Neuropsychiatry

I. Schizophrenia
II. Mood Disorders
III. Substance-Related Disorders
I. Schizophrenia
Important Initial Contributors

• Emil Kraepelin
  – Dementia praecox

• Eugene Bleuler
  – Schizophrenia
Positive Symptoms

• Delusions
• Hallucinations
• Disordered Thinking
• Disordered/Catatonic Behavior
• Inappropriate Affect

• Person showing primarily positive symptoms said to have Type I Schizophrenia
Negative Symptoms

• Flattened Emotional Response
• Poverty of Speech
• Lack of Initiative & Persistence
• Anhedonia
• Social Withdrawal

• Person showing primarily negative symptoms is said to have Type II Schizophrenia
Cognitive Symptoms

• Poor attention
• Low psychomotor speed
• Poor learning & memory
• Poor abstract thinking
• Poor problem solving skills
Prevalence Rates across the Lifespan

![Graph showing prevalence rates across the lifespan for males and females.](image)
Pharmacology of Schizophrenia

• The dopamine hypothesis

• Initial Evidence:
  – First antipsychotics (chlorpromazine) found to block D2 dopamine receptors
  – Some modern antipsychotics (Clozapine) block D4 dopamine receptors
  – Drugs that increase dopamine release (cocaine, amphetamines, Parkinson’s meds) can cause psychotic symptoms (particularly positive symptoms)
Pharmacology of Schizophrenia

• Modern evidence
  – Some schizophrenics show increased dopamine release in response to amphetamines
  – Evidence of extra D3 & D4 dopamine receptors in the nucleus accumbens
Dopamine Release in Response to Amphetamines

(a)

- Dopamine release (percent of baseline)
  - Controls
  - Schizophrenics

(response graph with data points and bars)
Brain Abnormalities
Schizophrenia & Brain Shrinkage

The diagram shows a scatter plot with two groups: comparison subjects and schizophrenia patients. The x-axis represents age (years), ranging from 20 to 70, and the y-axis represents the unstandardized residual of gray matter (ml), ranging from -300 to 200. The plot indicates a negative correlation between age and the unstandardized residual of gray matter, with schizophrenia patients generally having a lower gray matter volume compared to comparison subjects.
Prefrontal Cortex (PFC)

- Evidence that the PFC is underactive in many people with schizophrenia
- Called “hypofrontality”
Hypofrontality

Dorsal prefrontal cortex

Normal subjects

Schizophrenic patients
Disorganization in the Hippocampus
Theories for Schizophrenia

• Old editions of the book
  – positive symptoms caused by overactive dopamine (mesolimbic system)
  – negative symptoms cause by brain damage (to the PFC)

• My view (based on abnormal psych texts)
  – positive symptoms caused by overactive dopamine (mesolimbic system)
  – Negative symptoms caused by underactive dopamine (mesocortical system)
Problems with the Dopamine Hypothesis

- Many people with schizophrenia don’t respond to dopamine antagonists
- Some suggest that PCP (angel dust) simulates schizophrenia best; PCP is a glutamate antagonist
- Newer antipsychotics target glutamate and serotonin
Treatment with Glutamate (NMDA receptor) Agonists
Integrating Schizophrenia Theories

**Mesocortical System**
- Initial Brain Damage
  - Hypofrontality
  - MORE Hypofrontality

**Mesolimbic System**
- Glutamate neurons fail to excite GABA neurons in VTA
- Glutamate neurons fail to excite Mesocortical DA neurons

**Positive symptoms of schizophrenia**
- Nucleus accumbens

**Ventral tegmental area (VTA)**
- DA neuron
- GABA neuron
- DA neuron

**Prefrontal cortex**
- Glutamatergic neuron

**Mesolimbic System overactivates**
Integrating Schizophrenia Theories

• PFC is underactive (hypofrontality), perhaps because of abnormal brain development, negative symptoms produced

• PFC fails to excite DA neurons in the midbrain

• Underactive DA neurons in the midbrain create further underactivity in the PFC; more negative symptoms are produced

• PFC fails to inhibit the release of dopamine in the nucleus accumbens, making this area overactive; positive symptoms are produced
Heritability

<table>
<thead>
<tr>
<th></th>
<th>MZ (Identical Twins)</th>
<th>DZ (Fraternal Twins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordance rate:</td>
<td>46%</td>
<td>14%</td>
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</tbody>
</table>
Other Factors beyond Genetics that Appear to be Important

