Stress Impairs Prefrontal Cortex Function: Why Stress Can Produce an ADHD-Like Profile

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SOME IMAGES HAVE BEEN REMOVED TO REDUCE THE MEMORY REQUIREMENTS FOR THIS PRESENTATION
Disclosures

Dr. Arnsten and Yale University have license agreements with:

• Shire Pharmaceuticals for the development of guanfacine for the treatment of ADHD, and

• Marinus Pharmaceuticals for the development of chelerythrine for the treatment of bipolar disorder, schizophrenia, PTSD and related illnesses
Goals of Talk

• Learn about the prefrontal cortex, and why dysfunction of the prefrontal cortex produces symptoms of Attention Deficit Hyperactivity Disorder (ADHD).

• Learn about how brain cells (neurons) in prefrontal cortex communicate with each other, and how they form networks that allow high order regulation of behavior and thought.

• Learn about how sensitive prefrontal networks are to chemicals released according to our state of arousal, and how either too little (fatigue, boredom) or too much (stress) of these chemicals impairs prefrontal abilities.

• Understand how chemical changes in the prefrontal cortex produced by genetic and/or environmental insults associated with ADHD, bipolar disorder, schizophrenia and lead poisoning lead to weakened prefrontal function, and how optimal use of medications may be able to correct some of these insults.
Prefrontal Cortex
Prefrontal Cortex

The most highly evolved brain region
Prefrontal Cortex
Our Mental Sketchpad
Our Central Executive
Prefrontal Cortex

The ability to represent information that is not currently in the environment, and use that information to thoughtfully guide attention, actions and emotions.
Prefrontal Cortex

Inhibits inappropriate behaviors, thoughts, and emotions

Inhibits interference from external and internal distractions
Prefrontal Cortex

Allows us to make decisions, and have insight and judgment

Allows us to organize and plan for the future
Prefrontal Cortex

Understands what others are thinking (Theory of Mind)

Monitors errors, knows what is real vs. imagined
Prefrontal Cortex

Allows us to delay gratification

Allows us to multi-task and sort through high levels of information
Prefrontal Cortex

Increasingly needed for success in the Information Age and in school
Functional Organization of Prefrontal Cortex
Functional Organization of Prefrontal Cortex

Regulates attention and thoughts
Regulates attention and thoughts

Regulates motor behavior
Regulates attention and thoughts

Regulates motor behavior

Regulates emotions, social behavior
Regulates emotions, social behavior

Regulates attention and thoughts

Regulates motor behavior

projections lower brain systems that create motor patterns

projections to primitive brain regions that generate emotion

projections to sensory cortices

projections to motor cortices
Regulates emotions, social behavior

Regulates motor behavior

Regulates attention and thoughts

In humans, also organized by hemisphere

Functional Organization of Prefrontal Cortex
Functional Organization of Prefrontal Cortex

- Regulates attention and thoughts
- Regulates motor behavior
- Regulates emotions, social behavior

LEFT: GENERATION
Functional Organization of Prefrontal Cortex

Regulates attention and thoughts

Regulates motor behavior

Regulates emotions, social behavior

LEFT: GENERATION

language
Regulates attention and thoughts
Regulates motor behavior
Regulates emotions, social behavior

RIGHT: INHIBITION

Functional Organization of Prefrontal Cortex
Lesions to Right PFC Produce Symptoms of Disinhibition
Lesions to Right PFC Produce Symptoms of Disinhibition

distractibility, poor sustained attention, disorganized, poor planning

RIGHT: INHIBITION
Lesions to Right PFC Produce Symptoms of Disinhibition

distractibility, poor sustained attention, disorganized, poor planning

poor impulse control, locomotor hyperactivity

RIGHT: INHIBITION
Lesions to Right PFC Produce Symptoms of Disinhibition

distractibility, poor sustained attention, disorganized, poor planning

poor impulse control, locomotor hyperactivity

oppositionality, aggression
Lesions to Right PFC Produce Symptoms of Disinhibition

