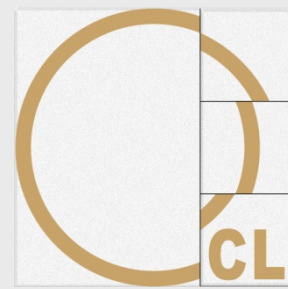




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VERNETZUNGSBEREICH

AFFECTIVE DISORDERS: DEPRESSION AND SOMATIC CO-MORBIDITY

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- General remarks
 - epidemiology
 - course of disorder
- Diagnosis – clinical appearance
- Depression and somatic co-morbidity
- Therapeutic aspects

Affective disorders

..... are mental disorders, which primarily affect the person's feelings and emotions but also have an effect on their way of thinking and on mental activity in general (concentration, retention)

Affective disorders

..... are potentially lethal: Up to 20% of patients suffering from depression commit suicide; 70% to 80% of all suicides are connected to depressive disorder.

....patients with depression have a 1.6 – 3x increased risk of mortality

Affective disorders

..... cause up to 7% of all disease burden in Europe und reduce the GDP by 1 percent.

..... are one of the main reasons for sick leave and early retirement.

Epidemiology

Life-time-risk: general population: 13-20 %
Females: 20 - 26 %
Males: 8 - 12 %

Prevalence of MDD –

general population: 5% - 8%
GP: 15 % - 20%

General Hospital: 30%

Psychiatric Hospital: 42% - 56%

- *Females : males = 2:1 (in unipolar depression;
in bipolar depression: 1:1)*
- *High individual suffering (also for relatives)*

