


Dysregulation of neurogenesis either alleviate or aggravate MDD and anxiety like behaviors

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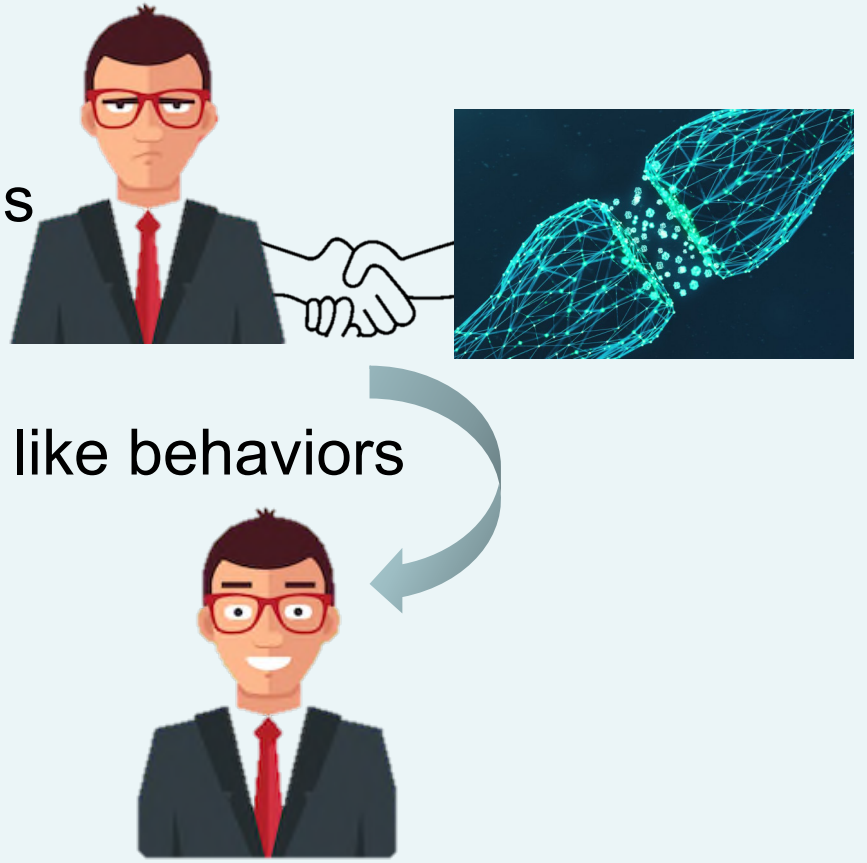
Outline

- Introduction to Depression and Anxiety like behaviors
- Overview of Adult Neurogenesis
- Key players and pathways involved in Neurogenesis
- Epigenetic regulation of Neurogenesis
- Dysregulation Neurogenesis and MDD and Anxiety like behaviors
- Summary
- References



Depression

- What is Depression?
- Symptoms
  - Loss of interest in daily activities
  - Dysfunctional sleep
  - Recurrent thoughts of death (Anderson et al. 2003; Ben-Zeev et al. 2012)
- Severity
  - 54 million YLDs worldwide
  - 10th leading cause of death in USA
  - 20% MDD patients commit suicide

  (Pratt et al. 2009)

“

A teen who gets 6 hours or less of sleep triples their risk **of depression**

Depression

- Prevalence
  - Worldwide >350 million
  - Sri Lanka > 800,000 people

(WHO 2015)

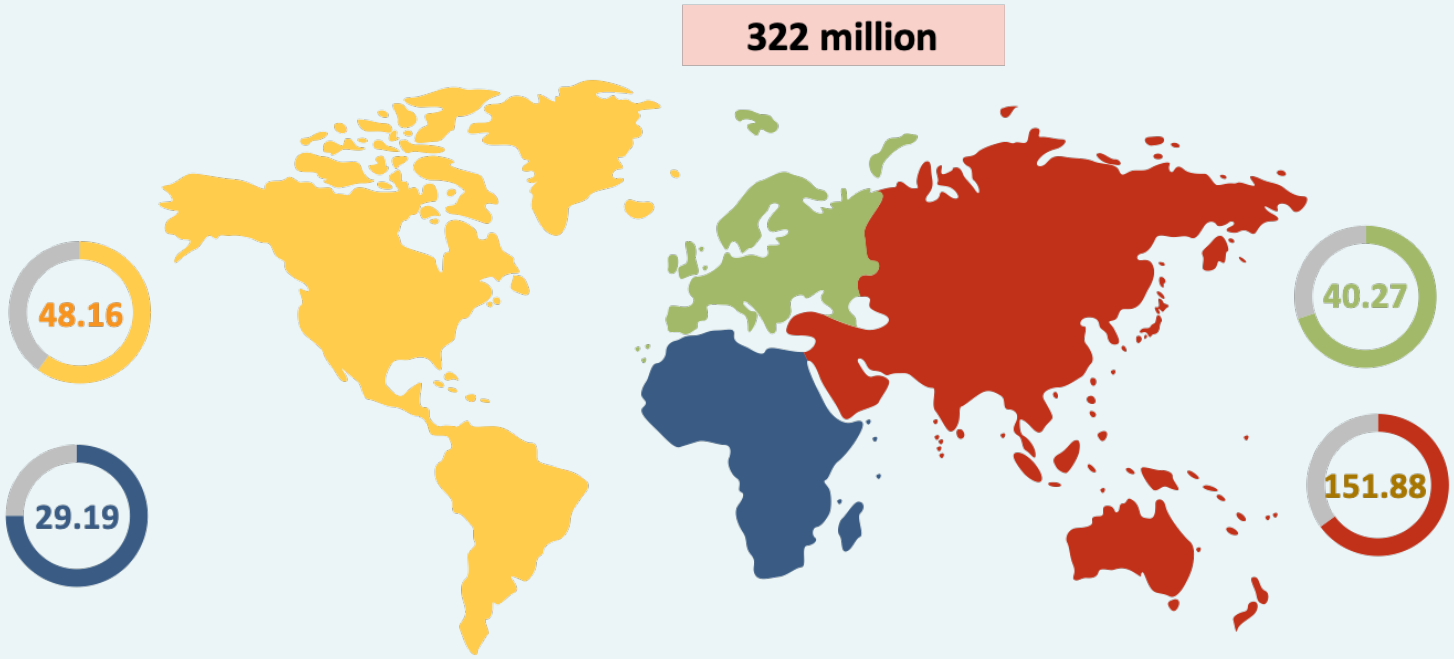


Figure 1 Prevalence of MDD in different parts of the world

Anxiety

- What is Anxiety?
- Symptoms
  - worry, excessive nervousness
  - somatic complaints
  - fear of heights and public speaking

