Are the offspring of parents with bipolar disorder too sensitive to their environment?

Studies of stress, cortisol levels, and the development of affective disorders

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When good hormones go bad:
Stress and mental health
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• No conflict of interest to disclose

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Outline

• Theoretical approach and background
• HPA functioning in offspring of parents with bipolar disorder
• **Longitudinal predictors of cortisol levels**: Environmental sensitization
• **Cross-sectional predictors of cortisol levels**: A biological sensitivity to stress
Prevalence of major affective disorders

National Comorbidity Study - Replication (n=9282)

- Depression: 16.2%
- Bipolar disorder: 2.1%
- Sub-threshold BD: 2.4%*

* Merikangas et al, 2007
## WHO Disease burden

<table>
<thead>
<tr>
<th>Region</th>
<th>Condition</th>
<th>% total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The Americas</strong></td>
<td>Unipolar depressive disorders</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Perinatal conditions</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Violence</td>
<td>4.7</td>
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<tr>
<td></td>
<td>Ischaemic heart disease</td>
<td>4.5</td>
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<tr>
<td></td>
<td>Alcohol use disorders</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Road traffic accidents</td>
<td>3.2</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Congenital anomalies</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory infections</td>
<td>2.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Condition</th>
<th>% total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>Ischaemic heart disease</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Unipolar depressive disorders</td>
<td>6.1</td>
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<tr>
<td></td>
<td>Alzheimer and other dementias</td>
<td>3.0</td>
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<tr>
<td></td>
<td>Alcohol use disorders</td>
<td>2.9</td>
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<td></td>
<td>Hearing loss, adult onset</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Road traffic accidents</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Self-inflicted injuries</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Üstün et al, 2004
Why are the affective disorders so burdensome?

• Among diseases, unique combination of
  – High prevalence
  – Early age of onset
  – High chronicity
  – High role impairment
Approaches to the problem of the affective disorders

LONGITUDINAL PROSPECTIVE RESEARCH

HIGH RISK POPULATIONS
## Risk for psychopathology in offspring of BD parents: Meta-Analysis (n=973)

<table>
<thead>
<tr>
<th></th>
<th>Offspring of BD parents</th>
<th>Offspring of control parents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any diagnosis</strong></td>
<td>52 %</td>
<td>29 %*</td>
</tr>
<tr>
<td><strong>All affective disorders</strong></td>
<td>26.5 %</td>
<td>8.3%*</td>
</tr>
<tr>
<td><strong>Bipolar disorder</strong></td>
<td>5.4%</td>
<td>0%*</td>
</tr>
</tbody>
</table>

* p<0.05, Lapalme & Hodgins, 1997
**More recent data:**
**Rates of affective disorders**

<table>
<thead>
<tr>
<th></th>
<th>OBD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent studies*</td>
<td>15-56%</td>
<td>2-10%</td>
</tr>
<tr>
<td>Concordia cohort at mean age of 20 years</td>
<td>32% (6% with BD)</td>
<td>10% (0% with BD)</td>
</tr>
</tbody>
</table>

* Birmaher et al, 2009
Henin et al, 2005
Duffy et al, 2007
Hillegers et al, 2005
Offspring of parents with bipolar disorder

• Very few studies (low prevalence)
• Evidence of abnormalities in…
  – Hypothalamic-pituitary-adrenal (HPA) axis (Ellenbogen et al, 2006, 2009)
  – Labeling emotions in faces (Brotman et al, 2008)
  – Executive functions, particularly inhibition and cognitive flexibility (Klimes-Dougan et al, 2006)
Offspring of parents with bipolar disorder

• Exposed to...
  – Elevated maternal negativity (Meyer et al, 2006)
  – More family conflict (Romero et al, 2005)
  – Less cohesion and more disorganization in the home (Chang et al, 2001; Ellenbogen & Hodgins, 2004; 2009)
  – Higher levels of chronic and episodic stress, as reported by the offspring (Ostiguy et al, 2009) and the parent (Ellenbogen et al, 2006)
Clinical staging model for the offspring of parents with BD

- Childhood:
  - Well
  - Non-mood disorders
- Adolescence:
  - Minor mood disturbances
  - Depression
- Mania