Symptoms of ADHD

distractibility, poor sustained attention, disorganized, poor planning

poor impulse control, locomotor hyperactivity

oppositionality, aggression

RIGHT: INHIBITION
Lesions to Right PFC Produce Symptoms of Disinhibition

**Symptoms of ADHD**
- distractibility, poor sustained attention, disorganized, poor planning
- poor impulse control, locomotor hyperactivity

**RIGHT: INHIBITION**

**Symptoms of conduct disorder**
- oppositionality, aggression
ALTERED PFC FUNCTION IN ADHD

Rubia et al, 1999
Reduced activity—especially in right hemisphere

Schulz et al, 2004

STOP

DELAY

TAPPING

Rubia et al, 1999
Reduced activity—especially in right hemisphere

Schulz et al, 2004
ALTERED PFC STRUCTURE IN ADHD

Mostofsky et al, 2002
Reduced volume

Makris et al, 2007
Disorganized white matter pathways
Lesions to Right PFC Produce Symptoms of Disinhibition

Severe distractibility, and inability to sustain attention, fractionated thought, disorganized, loss of insight, delusions

poor impulse control, locomotor hyperactivity

disinhibited emotions

RIGHT: INHIBITION

The manic phase of bipolar disorder is also associated with severe right prefrontal cortical dysfunction

Poor reality testing, error monitoring
Prefrontal cortex regulates behavior, thought and feelings through networks of interconnected neurons.
Networks of prefrontal pyramidal cells represent stimuli (e.g. I left my math book 90° from the TV), and represent goals and rules (I will finish my homework, I must sit in my seat). Network activity is used to guide correct choices, and to inhibit inappropriate responses. Networks maintain their activity through “recurrent excitation”; i.e. the cells excite each other in the absence of environmental stimulation.
Neurons also receive inputs from nonpreferred neurons, i.e. “noise”
How neurons communicate
PARTS OF THE NEURON
PARTS OF THE NEURON

Cell body
PARTS OF THE NEURON

- **Cell body**: The body of the neuron.
- **Dendrites**: Receive messages.
PARTS OF THE NEURON

- **Dendrites**: Receive messages from other neurons.
- **Dendritic spines**: Specialized for receiving messages, can readily change size/shape, spines can be lost or added.
PARTS OF THE NEURON

- **Dendritic spines**: Specialized for receiving messages, can readily change size/shape, spines can be lost or added.
- **Dendrites**: Receive messages.
- **Axon**: Sends messages; Cell “fires” off an action potential.

Cell body
**PARTS OF THE NEURON**

- **Cell body**
- **Dendrites** - Receive messages
- **Dendritic spines** - Specialized for receiving messages, can readily change size/shape, spines can be lost or added
- **Axon** - Sends messages, Cell “fires” off an action potential
- **Axon terminal** - Communicates with next cell, full of packets of chemical messages
A single neuron in the human prefrontal cortex often receives hundreds of thousands of connections.
TYPES OF NEURONS
TYPES OF NEURONS

excitatory cell
TYPES OF NEURONS

- Excitatory cell
- Inhibitory cell
A NETWORK OF EXCITATORY NEURONS
A NETWORK OF EXCITATORY NEURONS
A NETWORK OF EXCITATORY NEURONS
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A NETWORK OF EXCITATORY NEURONS
A NETWORK OF EXCITATORY NEURONS
Neurons Communicate Using Chemical Signals
Neurons Communicate Using Chemical Signals

Axon from excitatory neuron

PFC dendrite

Packets of neurotransmitter

Receptors

Spine
Neurons Communicate Using Chemical Signals

Axon from excitatory neuron

PFC dendrite

spine
Neurons Communicate Using Chemical Signals

Axon from excitatory neuron

PFC dendrite

spine
Neurons Communicate Using Chemical Signals

Axon from excitatory neuron
Neurons Communicate Using Chemical Signals
Neurons Communicate Using Chemical Signals