(Ettinger et al. 1998; Bell-Dolan et al. 1990)

- Severity
  - High mortality and IIry morbidity
  - 24.6 million YLDs worldwide

  (Almeida et al. 2014; Chaudhury et al. 2006)

Anxiety

- Prevalence
  - Worldwide >264 million
  - Sri Lanka > 600,000 people

(WHO 2015)

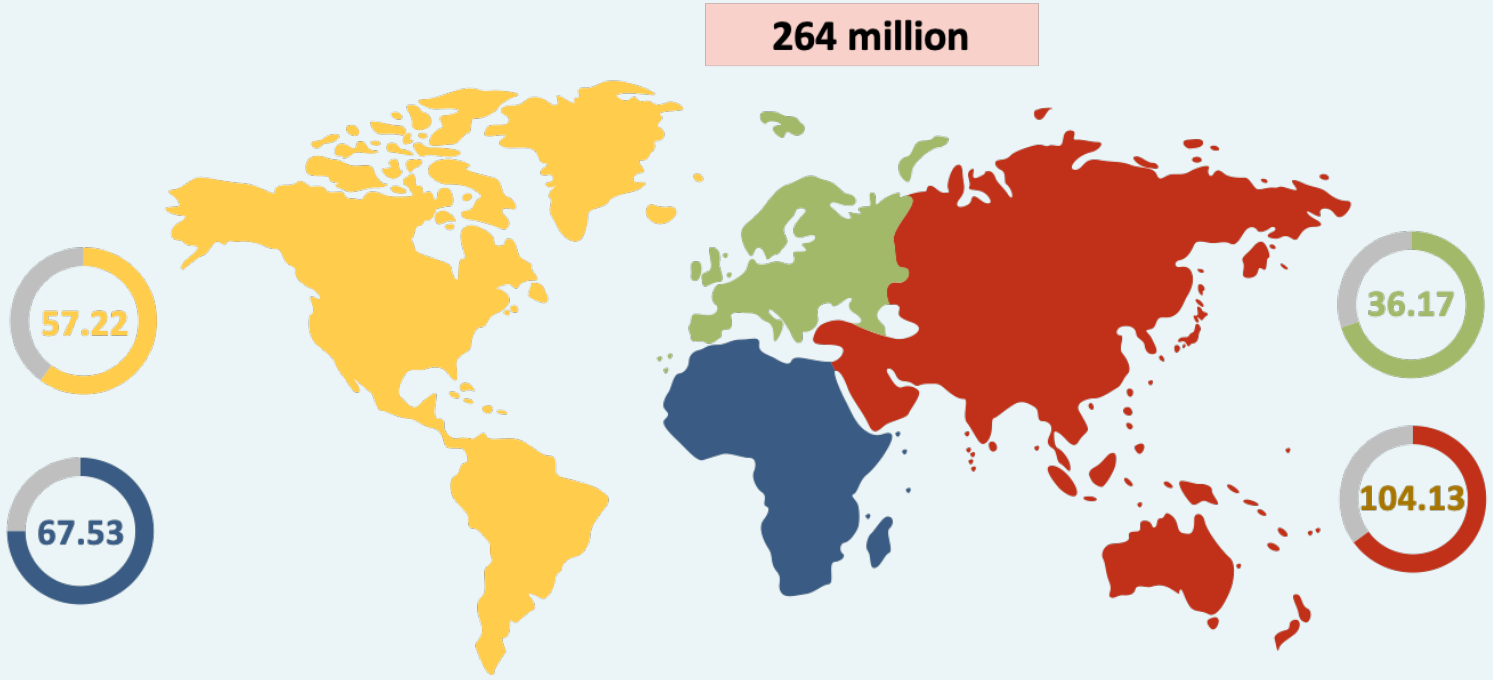
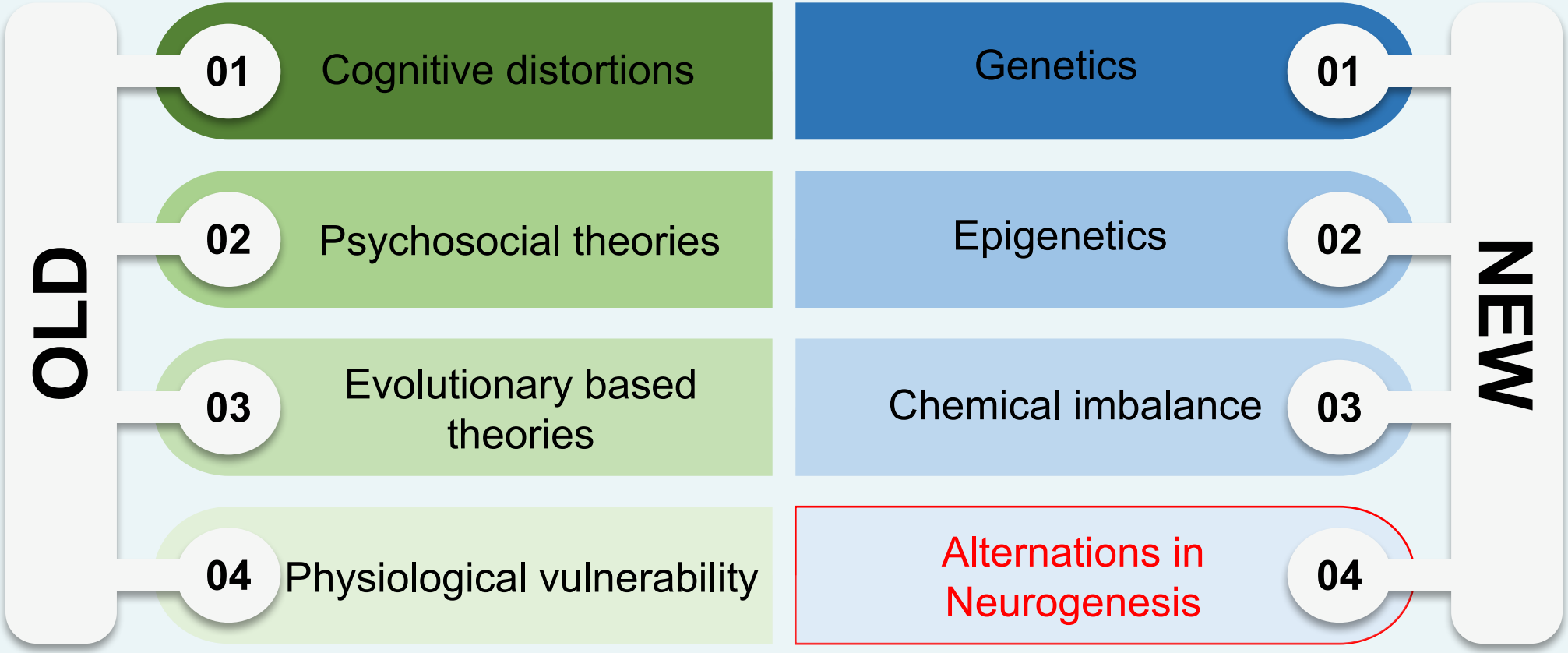


