The Psychopharmacology of Violence and Impulsivity

Part 1

Epidemiology, Neurobiology, and Genetics of Aggression
Learning Objective

• Understand the epidemiology, neurobiology, and genetics of violence, impulsivity, and aggression
Poll Question

I understand the epidemiology, neurobiology, and genetics of violence, impulsivity, and aggression.

A. 1 (strongly disagree)
B. 2
C. 3
D. 4
E. 5 (strongly agree)
Stacy is a 16-year-old patient with schizophrenia. She was recently sentenced to 6 months at a juvenile detention facility after physically assaulting a boy in her neighborhood. Approximately what percentage of girls at the detention facility likely have a mental illness?

A. 10%
B. 20%
C. 30%
D. 40%
E. 50%
Kevin is a 22-year-old patient with ADHD who often gets into fist fights when he feels threatened or angry. Which prefrontal brain area is most closely linked to impulsivity?

A. Dorsolateral prefrontal cortex
B. Ventromedial prefrontal cortex
C. Orbitofrontal cortex
D. Supplementary motor cortex
Charles is a 42-year-old patient with schizoaffective disorder and a history of childhood abuse. Genetic testing has revealed that Charles is homozygous for the short (3-repeat) allele of the MAO-A gene. Compared to another male patient with schizoaffective disorder and a history of child abuse who is homozygous for the long (4-repeat) allele of the MAO-A gene:

A. Charles has an increased risk for violent behavior
B. Charles has a decreased risk for violent behavior
C. The risk for violent behavior is the same for both of these male patients
WHAT IS VIOLENCE?
Definition of Aggression

- Hostile, injurious, or destructive behavior that is often caused by frustration

- Can be defined by the target
  - Self-directed
  - Other-directed

- Can be defined by the mode of aggression
  - Physical, verbal
  - Direct, indirect

- Can be defined by the cause
  - e.g., medical

Premeditated Aggression

- Planned behavior not typically associated with frustration or response to immediate threat
- Might not be accompanied by autonomic arousal
- Planned with clear goals in mind
- Also called:
  - Predatory
  - Instrumental
  - Proactive

Impulsive Aggression

- Characterized by high levels of autonomic arousal
- Precipitated by provocation
- Associated with negative emotions, such as anger or fear
- Usually represents response to perceived stress
- Also called:
  - Reactive aggression
  - Affective aggression
  - Hostile aggression

• Becomes pathological when aggressive responses are exaggerated in relation to emotional provocation

• Can be considered defensive aggression and appropriate if threat is dangerous and imminent and if aggressive response is unpremeditated

• Pathological aggression may be erroneously experienced or rationalized as being within the boundaries of normal protective or defensive aggression

WHO IS VIOLENT?
# Predictors of Violence

<table>
<thead>
<tr>
<th><strong>STATIC</strong></th>
<th><strong>DYNAMIC</strong></th>
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<tbody>
<tr>
<td>Factors that are unable to be altered</td>
<td>Factors that may be changed to improve outcome</td>
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<tr>
<td>• Previous history of violence</td>
<td>• Substance use</td>
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<tr>
<td>• Male gender</td>
<td>• Current symptoms of major mental illness</td>
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<tr>
<td>• Young adulthood</td>
<td>– Persecutory delusions</td>
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<tr>
<td>• Lower intelligence</td>
<td>– Command hallucinations</td>
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<tr>
<td>• History of head trauma</td>
<td>– Depression</td>
</tr>
<tr>
<td>• History of military service</td>
<td>• Hopelessness</td>
</tr>
<tr>
<td>• Weapons training</td>
<td>• Suicidality</td>
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<tr>
<td>• Past diagnosis of major mental illness</td>
<td>• Treatment nonadherence</td>
</tr>
<tr>
<td></td>
<td>• Impulsivity</td>
</tr>
<tr>
<td></td>
<td>• Access to weapons</td>
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Violence and Mental Illness

• Patients with mental illness are not generally violent toward others, but there is a subpopulation of patients who are at high risk for violence

