What Causes Them?

Pathophysiology of Psychiatric Disorders

Dr. Malay Dave

13-07-2019, Lonavla

MISSING LINK

MISSING LINK

Introduction

- Psychiatric illnesses have very complex pathophysiology
- Understanding psychiatric illnesses is a work in progress
- Neurosciences & molecular genetics have provided us with tools to understand brain processes better
- I don’t claim to know the complete pathophysiology of a single psychiatric disorder
- Cellphones to be shut off or on silent mode

MISSING LINK

Take home message

Predetermined epigenesis:

(Unidirectional structure–functional development)

genes → brain structure → brain function → experience

Probablistic epigenesis:

(Bidirectional structure–functional development)

genes ↔ brain structure ↔ brain function ↔ experience

What we shall discuss….

- What did the older theories tell us? - Sigmund Freud, B F Skinner and the rest
- What about Social & Family contributions?
- What is stress exactly? - Immunology, Endocrinology, Chronobiology
- What is happening in the brain? – Molecules, Cells, Areas & Networks
- Is there a second brain? - Gut Brain Axis
- What is the role of Development and Degeneration?
- What is the master control? – Genetics and Epigenetics
- Is there a common ground? – Chronic illnesses

MISSING LINK

What did the older theories tell us?

- Sigmund Freud
  - *Concept of Mind*
  - *Psychosexual development*
  - *Defence mechanisms*
  - *Conflict*
- Ivan Pavlov & B F Skinner
  - *Classical conditioning*
  - *Operant conditioning*
- Aaron Beck
  - *Cognition*

What did the older theories tell us?

- Drawbacks
  - *Observational*
  - *Incomplete understanding*
  - *Neuroscientific basis (?)*
  - *Partial therapies*

What about Social & Family contributions?

- Idea of a dysfunctional family
- Concepts of Skew, Schism, Double Bind
- Expressed Emotions
  - *Over-indulgence*
  - *Hostility*
  - *Over-protection*
- “Refrigerator Mother”
- Abuse

What is stress exactly?

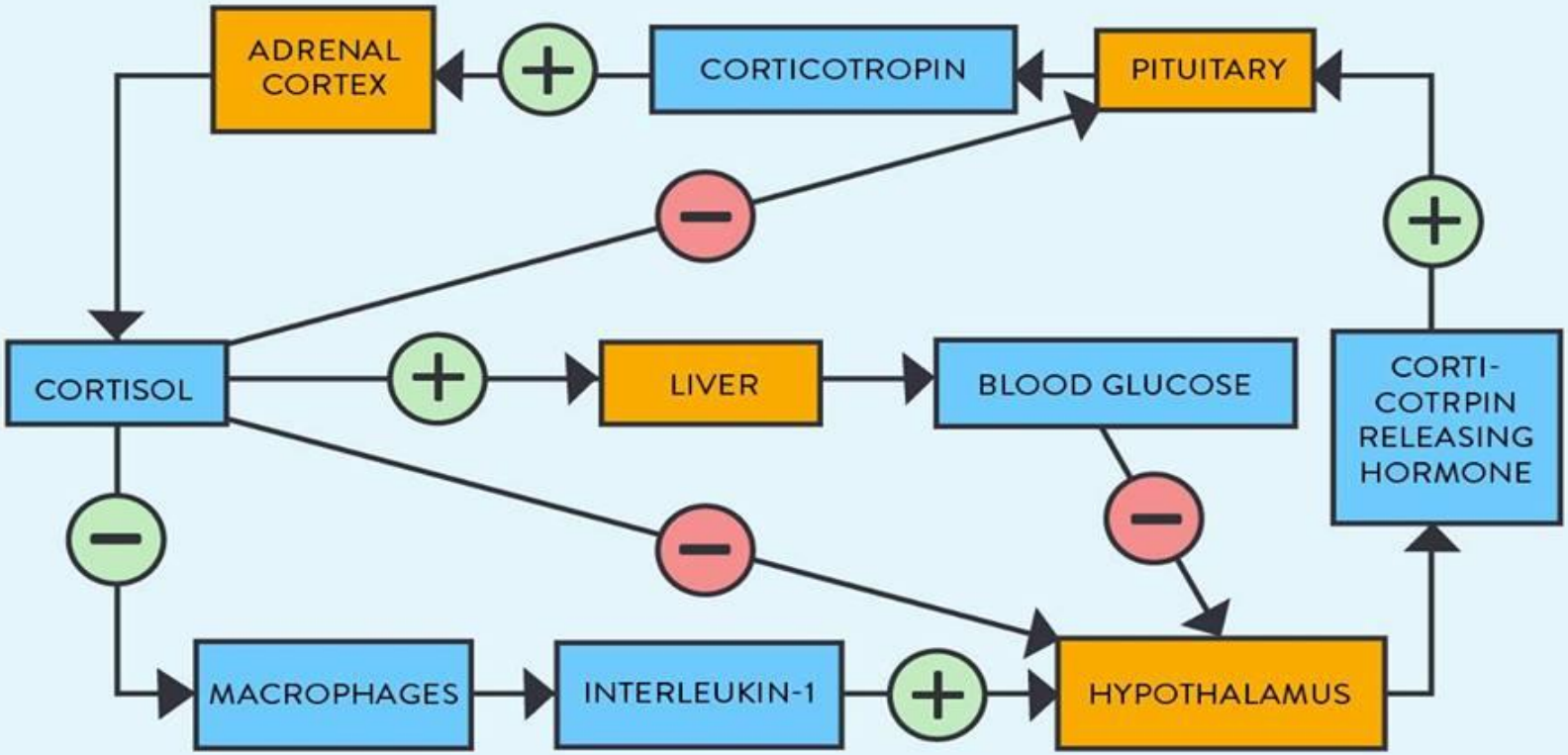
- Homeostasis
  - *Allostasis*
- Systems involved
  - *Hypothalamo-Pituitary-Adrenal Axis (HPA Axis) & Immune System*
  - *Hypothalamo-Pituitary-Thyroid Axis (HPT Axis)*
  - *Hypothalamo-Pituitary-Gonadal Axis (HPG Axis)*
- Complexity
- Genetic control & settings

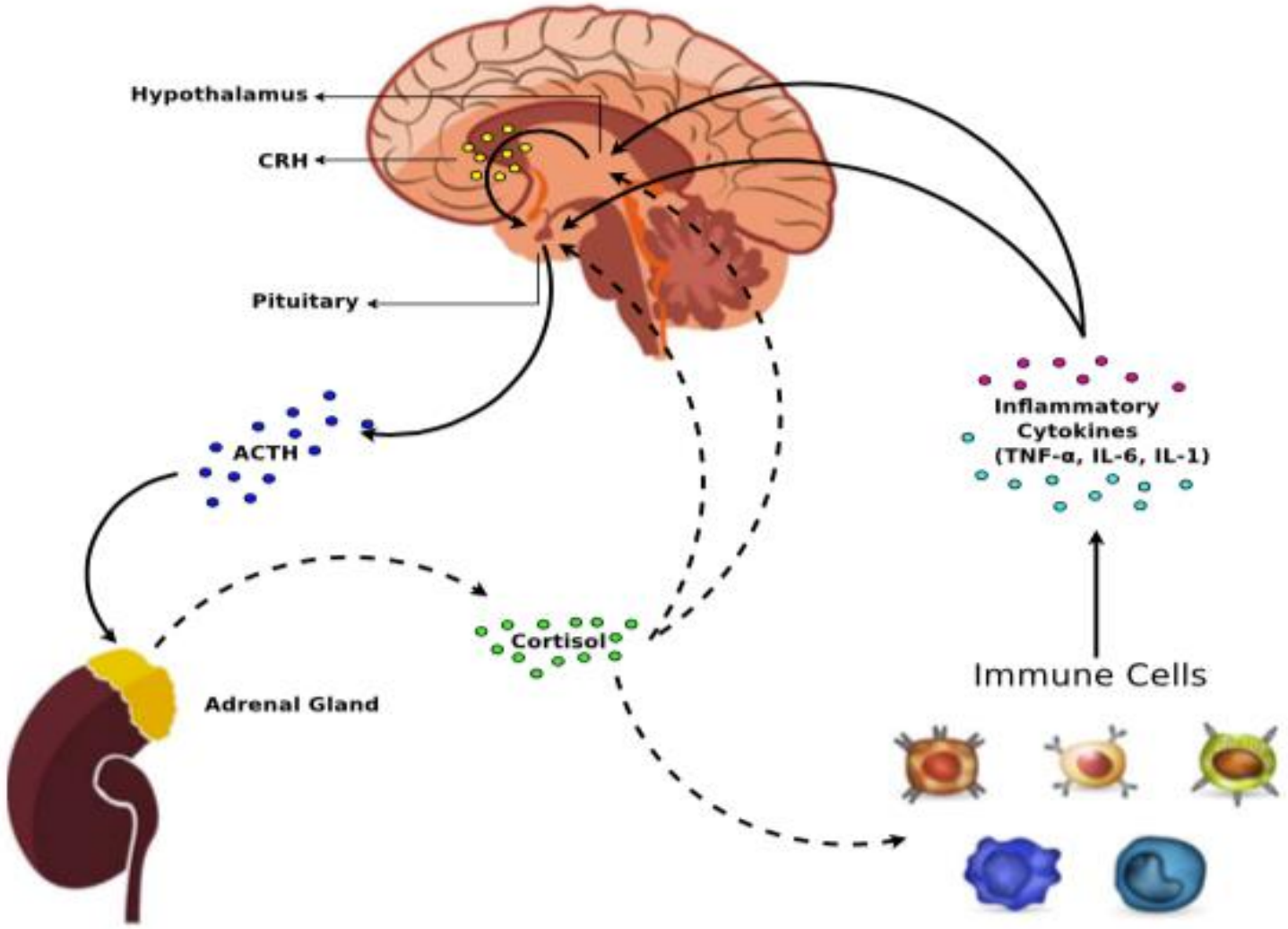
MISSING LINK

HPA Axis & Immunity - Inflammation

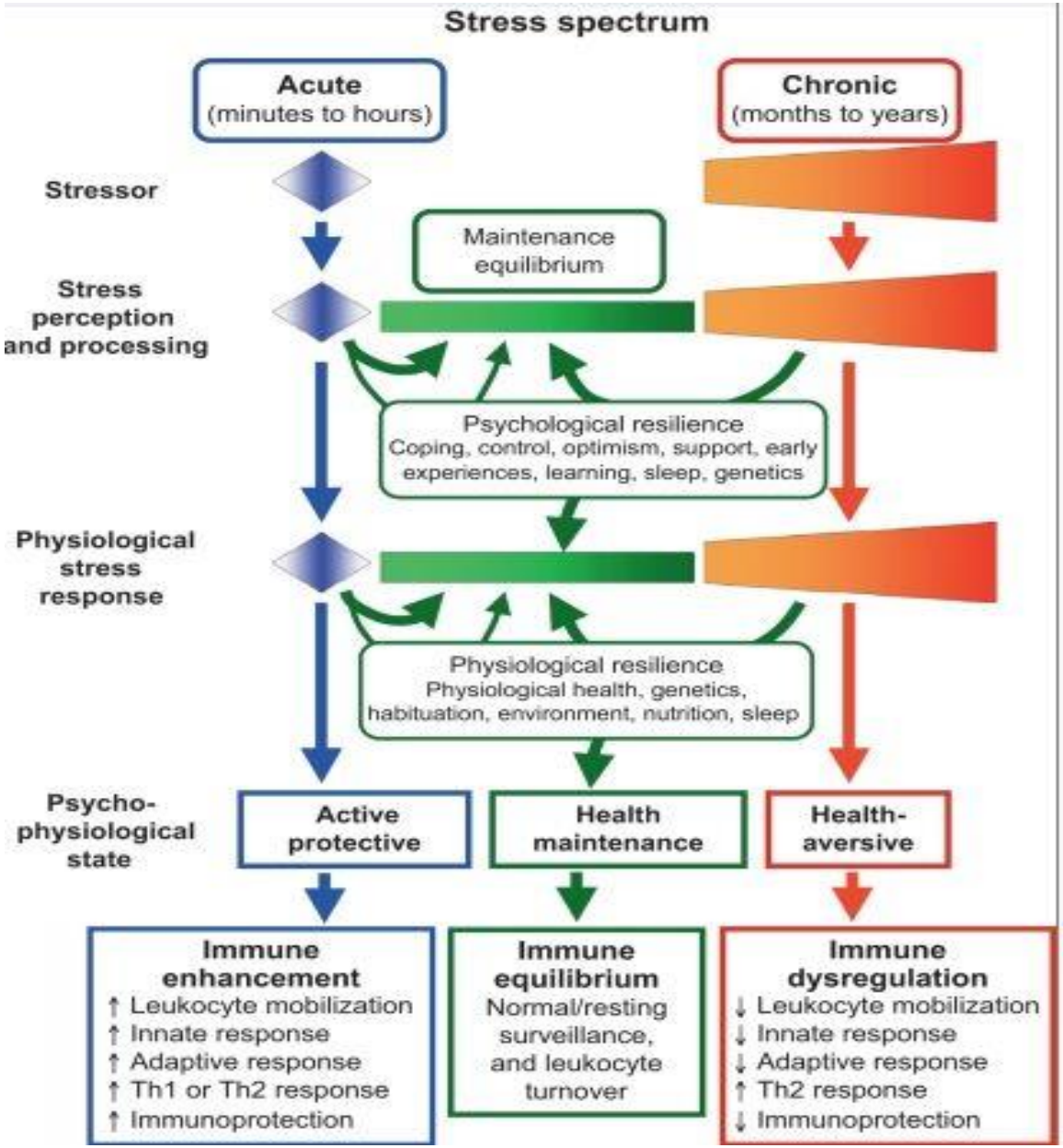
MISSING LINK

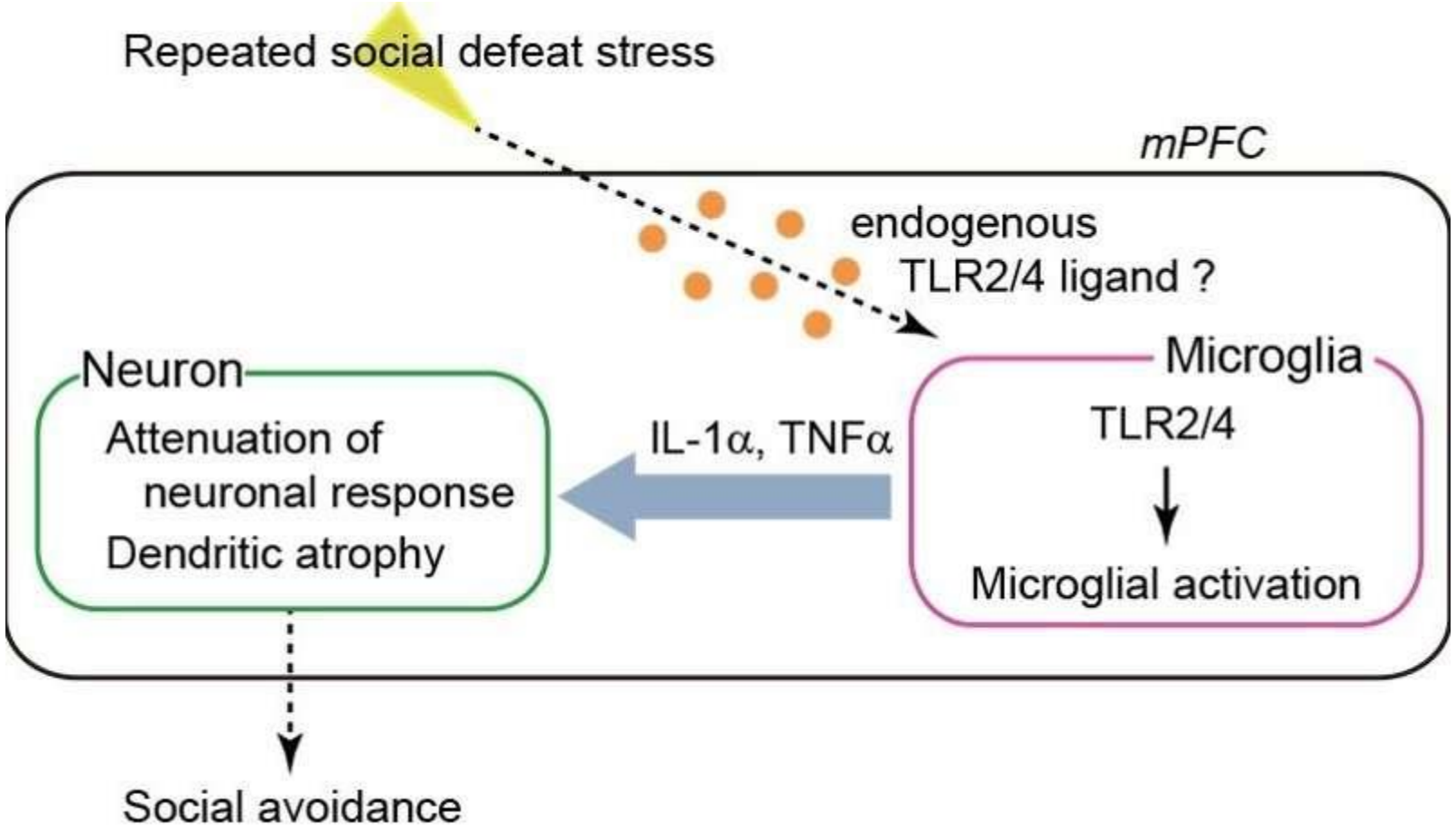
THE HPA AXIS

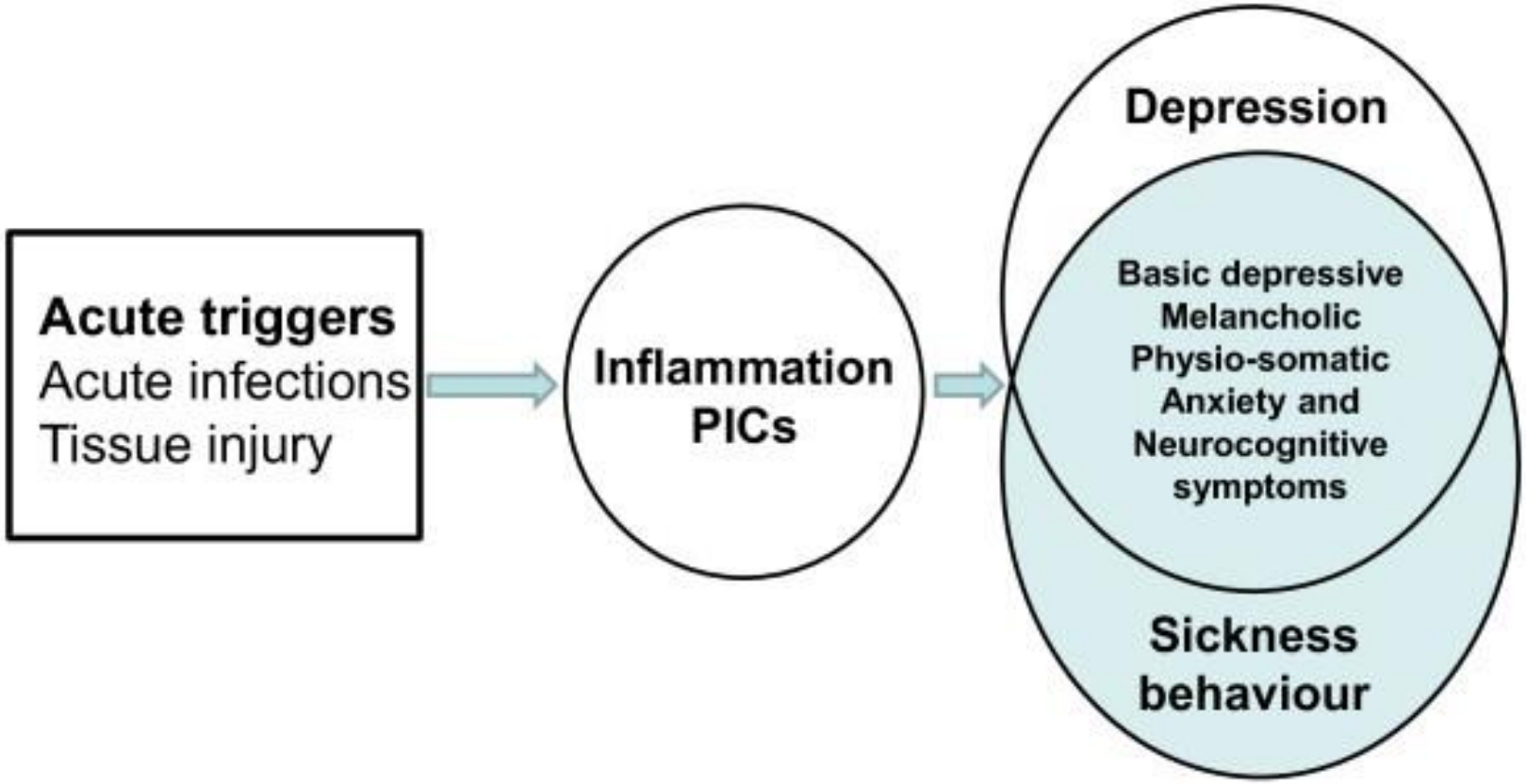

ADRENAL CORTEX
CORTICOTROPIN
PITUITARY
CORTISOL
LIVER
BLOOD GLUCOSE
CORTI-COTRPIN RELEASING HORMONE
MACROPHAGES
INTERLEUKIN-1
HYPOTHALAMUS



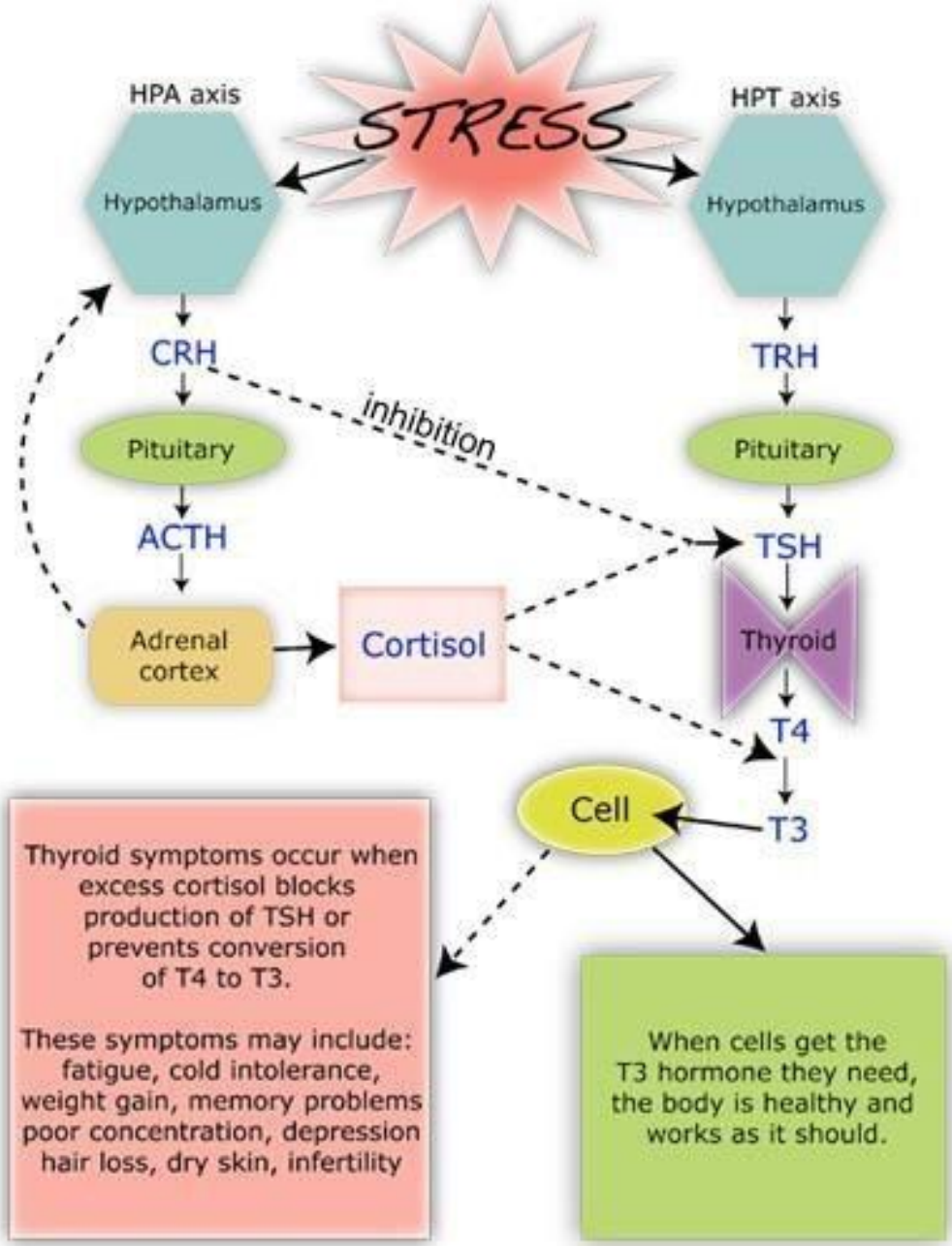
Schematic diagram of the interaction of innate immune cells with the HPA axis through inflammatory cytokines. Solid arrows indicate stimulation and dashed arrows indicate inhibition.

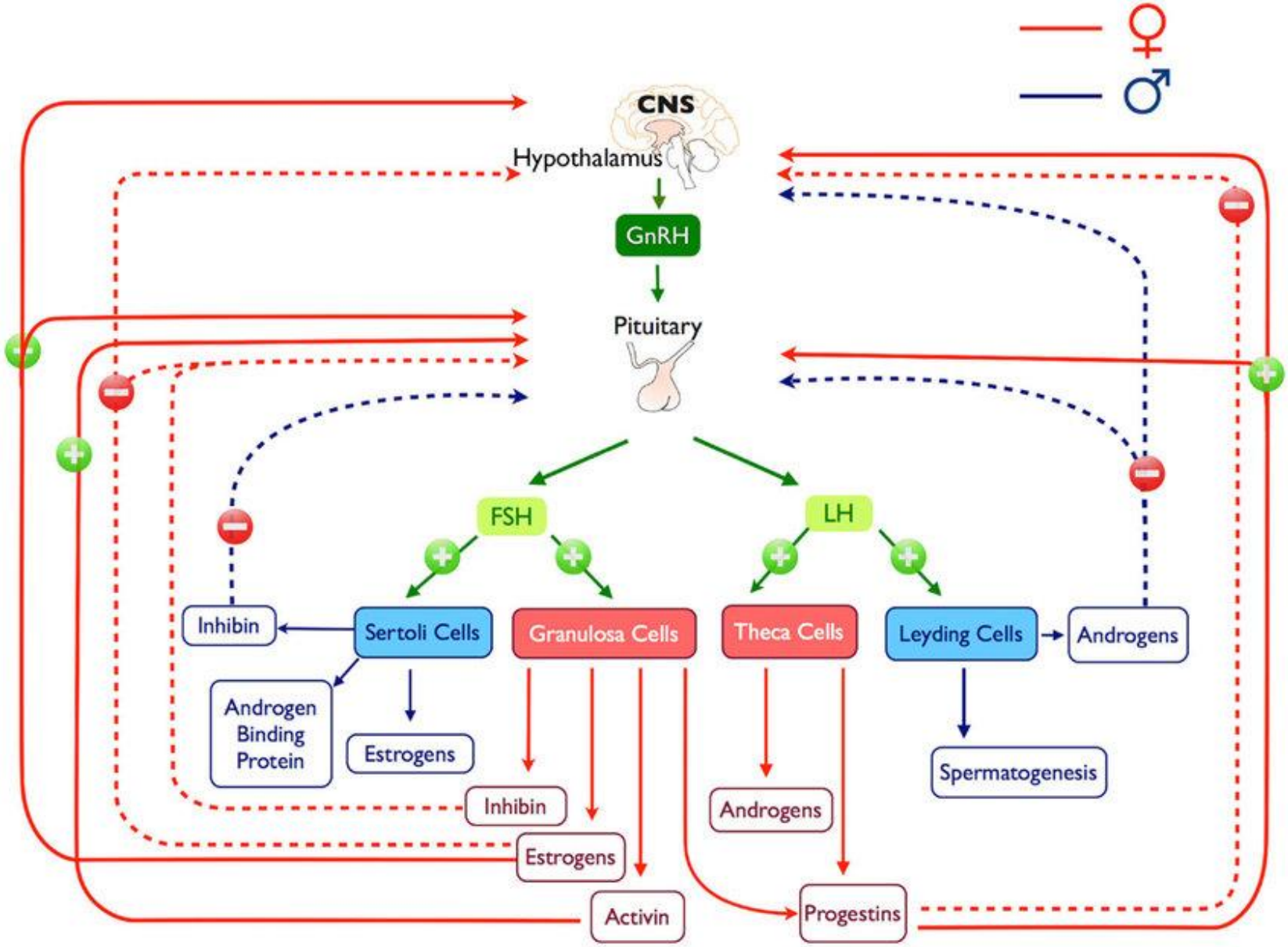

Stress spectrum
Acute
(minutes to hours)
Chronic
(months to years)
Stressor
Maintenance
equilibrium
Stress
perception
and processing
Psychological resilience
Coping, control, optimism, support, early
experiences, learning, sleep, genetics
Physiological
stress
response
Physiological resilience
Physiological health, genetics,
habituation, environment, nutrition, sleep
Psycho-
physiological
state
Active
protective
Health
maintenance
Health-
aversive
Immune
enhancement
↑ Leukocyte mobilization
↑ Innate response
↑ Adaptive response
↑ Th1 or Th2 response
↑ Immunoprotection
Immune
equilibrium
Normal/resting
surveillance,
and leukocyte
turnover
Immune
dysregulation
↓ Leukocyte mobilization
↓ Innate response
↓ Adaptive response
↑ Th2 response
↓ Immunoprotection


Repeated social defeat stress
mPFC
endogenous
TLR2/4 ligand ?
Neuron
Attenuation of
neuronal response
Dendritic atrophy
IL-1α, TNFα
Microglia
TLR2/4
Microglial activation
Social avoidance

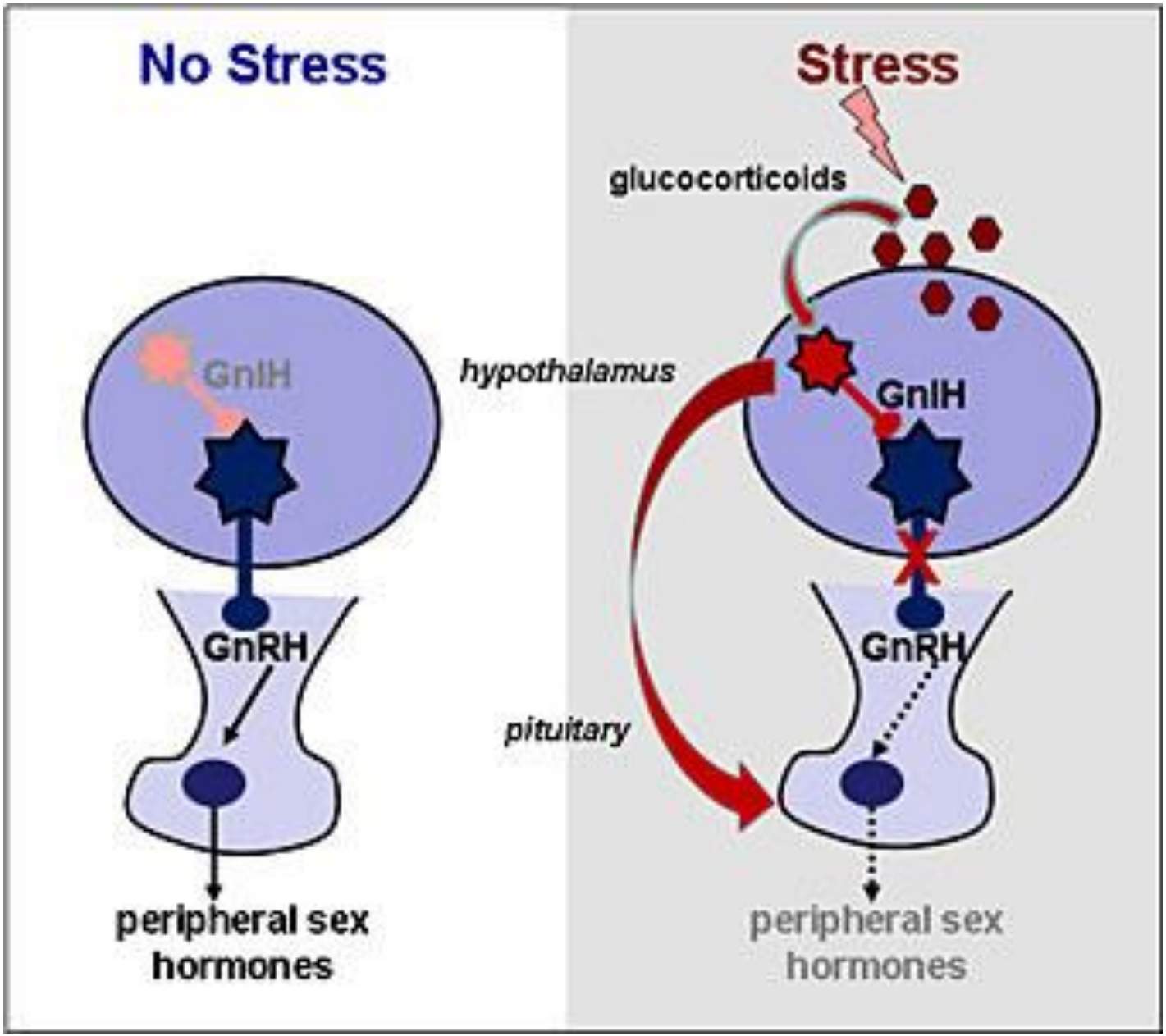

Acute triggers
Acute infections
Tissue injury
Inflammation
PICs
Depression
Basic depressive
Melancholic
Physio-somatic
Anxiety and
Neurocognitive
symptoms
Sickness
behaviour

Stress - Endocrinology


HPA axis
STRESS
HPT axis
Hypothalamus
Hypothalamus
CRH
TRH
inhibition
Pituitary
Pituitary
ACTH
TSH
Adrenal cortex
Cortisol
Thyroid
T4
Cell
T3
Thyroid symptoms occur when excess cortisol blocks production of TSH or prevents conversion of T4 to T3.
These symptoms may include: fatigue, cold intolerance, weight gain, memory problems poor concentration, depression hair loss, dry skin, infertility
When cells get the T3 hormone they need, the body is healthy and works as it should.



