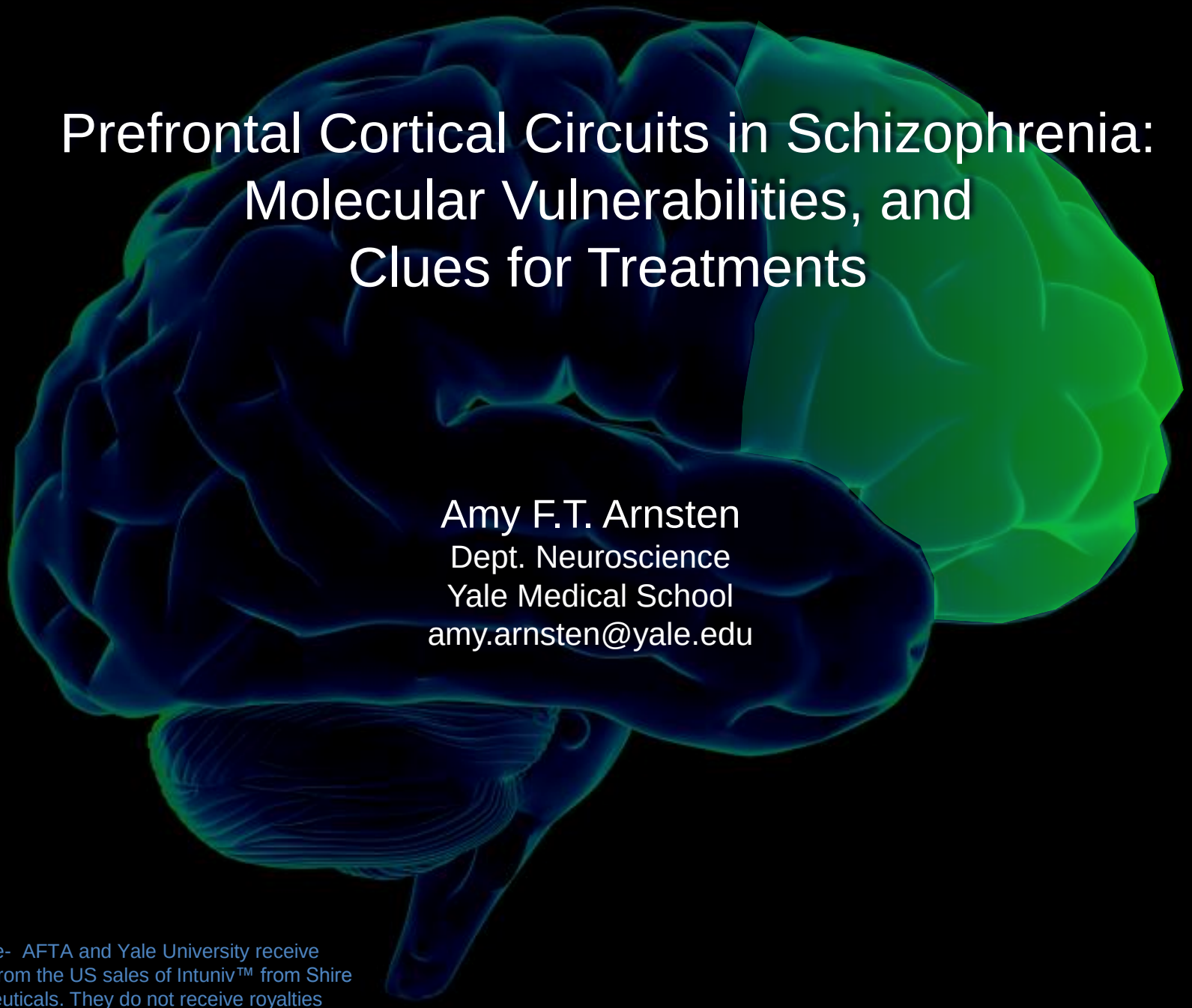
Prefrontal Cortical Circuits in Schizophrenia: Molecular Vulnerabilities, and Clues for Treatments



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Yale Medical School
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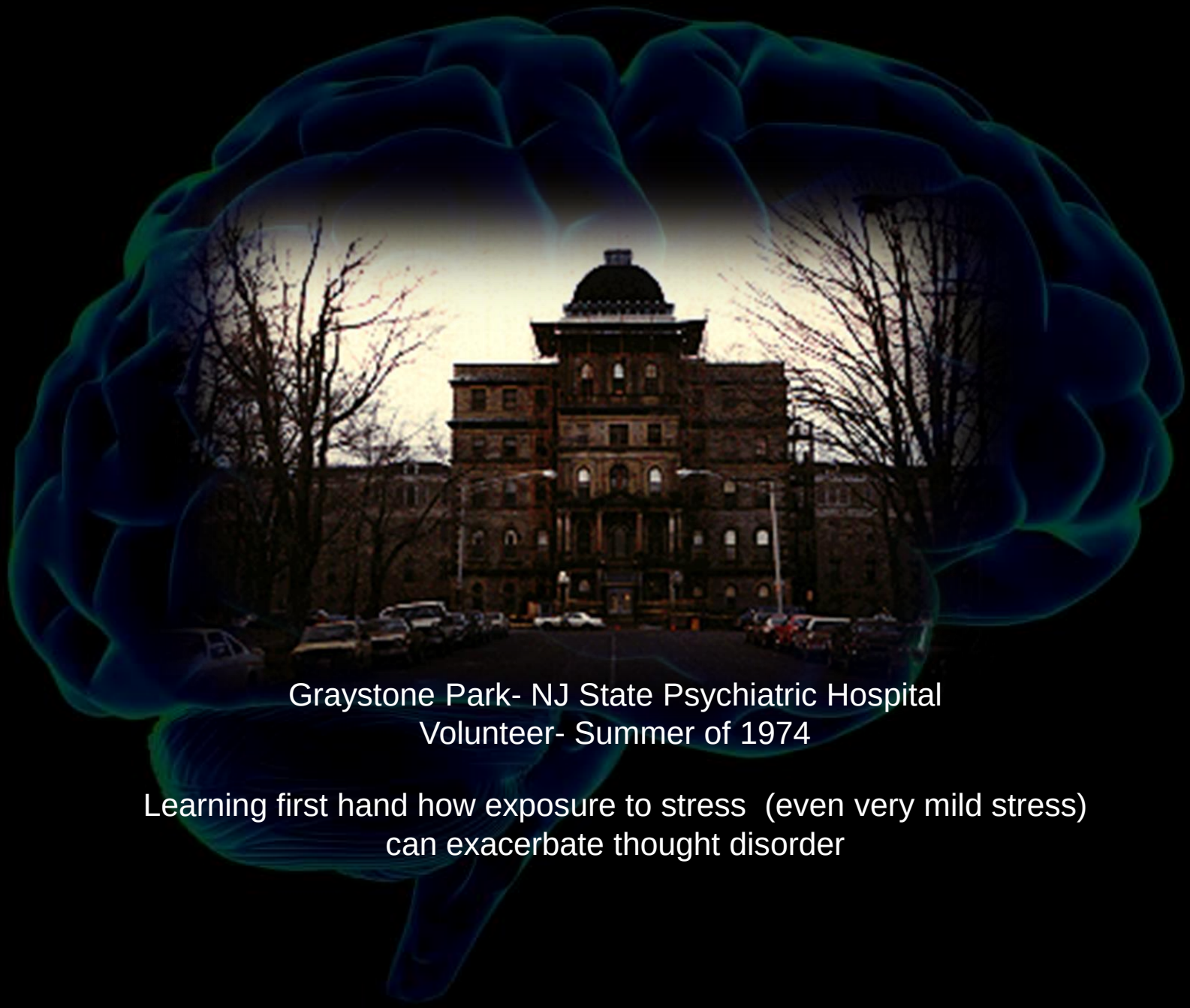
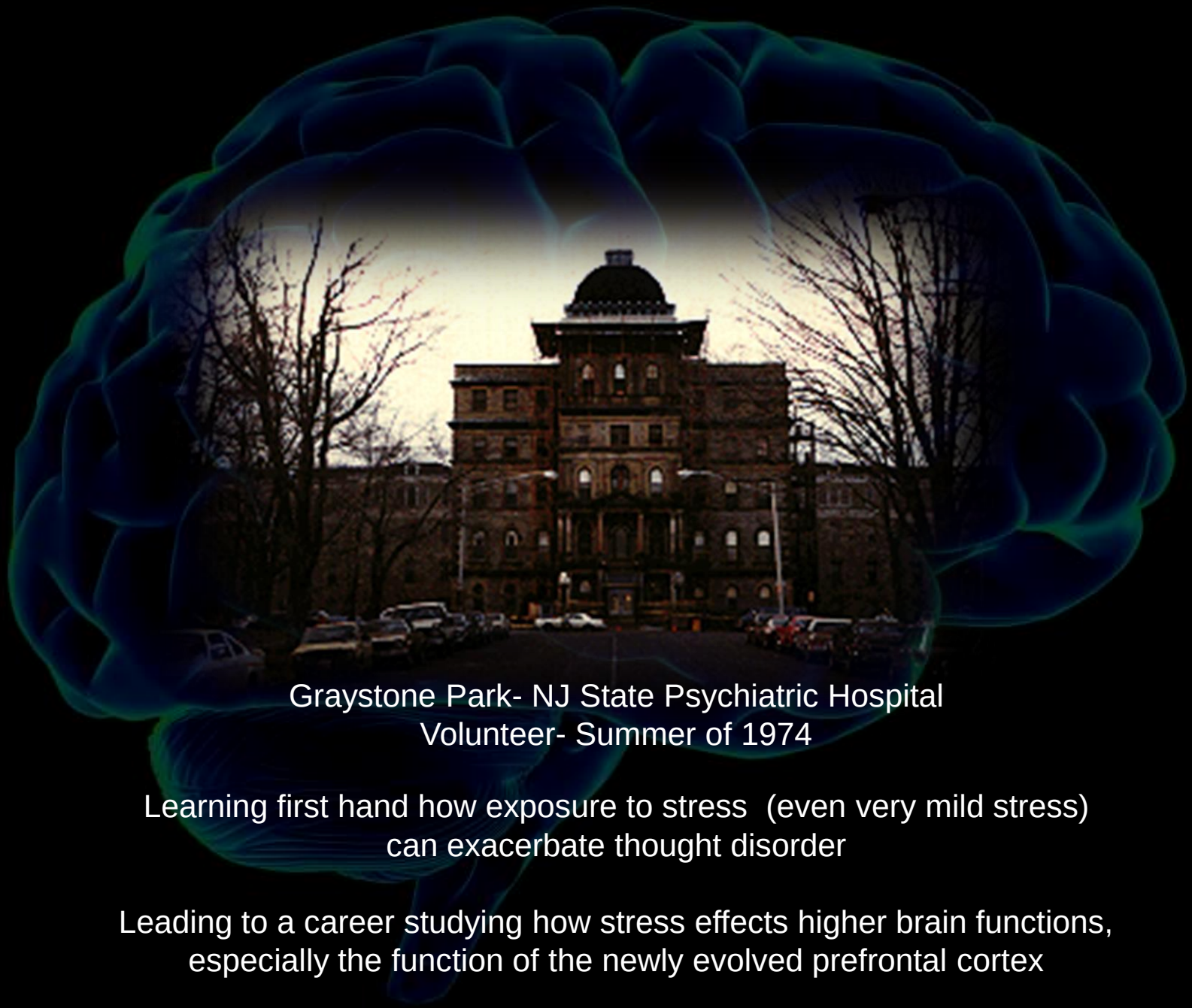
Disclosure- AFTA and Yale University receive royalties from the US sales of Intuniv™ from Shire Pharmaceuticals. They do not receive royalties from sales of generic Intuniv or guanfacine.



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

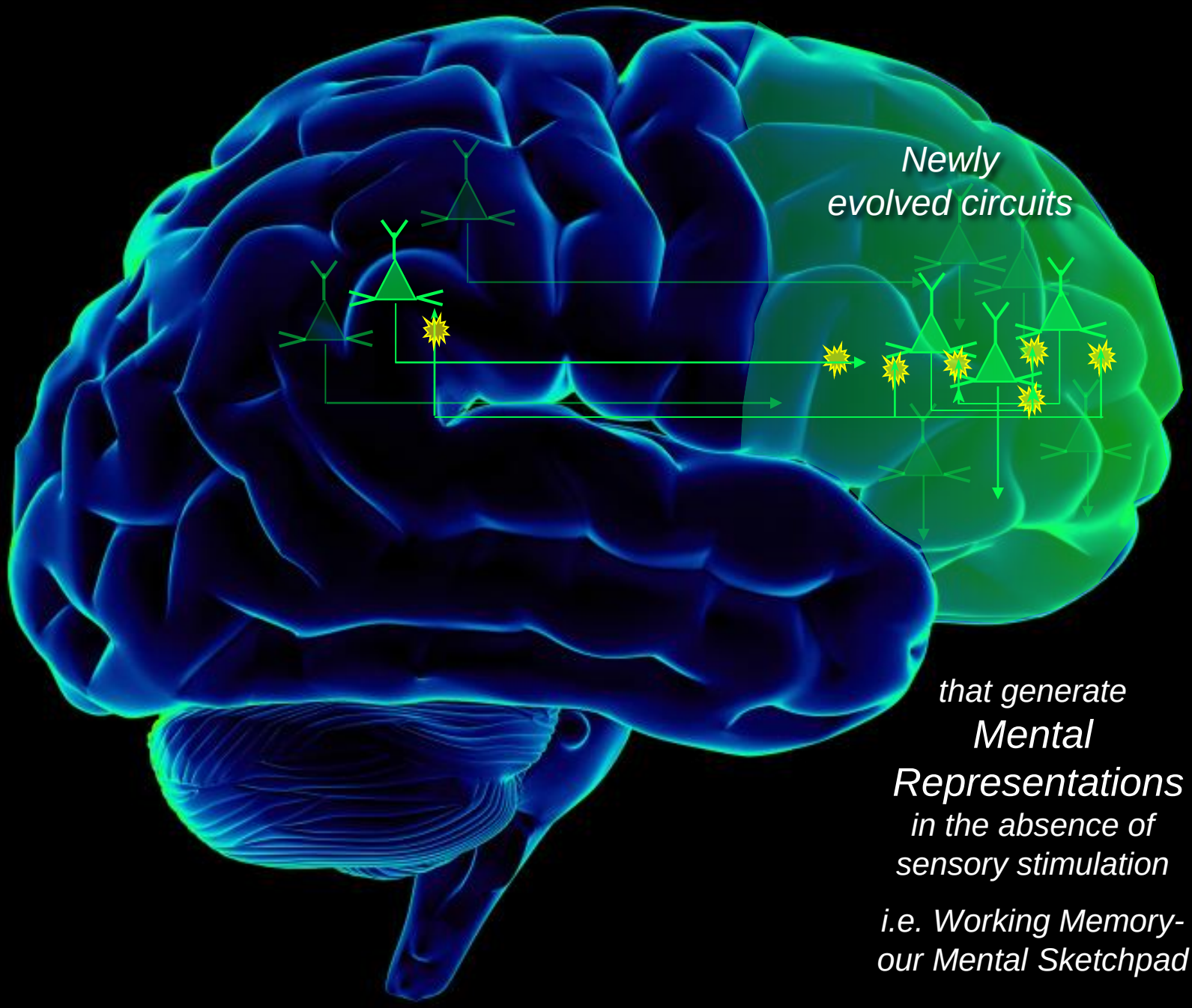


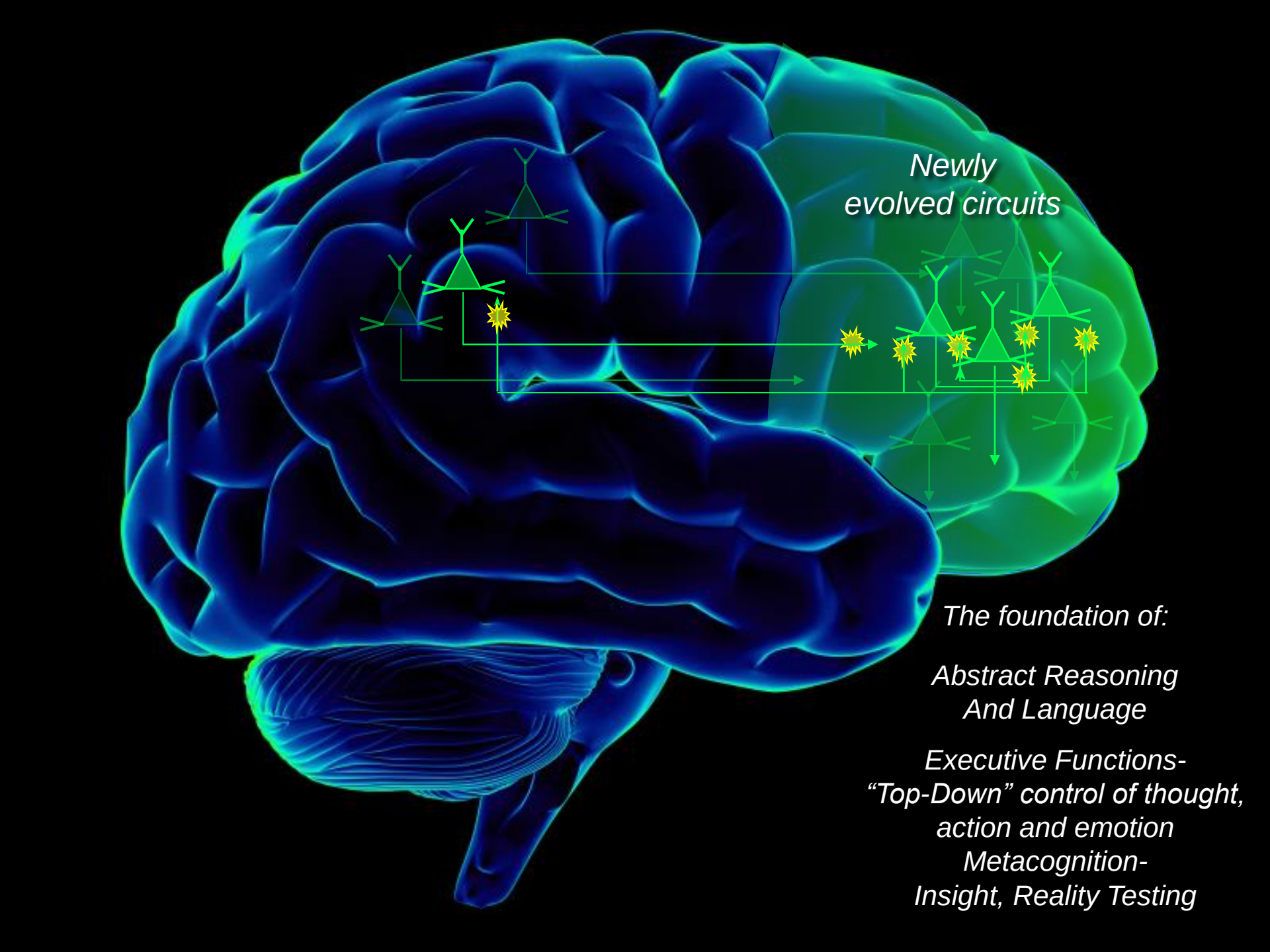
Graystone Park- NJ State Psychiatric Hospital
Volunteer- Summer of 1974

Learning first hand how exposure to stress (even very mild stress) can exacerbate thought disorder

Leading to a career studying how stress effects higher brain functions, especially the function of the newly evolved prefrontal cortex

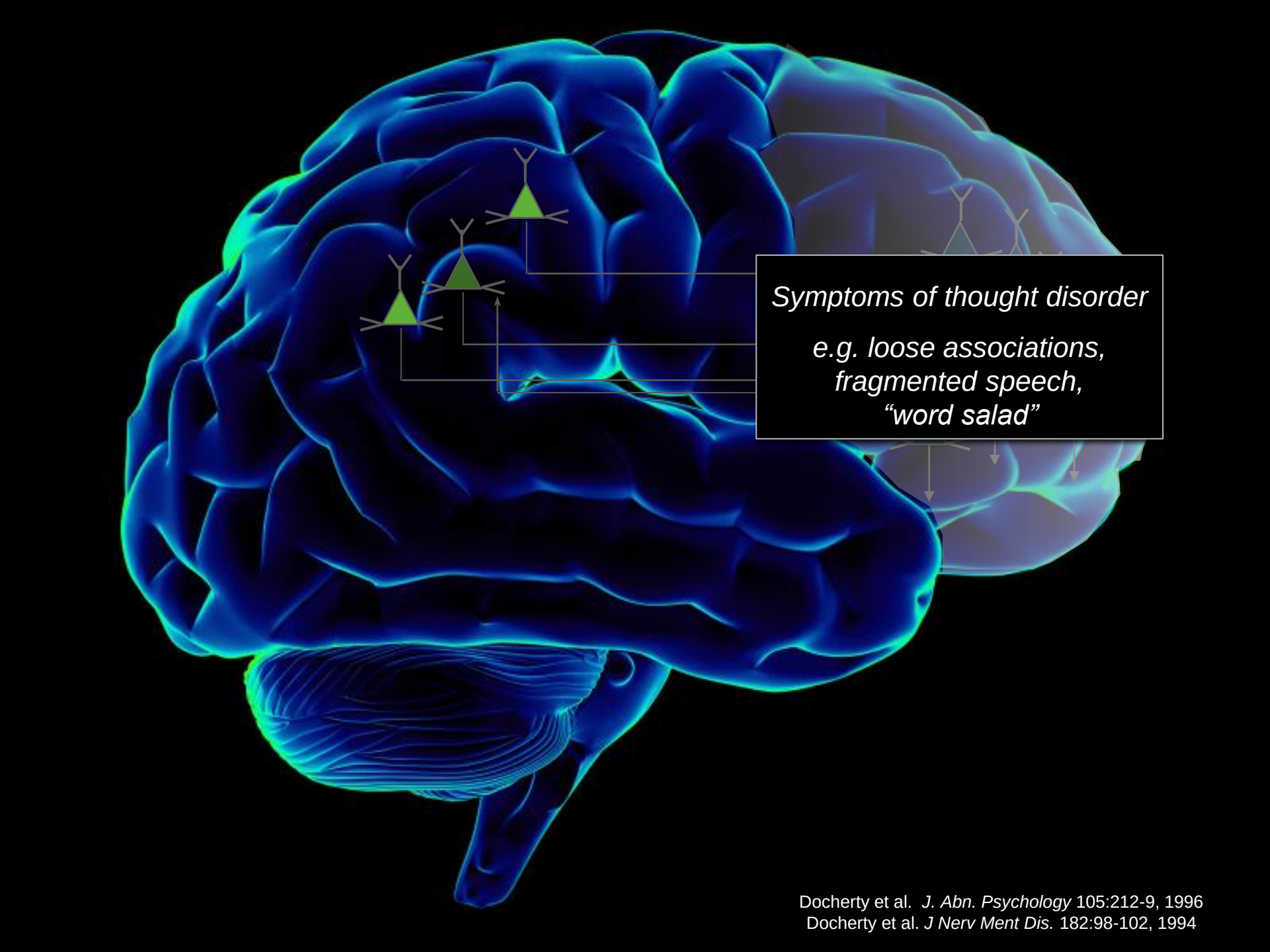

The Prefrontal Cortex
(PFC)