Figure 2 Prevalence of Anxiety in different parts of the world

Etiology of MDD and Anxiety like behaviors



(Allen and Badcock 2006; Billings et al. 1983; Silverman 1976)

Adult Neurogenesis

- The process of generating functionally integrated new neurons from progenitor cells (Kempermann et al. 2003; Petreanu and Alvarez-Buylla 2002)
- Takes place in 2 regions of the brain
  - SGZ of hippocampus → Interneurons
  - SVZ of olfactory bulb → Excitatory granules
- Electrically active and generate action potentials
- Integration of newborn neurons into existing neural network is extremely regulated
- Neurogenesis in both regions follow the same steps

(Kohwi et al. 2007; Cameron and McKay 2001; van Praag et al. 2002)

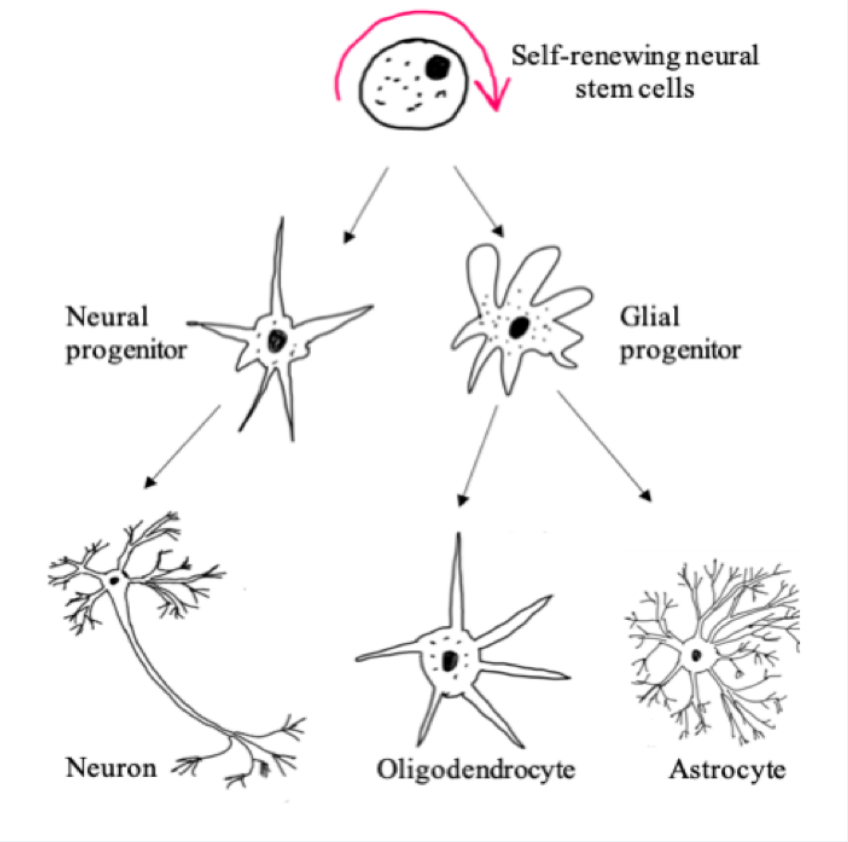
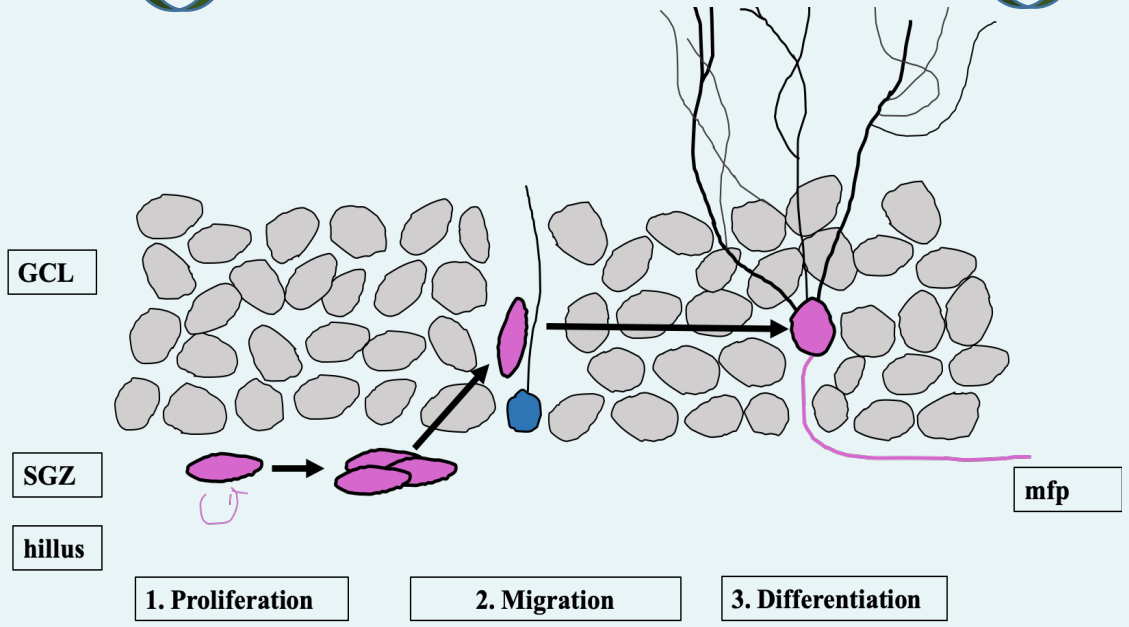