MISSING LINK


No Stress
Stress
glucocorticoids
GnIH
hypothalamus
GnIH
GnRH
GnRH
pituitary
peripheral sex hormones
peripheral sex hormones

Stress - Chronobiology

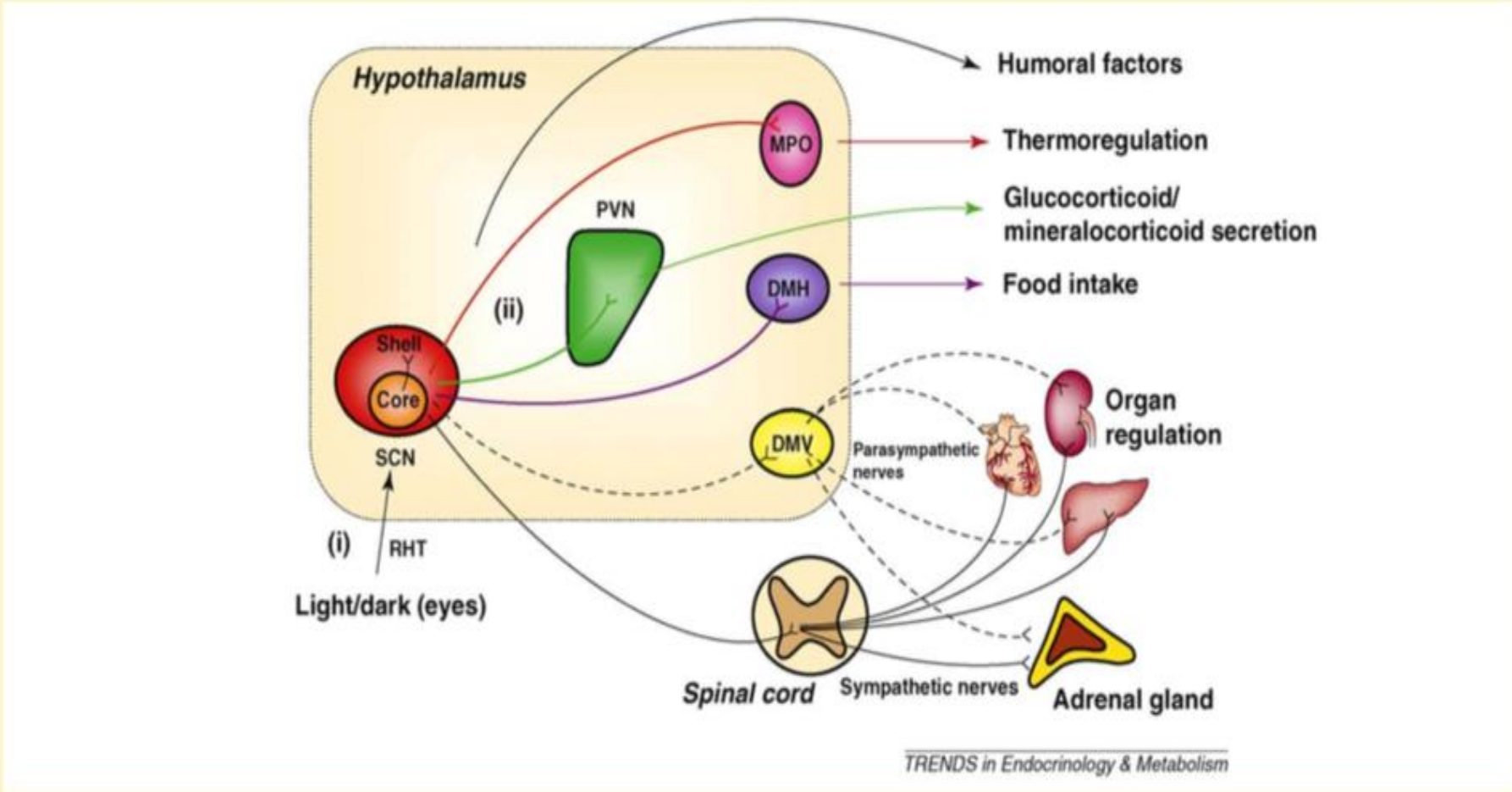


Figure I. Central CLOCK synchronizes the peripheral CLOCKs and regulates peripheral organ activities via neural and humoral interactions. **(i)** The central master CLOCK located in the SCN (core) obtains light/dark information from the retina through the retinohypothalamic track (RHT) and adjusts to synchronize its circadian rhythm, whereas **(ii)** it indirectly projects several efferent neurons to transmit timing information to other parts of the brain and distant organs their peripheral CLOCKs and influence their activities, such as secretion of pituitary hormones and melatonin, food intake, sleep and body temperature. The central master CLOCK employs the autonomic nervous system and humoral mediators for organ regulation. For simplicity, detailed anatomical structures for the sympathetic and parasympathetic nervous systems, such as nuclei located in the brain stem including the solitary nucleus and the ambiguous nucleus and the sympathetic and parasympathetic ganglia, are omitted. DMH: dorsomedial nucleus of hypothalamus, DMV: dorsal motor nucleus of vagus, MPO: medial preoptic region, PVN: paraventricular nucleus, SCN: suprachiasmatic nucleus.

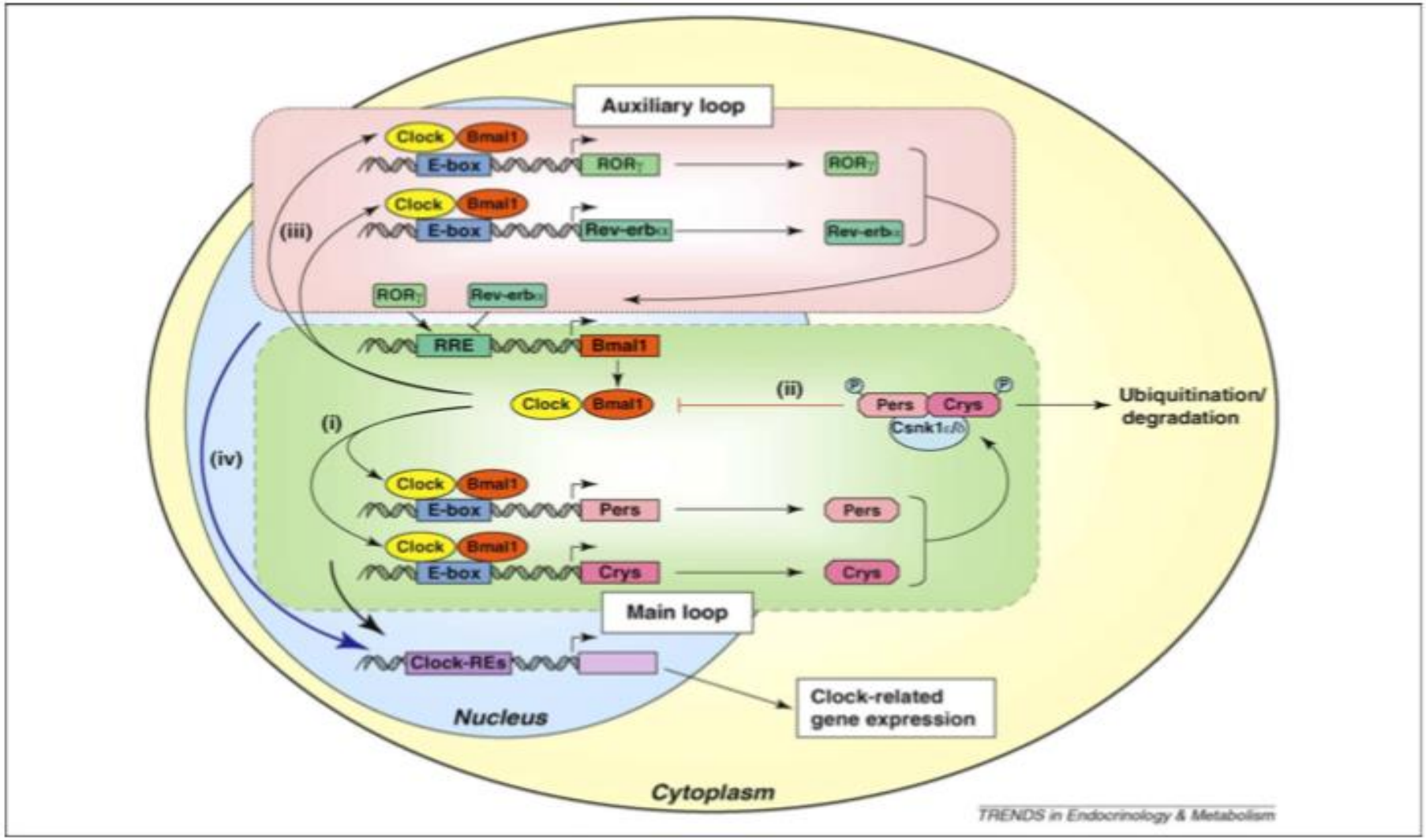


Figure 1. The circadian CLOCK system is regulated by a self-oscillating transcriptional loop. **(i)** The heterodimer Clock/Bmal1 binds to E-box elements located in the promoter region and stimulates expression of essential clock transcription factors Pers and Crys, which in turn **(ii)** repress the transcriptional activity of the Clock/Bmal1 heterodimer by inhibiting its binding to the E-box response elements located in their own promoters through formation of a complex with and subsequent phosphorylation by the casein kinase 1ε and δ. **(iii)** Clock/Bmal1 also stimulates expression of other CLOCK-related proteins, such as Rev–erbα, RORα, Dec1, Dec2 and Dbp, which create an auxiliary loop that helps stabilize the main regulatory loop. **(iv)** These CLOCK transcription factors control numerous "downstream" CLOCK-responsive genes to influence a variety of biologic activities. Bmal1: brain–muscle–arnt-like protein 1, Clock: circadian locomotor output cycle kaput, Crys: cryptochromes, Csnk1ε/δ: casein kinase 1ε/δ, P: phosphate residue on the phosphorylated molecules, Pers: periods, RORγ: retinoic acid receptor-related orphan nuclear receptor γ.

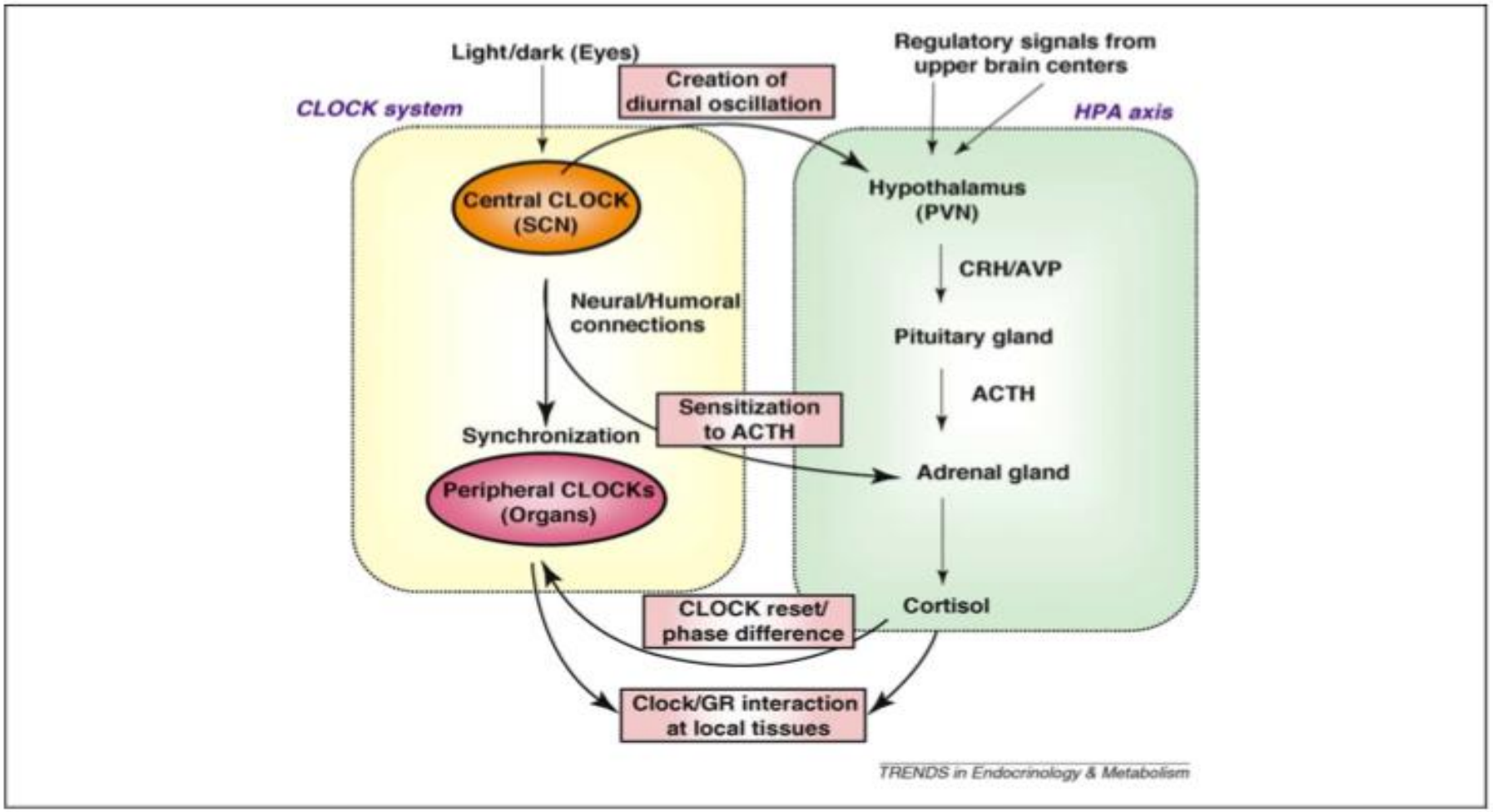
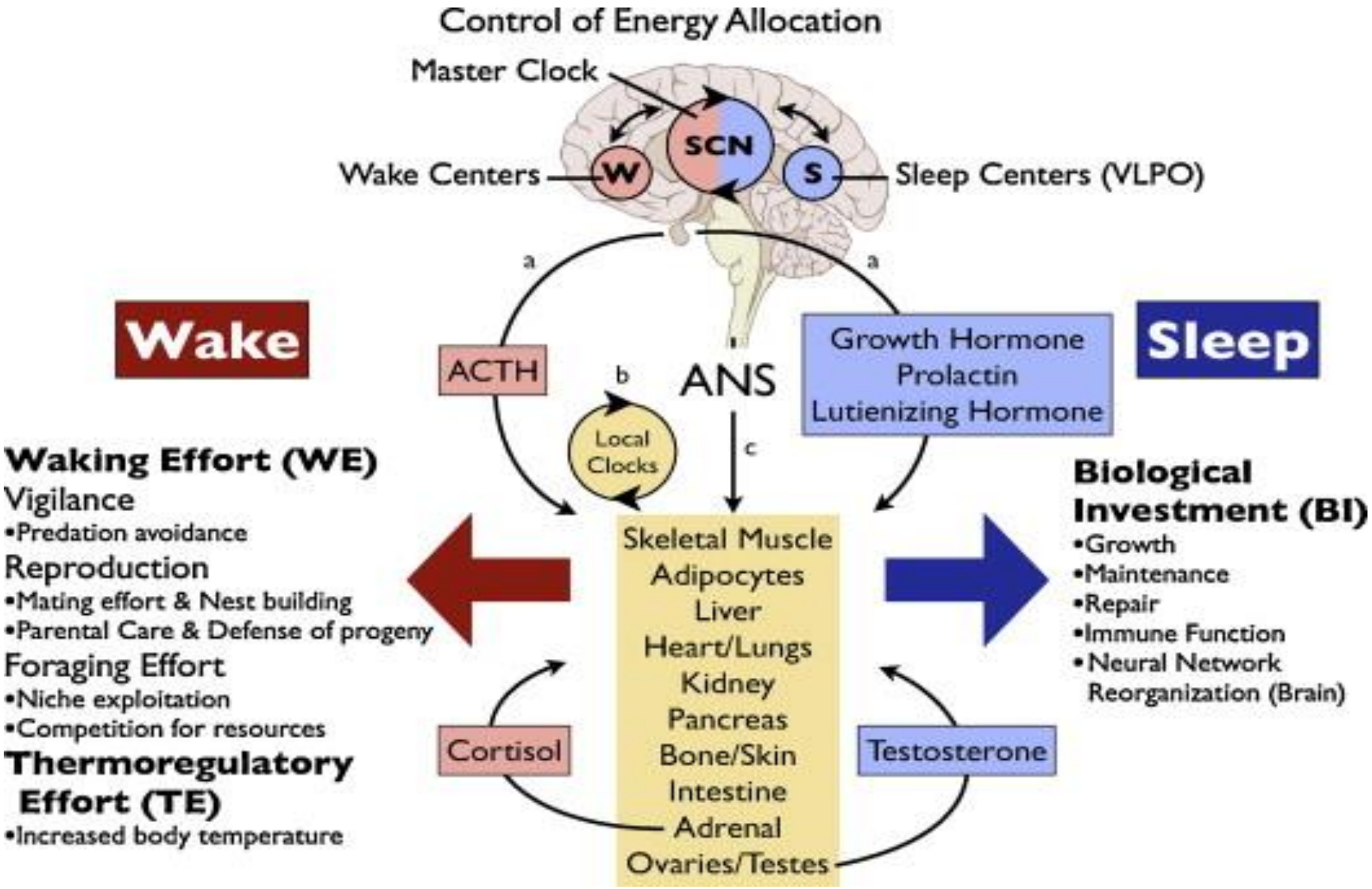
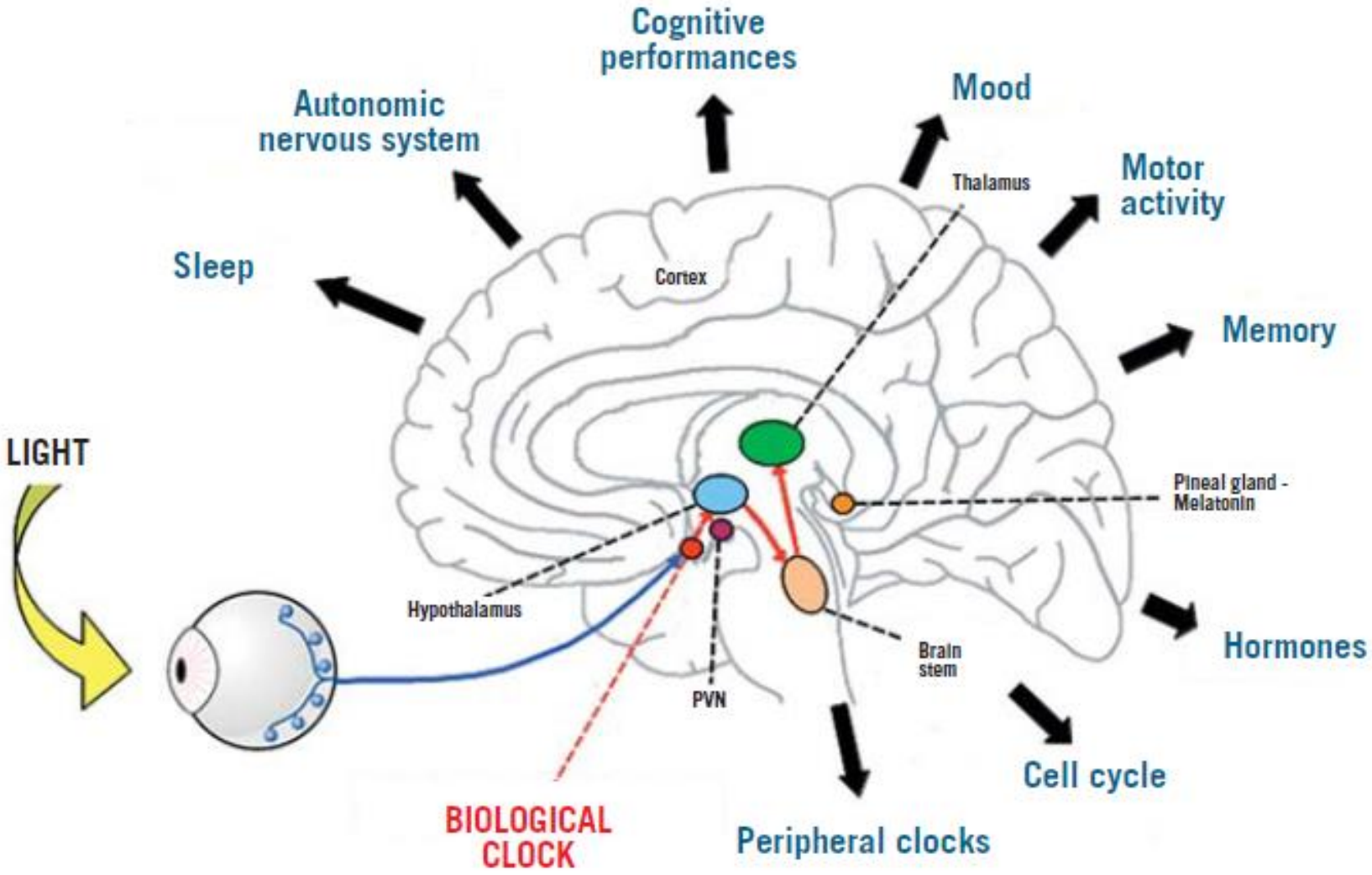


Figure 2. The circadian CLOCK system and the HPA axis influence the activity of one another at multiple levels. The central CLOCK under the regulation of the light input controls the HPA axis and produces regular diurnal secretion of glucocorticoid hormones from the adrenal glands, whereas the peripheral CLOCKs, which are located in the adrenal glands and other components of the HPA axis and are regulated by the central CLOCK through the sympathetic nervous system, also contribute to the rhythmic glucocorticoid secretion from these organs. Secreted glucocorticoids in turn reset and phase-shift the circadian rhythm of the peripheral CLOCKs by stimulating the expression of several CLOCK-related genes; this is particularly important for temporal adjustment of activity of the body against stress. The peripheral CLOCKs also regulate the glucocorticoid effect in local tissues through interaction between Clock/Bmal1 and the GR, providing a local counter regulatory feedback loop to the effect of central CLOCK on the HPA axis. ACTH: adrenocorticotropic hormone, AVP: arginine vasopressin, CRH: corticotropin-releasing hormone, PVN: paraventricular nucleus, SCN: suprachiasmatic nucleus.


Control of Energy Allocation
Master Clock
SCN
Wake Centers
W
S
Sleep Centers (VLPO)
a
a
Wake
Sleep
ACTH
b
ANS
Growth Hormone
Prolactin
Lutienizing Hormone
Local Clocks
c
Waking Effort (WE)
Vigilance
•Predation avoidance
Reproduction
•Mating effort & Nest building
•Parental Care & Defense of progeny
Foraging Effort
•Niche exploitation
•Competition for resources
Thermoregulatory Effort (TE)
•Increased body temperature
Skeletal Muscle
Adipocytes
Liver
Heart/Lungs
Kidney
Pancreas
Bone/Skin
Intestine
Adrenal
Ovaries/Testes
Biological Investment (BI)
•Growth
•Maintenance
•Repair
•Immune Function
•Neural Network Reorganization (Brain)
Cortisol
Testosterone


Cognitive performances
Mood
Autonomic nervous system
Thalamus
Motor activity
Sleep
Cortex
Memory
LIGHT
Pineal gland - Melatonin
Hypothalamus
Brain stem
Hormones
PVN
Cell cycle
BIOLOGICAL CLOCK
Peripheral clocks

What is happening in the brain?