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



Docherty et al. *J. Abn. Psychology* 105:212-9, 1996
Docherty et al. *J Nerv Ment Dis.* 182:98-102, 1994

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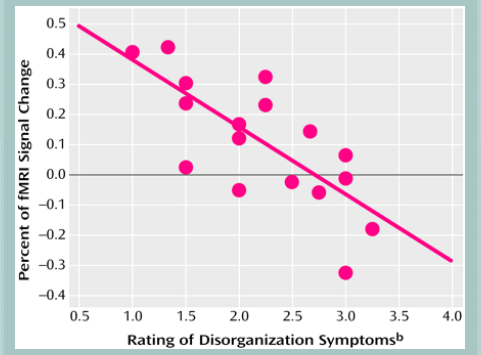
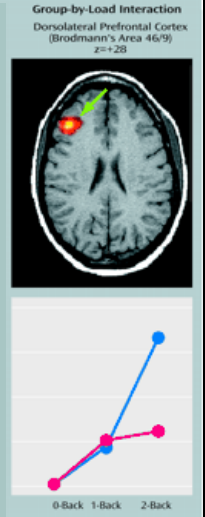
Perlstein et al. *Am J Psychiatry* 158:1105-13, 2001

Symptoms of thought disorder correlate with hypoactivity of the dorsolateral prefrontal cortex during working memory

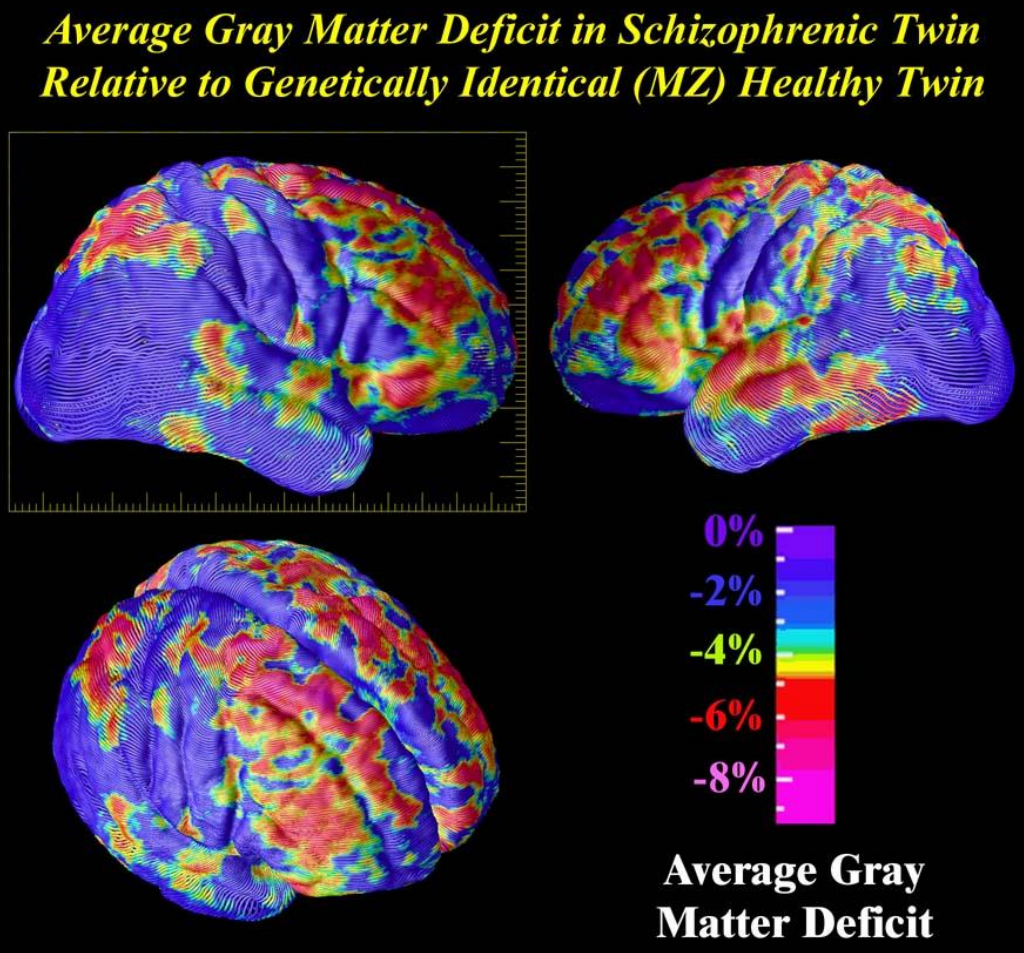
Correlations with symptoms of thought disorder





Perlstein et al. *Am J Psychiatry* 158:1105-13, 2001

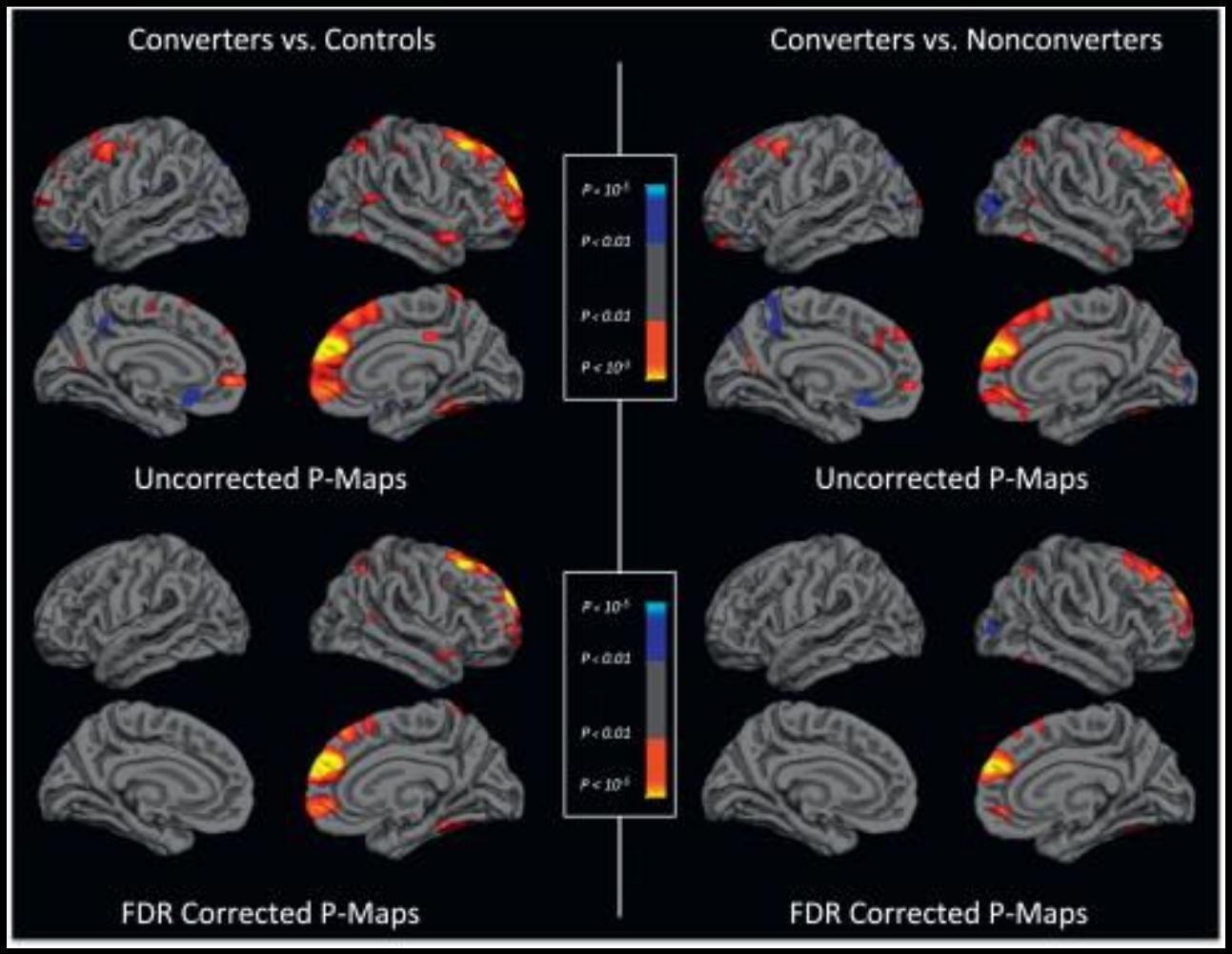
Gray Matter Loss in Schizophrenia Targets the Association Cortices, Especially Prefrontal Cortex



Cannon et al. *PNAS* 99: 3228-33, 2002

Prefrontal Cortical Gray Matter Loss During the Prodrome, as Patients Descend Into Illness

Often accompanied by stress, inflammation



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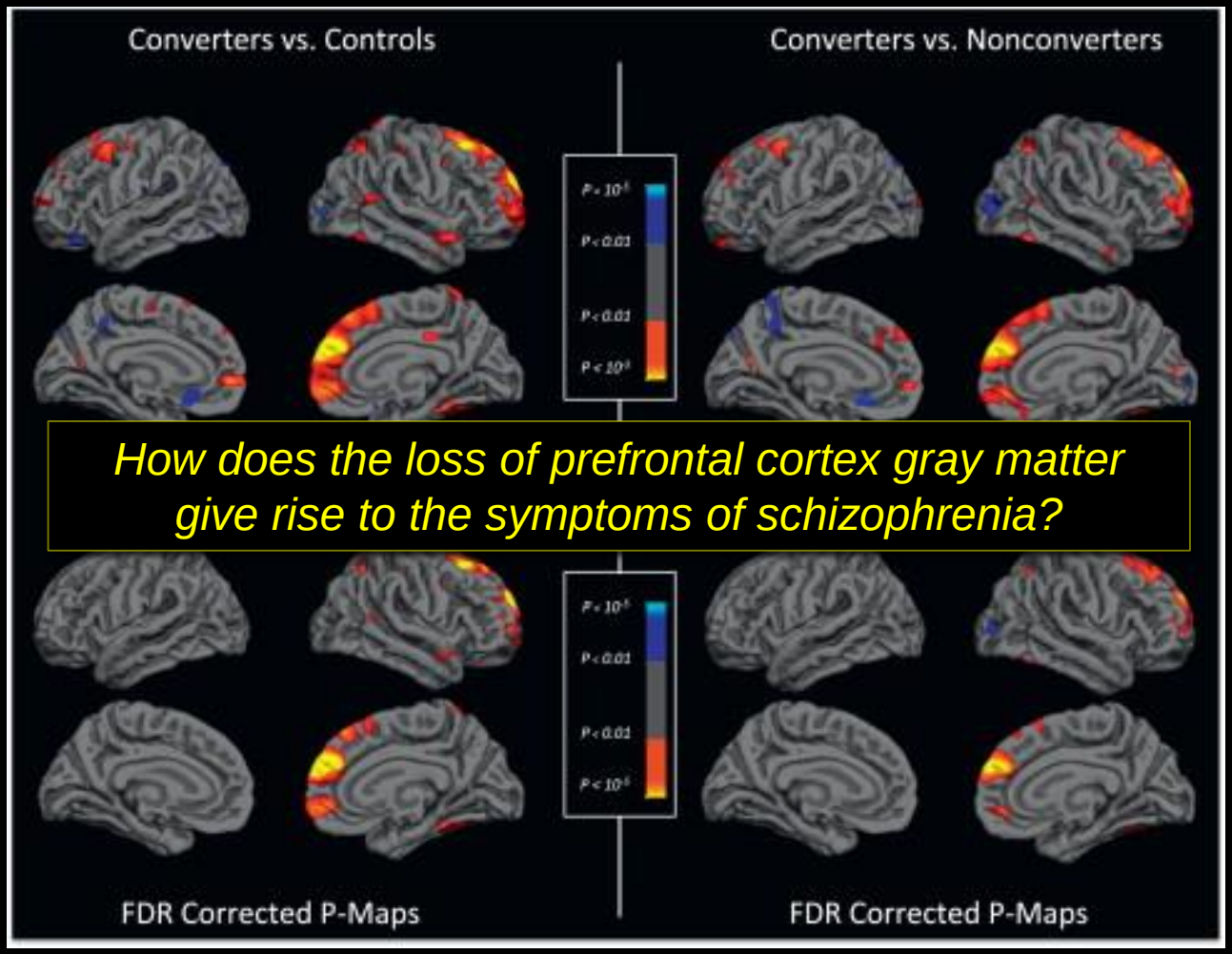

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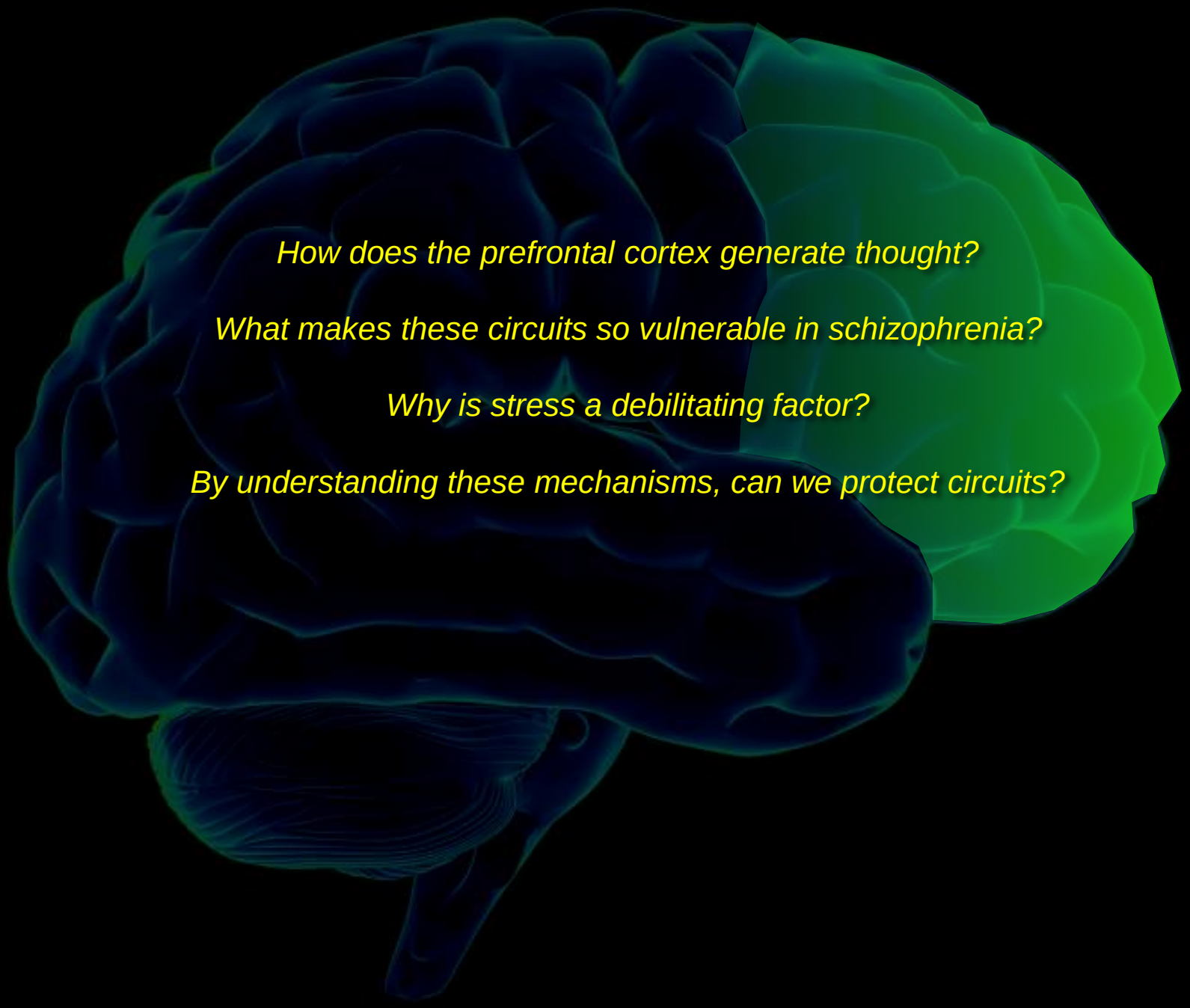
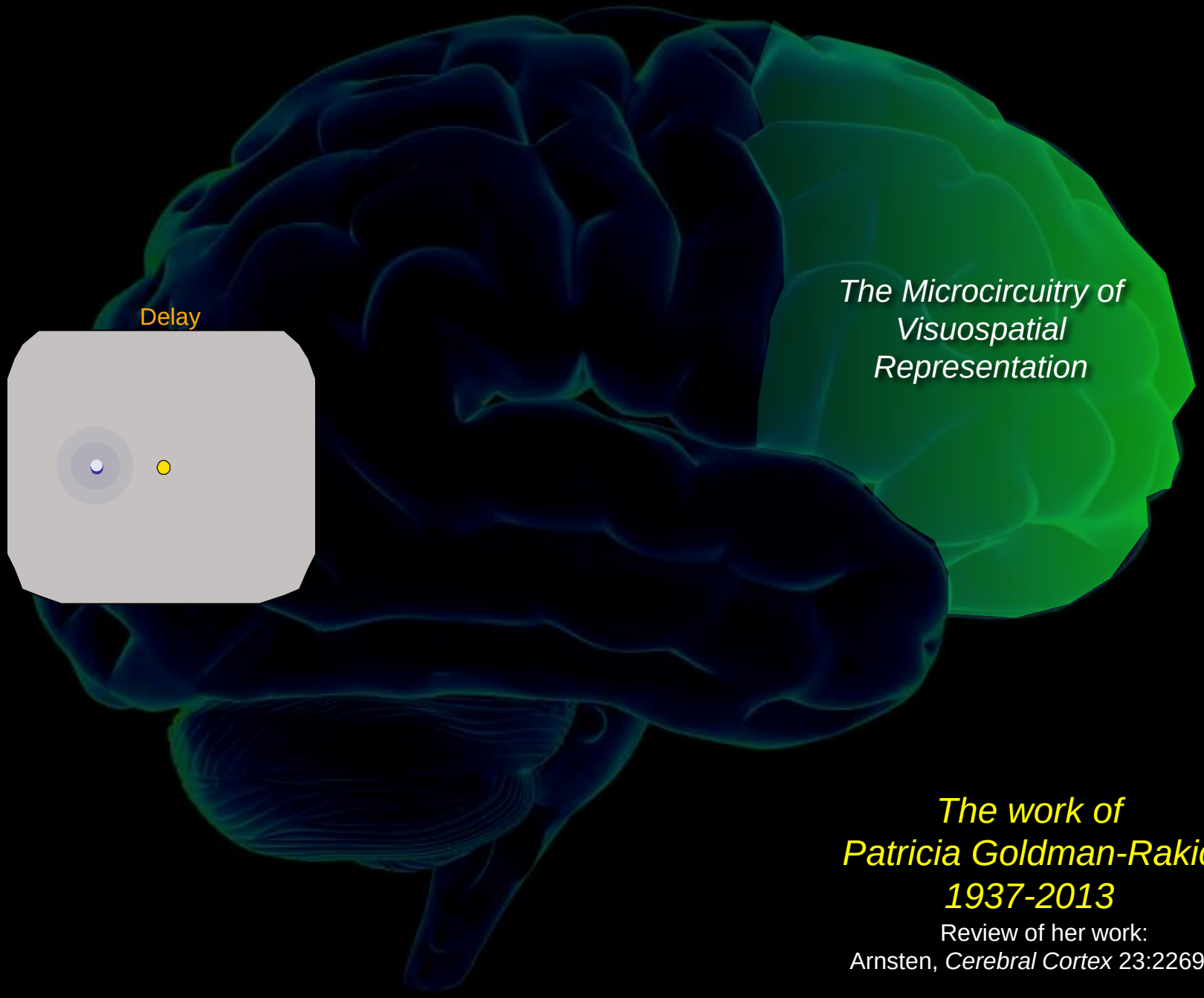
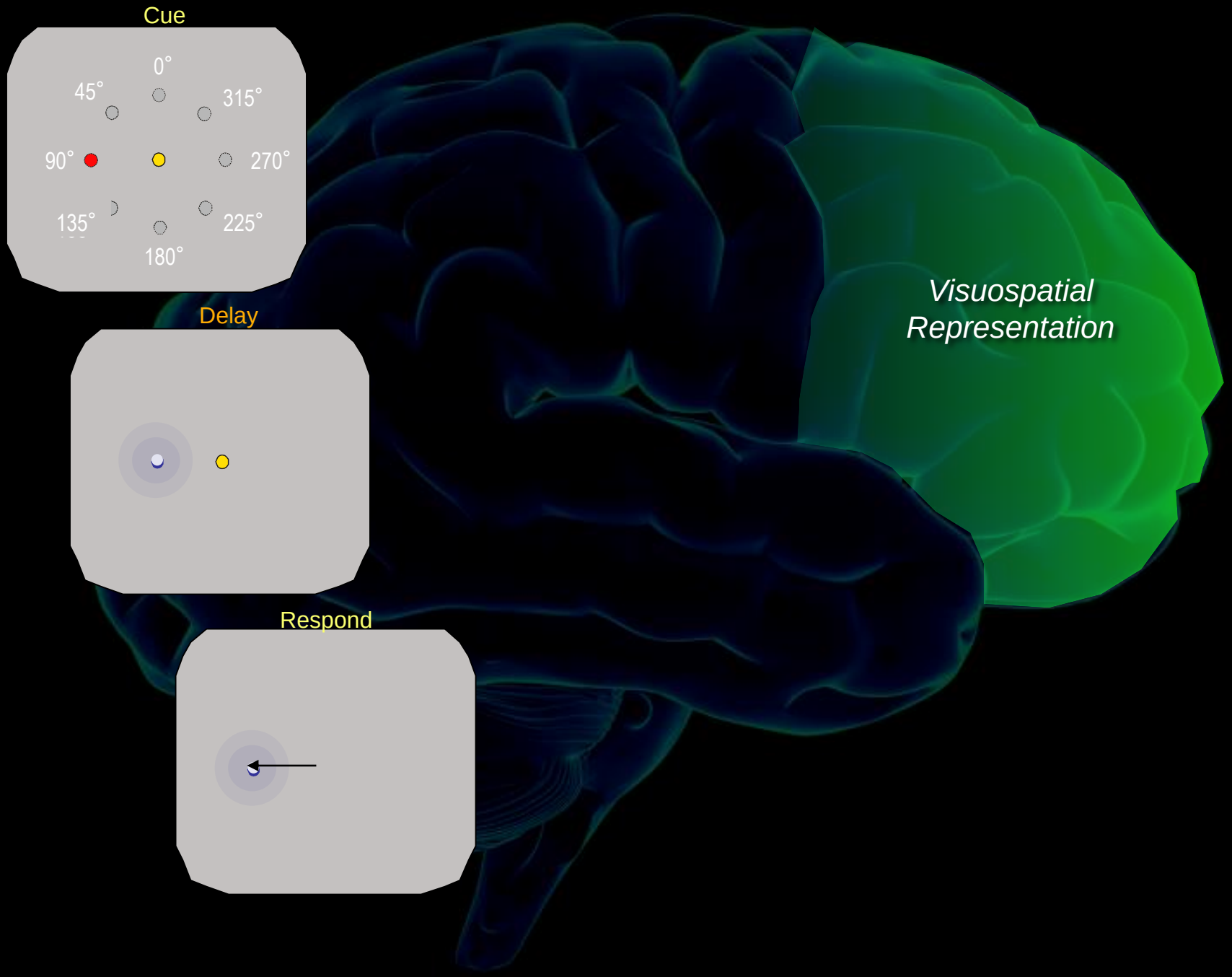
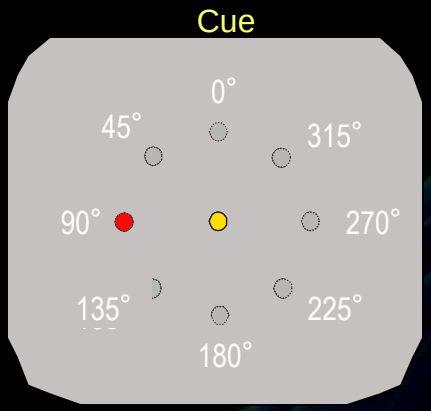

How does the prefrontal cortex generate thought?
What makes these circuits so vulnerable in schizophrenia?
Why is stress a debilitating factor?
By understanding these mechanisms, can we protect circuits?