Figure 3 Generation of neurons and glial cells from NSCs

Process of adult neurogenesis

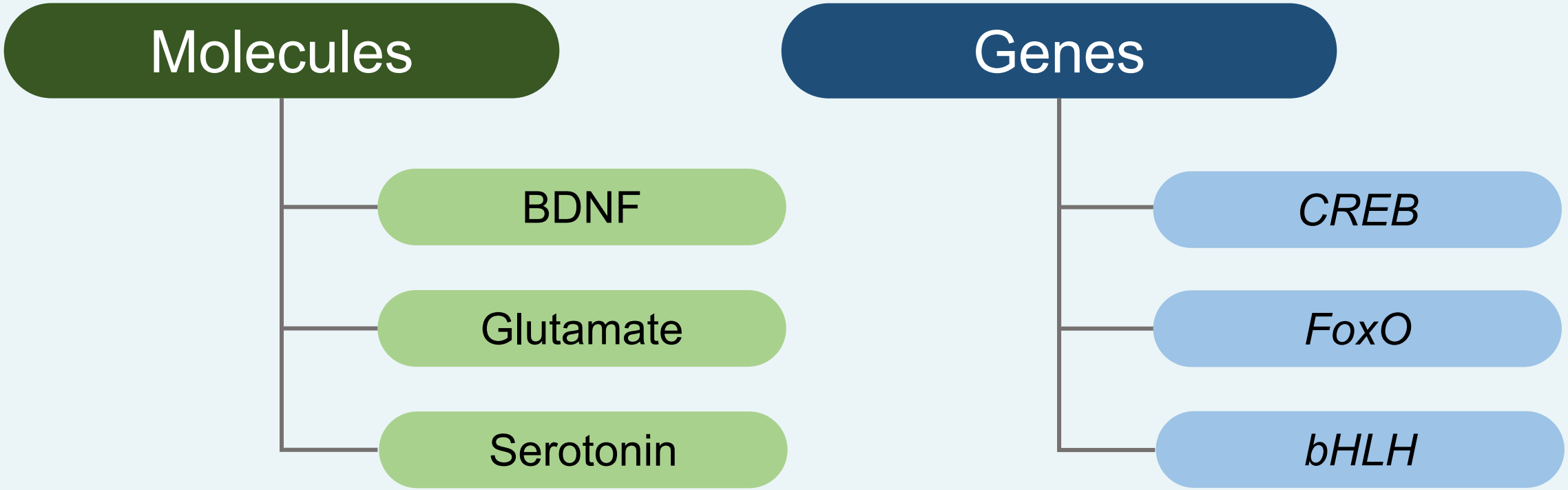
Proliferation of NSCs → Rapidly amplifying progenitor cells → Immature neurons → Migration to final location → Growth formation of synapses with other neurons → Fully functional neuron



(Goncalves et al. 2016; Hastings and Gould 1999; Seri et al. 2001)

Figure 4 Model representing the adult neurogenesis in the granule cell layer of hippocampus

Key molecules and genes involved in Neurogenesis



BDNF

- Neural growth Neurotrophin (Lie et al. 2004)
- Role
  - Growth
  - Proliferation
  - Survival and differentiation of neural progenitor cells
  - Activity- dependant synaptic plasticity (Scharfman et al. 2005)
- Effects neurogenesis as well as migration of neurons
- Major receptor- TrkB receptor (Li et al. 2008)

