Stress and vulnerability to depression
- An allostatic perspective

Cyril Rivat
Université de Montpellier

cyril.rivat@umontpellier.fr

The physiological response of stress

Stress describes experiences that are challenging emotionally and physiologically

« Good stress »

● Experiences that are of limited duration
● Sense of accomplishment
● Physiologically adapted

« Bad stress »

● Experiences that are of prolonged or recurrent
● Sense of control is lacking
● Emotionnaly/physically
Hans Selye (1907-1982) was the first to define the stress and the stress response.

General adaptation syndrome from Hans Selye

Our stress response system defends, then fatigues.

According to Hans Selye, the body reacts in three phases to a stressor. In the first phase, alarm, the body mobilizes to confront the threat, which temporarily expands resources and lowers resistance. In the resistance phase, the body is actively confronting the threat and resistance is high. If the threat continues, the body moves into exhaustion.
The physiological response of stress

Adaptive response (Fight or flight)

The physiological response of stress

Effects of cortisol on the organism

CRH - Corticotropin-releasing hormone
ACTH - Adrenocorticotropic hormone
The physiological response of stress

Effects of cortisol on brain structures

The physiological response of stress

Effects of cortisol on cognitive functions brain
The pathophysiological response of stress

Major depressive disorder (MDD) is one of the most prevalent and debilitating psychiatric disorders.

In 2014, 7% of Americans over the age of 12 reported depression within the past two weeks (Center for Disease Control and Prevention, 2014)

In 2003 the World Health Organization estimated a global lifetime prevalence of 16%

The economic burden of MDD in the United States in the year 2000 was estimated to be 83.1 billion dollars:

- 26.1 billion dollars (31%) directly related to medical costs,
- 5.4 billion dollars (7%) related to suicide,
- 51.5 billion dollars (62%) due to workplace costs including absenteeism and reduced productivity
Diagnosis of major depression

Based on the DSM-V

**Note:** Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). *(Note: In children and adolescents, can be irritable mood.)*

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. *(Note: In children, consider failure to make expected weight gain.)*

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

At least 5 out of 9 symptoms during the same period of two weeks

---

Diagnosis of major depression

**Hamilton Rating Scale for Depression**

At least 5 symptoms during the same period of two weeks
Pathophysiology of depression

Different mechanisms responsible for the occurrence of MDD

- Monoamine neurotransmission
- HPA axis dysregulation and the stress response
- Inflammation
- Reduced neurogenesis and neuroplasticity

Interaction between stress, inflammation, and neurogenesis

From Raison et al., TRENDS in Immunology Vol.27 No.1 January 2006
Stress and depression

Stress

- Physiological response
- Pathological response
- Vulnerability

Sustained or repetitive stress in adulthood may trigger maladaptive changes in some individuals. It acts as a trigger for mechanisms that leave predisposed individuals at increased risk of illness.
Allostasis

Allostatic responses are those physiological changes that occur in response to environmental perturbations.

They represent an important positive role in helping an organism adapt to a changing environment.

<table>
<thead>
<tr>
<th>Homeostasis</th>
<th>Allostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant or oscillating set point</td>
<td>Changing set point</td>
</tr>
<tr>
<td>Physiologic equilibrium</td>
<td>Compensated equilibrium</td>
</tr>
<tr>
<td>No or little anticipation of demand</td>
<td>Extensive anticipation of demand</td>
</tr>
<tr>
<td>No adjustment base on history</td>
<td>Adjustment based on history</td>
</tr>
<tr>
<td>Adjustment carries no price</td>
<td>Adjustment and accommodation</td>
</tr>
<tr>
<td></td>
<td>carry a price (allostatic load)</td>
</tr>
<tr>
<td>No pathology</td>
<td>Potentially leads to pathology</td>
</tr>
</tbody>
</table>

Allostasis = the active process by which the body responds to daily events and maintains homeostasis

« Stability through change »
Central role of the brain in the allostasis and the behavioral and physiological response to stressors

Allostasis and allostatic load

Stress Response

STOP
- Take a breath
- Observe / Open
- Proceed

Allostasis
Some stress can be energizing and toning to the system. Body systems adjust well to stressors without over taxing resources.

Stress Reaction

Allostatic Load
Body systems achieve a kind of balance, but everything is working too hard and we begin to slowly break down.