• 5.2% of severely violent acts are committed by mentally ill individuals

• There is as much as a 5-fold increase in violent offenses with mental illness compared to healthy individuals

• Prevalence of severe mental illness
  – 4% in adult prisoners
  – 30% in young girls in detention

Violence and Schizophrenia

- Violence in patients with psychosis (10%) vs. the general population (2%)

- Cost of schizophrenia includes $2.64 billion in direct non-health care costs for law enforcement (2002)

- Assault rate by patients with schizophrenia is 16-28%

- 59% of violence in schizophrenia is motivated by delusions
  - Especially if the delusions make the patient angry or upset
  - Especially if the delusions cause feelings of personal threat or are pathological thoughts that override self control

Tools for Assessing Aggression

- Historical Clinical Risk (HCR-20)
- Psychopathy Checklist – Revised (PCL-R)
- Psychopathy Checklist – Screening Version (PCL-SV)
- Brøset Violence Checklist

WHY ARE SOME PEOPLE VIOLENT?
Can One Inherit a Behavior or a Psychiatric Disorder?

- genotype

  - subtle molecular abnormality

  - abnormal information processing (biological endophenotype)

  - behavior with complex functional interactions and emergent phenomena (symptom endophenotype)
Hypothetical Path From Genes via Molecules, Circuits, and Information Processing to Symptoms, Syndromes, and Mental Illnesses

risk gene 1

risk gene 2

risk gene 3

altered enzyme for monoamine degradation

altered synaptic plasticity machinery

altered development in prefrontal cortex

biological endophenotype

symptom endophenotype

executive dysfunction

phenotype

delusions

schizophrenia

overactivation

normal

baseline

hypoactivation

F

From Genes via Molecules, Circuits, and Information Processing to Symptoms, Syndromes, and Mental Illnesses
Monoamine Oxidase A (MAO-A): The Warrior Gene

- 3-repeat (short) allele = low activity = elevated monoamines
- 4-repeat (long) allele = high activity = low monoamines
- Maltreated children have more aggression regardless of the type of MAO-A genotype
- In patients exposed to maltreatment as children:
  - Males: aggression linked to low-activity MAO-A variant
  - Females: aggression linked to high-activity MAO-A variant
- Testosterone lowers MAO-A levels by acting on the MAO-A promoter

MAO-A Genotype: Sex Matters

High Testosterone and Low MAO-A Activity in Antisocial Personality Disorder (ASPD)

Catechol-O-methyltransferase (COMT)

- Low-activity Met/Met genotype = increased dopamine in the PFC
- High-activity Val/Val genotype = decreased dopamine in the PFC
- Met allele is associated with enhanced aggressiveness and antisocial behavior in patients with schizophrenia
- S-adenosylmethionine (SAMe) treatment of Met/Met patients leads to a reduction in aggressive behavior
  - SAMe increases COMT activity (leading to less DA in the PFC)

Twin Studies

• Bullying behavior in younger middle-class children
  – Concordant in monozygotic twins of 0.72
  – Concordant in dizygotic twins of 0.42, indicating that 60% of the variance in bullying behavior is due to genetic factors

• Irritable/impulsive aggression (as differentiated from premeditated aggression) has substantial heritability (44-72%) in >20 twin studies

Born Fearful?
Serotonin Genetics and Life Stressors

- SERT I genotype
  - resilient circuit

- SERT s genotype
  - compromised circuit
  - fearful faces stressor
  - multiple adult life stressors
  - chronic stressors
  - MDD
  - anxiety disorder
  - brain atrophy

- Amygdala

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Born Callous?
MAO-A, Serotonin Genetics, and Life Stressors

Low-Risk Genes

- resilient circuit
  - amygdala
  - Learn to suppress short-term rewards for better long-term consequences

High-Risk Genes

- compromised circuit
  - amygdala
  - No fear conditioning for adverse consequences or reward conditioning for long-term rewards

