Dopamine System and Depression

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Depression and DSM?

- *At least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) or (2)*
  - ***Depressed mood : negative affect (but what about positive affect ?***
  - ***Diminished interest/pleasure : anhedonia (anticipatory and consummator)***
  - ***Weight changes***
  - ***Sleep disturbances***
  - ***Psychomotor agitation / retardation***
  - ***Fatigue / loss of energy***
  - ***Feelings of worthlessness or excessive or inappropriate guilt***
  - ***Diminished ability to think or concentrate, or indecisiveness***
  - ***Recurrent thoughts of death / suicidal ideation***
- ***Clinically significant distress or impairment***

DSM - depression research in MDD is hampered by the problem of heterogeneity

- **5 out of the 9 symptoms :**
  - 2 patients can be diagnosed with MDD while only sharing only 1 (or even 0) symptom of the disorder !

- **the problem of compound diagnostic criteria :**
  - **Insomnia or hypersomnia**
  - **Decreased appetite or increased appetite**
  - **Psychomotor retardation or agitation**
  - **Interest and pleasure**

The problem of heterogeneity

- Based on 9 DSM symptoms:
  - 227 unique profiles
- Cutting down sleep, appetite and psychomotor changes :
  - 945 unique profiles
- Cutting further down symptoms of DSM (STAR*D, N=3703) :
  - 1030 unique profiles
  - For those with 6 positive DSM symptoms : 188 unique profiles (86% endorsed by less than 5 patients)
  - **20,7% have anhedonia but not depressed mood**

Sibitz I et al., 2010; Fried EI et al., 2015


DEPRESSION

Who decides what is important in assessing change?

Physicians top 10 ranking

Negative feelings : blue mood, despair, anxiety, depression
Feeling down, depressed or hopeless
Little interest or pleasure in doing things
Symptoms disrupted social life / leisure activities
Feeling tired or having little energy
How satisfied are you with yourself
How much are you enjoying life
Symptoms have disrupted your work
To what extent life is meaningful
How satisfied are you with your personal relationships

Patients top 10 ranking

To what extent life is meaningful
How much do you enjoy life
How satisfied are you with yourself
How able are you to concentrate
Negative feelings : blue mood, despair, anxiety
Feeling tired or having little energy
Feeling down, depressed or hopeless
Feeling strong
How satisfied are you with your personal relationships
Feeling active

Demyttenaere K., Donneau AF, Albert A, Ansseau M., Constant E., van Heeringen K., J Affect Dis 2014

We know little

- **Knowledge about pathophysiology of depression is rudimentary – why?**

1. Heterogeneous syndromes with heterogeneous etiology -> weakness of trying to construct a “unifying” theory of depression
2. Observing pathological changes in the brain = difficult, limited techniques available (post mortem, neuroimaging, difficulties in transferring knowledge acquired from animal studies ✗)
3. Idiopathy of occurance of depression (various risk factors, no consistent genetic risk modifiers). Interaction of genetic predispositions and environmental risk factors.

1. **Neural circuitry of depression**

2. **Neurotrophines and Neurogenesis**

3. **Neuroendocrine and Neuroimmune systems**

4. **Monoamine Depletion**

1. **Neural circuitry of depression**

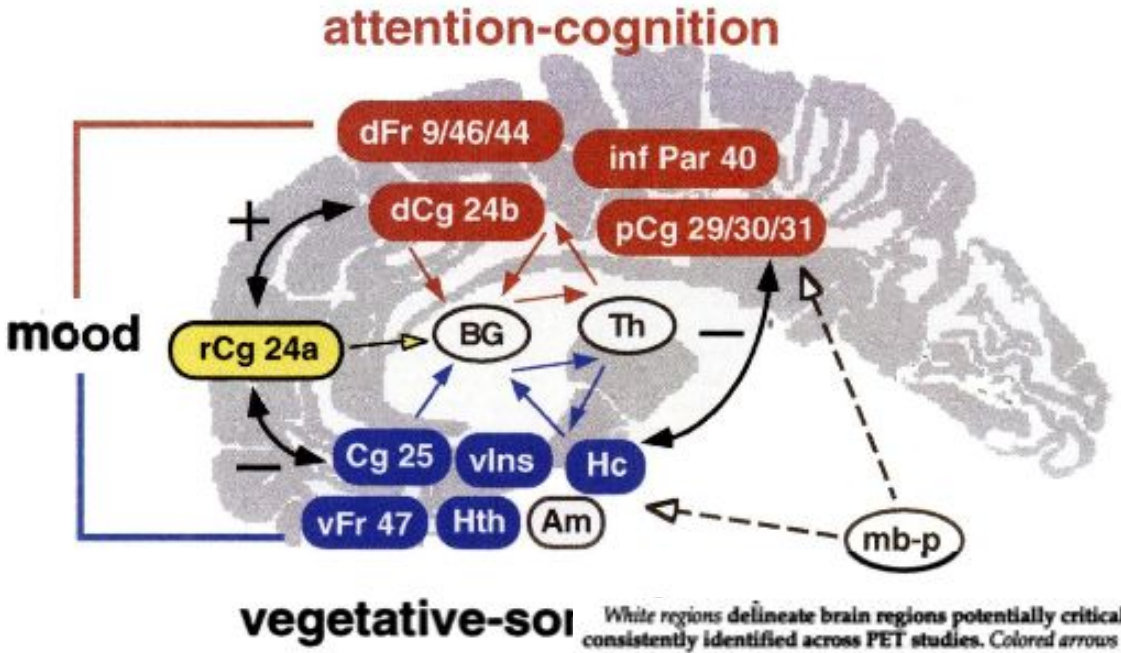
1. Neural circuits

- Hippocampus :
  - learning and memory
- Prefrontal cortex :
  - mood, working memory impairment, psychomotor retardation
- Amygdala :
  - allocation and assignment of emotional importance upon receiving psychological stimuli
- Mesolimbic dopamine system : (connected from ventral tegmental area to nucleus accumbens) :
  - motivation and reward, anhedonia an anergy
- Hypothalamus :
  - neurophysiological symptoms (insomnia, appetite, loss of sexual desire)