The work of Patricia Goldman-Rakic 1937-2013

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

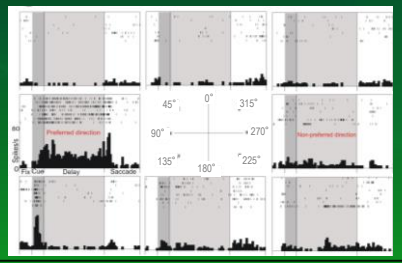

Cue
0°
45°
315°
90°
270°
135°
225°
180°
Delay
Respond
Visuospatial
Representation



I — dlPFC

II — Neural Representation of Visual Space

III — Delay cells



A "Delay cell" that represents 90º

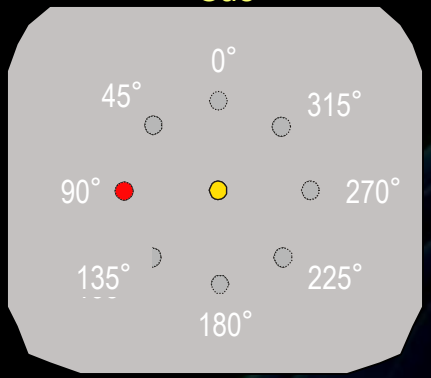
IV

V

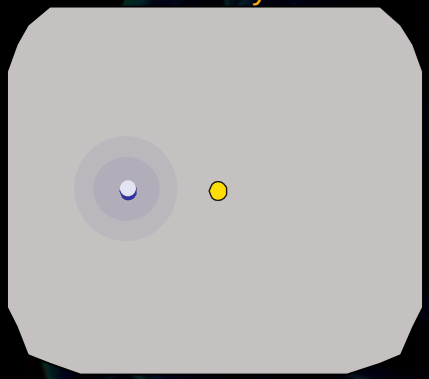
VI

Funahashi et al., *J. Neurophys*, 61:331-49 1989

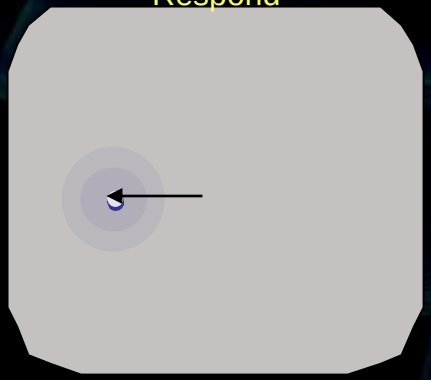
Cue



Delay



Respond



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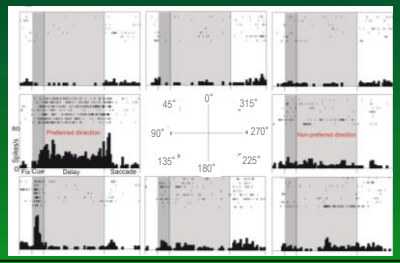
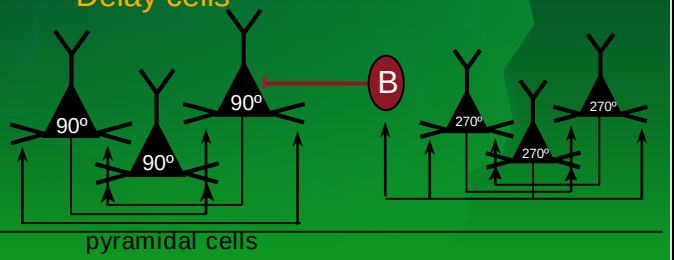
II Neural Representation of Visual Space

III



Delay cells



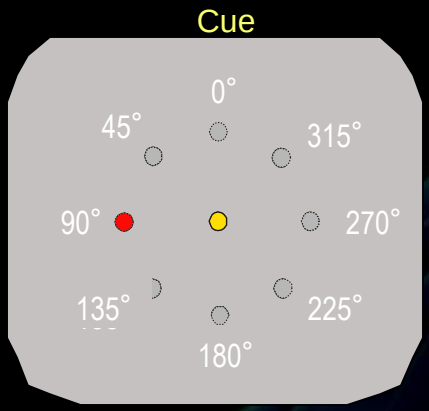
pyramidal cells

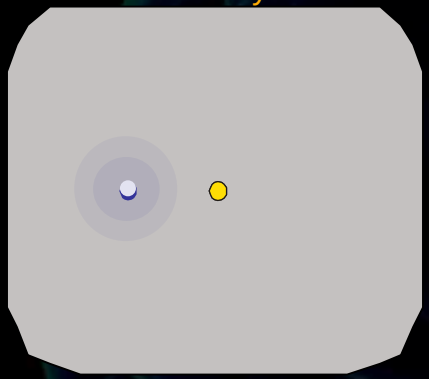
IV Prefrontal microcircuits

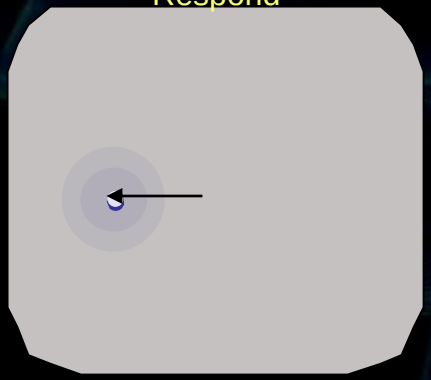
V

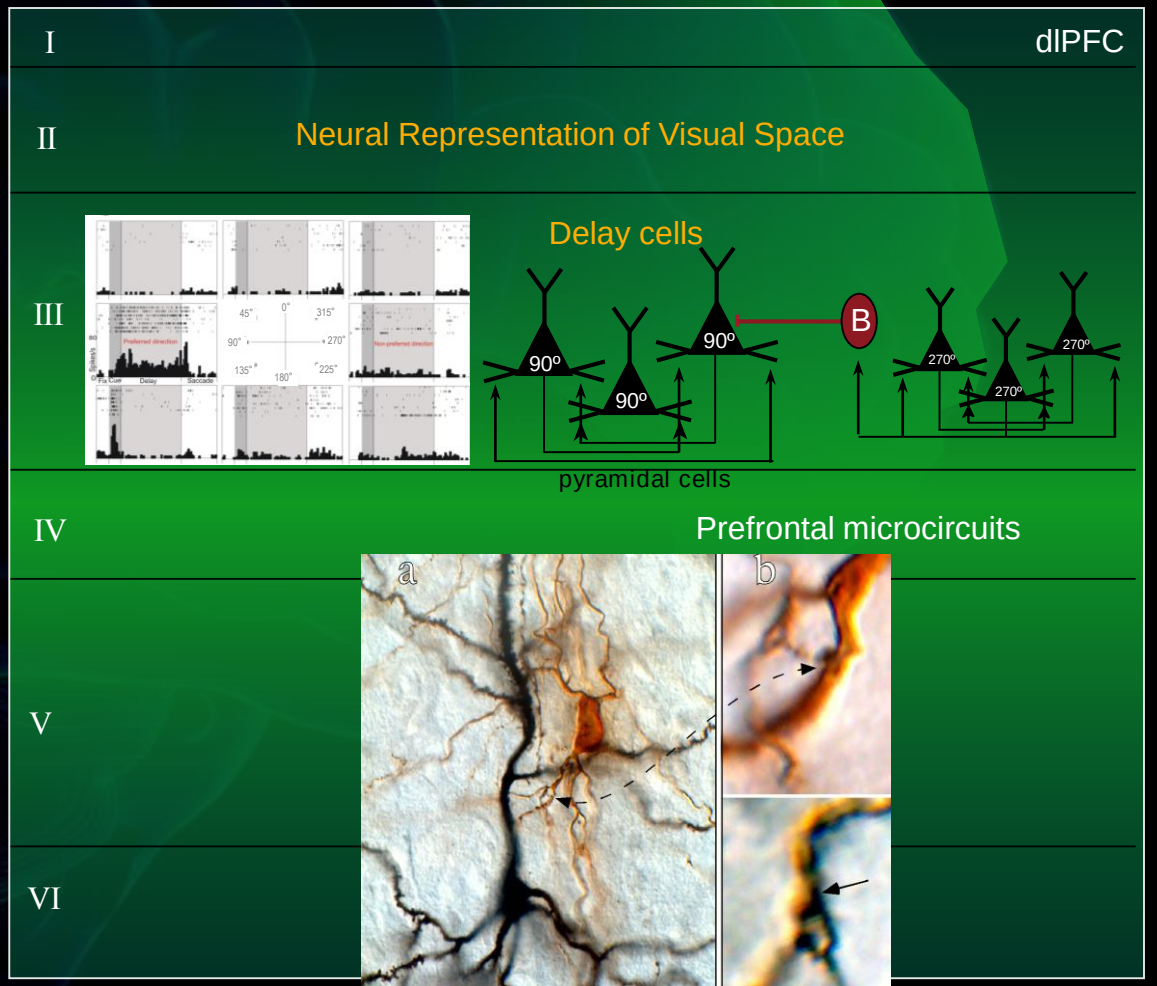
VI

Goldman-Rakic, *Neuron* 14:477, 1995

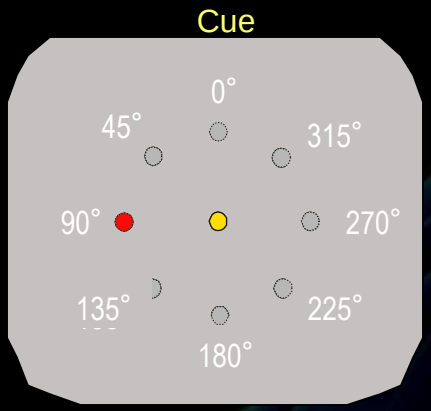


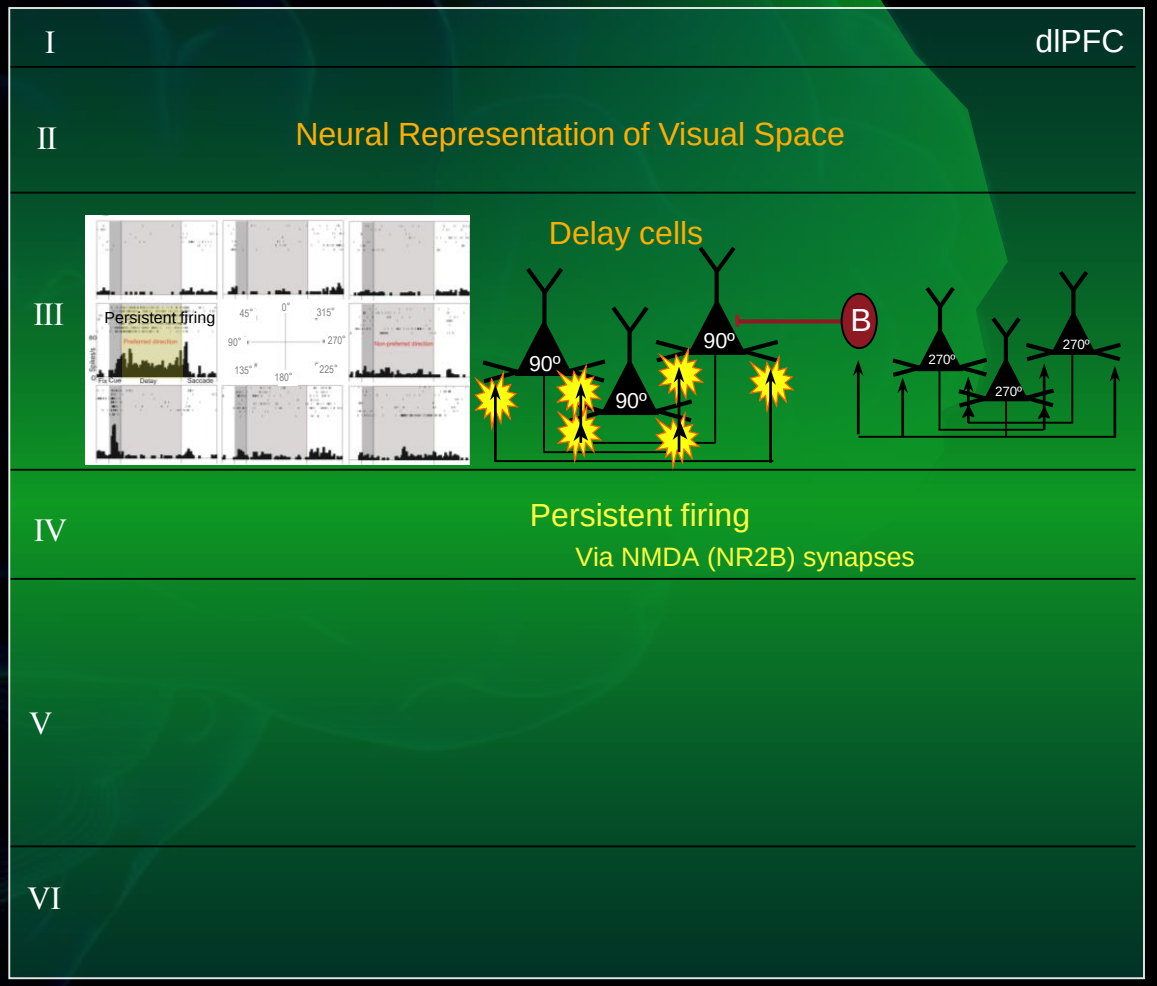




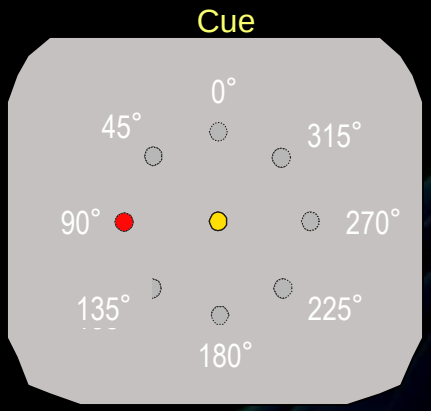


Goldman-Rakic, *Neuron* 14:477, 1995





Goldman-Rakic, *Neuron* 14:477, 1995
Wang et al., *Neuron* 77:736-49, 2013



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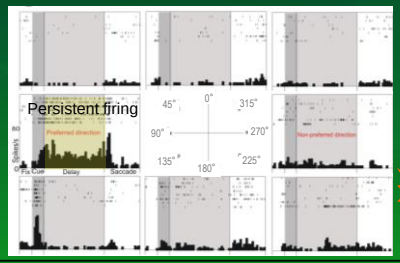
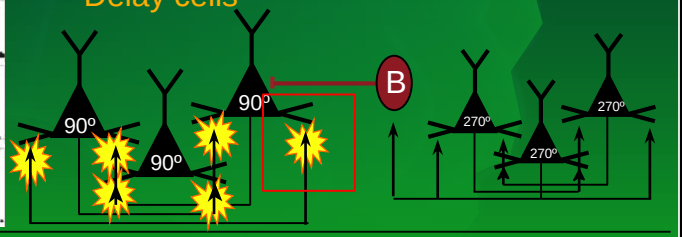


Delay cells



IV Persistent firing

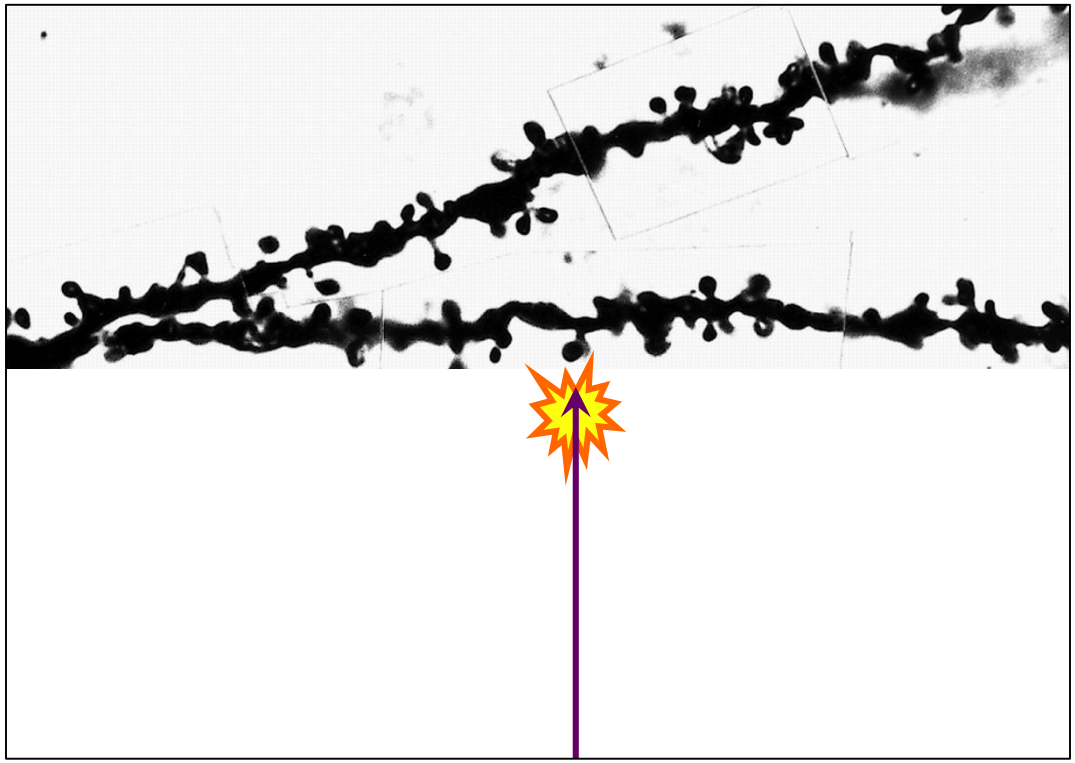
Via NMDA (NR2B) synapses

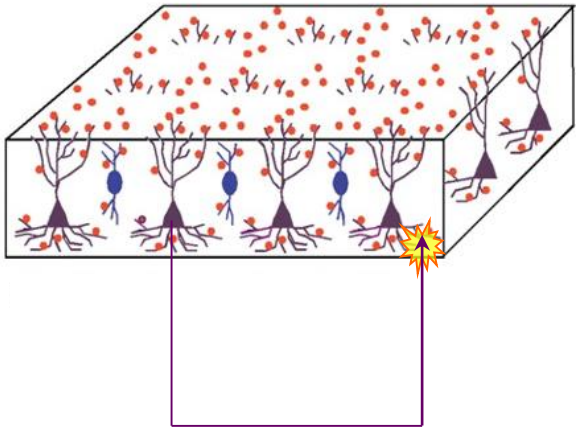
V

VI

Goldman-Rakic, *Neuron* 14:477, 1995
Wang et al., *Neuron* 77:736-49, 2013

Cells Excite Each Other via Connections on Dendritic Spines





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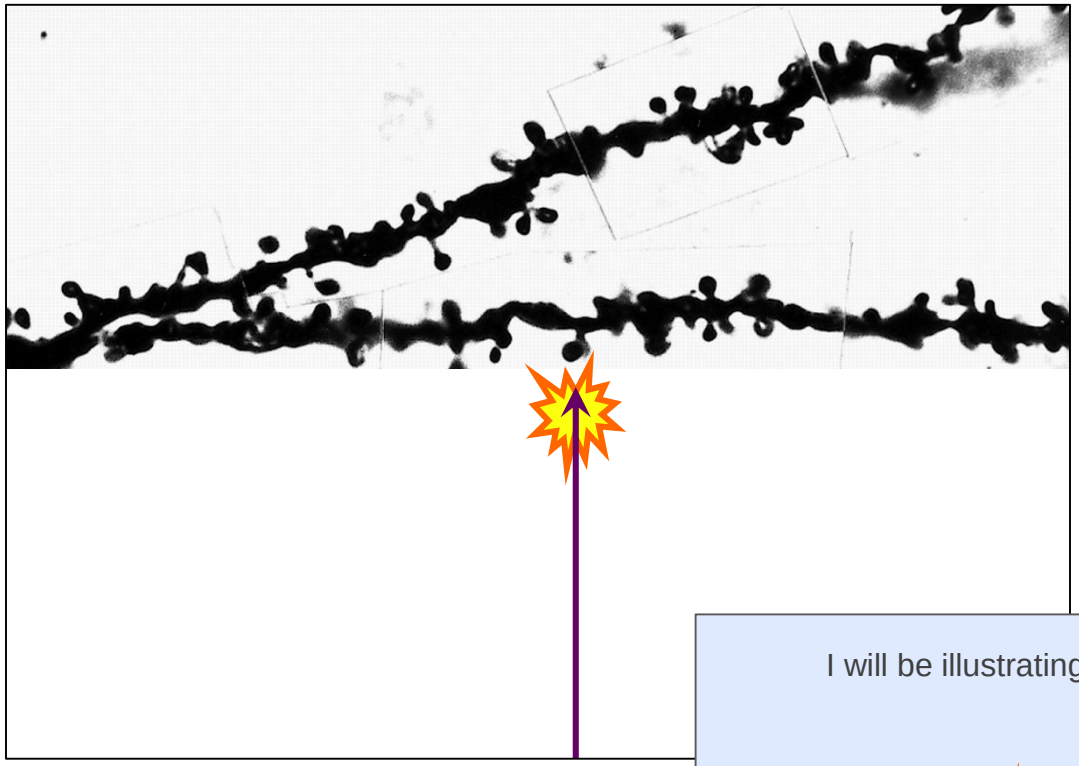