• Viral Exposure: influenza, rubella, toxoplasma gondii (toxoplasmosis), herpes, Lyme disease, polio, measles (prenatal and postnatal exposure)
  – Cause could be viruses themselves OR
  – Cause could be mother’s immune system response to the viruses

• Birth Complications
  – Prenatal hypoxia seen more often in the birth histories of people diagnosed with schizophrenia
The Seasonality Effect

Number of schizophrenic births (per 10,000 live births)

Adjusted Seasonality Effect

![Graph showing adjusted seasonality effect with months on the x-axis and schizophrenic births per 10,000 live births on the y-axis. The graph indicates a peak in February and a trough in August.]
Monochorionic vs. Dichorionic Twins

(a) Monochorionic Twins
- Placenta
- Amniotic sac

(b) Dichorionic Twins
- Placenta
Heritability

<table>
<thead>
<tr>
<th>Concordance rate:</th>
<th>MZ (Monochorionic)</th>
<th>MZ (Dichorionic)</th>
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<tbody>
<tr>
<td></td>
<td>60%</td>
<td>10.7%</td>
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II. Mood Disorders
Symptoms of Depression
(5/9 for at least 2 weeks)

- Depressed mood
- Weight loss/gain
- Motor agitation or impairment
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Change in sleep
- Concentration impairment
- Thoughts of death or suicide
- Loss of interest in previously pleasurable activities
Symptoms of Mania

• Elevated, expansive or irritable mood for at least 1 week, plus at least three of the following:
  • Inflated self-esteem or grandiosity
  • More talkative or pressure to keep talking
  • Flight of ideas or racing thoughts
  • Increase in goal-directed activity
  • Excessive involvement in potentially dangerous activities
Caspi et al. (2003)
Caspi et al. (2003)

![Graph showing the probability of suicide ideation/attempt against the number of stressful life events.](b)
MAO-A & Risk for Conduct Disorder
(Foley et al., 2004)
The Effect of Sleep on Depression

- REM deprivation
- Total sleep deprivation
Total Sleep Deprivation and Depression

Mood Rating

Depressed

Nonresponders

Responders

Night of sleep deprivation

Recovery night sleep

A.M. P.M.

9 1 5 9 1 5 9 1 5 9 1

60 70 80 90

Normal

Hours
Depression, Exercise, & Neurogenesis in the Hippocampus
III. Substance-Related Disorders
Substance Abuse

• Repeated problems as a result of the using the substance

• 1 or more of the following in a 1 year period:
  – Failure to fulfill important obligations at work, home, or school
  – Repeated use of the substance in hazardous situations
  – Repeated legal problems
  – Continued use of the substance despite repeated social and legal problems
Substance Dependence

• Closest thing in the DSM to “addiction”
• Often involves tolerance & withdrawal (if so, often referred to as physical/physiological dependence)
• But can be dependent without tolerance & withdrawal (if so, often referred to as psychological/psychic dependence)
### TABLE 14.4 DSM-IV-TR Criteria for Diagnosing Substance Dependence

Substance dependence often involves evidence of physiological dependence plus repeated problems due to the use of the substance.

A. Maladaptive pattern of substance use, leading to three or more of the following:
   1. Tolerance, as defined by either
      a. the need for markedly increased amounts of the substance to achieve intoxication or desired effect
      b. markedly diminished effect with continued use of the same amount of the substance
   2. Withdrawal, as manifested by either
      a. the characteristic withdrawal syndrome for the substance
      b. the same or a closely related substance is taken to relieve or avoid withdrawal symptoms
   3. The substance is often taken in larger amounts or over a longer period than was intended
   4. There is a persistent desire or unsuccessful effort to cut down or control substance use
   5. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
   6. Important social, occupational, or recreational activities are given up or reduced because of substance use
   7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem caused by or exacerbated by the substance.

