Epigenetic and environmental mechanisms of risk for psychiatric disorders

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Established environmental risk factors for schizophrenia

Urbanicity

Specific social stressors?

Social Status

Migration

Neuronal Mechanisms
Stress and its regulation

- Stress
  - CRF
  - ACTH
  - Catecholamines
  - Glucocorticoids

- Immune Function
  - ▼ Reproduction
  - ▼ SW Sleep
  - ▼ Eating
  - ▲ Grooming
  - ▲ Despair
  - ▲ Neophobia
  - ▲ Locomotor Activity
  - ▲ Startle
  - ▲ Locus Coeruleus FR
  - ◆ Nucleus Raphé FR

- Blood Pressure
- Heart Rate
- Platelet Activity
- Blood Sugar
- GI Blood Flow

Arborelius et al., *J Endocrinology* 1999

Lupien et al., *Nat Rev Neurosci* 2009
Environmental risk factor: social status

- Highly relevant for physical and mental health, critical for survival in primates
- Present throughout the animal kingdom
- Interacts with genetic risk for schizophrenia
Urbanicity and risk for schizophrenia

McGrath et al. BMC Medicine 2004

van Os et al. Nature 2010
Montreal Imaging Stress Task

\[4 \times 10 / 5 = ?\]

TIMEOUT!

City living and amygdala activation

Lederbogen*, Kirsch*, Haddad* et al., Nature 2011
Violence and urbanicity

Data from: Crime in the United States 2009, FBI

Urban birth tunes cingulate activation

Lederbogen*, Kirsch*, Haddad* et al., Nature 2011
Urban birth impairs cingulate-amygdala interactions

Lederbogen*, Kirsch*, Haddad* et al., Nature 2011
Causes ?
Neurogeography
Migration and schizophrenia

Cantor-Grae and Selten *Am J Psychiat* 2005
Social stress in migrants
Altered social stress processing in second-generation immigrants

Akdeniz*, Tost* et al., revision in preparation
Exaggerated dopamine release during psychosocial stress in immigrants

Mizrahi*, McKenzie*, Rusjan* et al., under review
Environmental and genetic risk factors converge on perigenual cingulate
Impact of stress on the brain across the life span

<table>
<thead>
<tr>
<th>Effect on HPA axis</th>
<th>Prenatal stress</th>
<th>Postnatal stress</th>
<th>Stress in adolescence</th>
<th>Stress in adulthood</th>
<th>Stress in aging</th>
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</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Programming effects</td>
<td>Differentiation effects</td>
<td>Potentiation/incubation effects</td>
<td>Maintenance/manifestation effects</td>
<td>Maintenance/manifestation effects</td>
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<tr>
<td></td>
<td>↑ Glucocorticoids</td>
<td>↑ Glucocorticoids (maternal separation)</td>
<td>↑↑ Glucocorticoids</td>
<td>↑ Glucocorticoids (depression)</td>
<td>↑ Glucocorticoids (cognitive decline)</td>
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<td>↓ Glucocorticoids (severe trauma)</td>
<td>↓↓ Glucocorticoids</td>
<td>↓ Glucocorticoids (PTSD)</td>
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<td>↓ Glucocorticoids (PTSD)</td>
</tr>
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</table>

Lupien et al., Nat Rev Neurosci 2009
Cellular mechanisms of GxE

Krishnan and Nestler *Nature* 2008
Stress and Hypermethylation of the neural glucocorticoid receptor (NR3C1)

Tyrka et al., *PLoS One* 2012

McGowan et al., *Nat Neurosci* 2009
Hypermethylation of NR3C1 and cingulate-amygdala connectivity

Tost*, Walter*, Nieratschker* et al., in progress
A decade for psychiatric disorders

There are many ways in which the understanding and treatment of conditions such as schizophrenia are ripe for a revolution.
Thanks

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- ZI-Community