STRESS AND DEPRESSION

Stress and Depression

- Depression ranks among the largest contributors to morbidity and lost productivity in the world.
- Among 60 countries (apx. 250.000 participants), depression produces larger decline in health than other chronic diseases such as asthma, diabetes, arthritis.
- Affects 15-20% of the population.

Major Depressive Disorder

- Impairment in functioning for most of the day, and nearly every day, for two weeks or more.
  - Depressed mood, sadness, or emptiness
  - Loss of pleasure in previously enjoyed activities
  - At least four of additional changes in functioning:
    - Alteration in weight, atypical sleep patterns, restlessness, low energy, feelings of worthlessness, difficulty concentrating, or preoccupation with death or suicide

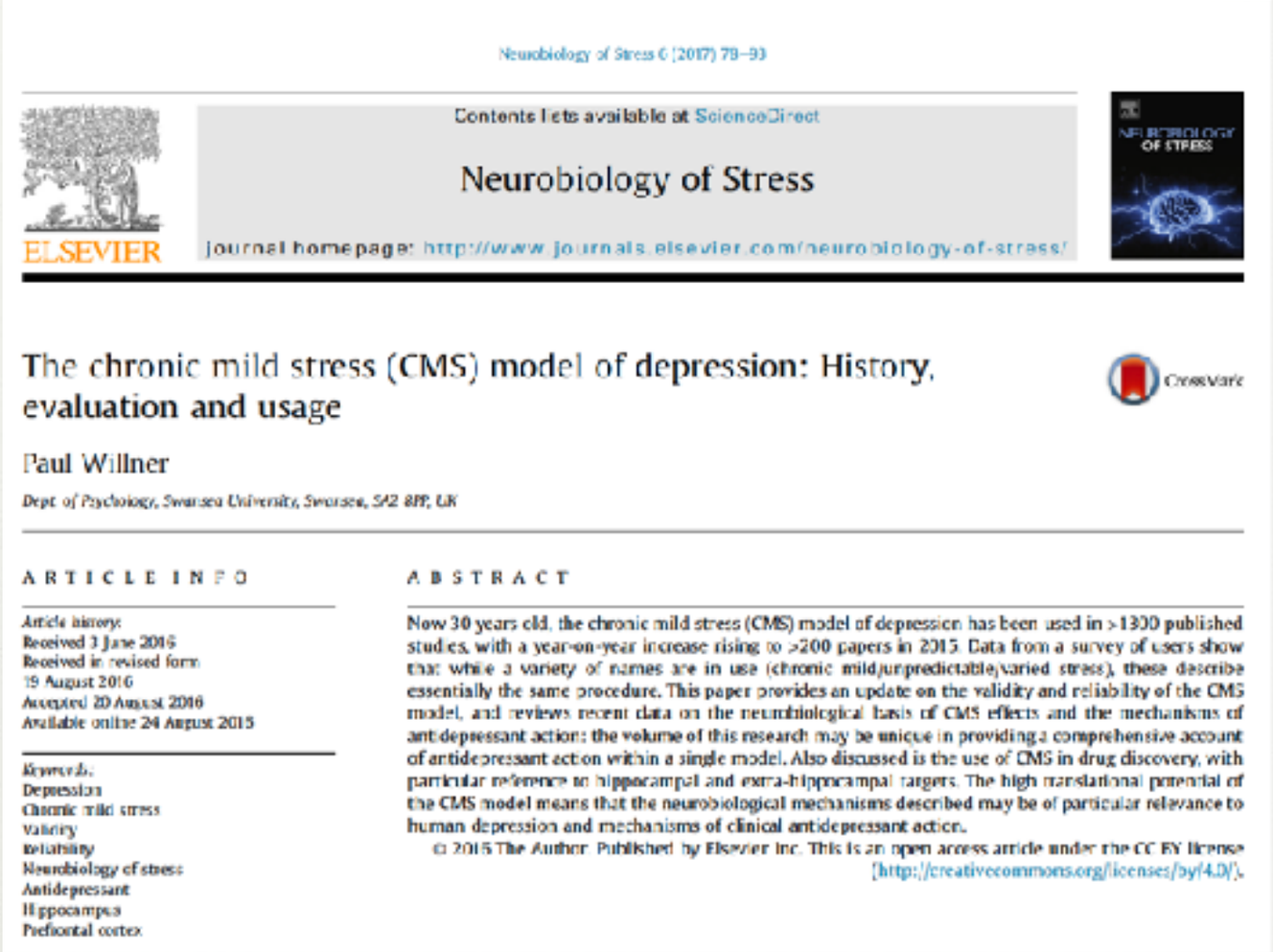
Major Depressive Disorder

Stress and Depression

- Stress and depression is linked.
- Chronic stress result in wear and tear on the body and the brain.
- In genetically vulnerable individuals, stress precipitate depression.
    - Recent life stressors
    - Cumulative effects of stress
    - Early life stress

