Effects of Drugs on the Developing Brain: Pregnancy, Adolescence and Beyond

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Overview of Lecture

- Effects of Drugs on the Developing Brain
  - Intrauterine Effects
  - Effects 2/2 Exposure in Adolescence
- Vulnerability to Drug Abuse
- Prevention

Effects of “Drugs” on the Developing Brain

“This is your brain on drugs.”

Intrauterine Effects

of Substances on the Developing Brain

Pregnancy-related Substance Use in the United States

- Between 1996-1998 in women of childbearing age (18 to 44 years old)
  - *(National Household Survey on Drug Abuse)*
- 6.4% of nonpregnant women used illicit drugs
- 2.8% of pregnant women used illicit drugs (possibly over 5%)[2]
- 113,000 Caucasian; 75,000 African American; 28,000 Hispanic women used drugs (etoh+cigs) during pregnancy[3]

Drugs of Choice

- Marijuana represented 3/4 of illicit drug use[1]
- Cocaine accounted for 1/10 of illicit drug use[1]
- Highest Rates of Drug Use:
  - Cocaine (4.5%) in AA
  - Alcohol (23%) + Cigarettes (24%) in Caucasian
  - >50% of pregnant women used alcohol and cigarettes.[1]
  - 25% of all pregnant women in U.S. smoke[2]
- Women who used both Alcohol and Cigarettes:[3]
  - 20% used Marijuana, 10% used cocaine
    - 0.2% and 0.1% in non-drinking /non-smoking

After Recognition of Pregnancy

- 28% of those who used drugs stopped in the first trimester
- 93% stopped by the third trimester
- Net postpartum reduction was only 24% due to relapse

Highest Rates of Use

- Younger age (18 to 30 years old)[1]
- Unmarried status[1]
- Less than high school education[1]
- Substance Abuse by Significant Other[2]
- Family Violence[2]

Acute Disruptions of Pregnancy

	Spontaneous Abortion	Abruptio Placentae	Premature Delivery	Fetal Demise
Nicotine	yes		yes	
Alcohol				
Cocaine	yes	yes	yes (PROM)	yes
THC				
Opiates				

Cocaine Outcome Based on Frequency of Use

- Erratic Use: highest rate of Vaginal Bleeding (22%), Abruptio Placentae (14%), Premature Delivery (36%), Still Birth (21%)
- Daily Use: highest rate of SGA births (33%), other endpoints (except premature delivery) significantly lower[1]
- Abruptio Placenta: due to chorionic villus edema and chorionic villus hemorrhage[2]

Neonatal Effects

	Growth Retardation[a]	Congenital Infections	Motor	Neonatal Withdrawal
Nicotine	yes		jittery	yes
Alcohol	yes[b]		jittery	yes
Cocaine	yes	HIV, HepC/B	jittery	yes
THC			jittery	yes
Opiates	yes[c]	HIV, HepC/B	Jittery/trouble bottle feeding[1]	yes

Neonatal Withdrawal

- 60% to 90% of infants prenatally exposed to drugs will experience withdrawal, (esp. with opiate exposure)
- signs and symptoms for opiates, alcohol, barbiturates (appearing within 72 hrs):
  - irritability, tremulousness, increased muscle tone, feeding difficulties (excessive, poorly coordinated sucking), tachypnea, diarrhea, disturbed sleep, fever, vomiting, high-pitched cry, seizures.

Neonatal Withdrawal

- Marijuana and Nicotine:
  - Increased startle, tremors, hypertonic, irritability, less responsiveness and poor habituation to light
- Cocaine: increased tone, drowsiness
- Polysubstance Use:
  - Increased tone, tachypnea, disturbed sleep, fever, excessive sucking, loose/watery stools.