- Neurotransmitters
- Relatively simple systems
  - *Dopamine – Psychosis, Impulsivity*
  - *Norepinephrine – Reward*
  - *Serotonin – Depression, OCRD*
- Complex
  - *Glutamate - Learning*
  - *GABA - Inhibition*

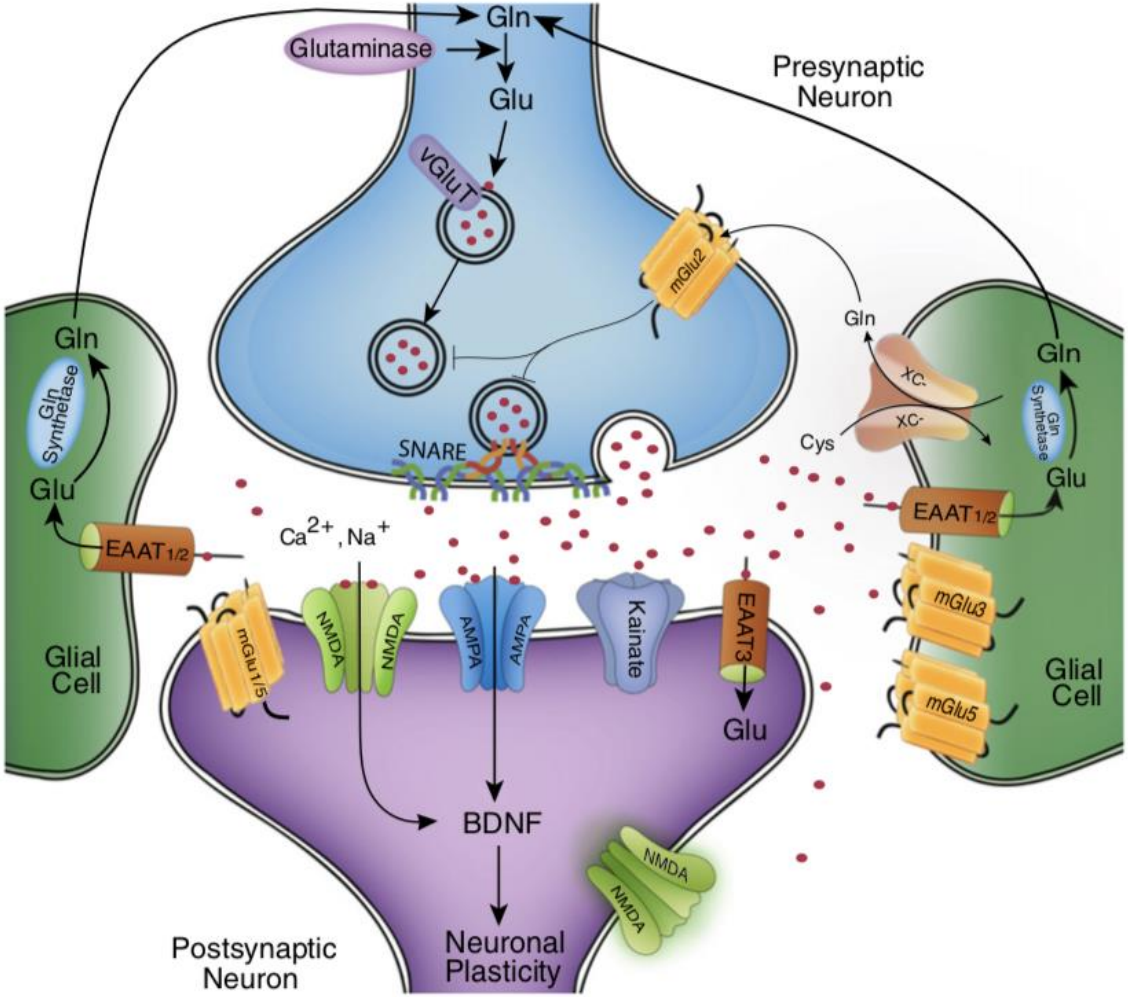
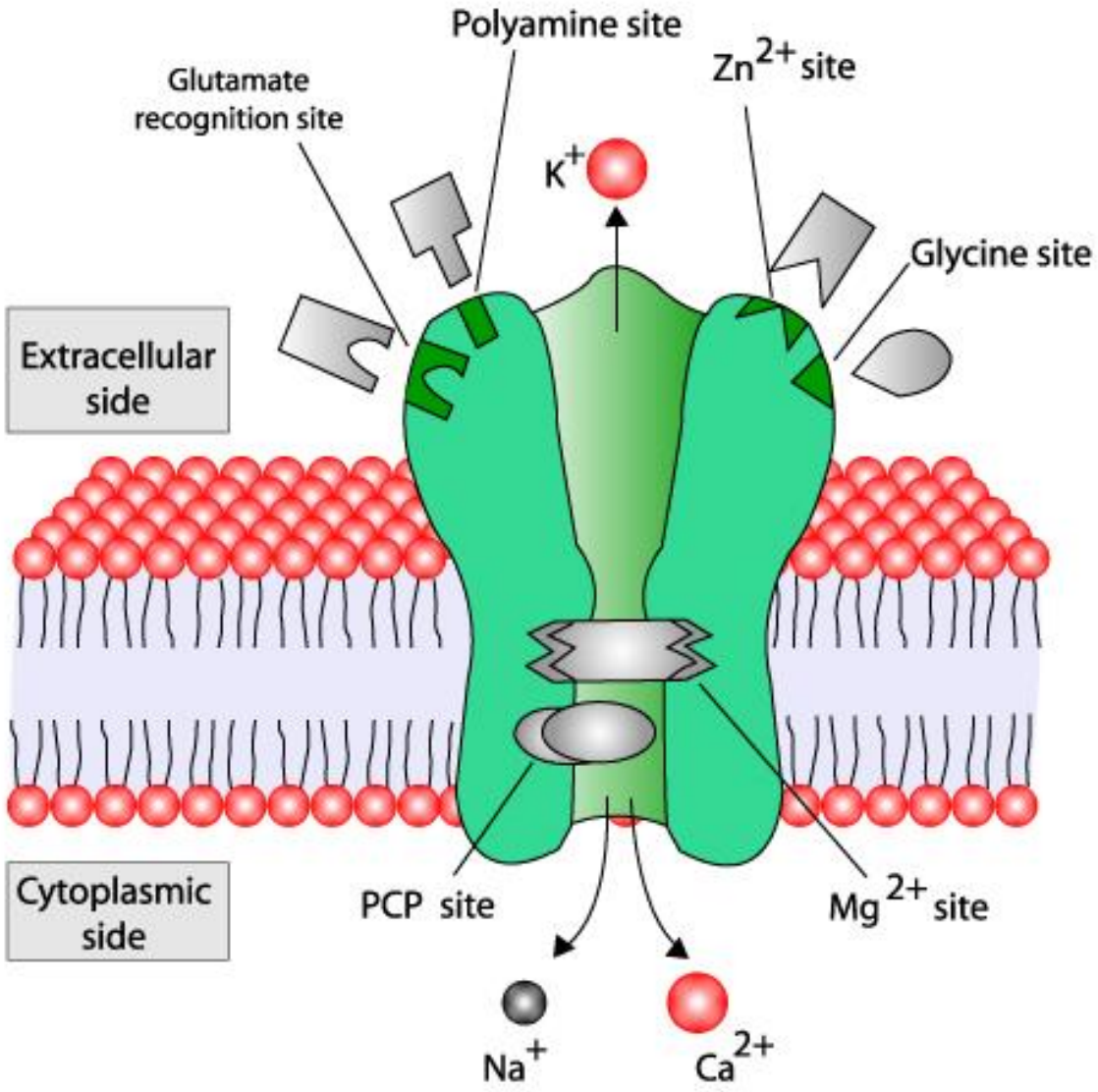
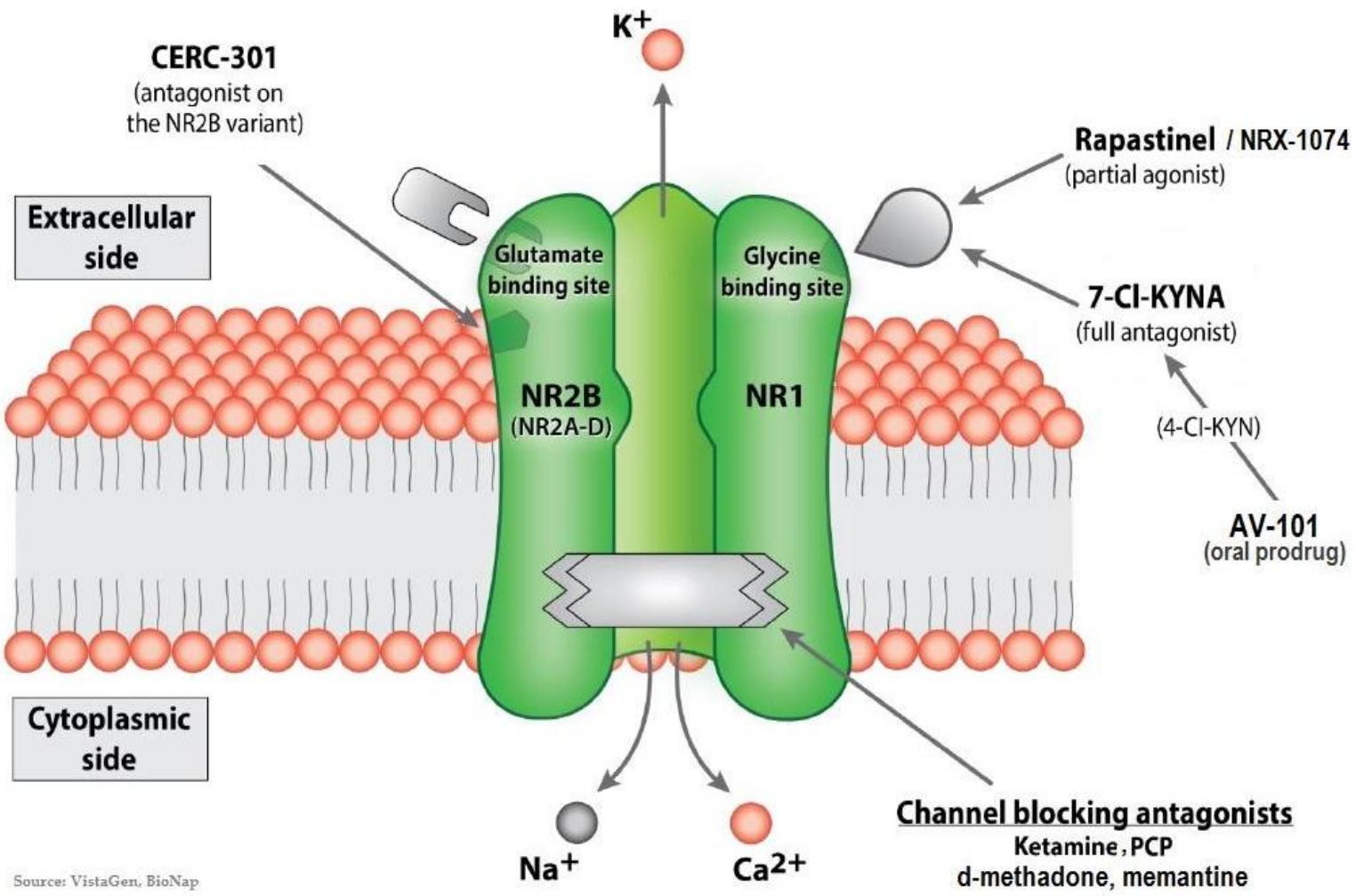


Fig. 1. Glutamatergic neurotransmission: due to the risk of excitotoxic damage in the wake of excessive glutamatergic stimulation, precise physiological control of glutamate must be maintained in the mammalian CNS. Glutamine (Gln) is converted to glutamate (Glu) by glutaminase [though glutamate may also be derived from the TCA cycle (not shown)]. Glu is packaged into presynaptic vesicles by vesicular Glu transporter (VGLUT) proteins and synaptically released in a voltage-dependent manner through vesicular interactions with SNARE proteins. Synaptically-released Glu is recycled from the extracellular space by excitatory amino acid transporters (EAATs) expressed predominantly on astroglia. In astrocytes, Glu is converted to Gln by Gln synthetase and exported extracellularly to be taken up again by neurons. Additionally, system x-C is a cystine/glutamate antiporter expressed on glia that also contributes to Glu recycling. Glu receptors are present on presynaptic and postsynaptic neurons as well as on glial cells. These include both ionotropic receptors (NMDA, AMPA/KA) and metabotropic receptors (mGluRs). The effect of Glu is determined by the receptor subtype, localization (synaptic, perisynaptic and extrasynaptic), and interactions with various scaffolding and signaling proteins (not shown) in the postsynaptic density. Glu receptor stimulation results not only in rapid ionotropic effects but also in synaptic plasticity, *e.g.* long-term potentiation (LTP) and long-term depression (LTD), via cognate signal transduction cascades.

Schematic representation of the NMDA (N - Methyl D- Aspartate) receptor complex

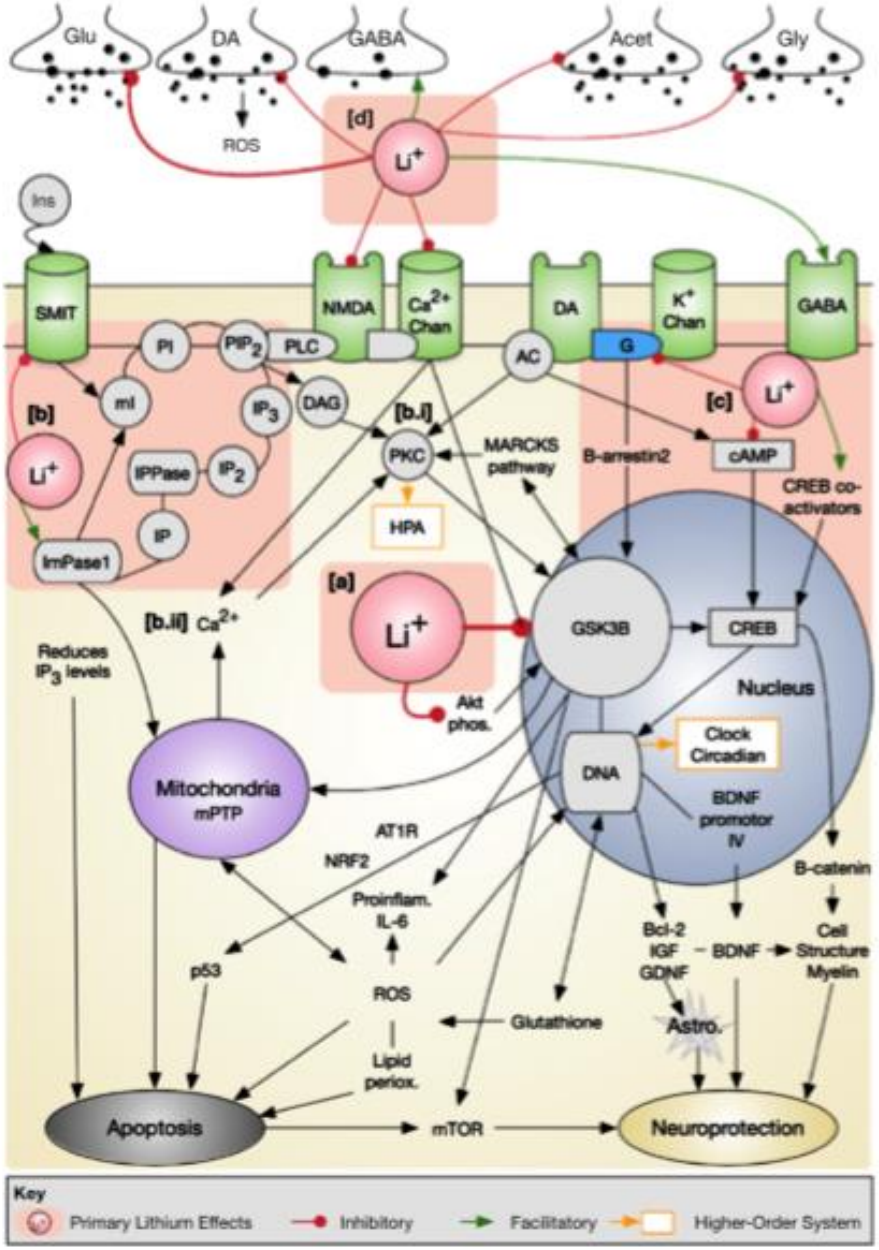


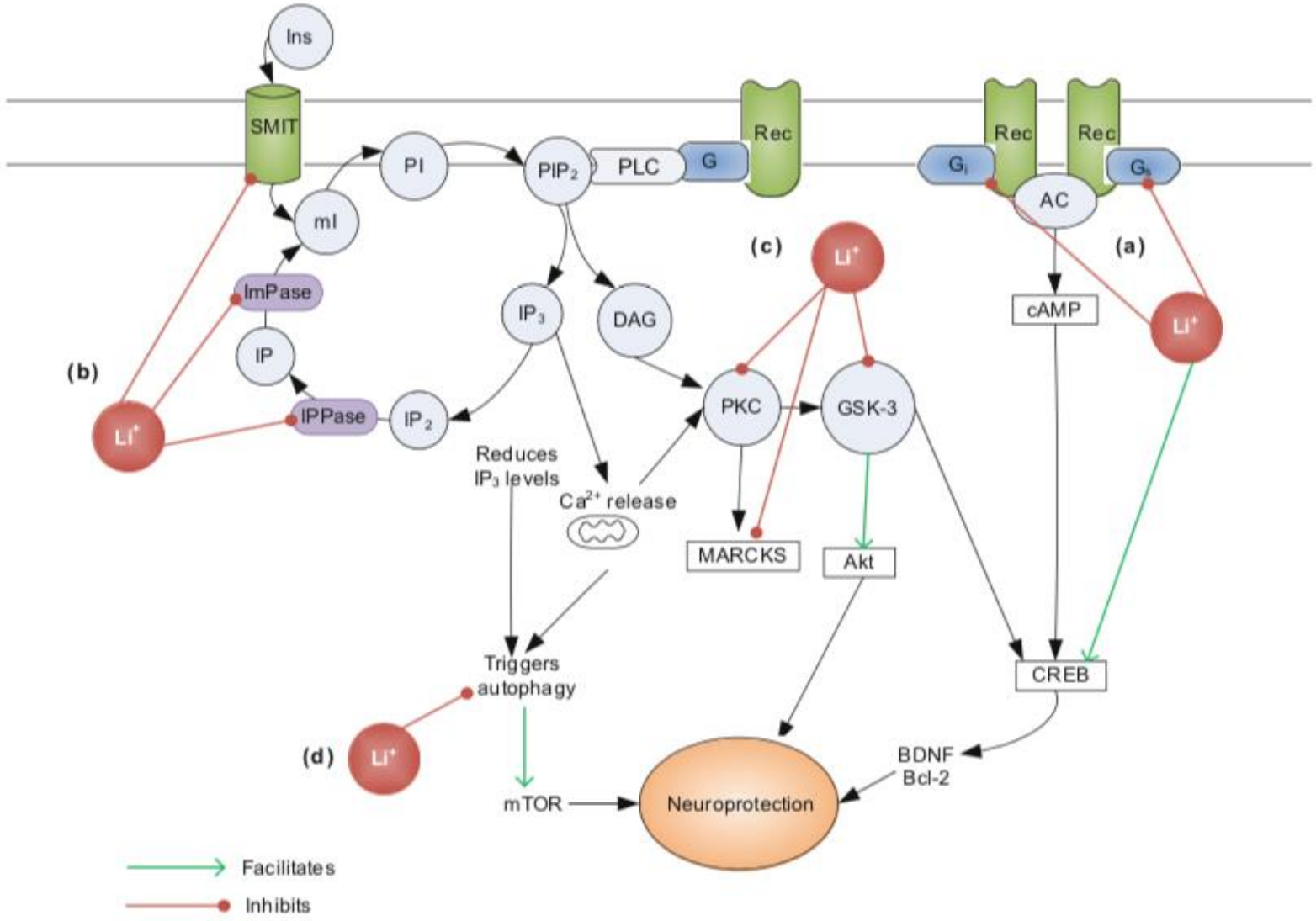
NMDA Receptor Pharmacology

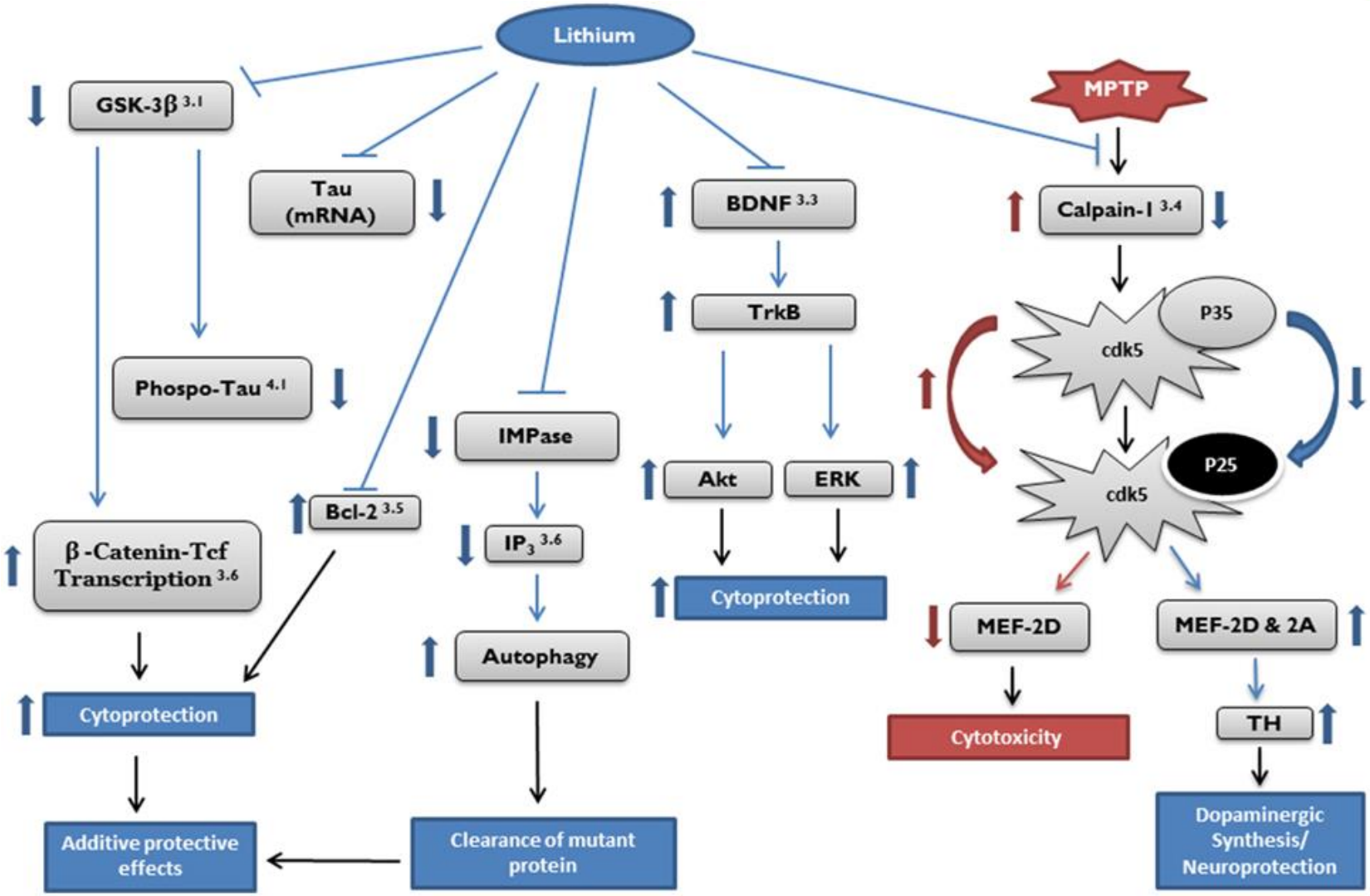


What is happening in the brain?

- Second messenger systems & beyond
  - *cAMP & cGMP, IP*
  - *Lithium and Bipolar disorder*


Glu
DA
GABA
Acet
Gly
ROS
[d]
Li+
Ins
SMIT
NMDA
Cs2+ Chan
DA
K+ Chan
GABA
PI
PIP2
PLC
AC
G
[b]
mI
IP3
DAG
[b.i]
[c]
Li+
PKC
MARCKS pathway
B-arrestin2
cAMP
CREB co-activators
IPPase
IP2
IP
HPA
ImPase1
[a]
Li+
GSK3B
CREB
[b.ii] Cs2+
Reduces IP3 levels
Nucleus
Akt phos.
Clock Circadian
DNA
Mitochondria
mPTP
BDNF promotor IV
AT1R
NRF2
B-catenin
Proinflam. IL-6
Bcl-2 IGF GDNF
BDNF
Cell Structure Myelin
p53
ROS
Glutathione
Astro.
Lipid perox.
Apoptosis
mTOR
Neuroprotection
Key
Primary Lithium Effects
Inhibitory
Facilitatory
Higher-Order System


Ins
SMIT
PI
PIP2
PLC
G
Rec
Rec
Rec
Gi
Gs
AC
mI
(c)
Li+
(a)
ImPase
IP3
DAG
cAMP
Li+
(b)
IP
IPPase
IP2
Li+
PKC
GSK-3
Reduces
IP3 levels
Ca2+ release
MARCKS
Akt
Triggers
autophagy
CREB
(d)
Li+
BDNF
Bcl-2
mTOR
Neuroprotection
Facilitates
Inhibits


Lithium
GSK-3β 3.1
Tau (mRNA)
Phospo-Tau 4.1
β-Catenin-Tcf Transcription 3.6
Bcl-2 3.5
Cytoprotection
Additive protective effects
IMPase
IP3 3.6
Autophagy
Clearance of mutant protein
BDNF 3.3
TrkB
Akt
ERK
Cytoprotection
MPTP
Calpain-I 3.4
P35
cdk5
P25
cdk5
MEF-2D
Cytotoxicity
MEF-2D & 2A
TH
Dopaminergic Synthesis/ Neuroprotection

What is happening in the brain?

- Mitochondria & bio-energetics
  - *Depression & Bipolar disorder*

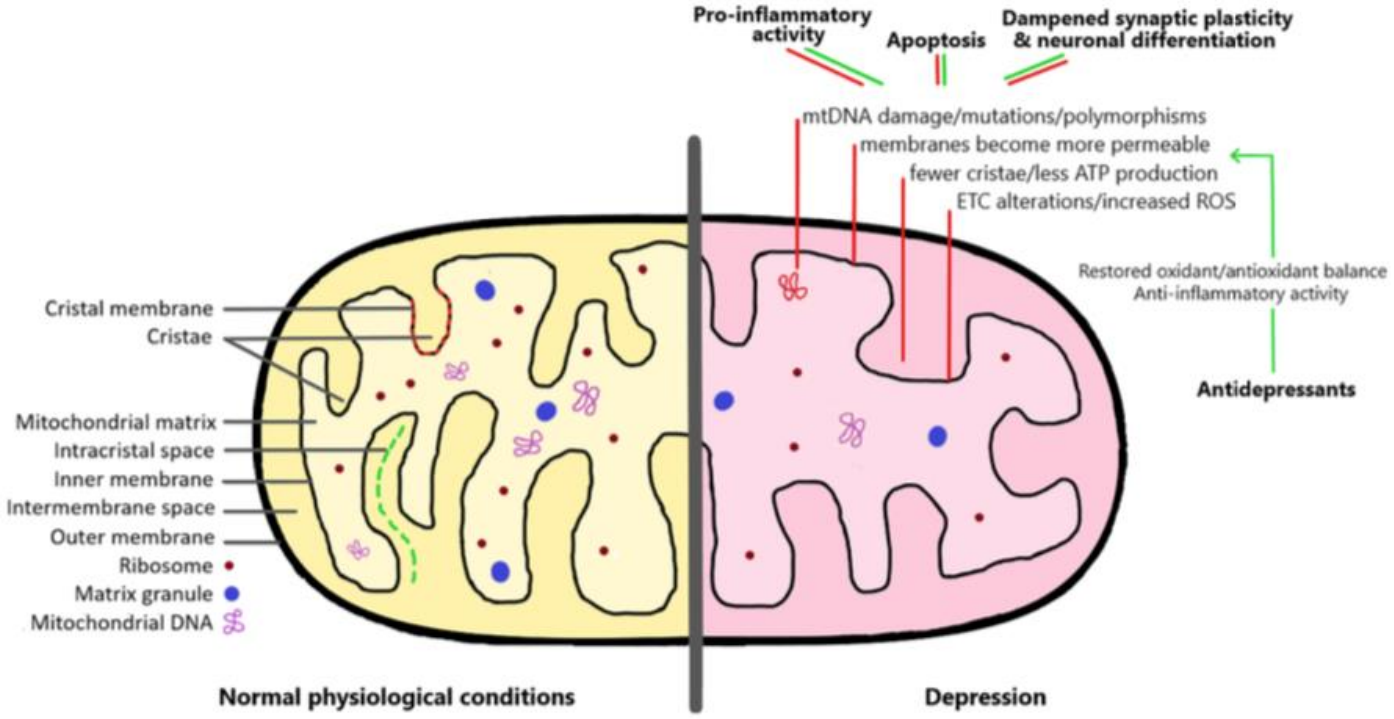
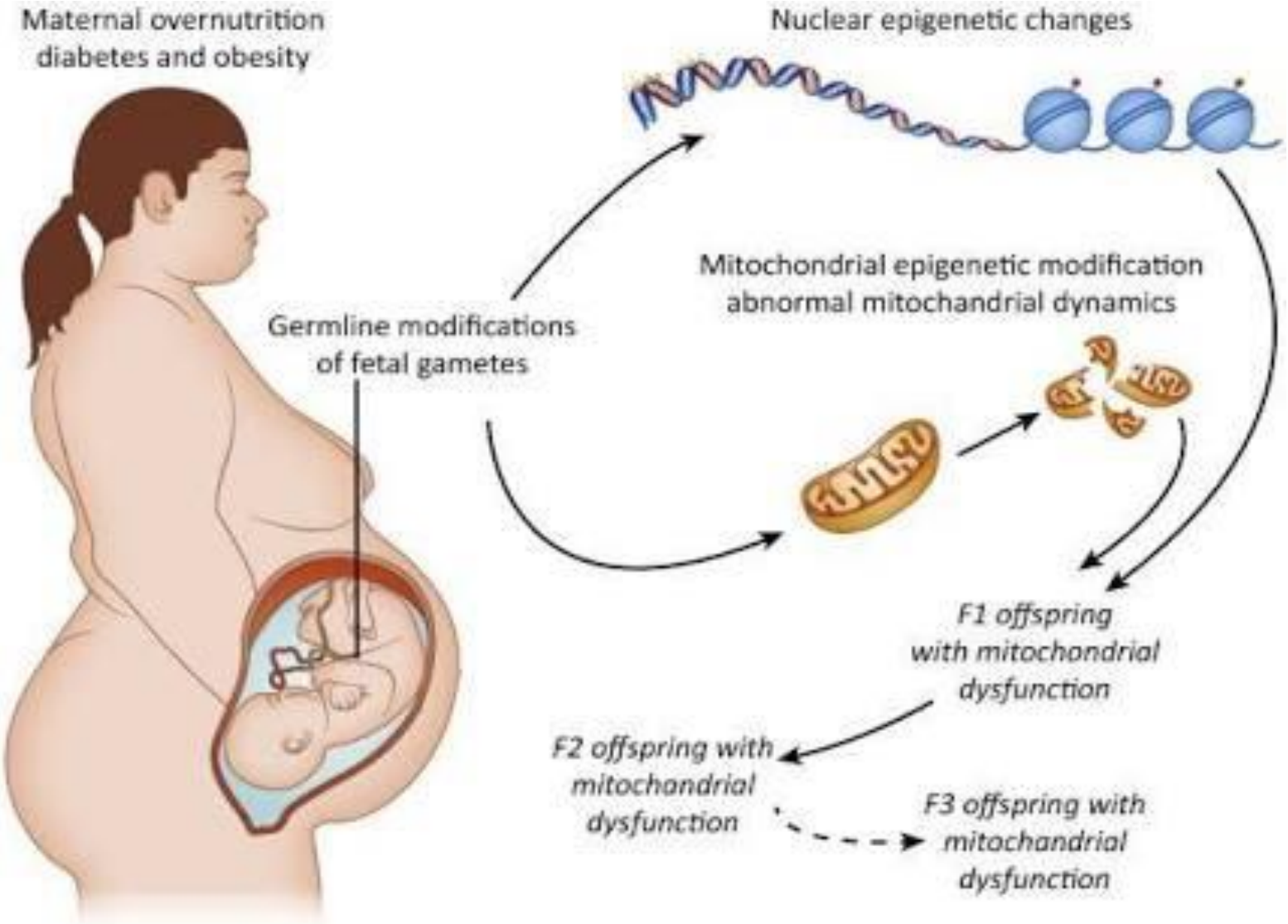
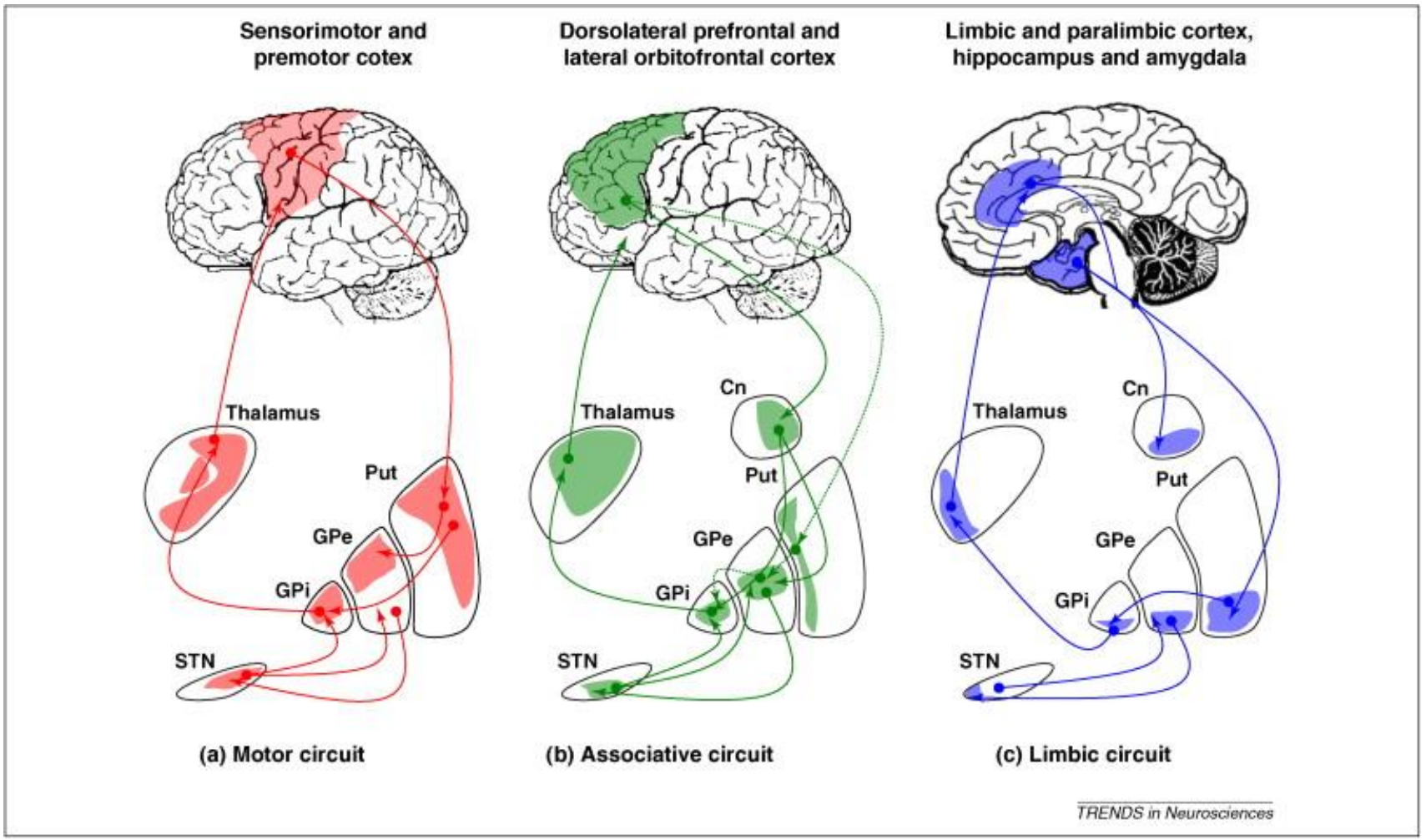


FIGURE 1 | The mitochondrion under normal physiological conditions and in the depression brain. As detailed in the right side of the image, there are a series of mitochondrial alterations that have been observed both in depressed patients and in animal models of depression (red lines). These include changes affecting mitochondrial DNA, membrane permeability, and increased formation of reactive oxygen species (ROS). As a consequence, these alterations lead to pro-inflammatory activity, increased apoptosis, and dampened synaptic plasticity and neuronal differentiation. Interestingly, antidepressant medication can restore the mitochondrial oxidant/antioxidant balance, and therefore help to rescue the negative effects of mitochondrial dysregulation (green lines). See the text for more detailed explanations.