Chronic Mild Stress (CMS) and Depression

- In CMS model (Katz et al., 1980), rats are exposed to sequentially a variety of stressors.
    - Noisy environments, unpredictable house conditions, changes in light dark cycles
    - Hedonic measures



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The chronic mild stress (CMS) model of depression: History, evaluation and usage

Paul Willner

Dept. of Psychology, Swansea University, Swansea, SA2 8PP, UK

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ABSTRACT

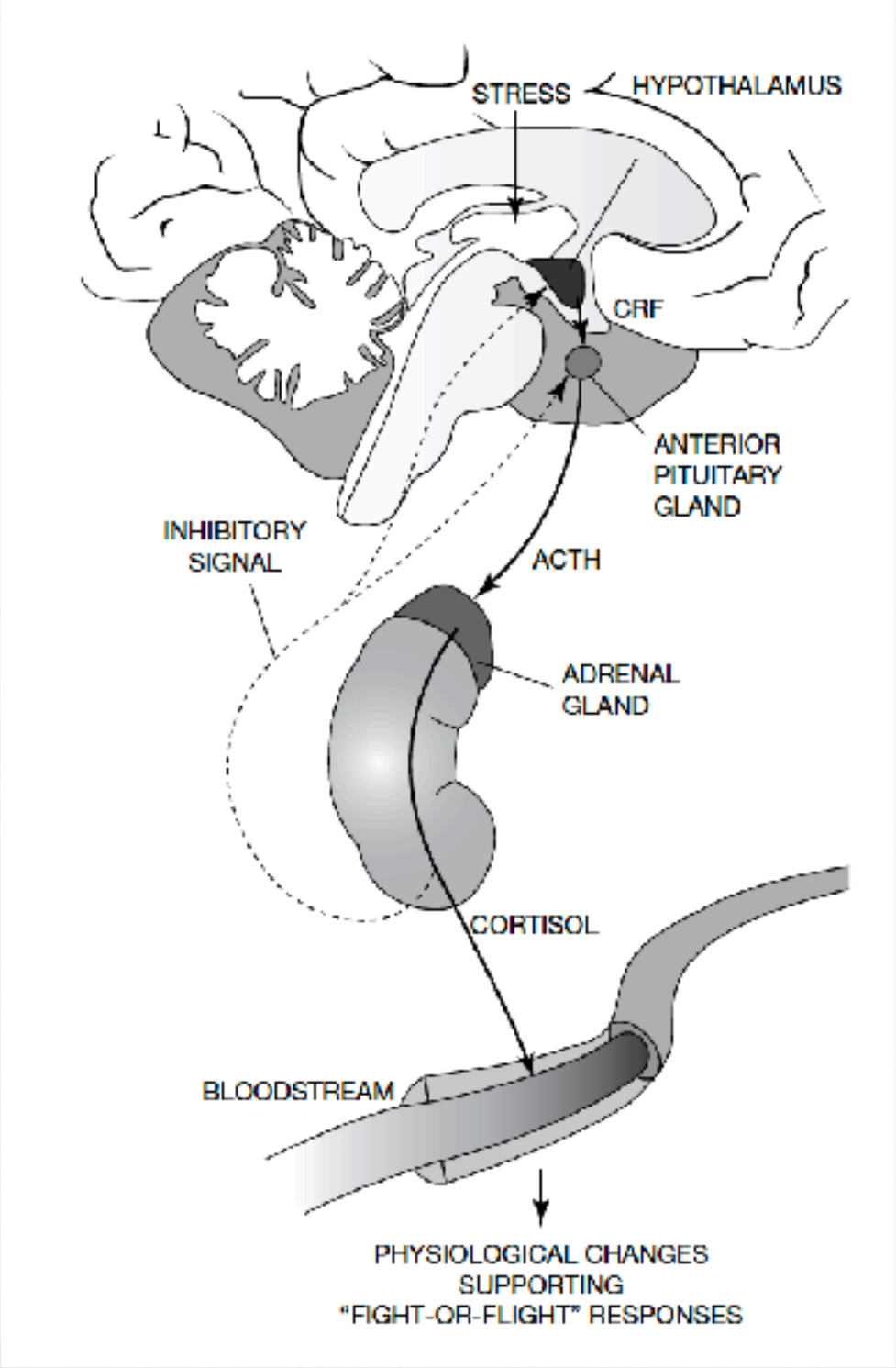
Now 30 years old, the chronic mild stress (CMS) model of depression has been used in >1300 published studies, with a year-on-year increase rising to >200 papers in 2015. Data from a survey of users show that while a variety of names are in use (chronic mild/unpredictable/varied stress), these describe essentially the same procedure. This paper provides an update on the validity and reliability of the CMS model, and reviews recent data on the neurobiological basis of CMS effects and the mechanisms of antidepressant action: the volume of this research may be unique in providing a comprehensive account of antidepressant action within a single model. Also discussed is the use of CMS in drug discovery, with particular reference to hippocampal and extra-hippocampal targets. The high translational potential of the CMS model means that the neurobiological mechanisms described may be of particular relevance to human depression and mechanisms of clinical antidepressant action.