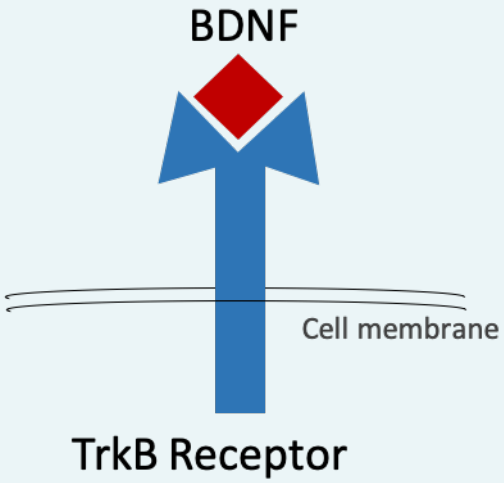


Figure 5 BDNF and its receptor

Mechanism of Action

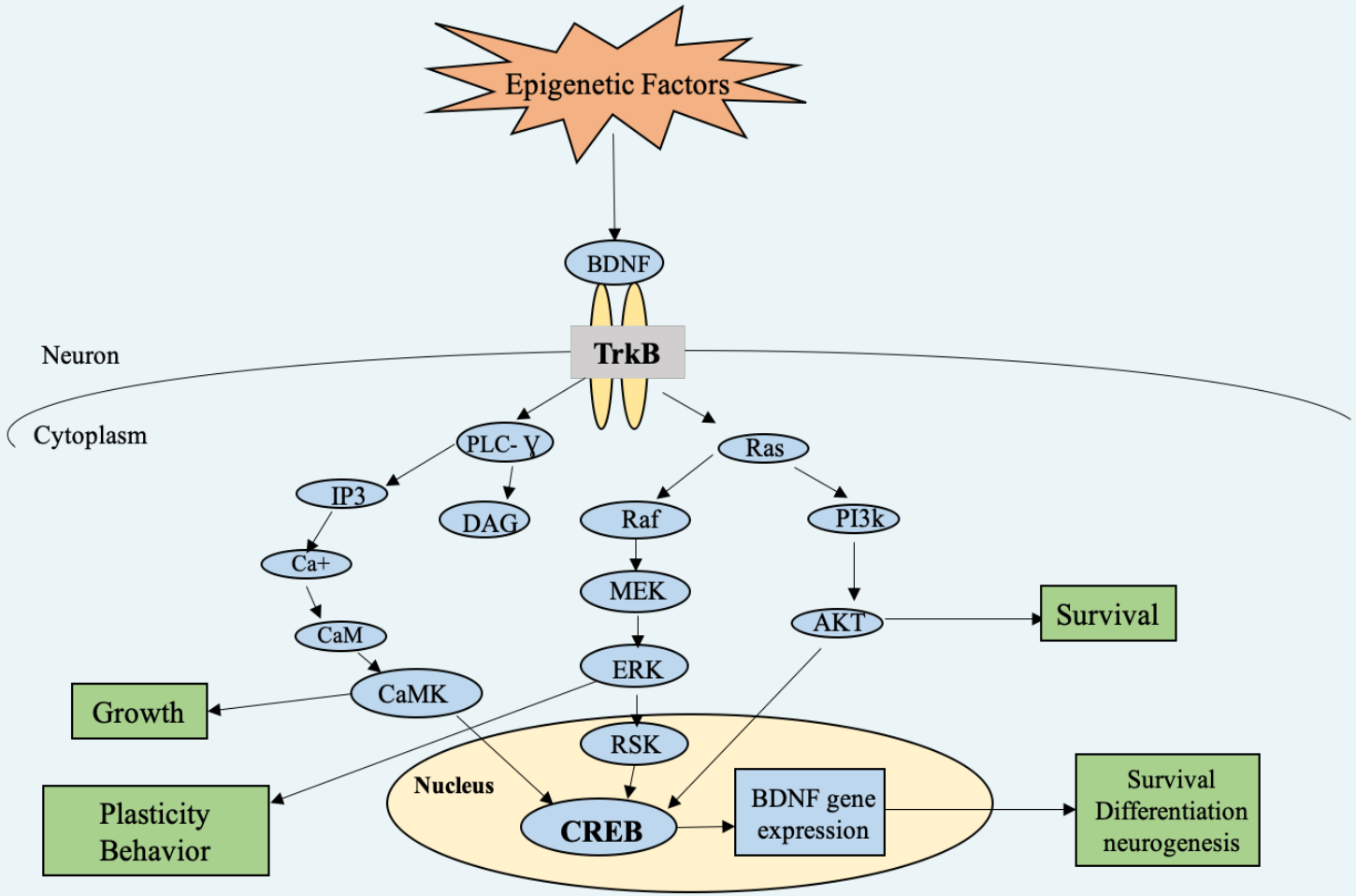


Figure 6 BDNF/TrkB signaling pathway

Overall affect of BDNF

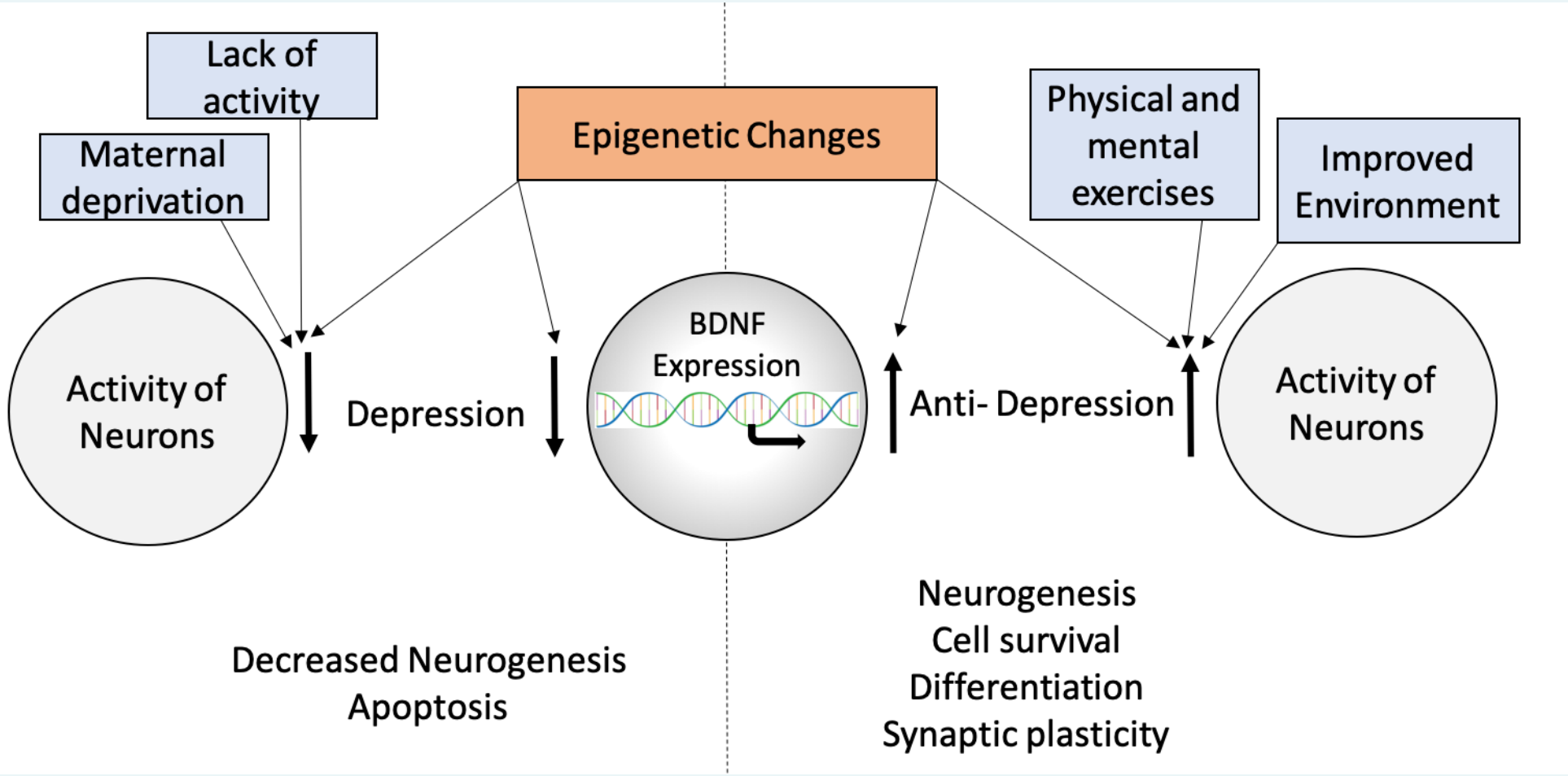


Figure 7 The overall effect of epigenetic factors on the expression of *BDNF*

Glutamate

- Amino acid – Neurotransmitter (Mitani et al. 2006)
- Role
  - learning, memory and regulating neuroplasticity

    (Malenka and Nicoll 1999)
- Receptors
  - ionotropic (iGluRs) - e.g. NMDA, AMPA
  - metabotropic receptors (mGluRs) – e.g. mGluR5 (Esposito et al. 2005)
- Biomarker of mood disorders
- Major neurotransmission system ⇢ Glutamate-GABA system (Sasaki et al. 1999)

