Neurobiology of Resilience

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Artwork by Jessica Ables
What is Resilience?

Resilience refers to the capacity of an individual to avoid negative social, psychological and biological consequences of extreme stress that would otherwise compromise their psychological or physical well being.

Russo et al, Nat Neurosci, 2012
How do we model psychiatric illness in rodents to study resilience?
Social defeat model of depression and anxiety

Chronic social defeat causes:

- Anxiety-like symptoms
- Hyperactivity of HPA axis
- Disrupted circadian rhythms
- Metabolic syndrome
- Greater addiction liability
- Anhedonia-like symptoms (decreased interest in sucrose and sex).
- Profound social avoidance

Berton et al., Science, 2006; Krishnan et al., Cell, 2007
Golden et al., Nat Protocol, 2011
Measuring social interaction

Hodes and Russo, Neurobiol Ment illness, 2013
Social defeat model: Susceptibility vs. Resilience

Roughly one-third of defeated mice are “resilient”:

Resilience for social avoidance is associated with resilience for other symptoms of chronic social defeat (e.g., anhedonia, metabolic syndrome), but not all symptoms (e.g., anxiety).

Krishnan et al., Cell, 2007
Chronic antidepressant treatment promotes resilience

Tsankova et al., Nat Neurosci, 2006
Circuit mechanisms of resilience

Russo and Nestler, Nat Rev Neurosci, 2013
Glutamatergic plasticity in the nucleus accumbens

-60,000 x normal size
-Adult human brain contains \(\approx 10^{14} \text{ to } 5 \times 10^{14}\) (100-500 trillion) synapses.

Russo et al., TiNs 2010
Increased glutamate transmission in susceptible mice

Christoffel et al., *J Neurosci*, 2011
Social defeat increases spines in susceptible mice

NeuronStudio available free at http://research.mssm.edu/cnic/tools-ns.html

Christoffel et al., J Neurosci, 2011
Increased VGlut2 containing presynaptic elements

Christoffel et al., *in preparation*
Ventral striatal microcircuit

mPFC (VGLUT 1 containing)

ILT (VGLUT 2 containing)

Russo and Nestler, Nat Rev Neurosci, 2013
Regulating thalamo-striatal glutamatergic transmission

Christoffel et al., in preparation
Regulating thalamo-striatal glutamatergic transmission

- evoked EPSC
- spontaneous EPSC
- oEPSC
- oEPSC + NBQX

Christoffel et al., in preparation
Silencing ILT-NAc reduces spine density

Christoffel et al., *in preparation*
Silencing ILT-Nac circuit promotes social interaction

Christoffel et al., in preparation
Activation of ILT-NAc circuit rapidly enhances susceptibility

Christoffel et al., *in preparation*, 2013
Summary

• There are individual differences in the development of social avoidance and synaptic plasticity of NAc neurons.

• Social defeat promotes excitatory spine synapse formation in susceptible mice.

• Resilient mice resist the development of social avoidance and lack measurable changes in excitatory synaptic plasticity.

• ILT inputs to the NAc control social avoidance and excitatory spine formation.
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Keithara Davis
Sam Golden
Georgia Hodes
Mitra Heshmati
Jane Magida
Madeline Pfau
Nicole Rebusi

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Morrison Lab
Deisseroth Lab
Neve Lab
Ibanez-Tallon and Heintz Lab
Han Lab
Tamminga Lab
Turecki Lab

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J&J/IMHRO Rising Star Award, Irma T. Hirschl/Monique Weill-Caulier Award,
Janssen Pharmaceutical Research Grant.
Silencing ILT-NAc inputs produces rapid antidepressant effects

Christoffel et al., in preparation
Activation of ILT terminals in NAc rapidly enhances susceptibility

10 mV
200 ms

Christoffel et al., in preparation
Thalamic projections to Nac
1 in every 10 persons suffer from depression in the US annually.

We have few, if any, diagnostic tests for depression available clinically based on *bona fide* disease mechanisms.

Classically prescribed monoaminergic modulators regularly lead to measurable improvement in only half of the depressed clinical population, and remission in less than 30-40%.

Psychiatric drug development over the past 50 years

From Discovery to Cure, Report of the National Advisory Mental Health Council’s Workgroup, August 2010
Disease mechanisms and experimental treatment strategies are heterogeneous.

- Glutamate (ketamine)
- Cytokines (antibodies against TNFa)
- Neurotrophic factors (pro-BDNF compounds)
- Histone acetylation or methylation (HDAC inhibitors, demethylases?)

A common feature of these mechanisms is that they strongly regulate synaptic plasticity.
Social defeat reduces inhibitory synapses in NAc

Heshmati et al., *in preparation*, 2013
Activation of thalamic-Nac circuit reduces social interaction

*NAc terminal stimulation also decreases social interaction

Christoffel et al., in preparation, 2013
Social defeat reduces spontaneous inhibitory postsynaptic current (sIPSC)

Heshmati et al., in preparation, 2013
Silencing parvalbumin neurons with CaV2.1 tethered toxins.

\[ Pvalb\text{-ires-Cre} \]
\[ B6;129P2-Pvalbtm1(cre)Arbr/J \]

Cre-dependent GFP
Social defeat model of depression

Golden et al., Nat Protoc, 2011
What is the mechanism?

Social defeat increase IκK protein

Christoffel et al., *J Neurosci.*, 2011
What is the mechanism?

