Prefrontal Cortical Circuits in Schizophrenia: Molecular Vulnerabilities, and Clues for Treatments

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Disclosure- AFTA and Yale University receive royalties from the US sales of Intuniv™ from Shire Pharmaceuticals. They do not receive royalties from sales of generic Intuniv or guanfacine.
Graystone Park- NJ State Psychiatric Hospital
Volunteer- Summer of 1974

Learning first hand how exposure to stress (even very mild stress) can exacerbate thought disorder
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Leading to a career studying how stress effects higher brain functions, especially the function of the newly evolved prefrontal cortex
The Prefrontal Cortex (PFC)
Newly evolved circuits that generate Mental Representations in the absence of sensory stimulation, i.e., Working Memory—our Mental Sketchpad.
Newly evolved circuits

The foundation of:

Abstract Reasoning
And Language

Executive Functions-
“Top-Down” control of thought, action and emotion

Metacognition-
Insight, Reality Testing
Rapidly taken “off-line” during uncontrollable stress.
The circuits most vulnerable in schizophrenia
Symptoms of thought disorder

- loose associations
- fragmented speech
- “word salad”

Symptoms of thought disorder are worsened by stress, and correlate with errors in working memory.
Symptoms of thought disorder correlate with hypoactivity of the dorsolateral prefrontal cortex during working memory.
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Correlations with symptoms of thought disorder

Gray Matter Loss in Schizophrenia Targets the Association Cortices, Especially Prefrontal Cortex
Prefrontal Cortical Gray Matter Loss During the Prodrome, as Patients Descend Into Illness

Often accompanied by stress, inflammation
Prefrontal Cortical Gray Matter Loss During the Prodrome, as Patients Descend Into Illness

Often accompanied by stress, inflammation

How does the loss of prefrontal cortex gray matter give rise to the symptoms of schizophrenia?
How does the prefrontal cortex generate thought?

What makes these circuits so vulnerable in schizophrenia?

Why is stress a debilitating factor?

By understanding these mechanisms, can we protect circuits?
The Microcircuitry of Visuospatial Representation

The work of Patricia Goldman-Rakic 1937-2013

Review of her work:
Arnsten, Cerebral Cortex 23:2269-81
Cue

Delay

Respond

Visuospatial Representation
A "Delay cell" that represents 90°
Neural Representation of Visual Space

Delay cells

Prefrontal microcircuits

Goldman-Rakic, Neuron 14:477, 1995
Neural Representation of Visual Space

Delay cells

Prefrontal microcircuits

Goldman-Rakic, Neuron 14:477, 1995
### Neural Representation of Visual Space

#### Delay cells
- Persistent firing via NMDA (NR2B) synapses

#### dIPFC

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Goldman-Rakic, Neuron 14:477, 1995
Cue

Delay

Respond

Neural Representation of Visual Space

Persistent firing
Via NMDA (NR2B) synapses

Goldman-Rakic, Neuron 14:477, 1995
Cells Excite Each Other via Connections on Dendritic Spines
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I will be illustrating this as a cartoon-

Cells Excite Each Other via Connections on Dendritic Spines
Loss of Spines and Dendrites in Schizophrenia

Postmortem dIPFC, Layer III

A. Control Subject

B. Schizophrenia

C. Schizophrenia

Healthy Comparison Subject

Schizophrenia Subject

Glantz, et al., Arch Gen Psychiatry, 57:65-73 2000
In schizophrenia:
- Loss of connections
- Neurons profoundly underactive
- Loss of persistent firing needed for strong mental representations (seen as reduced BOLD response in fMRI studies)

A. Control Subject

B. Schizophrenia

C. Schizophrenia

Glantz, et al., Arch Gen Psychiatry, 57:65-73 2000
Loss of Spines and Dendrites in Schizophrenia

What is causing this???

In schizophrenia:
- Loss of connections
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A. Control Subject

Healthy Comparison Subject

Schizophrenia Subject

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Neuron 1 releases glutamate, which stimulates NMDA receptors and excites Neuron 2

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A chemical called acetylcholine is released when we are awake. Acetylcholine stimulates nicotinic α7 receptors, which electrifies the membrane and allows NMDA receptors to respond to glutamate.
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A chemical called acetylcholine is released when we are awake. Acetylcholine stimulates nicotinic α7 receptors, which electrifies the membrane and allows NMDA receptors to respond to glutamate. This allows conscious thought when we are awake.

Yang et al., PNAS 110:12078-83, 2013
Weaker NMDA receptor and nicotinic α7 receptors have both been linked with schizophrenia. This would weaken the neural connection.

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Why most patients with schizophrenia smoke cigarettes?
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Why most patients with schizophrenia smoke cigarettes?

Medications that stimulate nicotinic α7 receptors are currently under development as potential treatments for cognitive deficits in schizophrenia.
Low doses of drugs that stimulate nicotinic α7 receptors can strengthen connections and enhance mental representations.

A. Weak firing with inadequate nic-α7R stimulation
B. Strong representation with optimal nic-α7R stimulation
C. Loss of representation with excessive nic-α7R stimulation

The strength of these higher prefrontal cortical connections is also dynamically altered by potassium ion channels.
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Chemical messengers inside the cell (cAMP, protein kinase A (PKA)) open the potassium channels to weaken the connection (e.g. this prevents seizures).
Exposure to uncontrollable stress releases chemicals in brain (norepinephrine and dopamine - similar to epinephrine) that drive the production of cAMP and PKA. This rapidly opens potassium channels and disconnects prefrontal networks, taking the prefrontal cortex “off-line”.