Duffy et al, 2010
Poor interpersonal functioning
Affective symptoms
Psychopathology

↑ Internalizing and externalizing problems
Stress
Family Environment
Parenting

HPA abnormalities
Poor interpersonal functioning
Affective symptoms
Psychopathology

Ostiguy et al, In press, Development and Psychopathology

Parents:
High neuroticism
Genetic risk
The Montreal Longitudinal Study of Families with Bipolar Disorder
There are a 105 families in the study, 58 with a BD parent and 47 families with no mental illness:

- 211 parents:
  - 21 parents with major depression
  - 58 parents with bipolar disorder
  - 132 parents with no mental illness

- 154 offspring, 4 to 12 years old:
  - 80 with one parent having BD
  - 74 with both parents free of mental illness
Parents:
- Diagnostic assessment
- Psychosocial/ Stress
- Personality

Offspring (4 - 12 yrs):
- Diagnostic assessment
- Behavior (CBCL)

Offspring (15 - 25 yrs):
- Adrenal hormones
- Diagnostic assessment
- Information processing
- Chronic and episodic stress
Adrenal (Stress) Hormones
HPA axis

hypothalamus

pituitary
HPA System

Hypothalamus

CRH → Vasopressin

Hippocampus

PFC

Monoamines

GABA

Pituitary

ACTH

Adrenal cortex

BBB

Cortisol
Why do we care?

HPA abnormalities are associated with the affective disorders
HPA and depression

- Hypothalamus
  - CRH
  - Pituitary
    - ACTH
      - Adrenal cortex
        - GC receptors
          - Hippocampus
            - Volume
            - Reactivity to stress
              - Awakening response

Cortisol

- Volume
- CORT
HPA axis and major affective disorders

• HPA axis is compromised at many levels in major depressive (Holsboer, 1995) and bipolar disorders (Rybakowski & Twardowska, 1999).

• Do HPA abnormalities precede the onset of a major affective disorder?
Mean cortisol levels: Age 16

Ellenbogen, Hodgins, & Walker, 2004; 2006
Mean cortisol levels: Age 18

Ellenbogen et al, 2010
Mean cortisol levels: Age 20

- ○ - Any disorder (n=32)
- ■ - OBD / no disorder (n=37)
- ▲ - control (n=43)

Day Profile

Cortisol response to awakening

n=112; unpublished data
Summary

• Offspring of parent with BD have persistently elevated daytime cortisol

• Not simply due to the presence of a disorder

• Marker of vulnerability?
Are high cortisol levels associated with early environment influences?
Environmental influences

• Animal research has demonstrated that the HPA axis is calibrated by the prenatal and postnatal environment (Sanchez et al, 2001).

• Human studies suggest that early environmental adversity is associated with HPA sensitization later in life
  – O’Connor et al, 2004 Prenatal anxiety
  – Halligan et al, 2004 Postnatal depression
  – Essex et al, 2002 Postnatal stress
  – Nicolson, 2004 Parental loss

• Is the relationship between early environmental adversity and alterations in HPA function mediated by parenting?
Offspring: 6 – 13 years
Offspring: 13 – 21 years

Parenting practices

7-8 years
HPA reactivity

Controlling for
- Parent mental health
- Parent functioning, neuroticism
- Child mental health, behavior
- Adherence to sampling protocol
- Other sampling factors (i.e. time of awakening, etc).
Both parents completed the Parenting Dimensions Inventory (Slater & Power, 1987):

- **Support**: the affective quality and nurturance
- **Structure**: the organization and consistency
- **Control**: the type and frequency of disciplinary practices
Two measures of HPA reactivity in adolescence (Time 2)

- Rise in cortisol following awakening
- Cortisol response to the Trier Social Stress Test
Cortisol rise following awakening

Multiple regression, cort AUC; parent structure: $\beta=-0.36; p<0.05, n=54$; Ellenbogen & Hodgins, 2009
Trier Social Stress Test

Relaxation
30 min.

Anticipation
10 min.

Public Speech/
Mental arithmetic
10 minutes
- in front of 2 “experts”

Recovery
45 min.