Prolonged Effects on the Central Nervous System of Intrauterine Drug Exposure

By Drug: Nicotine, Alcohol, Cocaine, PCP, Barbiturates, Benzodiazepines

Neonatal Brain on Drugs

- Synaptogenesis (brain growth spurt) occurs from 6 mo gestation to several years post birth.
- Drugs that block NMDA glutamate receptors and those that activate $GABA_A$ receptors trigger widespread apoptosis of neurons[1]
  - Causing pathologic rather than physiologic cell death.
  - e.g.: alcohol, PCP, Special K, Barbiturates, Benzodiazepines

Neonatal Cocaine

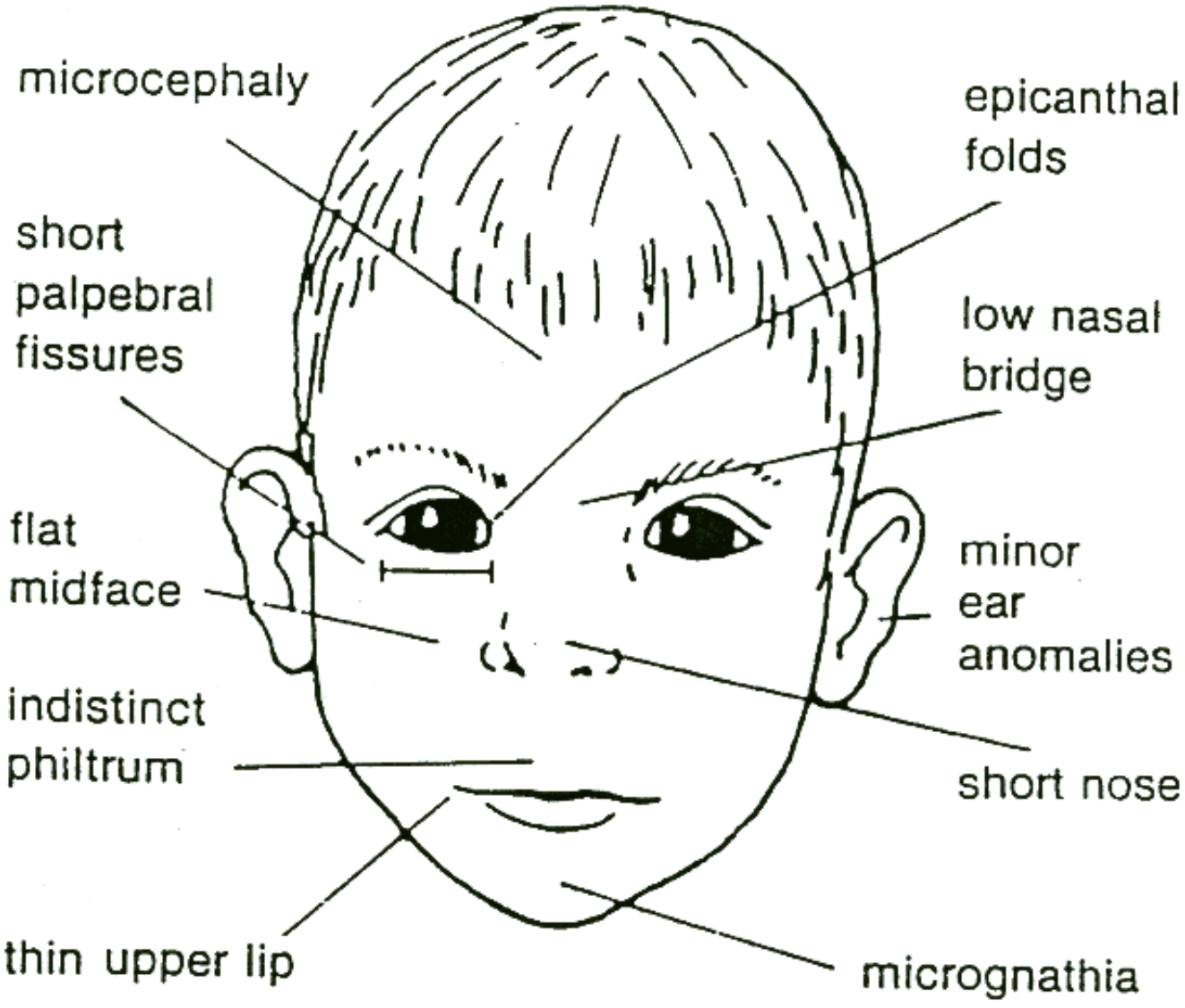
- Dopamine System:
  - Produces dysfunctions in the signaling of the D1 receptor and abnormalities in the development of the frontocingulate cortex leading to difficulties with attentional focus and stimulus processing by the cingulate cortex.[1]
- Suppression of frontal 5-HT system with resultant poor response inhibition.[2]