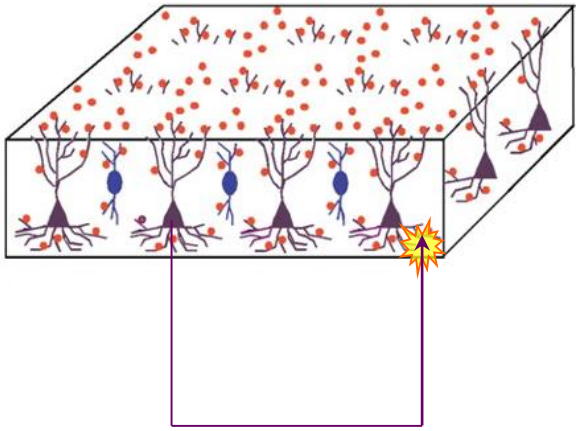

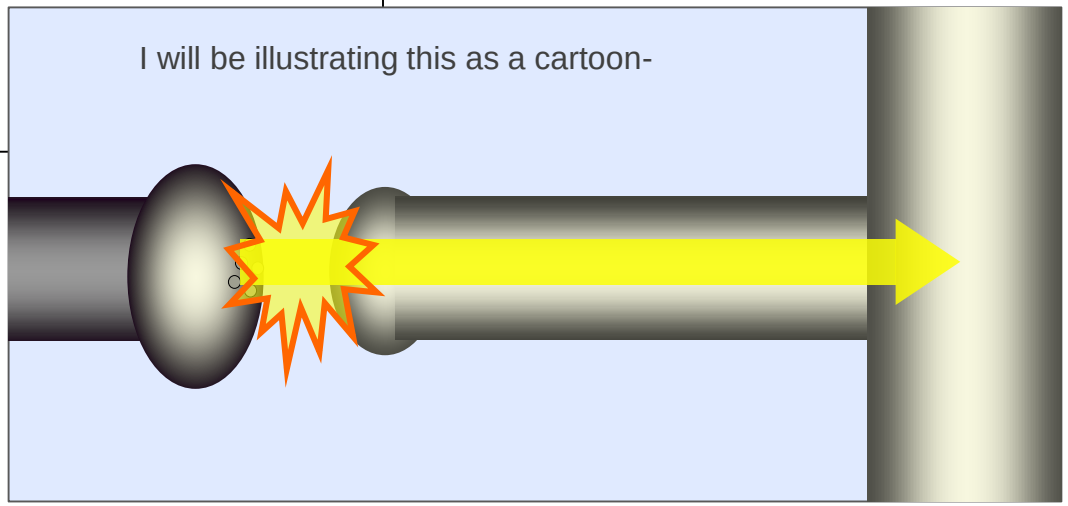

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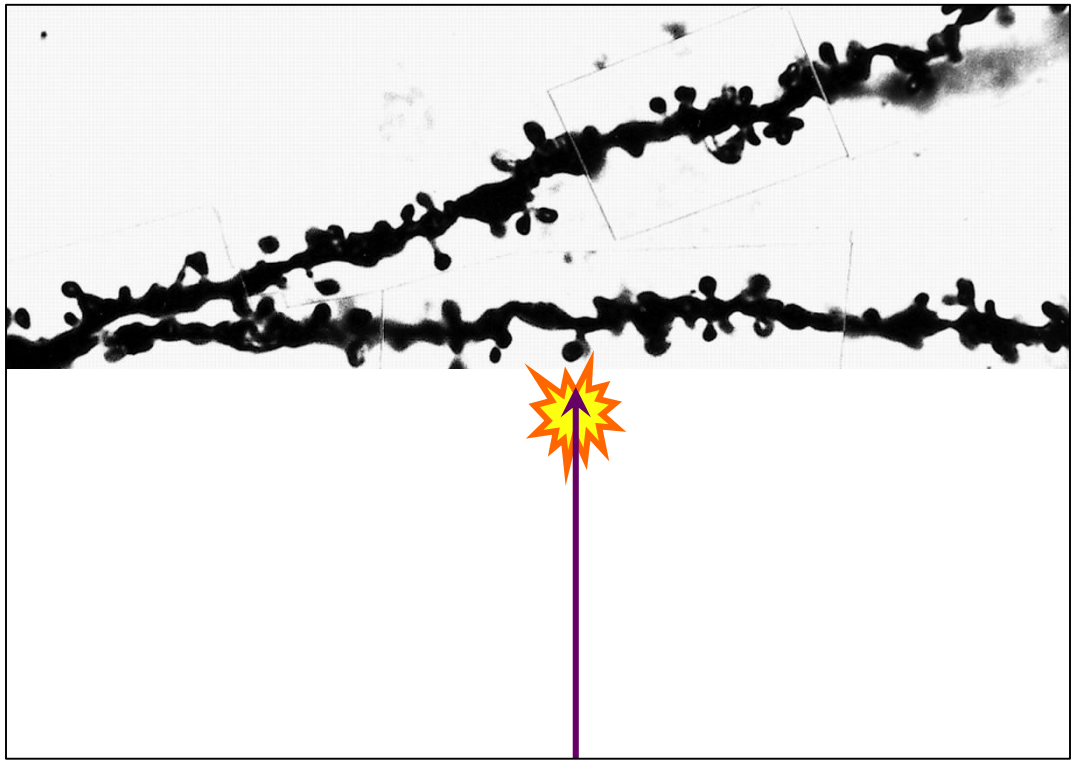
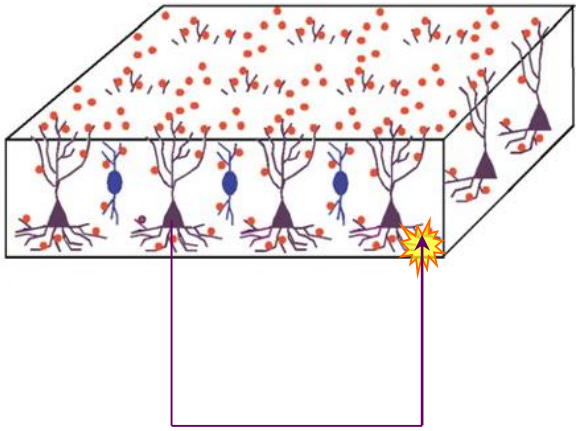
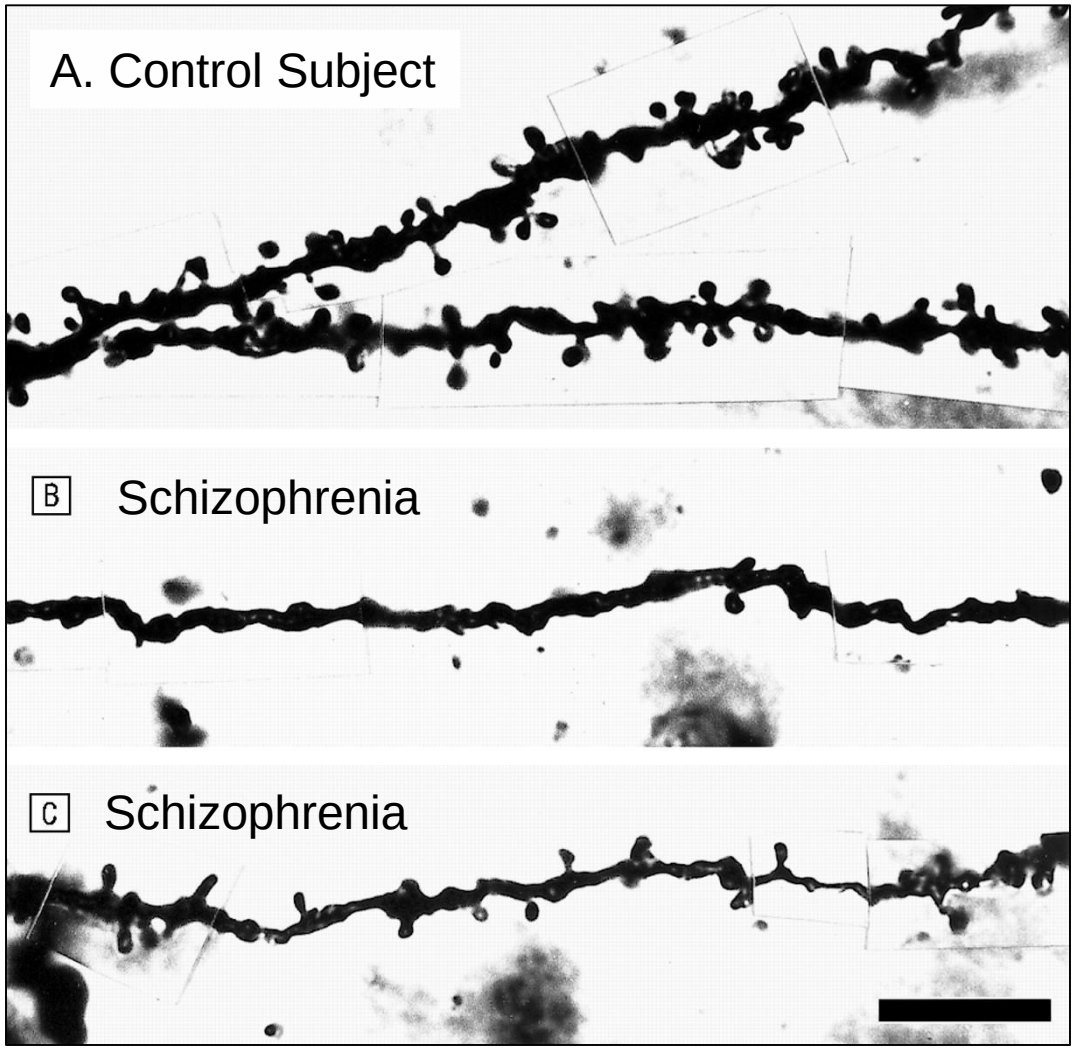
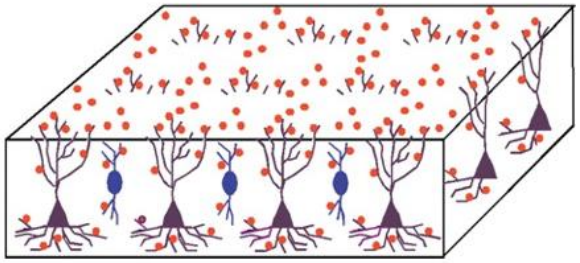




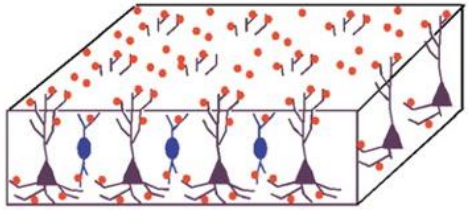
Loss of Spines and Dendrites in Schizophrenia

Postmortem dlPFC, Layer III





Healthy Comparison Subject



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Glantz, et al., *Arch Gen Psychiatry,* 57:65-73 2000

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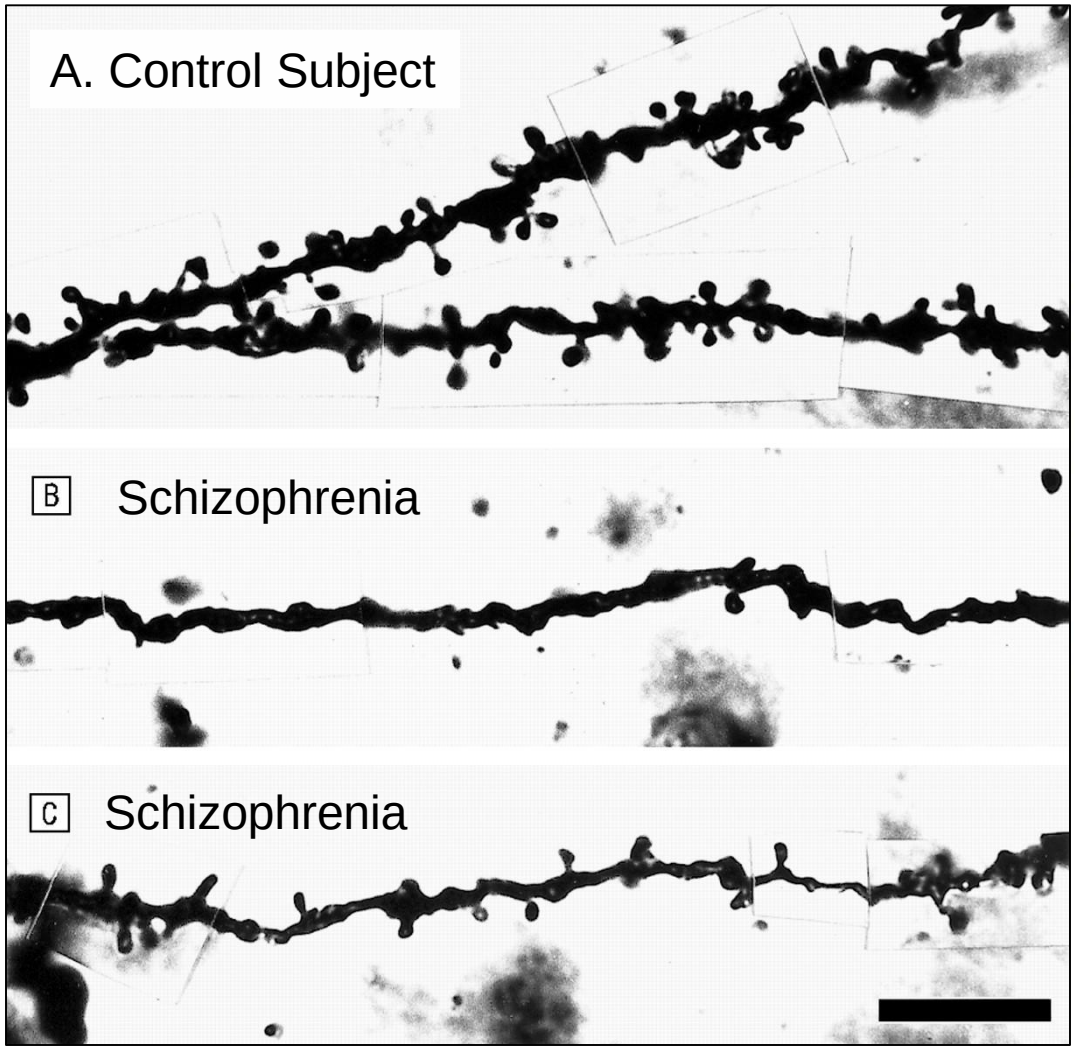
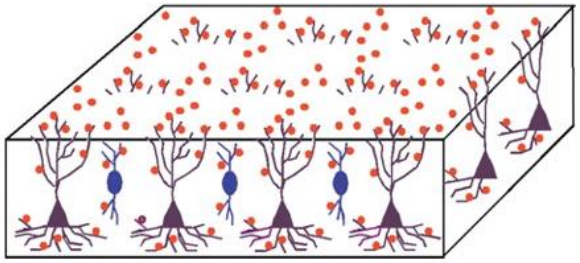
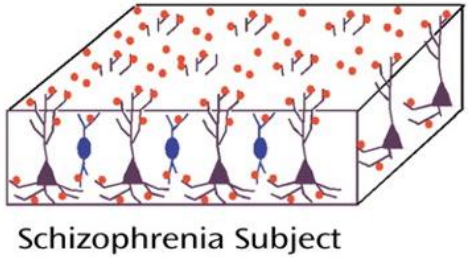






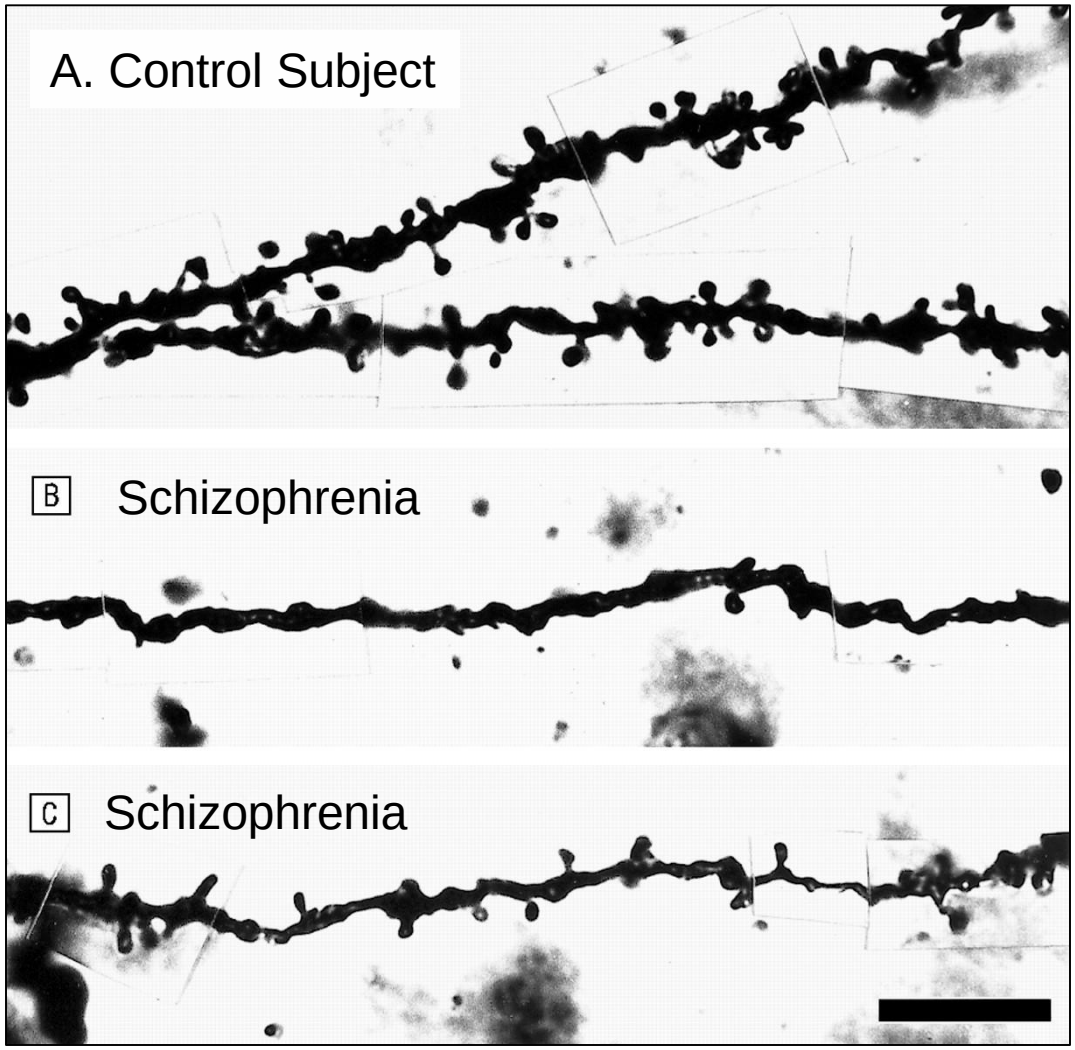
In schizophrenia:

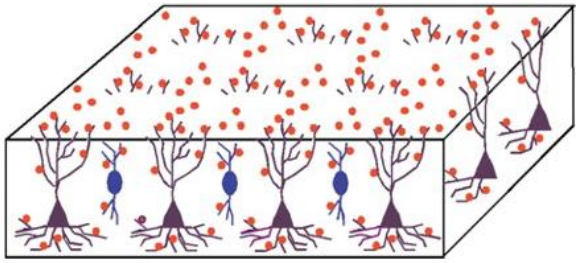
- Loss of connections
- Neurons profoundly underactive
- Loss of persistent firing needed for strong mental representations (seen as reduced BOLD response in fMRI studies)

Arion, et al., *Mol Psychiatry,* 20:1397-405, 2015
Glantz, et al., *Arch Gen Psychiatry,* 57:65-73 2000

Loss of Spines and Dendrites in Schizophrenia

What is causing this???