Explanations for Addictive Behavior

• Positive reinforcement
  – Activation of pleasure areas via opiates and/or endocannabinoids
  – Activation of craving/wanting areas via dopamine release in the nucleus accumbens

• Negative reinforcement

• Classical Conditioning
Addictive Behaviors and Classical Conditioning

Drug (UCS) $\rightarrow$ Compensatory response (UCR)

Drug paraphernalia & environment (CS) $\rightarrow$ Compensatory response (CR)

Many fatal drug overdoses occur when the person uses in a non-familiar environment. Why?
Commonly Abused Substances
Opiates

• Examples: morphine, heroin, codeine, methadone

• Effects (site of action)
  – Analgesia (periaqueductal gray matter)
  – Hypothermia (preoptic area)
  – Sedation (reticular formation)
  – Reinforcement/craving/wanting (mesolimbic system and nucleus accumbens)
Cocaine & Amphetamines

• Classified as stimulants
• Cocaine: blocks reuptake of dopamine in the nucleus accumbens
• Amphetamines: cause dopamine transporters to run in reverse, providing additional dopamine to the synapse
Nicotine

• Impersonates the neurotransmitter ACh (it’s an acetylcholine agonist)
• Mesolimbic system has nicotinic ACh receptors
• Conditioned place preference: animals learn to prefer places where they receive nicotine
• Brain area related to nicotine dependence: the insula
The Insula & Addiction

Degree of correlation with smoking cessation
Alcohol

• Likely has the largest negative effect on society of any substance, with the possible exception of nicotine

• Alcohol affects at least two receptors:
  – NMDA receptor
  – $\text{GABA}_A$ receptor
Alcohol & the NMDA Receptor

• Alcohol is an indirect antagonist of the NMDA receptor
• Alcohol impairs LTP
• Other NMDA antagonist drugs...
  – produce sedative effects
  – produce anxiety reducing effects
  – stimulate the release of DA in the nucleus accumbens
Alcohol & the GABA$_A$ Receptor

- Indirect agonist for the GABA$_A$ receptor
- With alcohol, more inhibitory potentials are created and thus more neurons are hyperpolarized
- Drug Ro-15-4513 blocks this binding site for alcohol on the GABA$_A$ receptor
- Impairment of GABA$_A$ receptors in the cerebellum disrupts balance and coordination
Effect of Ro15-4513
Cannabis/Marijuana

• Active agents:
  – THC (tetrahydrocannabinol)
  – CBD (cannabidiol)

• Both impersonate endocannabinoids such as anandamide and 2-AG

• Receptors for endocannabinoids found all over the brain, including the mesolimbic system and the hippocampus
Heritability of Various Addictive Substances

Heritability of addiction ($h^2$)

Addictive agents

Hallucinogens, Stimulants, Cannabis, Sedatives, Gambling, Smoking, Alcohol, Caffeine, Opiates, Cocaine
More on Alcohol Dependence

• Steady drinkers
  – Drink consistently/have trouble abstaining
  – Start drinking before age 25
  – Correlated with antisocial behaviors: impulsiveness, fighting, lack of guilt/remorse

• Binge drinkers
  – Go for long periods without drinking, but when they start again, they have trouble stopping
  – Start drinking after age 25
  – Personality: dependent, perfectionistic, excessive guilt
Treatments
Treatments for Opiate Dependence

• Methadone & methadone maintenance therapy (agonist substitution)
• Buprenorphine: partial opiate agonist
Treatments for Cocaine & Amphetamine Dependence

• Initially tried dopamine receptor blocker meds but these proved problematic

• Also have tried agonist substitutions, but substitutes are also highly addictive

• Immune system & “vaccinating” against dependence (Carrera et al. (1995))
Treatments for Nicotine Dependence

- **Rimonabant**: cannabinoid CB1 receptor blocker
- **Bupripion/Wellbutrin**: antidepressant, NE & DA reuptake inhibitor, ACh antagonist
- **Varenicline/Chantix**: partial agonist for the nicotinic ACh receptor; book evidence makes this medication look pretty good
Treatments for Nicotine Dependence

<table>
<thead>
<tr>
<th>Weeks of abstinence</th>
<th>Percentage who abstained</th>
</tr>
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<tbody>
<tr>
<td>4–7</td>
<td>Varenicline</td>
</tr>
<tr>
<td>4–12</td>
<td>Bupropion</td>
</tr>
<tr>
<td>4–24</td>
<td>Placebo</td>
</tr>
<tr>
<td>4–52</td>
<td></td>
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</tbody>
</table>
Treatment for Alcohol Dependence

• Naltrexone: opiate antagonist
• Acamprosate: NMDA receptor antagonist (1\textsuperscript{st} used to treat alcohol withdrawal seizures, later found it reduced likelihood of returning to drinking)
Treatments for Alcohol Dependence

[Graphs showing the comparison of mean craving scores and proportion of subjects who continued to abstain between Placebo-treated and Naltrexone-treated groups over 12 weeks of medication.]

Mean craving score (0–9)

Proportion of subjects who continued to abstain

Number of weeks receiving medication