Neonatal Nicotine[1]

- Nicotine triggers abnormal neuronal cell proliferation and differentiation,
- Disrupts the development of cholinergic and catecholaminergic systems

Fetal Alcohol Syndrome-1973

- Severe developmental disorder associated with maternal drinking
  - Growth Retardation (height/weight below 5 %)
  - CNS dysfunction (impaired motor, LD, behav d/o)
  - Characteristic craniofacial abnormalities (need 2)
    - Short palpebral fissures
    - Flat midface
    - Short nose
    - Indistinct Philtrum
    - Thin upper lip


microcephaly
short palpebral fissures
flat midface
indistinct philtrum
thin upper lip
epicanthal folds
low nasal bridge
minor ear anomalies
short nose
micrognathia

Fetal Alcohol Syndrome

- 1-3/ 1000 live births
  - 2X > Down's Syndrome
  - 5X > spina bifida
  - highest rates in Native Americans and African Americans
- Direct toxic effects of alcohol and acetaldehyde on the embryo and placenta

Prenatal Exposure and Developmental Effects in Human Studies

- Nicotine: association with ADHD and Conduct Disorder[1]
  - unclear if genetic or environmental
- Marijuana: high hyperactivity, impulsivity, delinquency, poor sustained attention and visual memory[4]
- Cocaine: “crack babies” by age 6 show no gross differences c/w controls.[2]
  - May have more subtle problems with arousal regulation affecting orientation, selective attention, information processing, learning and memory[3]

Treatment - Secondary Prevention

- Abstinence-based AA-model (all substances except opiates)
  - Success hinges on retention
  - Retention is facilitated by provision of support services
    - child care, parenting classes, vocational training
    - addressing violence, abuse, safety issues and mood disorders
- Opiates: abstinence vs. methadone maintenance (based on likely hood of successful abstinence)

Treatment - Neonatal Withdrawal and Beyond

- Supportive Measure in the Infant Nursery
  - Provide containment by swaddling with blankets (tremors, increased tone)
  - Gentle moving and awakening of infant to reduce startle
  - Quiet environment with reduced lights
  - Dress in light clothing to reduce overheating
- Loose/watery stools may require treatment with opiods (tincture of opium, oral morphine or methadone)
- Provide access to addiction treatment for the mother and/ father
- Provide parenting education and support
- Provide early intervention/ enriched environment for the child

Impact of Adolescent Substance Use on the Developing Brain

By Drug: Nicotine, Alcohol, Marijuana, Cocaine

Adolescence: from age 11 to early 20's

- More likely to experiment with a variety of risky behaviors including drug use
- Often the time of first use of alcohol and tobacco
- Continued cortical and subcortical brain development
- On average about 10% of Adolescents develop substance abuse, higher rates in high risk groups.

Nicotine

- Female rats exposed to nicotine in adolescence self-administered 2X the amount of drug/kg weight than those exposed as adults and this escalation persisted into adulthood
- Persistent learning impairments were seen in adulthood after adolescent nicotine exposure

Alcohol and Hippocampus

- Adolescents are more vulnerable than adults to the effects of alcohol on learning and memory at lower doses of alcohol
  - Replicated in human subjects in early 20's vs. late 20's (worse memory at same dose of etoh)
  - Teens w/ Etoh abuse have smaller hippocampus on MRI*
  - Glutamatergic (NMDA) receptor-mediated neurotransmission in hippocampus inhibited more powerfully by acute etoh during adolescents than adulthood

Double Hit of Alcohol on Adolescent Brain

Adolescents have less sensitivity to the sedative and motor-impairing effects of etoh