- **Mayberg's model of depression: limbic-cortical dysregulation**

(Mayberg, 1997)

- Sadness + depressive illness:
  - ↓ dorsal limbic & neocortical regions (red)
  - ↑ ventral paralimbic areas (blue)
- Remission
  - Reversal of these findings
  - Inhibtion / activation (black arrows), effect facilitated by fluoxetine action in dorsal raphe and projection side (dotted lines)
  - Integrity of the rostral cingulate (yellow) -> required for adaptive changes -> pretreatment metabolism predicts antidepressant treatment respons



Dorsal (red)
Ventral (blue)
Rostral (yellow)

White regions delineate brain regions potentially critical to the evolution of the model but where changes have not been consistently identified across PET studies. *Colored arrows* identify segregated ventral and dorsal compartment afferents and efferents to and from the striatum (caudate, putamen, nucleus accumbens) and thalamus (predominantly mediodorsal and anterior thalamus), although individual cortical-striatal-thalamic pathways are not delineated. *Black arrows* indicate reciprocal connections through the anterior and posterior cingulate linking the dorsal and ventral compartments. *Dotted lines* indicate serotonergic projections to limbic, paralimbic, subcortical, and cortical regions in both compartments. *Red:* dFr = dorsolateral prefrontal; inf Par = inferior parietal; dCg = dorsal anterior cingulate; pCg = posterior cingulate. *Blue:* Cg 25 = subgenual (infralimbic) cingulate; vIns = ventral anterior insula, Hc = hippocampus; vFr = ventral frontal; Hth = hypothalamus. *Yellow:* rCg = rostral anterior cingulate. *White:* mb-p = midbrain-pons; BG = basal ganglia; Th = thalamus; Am = amygdala. Numbers are Brodmann designations.

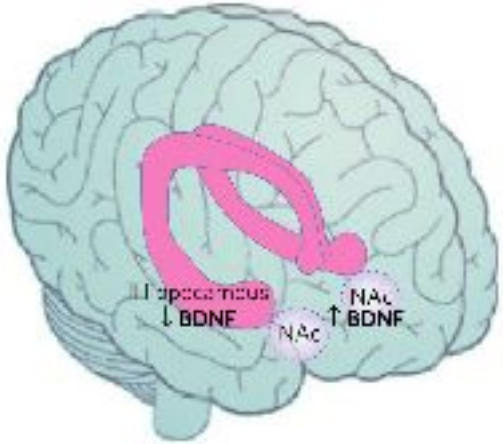
3. Neurotrophins and neurogenesis

- Neurotrophic factors: neurodevelopmentally expressed growth factors that also regulate plasticity within adult brain

« BDNF hypothesis »

- Brain-derived Neurotrophic Factor = abundantly expressed in adult limbic structures
- Preclinical studies show
  - Several forms of stress reduce BDNF-mediated signalling in the hippocampus
  - Chronic treatment with antidepressants increase BDNF-mediated signalling

- Post mortem data from depressed humans
  - Decrease in the amount of BDNF in the hippocampus
  - Increase in the NAc



- BUT: recent findings suggest that BDNF hypothesis: too simplistic

- Knock-in mice that express Met-66 BDNF (**Val66Met** is a gene variation, a single nucleotide polymorphism (SNP) in the BDNF gene that codes for BDNF)
  - Equivalent response in forced swim test
  - Increased anxiety like behaviour
  - Increased resilience (behavioral and molecular changes) to social defeat