Axon from excitatory neuron

PFC dendrite

spine

excitatory
Neurons Communicate Using Chemical Signals

If there are enough excitatory inputs, the axon fires and action potential.
INHIBITORY NEURONS STOP CELL FIRING
Neurons Communicate Using Chemical Signals

Input from inhibitory neuron

PFC dendrite

spine
Neurons Communicate Using Chemical Signals

PFC dendrite

Input from inhibitory neuron
Neurons Communicate Using Chemical Signals

- PFC dendrite
- Input from inhibitory neuron
- Spine
Neurons Communicate Using Chemical Signals

- **Inhibitory**: makes neuron stop firing
- **Input from inhibitory neuron**
- **PFC dendrite**
- **Spine**
Neurons Communicate Using Chemical Signals

Inhibitory: makes neuron stop firing

Input from inhibitory neuron

PFC dendrite

Not the focus of today’s talk

spine
NEUROMODULATORS HAVE INDIRECT INFLUENCES
NEUROMODULATORS HAVE INDIRECT INFLUENCES

e.g. norepinephrine, dopamine and other chemicals released based on our state of arousal
Neurons Communicate Using Chemical Signals

PFC dendrite

spine
Neurons Communicate Using Chemical Signals
Neurons Communicate Using Chemical Signals

Norepinephrine-

A substance released when an interesting stimulus occurs, and according to our state of arousal.
Neurons Communicate Using Chemical Signals

Neuromodulator

Norepinephrine

PFC dendrite

spine
Neurons Communicate Using Chemical Signals

Norepinephrine receptor

PFC dendrite

Neuromodulator
Neurons Communicate Using Chemical Signals

Neuromodulator

Ion channel—an open pore

PFC dendrite

spine

α2A Ion channel
Neurons Communicate Using Chemical Signals

PFC dendrite

Ion channel open

spine

Neuromodulator

α2A Ion channel open
Neurons Communicate Using Chemical Signals

Norepinephrine binds to receptor- \( \alpha_2 \)A ion channel closes

PFC dendrite

spine

Neuromodulator
Neurons Communicate Using Chemical Signals

Norepinephrine binds to receptor-ion channel closed
ELECTRON MICROSCOPY OF $\alpha_{2A}$ RECEPTORS AND HCN ION CHANNELS ON THE SPINES (sp) OF PFC NEURONS
Summary:

Networks maintain representations through “recurrent excitation”; i.e. the cells excite each other to maintain firing even with no stimulation from the outside world. The neurons in the networks interact through synapses on dendritic spines.

The spines in prefrontal cortex often contain receptors for neuro-modulators such as norepinephrine, and contain ion channels that can alter the strength of input connections onto the spine.

The chemical environment influences whether PFC cells can engage with correct networks, and disconnect from irrelevant inputs.
PFC network connections are very sensitive to their chemical environment.
Goldilocks
Too much

Too little

Just right
Just right

Too little

Too much
Soup = Norepinephrine (NE) and dopamine (DA)
These chemicals are released in the prefrontal cortex according to our state of arousal.
Norepinephrine and dopamine are part of a family of chemicals called catecholamines.
The Inverted U
The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function
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The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function

levels of catecholamine release increase with arousal state

Focused
Organized
Responsible

Distracted
Disorganized
Forgetful
Disinhibited

PFC Abilities
The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function

levels of catecholamine release increase with arousal state
The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function

- Inadequate catecholamines
- fatigued
- bored

levels of catecholamine release increase with arousal state
The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function

Moderate amounts of NE engage $\alpha_2$A receptors
Moderate amounts of dopamine stimulate some D1 receptors

levels of catecholamine release increase with arousal state
The Prefrontal Cortex Requires A Proper Level of Catecholamines for Optimal Function