- Adolescent GABA receptor less sensitive to etoh (theory)
- Normal “STOP DRINKING” brakes are absent
- Allowing adolescents to consume more etoh over longer periods w/higher blood etoh levels

Marijuana

- Initiation before age 17:
- was associated with lower verbal IQ scores[1]
- impaired working memory[2]
- smaller whole brain and cortical gray[3] matter volumes
  - Both males and females were smaller in height and weight (males>females)

Cocaine and Aggression

- Adolescent hamsters repeatedly exposed to cocaine in adolescence have higher offensive aggression (attacks, bites, latency to bite) than control littermates.
- Effect mediated through cocaine activating prefrontal neurons critical for aggression and decrease in serotonin inhibition signal to this brain region to help regulate aggression

Vulnerability to Substance Abuse

A. Incidence of Substance Use Disorder among adolescents
B. Family studies and predisposing risk factors
C. Co morbid Disorders and predisposing risk factors

Vulnerability to Drug Abuse

- Children of Parents with Substance Abuse Disorder have a 4 to 7 fold higher risk of developing Substance Use Disorder.[1]
- Genetic Component of liability to SUD estimated at 0.31 in males and 0.22 in females and can reach as high as 0.79 in some studies. (higher for stimulants 0.44)
- The Environmental Component carries the remainder of liability to SUD
  - Environment easier to change than genetics

Environmental Risk Factors

- Access to drugs[1]
  - 27% of those who experiment with drugs >6 times will become daily users
  - 50% of daily users will develop drug abuse or dependence
- Early age of first use[2]
  - Drug experimentation before age 13 significantly increased probability of developing SUD by age 17
- Negative parent-child interactions[3]
- Problems at school and with peers
- Peers who use drugs

Identifying High Risk Kids

- Externalizing Disorders
  - Neurobehavioral Disinhibition[1]
    - Difficult temperament, aggression, violation of rules, noncompliance with authority figures, hyperactive/impulsive behavior, sensation seeking, high response to reward, poor response to punishment, poor cognitive control over behavior and emotion.
  - Conduct Disorder[2]
    - Especially when persists beyond age 15, increased the relative likelihood of substance use disorders **five-to six fold**
- Other Psychiatric Disorders
  - Depression, Anxiety

Age appropriate use?

College binge drinking and behavioral consequences: rape, violence, accidents.

College Binge Drinking

- Prevalence of drinking and heavy drinking higher among college students than their peers not in college.
  - Easy access, influence of fraternities and sororities, more unstructured time, special advertising to college students
- Yearly consequences of college drinking:
  - 1400 deaths, 500,000 unintentional injuries, 600,000 assaults, 70,000 sexual assaults, 2.1 million drive while intoxicated, 400,000 have unprotected sex while drinking.

Prevention programs: do they work?

- Protective Factors
- Why it is hard to study the outcome, what is the target, who are we trying to protect and why and when?
- Better ways to identify who is at risk.

Primary Prevention Programs

- Protective Factors
  - Higher level of emotional support and warmth within child-parent relationship
  - Higher level of appropriate monitoring and limit setting
  - More parental time spent with adolescents
  - Higher level of parent-adolescent communication
  - Better social skills and peer relationships
  - Better problems solving/ executive function skills

Primary Prevention Programs

- Universal Intervention Programs
  - Difficult to say whether effective
- Targeted Intervention Programs
  - Parents with drug abuse problems
  - Youth with high risk behaviors and/or drug experimentation
  - Community Based Programs
  - Show some short term effectiveness but no long term follow up data available

Review Questions

- 1) List three types of acute disruptions of pregnancy related to substance abuse and the substances responsible.
- 2) List three neonatal complications related to substance abuse and substances responsible.
- 3) Identify one type of prolonged effect secondary to prenatal substance exposure for at least three substances of abuse.
- 4) Identify three risk factors and three protective factors for substance abuse in adolescence.
- 5) Identify three risk factors for substance use/abuse during pregnancy.