Type of Stress and Clinical Representation

- Recent life stressor;
  - Guilt, anhedonia, sadness, appetite loss
- Unable to identify a specific stressor;
  - Fatigue, hypersomnia

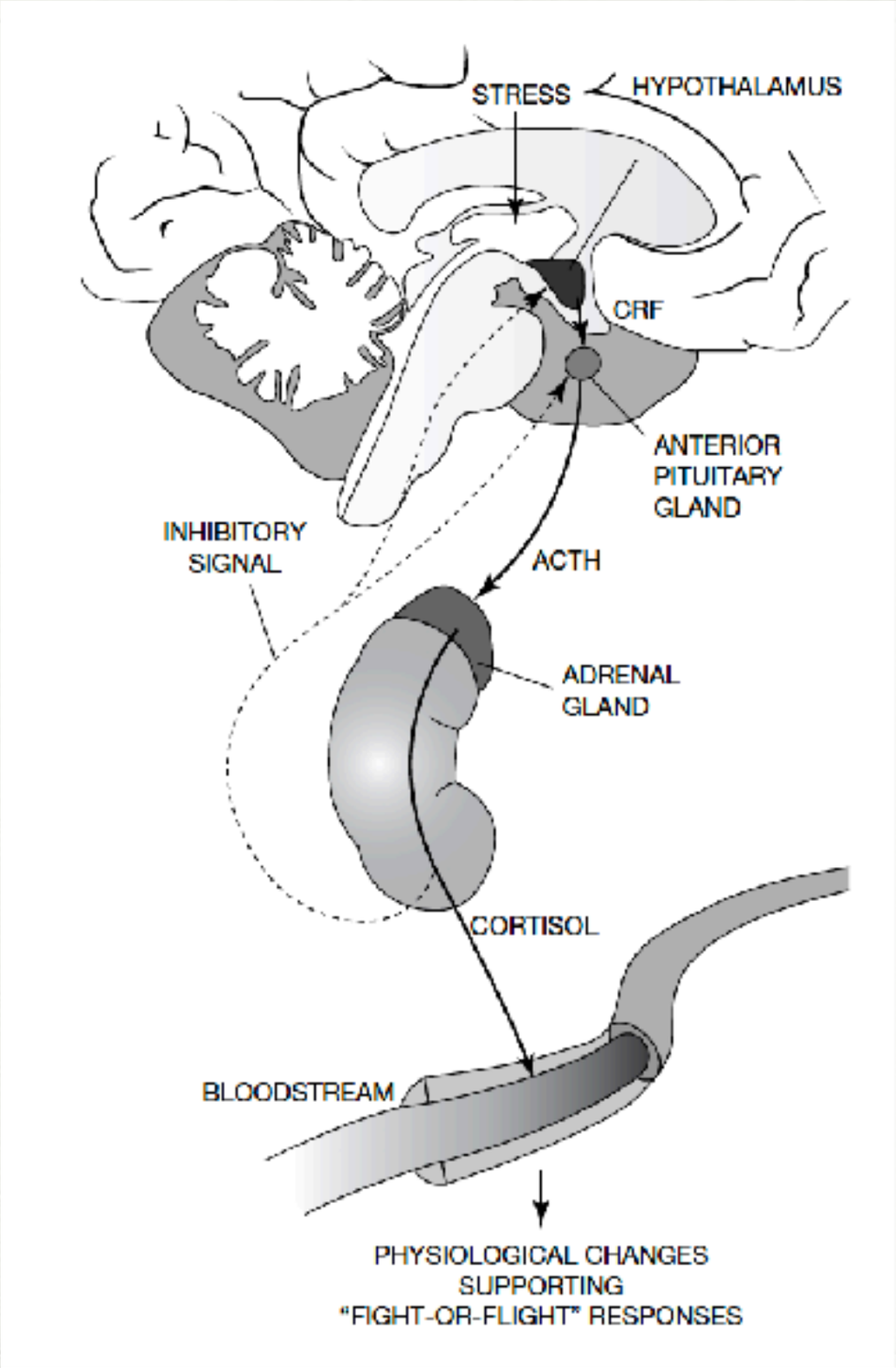
BASIC BIOLOGY OF STRESS RESPONSE

- Interoceptive or exteroceptive stressors may create a threat to the organism's homeostasis.
- Body activates two separate but interrelated systems.
    - SAM and HPA