MAO-A, Serotonin Genetics, and Life Stressors

- overactivation
- normal
- baseline
- hypoactivation

amygdala

- rewards
- conduct disorder
Stress-Diathesis Model, Part 1: no risk gene, normal function

no stressor

mild stressor

severe stressor

no stressor

normal function

normal function
Stress-Diathesis Model, Part 2: 1 risk gene, normal function
Stress-Diathesis Model, Part 3:  
2 risk genes, slowing of function, but compensation and no breakdown

no stressor

risk gene 1

risk gene 2

mild stressor

severe stressor

normal function

normal function
Stress-Diathesis Model, Part 4:
multiple risk genes, slowing of function with mild stressor, but decompensation and breakdown with severe stressor

- **no stressor**
- **slowing of function**
- **breakdown**
Is Violence Acquired?

• Parental violence is a predictor of violence in patients with schizophrenia

• Among violent offenders, 47% of men and 21% of women have antisocial personality disorder
  – Are personality disorders acquired or inherited?

Child Abuse Sensitizes Circuits to Adult Stressors

- no stress in infancy
- mild stress in infancy
- child abuse

- normal stress activation
- reduced reactivity to stress
- stress sensitization but no symptoms of anxiety or depression

- multiple adult life stressors

- no psychiatric disorder

MDD, anxiety disorder
Susceptibility to Aggression and Psychiatric Diagnosis

- co-occurring psychopathology
  - psychosis and cognitive impairment
  - anxiety and adult trauma
  - emotional sensitivity and dysregulation
  - psychopathy

- type of aggression
  - deviant behaviors
  - impulsive, triggered by cues associated with the trauma
  - impulsive or reactive; borderline personality disorder
  - premeditated; antisocial personality disorder

Are Violence and Aggression Hypothetically Linked to Specific Brain Regions?

Lack of top-down inhibition of impulses and callous thoughts

delusions hallucinations drug rewards motivation

provocation

A: amygdala
BF: basal forebrain
C: cerebellum
H: hippocampus
Hy: hypothalamus
NA: nucleus accumbens
NT: brainstem neurotransmitter centers
PFC: prefrontal cortex
S: striatum
SC: spinal cord
T: thalamus

no fear conditioning excessive fear conditioning
reexperiencing

autonomic drives
Serotonin and Aggression

- Low 5HT metabolite 5HIAA
  - Suicide attempters, particularly those who make violent attempts
  - Patients with personality disorders; correlates with lifetime history of aggression
  - Impulsive murderers, arsonists, those who commit infanticide

- 5HT1A and 5HT1B autoreceptors
  - Inhibit serotonergic neurotransmission
  - Overexpressed in highly aggressive rats
  - Density increased following victorious aggressive experiences

Abnormalities in the Pathophysiology of Aggression

Bottom-Up: Temptation With Impulsive Action

1. anticipation of threat
2. impulsive choice
3. threat sensitivity
4. protection
5. Lack of cognitive flexibility

Overactivation
Normal
Baseline
Hypoactivation

Temptation With Impulsive Action

Hit that guy

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Top-Down: Willpower When Provoked

1. Amygdala
2. Don't hit that guy

Red: overactivation
Purple: normal
Gray: baseline
Blue: hypoactivation
# Mechanisms of Aggression in Different Psychiatric Disorders

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Match Each Symptom to Hypothetically Malfunctioning Brain Circuits

- **Positive symptoms**
  - mesocortical/prefrontal cortex
  - nucleus accumbens reward circuits

- **Negative symptoms**
  - mesolimbic

- **Affective symptoms**
  - ventromedial prefrontal cortex

- **Aggressive symptoms**
  - orbito-frontal cortex

- **Cognitive symptoms**
  - amygdala
  - dorsolateral prefrontal cortex
Psychotic Aggression: Bottom-Up Out of Control

1. That guy is going to hurt me – paranoid threat generated internally by psychosis (schizophrenia, bipolar, drug abuse)

2. Go for it!

3. Is this a real threat?

4. Remember, I got in trouble the last time

- amygdala
- OFC
- VMPFC
- DLPFC
- PFC
- NA
- VTA

- overactivation
- normal baseline
- hypoactivation

Hit that guy
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Impulsive Aggression: Bottom-Up Out of Control