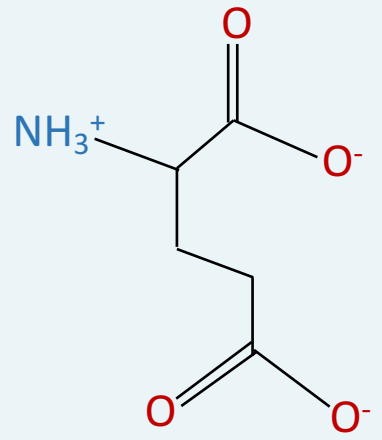


Figure 8 Structure of glutamate

Mechanism of action

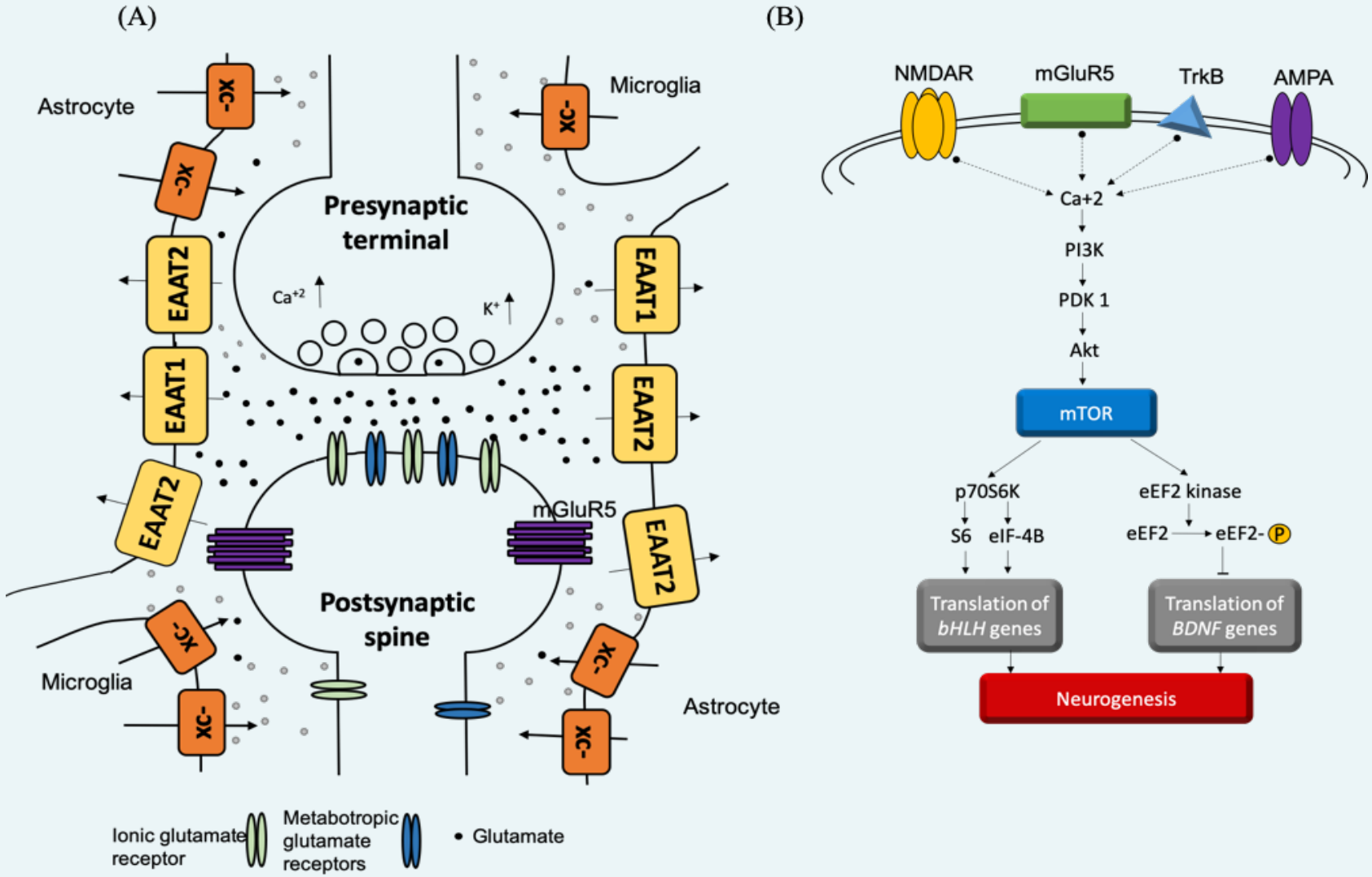


Figure 9 (A) Glutamate uptake by glutamate receptors (B) mTOR signaling pathway

Serotonin

- 5-hydroxytryptamine (5-HT), is a catecholamine
- Neurotransmitter and a neuromodulator (Herve et al. 1995)
- Role of serotoninergic systems
  - maintain the feelings of anxiety, fear, depression and helplessness (Meltzer 1990)
- Tryptophan experiment
  - tryptophan $\xrightarrow{\text{TPH 2}}$ serotonin (Robinson et al. 2012)
- 3 major receptors
  - The 5-$HT_{1A,1B,1D}$, 5-HT_4 , 5-HT_2 (Dwivedi et al. 2001)