10 Saliva samples
Cortisol response to psychosocial stress

Multiple regression, cort AUC; parent structure: $\beta=-0.33; p<0.05$, $n=46$; Ellenbogen & Hodgins, 2009
Summary

• Early environmental predictors

  – Parental organization and consistency during CHILDHOOD predicts CORT reactivity in ADOLESCENCE

  – Consistent with the view that early environmental influences sensitize developing psychobiological systems IN HUMANS
Are high cortisol levels associated with concurrent environmental influences?
Interpersonal stress and the affective disorders

- Stress generation theory (Hammen)

- At risk individuals are exposed to increased chronic and episodic interpersonal stress (Hammen, 1991; Adrian and Hammen, 1993; Rudolph et al, 2000; Ostiguy et al, 2009)

- Interpersonal stress predicts depression (Eberhart & Hammen, 2006).
Question

- Are high risk offspring more biologically sensitive to interpersonal stress occurring in the natural environment than low risk offspring?
### Sample

<table>
<thead>
<tr>
<th></th>
<th>Offspring of BD parents</th>
<th>Offspring of control parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>Gender</td>
<td>36M/26F</td>
<td>28M/32F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.3 ± 3.4 (14-28)*</td>
<td>18.7 ± 3.2 (14-28)</td>
</tr>
<tr>
<td>Number (%) affective dx: <strong>lifetime</strong></td>
<td>20 (32%) *</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Number (%) affective dx: <strong>current</strong></td>
<td>5 (8%)*</td>
<td>0</td>
</tr>
<tr>
<td>Number (%) non-affective dx: <strong>lifetime</strong></td>
<td>22 (35%) *</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Number (%) non-affective dx: <strong>current</strong></td>
<td>15 (24%)*</td>
<td>6 (10%)</td>
</tr>
</tbody>
</table>

* p < 0.05
Methods

• UCLA Life Stress interview
  – Chronic....clinician rated
  – Episodic.... team ratings (blind)

• Structured Clinical Interview for DSM-IV and Kiddie-SADS

• Cortisol sampling in the natural environment
  – 3 days, 7 samples / day
  – objective compliance
Predicting cortisol

- Predictors
  - Chronic (Episodic) Stress
  - Group (OBD vs control)
  - Lifetime affective disorders
  - Gender
  - Age
  - Group X Stress \(\rightarrow\) Increased biological sensitivity

- Dependent measures
  - AUC awakening and daytime cortisol
Interpersonal chronic stress

Chronic Stress X Group interaction: $\beta = -0.36; \ p<0.01$; Ostiguy et al, 2011
Interpersonal episodic stress (severity)

Episodic Stress X Group interaction: $\beta = -0.28$; $p < 0.05$:
Ostiguy et al, 2011
Summary and conclusions

- Increased reactivity at awakening and higher daytime cortisol levels in the offspring of parents with BD exposed to high interpersonal stress
- The relationship was not present in controls

- Biological sensitivity to naturalistic interpersonal stress relative to controls
Implications

• Consistent with Ellis and Boyce’s (2008, 2005) view of a “biological sensitivity to context”

• Are high cortisol levels, therefore, maladaptive?
Cortisol levels and the prospective development of affective disorders

Logistic regression, controlling for past disorders and risk status, odds ratio 2.1; p< 0.05; Ellenbogen et al, 2011
Final summary

• The adolescent offspring of parents with BD have persistently elevated HPA activity

• High cortisol levels arise, in part, from exposure to family stress and parenting style in childhood

• High cortisol levels arise, in part, from a biological sensitivity to naturalistic stress in high risk offspring

• Increased sensitivity to stress may be an important risk mechanism
Take-home message

Good hormones $\rightarrow$ Bad hormones

Normal adaptations of the HPA axis to a stressful and chaotic environment evolve…..

….into changes that later become a vulnerability factor for an affective disorder
Clinical implications

- Pay attention to offspring (ask parents with BD about their children)

- (Preventative) interventions should probably occur early and target non-affective symptoms. Need empirical studies

- Targeted stress-coping interventions may be particularly useful in this population. Need empirical studies
THANK YOU