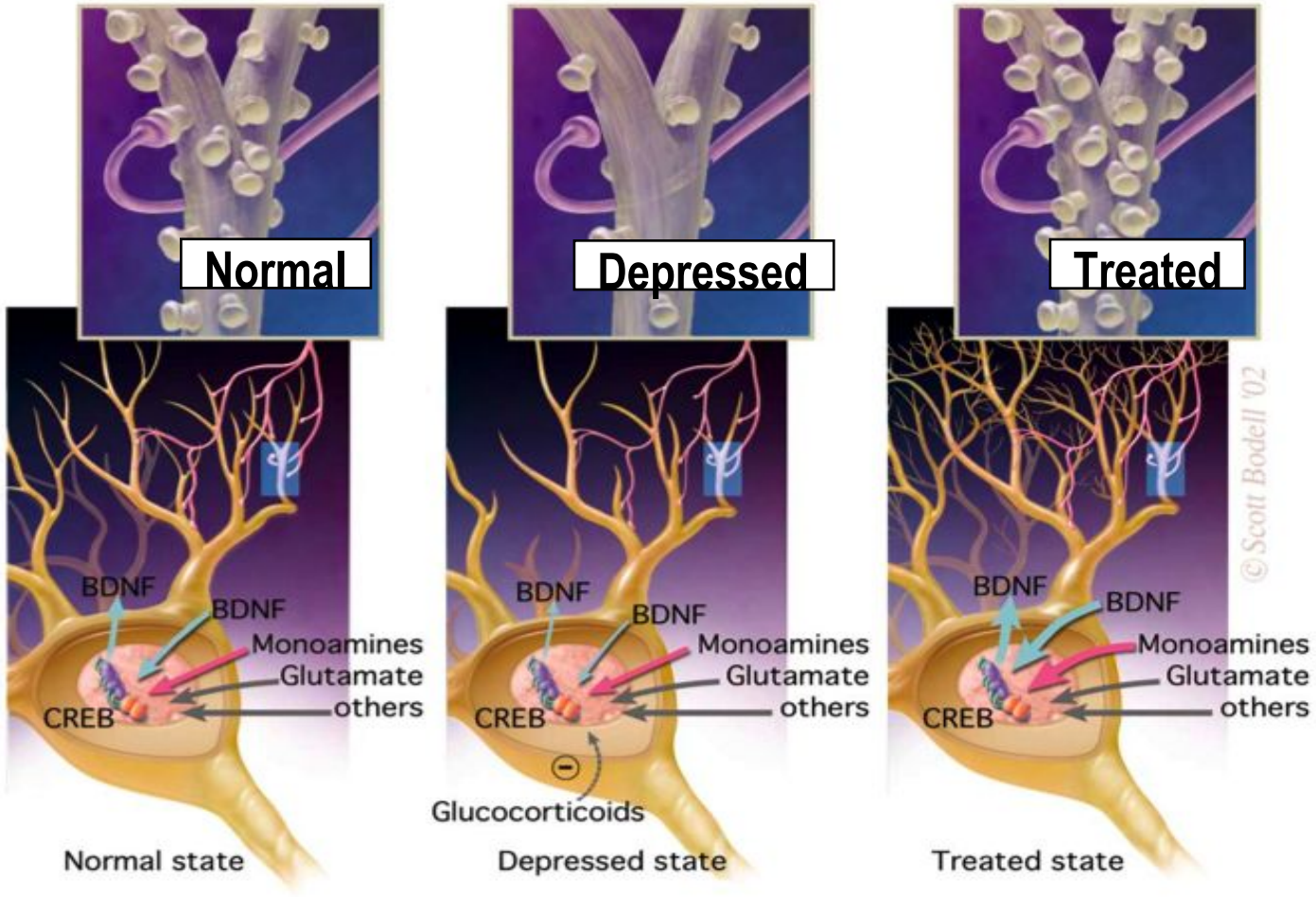
BDNF Met 66/Met 66

➔ BDNF-mediated signalling is involved in neuroplastic responses to stress and antidepressants

BUT: effects = **region specific** and **antidepressant-specific** and function in the background of potent genetic and environmental modifiers

Illustration of …the proposed facts…

Antidepressants / neurotrophic factors may help restore communication in MDD



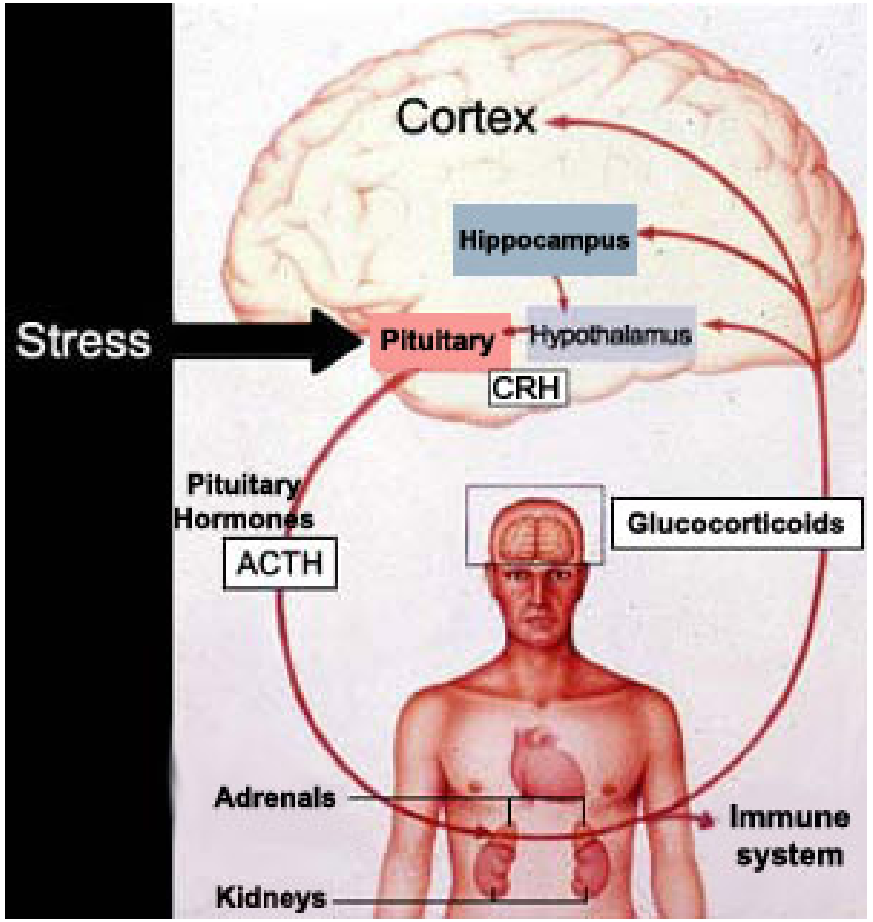
Nestler EJ, et al. *Neuron.* 2002;34(1):13-25.

3. Neuroendocrine and neuroimmune interactions

(a) **Hypothalamic-pituitary-adrenal (HPA) axis dysfunction**

(b) **“Cytokine hypothesis”**

(a) **Hypothalamic-pituitary-adrenal (HPA) axis dysfunction**



CRH = Corticotropin-releasing hormone
ACTH = adrenocorticotropic hormone

Dysfunctional Hypothalamic-pituitary-adrenal (HPA) axis

- Chronic administration of glucocorticoides can lead to depression-like symptoms in rodents