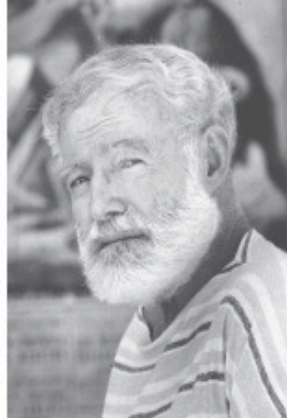
Well-known people suffering from MDD



Abraham Lincoln
Präsident der USA



Elisabeth Eugenie
Amalie von Wittelsbach,
genannt Sisi
Österreichische Kaiserin



Ernest Hemingway
Schriftsteller



Hermann Hesse
Schriftsteller

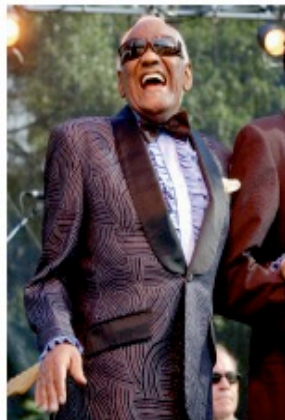


Pablo Picasso
Maler



© mmic collection, 2006

Marilyn Monroe
Schauspielerin



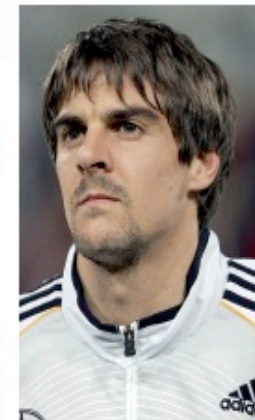
Ray Charles
Musiker



Kurt Cobain
Musiker,
Bandmitglied »Nirvana«

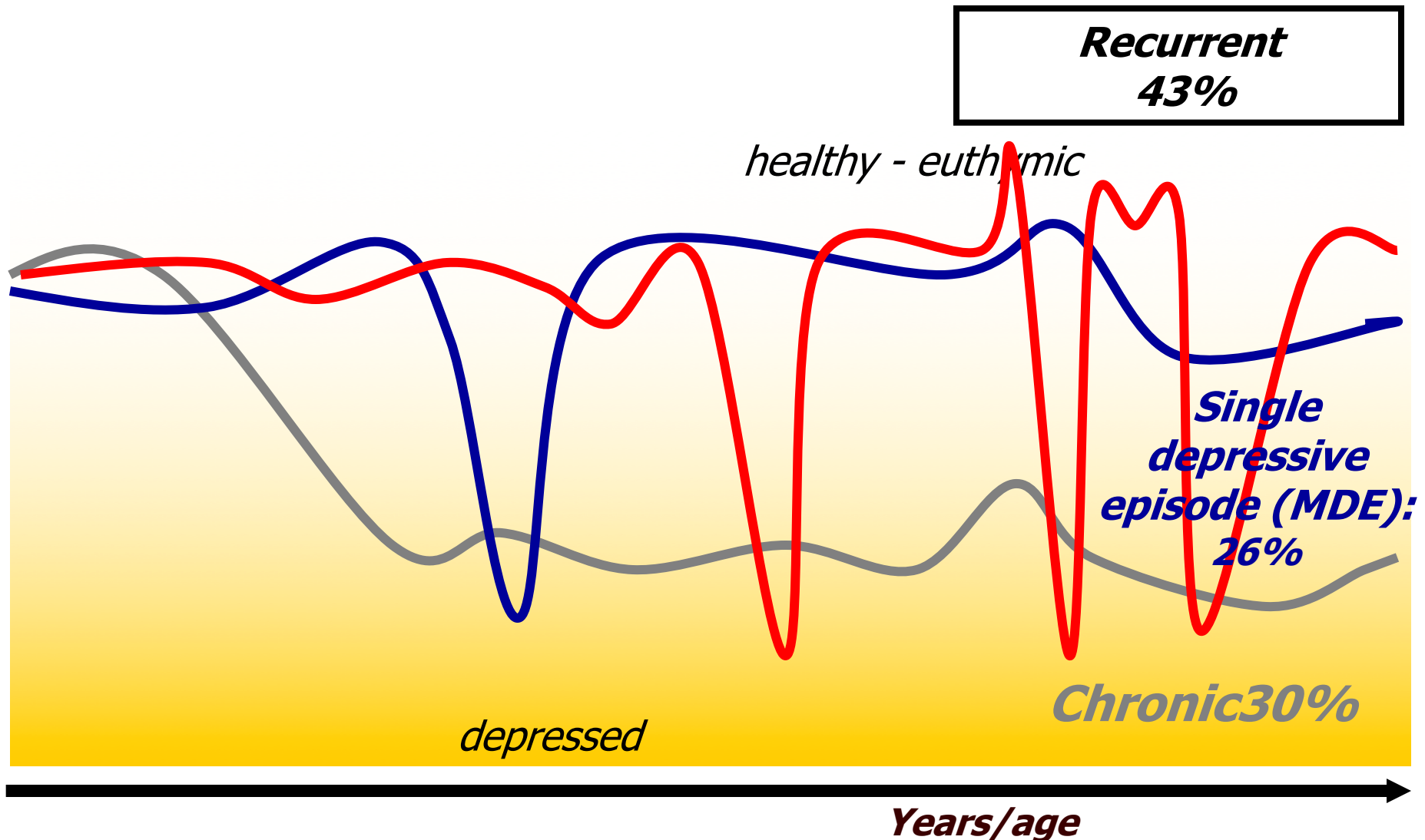


Eric Clapton
Musiker



Sebastian Deisler
Fußballer

Typical course of depression



Symptoms of Depression

Depressed mood

Lack of interest, inability to enjoy

Lack of energy

Feelings:

sadness, anxiety, anger, guilt, hopelessness
feelings of inner emptiness

Behaviour:

social withdrawal, lack of energy, low motivation,
poor concentration, sleep problems, sign. changes
in appetite

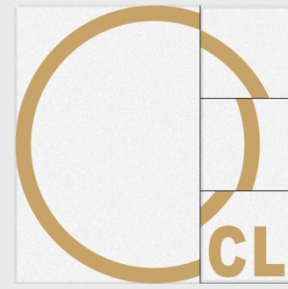
Thoughts:

poor self esteem, thoughts of suicide,
loss of interests, pessimistic future perspectives