Mechanism of action

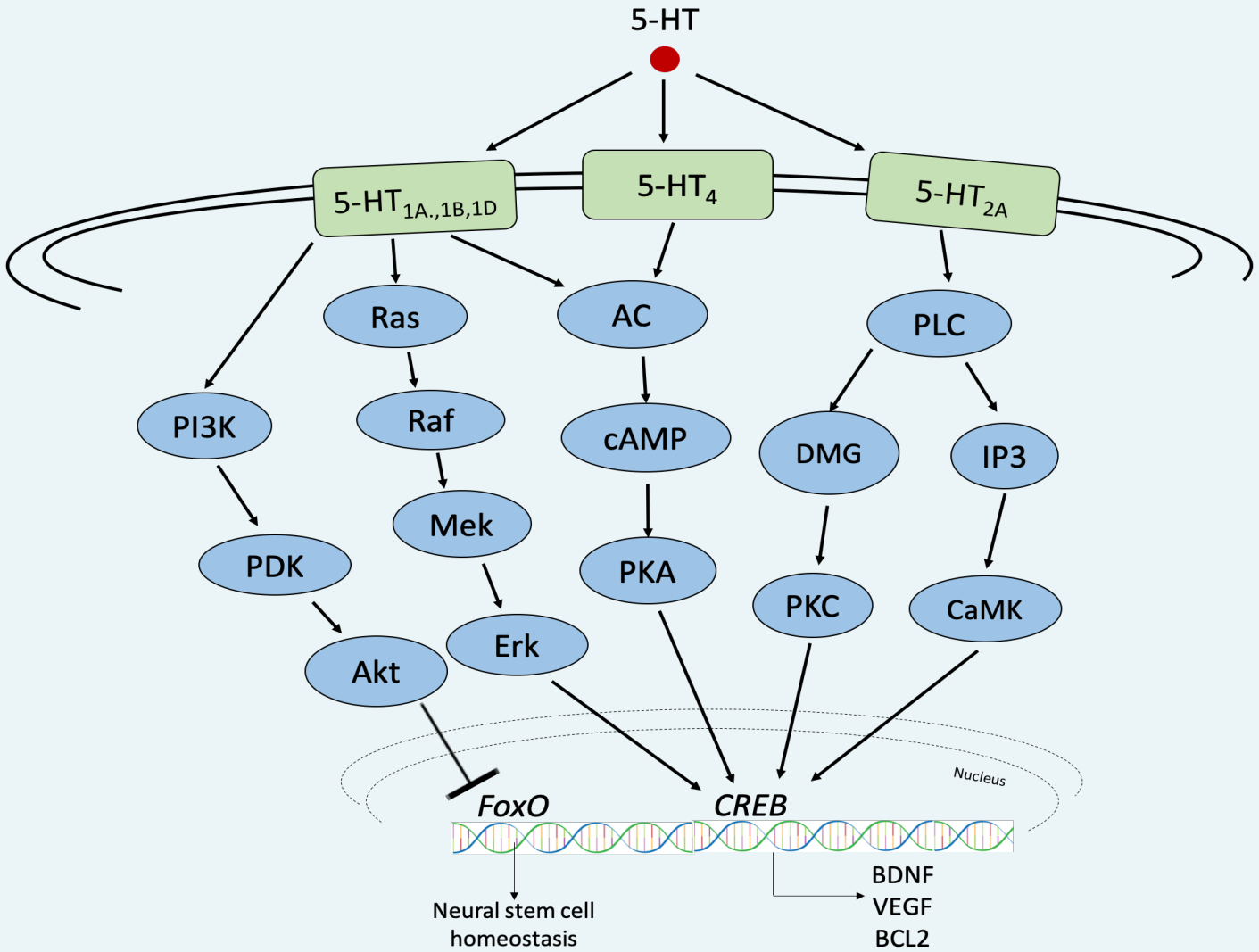


Figure 10 The pathways by which serotonin exerts its effect towards neurogenesis

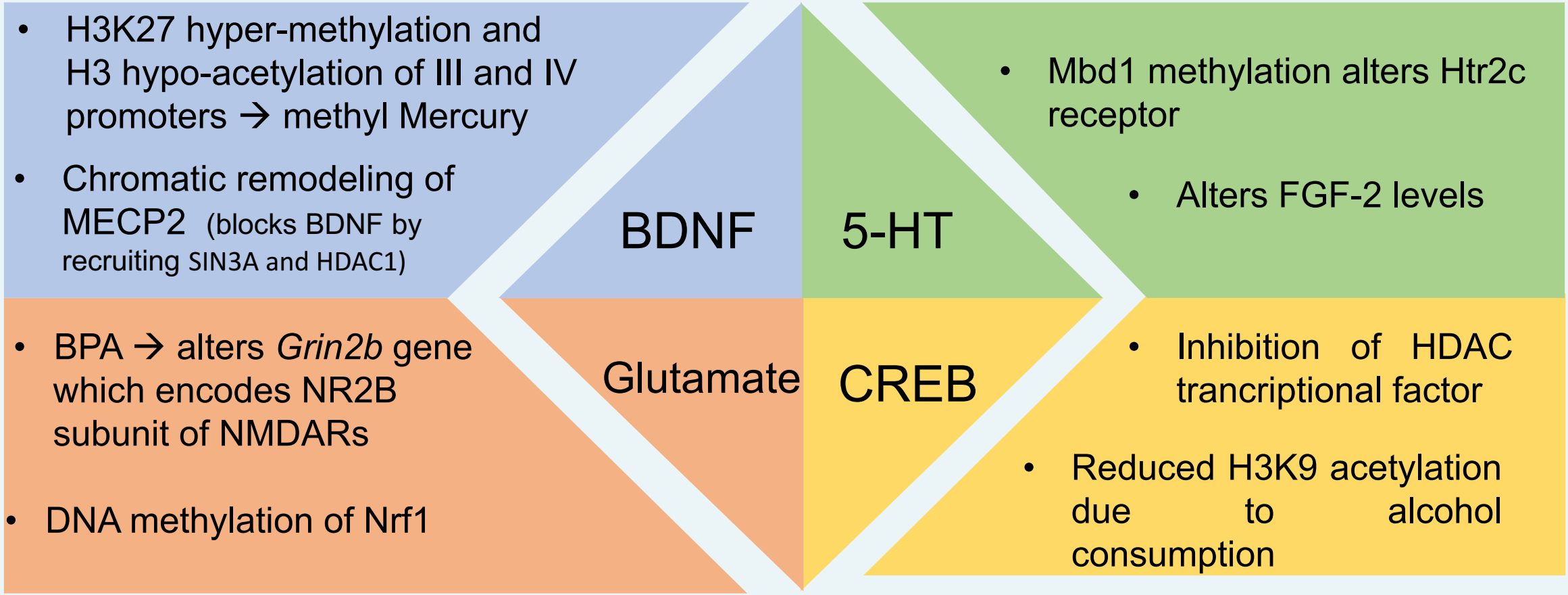
Three major genes identified !

Table 1 Downstream target genes of *bHLH*, *CREB* and *FoxO* and their functions

Gene	Downstream Targets	Function	References
FoxO	p21	Inhibit cell cycle progression	Pechnick et al. 2008
	Bim-1	Maintenance of neural stem cell homeostasis	Molofsky et al. 2005
	GADD 45	Regulate neural development and exit pluripotency and enter differentiation	Kaufmann et al. 2011
CREB	BDNF	Required for cell differentiation, nerve growth and neuronal development	Yoo et al. 2017
	ATF-3	Fear memory formation	Sakamoto and Frank 2009
	Bcl-2	Cell survival and cell cycle progression thereby promote neurogenesis and inhibits apoptosis	Zhang et al. 2006
bHLH	BDNF	Required for cell differentiation, nerve growth and neuronal development	Yoo et al. 2017

What causes the alterations in the levels of these molecules?

- Among many factors Epigenetics play a major role!



(Fasolino and Zhou 2017; Priya et al. 1833; Alavian-Ghavanini et al 2018; Zhao et al. 2003; Li et al. 2007; Vecsey et al. 2007; Alarcon et al. 2004)

Dysregulation of neurogenesis either alleviate or aggravate MDD and anxiety like behaviors

