Abelson Seminar 2008
How Does Stress Get Under the Skin?

Steven E. Hyman

- Unipolar depressive disorders
- Alcohol-use disorders
- Schizophrenia
- Iron-deficiency anemia
- Bipolar disorder
- Hearing loss (adult onset)
- HIV/AIDS
- Chronic obstructive pulmonary disease
- Osteoarthritis
- Traffic accidents
Rene Descartes thought us out of our bodies with his “cogito ergo sum”

What are the mechanisms by which lived experiences, such as psychological and social stressors affect the body and influence health?

Learning mechanisms will give us insight into interventions.
Most disease results from a combination of genes, environment, behavior and bad luck.

Source: David Altshuler 2005
## Genetic Risk of Neuropsychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence in the population (%)</th>
<th>Relative risk, $\lambda_1$</th>
<th>Heritability†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autism (narrow)</td>
<td>0.2</td>
<td>25</td>
<td>0.9</td>
</tr>
<tr>
<td>Autism (broad)</td>
<td>0.7</td>
<td>25</td>
<td>0.9</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1.0</td>
<td>9</td>
<td>0.8–0.9</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1.0</td>
<td>8</td>
<td>0.7–0.8</td>
</tr>
<tr>
<td>Major depression</td>
<td>17</td>
<td>2–5</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Polygenic model relevant to depression, Anxiety, and substance use disorders
Stress Getting Under the Skin

Threat

Transduction
Sensory Inputs and processing
Sensory Thalamus and Cortex

Appraisal and Response
Emotion Processing Circuits and Outputs
Amygdala, Hypothalamus, Brainstem

Safety Signals
Hippocampus (Context)
Reappraisal
Medial Prefrontal Cortex
Cortex

Hippocampus

Thalamus

Lateral Nuclear Complex

Frontal Cortex

Hippocampus

Striatum

Hypothalamus

Brainstem

Sensory and Contextual Inputs

Outputs

Response selection

Contextual Memory

Learned avoidance behaviors

Sympathetic activation, CRF release

Freezing, startle, facial expressions

Arousal, vigilance

Monoamine Nuclei

PAG
Norepinephrine Projections
β-adrenergic receptor

NE dependent phosphorylation of GluR1 Facilitates synaptic delivery of AMPARs and LTP
AMPA Receptor Trafficking in LTP and LTD

Source: Citri and Malenka Neuropsychopharmacology 2007
Signals that can be initiated by experience or drugs can regulate gene expression.
Epigenetic Regulation: Chromatin Remodeling by a Stressor

(a) Normal

Basal BDNF expression:

(b) Chronic defeat stress

H3 acetylation
H3-K27 dimethylation

(c) Antidepressant-treated
Meta-analysis: Areas of Hyper- and Hypo-activation in Anxiety Disorders Compared with Healthy Subjects (diverse fear stimuli)

Lack of Validated Targets for Psychopharmacology

- The drugs used in psychopharmacology were discovered serendipitously.
- The initial molecular targets of these drugs were discovered based on reverse engineering of existing drug mechanisms.
- Learning “where” in the brain identifies the cells, synapses, and circuits that can be targeted by treatment interventions.
Knowing “where” in the brain identifies the cells, synapses, and circuits that provide targets of intervention.
Cg25WM Deep Brain Stimulation

Stereotaxic targeting  Cg25 target  Bilateral electrodes  hi Freq DBS

Baseline PET  
Ham17 = 27±2

Bilateral electrodes

3 months DBS  
Ham17 = 9±6

Mayberg et al. Neuron, 45:651-660, 2005