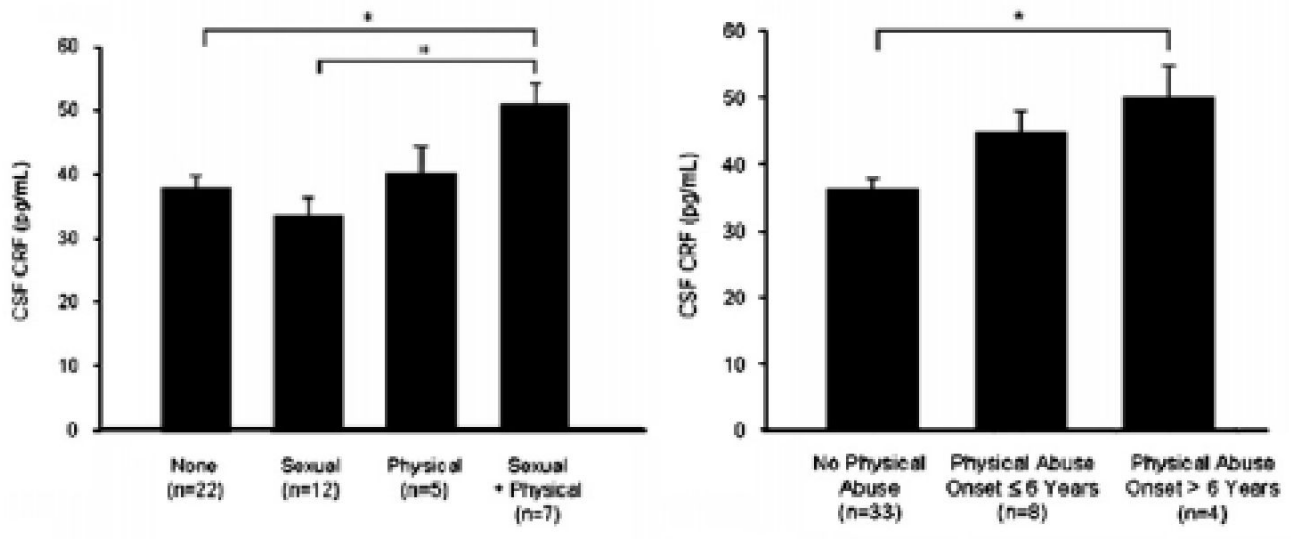
- Excess in glucocorticoides can reduce subgranular zone profileration (one of two major zones of adult neurogenesis) and produce atrophic changes in hippocampal subregions
    - this could lead to hippocampal volume reduction seen in depression

- Hypercortisolaemia is manifest at many levels in depressed patients

- **Early adverse experiences** play a preeminent role in the development of mood and anxiety disorders
    - Association mediated by **corticotropin-releasing factor (CRF)** system?
    - Evidence from preclinical studies (rats, non human primates): increased CRF may be the persisting neurobiological consequence of stress early in development

CRF in cerebospinal fluid

Severe stress early in life ➔ persistent sensitization of the pituitary-adrenal and autonomic stress response ➔ probably a risk factor for adulthood psychopathology



Heim C et al., JAMA 2000

(b) « Cytokine hypothesis »

- act as hormonal regulators or signaling molecules at nano- to-picomolar concentrations and help in cell signaling
- humoral mediators of innate and adaptive immunity
- important modulators of mood

- Some evidence from clinical and preclinical studies for a role in depression
  - 30% of patients treated with recombinant interferons develop depression as side effects
  - In rodents: blocking pro-inflammatory cytokine-mediated signalling can produce antidepressant effects

4. Monoamine Depletion

- 1950: Reserpine → Induce depression
- Study: Reserpine depletes storage or amine neurotransmitters such as serotonin and norepinephrine
- Break-through: MAOI and TCA
- Then: Depression ←→ ⇩Amine-dependent synaptic transmission

  (Antidepressants → ⇧Amine by means of reuptake and metabolism)
- Conclusion: Major model for the subsequent antidepressants

Neurotransmitter Deficiency Hypotheses of Depression

- Serotonin
- Norepinephrine
- Dopamine
- Gamma-aminobutyric acid (GABA)
- Brain-derived neurotrophic factor (BDNF)
- Somatostatin

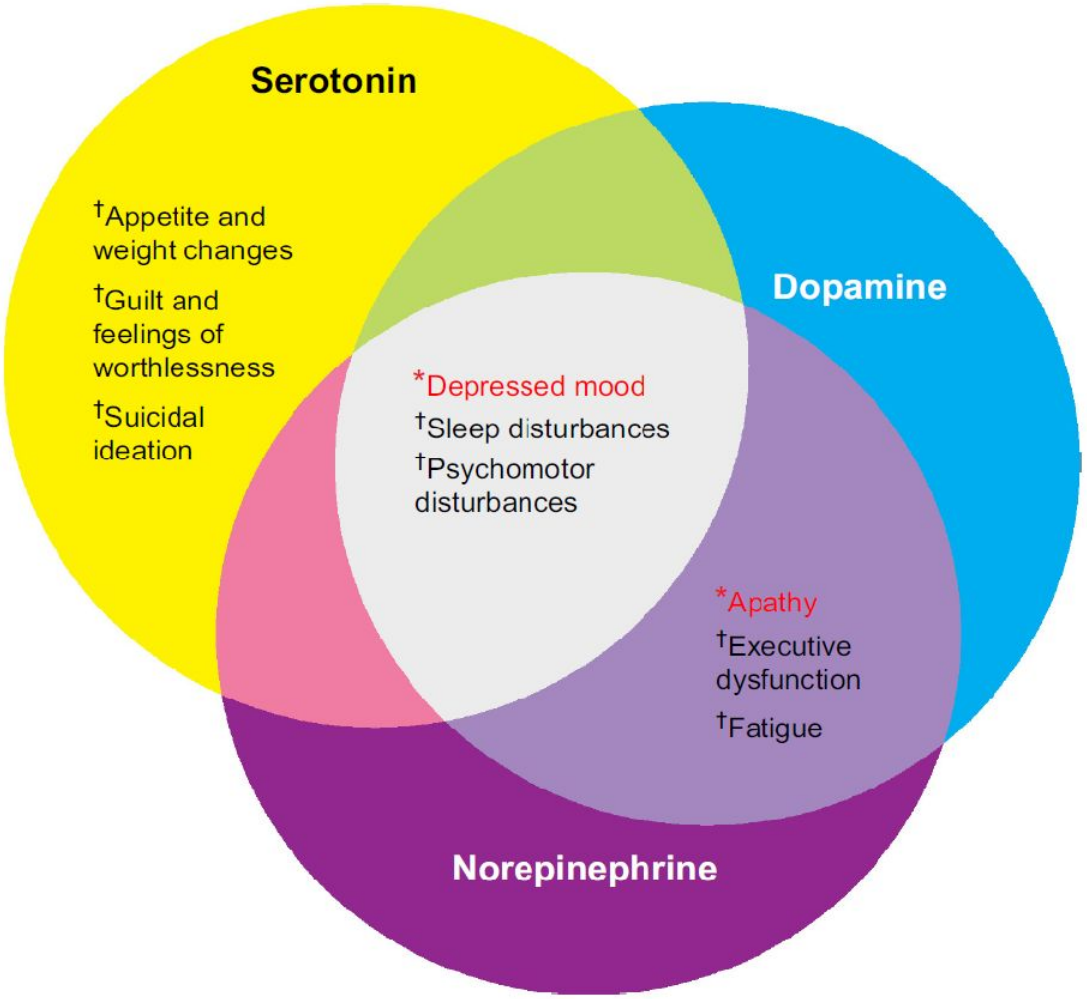
Neurotransmitter Excess Hypotheses of Depression