Somatic symptoms:

pain, „chest-pressure“, dizziness,
digestive-problems

What do depressed people think/say



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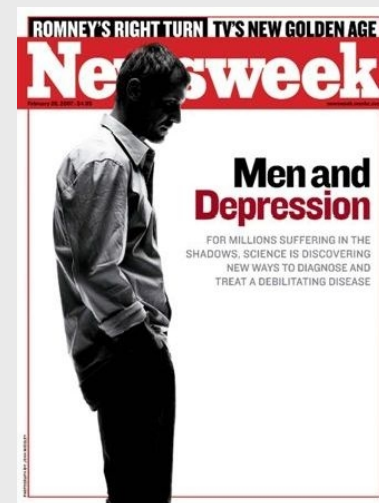
- *I have lost all my self-esteem, feeling of self-worth*
- *I cannot distract myself*
- *I have lost all my humor*
- *Something has changed inside myself: I have lost all my love and feelings for my own children, my partner*
- *Everything makes me feel so exhausted*



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What do depressed people think/say

- *I cannot experience joy anymore*
- *I can't think or read anymore and I can't concentrate at all*
- *I feel so empty inside*
- *I want to be free of all my thoughts once and for all, fall asleep and never wake up again*



Questions for screening of depression



- Have you been able to experience joy lately?
- Do you often have the feeling that you lack the incentive to do anything in particular?
- Do regular activities feel more difficult than usual? (work, household, sport etc.)
- Do you often feel „empty inside“?
- Did your sleeping pattern change lately?
- Do you withdraw from your friends and your social environment?
- Do you find it difficult to concentrate?
- Do you experience (vague/general) anxiety or fear?
- Do you sometimes think it would be better to be dead in your current situation? Do you think of taking your life?

Risik factors for depressive episodes

- Prior depressive episodes
- Family history of affective disorders
- Prior suicide attempts, or family history of suicide
- Somatic co-morbidity (esp. chronic somatic disorders)
- Co-morbidity of addiction or substance abuse
- Negative life events
- Lack of social support
- Early-life trauma

Causal factors/associated:

- Genetics
- Neurotransmitters: serotonin and/or norepinephrine deficiency/imbalance; receptor dysregulations
- Chronic dysadaptation to stress
- Chronobiological alterations (circadianic rhythms)
- Rigid, anancastic personality (Tellenbach)
- Early psychic trauma/losses
- ‚Learned helplessness‘

Co-morbidity between somatic disorders and depression

- Somatic diseases increase the risk of depression
- Depressive disorders increase the risk of somatic diseases
- Depressive disorders have a negative impact on the course of somatic diseases

Somatic diseases with frequent depressive co-morbidity

Disorder	Authors	Prevalence of depression
Cardiovascular diseases	Rudisch & Nemeroff, 2003	17 - 27 %
Diabetes	Anderson et al., 2001	9 - 26 %
Cancer	Pril, 2004	10 – 25 %
Chronic renal diseases (Haemodialyse)	Kim et al., 2002	20 – 30 %
Alzheimer disease	Lee, 2003	30 – 50 %
Cerebrovasculare diseases	Robinson, 2003	14 – 19 %
Parkinson's disease	McDonald et al., 2003	4 – 75 %
Pain	Campbell et al., 2003	30 – 54 %

CVD & Depression

CVD: 17 – 27% Major Depression

- Depression and CVD = risk for MCI ↑ (2-3x)
- Depression and MCI = mortality ↑ (3-4x)

[Carney et al, 1988; Ladwig et al, 1991; Frasure-Smith et al, 1993;
Frasure-Smith et al, 1995; Lesperance et al, 2000; Welin et al, 2000;
Bush et al, 2001]

- Depression = risk for CVD ↑ (1,5-2x)

[Anda et al, 1993; Aromaa et al, 1994; Barefoot et al, 1996; Everson et al, 1996;
Ford et al, 1998 ; Ferketich et al, 2000; Ariyo et al, 2000; Schulz et al, **2000 Rudisch B,**

**Nemeroff CB. Epidemiology of comorbid coronary artery disease and
depression. Biol Psychiatry. 2003 Aug 1;54(3):227-40]**