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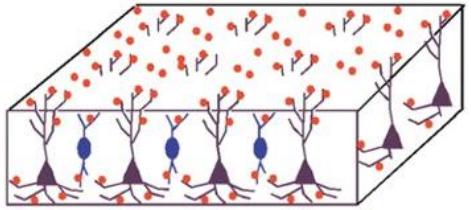

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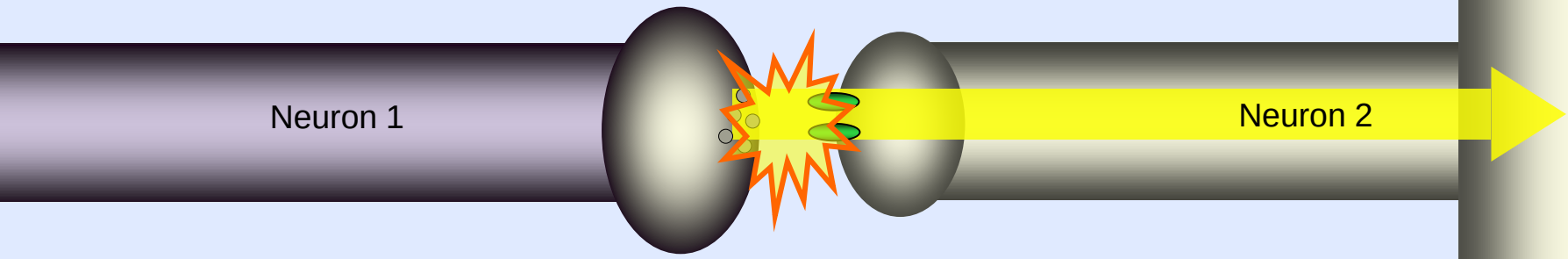
Healthy connection

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



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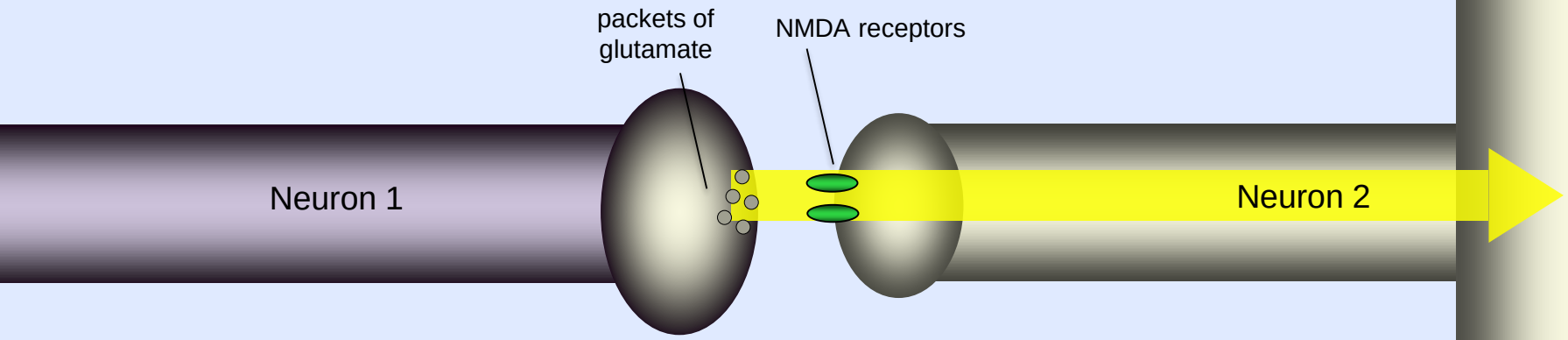

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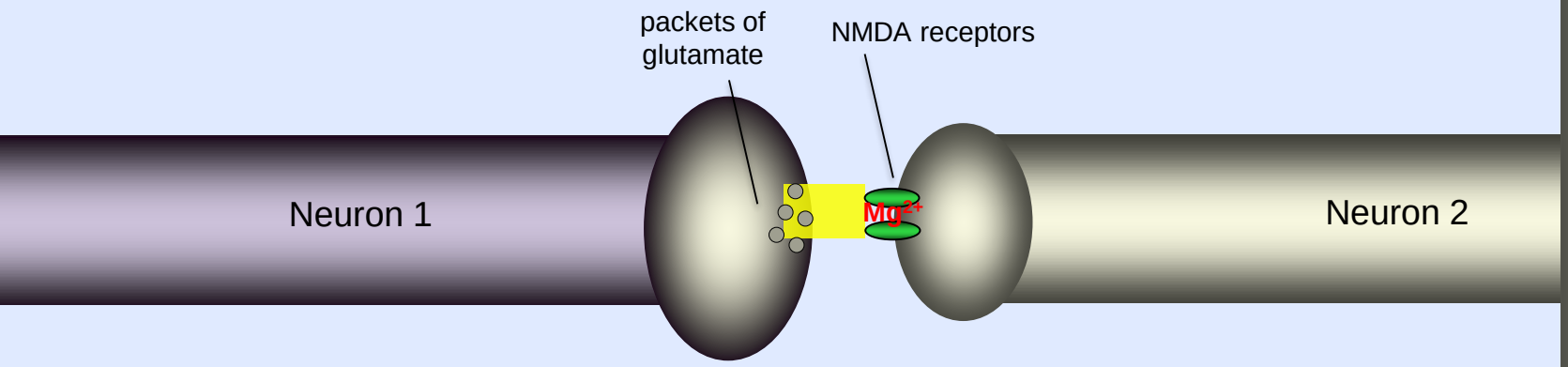
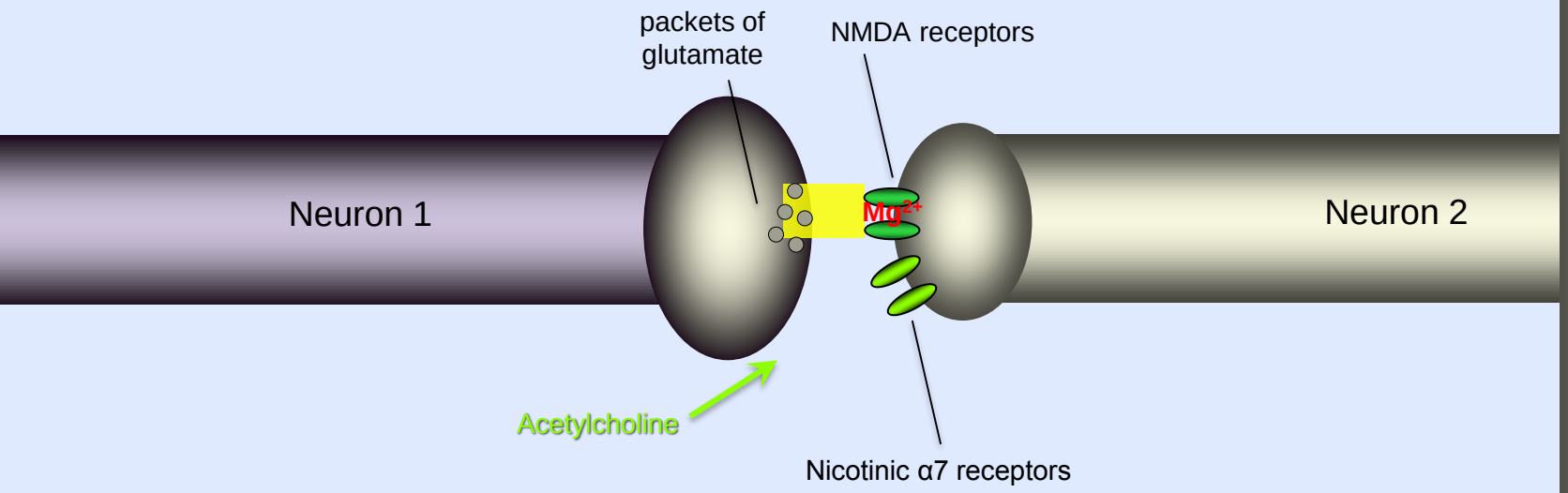


Wang et al., *Neuron* 77:736-49, 2013

Healthy connection

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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Yang et al., *PNAS* 110:12078-83, 2013

Healthy connection

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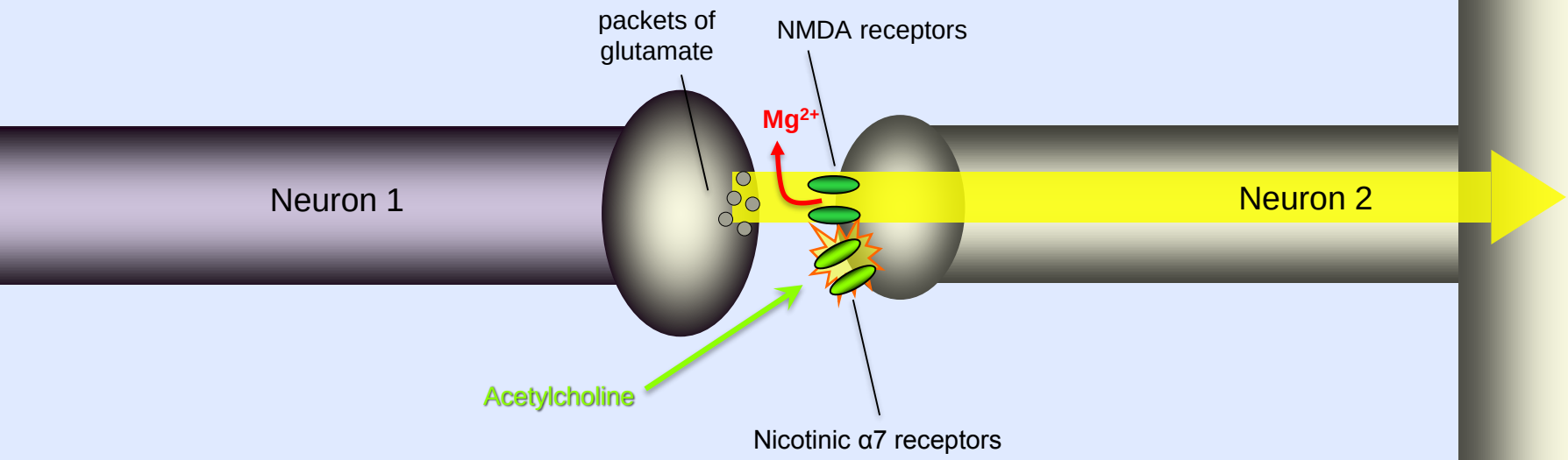

Wang et al., *Neuron* 77:736-49, 2013
Yang et al., *PNAS* 110:12078-83, 2013

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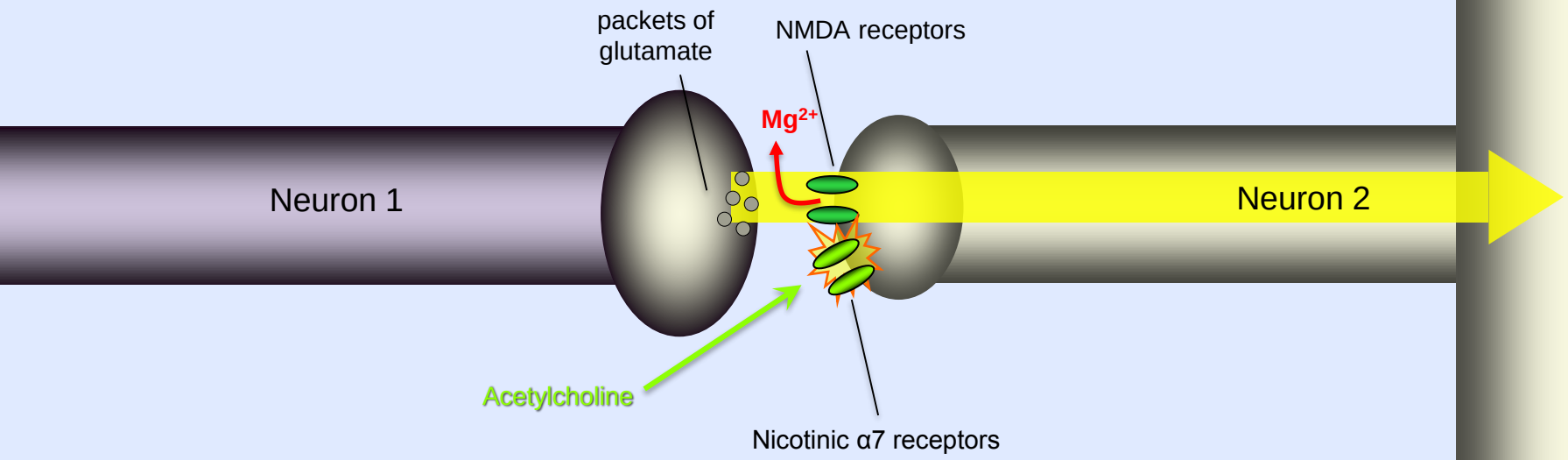
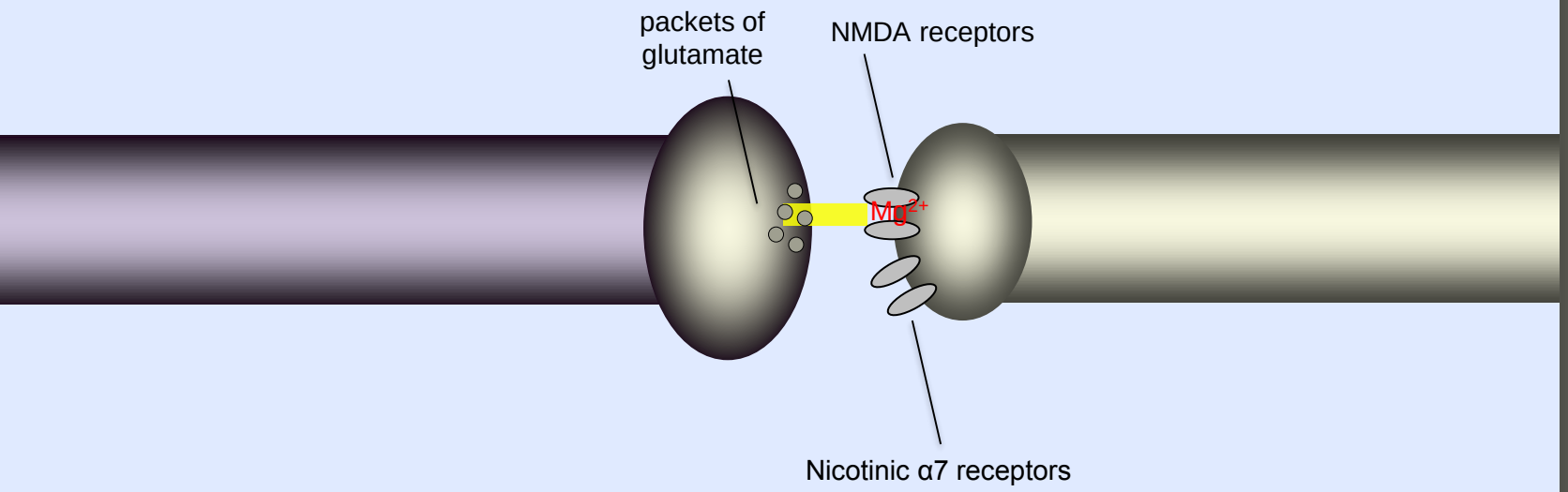


This allows conscious thought when we are awake

Wang et al., *Neuron* 77:736-49, 2013
Yang et al., *PNAS* 110:12078-83, 2013

Schizophrenia

Weaker NMDA receptor and nicotinic α7 receptors have both been linked with schizophrenia. This would weaken the neural connection.



Arnsten and Wang, *Ann Rev Pharm Tox* 56:339-56, 2016

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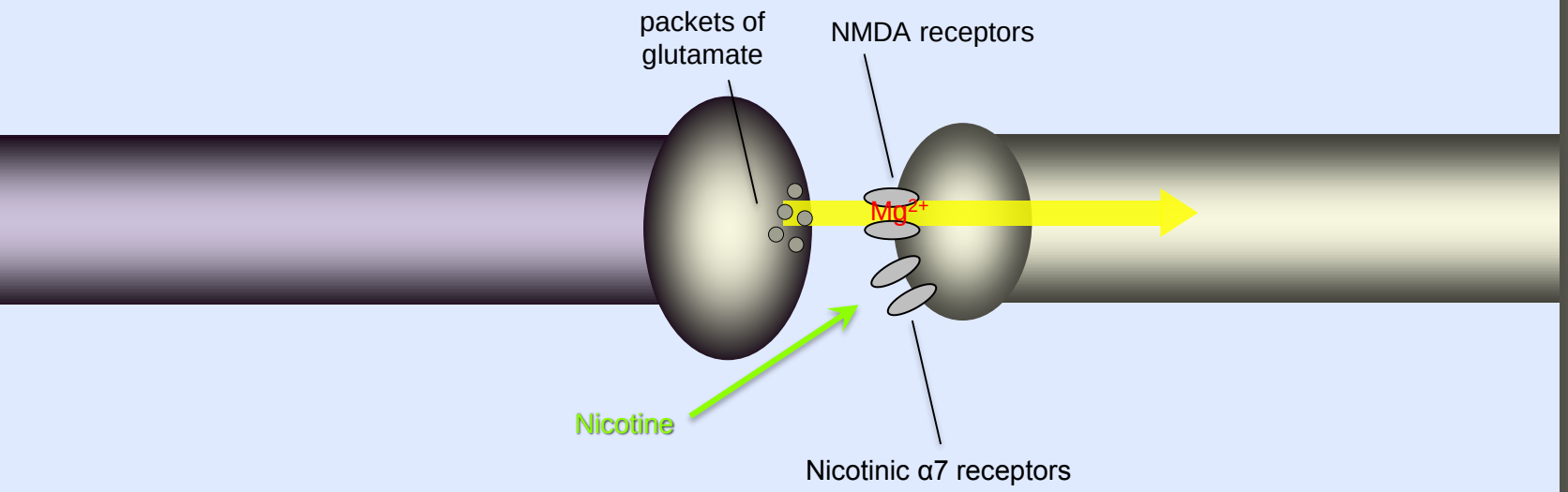

Why most patients with schizophrenia smoke cigarettes?

Arnsten and Wang, *Ann Rev Pharm Tox* 56:339-56, 2016

Schizophrenia

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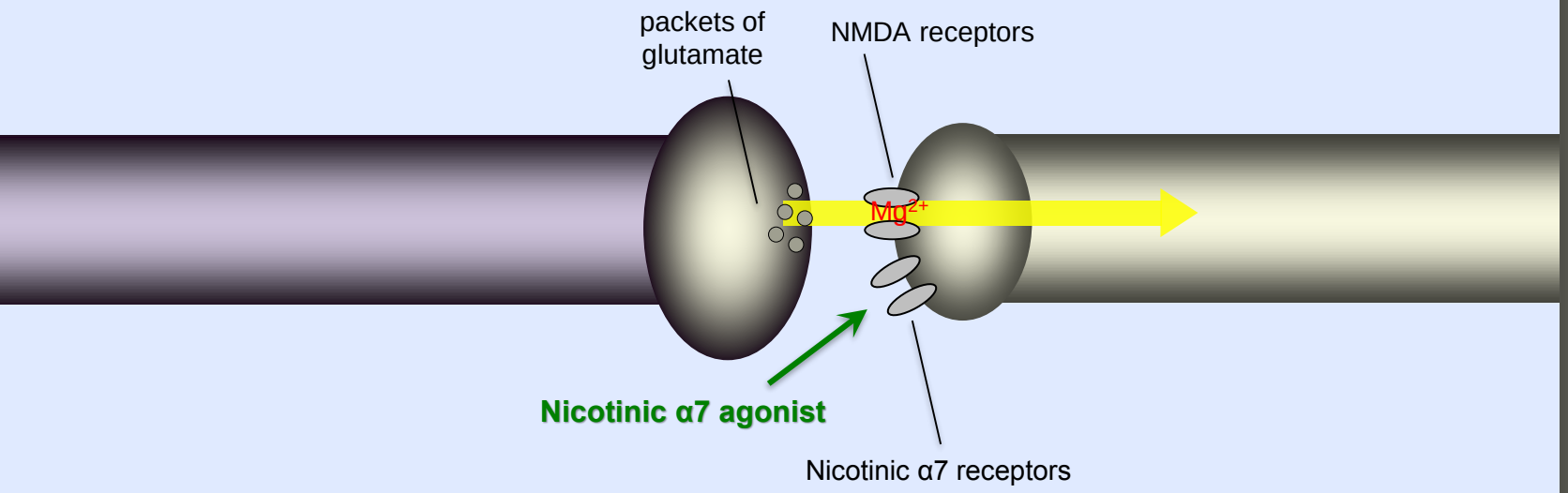
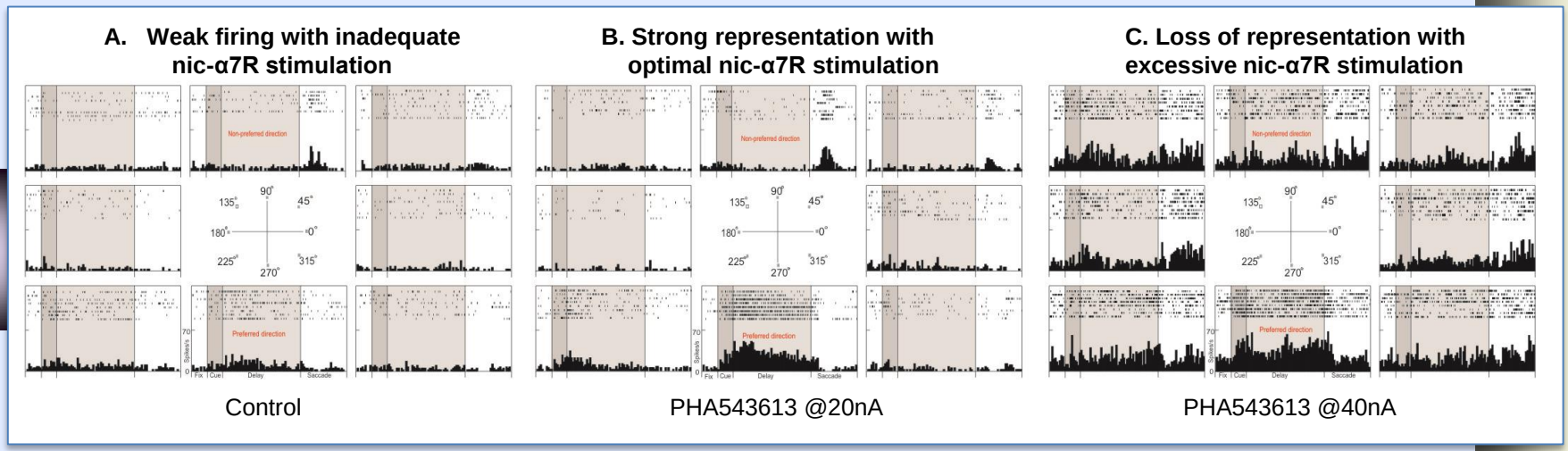


Why most patients with schizophrenia smoke cigarettes?