- Acetylcholine
- Substance P
- Corticotrophin Releasing Hormone (CRH)

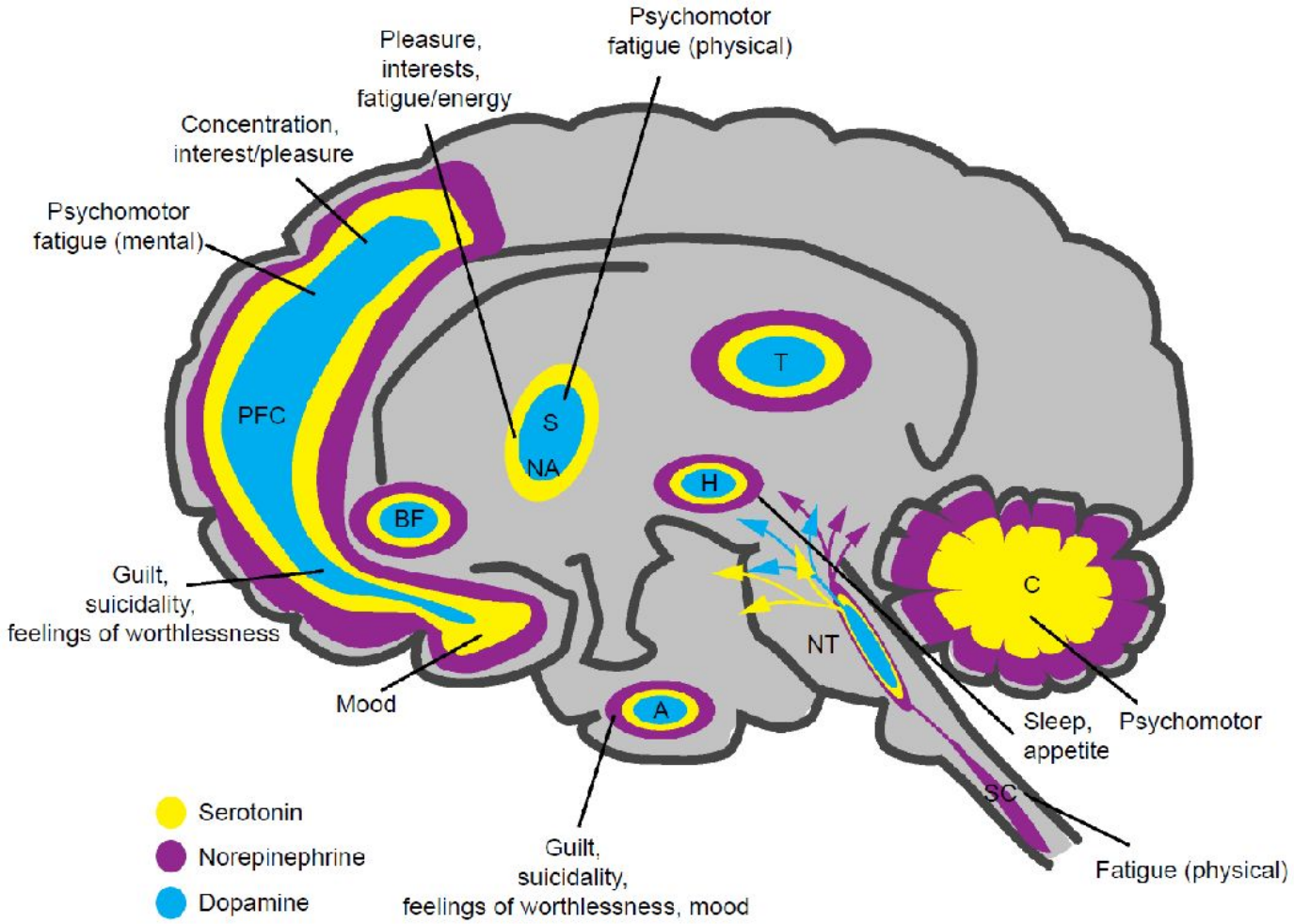
ANTIDEPRESSANT ACTION

- Enhance serotonin function by SSRI, MAOI, lithium or tricyclic antidepressant medication.
- Enhance norepinephrine or dopamine function by NERI or MAOI.
- Increased receptor number induced by ECT or enhance signal by second messenger effects.
- Enhance GABA function (anticonvulsants).
- Infuse BDNFintrathecally (serotonin growth).