1. Staff is telling me to change my behavior and is refusing my request
2. Act first, think later – ADHD, psychosis, cognitive dysfunction, substance abuse, child abuse
3. Do I really need to hit somebody to get my way?
4. Remember, I got in trouble the last time

OFC, VMPFC, DLPFC, PFC, NA, amygdala, VTA

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Circuits of Impulsivity, Hyperactivity, and Attention: Regional Problems of PFC "Tuning"

- **OFC**
  - Limbic
    - Interrupt
    - Blurt out
    - Not waiting turn
  - Motor
    - Fidget
    - Leave seat
    - Climb

- **DLPFC**
  - Cognitive
    - Does not finish
don't disorganized
    - Avoids sustained
effort

- **Dorsal ACC**
  - Does not listen
distracted
  - Forgetful
  - Careless

**Impulsivity**

**Hyperactivity**

**Problems of Sustained Attention & Problem Solving**

**Problems of Selective Attention**
How DA and NE Hypothetically "Tune" the PFC: Signal Increased and Noise Reduced
How DA and NE Hypothetically "Tune" the PFC:
Low NE and Low DA: ADHD With Signals Reduced and Noise Increased
ADHD: Hypothetically Low Signals and/or High Noise in PFC

- Noise
- Signal

Fidget / Shift attention

Sit in seat / Focus

PFC strength of output

NE concentration

DA concentration

NE low – Signal reduced

DA low – Noise increased
Treatment: Increase NE, Increase DA

- NE optimized – signal increased
- DA optimized – noise reduced
ADHD and Stress: Hypothetically Low Signals and/or High Noise in PFC

at first, high NE and DA

NE high – signal reduced
DA high – noise increased
eventually, **NE and DA depletion**

- **NE concentration**
  - NE low – signal reduced

- **DA concentration**
  - DA low – noise increased
Treatment: Increase NE, Increase DA

PFC

noise

signal

fidget / shift attention

sit in seat / focus

NE optimized – signal increased

DA optimized – noise reduced

PFC strength of output

NE concentration

DA concentration
ADHD: Hypothetically Low Signals due to Low NE

- **NE low** – signal reduced
- **DA optimized** – noise reduced

**PFC**

noise → signal

hyperactivity
impulsivity
inattention

sit still
behave
pay attention

DA concentration

NE concentration

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Treatment With Alpha 2 Agonist

- PFC strength of output
- NE concentration
  - NE optimized – signal increased
- DA concentration
  - DA optimized – noise reduced
ADHD and Oppositional Symptoms: Hypothetically Very Low Signals in VMPFC

- NE concentration very low – signal much reduced
- DA concentration low – noise increased

VMPFC

noise
signal

temper tantrums
argumentative
disobedient
aggressive

behavior cooperate
Treatment: Stimulant

VMPFC

Neurotransmitters:
- NE: NE concentration
- DA: DA concentration

Graphs:
- NE concentration: NE still low – signal reduced
- DA concentration: DA optimized – noise reduced

Behavioral Changes:
- Cooperate
- Temper tantrums, argumentative, disobedient, aggressive

Diagram:
- Noise to Signal ratio
- Behaviors: Cooperate vs. Temper tantrums, argumentative, disobedient, aggressive

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Treatment: Augment Stimulant With Alpha 2A Agonist

NE optimized – signal increased
DA optimized – noise reduced

VMPFC

noise signal

temper tantrums argumentative disobedient aggressive

behave cooperate

NE concentration

DA concentration

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Substance Use and Violence

• The association between schizophrenia and violent crime may be minimal unless the patient has a comorbid substance use disorder.

• Individuals with a substance use disorder have the same risk of violent behavior as patients with psychosis or psychosis and comorbid substance abuse.