Excessive norepinephrine engages α1, β1 receptors
Excessive dopamine stimulation of too many D1 receptors

levels of catecholamine release increase with arousal state
Chemical Cascades That Alter Network Firing
Chemical Cascades That Alter Network Firing
Chemical Cascades That Alter Network Firing

OPTIMAL PFC FUNCTION
MODERATE LEVELS OF CATECHOLAMINES

STRENGTHEN NETWORKS
BRINGING IN “SIGNALS”

<table>
<thead>
<tr>
<th>HCN closed</th>
<th>AC</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>cAMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gs</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>HCN open</th>
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<td></td>
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<tr>
<td>Gi</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WEaken NETWORKS
BRINGING IN “NOISE”

NE α2A
Moderate D1

Alert
Interested

OPTIMAL
$\alpha_2A$ increases "signal"
OPTIMAL CATECHOLAMINE REGULATION

α2A increases “signal”
OPTIMAL CATECHOLAMINE REGULATION

α2A increases “signal”
\( \alpha_2A \) increases "signal"
α2A increases “signal”
OPTIMAL CATECHOLAMINE REGULATION

α2A increases “signal”
OPTIMAL CATECHOLAMINE REGULATION

α2A increases “signal”

D1 decreases “noise”

INAPPROPRIATE INPUT

DOPAMINE

NET

PFC dendrite

DAT

glutamate

APPROPRIATE INPUT

NOREPINEPHRINE

α2A increases “signal”
INAPPROPRIATE INPUT

OPTIMAL CATECHOLAMINE REGULATION

- **NOREPINEPHRINE**
  - NET

- **DOPAMINE**
  - DAT

- **PFC dendrite**
  - D1
  - cAMP

- **spine**
  - glutamate

- **INAPPROPRIATE INPUT**
  - glutamate

- **APPROPRIATE INPUT**
  - $\alpha 2A$

  - $\alpha 2A$ increases "signal"

  - D1 decreases "noise"
OPTIMAL CATECHOLAMINE REGULATION

α2A increases “signal”

D1 decreases “noise”

α2A increases “signal”

DOPAMINE

INAPPROPRIATE INPUT

glutamate

INAPPROPRIATE INPUT

APPROPRIATE INPUT

cAMP

PFC dendrite

DAT

DOPAMINE

NET

NOREPINEPHRINE
OPTIMAL CATECHOLAMINE REGULATION

- APPROPRIATE INPUT
  - $\alpha 2A$ increases "signal"
- INAPPROPRIATE INPUT
  - D1 decreases "noise"
  - glutamate

- Norepinephrine (NET)
- Dopamine (DAT)

PFC dendrite

- cAMP

Inappropriate input leads to increased noise, while appropriate input increases signal through $\alpha 2A$ receptors.
OPTIMAL CATECHOLAMINE REGULATION

- α2A increases "signal"
- D1 decreases "noise"
- INAPPROPRIATE INPUT
- glutamate
- DOPAMINE
- NET
- NOREPI-NEPHRINE
- APPROPRIATE INPUT
- cAMP
- PFC dendrite
- spine
- DAT

α2A increases "signal"
OPTIMAL CATECHOLAMINE REGULATION

α2A increases “signal”

D1 decreases “noise”

INAPPROPRIATE INPUT

INAPPROPRIATE CATECHOLAMINE REGULATION

APPROPRIATE INPUT

α2A increases “signal”

PFC dendrite

cAMP

spine

glutamate

D1 decreases “noise”

DAT

DOPAMINE

NOREPINEPHRINE

APPROPRIATE INPUT

INAPPROPRIATE INPUT
Chemical Cascades That Alter Network Firing

OPTIMAL PFC FUNCTION
MODERATE LEVELS OF CATECHOLAMINES

HCN closed

HCN open

STRENGTHEN NETWORKS BRINGING IN “SIGNALS”

WEAKEN NETWORKS BRINGING IN “NOISE”