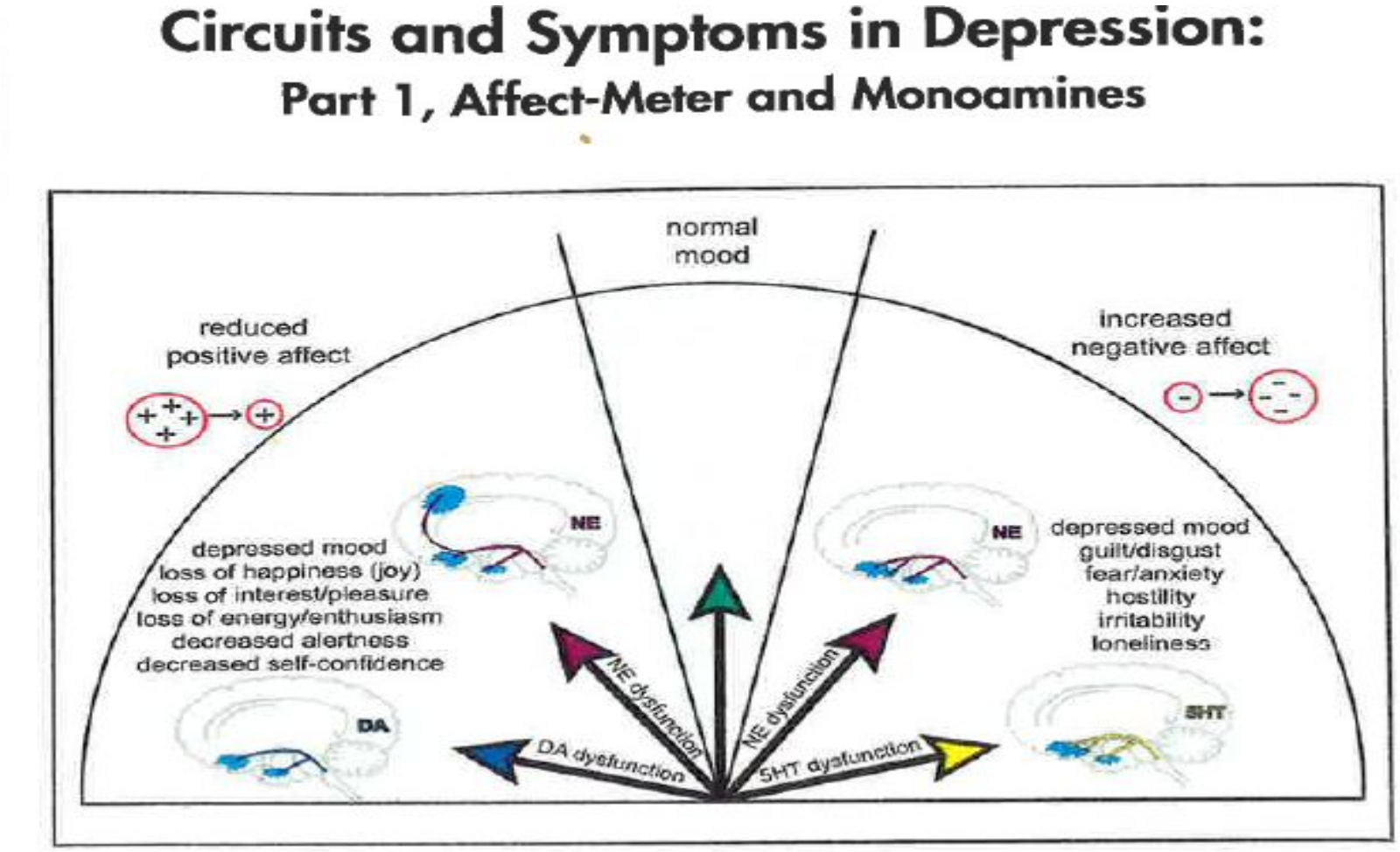
Serotonergic-noradrenergic-dopaminergic symptoms ?