Maternal overnutrition
diabetes and obesity
Nuclear epigenetic changes
Mitochondrial epigenetic modification
abnormal mitochandrial dynamics
Germline modifications
of fetal gametes
F1 offspring
with mitochondrial
dysfunction
F2 offspring with
mitochondrial
dysfunction
F3 offspring with
mitochandrial
dysfunction

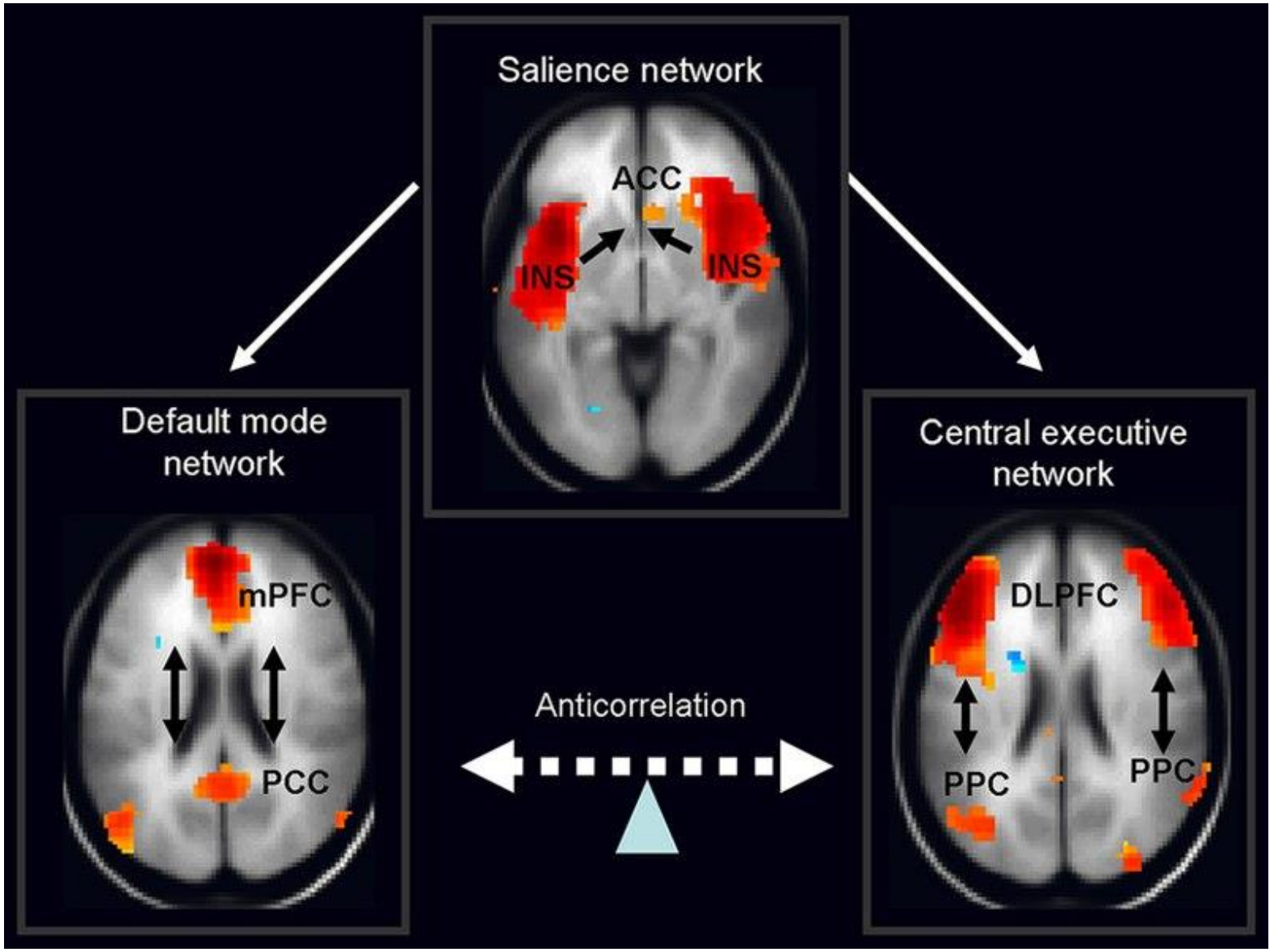
What is happening in the brain?

- Areas in isolation – no
- Areas in unison – yes
- The CSTC loops
  - *Cognition - Schizophrenia*
  - *Emotion processing - Mood Disorders*
  - *Motor behavior - OCRD*


Sensorimotor and premotor cotex
Dorsolateral prefrontal and lateral orbitofrontal cortex
Limbic and paralimbic cortex, hippocampus and amygdala
Thalamus
Put
GPe
GPi
STN
Cn
(a) Motor circuit
(b) Associative circuit
(c) Limbic circuit
TRENDS in Neurosciences

What is happening in the brain?

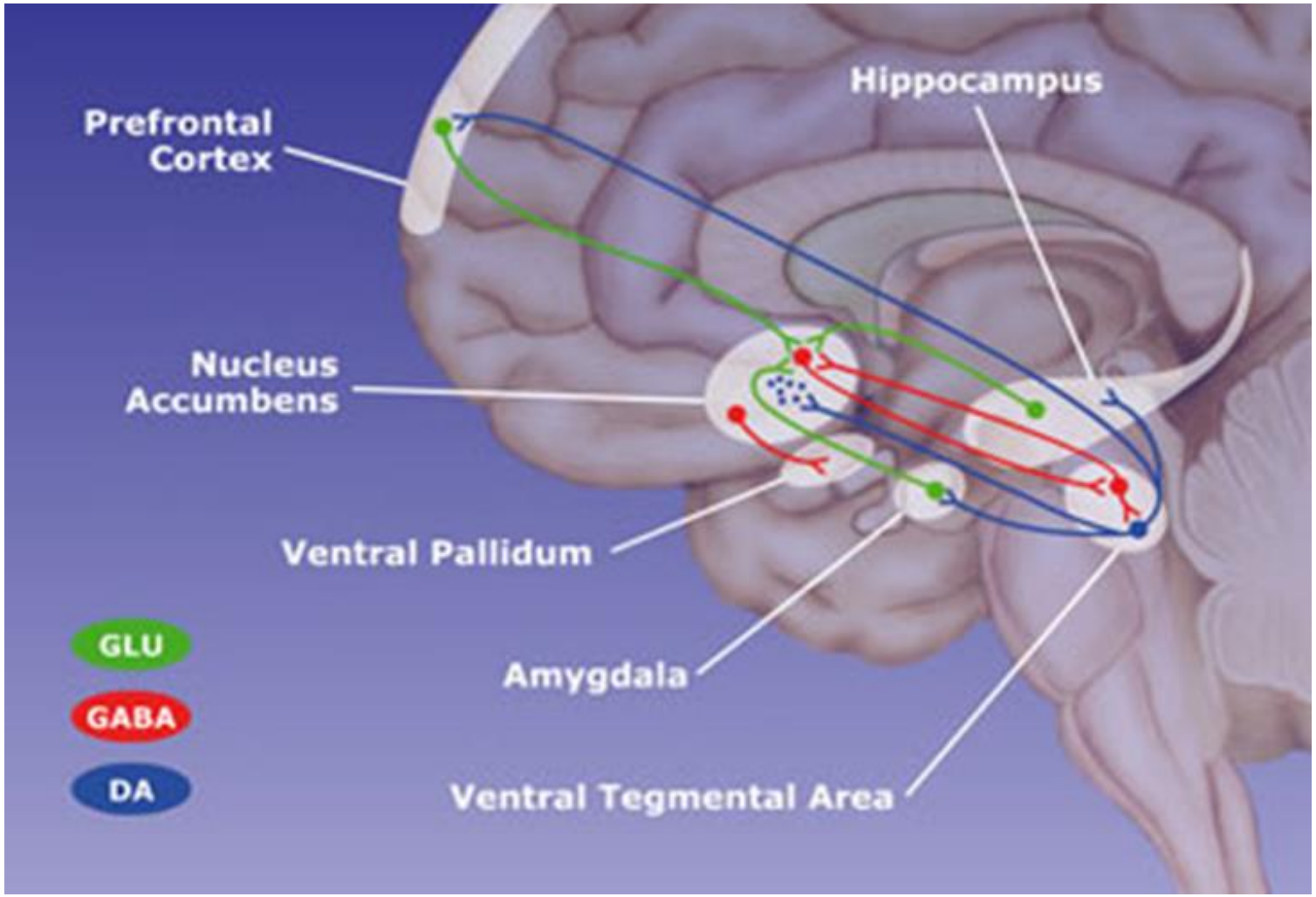
- Networks
  - *Nodes*
  - *Connections*
- Default Mode Network
  - *Consciousness, Autobiographical Memory, Self*
- Salience Network
  - *Attention*
- Central Executive Network
  - *Processing & execution*


Salience network
ACC
INS
INS
Default mode network
mPFC
PCC
Central executive network
DLPFC
PPC
PPC
Anticorrelation

What is happening in the brain?

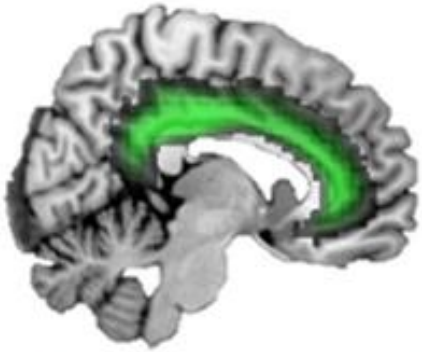
- Reward Circuit
  - *Basis of addictions*

The Reward Circuit



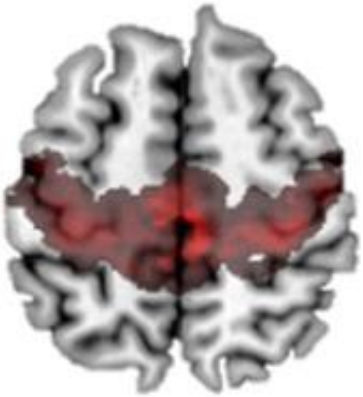
And what is cerebellum doing here?

As in motion, so in cognition



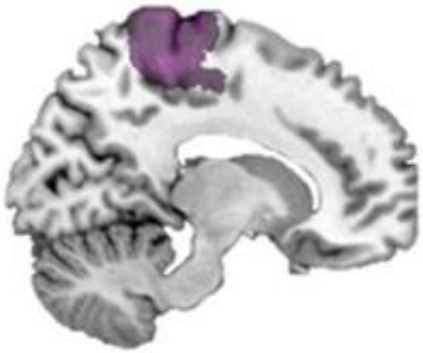
Posterior Vermis

- Affective dysregulation
- Social processing deficits
- Irritability



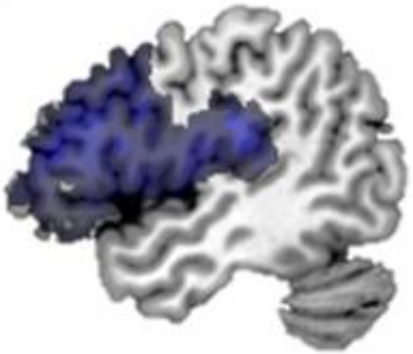
Anterior lobe

- Stereotyped and repetitive behaviors
- Motor impairments



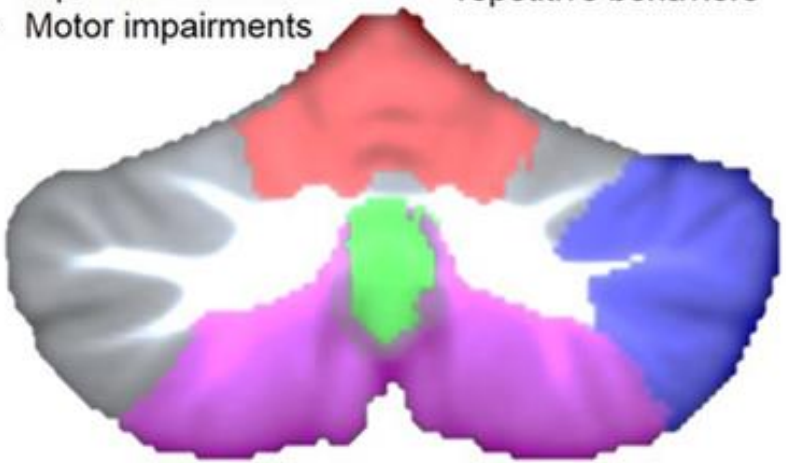
VIIIA & VIIIB

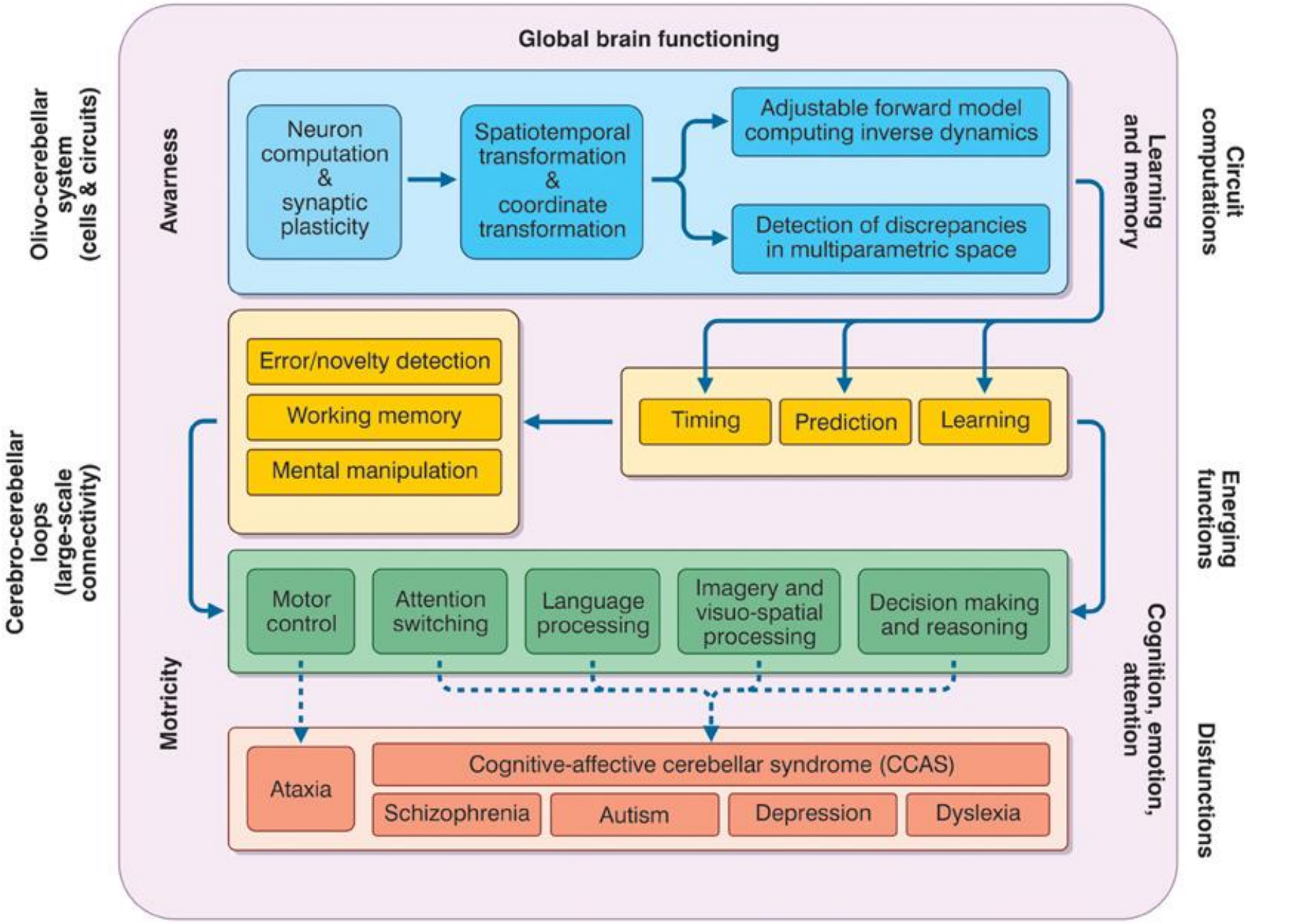
- Stereotyped and repetitive behaviors



Right Crus I & II

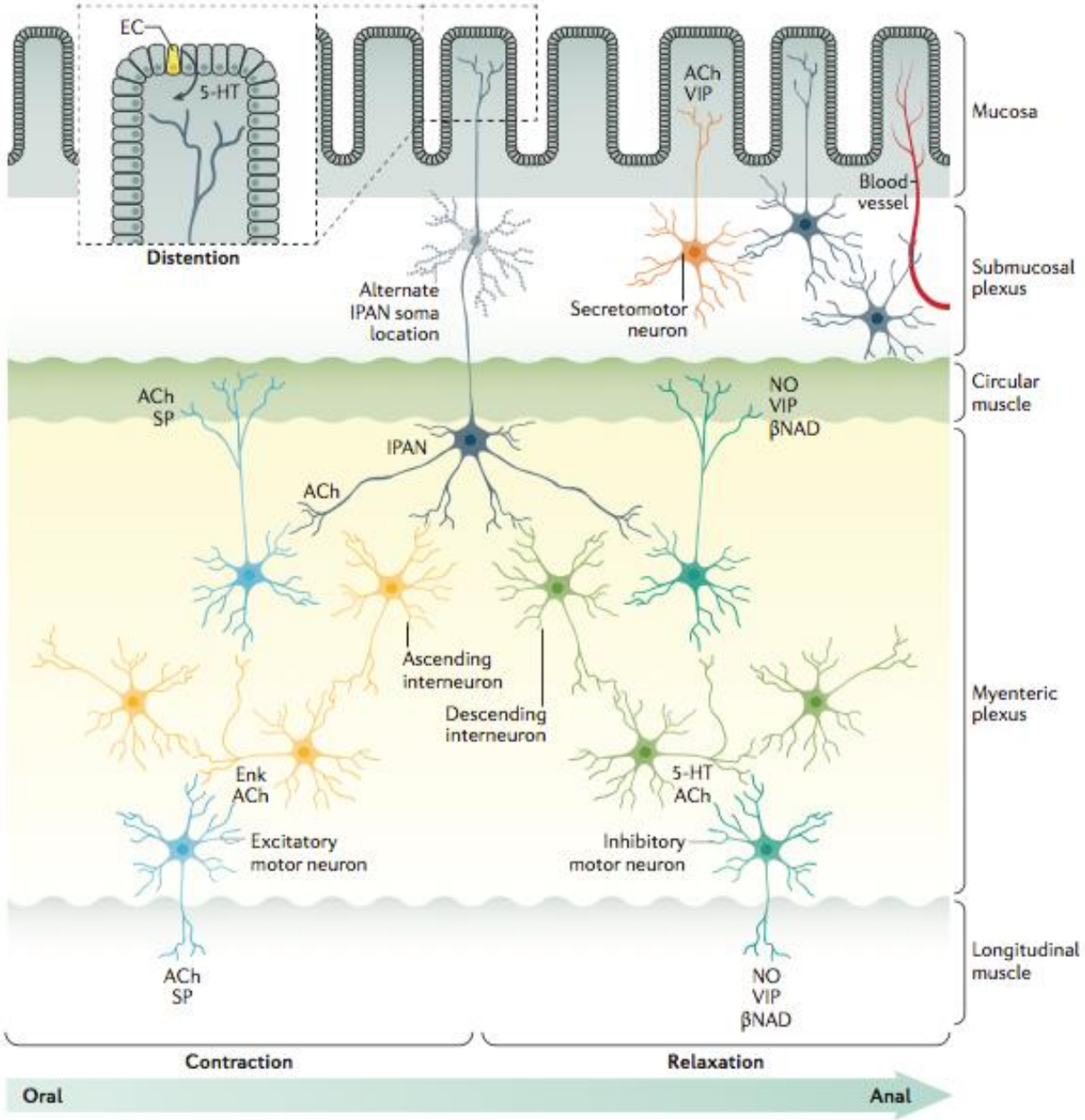
- Language deficits
- Social cognition deficits
- Theory of mind deficits
- Face processing impairments
- Imitation impairments
- Stereotyped and repetitive behaviors

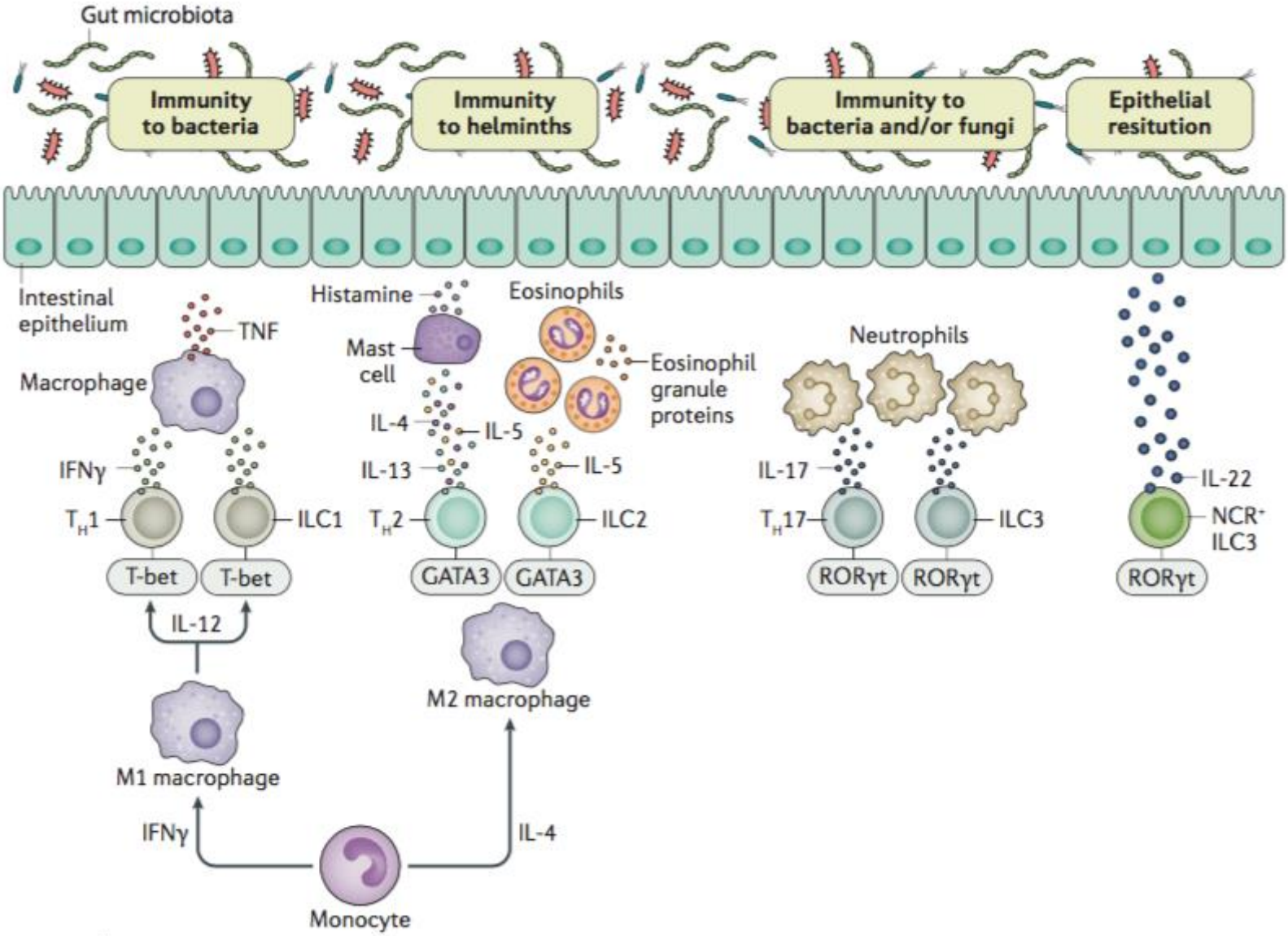


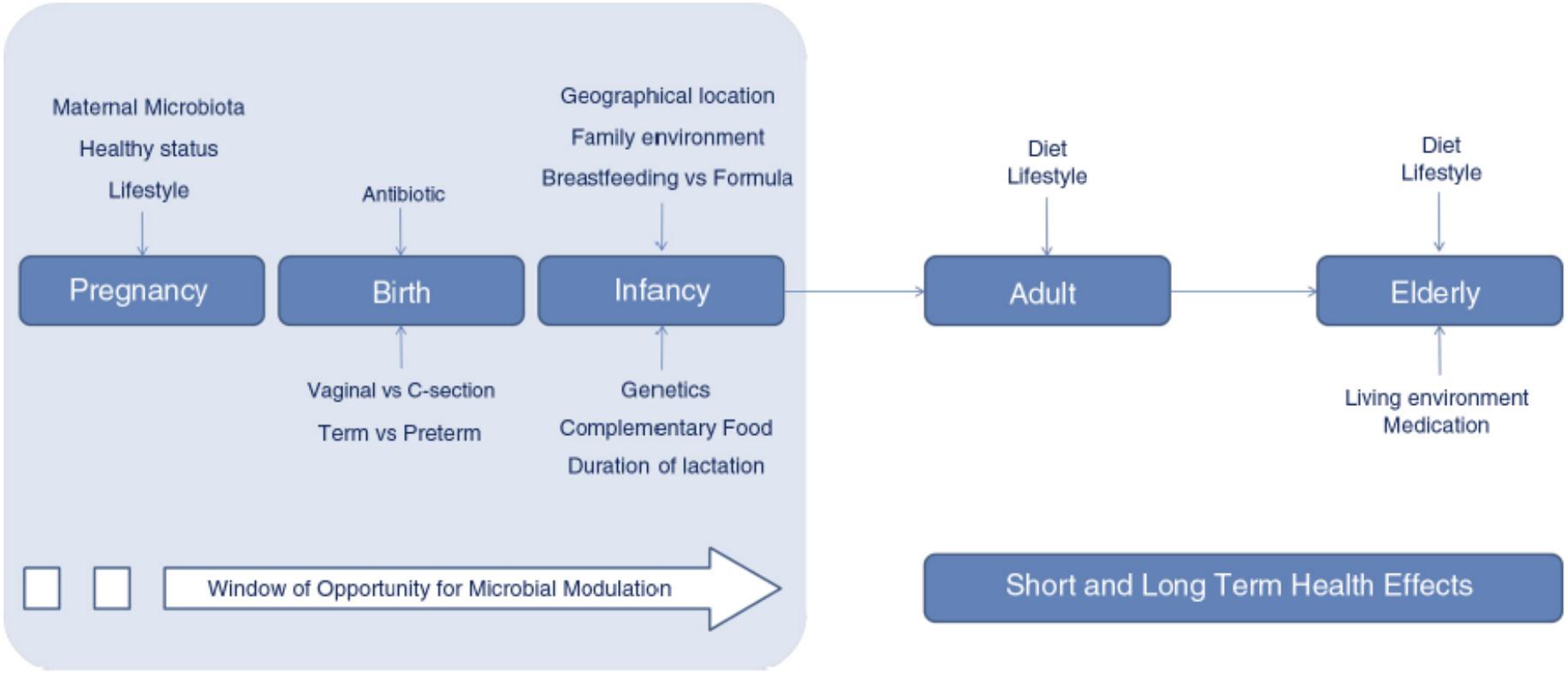

Global brain functioning
Olivo-cerebellar system (cells & circuits)
Awarness
Neuron computation & synaptic plasticity
Spatiotemporal transformation & coordinate transformation
Adjustable forward model computing inverse dynamics
Detection of discrepancies in multiparametric space
Learning and memory
Circuit computations
Error/novelty detection
Working memory
Mental manipulation
Timing
Prediction
Learning
Cerebro-cerebellar loops (large-scale connectivity)
Energing functions
Motricity
Motor control
Attention switching
Language processing
Imagery and visuo-spatial processing
Decision making and reasoning
Cognition, emotion, attention
Ataxia
Cognitive-affective cerebellar syndrome (CCAS)
Schizophrenia
Autism
Depression
Dyslexia
Disfunctions