NE α2A
Moderate D1

Alert
Interested

Chemical Cascades That Alter Network Firing

OPTIMAL PFC FUNCTION
MODERATE LEVELS OF CATECHOLAMINES

HCN closed

HCN open

STRENGTHEN NETWORKS BRINGING IN “SIGNALS”

WEAKEN NETWORKS BRINGING IN “NOISE”

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Chemical Cascades That Alter Network Firing

OPTIMAL PFC FUNCTION
MODERATE LEVELS OF CATECHOLAMINES

HCN closed

HCN open

STRENGTHEN NETWORKS BRINGING IN “SIGNALS”

WEAKEN NETWORKS BRINGING IN “NOISE”

NE α2A
Moderate D1

Alert
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Chemical Cascades That Alter Network Firing

OPTIMAL PFC FUNCTION
MODERATE LEVELS OF CATECHOLAMINES

HCN closed

HCN open

STRENGTHEN NETWORKS BRINGING IN “SIGNALS”

WEAKEN NETWORKS BRINGING IN “NOISE”

NE α2A
Moderate D1

Alert
Interested

Chemical Cascades That Alter Network Firing

OPTIMAL PFC FUNCTION
MODERATE LEVELS OF CATECHOLAMINES

HCN closed

HCN open

STRENGTHEN NETWORKS BRINGING IN “SIGNALS”

WEAKEN NETWORKS BRINGING IN “NOISE”

NE α2A
Moderate D1

Alert
Interested
ADHD May Involve Inadequate Catecholamines

Optimal PFC Function

Genetic Changes in ADHD

- HCN closed
- HCN open

Weakened “Signals”
- cAMP
- AC
- α2A

Strengthened “Noise”
- cAMP
- AC
- D1/5

ADHD
Inadequate catecholamines
ADHD Medications Normalize Catecholamines in PFC

**OPTIMAL PFC FUNCTION**

<table>
<thead>
<tr>
<th>Genetic Changes in ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCN closed</td>
</tr>
<tr>
<td>cAMP up</td>
</tr>
<tr>
<td>AC up</td>
</tr>
</tbody>
</table>

**STRENGTHEN NETWORKS**

- Bringing in “Signals”
- Guanfacine

**WEAKEN NETWORKS**

- Bringing in “Noise”
- Methylphenidate
- Amphetamines
- Atomoxetine

**ADHD + meds**

- ADHD

---

**Key Compounds**

- NE (Norepinephrine)
- DA (Dopamine)
- NET (Norepinephrine Transporter)
- NETdβH (Dopamine Transporter)
- DAT (Dopamine Transporter)

---

**Additional Information**

- α2A and D1/5 receptors
- Gs and Gi signaling pathways
OPTIMAL CATECHOLAMINE REGULATION

NOREPINEPHRINE

NET

NP

APPROPRIATE INPUT

α2A increases “signal”

INAPPROPRIATE INPUT

DOPAMINE

DAT

cAMP

D1 decreases “noise”

glutamate

PFC dendrite

spine

α2A increases “signal”

APPROPRIATE INPUT

OUTPUT

OPTIMAL CATECHOLAMINE REGULATION
GENETIC WEAKENING OF CATECHOLAMINES IN ADHD

NET

NOREPINEPHRINE

DGH

NET

APPROPRIATE INPUT

cAMP

PFC dendrite

32A

DAT

DOPAMINE

INAPPROPRIATE INPUT

glutamate

spine
GENETIC WEAKENING OF CATECHOLAMINES IN ADHD

NET/DAH
NOREPINEPHRINE

DOPAMINE

APPROPRIATE INPUT

INAPPROPRIATE INPUT
glutamate

PFC dendrite

AcAMP

32A

spine
Alterations in DBH are associated with weak sustained attention and poor executive function in patients with ADHD (Bellgrove et al, 2005; Kieling et al, 2007)
GENETIC WEAKENING OF CATECHOLAMINES IN ADHD