Interaction between DM & MD

- Patients with depression have a greater risk to develop type II diabetes
- Compared to GP patients with typ II diabetes have 2x higher risk to develop depression (Anderson et al. 2001, Zhao et al. 2006)
- Patients with typ II diabetes and depression are more often hospitalized (Rosenthal et al. 1998)
- Mortality is significantly increased in patients with typ II diabetes and depression

Influence of depression on mortality in patients with type II diabetes

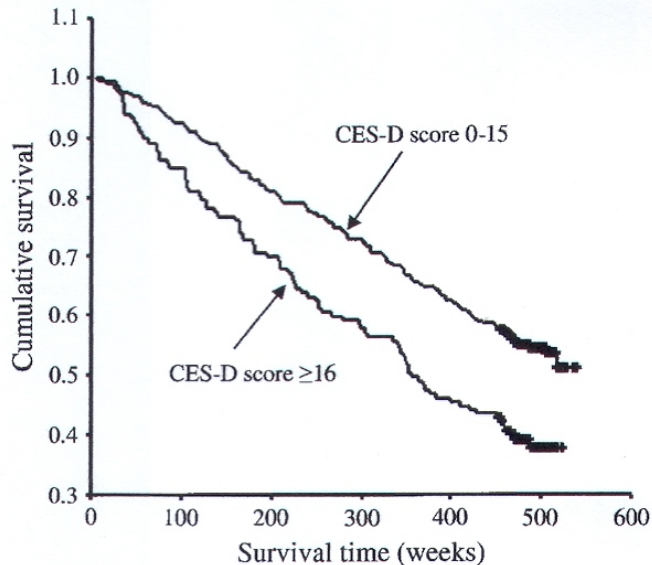


FIGURE 1. Survival functions in a diabetic population stratified by Centers for Epidemiologic Studies Depression (CES-D) Scale score, NHANES I Epidemiologic Follow-up Study, 1982–1992.

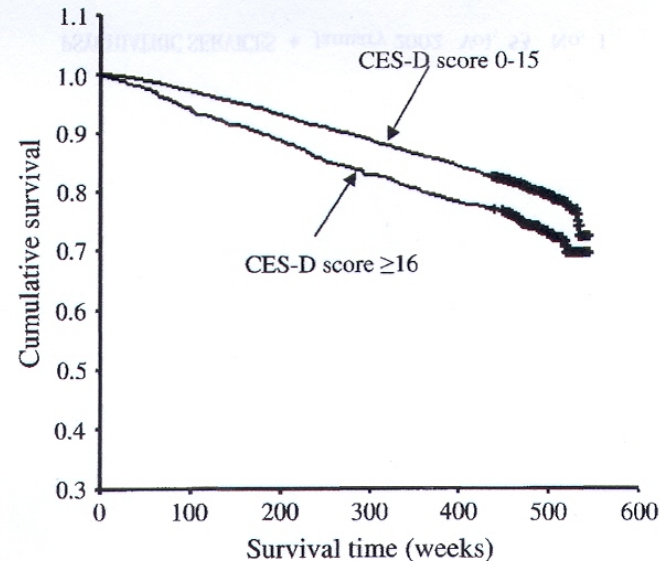


FIGURE 2. Survival functions in a nondiabetic population stratified by Centers for Epidemiologic Studies Depression (CES-D) Scale score, NHANES I Epidemiologic Follow-up Study, 1982–1992.

- *NHANES Epidemiologic Follow-up Study*
- *9.990 Persons (714 with diabetes)*
- *Follow-up: 10 a (1982-1992)*
- *10-years-mortality: 49,5% (Diabetes) vs. 21,2% (Non-Diabetes)*

Cancer and depression: Neuroendocrine-immune mechanisms as mediators of psychopathology

Cancer and its treatment

Tumor
Metastases
Chemotherapy
Psychological
Stress
Surgery
Radiation

Neuroendocrine System

Flattened cortisol slope
↓ Glucocorticoid
sensitivity
↓ Cortisol responsiveness
to stress