Medications that stimulate nicotinic α7 receptors are currently under development as potential treatments for cognitive deficits in schizophrenia

Healthy connection

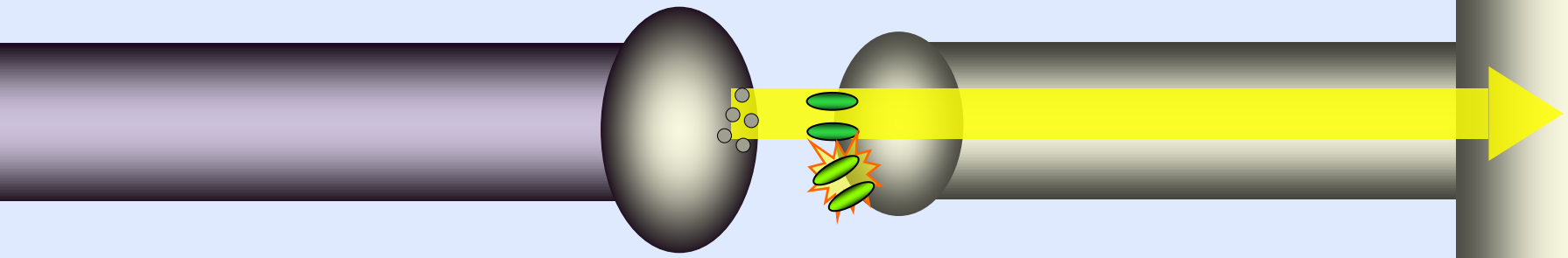
Low doses of drugs that stimulate nicotinic α7 receptors can strengthen connections and enhance mental representations



Arnsten and Wang, *Ann Rev Pharm Tox* 56:339-56, 2016

Healthy connection

The strength of these higher prefrontal cortical connections is also dynamically altered by potassium ion channels



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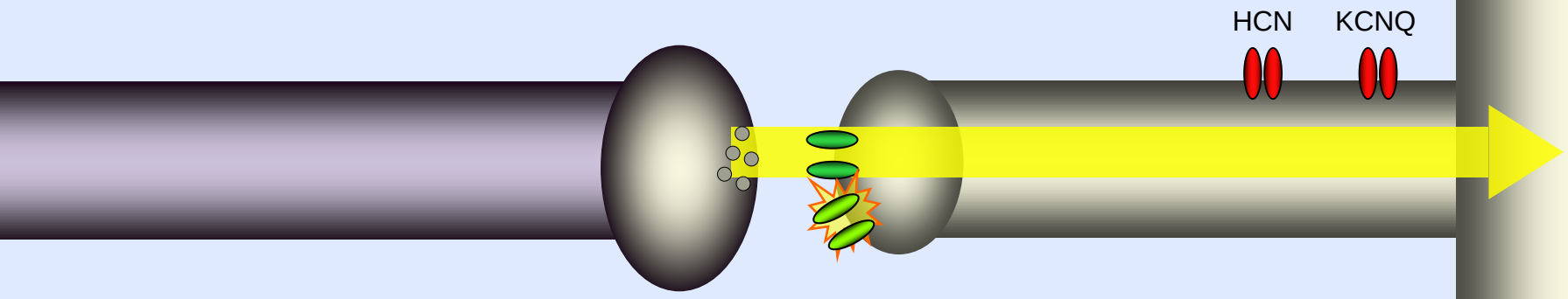
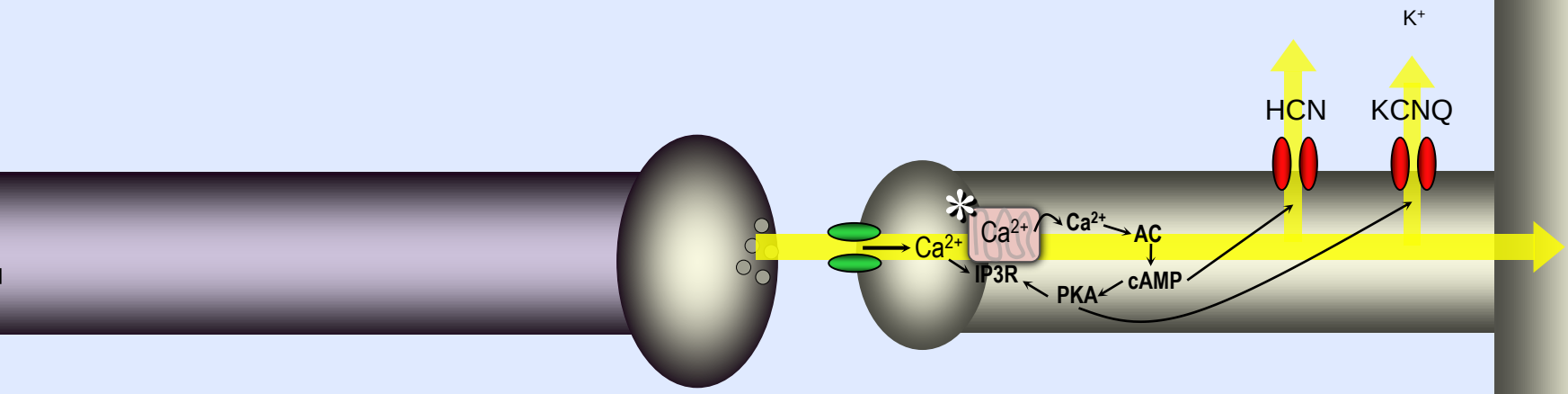


Healthy connection

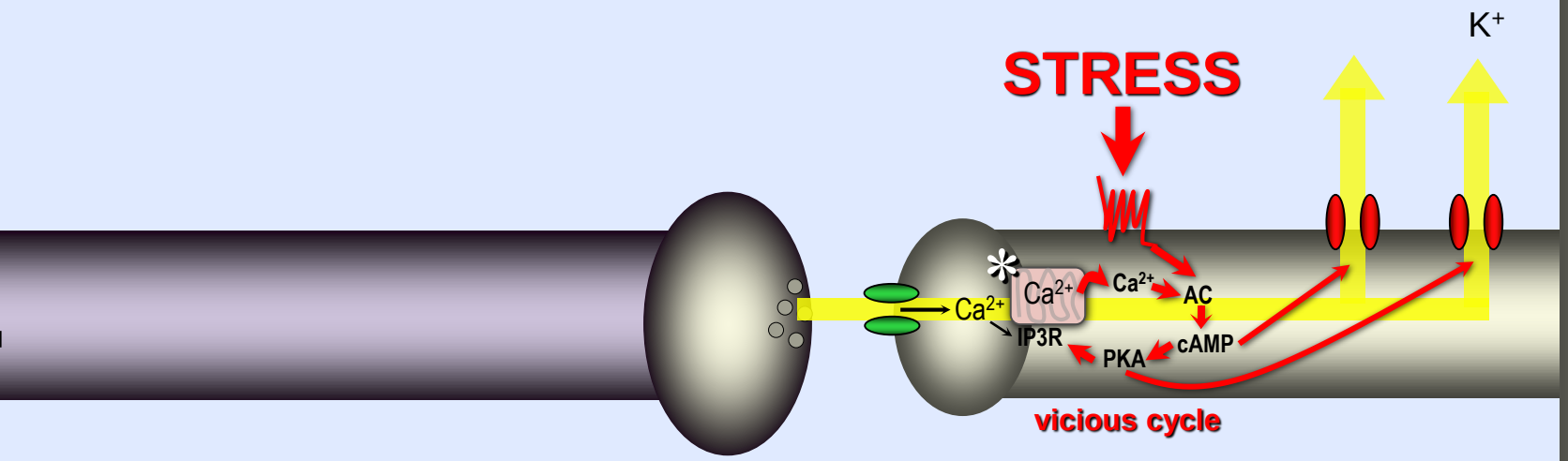
Chemical messengers inside the cell (cAMP, protein kinase A (PKA))
open the potassium channels to weaken the connection
(e.g. this prevents seizures)



Arnsten et al, *Neuron* 76:223-39, 2012

Healthy connection

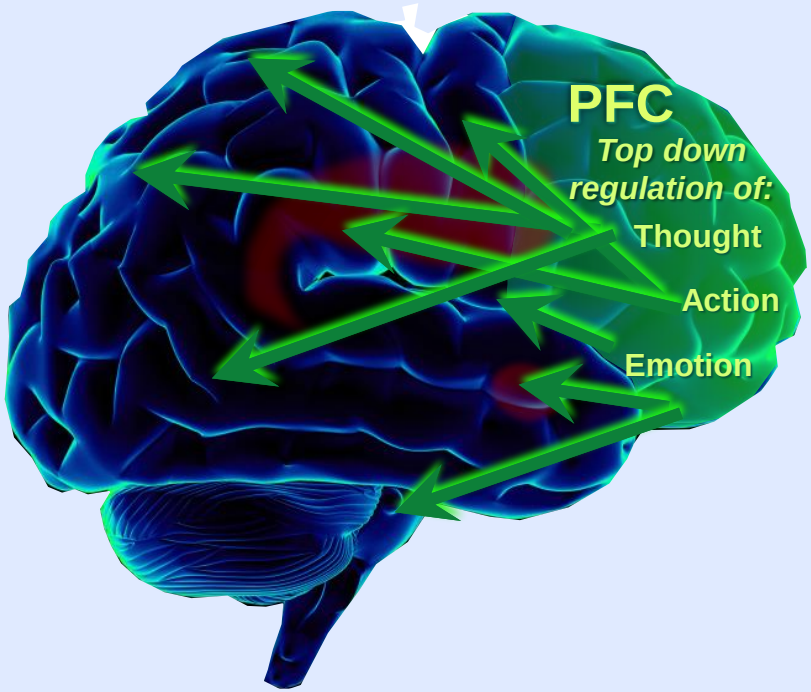
Exposure to uncontrollable stress releases chemicals in brain
(norepinephrine and dopamine- similar to epinephrine)
that drive the production of cAMP and PKA. This rapidly opens potassium channels
and disconnects prefrontal networks, taking the prefrontal cortex “off-line”.



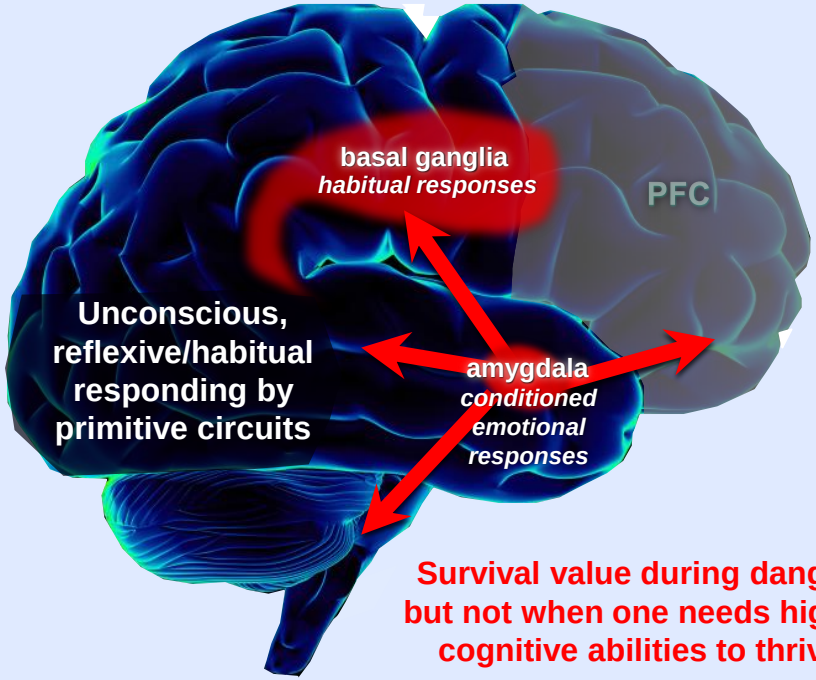
Arnsten et al, *Neuron* 76:223-39, 2012

Summary- Stress Effects on Brain State

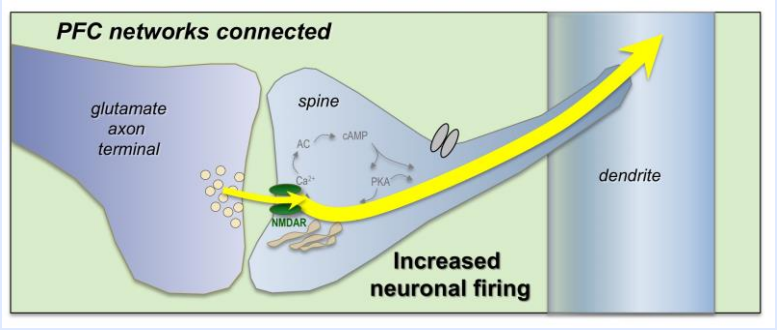
Alert, Safe and Interested

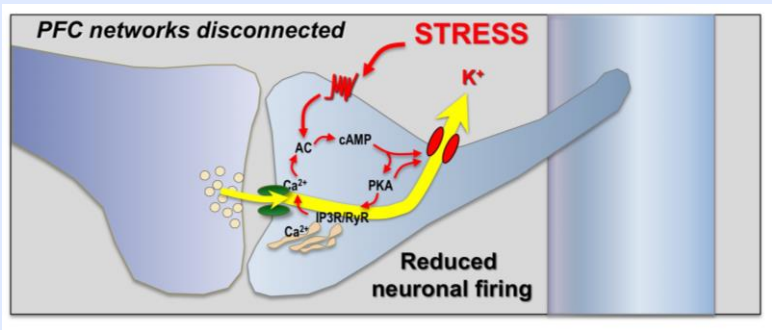


Uncontrollable Stress



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





Arnsten, *Nat Neuroscience* 18:1376-85, 2015

Summary- Stress Effects on Brain State

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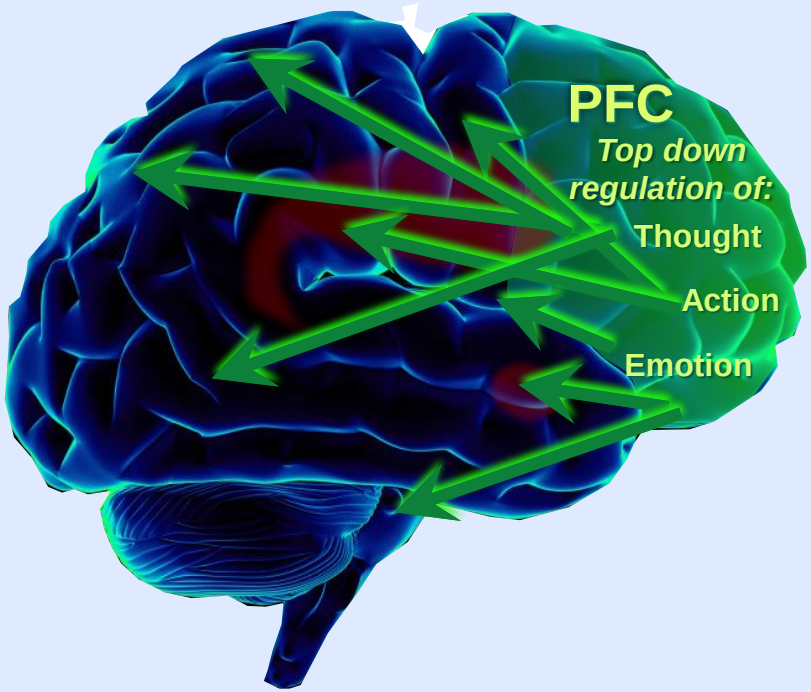
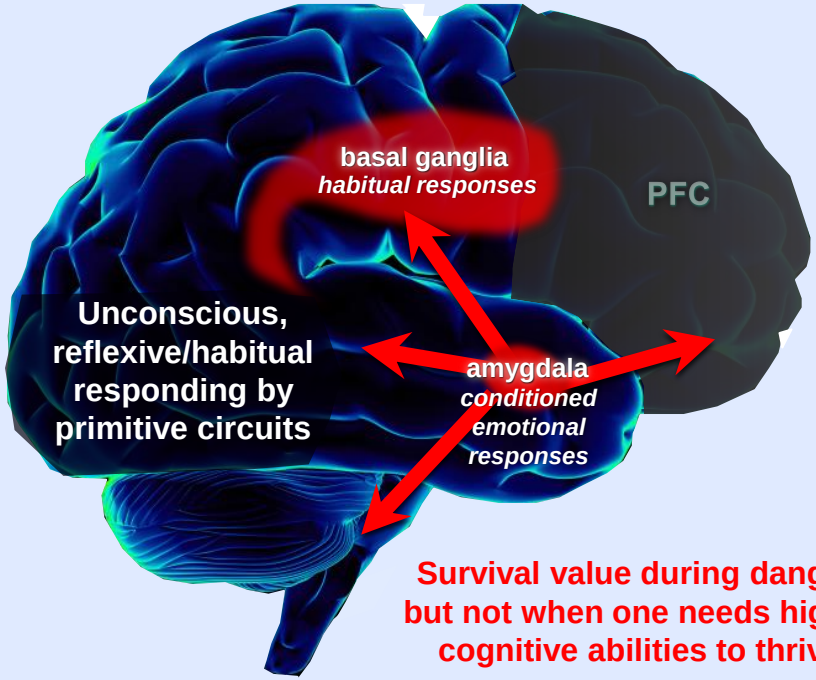


Chronic Uncontrollable Stress



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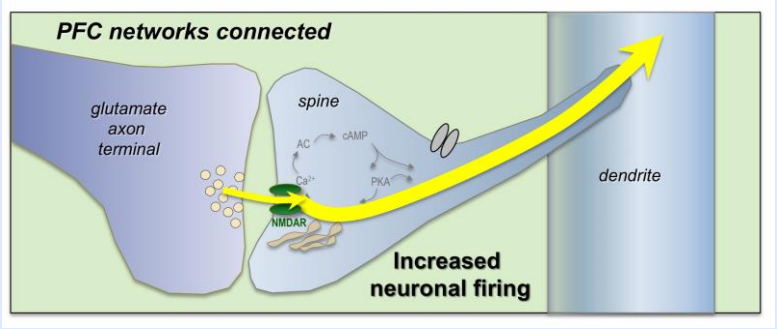
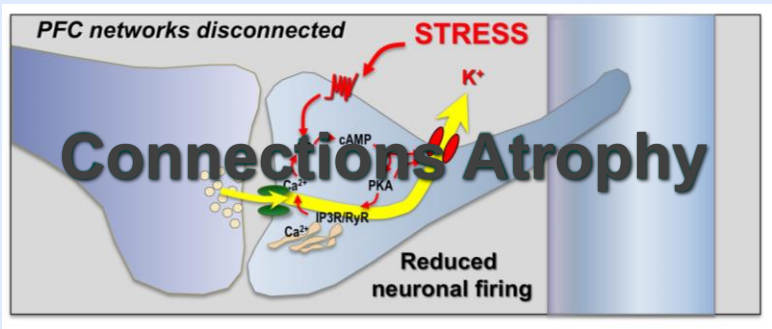
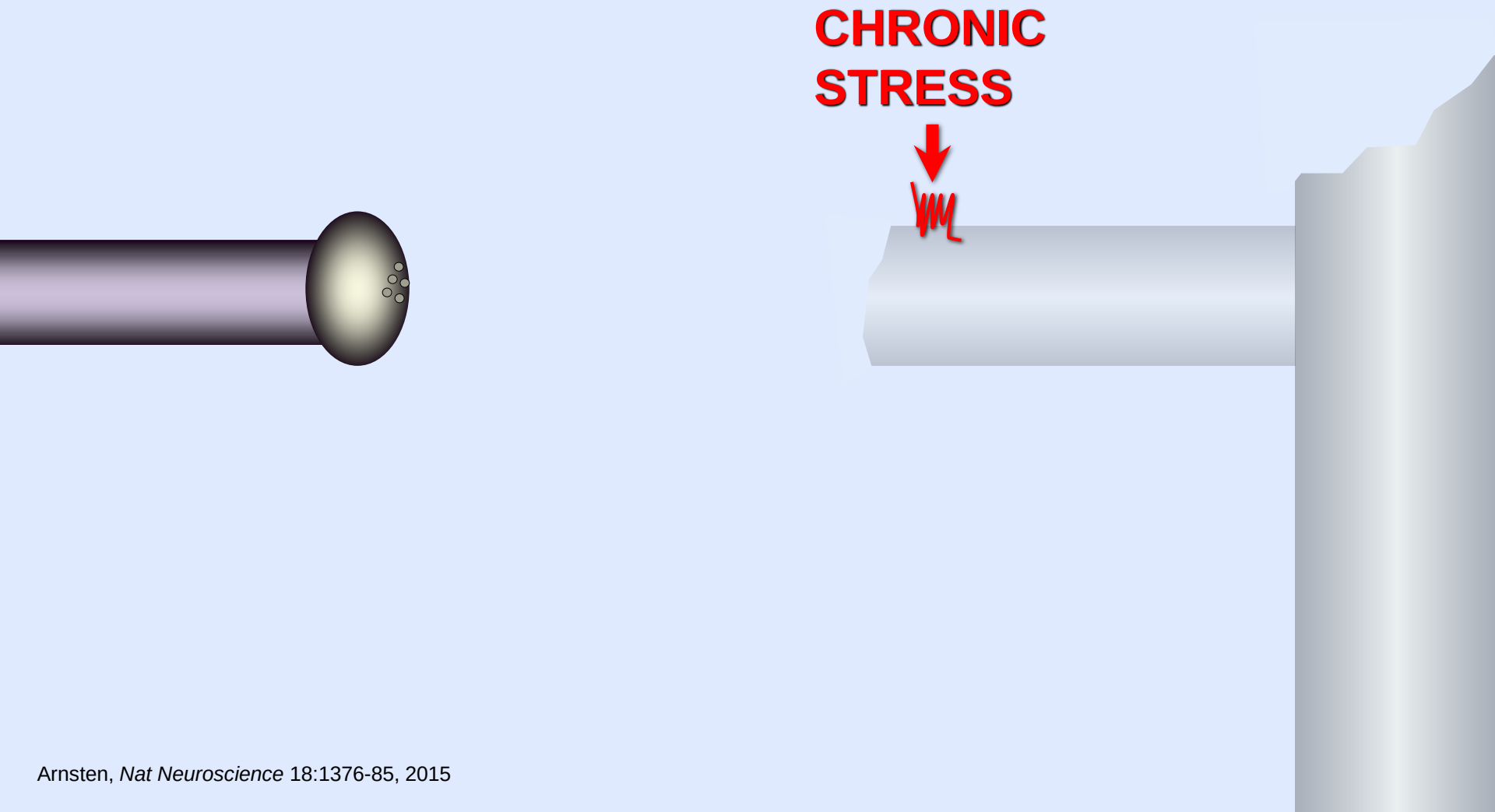




Arnsten, *Nat Neuroscience* 18:1376-85, 2015

Lose dendrites and spines



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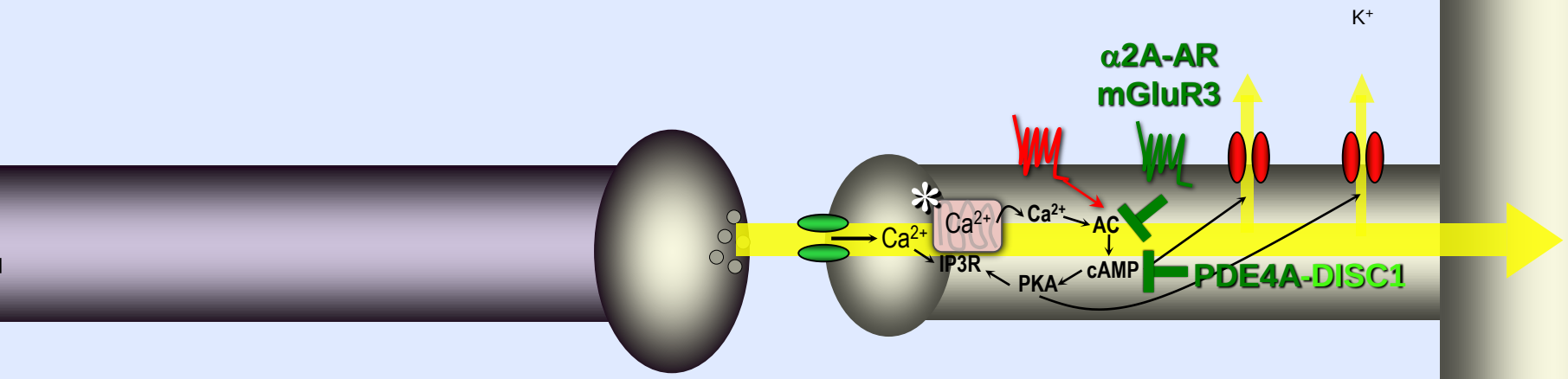
Healthy connection