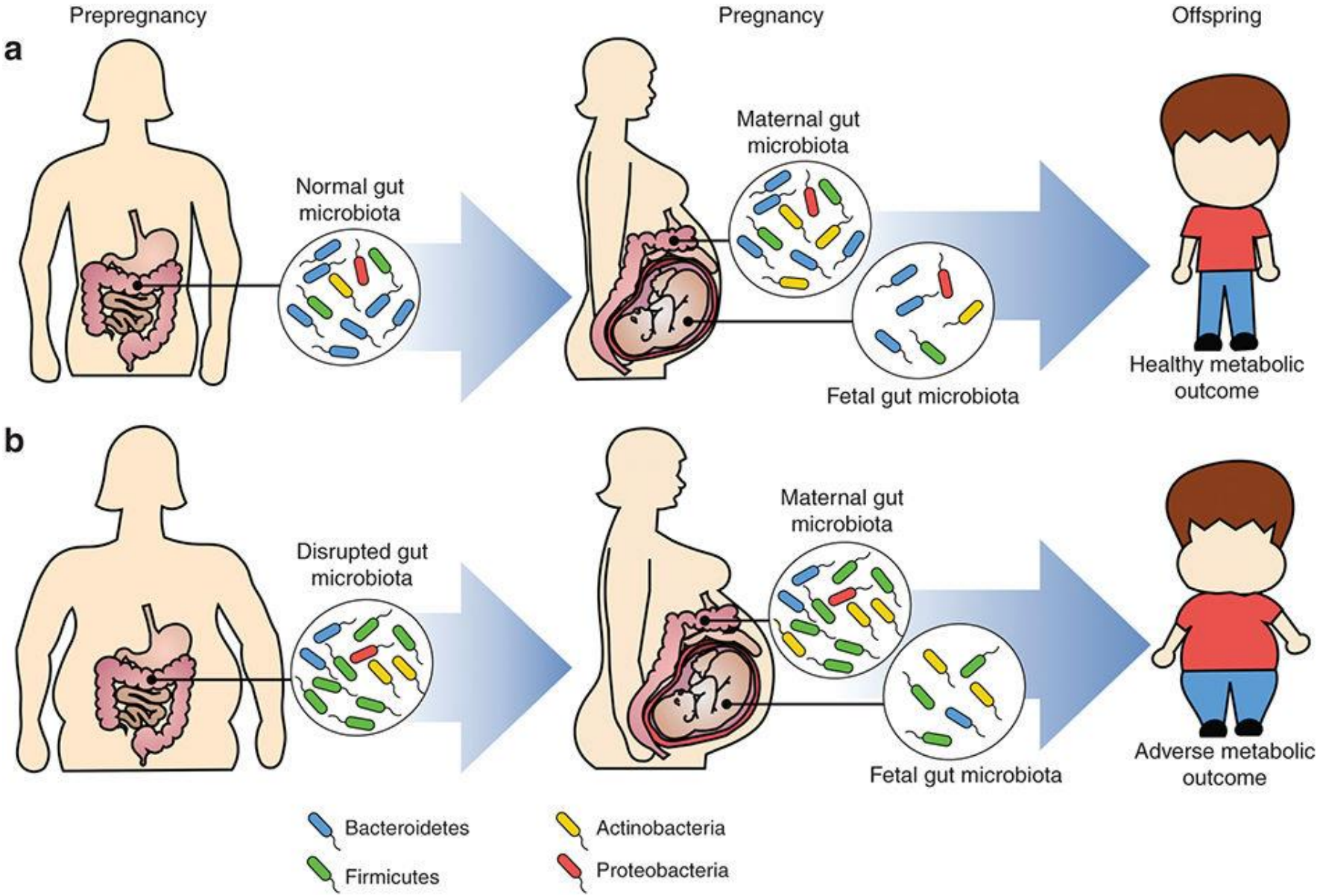
Is there a second brain?

- Discovered in the late 1900's
- Part of the autonomic nervous system
- "On Site" control of gut behavior
- Can alert the organism to danger & influence response (Unconscious)
- 90% of Vagus Nerve information flow is from the gut to the brain


EC
5-HT
Distention
ACh
VIP
Blood vessel
Mucosa
Alternate IPAN soma location
Secretomotor neuron
Submucosal plexus
Circular muscle
ACh
SP
IPAN
ACh
NO
VIP
βNAD
Ascending interneuron
Descending interneuron
Myenteric plexus
Enk
ACh
Excitatory motor neuron
5-HT
ACh
Inhibitory motor neuron
ACh
SP
NO
VIP
βNAD
Longitudinal muscle
Contraction
Relaxation
Oral
Anal


Gut microbiota
Immunity to bacteria
Immunity to helminths
Immunity to bacteria and/or fungi
Epithelial resitution
Intestinal epithelium
TNF
Macrophage
IFNγ
T_H1
ILC1
T-bet
T-bet
IL-12
M1 macrophage
Histamine
Mast cell
Eosinophils
Eosinophil granule proteins
IL-4
IL-5
IL-13
IL-5
T_H2
ILC2
GATA3
GATA3
M2 macrophage
Neutrophils
IL-17
T_H17
ILC3
RORγt
RORγt
IL-22
NCR+ ILC3
RORγt
IFNγ
IL-4
Monocyte

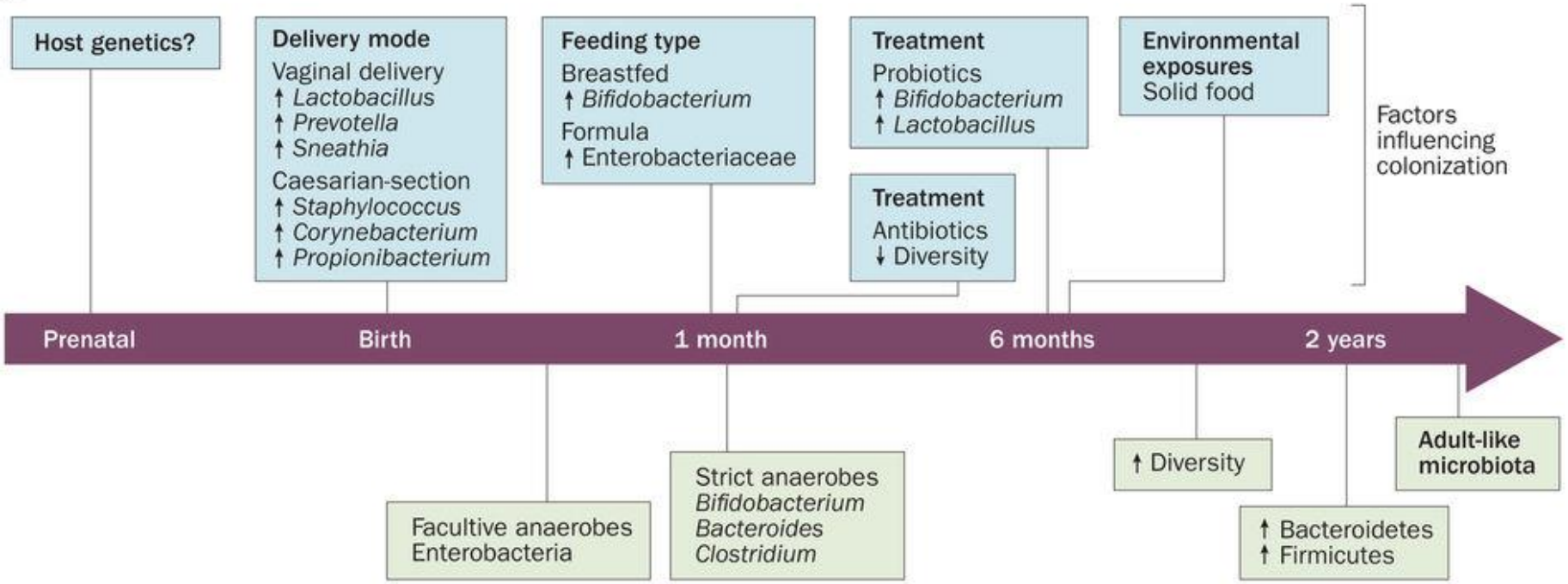

Maternal Microbiota
Healthy status
Lifestyle
Antibiotic
Geographical location
Family environment
Breastfeeding vs Formula
Diet
Lifestyle
Diet
Lifestyle
Pregnancy
Birth
Infancy
Adult
Elderly
Vaginal vs C-section
Term vs Preterm
Genetics
Complementary Food
Duration of lactation
Living environment
Medication
Window of Opportunity for Microbial Modulation
Short and Long Term Health Effects


Prepregnancy
Pregnancy
Offspring
a
Normal gut microbiota
Maternal gut microbiota
Fetal gut microbiota
Healthy metabolic outcome
b
Disrupted gut microbiota
Maternal gut microbiota
Fetal gut microbiota
Adverse metabolic outcome
Bacteroidetes
Firmicutes
Actinobacteria
Proteobacteria

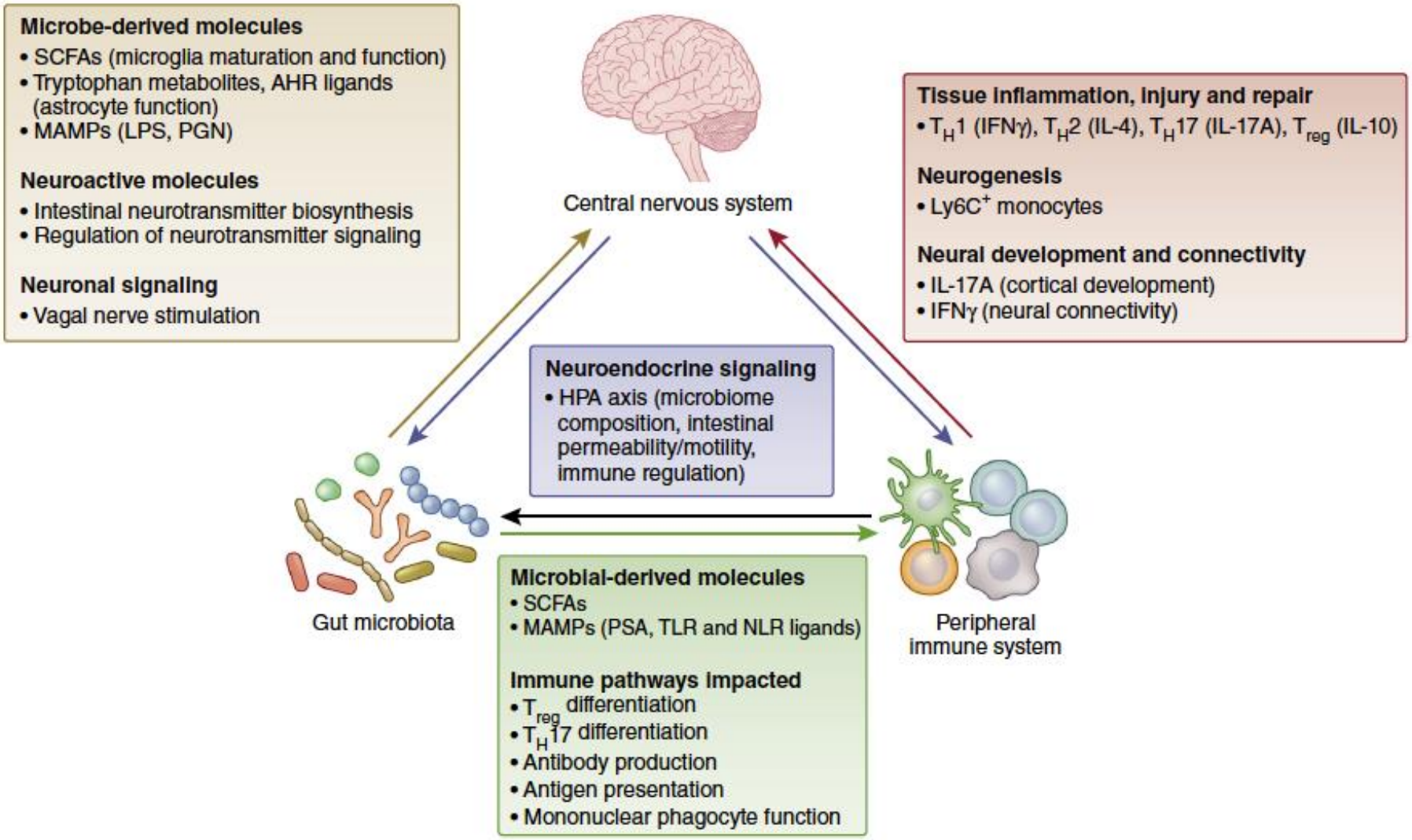
a

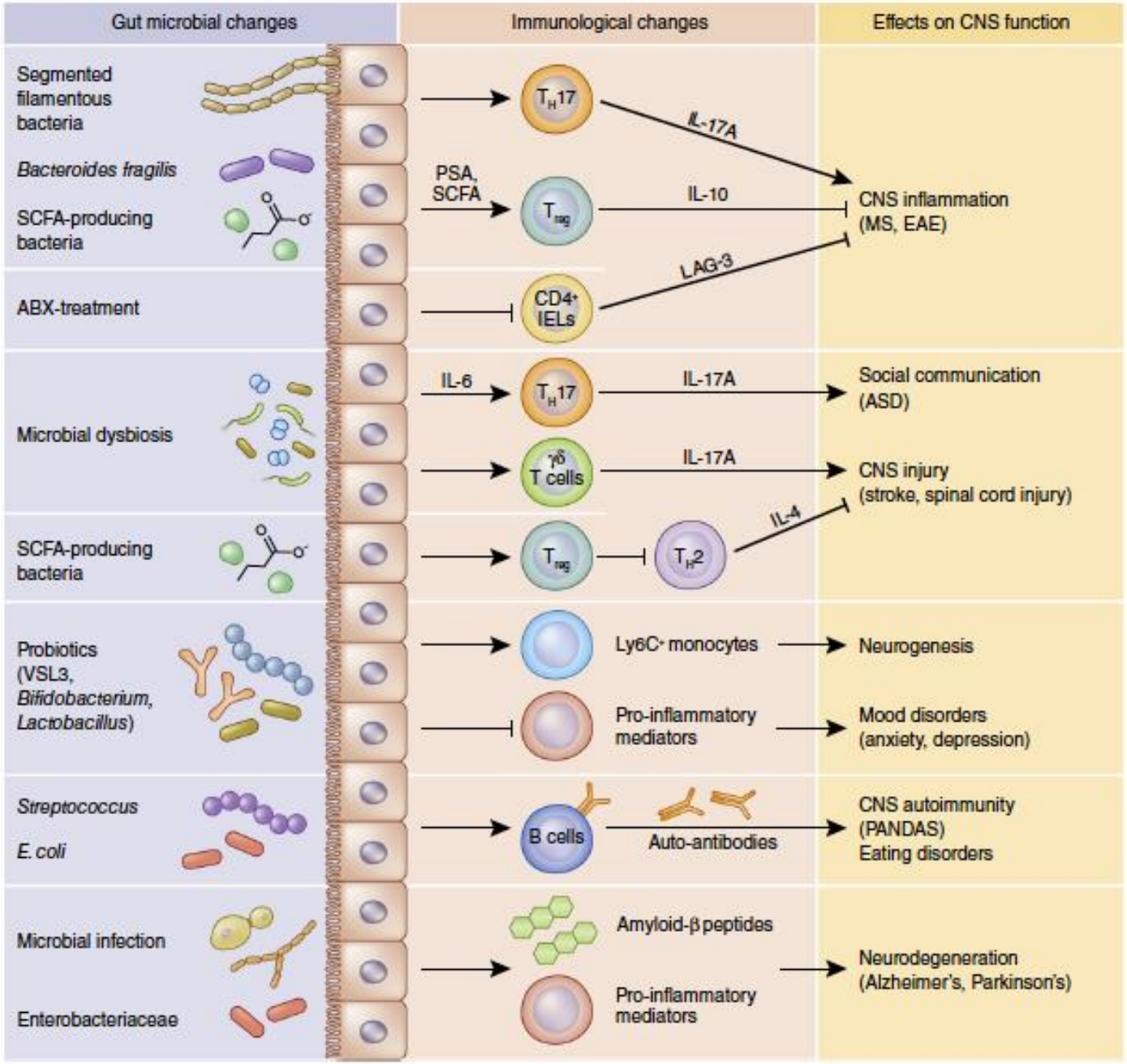
Intestinal location	Stomach	Duodenum	Jejunum	Ileum	Colon
Microbes/gram	1×10^{1}	1×10^{3}	1×10^{4}	1×10^{7}	1×10^{12}
Composition	*Lactobacillus* *Helicobacter* *Veillonella*	*Streptococcus* *Lactococcus* *Staphylococcus*	*Lactobacillus* *Streptococcus* *Enterococcus*	SFB Enterobacteriaceae *Bacteroides* *Clostridium*	*Bacteroides* *Clostridium* Lachnospiraceae Proteobacteria Actinobacteria Prevotellaceae

b



Nature Reviews | Gastroenterology & Hepatology


Microbe-derived molecules
• SCFAs (microglia maturation and function)
• Tryptophan metabolites, AHR ligands (astrocyte function)
• MAMPs (LPS, PGN)
Neuroactive molecules
• Intestinal neurotransmitter biosynthesis
• Regulation of neurotransmitter signaling
Neuronal signaling
• Vagal nerve stimulation
Central nervous system
Tissue inflammation, injury and repair
• T_H1 (IFNγ), T_H2 (IL-4), T_H17 (IL-17A), T_{reg} (IL-10)
Neurogenesis
• Ly6C$^+$ monocytes
Neural development and connectivity
• IL-17A (cortical development)
• IFNγ (neural connectivity)
Neuroendocrine signaling
• HPA axis (microbiome composition, intestinal permeability/motility, immune regulation)
Gut microbiota
Peripheral immune system
Microbial-derived molecules
• SCFAs
• MAMPs (PSA, TLR and NLR ligands)
Immune pathways impacted
• T_{reg} differentiation
• T_H17 differentiation
• Antibody production
• Antigen presentation
• Mononuclear phagocyte function


Gut microbial changes
Immunological changes
Effects on CNS function
Segmented filamentous bacteria
Bacteroides fragilis
SCFA-producing bacteria
ABX-treatment
PSA, SCFA
T_H17
T_{reg}
CD4+ IELs
IL-17A
IL-10
LAG-3
CNS inflammation (MS, EAE)
Microbial dysbiosis
SCFA-producing bacteria
IL-6
T_H17
γδ T cells
T_{reg}
T_H2
IL-17A
IL-17A
IL-4
Social communication (ASD)
CNS injury (stroke, spinal cord injury)
Probiotics (VSL3, Bifidobacterium, Lactobacillus)
Ly6C+ monocytes
Pro-inflammatory mediators
Neurogenesis
Mood disorders (anxiety, depression)
Streptococcus
E. coli
B cells
Auto-antibodies
CNS autoimmunity (PANDAS)
Eating disorders
Microbial infection
Enterobacteriaceae
Amyloid-β peptides
Pro-inflammatory mediators
Neurodegeneration (Alzheimer's, Parkinson's)

What is the role of Development and Degeneration?

- Many psychiatric illnesses are developmental in origin
  - *ADHD, ASD, IDD, SLD*
- Many psychiatric illnesses are degenerative in origin
  - *Dementias*
- Most psychiatric illnesses are a combination of the two
- Genetically determined

Predetermined epigenesis:

(Unidirectional structure–functional development)

genes → brain structure → brain function → experience

Probablistic epigenesis:

(Bidirectional structure–functional development)

genes ↔ brain structure ↔ brain function ↔ experience

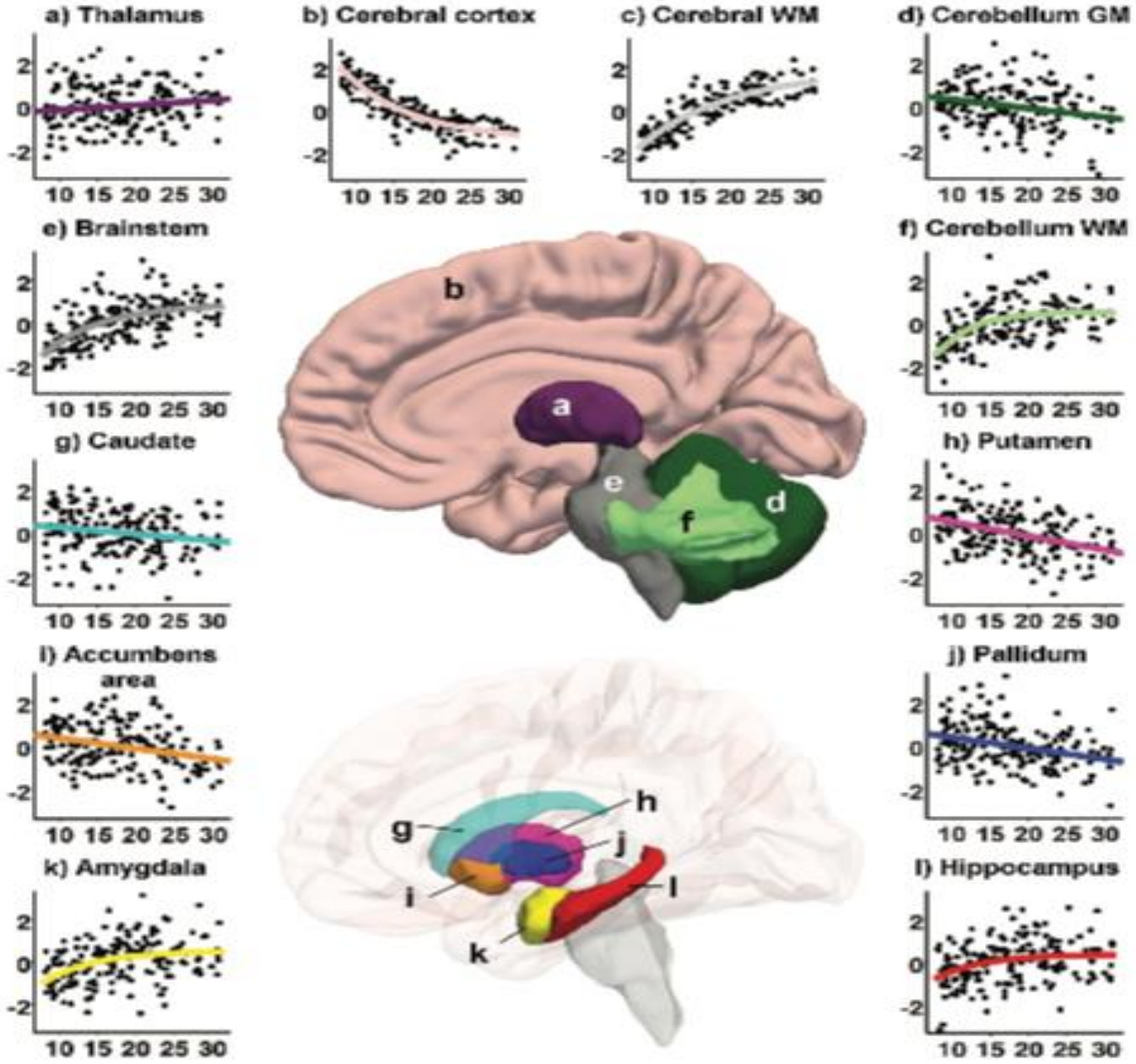
Development

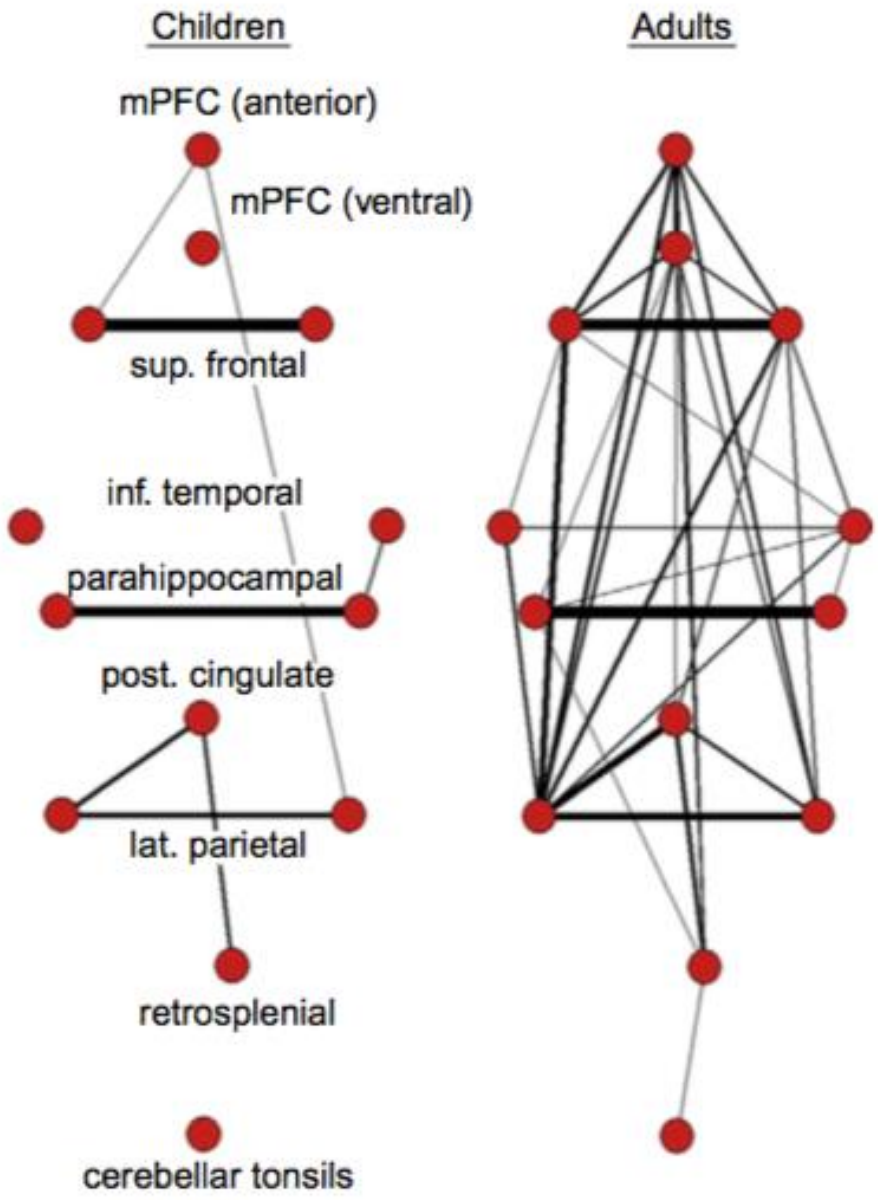
- Nature – **Genetics**
- Nurture – **Tabula rasa**
- **BOTH** genes and environment make significant contributions to the regulation of how development unfolds
- Epigenesis – **G x E** interactions
- **Plasticity**
- **Chronobiology** – Periodicity
- Individual **variations**

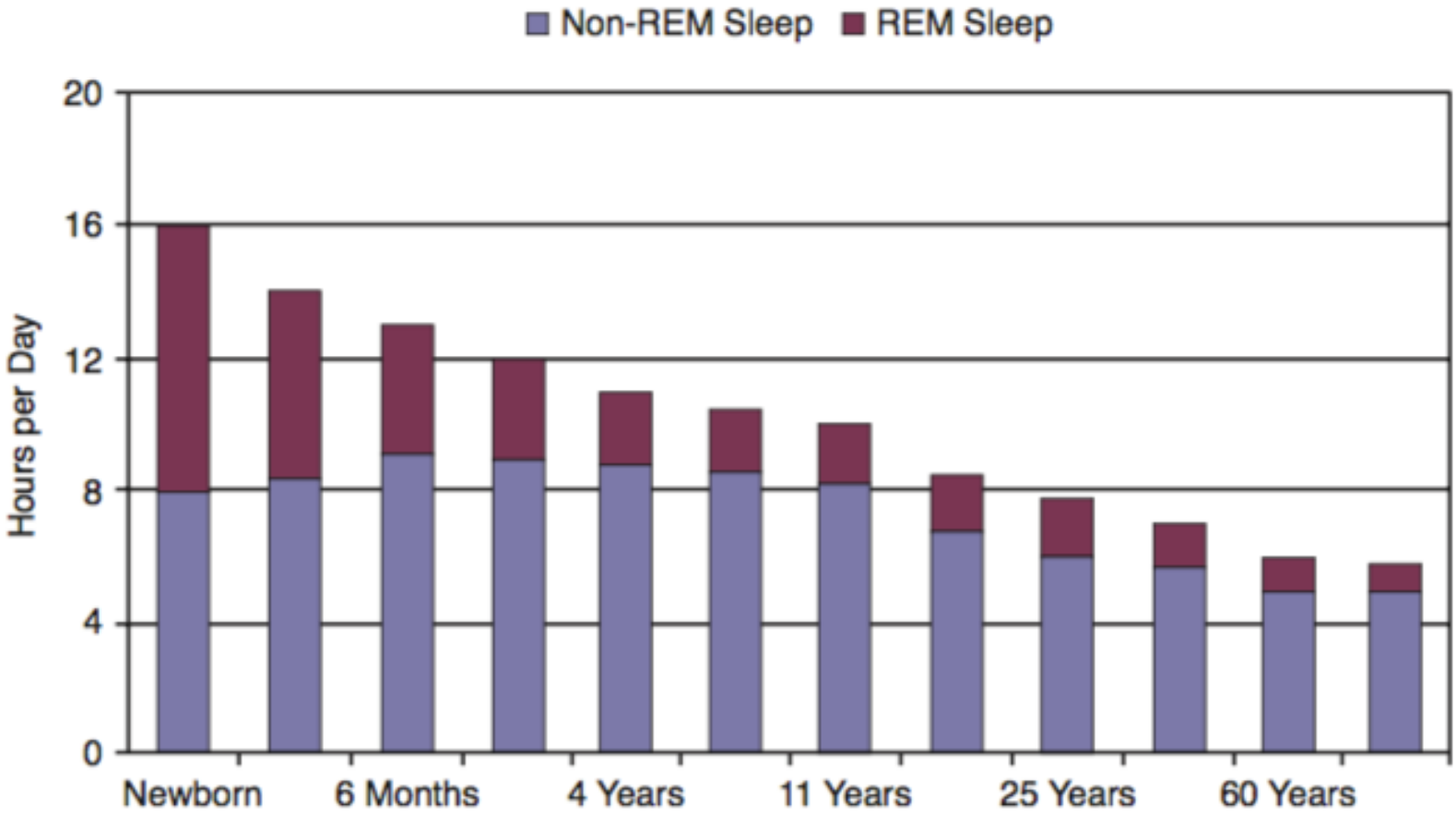
Development

- **Differential** growth – Intraregional, Interregional, Hemispherical
- **Protracted** growth – into adulthood
- **Pruning – “**Use it Or Lose it”
- **Nodes** & networks
- **Lateralization** – “Logical thinking”
- **Efficiency**
- **Sexual** differentiation