NOREPINEPHRINE

INAPPROPRIATE INPUT

PFC dendrite

ACMP

spine

APPROPRIATE INPUT

DOPAMINE

DAT

glutamate

α2A

cAMP
ADHD TREATMENTS ENHANCE CATECHOLAMINES IN PFC

NET/NET/NET

methylphenidate
amphetamine
atomoxetine

guanfacine

32A

PFC dendrite

GABA

CAMP

INAPPROPRIATE INPUT

NOREPINEPHRINE

DOPAMINE

DOPAMINE

APPROPRIATE INPUT

glutamate

spine
Stress Impairs Prefrontal Function

levels of catecholamine release

stressed
Epinephrine released into blood
Norepinephrine released by sympathetic nervous system and throughout most of brain
Turning off prefrontal cortical control of behavior during stress may have survival value, but may make us more vulnerable to neuropsychiatric illness.
Even mild stress impairs prefrontal function, if we feel **out of control**. The prefrontal cortex is the brain region that assesses whether we are in control, and shuts off the stress response if it thinks we are.
Stress Impairs Prefrontal Function

Excessive D1

NE $\alpha_1, \beta_1$

levels of catecholamine release

stressed
Stress Impairs Prefrontal Function

Excessive levels of catecholamine release

**IMPARED PFC FUNCTION**
EXCESSIVE LEVELS OF CATECHOLAMINES

- all HCN open
- cAMP
- AC
- Gs
- β1 or D1/5

DISCONNECTS ALL NETWORK CONNECTIONS

**NE α1, β1**
**Excessive D1**

levels of catecholamine release

stressed
Stress Impairs Prefrontal Function

Excessive levels of catecholamine release lead to impaired PFC function. The diagram shows the mechanisms involved:

- **Excessive levels of catecholamines**
- **NE α1, β1**
- **Excessive D1**

The diagram illustrates the following pathways:

- **Ca^2+** activates PKC, which suppresses cell firing.
- **DAG** and **IP3** activate PLC, leading to the release of cAMP, which in turn activates AC, leading to the suppression of all HCN channels.
- **All network connections** are disconnected.

The diagram also highlights the role of the sympathetic nervous system (SNS) in stress, showing an increased release of NE (norepinephrine) and DA (dopamine), further impairing PFC function.
Stress Impairs Prefrontal Function

Excessive levels of catecholamine release

It takes very high levels of NE to engage these receptors, and thus they seem to only kick in during stress.

NE $\alpha_1$, $\beta_1$ Excessive D1

DISCONNECTS ALL NETWORK CONNECTIONS

IMPAIRED PFC FUNCTION

EXCESSIVE LEVELS OF CATECHOLAMINES

Ca$^{2+}$

PKC

DAG

IP3

PLC

Gs

Gq

AC

cAMP

It takes very high levels of NE to engage these receptors, and thus they seem to only kick in during stress.

NE $\alpha_1$, $\beta_1$ Excessive D1

levels of catecholamine release

stressed
Stress Impairs Prefrontal Function

Excessive levels of catecholamine release impair prefrontal function. NE, α1, β1, or D1/5 receptors are activated, leading to increased cAMP production through AC and PKC. This results in suppressed cell firing and disconnection of all network connections.
Stress Impairs Prefrontal Function

- Excessive levels of catecholamine release
- NE $\alpha_1$, $\beta_1$
- Excessive D1
- IMPAIRED PFC FUNCTION
- SUPPRESSES CELL FIRING
- DISCONNECTS ALL NETWORK CONNECTIONS

Diagram:
- NE $\alpha_1$, $\beta_1$
- Excessive D1
- SUPPRESSES CELL FIRING
- DISCONNECTS ALL NETWORK CONNECTIONS

Chemical Pathways:
- PKC
- Ca$^{2+}$
- DAG
- IP3
- cAMP
- AC
- Gs
- Gq
EXCESSIVE CATECHOLAMINES (eg STRESS)