Allostatic load refers to the wear and tear that result from either exaggerated stress or from inefficient management of allostasis.
Allostasis and allostatic load

Four types of allostatic load

Vulnerability to disease

Proper functioning of the stress and glucocorticoid system is critical for normal brain function but excessive and long-term activation of this system can lead to disease.
Allostasis and allostatic load

Alteration of synaptic plasticity in the hippocampus

Acceleration of aging process

Allostasis and allostatic load

Development of long-term vulnerability

From McEwen et al., nature neuroscience VOLUME 18 | NUMBER 10 | OCTOBER 2015 1353
Modelization of vulnerability to depression

Model of social defeat

1. Anticipation (30 mn)  2. Confrontation (15 mn)

Alteration in the HPA axis

Depression model (Becker et al., 2008 Molecular Psychiatry)
Anxiety model (Becker et al., 2001 J. Neurosci.)

Modelization of vulnerability to depression

Neurobiology of Disease

Vulnerability to Depression: From Brain Neuroplasticity to Identification of Biomarkers

Aurélie Blageot,1,2,3*, Cyril Rivat,1,2,3* Elodie Bouvier,1,2,3* Jenny Molet,1,2,3 Amandine Mouchard,1,2,3 Brigitte Zeau,1,2,3 Christophe Bernard,1* Jean-Jacques Benaliel,1,2,3 and Chrystel Becker1,2,3,6

1Université Pierre et Marie Curie-Paris 6, UMR 973, Pain Team, Site Pitié-Salpêtrière, Paris 75013, France; 2Inserm, U 975, Paris 75013, France; 3CNRS, UMR 7225, Paris 75013, France; 4Inserm, U 751, Marseille 13385, France; 5Service de Biochimie Endocrinienne et Oncologique, Hôpital de la Pitié-Salpêtrière, Paris 75013, France; and 6Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris 75006, France

OPEN

Molecular Psychiatry (2016) 00, 1–13

www.nature.com/mp

ORIGINAL ARTICLE

Nrf2-dependent persistent oxidative stress results in stress-induced vulnerability to depression

E Bovier1,2,3, F Brouillard4,5, J Molet1,2,3, D Claverie1,2,3,6, MM Cabungcal7, N Cresto1,2,3, N Doligez1,2,3, C Rivat1,2,3, KQ Oo1, C Bernard4

1,2,3,6 and C Becker1,2,3,6,10
Modelization of vulnerability to depression

« Double hit » model

DS
7 days 4 days

Rest
1 month

CMS
3 weeks

5 days

7 days

57 days

a

Adrenal gland weight:
C: 10.28 ± 0.31 mg/100g
DF: 13.62 ± 0.45 mg/100g

b

Serum glucose (mg/dl)
c

Hippocampal volume:
C: 9.15 ± 0.26 mm³
DF: 8.10 ± 0.31 mm³

Modelization of vulnerability to depression

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday-Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>housing in small cage (10&quot;x16&quot;x15 cm) during 1h</td>
<td></td>
<td></td>
<td></td>
<td>cycle dark/light</td>
</tr>
<tr>
<td>Afternoon</td>
<td>shaking (5 min)/rest (2 min)/shaking (5 min)/rest (2 min)</td>
<td>housing in small cage during 30 min with water (2 cm high)</td>
<td>rat 1 in cage of rat 2 (and vice-versa) from 1 pm to 17 pm</td>
<td>shaking (5 min)/rest (2 min)/shaking (5 min)/rest (2 min)</td>
<td>rat 1 in cage of rat 2 (and vice-versa) from 1 pm to 17 pm</td>
</tr>
<tr>
<td>Night</td>
<td>cage inclination (45°)</td>
<td>wet bedding</td>
<td>cage inclination (45°)</td>
<td>wet bedding</td>
<td>every 3 hours</td>
</tr>
</tbody>
</table>

CMS procedure does not produce depressive-like behaviors
Modelization of vulnerability to depression

Forced-swimming test

Identification of two different populations after the CMS procedure

NR = Non responders
R = Responders

60% 40%

a. SSP (D57)

Adrenal gland weight:
C: 10.07 ± 0.40 mg/100g
NR: 9.28 ± 0.23 mg/100g
R: 12.59 ± 0.19 mg/100g

b. SSP (D57)

c. SSP (D57)
Modelization of vulnerability to depression

The level of serum BDNF is a biomarker of vulnerability to depression

Modelization of vulnerability to depression

SD induces sustained alteration of dendritic arborization in the hippocampus of responder animals
Modelization of vulnerability to depression

Effects of BDNF agonist

7,8-DHF icv

BDNF agonist reverses SD-induced sustained alterations and vu of dendritic arborization in the hippocampus of responder animals

Modelization of vulnerability to depression

Blugeot, Rivat et al., JNS, 2011