Summary - Stress Effects on Brain State

Alert, Safe and Interested

Uncontrollable Stress

PFC
Top down regulation of:
- Thought
- Action
- Emotion

basal ganglia
habitual responses

Unconscious, reflexive/habitual responding by primitive circuits

Survival value during danger, but not when one needs higher cognitive abilities to thrive

PFC networks connected

Increased neuronal firing

PFC networks disconnected

Reduced neuronal firing

Arnsten, Nat Neuroscience 18:1376-85, 2015
**Summary - Stress Effects on Brain State**

**Alert, Safe and Interested**

- **PFC**
  - Top down regulation of:
    - Thought
    - Action
    - Emotion

**Chronic Uncontrollable Stress**

- **basal ganglia**
  - habitual responses

- **amygdala**
  - conditioned emotional responses

- Unconscious, reflexive/habitual responding by primitive circuits

**Survival value during danger, but not when one needs higher cognitive abilities to thrive**

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Arnsten, Nat Neuroscience 18:1376-85, 2015
Lose dendrites and spines

CHRONIC STRESS

Arnsten, Nat Neuroscience 18:1376-85, 2015
Mechanisms that rein in the stress response and restore prefrontal connections

Healthy connection

Arnsten, Nat Neuroscience 18:1376-85, 2015
Mechanisms that rein in the stress response and restore prefrontal connections

Many are the target of genetic insults in schizophrenia

Arnsten, Nat Neuroscience 18:1376-85, 2015
The phosphodiesterase PDE4A is an enzyme that destroys cAMP.
It is anchored near cAMP by DISC1 (Disrupted In Schizophrenia)

Mechanisms that rein in the stress response and restore prefrontal connections

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Healthy connection

Mechanisms that rein in the stress response and restore prefrontal connections

The phosphodiesterase PDE4A is an enzyme that destroys cAMP.

It is anchored near cAMP by DISC1 (Disrupted In Schizophrenia)

Genetic alterations to both PDE4A and DISC1 have been linked to schizophrenia and autism.

Healthy connection

Mechanisms that rein in the stress response and restore prefrontal connections
Mechanisms that rein in the stress response and restore prefrontal connections

Genetic links with mGluR3 (GRM3) in both schizophrenia and autism

Healthy connection

Mechanisms that rein in the stress response and restore prefrontal connections

NAAG = N-acetyl-aspartyl-glutamate
Healthy connection

Mechanisms that rein in the stress response and restore prefrontal connections

Jin et al, Cerebral Cortex epub, Jan 19, 2017
Endogenous mGluR3 agonist, NAAG, greatly enhances the firing of Delay cells

Jin et al, Cerebral Cortex epub, Jan 19, 2017
Increases in the enzyme that destroys NAAG, and reduced expression of mGluR3 in the PFC of patients with schizophrenia

Jin et al, *Cerebral Cortex* epub, Jan 19, 2017
Schizophrenia
Potential treatment?

Endogenous mGluR3 agonist, NAAG, greatly enhances the firing of Delay cells

Jin et al, Cerebral Cortex epub, Jan 19, 2017
Potential therapeutic mechanism to strengthen and protect dIPFC connections

The receptor engaged when we feel alert, safe and interested

The receptor engaged when we feel alert, safe and interested

Potential therapeutic mechanism to strengthen and protect dIPFC connections

Potential therapeutic mechanism to strengthen and protect dlPFC connections

Stimulation of the α2A-AR strengthens connectivity and enhances dlPFC Delay cell firing

Potential therapeutic mechanism to strengthen and protect dIPFC connections

Improved Working Memory and Reduced Distractibility in Monkeys

Guanfacine improves a variety of PFC cognitive functions in rodents, monkeys and humans

Reviewed in:

Kim et al. (2012) Psychopharm 219:363-75
Potential therapeutic mechanism to strengthen and protect dIPFC connections

Daily guanfacine protects PFC dendritic spines and cognitive function from chronic stress exposure in rats

(guanfacine also reduces neuroinflammation, which is increased at the onset of illness)
Guanfacine is in widespread use for a number of PFC disorders, e.g.:

- ADHD (FDA-approved 2009; Intuniv™)
- Tourettes Syndrome (Scahill, Yale)
- Autism spectrum disorders (Scahill, Yale; McCracken, UCLA)
- Oppositional/aggressive symptoms (Connor, UConn)
- Emotional trauma, e.g. PTSD in children (Connor, UConn)

Guanfacine is also being tested in the treatment of other PFC disorders, including:

- Mild Traumatic Brain Injury (McAllister, Dartmouth, Indiana)
- Substance abuse (Fox/McKee/Sinha, Yale)
- Emergence Delirium (Blair, Vanderbilt)
- Strokes/Infections afflicting the association cortices (Singh-Curry et al, UCL, London)

- Helpful in prodromal schizophrenia?
A variety of molecules that normally serve to strengthen prefrontal connections and protect them from stress are genetically weakened or have reduced expression in schizophrenia.

This may help to explain why many different kinds of genetic insults can produce the same phenotype, and why these insults particularly afflict the newly evolved circuits in prefrontal cortex.
Learning about these molecular mechanisms has identified new potential therapeutic targets to strengthen the prefrontal circuits most at risk in schizophrenia.
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Take Home Message

We are learning about how molecular insults lead to prefrontal dysfunction in schizophrenia, which may identify new strategies to protect these vital circuits.
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