INAPPROPRIATE INPUT

PFC dendrite

D1

DAT

DOPAMINE

NOREPINEPHRINE

NET

NET

APPROPRIATE INPUT

glutamate

INAPPROPRIATE INPUT

cAMP

β1

cAMP

cAMP

cAMP

cAMP

spine
EXCESSIVE CATECHOLAMINES (eg STRESS)
EXCESSIVE CATECHOLAMINES (eg STRESS)

- INAPPROPRIATE INPUT
- DOPAMINE
- D1

APPROPRIATE INPUT

- NET
- NOREPINEPHRINE

PFC dendrite

- cAMP
- spine
- glutamate

INAPPROPRIATE INPUT
EXCESSIVE CATECHOLAMINES (eg STRESS)

APPROPRIATE INPUT

INAPPROPRIATE INPUT

NOREPINEPHRINE

DOPAMINE

NET

NET

PFC dendrite

DAT

cAMP

DAT

cAMP

GLUTAMATE

cAMP

spine
EXCESSIVE CATECHOLAMINES (eg STRESS)

- NET/1
- NOREPINEPHRINE
- DAT

APPROPRIATE INPUT

INAPPROPRIATE INPUT

PFC dendrite

α₁
β₁

cAMP

dendrite

INAPPROPRIATE INPUT

glutamate
EXCESSIVE CATECHOLAMINES (eg STRESS)

- Excessive catecholamines (e.g., stress) can lead to increased activity in the brain.
- This can be caused by excessive noradrenaline (NET), dopamine (DOPAMINE), and other neurotransmitters.
- Inappropriate input (INAPPROPRIATE INPUT) can also contribute to this state.
- The diagram shows the flow of neurotransmitters, including dopamine (D1) and Noradrenaline (NET), as well as the production of cAMP and the involvement of PKC and Ca^2+.
- The spine and dendrite regions are highlighted to show the sites of interaction and signal transduction.
- Glutamate is also depicted as a neurotransmitter involved in this process.
EXCESSIVE CATECHOLAMINES (eg STRESS)

- NORADRENALINE (norepinephrine)
- NET (netransmitter)
- APPROPRIATE INPUT
- DOPAMINE
- DAT (dopamine transporter)
- INAPPROPRIATE INPUT
- glutamate

PKC
Ca^{+2}

PFC dendrite

D1

D1

INAPPROPRIATE INPUT

cAMP

APPROPRIATE INPUT

NOREPINEPHRINE

D1
**EXCESSIVE CATECHOLAMINES (e.g., STRESS)**

- **NOREPINEPHRINE**
  - NET

- **DOPAMINE**
  - DAT

- **APPROPRIATE INPUT**
  - glutamate
  - cAMP

- **INAPPROPRIATE INPUT**
  - cAMP

- **PKC**
  - Ca^{+2}

- **PFC dendrite**
  - D1

- **Stop cell firing**
  - cAMP

- **spine**
  - cAMP
Stress Impairs Prefrontal Function

Excessive levels of catecholamines:
- NE
- DA

Impaired PFC function due to all HCN open and excessive levels of cAMP, Ca^{2+}, DAG, IP3, and PLC.

Mechanisms:
- Gs
- Gq
- PKC
- AC
- IP3
- DAG
Important Molecules Inside of Cells Provide Brakes On These Stress Pathways

DGKH=DAG Kinase

IMPAIRED PFC FUNCTION
EXCESSIVE LEVELS OF CATECHOLAMINES

PKC ← Ca^{2+} ↓
DAG ↓
IP3 ↘
PLC ↗
cAMP ↗
AC ↘

DGKH

Gq
Gs

α1
β1 or D1/5

NE
DA

stressed
Bipolar disorder (mania)
Molecular Brakes Altered in Mental Illness

Right prefrontal dysfunction in mania
Blumberg et al. 1999

Bipolar disorder (mania)
Molecular Brakes Altered in Mental Illness

Normalized by medications that inhibits PKC signaling
Blumberg et al. 2005

Bipolar disorder (mania)
Molecular Brakes Altered in Mental Illness

DISC1=Disrupted In Schizophrenia

Bipolar disorder (mania)
Schizophrenia
Molecular Brakes Altered in Mental Illness

Bipolar disorder (mania)
Schizophrenia
Molecular Brakes Altered in Mental Illness

Could guanfacine treatment substitute for loss of DISC1 function?