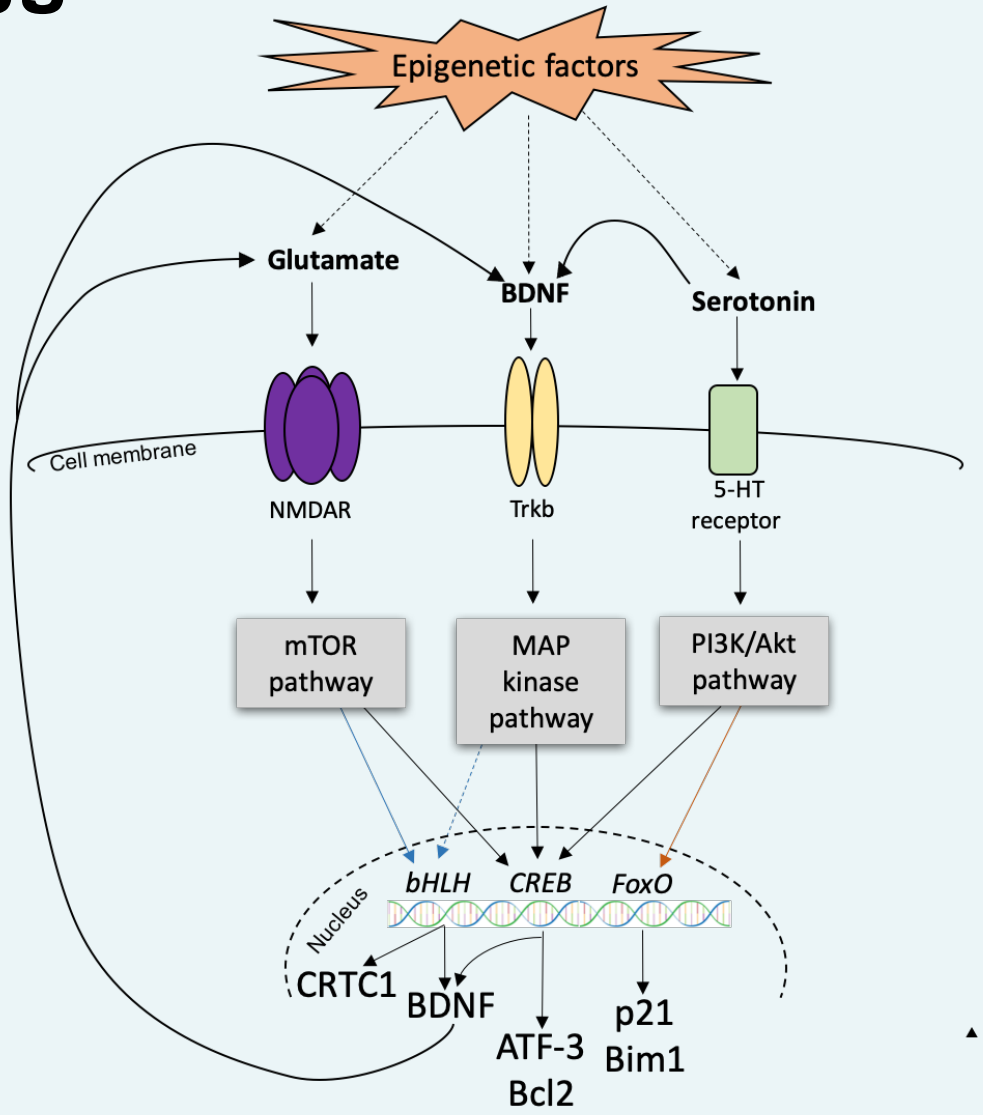
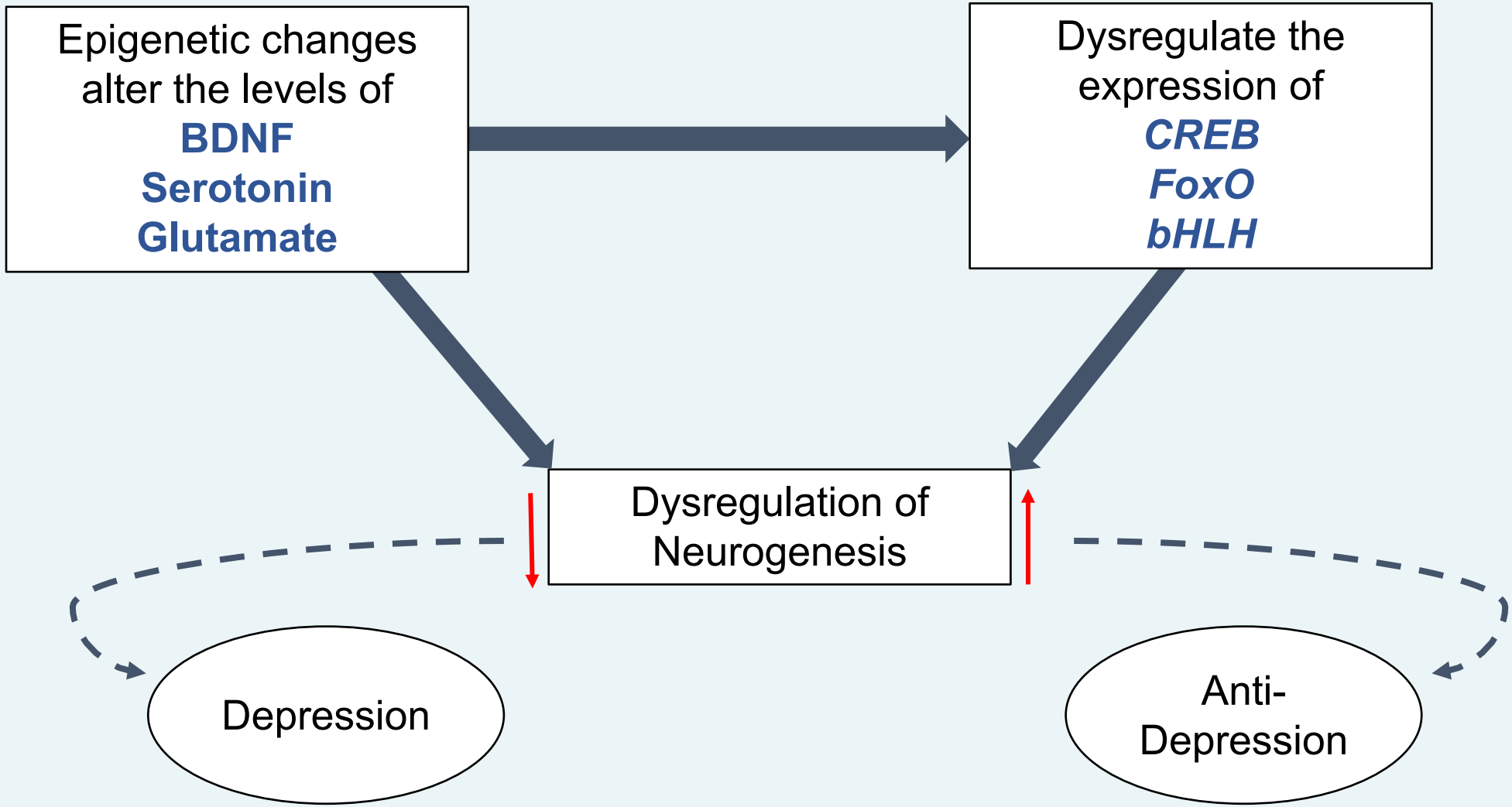


Figure 11 The major processes involved in the dysregulation of neurogenesis leading to depression

Summary


Epigenetic changes alter the levels of
BDNF
Serotonin
Glutamate
Dysregulate the expression of
CREB
FoxO
bHLH
Dysregulation of Neurogenesis
Depression
Anti-Depression

Conclusion

- Dysregulation of adult neurogenesis may perhaps be a frequent natural method of developing MDD and other related mental disorders.
- THREE genes and THREE key molecules have been identified to play a major role in the pathophysiology of MDD
- The identified molecules and genes can be used as therapeutic targets when creating drugs and treatments to fight against these diseases

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Thank you