Mechanisms that rein in the stress response and restore prefrontal connections



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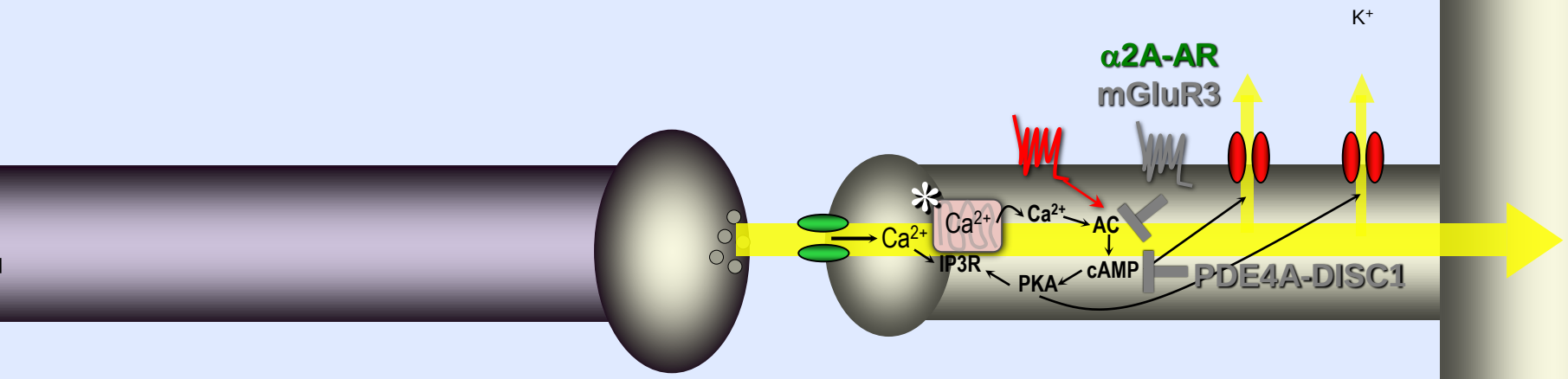
Mechanisms that rein in the stress response and restore prefrontal connections

Many are the target of genetic insults in schizophrenia



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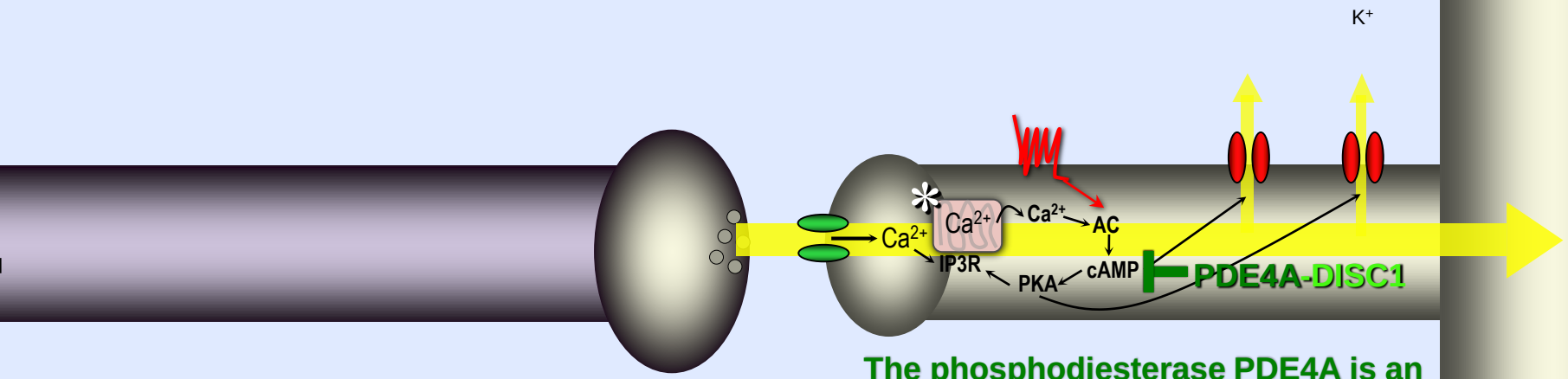

The phosphodiesterase PDE4A is an enzyme that destroys cAMP.

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

Arnsten, *Nat Neuroscience* 18:1376-85, 2015

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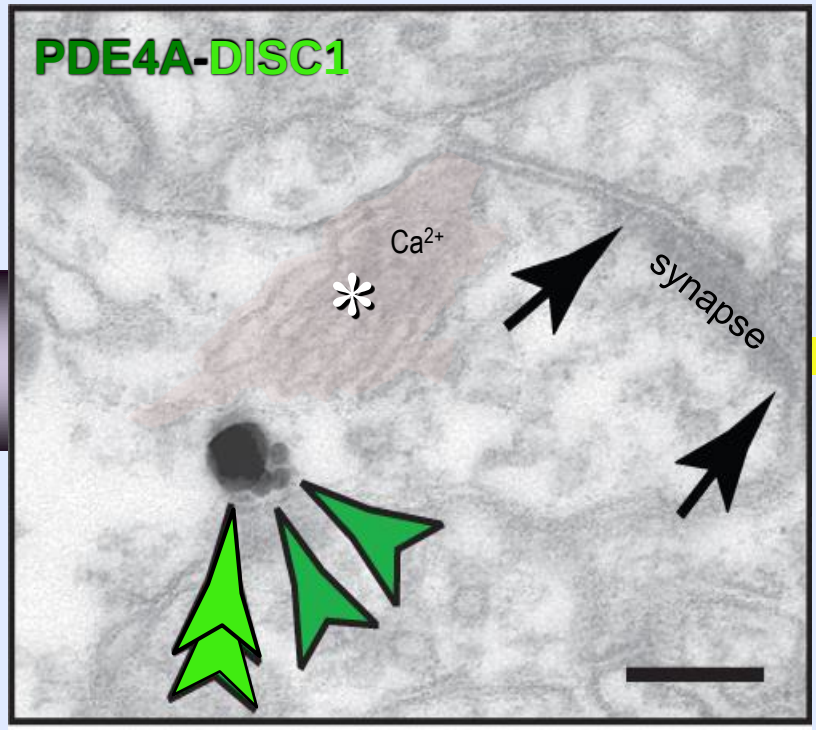

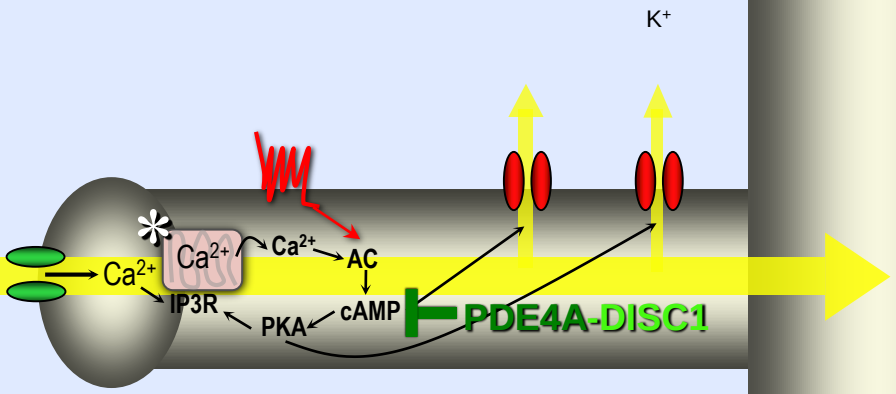

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Paspalas et al (2013) *Cerebral Cortex* 23:1643-54

Schizophrenia

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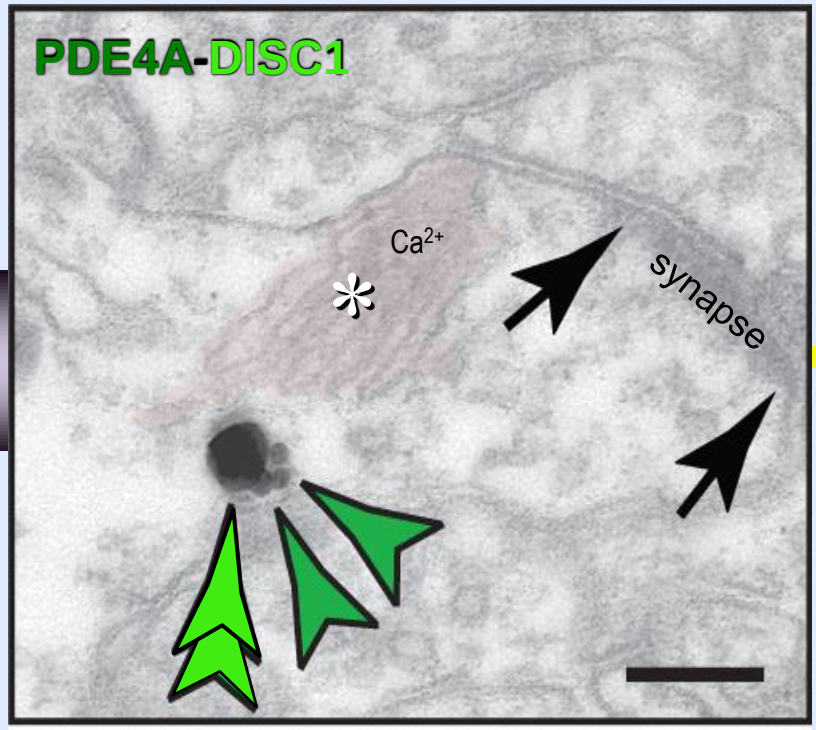

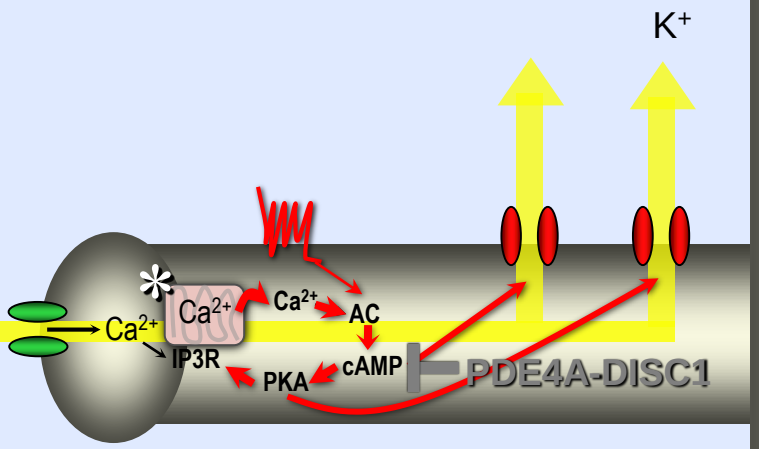

Reduced ability to hold the stress response in check

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

Millar et at., *Science* 310:1187-91, 2005; Deng et al., *Am J Med Genet B Neuropsychiatr Genet.* 156B:850-8 2011; Braun et al., *Neuroreport* 18:1841-4,2007; Kilpinen et al., *Mol Psychiatry*13:187-96, 2008

Healthy connection

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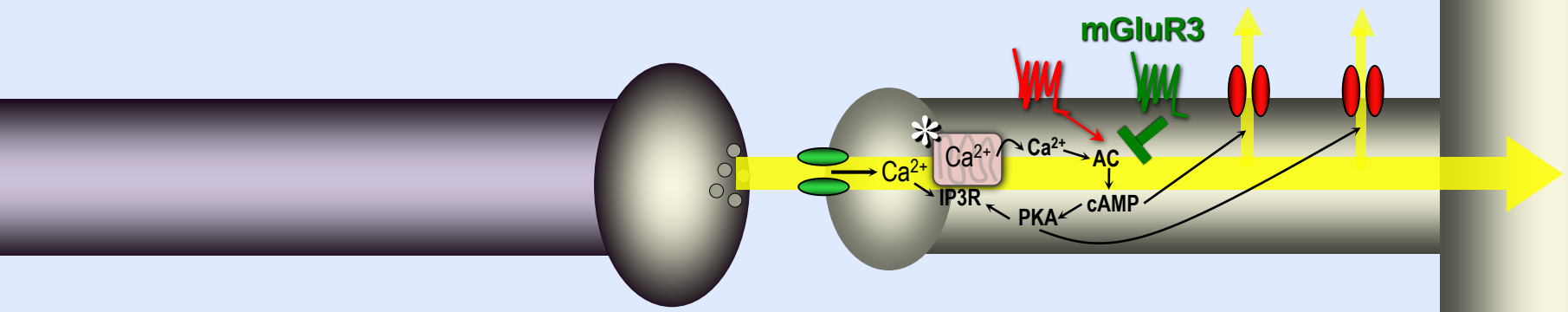

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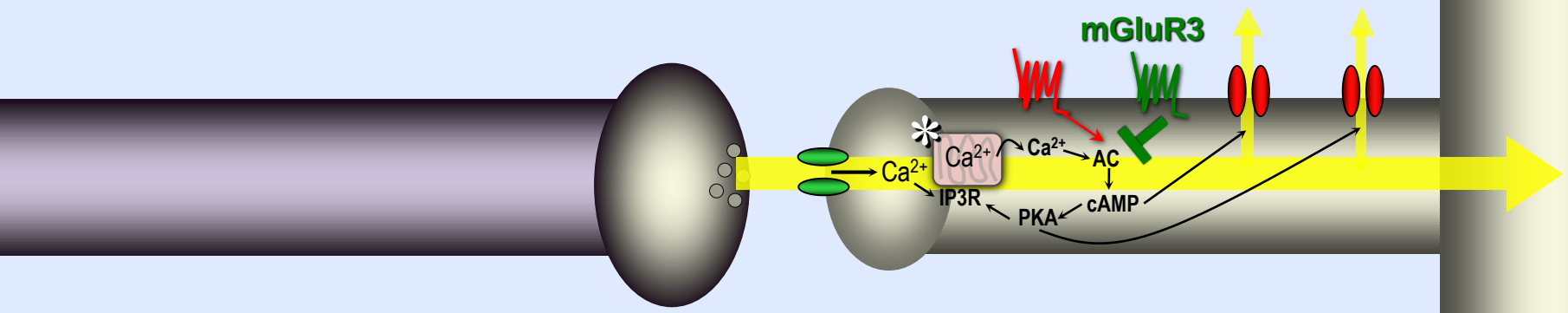

Genetic links with mGluR3 (GRM3) in both schizophrenia and autism

Schizophrenia Working Group, *Nature* 511: 421–427, 2014
Casey et al, *Hum Genet.* 131:565–79, 2012

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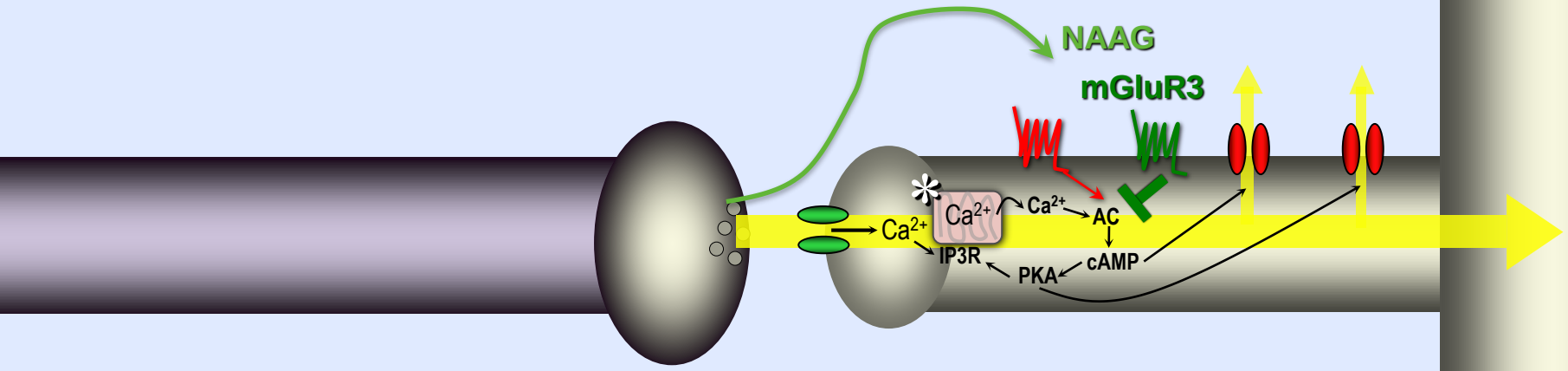

NAAG = N-acetyl-aspartyl-glutamate

Healthy connection

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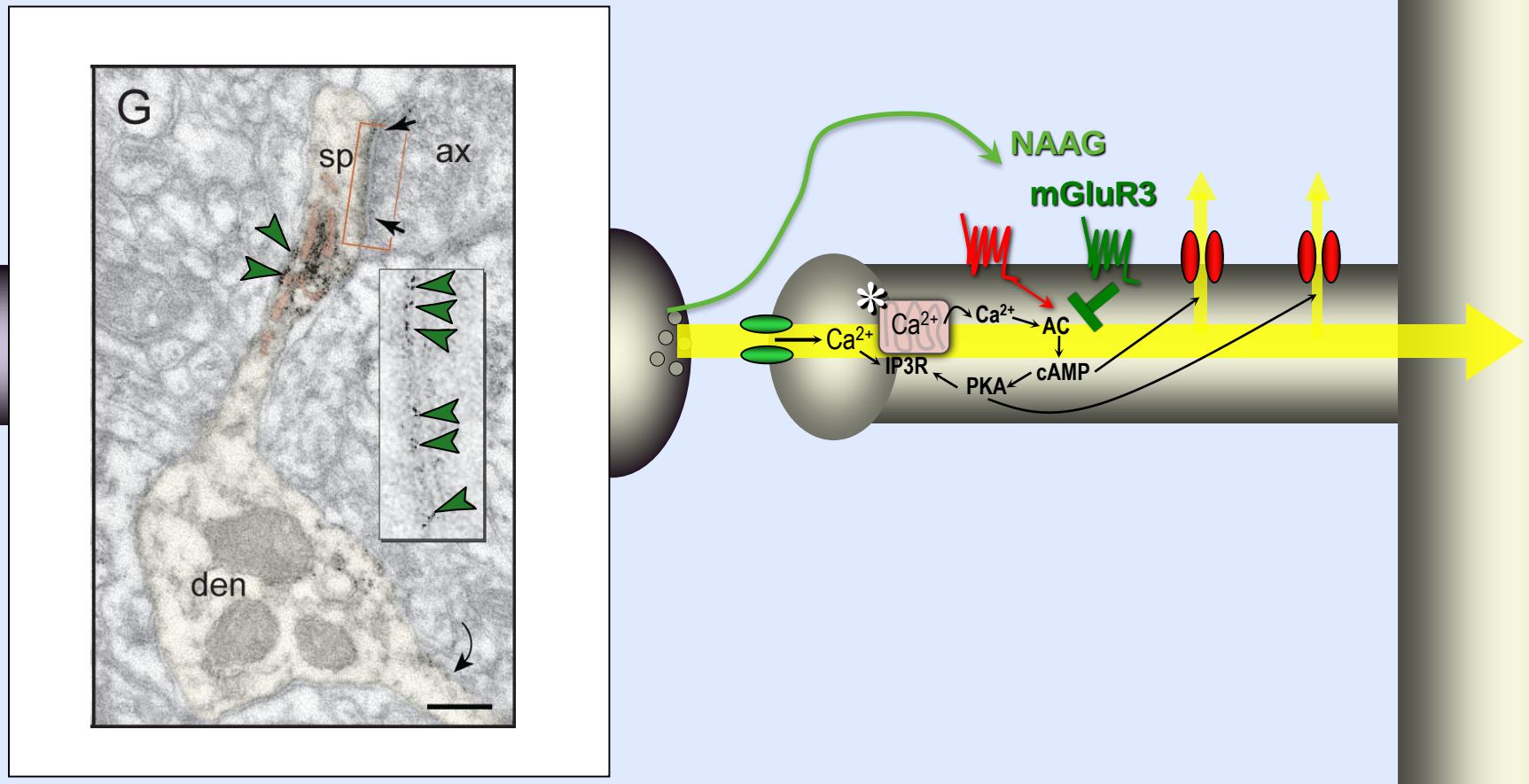
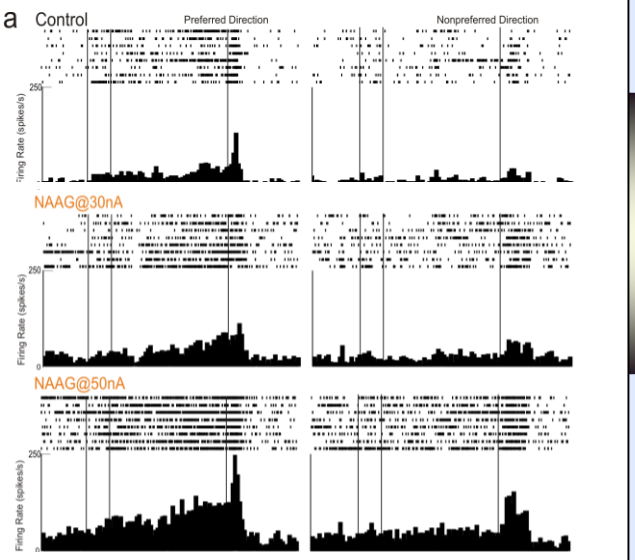


Jin et al, *Cerebral Cortex* epub, Jan 19, 2017

Healthy connection

Mechanisms that rein in the stress response and restore prefrontal connections

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

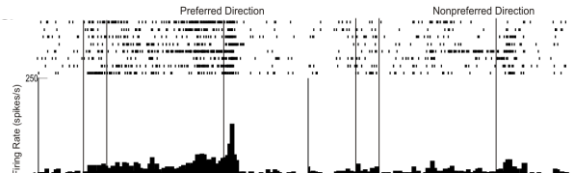


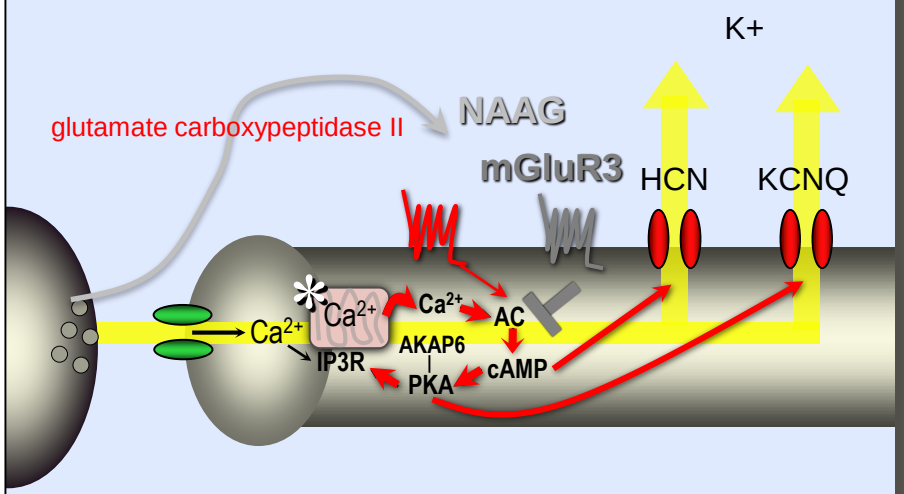
Jin et al, *Cerebral Cortex* epub, Jan 19, 2017

Schizophrenia

Increases in the enzyme that destroys NAAG, and reduced expression of mGluR3 in the PFC of patients with schizophrenia

Reduced firing without mGluR3 stimulation





Jin et al, *Cerebral Cortex* epub, Jan 19, 2017

Ghose et al, *Am J Psychiatry* 166:812-20, 2009

Schizophrenia

Potential treatment?