Bipolar disorder (mania)
Schizophrenia

IMPAIRED PFC FUNCTION
EXCESSIVE LEVELS OF CATECHOLAMINES

- PKC
- Ca²⁺
- DAG
- IP₃
- PLC
- cAMP
- AC
- Gq
- Gs
- α₁
- β₁ or D₁/₅
- NE
- DA

all HCN open

guanfacine

DISC1
Molecular Brakes Altered in Mental Illness

DISC1 is also needed for the normal development of the PFC

Bipolar disorder (mania)
Schizophrenia
Lead Poisoning Mimics ADHD

Lead poisoning
Lead Poisoning Mimics ADHD

Lead poisoning

Pb\(^{2+}\)
Lead poisoning mimics ADHD

Lead poisoning is associated with criminal behavior and out of wedlock pregnancy. Even low levels cause impaired attention regulation.
Lead Poisoning Mimics ADHD

Lead poisoning is associated with reduced PFC gray matter. 

Destruction to this area in early childhood (e.g. falling out a window, hit by a car) causes sociopathy.

Cecil et al, PLOS 2008
Increased PKC Signaling Decreases PFC Gray Matter

Lead poisoning

Pb$^{2+}$

PKC

Ca$^{2+}$

PLC

IP3

DAG

Pb$^{2+}$

α1

NE
Increased PKC Signaling Decreases PFC Gray Matter

Lead poisoning

\( \text{Pb}^{2+} \)
Increased PKC Signaling Decreases PFC Gray Matter

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$\text{Pb}^{2+}$
Increased PKC Signaling Decreases PFC Gray Matter
Loss of PFC Activity/Gray Matter In Conditions that Resemble ADHD

STOP

DELAY

TAPPING

ADHD

Mania

Lead Poisoning
Medications That Inhibit PKC Protect PFC Gray Matter In Bipolar Disorder

Blumberg et al. *Biol Psychiatry* 2006
Medications= Lithium, Depakote

Ventral Prefrontal Cortex
Medications That Inhibit PKC Protect PFC Gray Matter In Bipolar Disorder

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Medications = Lithium, Depakote

Might these medications be helpful in treating children with lead poisoning as well, especially if chelation is unable to remove all the lead from their systems?
SUMMARY: Prefrontal Dysfunction Resembles ADHD

A normal child when stressed
Genetic mutations that weaken brakes on stress pathways
e.g. DAG kinase (bipolar disorder)
DISC1 (schizophrenia)
Lead poisoning
SUMMARY: Prefrontal Dysfunction Resembles ADHD

A normal child when tired
Genetic mutations that reduce catecholamine levels in PFC

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SUMMARY: Prefrontal Dysfunction Resembles ADHD

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Head injury to PFC
Genetic mutations that slow or impair the development of the PFC or its connections

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True ADHD?
SUMMARY: Prefrontal Dysfunction Resembles ADHD

Important to distinguish the true cause of “ADHD-like” behaviors, in order to plan the correct treatment

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Genetic mutations that reduce catecholamine levels in PFC

Head injury to PFC
Genetic mutations that slow or impair the development of the PFC or its connections

A normal child when stressed
Genetic mutations that weaken brakes on stress pathways e.g. DAG kinase (bipolar disorder) DISC1 (schizophrenia) Lead poisoning

True ADHD?
The future: A more rational approach to neuropsychiatry
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NIMH
NIA
NARSAD