Neurotransmitters and depressive symptoms



Circuits and symptoms in depression

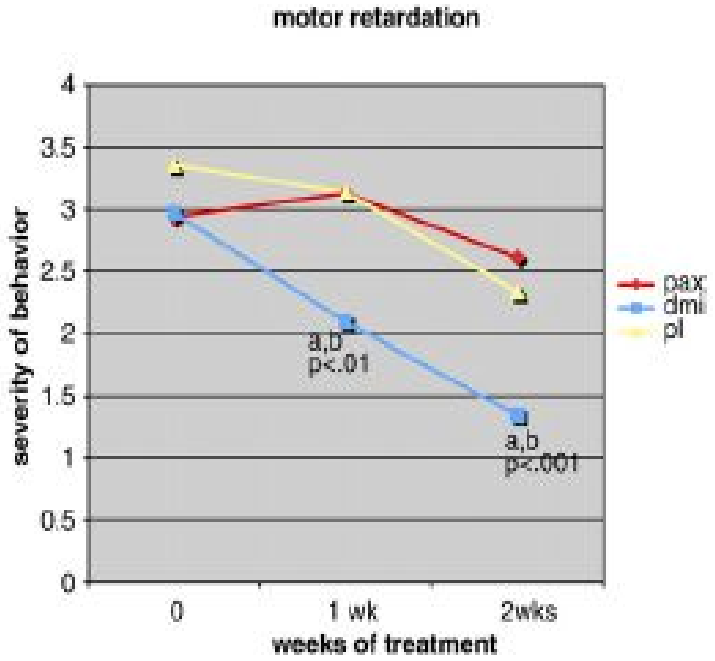


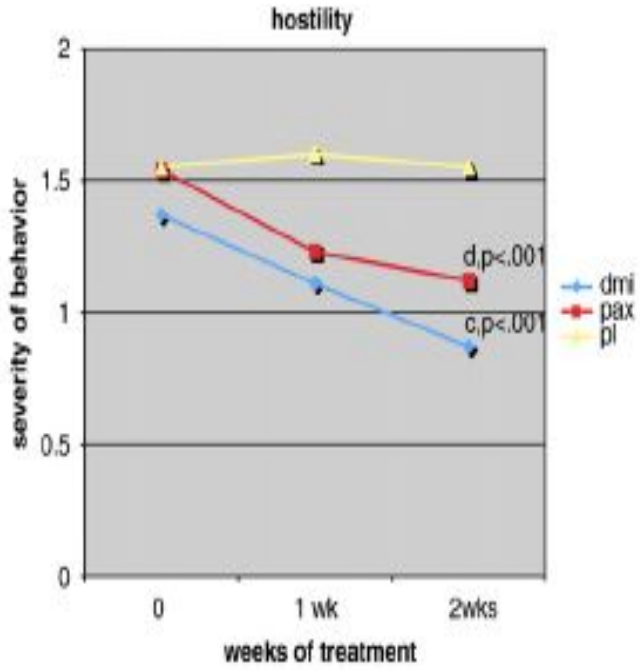
Stahl SM, Essential Psychopharmacology

Heterogeneity of MDD and neurotransmitters :
believers and non-believers ?

‘Neurotransmitter Specificity’ versus ‘Chemical Soup’

Are antidepressants component-specific rather than disorder-specific?





Katz MM et al., 2010

Dopamine

Dopamine Function is Deficient in Major Depression

- Parkinson's Disease associated with depression.
- CSF shows low homovanillic acid (HVA).
- Neuroendocrine challenges: blunted responses to dopamine agonists
- Depletion of dopamine with AMPT causes depression in recovered patients but not normals.
- Genes: TH, COMT & MAO

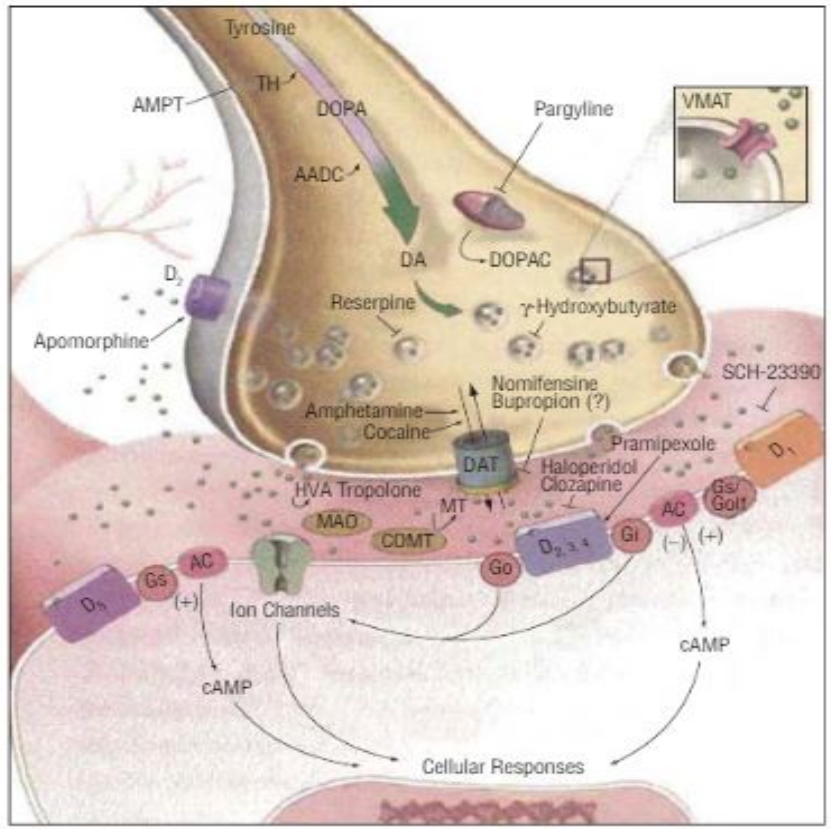


Figure 2. Dopaminergic synaptic signaling. Reprinted with permission from Szabo et al (2004).[5] AADC indicates aromatic acid decarboxylase; AMPT, α-methylparatyrosine; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; COMT, catechol-O-methyltransferase; D_1-D_5, dopamine receptors 1 through 5; DA, dopamine; DAT, dopamine transporter; DOPA, 3,4-dihydroxyphenylalanine; DOPAC, dihydroxyphenylacetic acid; Gi, Go, and Gs, protein subunits; HVA, homovanillic acid; MAO, monoamine oxidase; MT, 3-methoxytyramine; TH, tyrosine hydroxylase; and VMAT, vesicular monoamine transporter.