Region	Functions	Girls / Boys
Frontal plobes	Planning, organizing, strateging, initiating, shifting, sustaining, attention	11.0 years / 12.1 years
Temporal lobes	Language, emotional, memory	16.7 years / 16.2 years
Parietal lobes	Receiving and processing sensory input	10.2 years / 11.8 years


a) Thalamus
b) Cerebral cortex
c) Cerebral WM
d) Cerebellum GM
e) Brainstem
f) Cerebellum WM
g) Caudate
h) Putamen
i) Accumbens area
j) Pallidum
k) Amygdala
l) Hippocampus
2
0
-2
10 15 20 25 30
a
b
d
e
f
g
h
i
j
k
l


Children
Adults
mPFC (anterior)
mPFC (ventral)
sup. frontal
inf. temporal
parahippocampal
post. cingulate
lat. parietal
retrosplenial
cerebellar tonsils


Non-REM Sleep
REM Sleep
Hours per Day
20
16
12
8
4
0
Newborn
6 Months
4 Years
11 Years
25 Years
60 Years

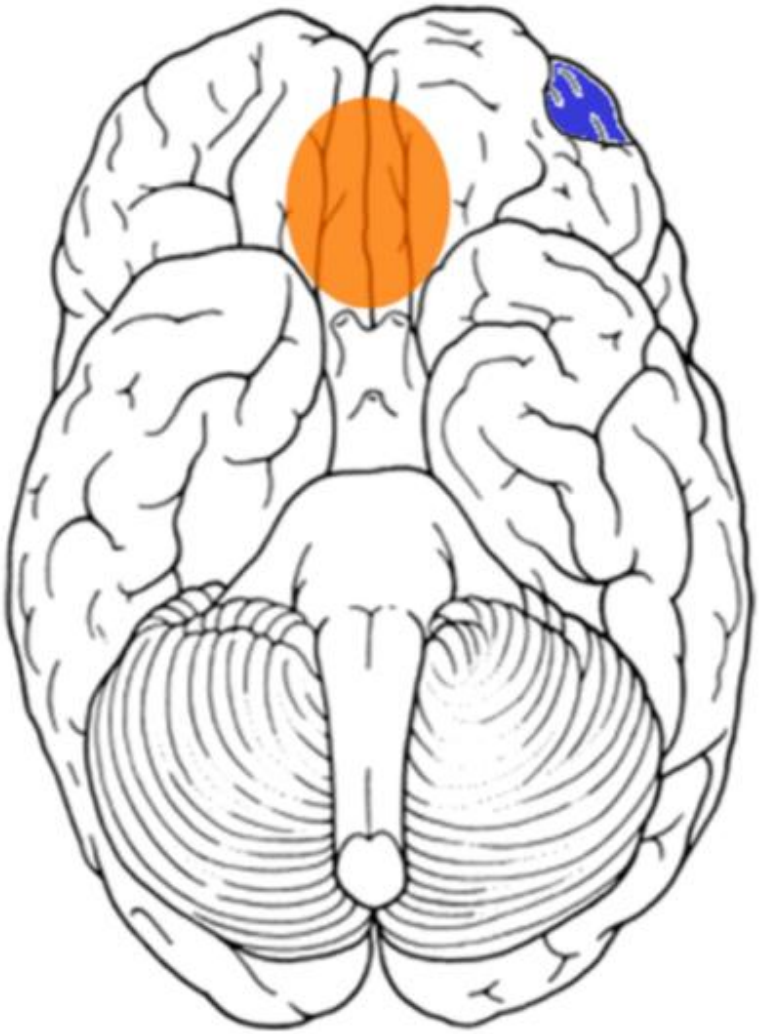
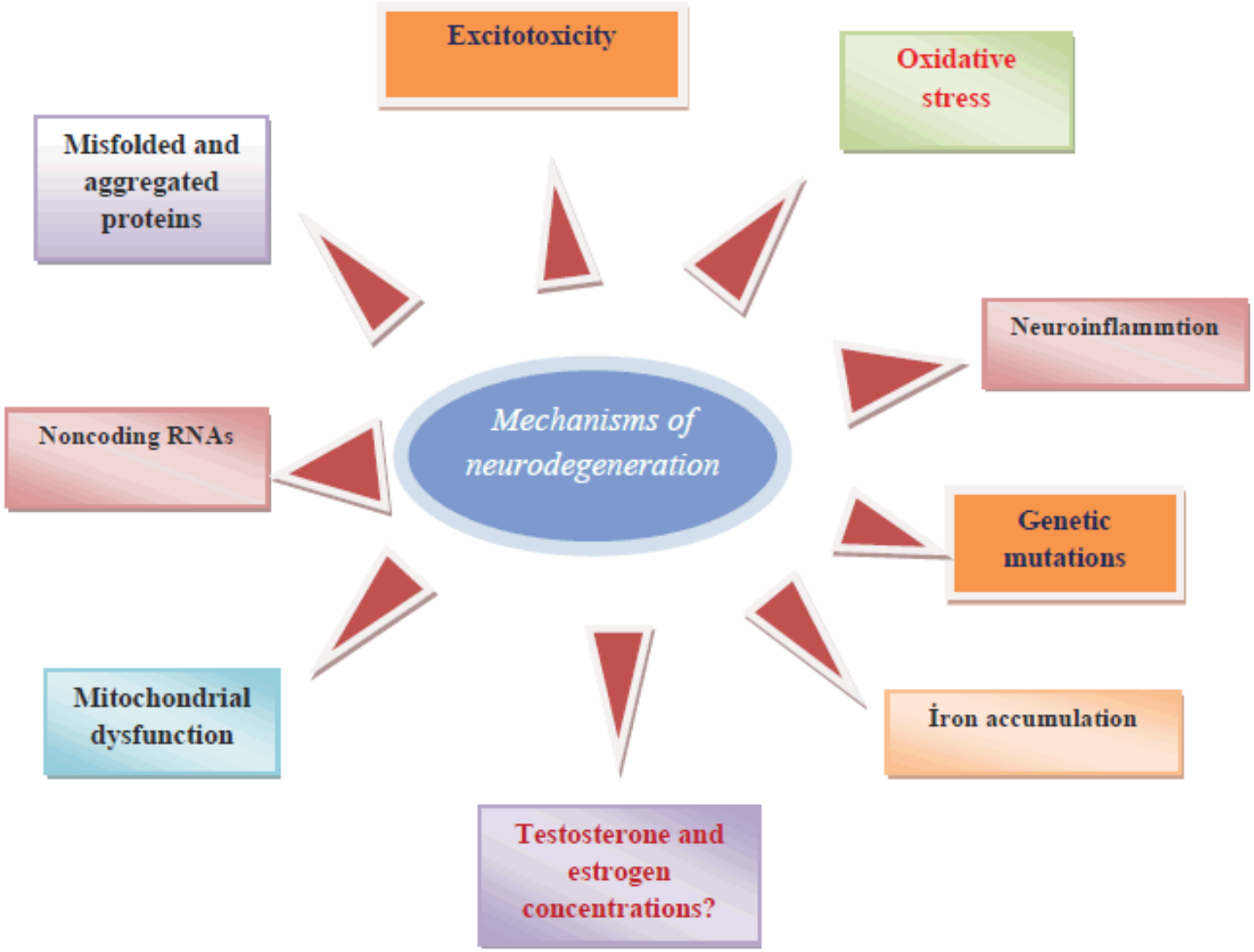


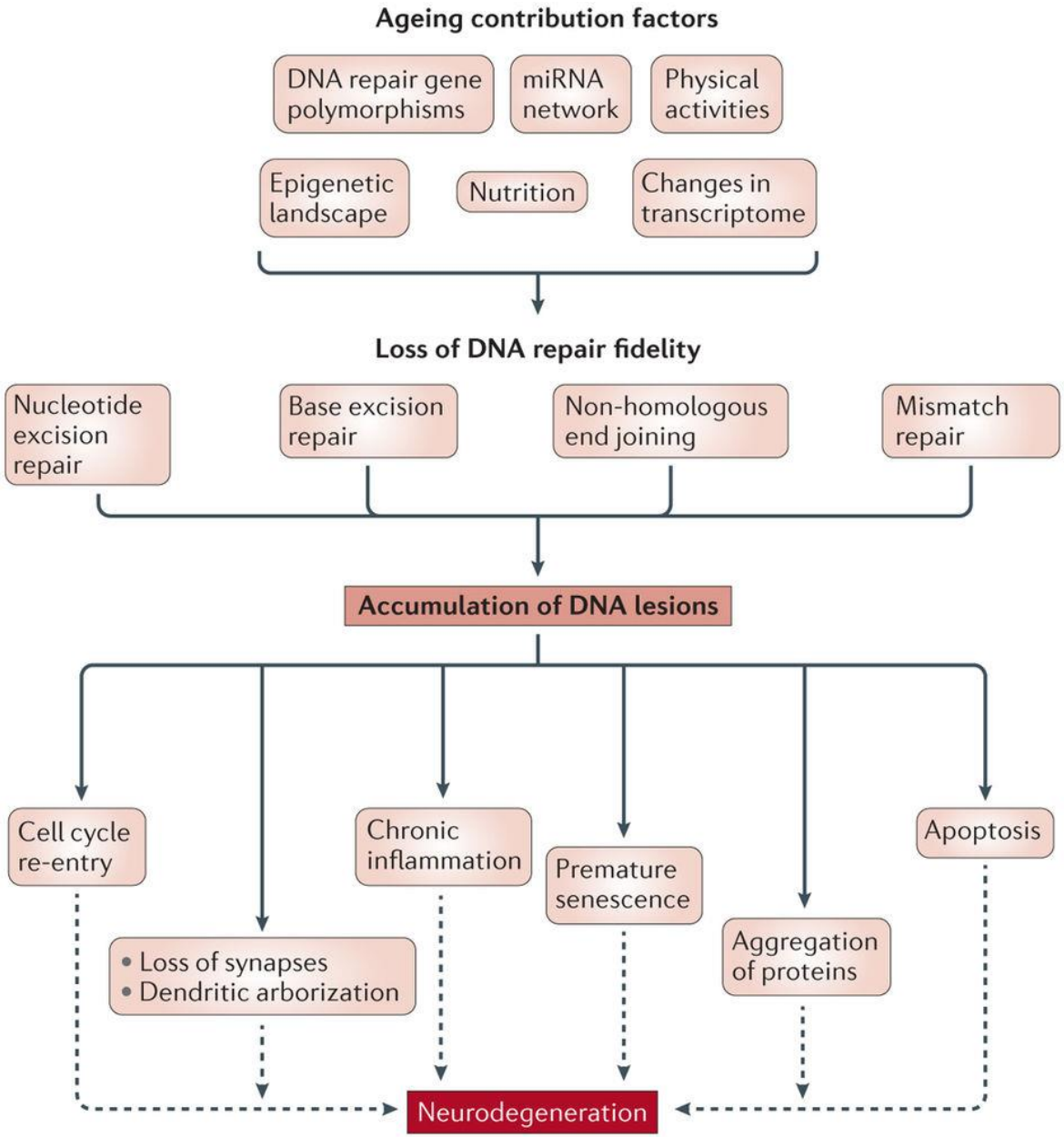
Fig. 3.3. The areas of the frontal cortex active during empathic responses change from the ventromedial portion (in orange) of the orbitofrontal cortex (OFC) in childhood to the lateral OFC (colored blue) in adulthood, with a gradual shift from 10 to 40 years. (*Source*: See Ref. 77 for original data.)

Degeneration

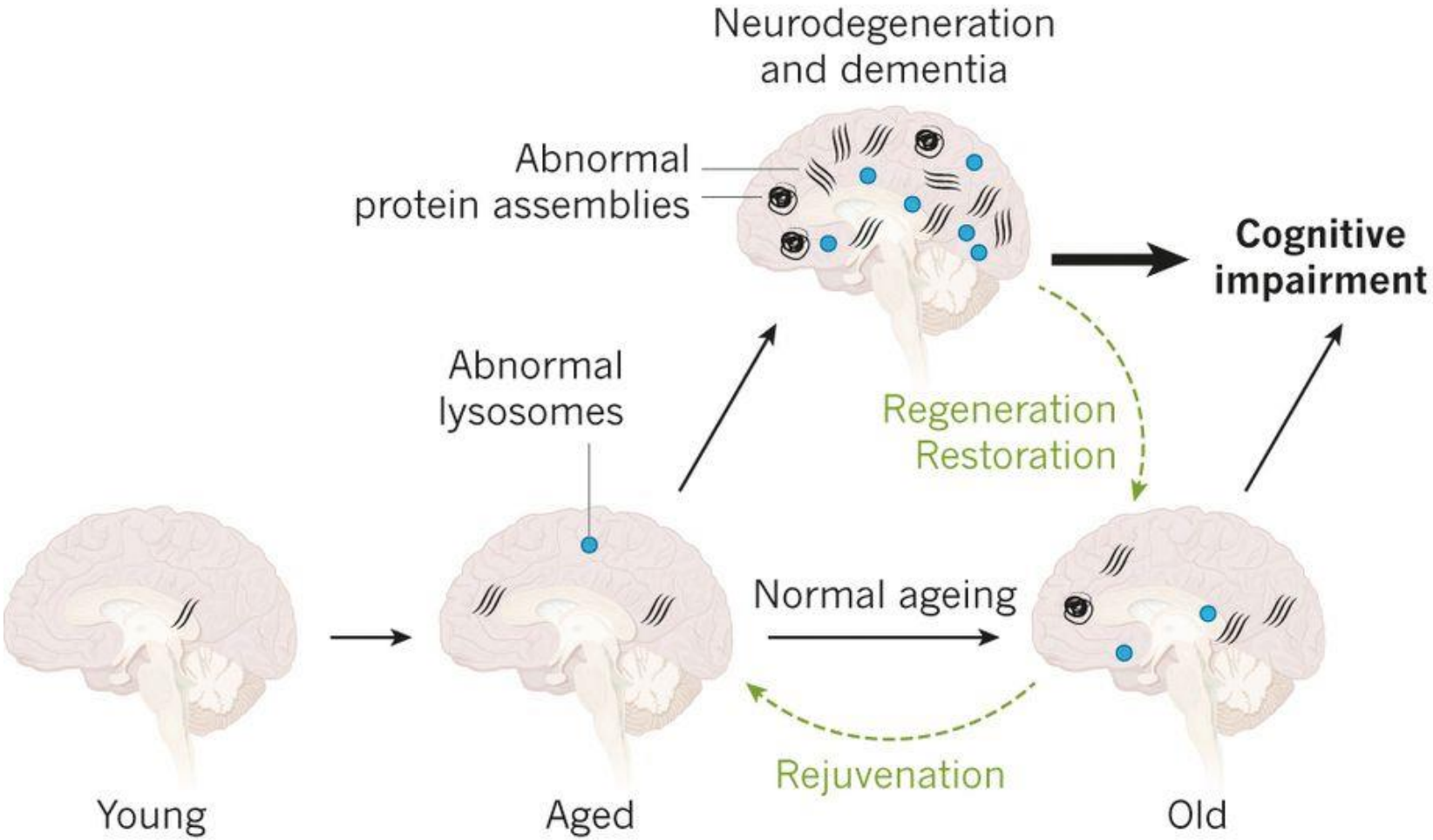
- Multifactorial
- Genetically determined



Different biological process which are involved in the development of neurodegeneration



Nature Reviews | Neuroscience


Neurodegeneration
and dementia
Abnormal
protein assemblies
Cognitive
impairment
Abnormal
lysosomes
Regeneration
Restoration
Normal ageing
Rejuvenation
Young
Aged
Old

What is the master control?

Heritability of Psychiatric Disorders

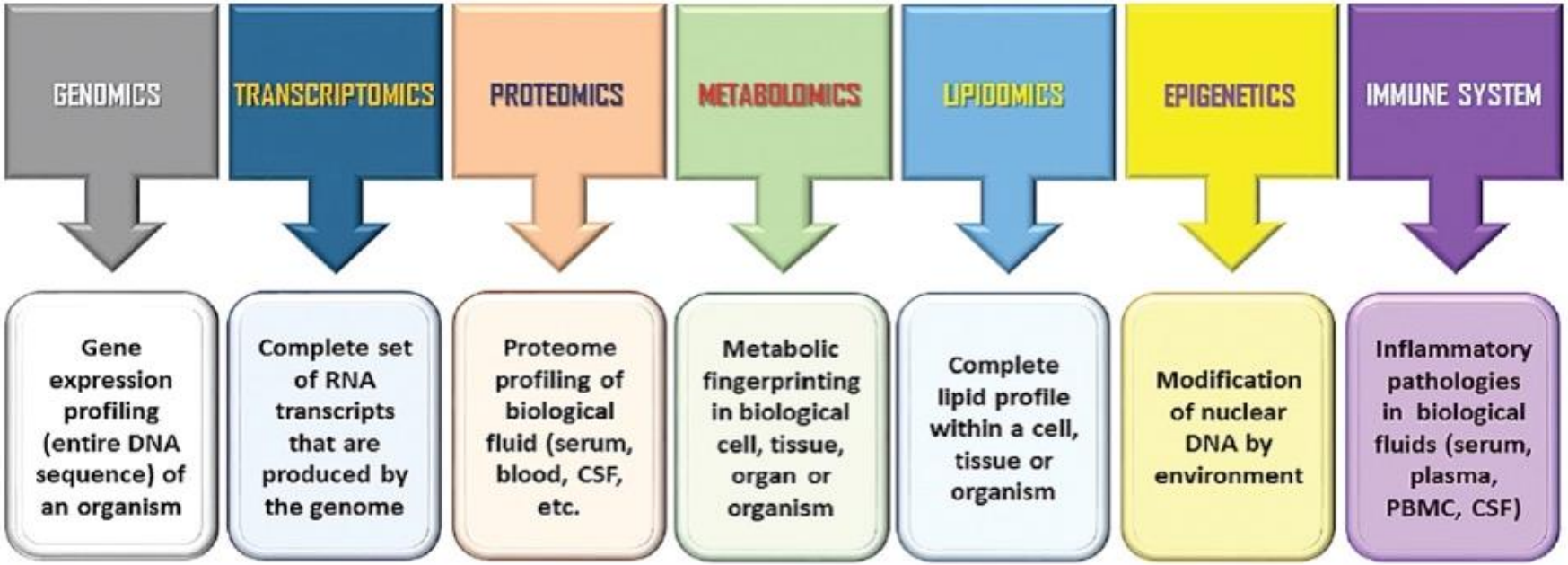
Disease	Heritability
Schizophrenia	0.81
Autism spectrum disorder	0.80
Bipolar disorder	0.75
Major depression	0.37
Attention deficit disorder	0.75
Alzheimer's disease	0.58

Source: Sullivan PF, et al. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet 2012;13:537-52.

What is the master control?

- Genetics
  - *Single gene – rare*
  - *Multiple genes – small effects*
  - *G X E*
- Variability
- Concordance

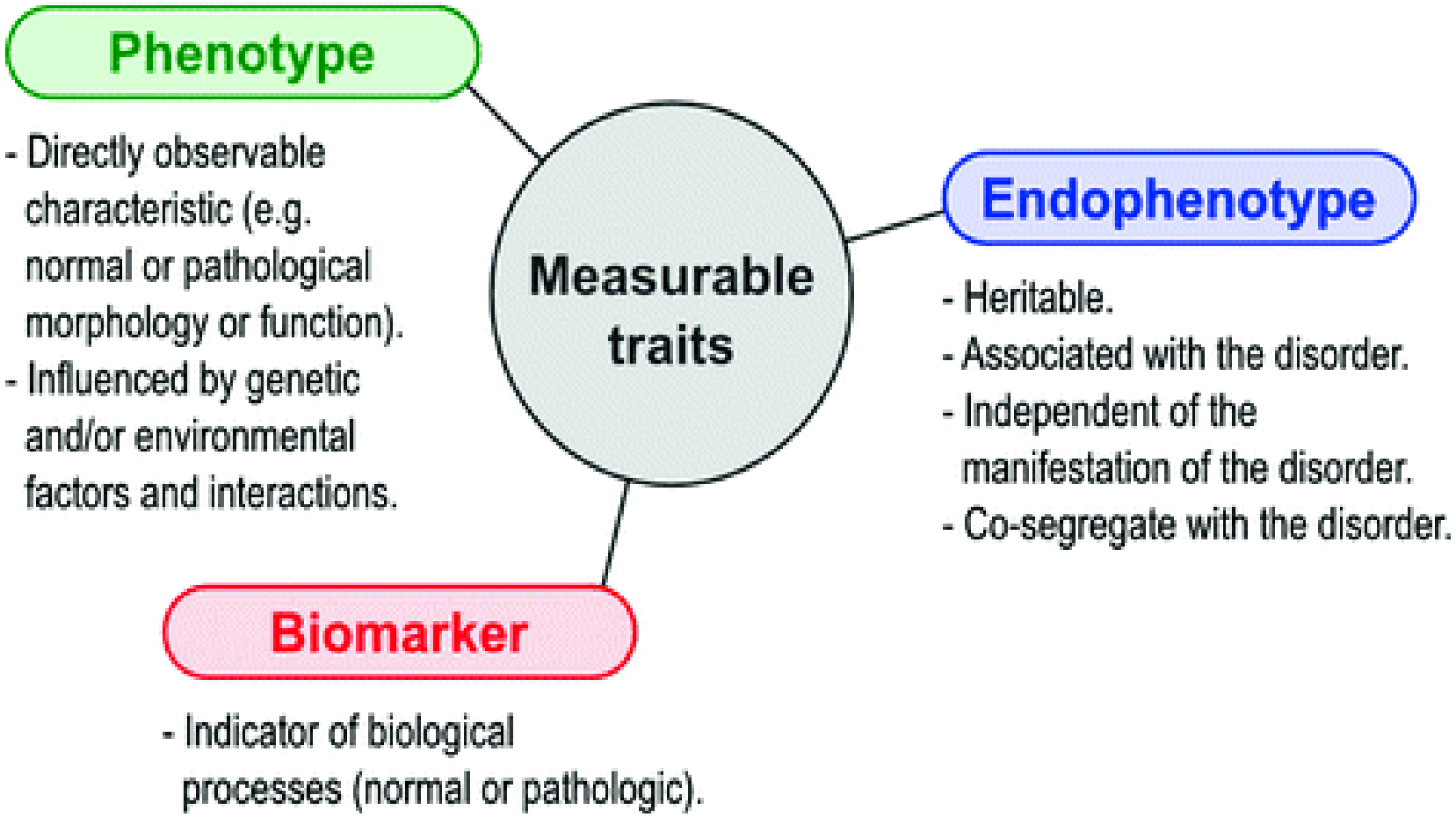
BIOMARKER DISCOVERY RESEARCH



NEUROPSYCHIATRIC DISORDERS

(bipolar disorder, depression, schizophrenia, addictive disorder)

MISSING LINK


Phenotype
- Directly observable characteristic (e.g. normal or pathological morphology or function).
- Influenced by genetic and/or environmental factors and interactions.
Measurable traits
Endophenotype
- Heritable.
- Associated with the disorder.
- Independent of the manifestation of the disorder.
- Co-segregate with the disorder.
Biomarker
- Indicator of biological processes (normal or pathologic).

Table

Candidate Genes With the Strongest Evidence for a Role in the Genesis of Schizophrenia

Gene	Chromosomal Locus	Hypothesized Role
Dysbindin (*DTNBP1*)	6p22.3	Via synaptic glutamate release
Neuregulin 1 (*NRG1*)	8p12-21	Multiple, including effects on synaptic plasticity, neuro-development and transmitter activitity
Catechol O-methyl-transferase (*COMT*)	22q11.2	Metabolizes cerebral monoamines including dopamine
Disrupted in schizophrenia 1 (*DISC1*)	1q42	Poorly understood; possible roles suggested in synapto-genesis and neurodevelopment
Metabotropic glutamate receptor 3 (*mGluR3* as well as *GRM3*)	7q21-22	NMDA receptor effects via affecting presynaptic glutamate release
Proline dehydrogenase (*PRODH*)	22q11.2	Modulation of synaptic transmission
D-amino acid oxidase activator (*DAOA*), also known as *G72*	13q32-34	Possibly affects ratio of L- to D-serine ratio, which may have a role in regulation of NMDA receptor

Source: Picker J (2005)

Chromosomal loci reported by linkage studies for bipolar disorder

Location	LOD score	Reference
1q31-q32	2,6	Detera-Wadleigh et al, 1999
4p16	4,8	Blackwood et al, 1996
12q23-24	3,4	Ewald et al, 1998
13q32	3,5	Detera-Wadleigh et al, 1999
18q22	4,0	McInnes et al, 1996
20p11.2-q11.2	4,3	Radhakrishna et al, 2001
21q22	3,4	Vallada et al, 1996
22q11-q13	3,8	Kelsoe et al, 2001

Modified from Tsuang et al

Candidate genes with replicated association in anxiety disorders

Anxiety Disorder	Gene Name	Gene Symbol	Function
OCD	Glutamate transporter	SLC1A1	Neurotransmission
Panic disorder	Catechol-O-methyltransferase	COMT	Neurotransmission
	Neuropeptide S receptor gene	NPSR	Neuronal signaling
	Transmembrane protein 132D	TMEM132D	Unknown
PTSD	FK-506 binding protein	FKBPS	Glucocorticoid chaperone

Genetic variations affecting substance abuse risk

Gene	SNPs (Major / Minor)	Substance	Minor Allel Effect
ALDH2	rs671 (A>G)	Alcohol	Protective
ADH1B	rs1229984 (A?G)	Alcohol	Protective
ADH1C	rs1693482 (C>T) rs698 (A>G/T)	Alcohol Alcohol	Protective Protective
CHRNA5/A3/B4	rs16969968 (A>G)	Cocaine; nicotine*	Protective; risk*
CHRNB3-CHRNA6	rs6474412 (C>T) rs13273442	Nicotine	Risk Protective
CYP2A6	rs1801272 (A>T)	Alcohol; nicotine	Risk
FKBP5	rs1360780 (C>T) rs3800373 (G>T)	Heroin Heroin	Protective Protective
GABRA2	rs279858 (A>G) rs279826 (A>G) rs279871 (A>G)	Alcohol; illicit drugs	Risk Risk Risk
OPRM1	rs1799971 (A>G)	Alcohol; opioids; nicotine	Risk

MISSING LINK

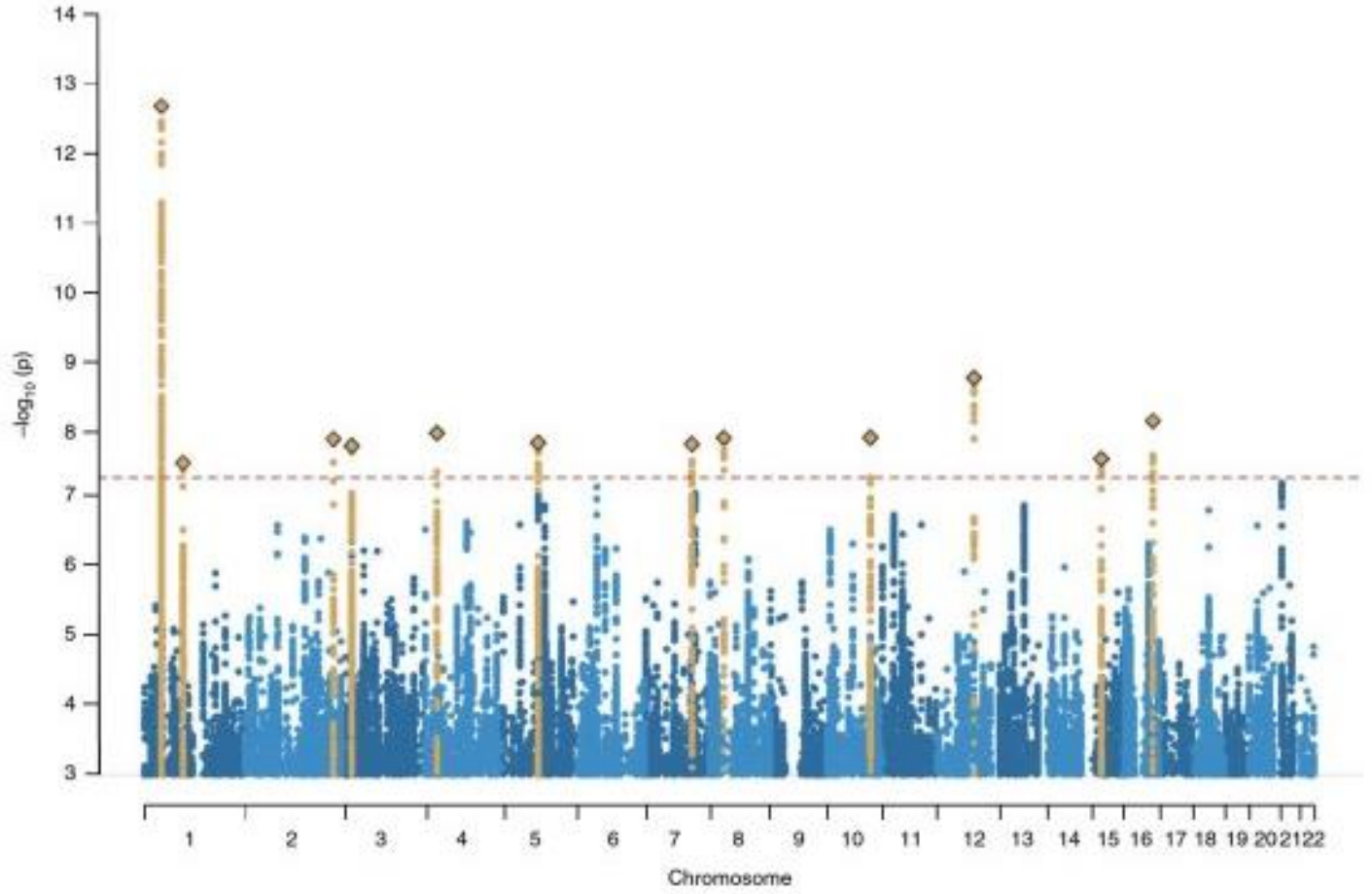


Fig. 1 | Manhattan plot of the results from the GWAS meta-analysis of ADHD. The index variants in the 12 genome-wide significant loci are highlighted as an orange diamond. Index variants located with a distance <400 kb are considered as one locus. The *y* axis represents -log(two-sided *P* values) for association of variants with ADHD, from meta-analysis using an inverse-variance weighted fixed effects model and a total sample size of 20,183 individuals with ADHD and 35,191 controls. The horizontal red line represents the threshold for genome-wide significance.