• Substance abuse may increase the risk of violence in mental illness by:
  – Further impairing impulse control
  – Further impairing threat perception
  – Further impairing treatment adherence

Fazel et al. JAMA 2009;301(19):2016-23;  
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Stress and the Normal Circuit

biological endophenotype
- unprovoked
- provoked - compensated
- unprovoked

symptom endophenotype or phenotype
- no symptoms
- no symptoms - resilient
- no symptoms

overactivation
normal
baseline
hypoaactivation
Development of Stress Sensitization in the Normal Circuit

**Biological Endophenotype**
- Unprovoked
  - Emotional trauma
  - Repeatedly provoked – still compensation
- Provoked – compensation

**Symptom Endophenotype or Phenotype**
- No symptoms
  - No symptoms – resilient
  - No symptoms – loss of resilience
  - No symptoms – vulnerable but presymptomatic

Colors:
- Red: Overactivation
- Normal
- Baseline
- Hypoactivation

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Model of Progression From Stress Sensitization

**biological endophenotype**

- **unprovoked** – irreversible stress sensitization
- **provoked** – lack of compensation
- **provoked** – decompensation with either overactivation or circuit breakdown
- **unprovoked but decompensation is sustained**

**symptom endophenotype or phenotype**

- no symptoms – vulnerable but presymptomatic
- prodromal symptoms begin
- definite but subtle/subsyndromal symptoms
- psychiatric symptom of a full syndrome/psychiatric disorder

- overactivation
- normal
- baseline
- hypoactivation

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That guy disrespected me; I want more cigarettes, drugs, and respect – a cell phone would be nice, too; good thing the rules don't apply to me

Unemotional planning and execution; no fear of carrying this out or of the consequences

I don't need to do anything that is frustrating to me

Can I get away with it? Callous disregard for others

Hit that guy when he is not expecting it and when I can get away with it

Suppress the action until it is time
Fear Conditioning

• Excessive in anxiety disorders
  – Overvalued consequences

• Deficient in conduct disorder
  – Lack ability to accurately predict impending harm from signals of threat
  – Unable to flexibly adjust to changes in reinforcement
  – May explain why these patients never develop a "conscience"
Fear Conditioning vs. Fear Extinction
Fear Conditioning vs. Fear Extinction

VMPFC
hippocampus

no fear response

VMPFC
hippocampus
sensory cortex
thalamus

= glutamate
= GABA

fear response!!!
fear conditioning

fear extinction
new learning

no fear response
Circuits of Conduct Disorder, Antisocial Behavior, Mood Instability, and Oppositional Behavior: Additional Problems in the PFC

- **Steal a car**
- **Cruelty**
- **Pick a fight**

**Conduct Disorder**

- **Mood Instability**
- **Mania**
- **Anxiety**

**Bipolar/Anxiety Spectrum**

- **Temper Tantrums**
- **Argumentative**
- **Disobedient**
- **Aggressive**

**Oppositional Defiant Disorder**
## Treatment of Aggression

<table>
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<tr>
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<th>Target</th>
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<tr>
<td></td>
<td>Drive</td>
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<tr>
<td>Serotonin reuptake</td>
<td></td>
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<tr>
<td>Anticonvulsants</td>
<td>↓ (limbic irritability)</td>
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<tr>
<td>Atypical antipsychotics</td>
<td>↓ (subcortical dopaminergic stimulation)</td>
</tr>
<tr>
<td>Stimulants</td>
<td></td>
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<tr>
<td>Opiate antagonists</td>
<td>↓ (opiates)</td>
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• Violence can be either impulsive or instrumental, inherited or acquired

• There is a high association of violence with genetic susceptibility plus an unfavorable environment

• There are many routes to violence (e.g., mental illnesses and unfavorable factors such as substance abuse)

• Various areas of the prefrontal cortex and the amygdala are hypothetically linked to symptoms of psychotic, impulsive, and instrumental violence

• Understanding the topographical distribution of symptoms and their regulation by neurotransmitters provides a rationale for psychopharmacological treatment of the symptoms of violence