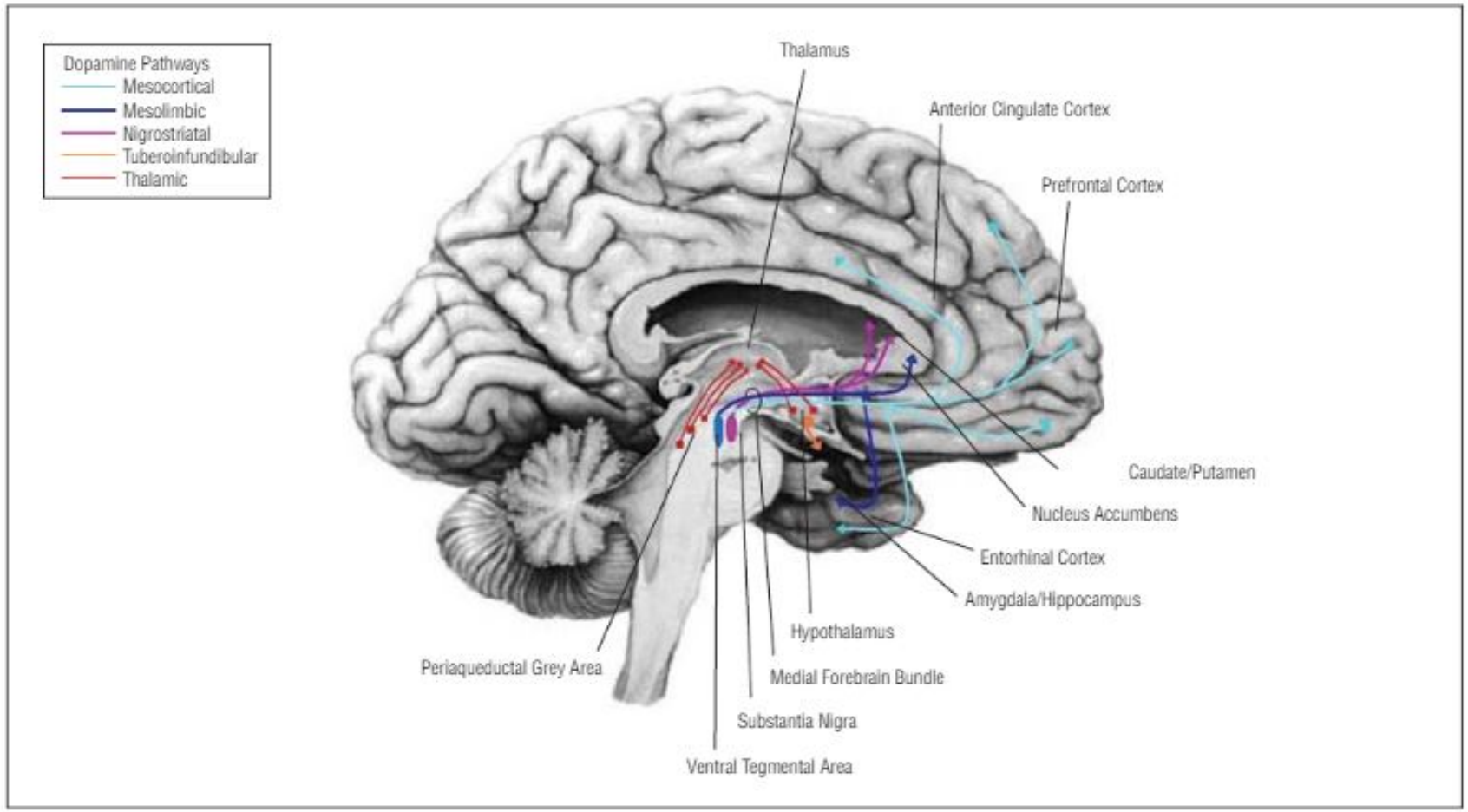
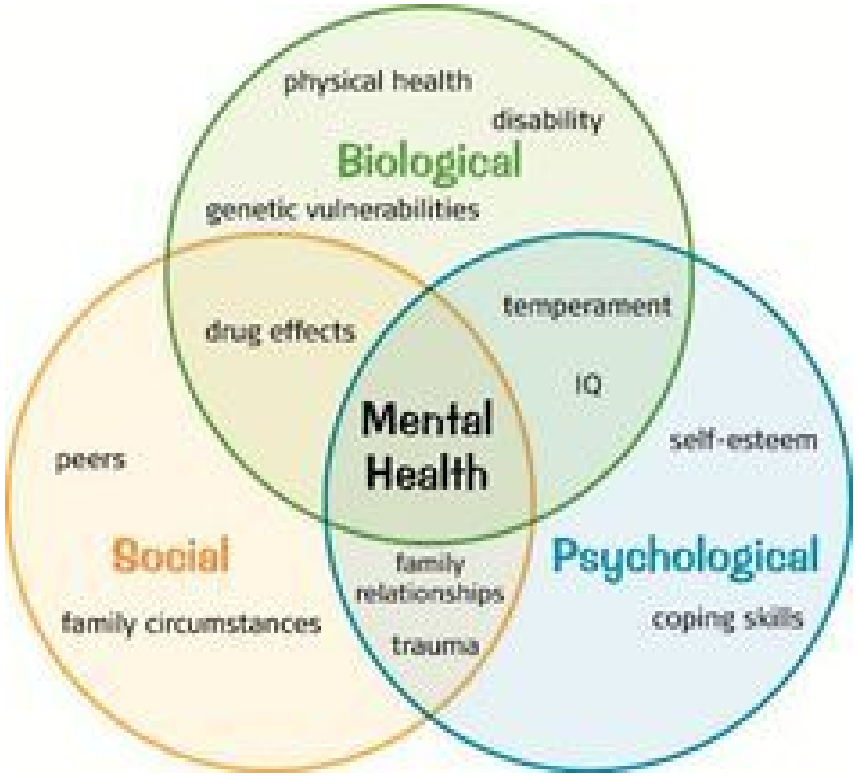


Figure 1. Dopaminergic pathways in the human brain. Reprinted with permission from Szabo et al (2004)[5] and Sanchez-Gonzalez et al (2005).[6] (Brain drawing used with the permission of Robert Finkbeiner.) Note that this image is a midline sagittal section of the brain. Many of the structures identified are located more laterally than the drawing indicates.

Dopamine importance in treatment of depression

- Anhedonia
- Postmortem studies of patients with suicides
- Dopamine agents like nomifencine, bromocriptine,prmipixole
- Serotonin dopamine interaction

Depression :
an individualized biopsychosocial disorder




HOPE