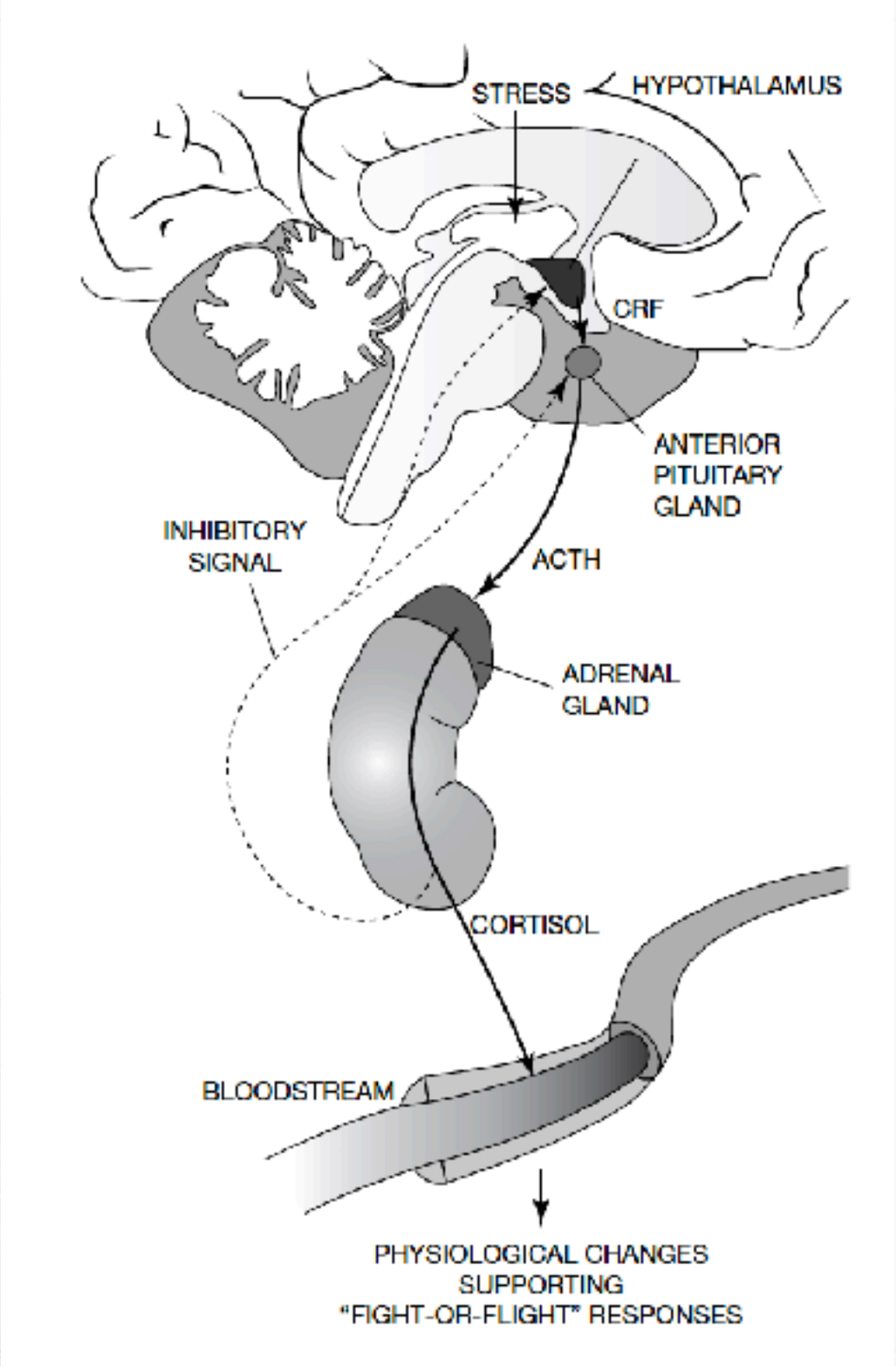
Stress Response and Depression

- SAM- within milliseconds but short live
- HPA- seconds to minutes but long live
- CRF provides key link between stress and depression.
- Intro-ventricular injection of CRF
    - Decreased libido, Reduced appetite, Weight loss, Sleep disturbances, Neophobia



HPA Axis and CRF

- Hyper-secretion of CRH;
  - Increased cortisol, glucose production, breakdown of lipids, gastrointestinal problems
  - Suicide ideation
  - Pituitary gland and adrenal glands enlargement
  - Reduction in size of hippocampus



HPA Axis and Depression

EVIDENCE FOR HYPOTHALAMUS–PITUITARY ADRENAL AXIS DYSFUNCTION IN DEPRESSION

1. Urinary free cortisol is increased in depression and returns to normal after resolution of depression.
2. Dexamethasone, a glucocorticoid antagonist, does not suppress cortisol to the same extent in severely depressed patients compared to normal.
3. Adrenal gland is enlarged in depressed patients when compared with normal individuals.
4. Pituitary gland is enlarged in depressed patients, especially in those with elevated HPA function.

Dinan TG, Scott LV. Anatomy of melancholia: focus on hypothalamic-pituitary-adrenal axis overactivity and the role of vasopressin. J Anat September 2005; 207(3):259–64 [Review].

SAM Axis and NE

EVIDENCE FOR NOREPINEPHRINE IN DEPRESSION

1. Depleting norepinephrine leads to depressive symptoms in patients on antidepressants.
2. Decreased norepinephrine transporter binding in locus coeruleus of depressed patients.
3. Polymorphism of norepinephrine transporter 182c is linked to risk for depression.
4. Norepinephrine transporter inhibitors that increase norepinephrine in the synapse treat depression.