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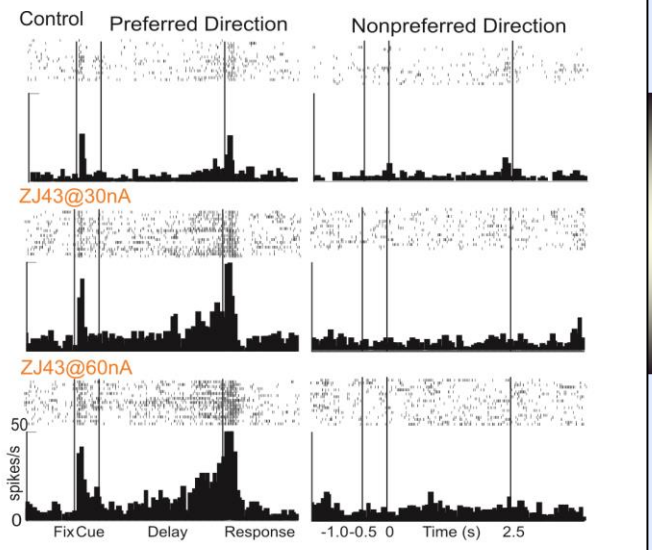

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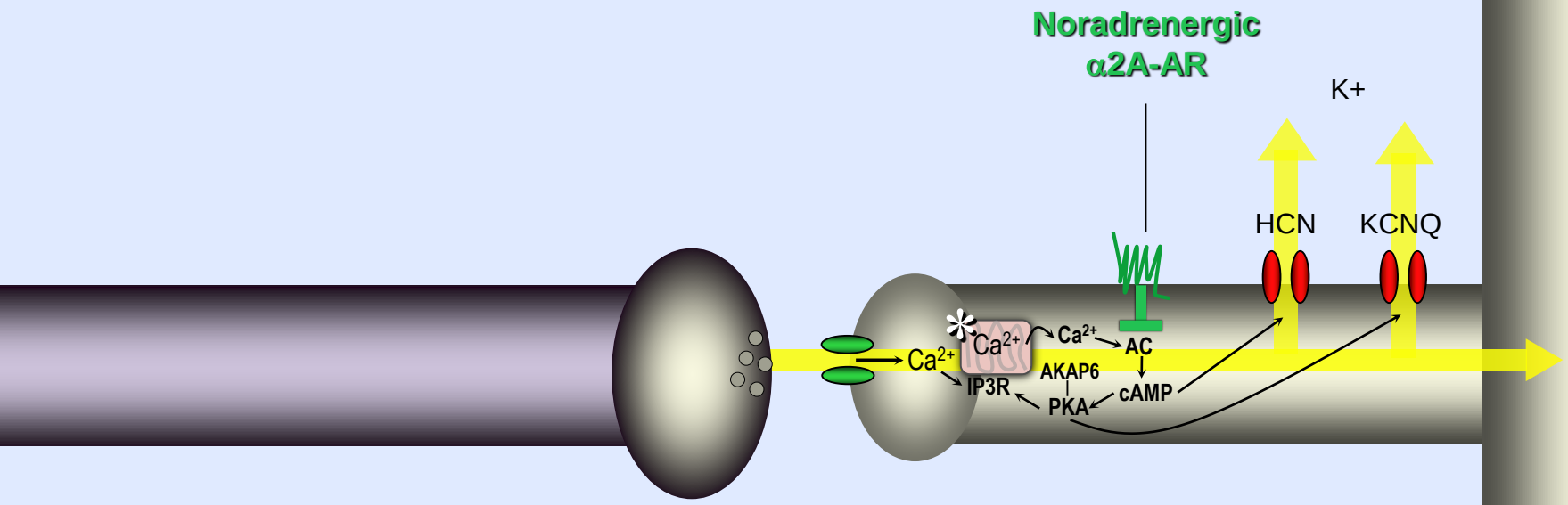
Potential therapeutic mechanism to strengthen and protect dlPFC connections



The receptor engaged when we feel alert, safe and interested

Wang et al (2007) *Cell* 129: 397-410

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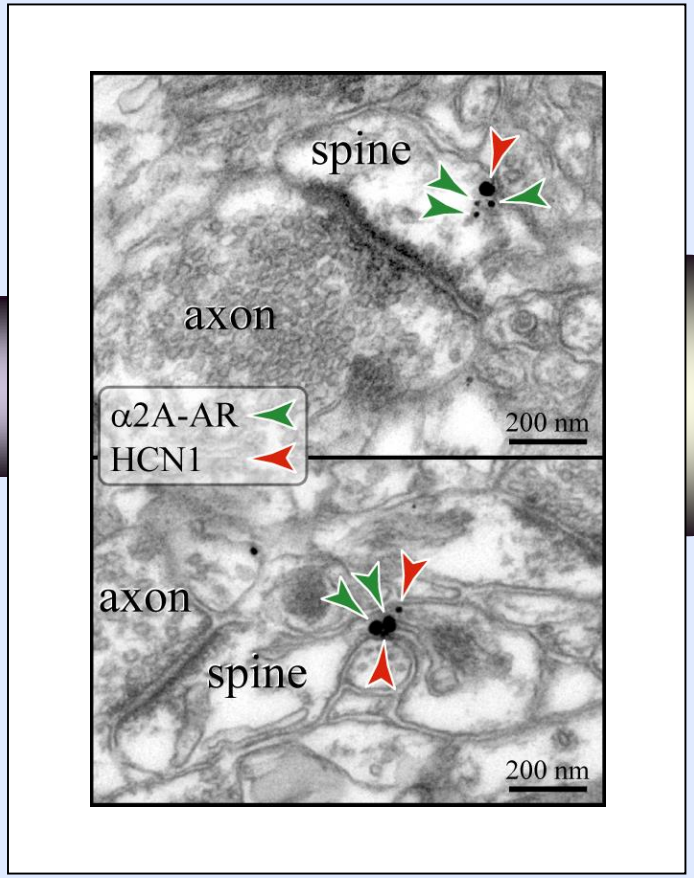

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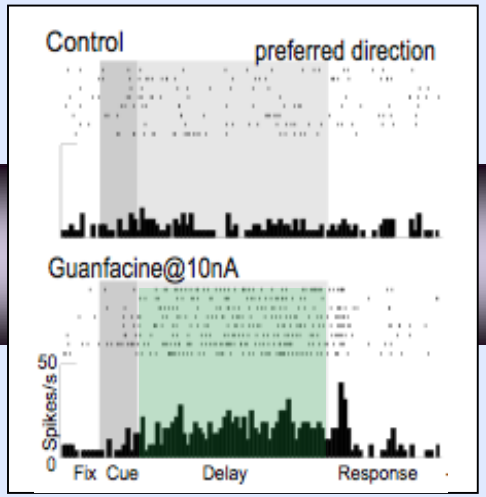
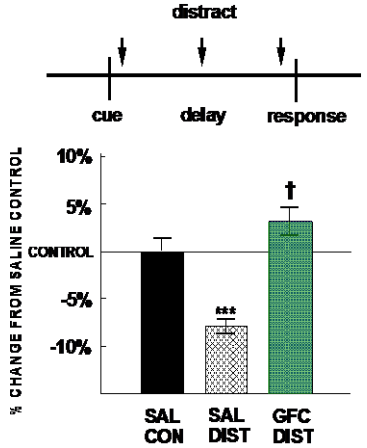


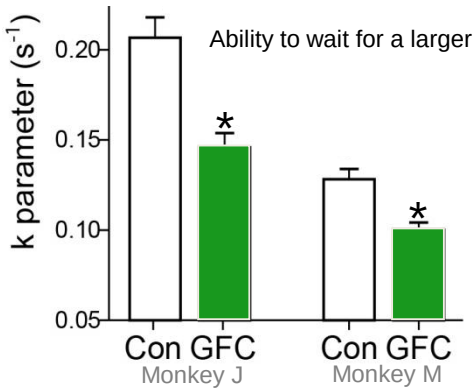
Stimulation of the α2A-AR strengthens connectivity and enhances dlPFC Delay cell firing

Wang et al (2007) *Cell* 129: 397-410

Potential therapeutic mechanism to strengthen and protect dlPFC connections

Improved Working Memory and Reduced Distractibility in Monkeys





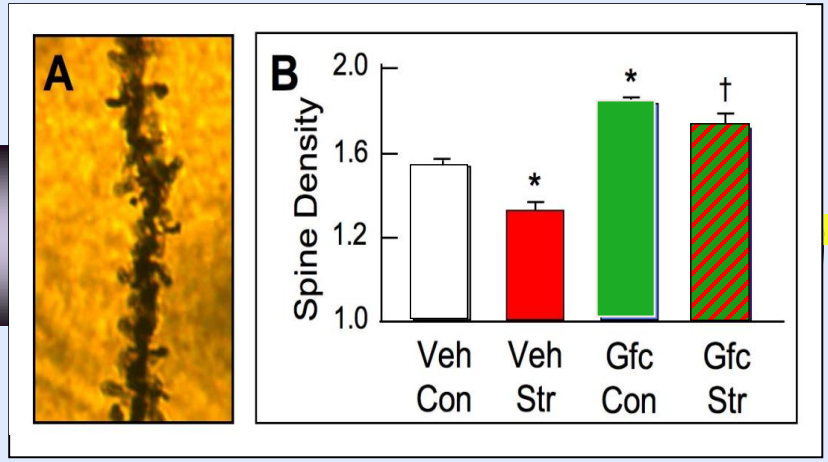
Ability to wait for a larger reward

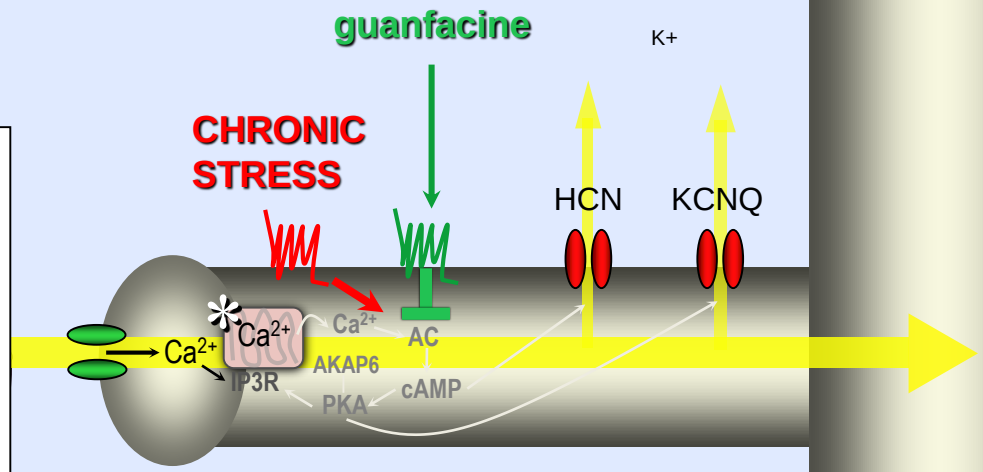
Arnsten & Contant (1992) *Psychopharm* 108:159-69.
Kim et al. (2012) *Psychopharm* 219:363-75

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

Reviewed in:
Arnsten (2010) *Exp. Rev. Neurother.* 10:1595-605

Potential therapeutic mechanism to strengthen and protect dlPFC 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)

Hains et al. *Neurobiol Stress* 2:1-9, 2015

Treatment of PFC disorders

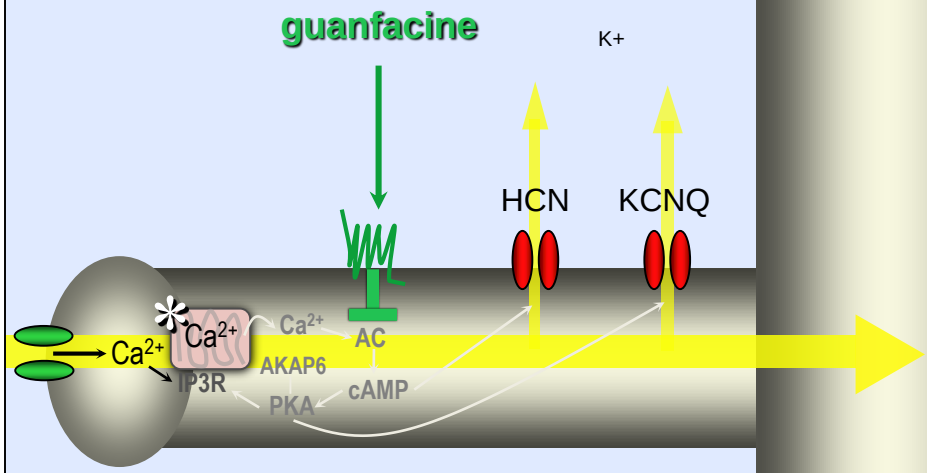
Guanfacine is in widespread use for a number of PFC disorders, e.g.:

- 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:

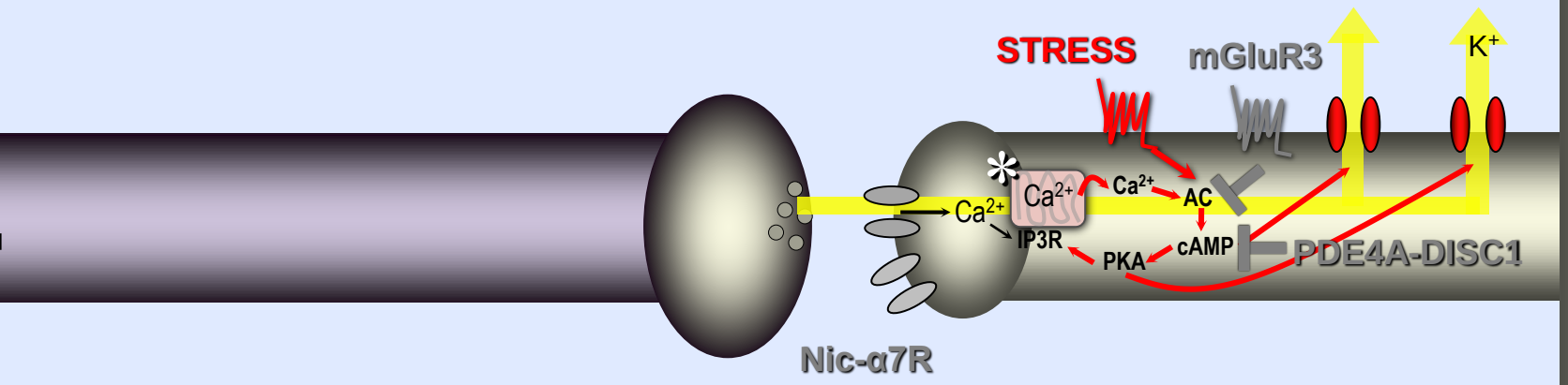
- Mild Traumatic Brain Injury (McAllister, Dartmouth, Indiana)
- Substance abuse (Fox/McKee/Sinha, Yale)
- Emergence Delirium (Blair, Vanderbilt)
- Strokes/Infections afflicting the association cortices (Singh-Curry et al , UCL, London)

- Helpful in prodromal schizophrenia?



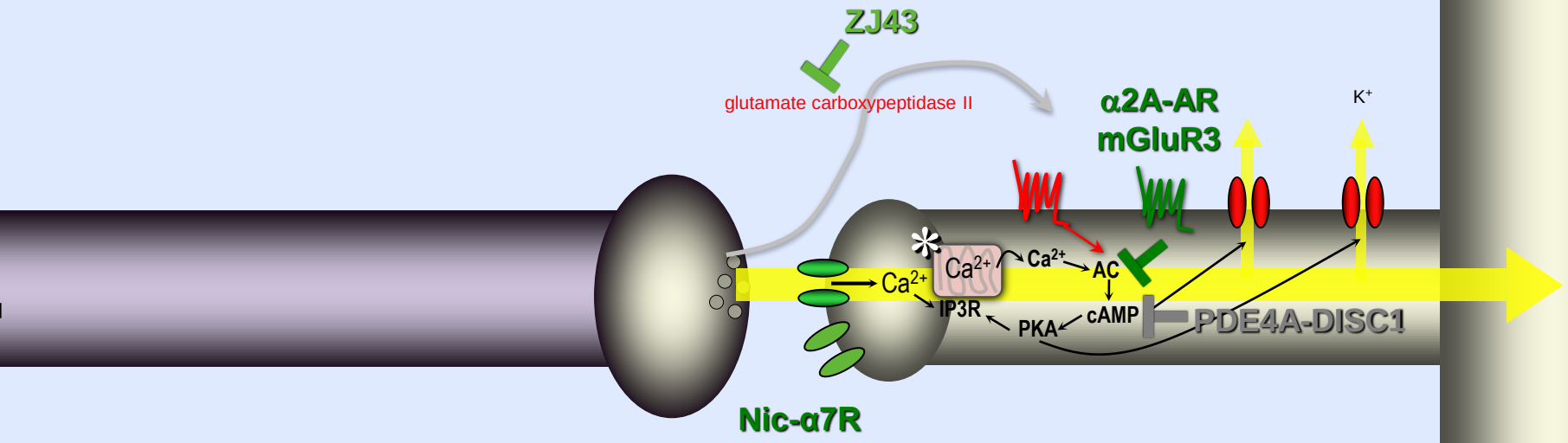
A variety of molecules that normally serve to strengthen prefrontal connections and protect them from stress are genetically weakened or have reduced expression in schizophrenia.

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



Arnsten, *Nat Neuroscience* 18:1376-85, 2015

Learning about these molecular mechanisms has identified new potential therapeutic targets to strengthen the prefrontal circuits most at risk in schizophrenia



Arnsten, *Nat Neuroscience* 18:1376-85, 2015

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NIA MERIT Award AG06036
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NIMH MH093354
NIA R01AG043430
NIH Pioneer Award DP1AG047744

Electron Microscopy

Constantinos Paspalas
Yury Morisov
Dibyadeep Datta
Johanna Crimins

Behavior/Dendrites

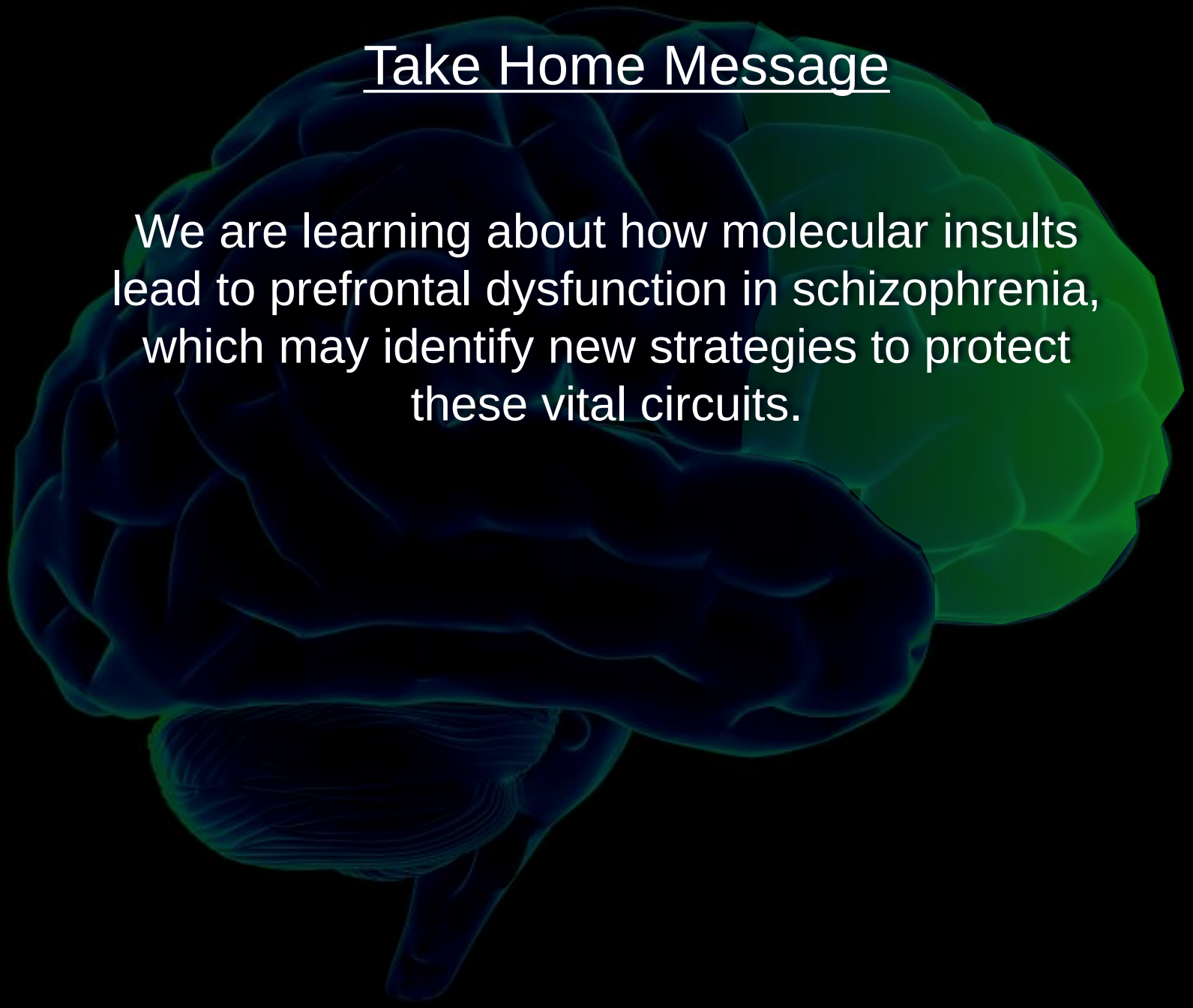
Avis Hains
Yoko Yabe
Jenna Franowicz
Shari Birnbaum
Brian Ramos
Rebecca Shansky
JingXia Cai

Physiology

Min Wang
Lu Jin
Yang Yang
Sheng-Tao Yang
Veronica Galvin
Taber Lightbourne
James Mazer
Daeyeol Lee

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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QUESTIONS?