Gene	Protein description	Nature of abnormality	Reference
NRXN1	Transmembrane	Mutation, CNVs	Feng et al. (2006)
NRXN2	Transmembrane	Mutation	Arstikaitis et al. (2011)
NRXN3	Transmembrane	Mutation	Vaags et al. (2012)
NLGN1	Transmembrane	Genetic association	Glessner et al. (2009)
NLGN3	Transmembrane	Mutation	Jamain et al. (2003)
NLGN4	Transmembrane	Mutation, CNVs	Jamain et al. (2003)
CNTN3	Ig-CAM	Mutation, CNVs	Morrow et al. (2008)
CNTN 4	Ig-CAM	Mutation	Roohi et al. (2009)
CNTNAP2	Transmembrane	Mutation, genetic association	Arking et al. (2008)
NrCAM	Ig-CAM	Genetic association	Marui et al. (2009)
CDH9/10	Transmembrane	Genetic association	Bucan et al. (2009)
CDH18	Transmembrane	Chromosomal abnormality	Marshall et al. (2008)
PCDH9	Transmembrane	Mutation	Marshall et al. (2008)
PCDH10	Transmembrane	Mutation	Morrow et al. (2008)
PCDH19	Transmembrane	Mutation	Dibbens et al. (2008)
SHANK1	Scaffolding	Mutation	Sato et al. (2012)
SHANK2	Scaffolding	Mutation	Berkel et al. (2010)
SHANK3	Scaffolding	Mutation	Durand et al. (2007)
DLG4 (disk large homolog 4)	Scaffolding	SNPs	Feyder et al. (2010)
HOMER1	Scaffolding	Mutation	Kelleher et al. (2012)
cAMP-GEF (guanine exchange factor)	Cytoskeletal	Mutation	Bacchelli et al. (2003)
RELN (Reelin)	Secreted	Genetic association	Persico et al. (2001)
EN2 (Engrailed 2)	Transcription factor	Genetic association	Gharani et al. (2004)

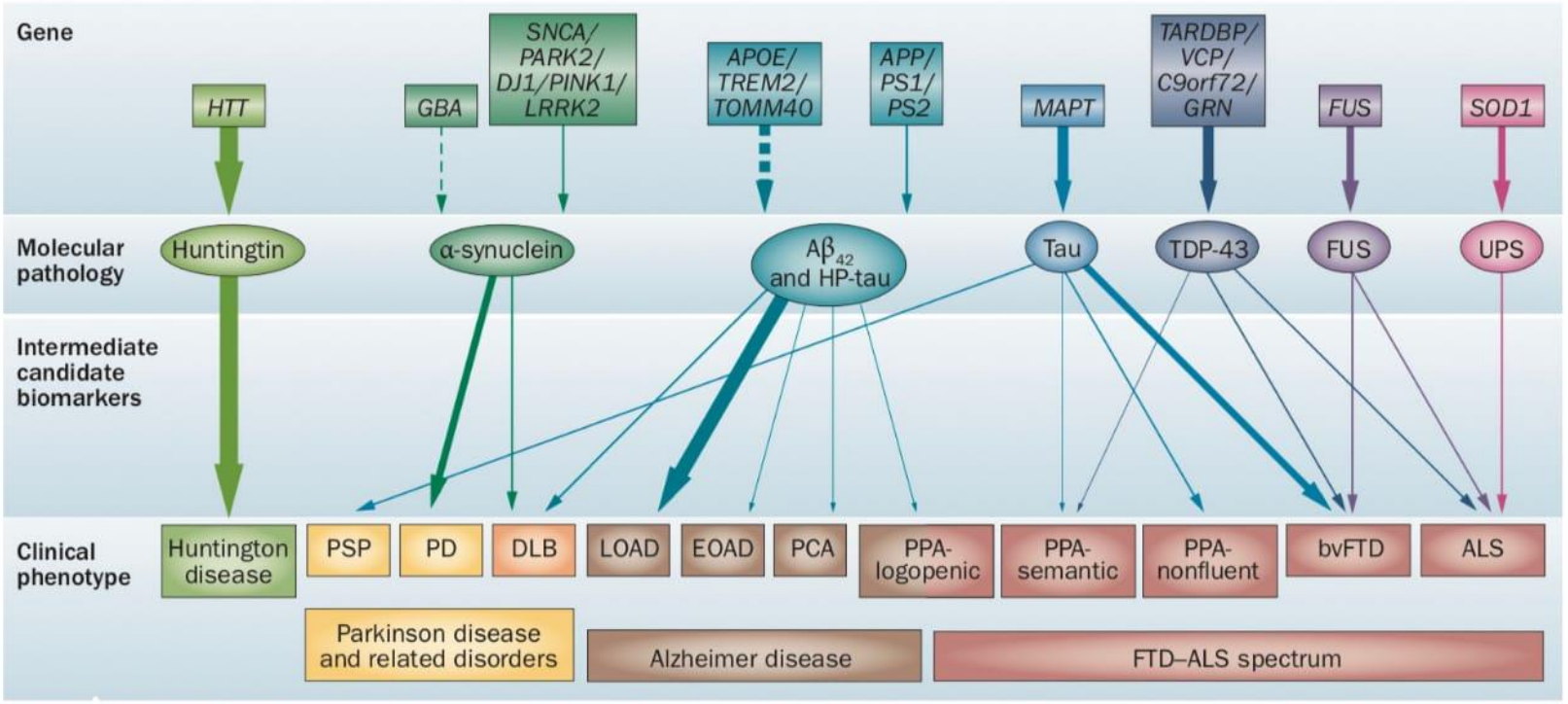
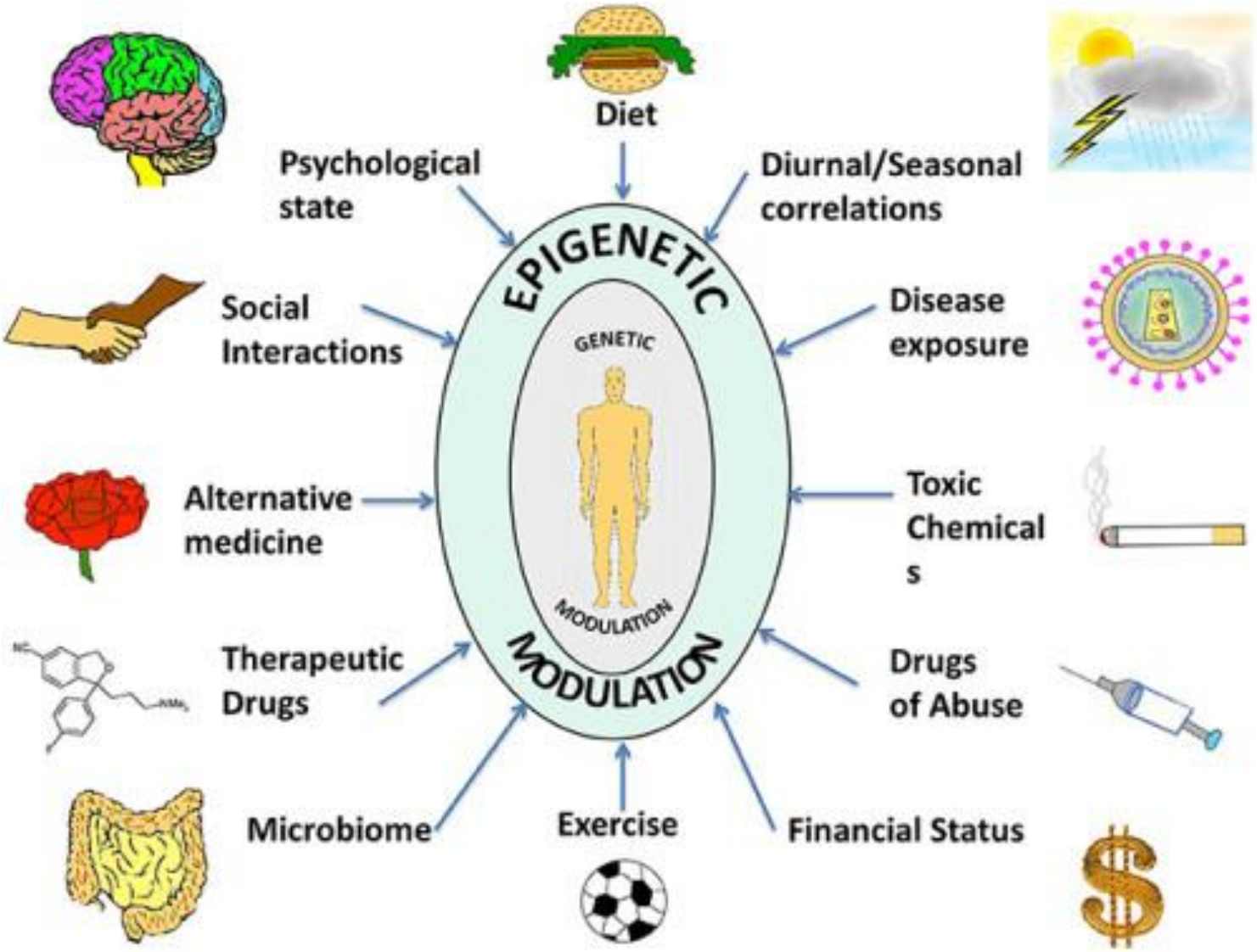
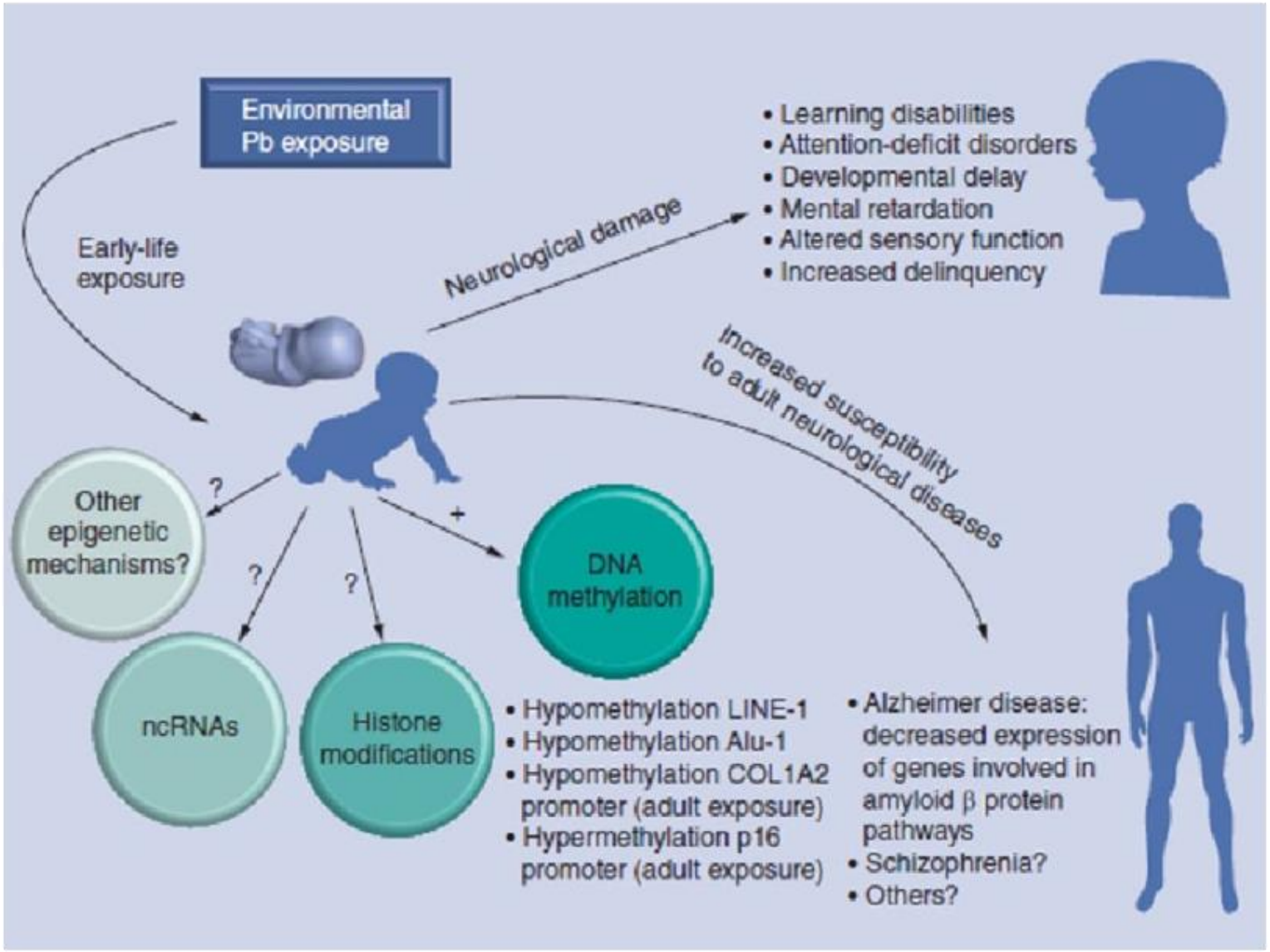


Figure Upstream determinants (genes and molecular pathology) and downstream effects (clinical phenotypes) for the main neurodegenerative disorders. Functional and structural brain connectivity might act as intermediate biomarkers. Causative genetic mutations are shown by solid arrows and genetic risk factors by dotted arrows. The size of the arrow is roughly proportional to the population attributable fraction. The size of arrows linking molecular pathology to clinical phenotypes are roughly proportional to the prevalence of the clinical phenotype in the pertinent molecular pathology. Abbreviations: $A\beta_{42}$, amyloid-β_{42}; ALS, amyotrophic lateral sclerosis; *APOE*, apolipoprotein E; *APP*, amyloid precursor protein; bvFTD, behavioural variant frontotemporal dementia; *DJ1*, parkinson protein 7; DLB, dementia with Lewy bodies; EOAD, early-onset Alzheimer disease; FUS, fused in sarcoma; *GBA*, glucocerebrosidase; *GRN*, granulin; HP-tau, hyperphosphorylated-tau; LOAD, late-onset Alzheimer disease; *LRRK2*, leucine-rich repeat kinase 2; *MAPT*, microtubule-associated protein tau; *PARK2*, parkin RBR E3 ubiquitin protein ligase; PCA, posterior cortical atrophy; PD, Parkinson disease; *PINK1*, PTEN induced putative kinase 1; PPA, primary progressive aphasia; *PS*, presenilin; PSP, progressive supranuclear palsy; *SNCA*, α-synuclein; *SOD1*, superoxide dismutase 1; *TARDBP*/TDP-43, TAR DNA-binding protein 43; *TOMM40*, translocase of outer mitochondrial membrane 40 homologue; *TREM2*, triggering receptor expressed on myeloid cells 2; UPS, ubiquitin proteasome system; *VCP*, valosin containing protein.

What is the master control?

- Epigenetics
- Holy grail of pathophysiology (?)


Diet
Psychological state
Diurnal/Seasonal correlations
Social Interactions
Disease exposure
Alternative medicine
Toxic Chemicals
Therapeutic Drugs
Drugs of Abuse
Microbiome
Exercise
Financial Status
EPIGENETIC
GENETIC
MODULATION
MODULATION


Environmental Pb exposure
Early-life exposure
Neurological damage
• Learning disabilities
• Attention-deficit disorders
• Developmental delay
• Mental retardation
• Altered sensory function
• Increased delinquency
Increased susceptibility to adult neurological diseases
Other epigenetic mechanisms?
?
?
?
+
DNA methylation
ncRNAs
Histone modifications
• Hypomethylation LINE-1
• Hypomethylation Alu-1
• Hypomethylation COL1A2 promoter (adult exposure)
• Hypermethylation p16 promoter (adult exposure)
• Alzheimer disease: decreased expression of genes involved in amyloid β protein pathways
• Schizophrenia?
• Others?

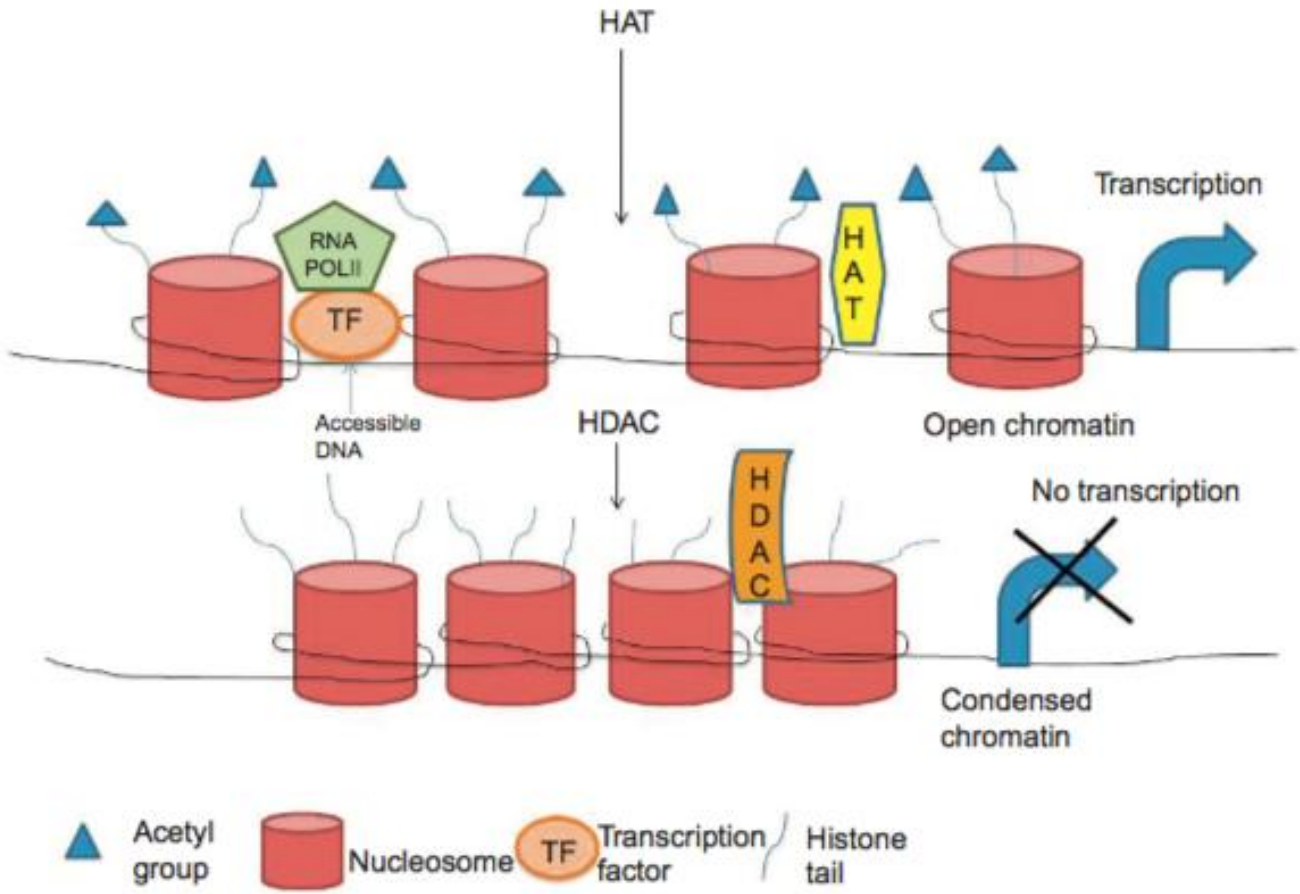


FIGURE 2.3

Acetylation of histones by histone acetyltransferase (HAT) generally leads to an open chromatin structure; thus, transcription factors and RNA polymerase can bind to DNA and activate transcription. Histone deacetylases (HDACs) deacetylate histone and lead to a closed chromatin state where the transcription factors cannot bind.

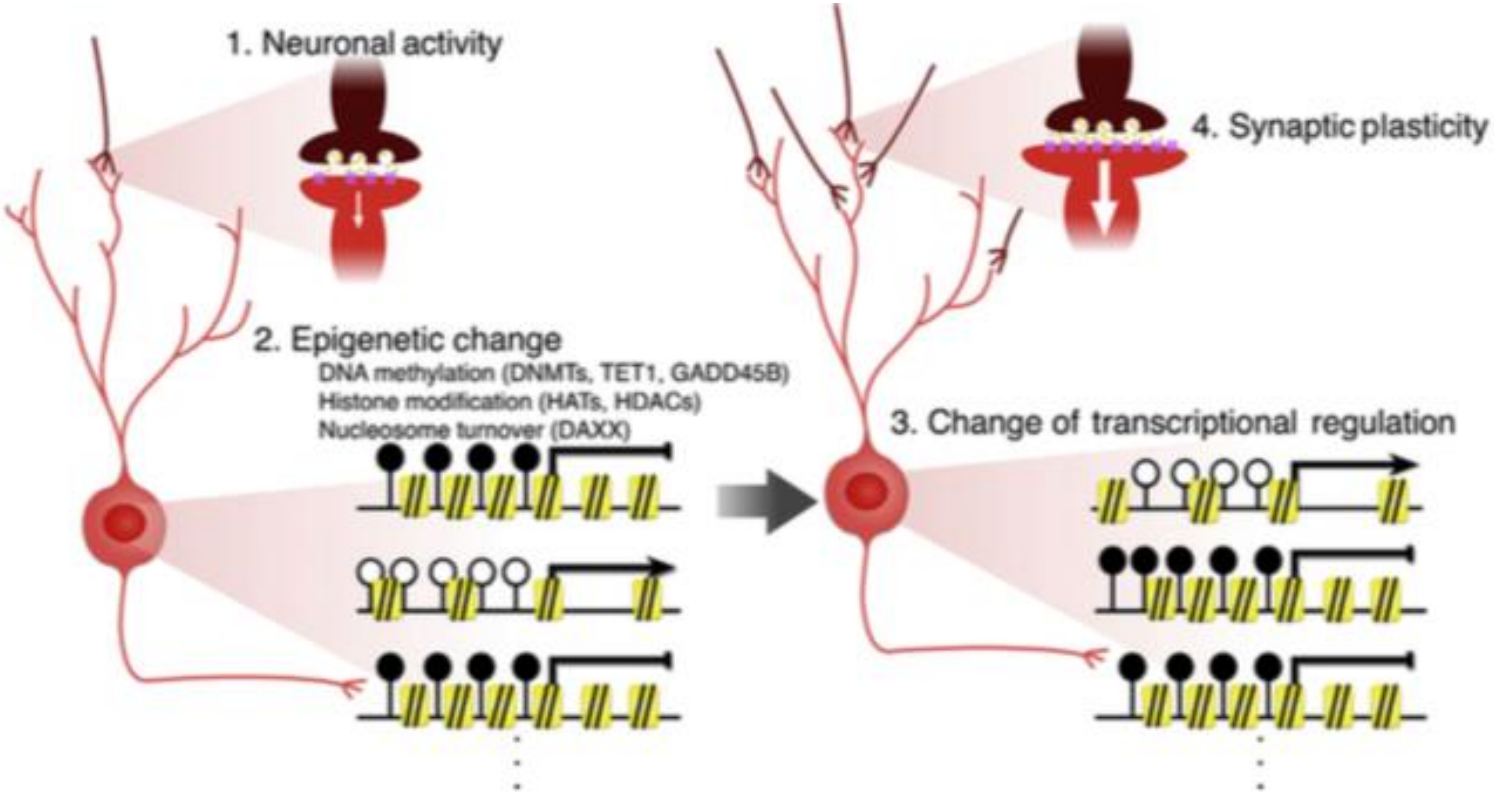
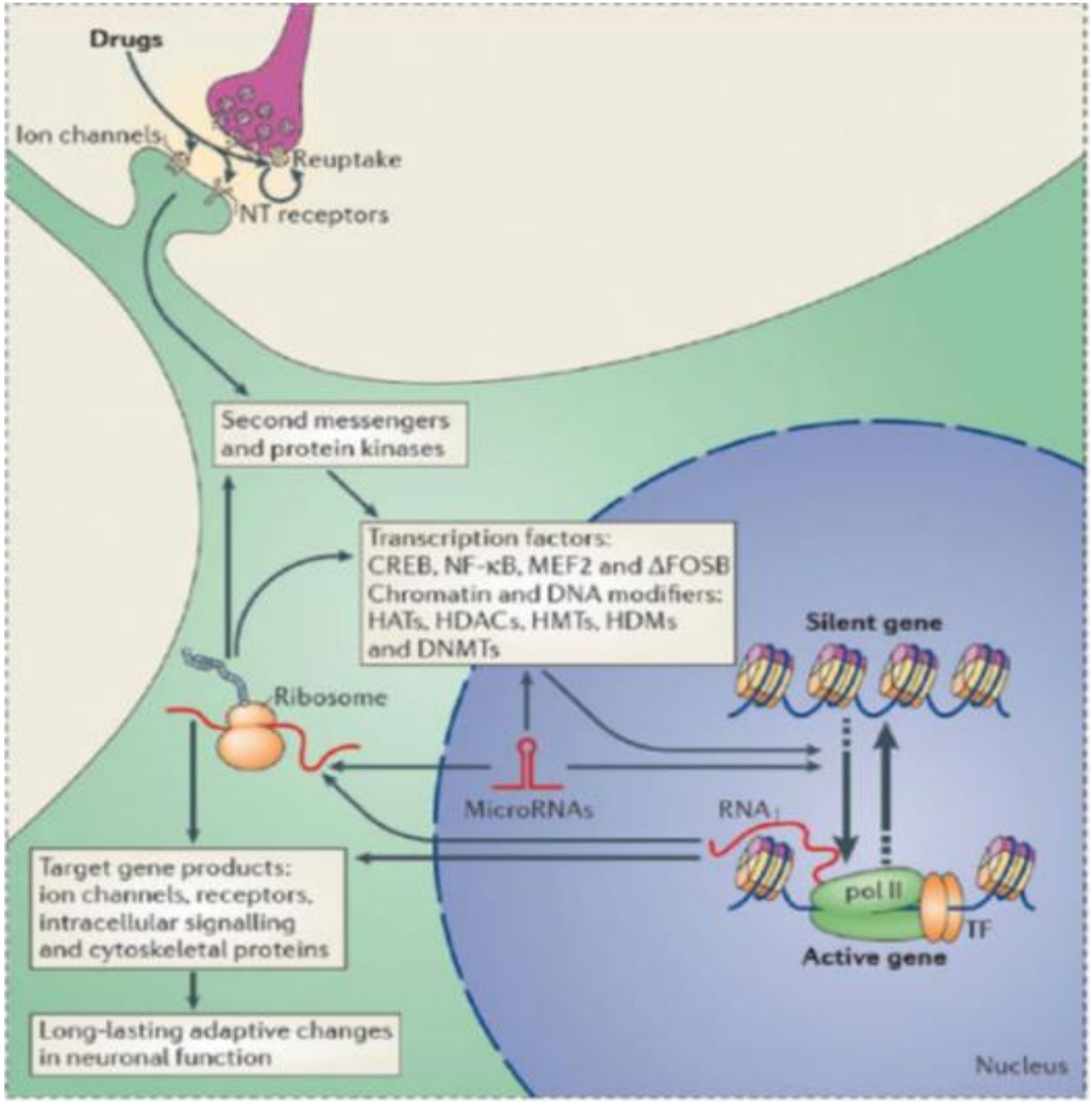
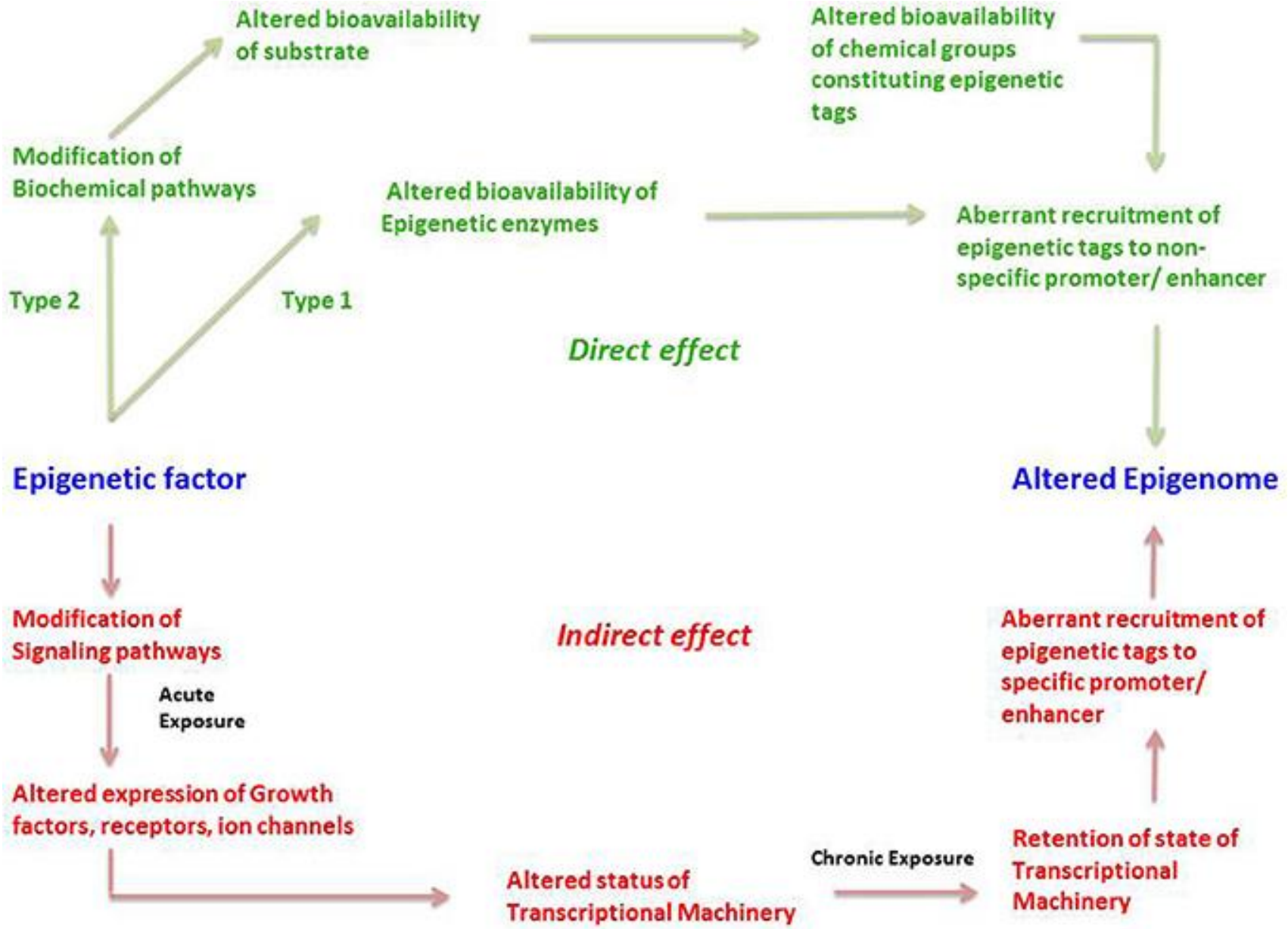
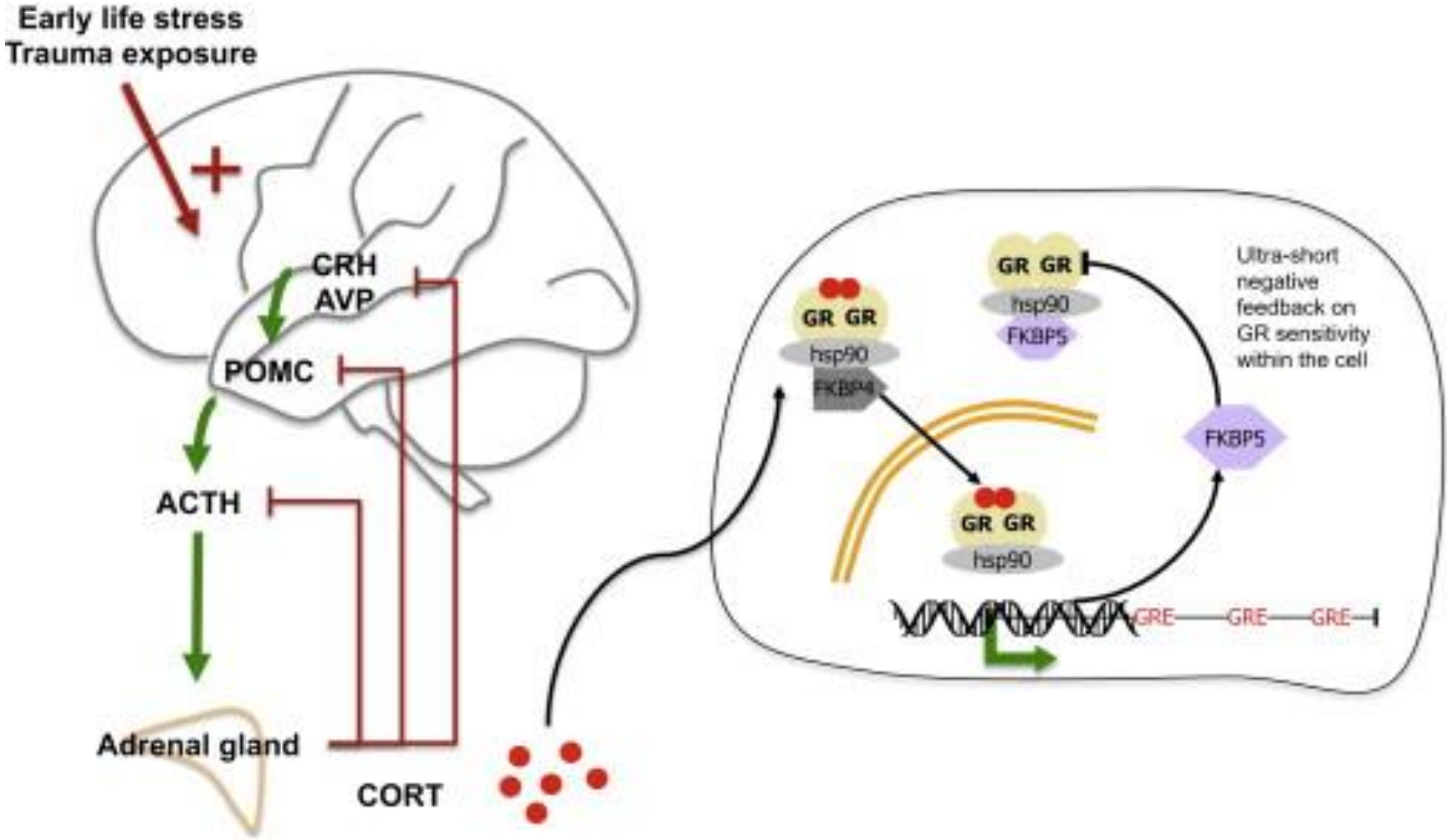