Moret C, Briley M. The importance of norepinephrine in depression. Neuropsychiatr Dis Treat 2011;7(Suppl. 1):9–13. http://dx.doi.org/10.2147/NDT.S19619 [Epub 2011 May 31].

Stress Response and Serotonin

EVIDENCE FOR SEROTONIN IN DEPRESSION

1. Depleting tryptophan, a precursor for serotonin, in patients on antidepressants can induce depressive symptoms.
2. Serotonin transporter (5HTT) inhibitors that increase serotonin in the synapse treat depression.
3. Decreased serotonin metabolites in the spinal fluid of depressed patients.
4. 5HTT polymorphism related to risk of depression.
5. Altered serotonin receptors in the brains of depressed patients.

Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, et al. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. Arch Gen Psychiatry November 1994; 51(11):865–74.

Stress Response and Brain Derived Neurotrophic Factor (BDNF)

BRAIN-DERIVED NEUROTROPHIC FACTOR AND DEPRESSION

1. BDNF in hippocampus is reduced by stress in animal studies.
2. BDNF is increased by antidepressants in human blood.
3. Depression leads to reduced BDNF in blood.
4. BDNF modulates neurogenesis in the brain and in modifying neuroplasticity and that is believed to be the presumed mechanism.
5. Decreased peripheral BDNF levels and selected *BDNF* gene variants are associated with the risk of developing mood disorders in individuals with early trauma [9,10].
6. The combination of BDNF Met allele carrier status and exposure to trauma early in life predicted reduced gray matter in the hippocampus, lateral PFC and greater depression.
7. The *BDNF* gene is a risk locus for depression [11,12] and with antidepressant response [11,13].

