent Substance Use?

• Is risk greatest for those with a genetic predisposition to psychiatric disorders or substance use disorders, or is it common across all adolescents?


• Are there neurotoxic effects of drugs to which adolescent users are most susceptible?
Decreased Brain Volume in Adolescents and Young Adults with Alcohol Use Disorder

Decreased PFC volume in males with adolescent alcohol use disorder (AUD) compared to adolescent males without AUD

Decreased PFC grey matter as a function of the number of alcohol drinks consumed in a single drinking episode

De Bellis et al., 2005
Age of Onset of Alcohol Consumption Predicts Later Abuse and Dependence

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Lifetime Dependence: % (Standard Error)</th>
<th>Lifetime Abuse: % (Standard Error)</th>
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<td>8.3 (1.1)</td>
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<tr>
<td>13</td>
<td>41.3 (2.7)</td>
<td>11.5 (1.8)</td>
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<tr>
<td>14</td>
<td>40.8 (1.9)</td>
<td>13.8 (1.5)</td>
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<tr>
<td>15</td>
<td>38.7 (1.4)</td>
<td>11.9 (0.9)</td>
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<td>30.6 (0.9)</td>
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<td>24.5 (1.0)</td>
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<tr>
<td>25 or Older</td>
<td>7.9 (0.6)</td>
<td>2.5 (0.4)</td>
</tr>
</tbody>
</table>

Younger onset of alcohol consumption correlates with higher rates of lifetime substance dependence and abuse. Grant and Dawson, 1997
Binge Drinking in Adolescents and Young Adults

• 30-40% of college students are binge drinkers
  – 10-20% drink more than twice the binge threshold (White et al., 2006)

• Heavy binge drinking reduces decision-making skills
  – Especially ages 18-19 (Goudriaan et al., 2007)

• Heavy college drinking is associated with greater use of other illicit drugs, including cocaine, amphetamines, and analgesics (O’Grady et al., 2008)

• Heavy college drinking is associated with risks of:
  – Later alcohol dependence and abuse
  – Early departure from college/attrition (Jennison, 2004; O’Neill et al., 2001)
Therapeutic Implications

• For treatment of substance use disorder within psychiatric disorders (e.g., schizophrenia):
  -- encouragement of abstinence
  -- use of pharmacologic agents that ameliorate brain reward circuit dysfunction
  -- use of psychosocial interventions to compensate for brain reward circuit dysfunction

Roth et al, 2005
Therapeutic Implications

• For adolescents?

Controlled use advised

Identify high risk individuals and caution against use?

Psychosocial interventions to aid in healthy choices?

Role of pharmacologic/psychosocial intervention in high risk?

Ferdinand et al, 2005; Caspi et al, 2005
Conclusions: Substance Use and the Vulnerable Brain

• Adolescence appears to be a time of heightened vulnerability to risks of substance use – especially for those with family history of SUD or genetic risk of poorly regulated PFC.

• Long-term consequences of adolescent substance use may continue into adulthood.

• Patients with schizophrenia have heightened vulnerability to risks of substance use.

• Long-term consequence may involve poorer outcome in schizophrenia.

• Common mechanism may involve organization of mesocorticolimbic circuitry.