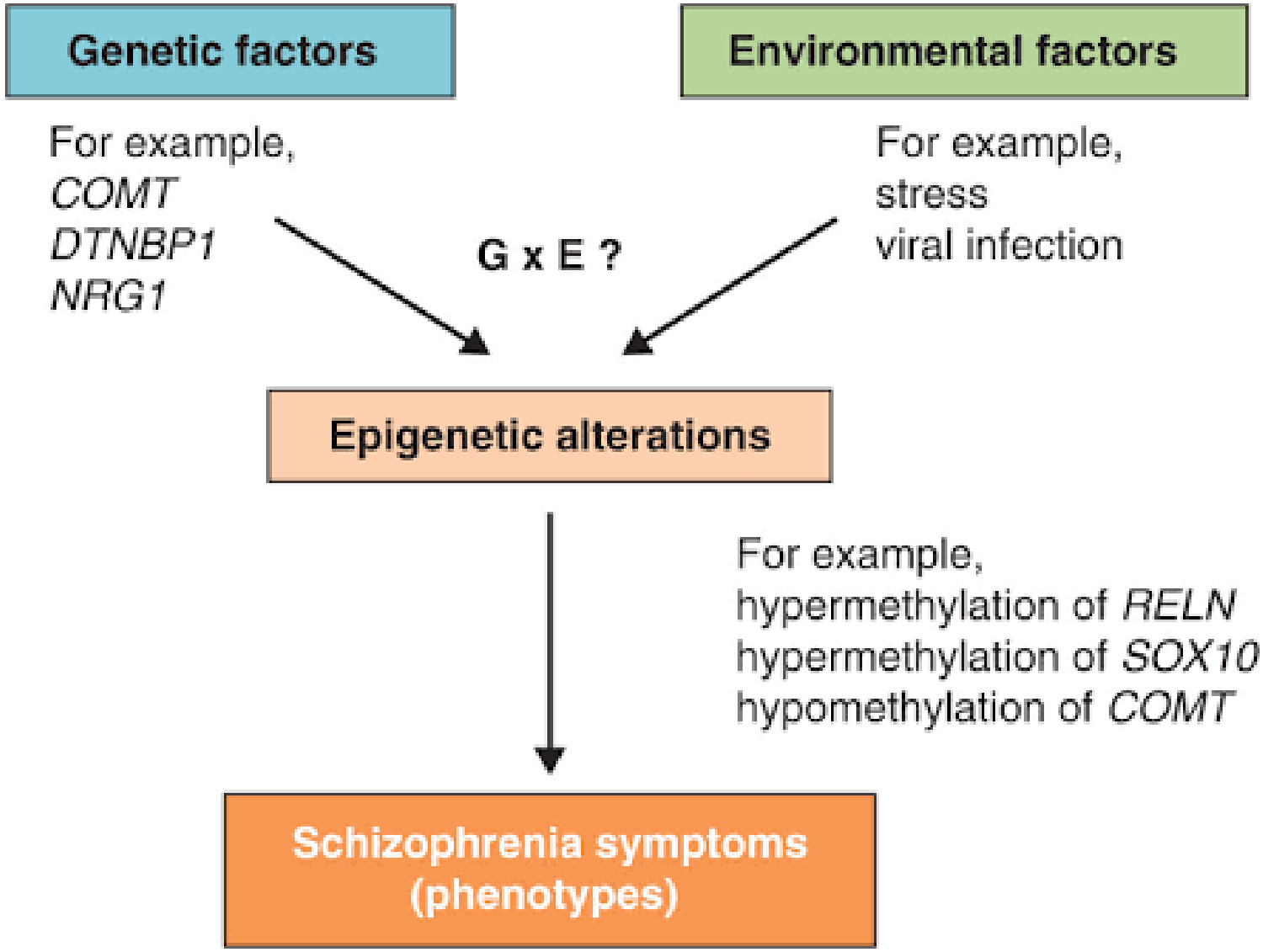
FIGURE 4.3

Epigenetic changes observed in postmitotic neurons. Neuronal activity can induce several changes of biological processes, such as the expression levels of epigenetic modifiers, leading to global and local changes of the epigenetic status. These epigenetic changes alter transcriptional regulation at several gene loci (e.g., *BDNF*), followed by enhancement of synaptic plasticity. Filled and open lollipops denote methylated and unmethylated cytosine, respectively. Arrows and hammers indicate expression and repression of downstream genes, respectively.


Drugs
Ion channels
Reuptake
NT receptors
Second messengers
and protein kinases
Transcription factors:
CREB, NF-κB, MEF2 and ΔFOSB
Chromatin and DNA modifiers:
HATs, HDACs, HMTs, HDMs
and DNMTs
Silent gene
Ribosome
MicroRNAs
RNA
pol II
TF
Active gene
Target gene products:
ion channels, receptors,
intracellular signalling
and cytoskeletal proteins
Long-lasting adaptive changes
in neuronal function
Nucleus


Altered bioavailability of substrate
Altered bioavailability of chemical groups constituting epigenetic tags
Modification of Biochemical pathways
Altered bioavailability of Epigenetic enzymes
Aberrant recruitment of epigenetic tags to non-specific promoter/ enhancer
Type 2
Type 1
Direct effect
Epigenetic factor
Altered Epigenome
Modification of Signaling pathways
Indirect effect
Aberrant recruitment of epigenetic tags to specific promoter/ enhancer
Acute Exposure
Altered expression of Growth factors, receptors, ion channels
Chronic Exposure
Retention of state of Transcriptional Machinery
Altered status of Transcriptional Machinery


Early life stress
Trauma exposure
CRH
AVP
POMC
ACTH
Adrenal gland
CORT
GR GR
hsp90
FKBP4
GR GR
hsp90
FKBP5
Ultra-short
negative
feedback on
GR sensitivity
within the cell
FKBP5
GR GR
hsp90
GRE
GRE
GRE


Genetic factors
Environmental factors
For example,
COMT
DTNBP1
NRG1
G x E ?
For example,
stress
viral infection
Epigenetic alterations
For example,
hypermethylation of RELN
hypermethylation of SOX10
hypomethylation of COMT
Schizophrenia symptoms
(phenotypes)

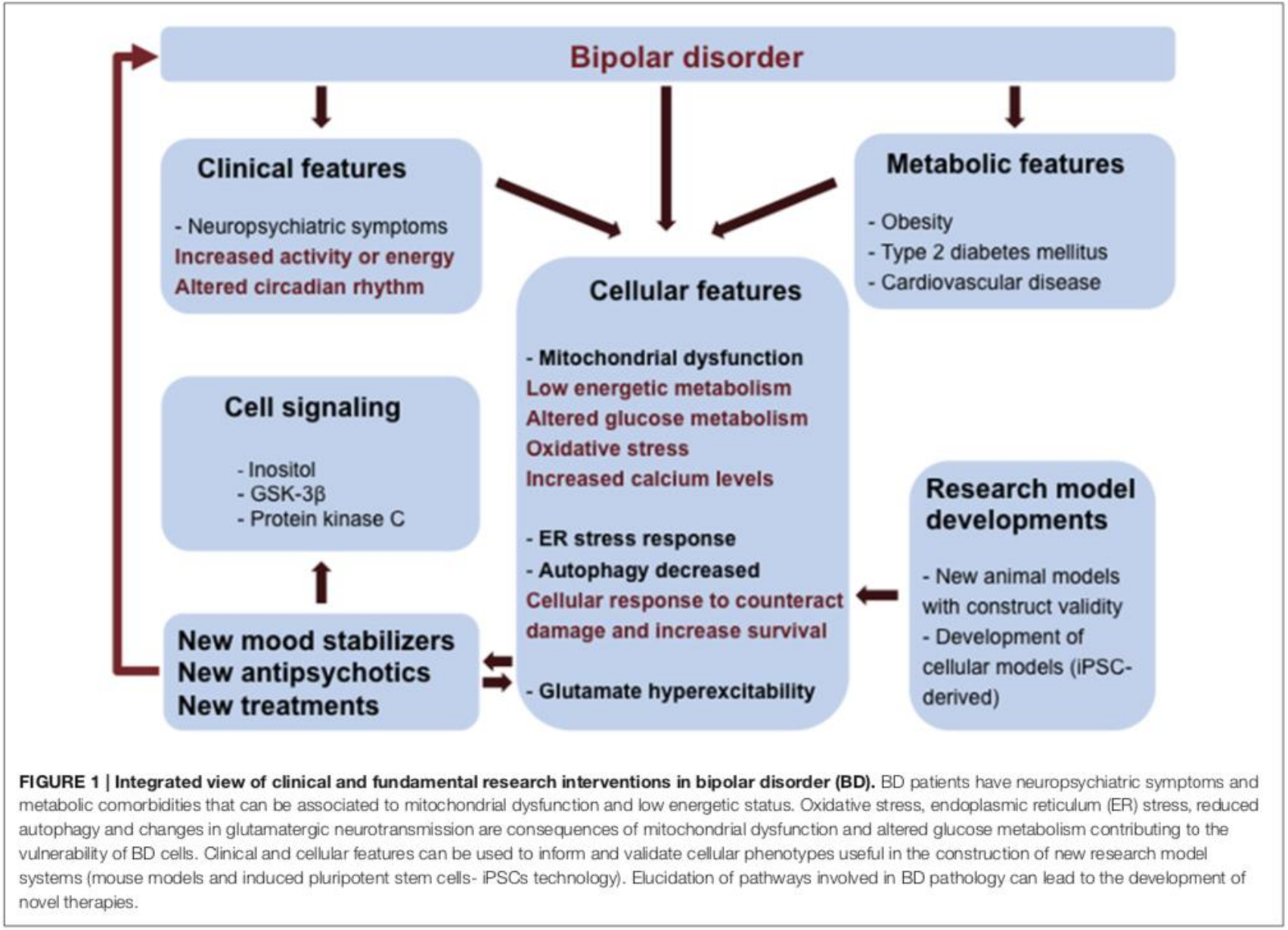
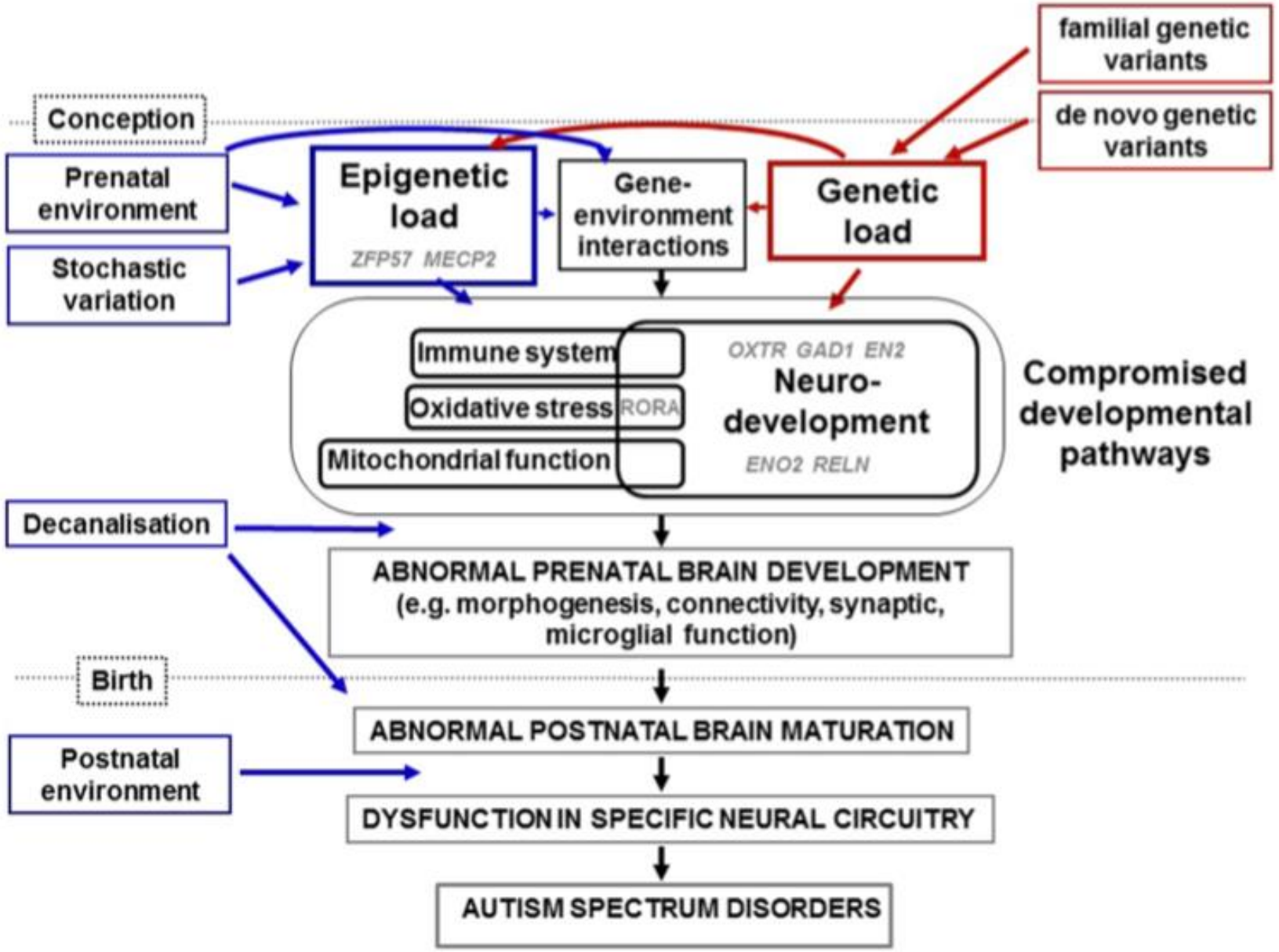
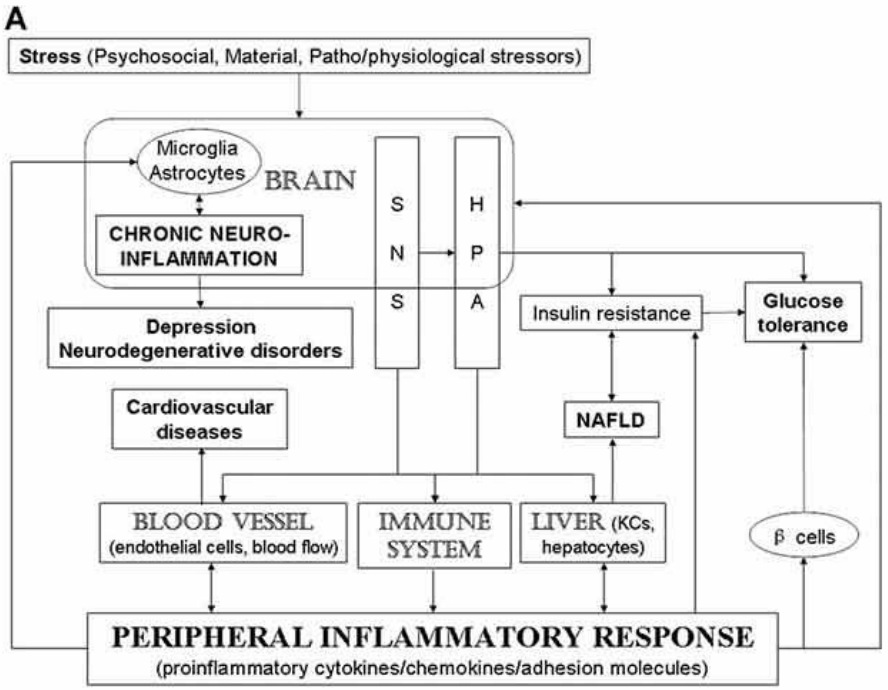


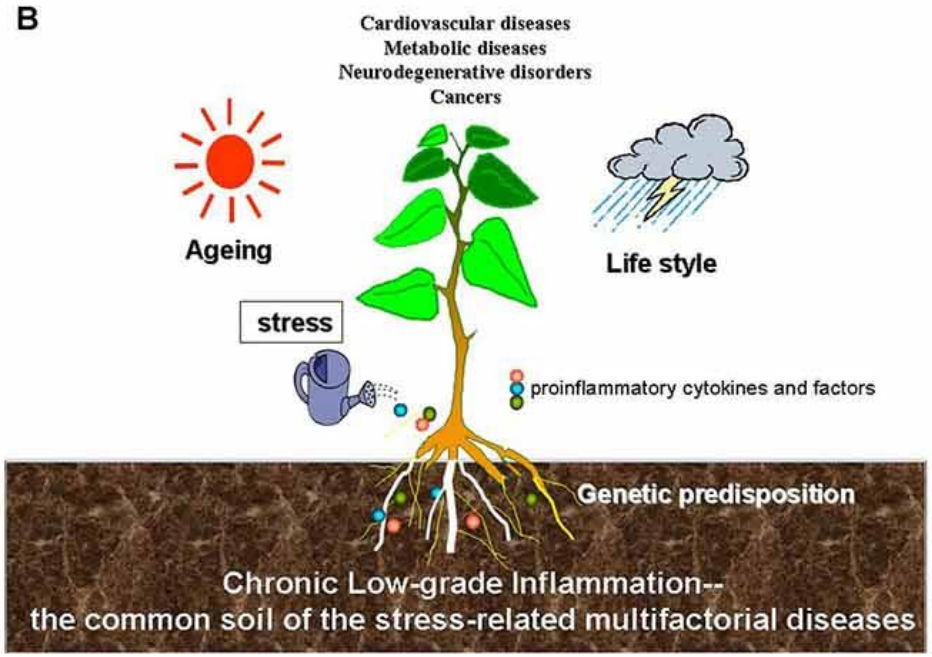
FIGURE 1 | Integrated view of clinical and fundamental research interventions in bipolar disorder (BD). BD patients have neuropsychiatric symptoms and metabolic comorbidities that can be associated to mitochondrial dysfunction and low energetic status. Oxidative stress, endoplasmic reticulum (ER) stress, reduced autophagy and changes in glutamatergic neurotransmission are consequences of mitochondrial dysfunction and altered glucose metabolism contributing to the vulnerability of BD cells. Clinical and cellular features can be used to inform and validate cellular phenotypes useful in the construction of new research model systems (mouse models and induced pluripotent stem cells- iPSCs technology). Elucidation of pathways involved in BD pathology can lead to the development of novel therapies.

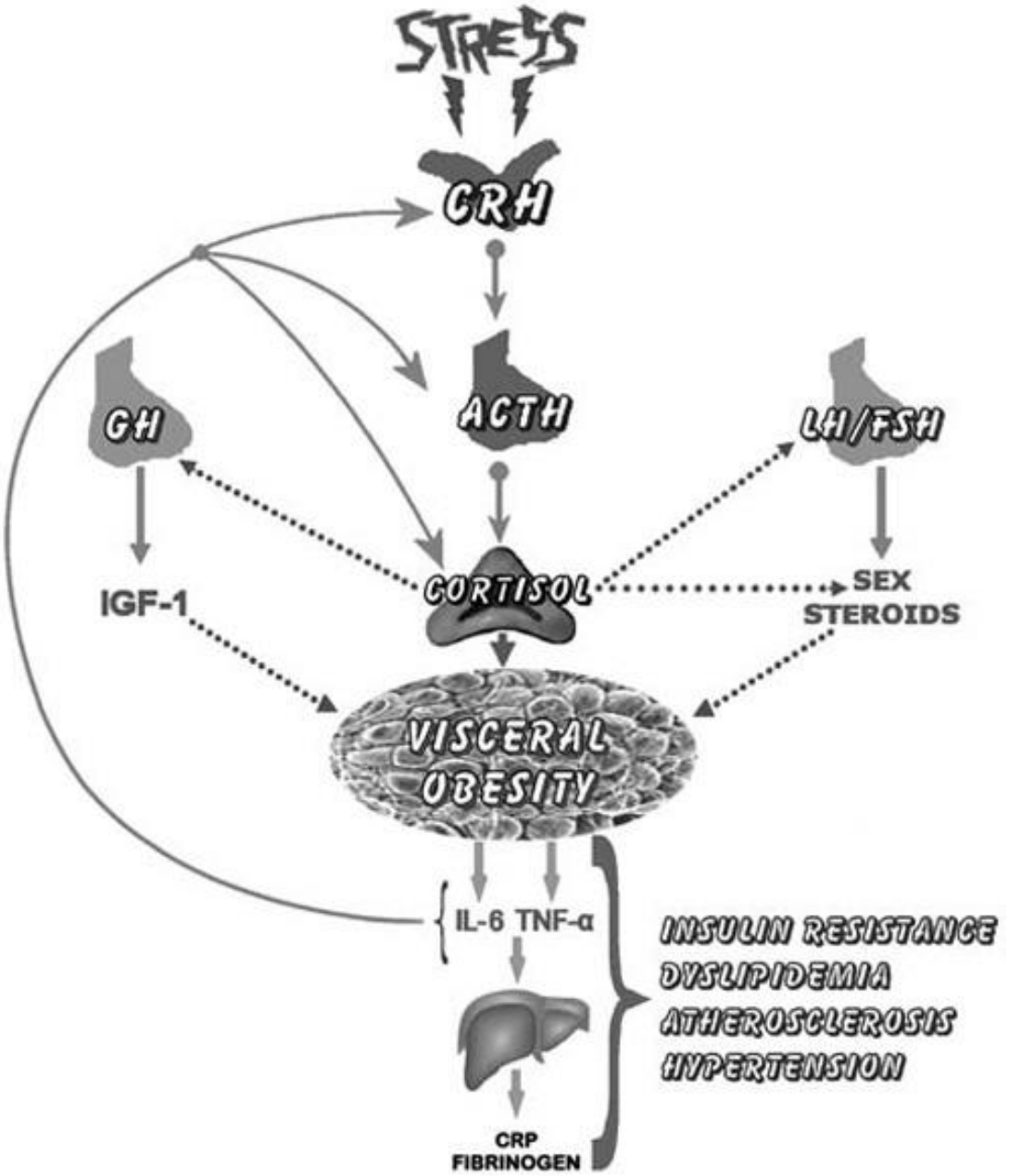

familial genetic variants
de novo genetic variants
Conception
Prenatal environment
Stochastic variation
Epigenetic load
ZFP57 MECP2
Gene-environment interactions
Genetic load
Immune system
Oxidative stress
Mitochondrial function
OXTR GAD1 EN2
Neuro-development
RORA
ENO2 RELN
Compromised developmental pathways
Decanalisation
ABNORMAL PRENATAL BRAIN DEVELOPMENT
(e.g. morphogenesis, connectivity, synaptic, microglial function)
Birth
ABNORMAL POSTNATAL BRAIN MATURATION
Postnatal environment
DYSFUNCTION IN SPECIFIC NEURAL CIRCUITRY
AUTISM SPECTRUM DISORDERS

Is there a common ground?

- Similarities between psychiatric illnesses & chronic medical conditions


A
Stress (Psychosocial, Material, Patho/physiological stressors)
Microglia
Astrocytes
BRAIN
CHRONIC NEURO-INFLAMMATION
S
N
S
H
P
A
Depression
Neurodegenerative disorders
Insulin resistance
Glucose tolerance
Cardiovascular diseases
NAFLD
BLOOD VESSEL (endothelial cells, blood flow)
IMMUNE SYSTEM
LIVER (KCs, hepatocytes)
β cells
PERIPHERAL INFLAMMATORY RESPONSE
(proinflammatory cytokines/chemokines/adhesion molecules)


B
Cardiovascular diseases
Metabolic diseases
Neurodegenerative disorders
Cancers
Ageing
Life style
stress
proinflammatory cytokines and factors
Genetic predisposition
Chronic Low-grade Inflammation--
the common soil of the stress-related multifactorial diseases


STRESS
CRH
ACTH
GH
LH/FSH
IGF-1
CORTISOL
SEX STEROIDS
VISCERAL OBESITY
IL-6 TNF-α
CRP FIBRINOGEN
INSULIN RESISTANCE
DYSLIPIDEMIA
ATHEROSCLEROSIS
HYPERTENSION

Thank You

MISSING LINK

Suggested reading

- Synopsis of Psychiatry, 11th edition
- Etiology in psychiatry: embracing the reality of poly-gene-environmental causation of mental illness. *Rudolf Uher, Alyson Zwicker, World Psychiatry 2017;16:121–129*
- Adolescent Brain Development. Lisa Wright, Stan Kutcher
- Developmental Cognitive Neuroscience, 4th edition. Mark Johnson, Michelle de Haan
- Epigenetics in Psychiatry. Jacob Pedicaayil, Dennis Grayson, Dimitrios Avramopoulos