Duman RS. Pathophysiology of depression: the concept of synaptic plasticity. Eur Psychiatry 2002;17(Suppl. 3):306–31 [14].

Early Life Stress and Depression

- 30-40% of depression is known to be heritable.
- Early life stress such as abuse and neglect make individuals vulnerable to CRH, ACTH, cathecolamine, glucocorticoid dysregulation.

Early Life Stress and Depression

- Rhesus monkeys that spent first 6 months in isolation
  - Exaggerated oral behaviors
  - Heightened fear and anxiety
  - Reduced ability to dealt with stressors

Levine, Wiener, & Coe, 1993

Early Life Stress and Depression

- Three conditions - CSF CRF
  - Low foraging demand
  - High foraging demand
  - Variable foraging demand
- Predictability and stability of mother-child bond is important.

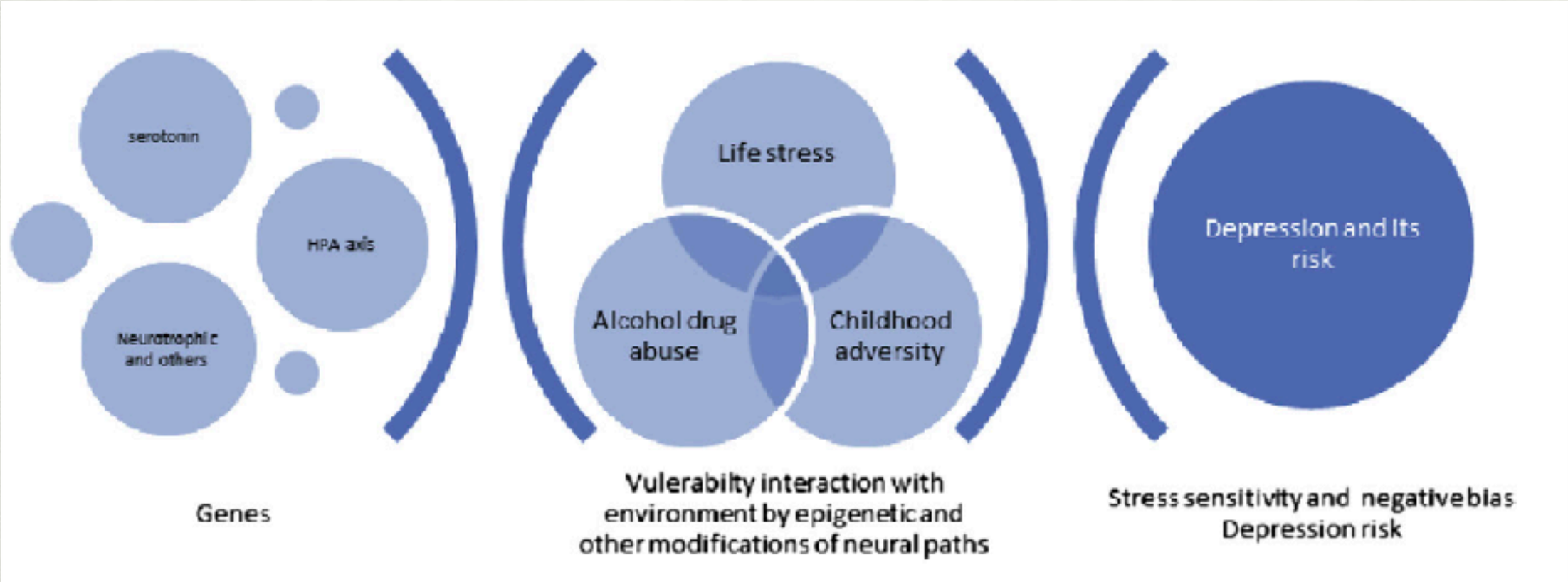
Coplan et al., 1996

Early Life Stress and Depression

- Parental loss (prior to age 16) and elevated cortisol secretion in public speaking task.
- No association between parental conflict and level of cortisol secretion.

Luecken, 1998; 2000

Integrative Model of the link between Stress and Depression



Amygdala	Orbital PFC	Medial PFC	Hippocampus
• Dendrite growth increase • Increased synaptic remodeling	• Dendritic branching increased	• Decreased dendrites • Decreased spine density	• Decreased neurogenesis • Decreased glia • Decreased spine density • aaaaaaaa dendrites