Rho-GTPase signaling pathway

Christoffel et al., *J. Neurosci.*, 2011
Silencing PFC-NAc inputs has no effect
IkK is necessary and sufficient for social avoidance

Christoffel et al., J Neurosci., 2011
100 Hz frequency stimulation of PFC-NAc inputs is antidepressant
\( \textit{\textbf{I\kappa K regulates immature spine formation}} \)

*\( \textit{\textbf{I\kappa Kca promotes immature spine formation}} \)
Susceptible mice have smaller glutamatergic synapses

Christoffel et al., J Neurosci., 2011
Human Depression - ChIP

Micrococcal Nuclease (S7 Nuclease or MNase)

Golden et al., submitted, 2012
## Human NAc depression samples

<table>
<thead>
<tr>
<th>gender</th>
<th>age</th>
<th>race</th>
<th>PMI</th>
<th>RIN</th>
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**Control**

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**Depressed**

HTCVD = hypertensive cardiovascular disease
ASCVD = atherosclerotic cardiovascular disease

Carol Tamminga
Subroto Ghose
Rac1 mRNA and protein down at 48 hrs post stress

Golden et al., Nat Med, 2013
Rac1 is necessary and sufficient for social avoidance

Golden et al., Nat Med, 2013
Rac1 deletion promotes immature spine formation.

*Rac1 replacement after chronic social defeat prunes away immature spines*
Mechanism of chromatin regulation at the Rac1 gene

Stress increases cofilin in stubby spines

Golden et al., submitted, 2012
Major Depressive Disorder

Statistics:

1 in every 10 persons suffer from depression in the US annually.

We have no diagnostic tests for depression based on *bona fide* disease mechanisms.

Classical antidepressant Tx leads to measurable improvement in only half of depressed people and remission in less than 30-40%.

Psychiatric drug development over the past 50 years

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Disease mechanisms and experimental treatment strategies are heterogeneous.

- Glutamate (ketamine)
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- Neurotrophic factors (pro-BDNF compounds)
- Histone acetylation or methylation (HDAC inhibitors, demethylases?)

A common feature is that they all strongly regulate glutamatergic circuits in the nervous system.
Rac1 CA restores normal social interaction

Golden et al., submitted, 2012
Rac1 CA prunes away stubby spines

Golden et al., submitted, 2012
Is Rac1 necessary and sufficient for stress-induced behavior?
What is the chromatin state surrounding the Rac1 gene?
Optogenetic activation of PV cells

AAV-DIO-ChR2 or EYFP in PV-Cre line

Intra-NAc stimulation during a 2nd SI test

Check viral expression & cannulae placement
Stimulation of PFC-NAc inputs is antidepressant

Christoffel et al., in preparation
Silencing PV cells promotes social avoidance
Box 1. Dendritic spine morphology

Psychostimulant-induced structural plasticity is generally characterized by three parameters: (1) dendritic spine density, (2) dendritic spine size and shape (morphology) and, (3) dendritic arborization or complexity. Recent advances in methodology (see Box 1) have greatly increased our ability to identify more discrete and subtle changes in dendritic spine morphology. Rather than simply measuring spine density, these tools allow for the characterization of dendritic spines by type (i.e., thin, mushroom or stubby) or volume, which more accurately reflects the functional outcome of experience-dependent plasticity (Petrak et al. 2005; Holtmaat and Svoboda 2009). Further, synaptic activity at individual dendritic spines is directly coupled to structural re-organization (Matsuzaki et al. 2004). (A) A 3-dimensional recreation of a LY filled dendritic segment from a MSN located in the NAc. As can be easily observed, there is a large dynamic continuum along which dendritic spine morphology falls. (B) Stubby spines, or spines whose total length is nearly equal to their spine head diameter, are the least well understood. They are most prominent during development and generally considered to be immature and plastic synaptic elements, while also strongly coupled to their parent dendrite (Schmidt and Eliers 2009). This strong coupling suggests that changes in frequency of stubby spines may disproportionally impact neuronal excitability relative to other spine types (Noguchi et al. 2005). Further, the lack of a spine neck is believed to preclude direct innervations by inhibitory connections. It is critical to point out that most common methods for assessing spine morphology (i.e., Golgi-Cox stain) are unable to reliably detect stubby spines. (C) Thin spines, whose total length is greater than their head width and head width is greater than their neck width, are also considered to be immature, plastic elements. (D) Mushroom spines, whose head width are greater than their neck width, are considered to be the most stable and non-plastic spine types along the continuum. Mushroom spines also exhibit increased AMPAR frequency along the PSD, relative to stubby spines. Due to their differential physiological properties, these kinds of detailed morphological assessments of spine are more accurate than total spine density. Panel A is modified with permission from Russo et al. 2010.
Social defeat reduces Rac1 transcription

*Rac1 protein is also selectively decreased

Golden et al., *Nat Med*, 2013
Rac1 gene is in a repressed state

Golden et al., Nat Med, 2013
Silencing PFC-NAc circuit increases stubby spine density

Christoffel et al., *in preparation*
Silencing PFC-NAc circuit promotes social avoidance.

Rapid reversible silencing with NpHr2 has no effect on social avoidance.
Regulating neuronal activity in a circuit specific manner

Christoffel et al., in preparation
HDAC inhibitor normalizes Rac1 and social interaction

Golden et al., *Nat Med*, 2013
Effects are long-lasting and partially reversed by chronic antidepressant treatment.

Golden et al., *Nat Med*, 2013
Who Cares? Is social defeat relevant to human depression?
Rac1 is decreased in human NAc from depressed subjects

Golden et al., Nat Med, 2013
Chromatin is in a repressed state

Golden et al., *Nat Med*, 2013
**Box 1. Dendritic spine morphology**

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Circuit mechanisms of resilience

Russo and Nestler, 2013
Back to mice. What’s the functional significance?