Sleep-Wake Cycle

↓ Sleep efficiency
↑ Awake time
↑ Latency to sleep
Disrupted rhythm

Behavioral Alterations

Depression
Fatigue
Impaired
Sleep
Cognitive
Dysfunction

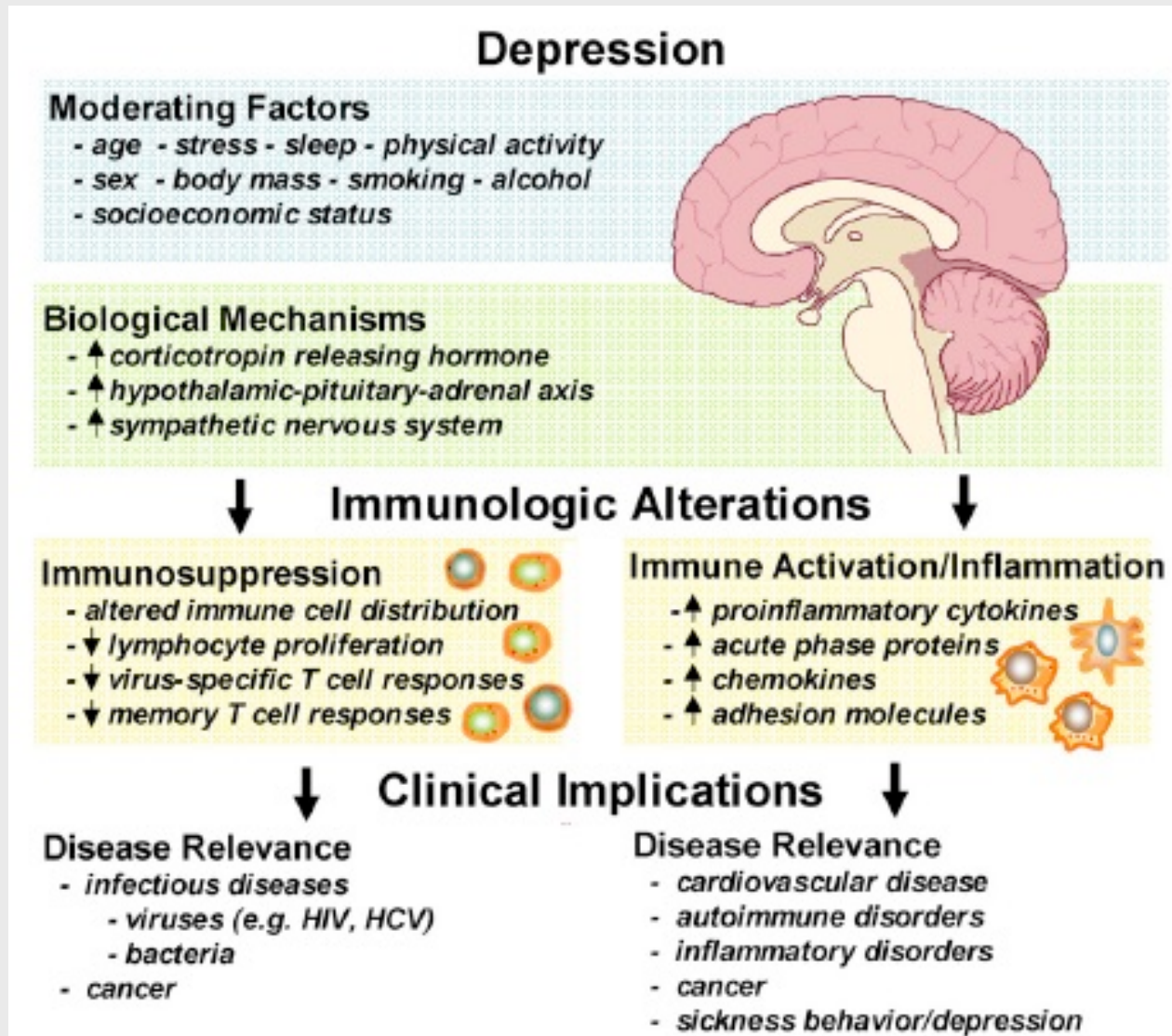
Inflammation

↑ Proinflammatory cytokines
↑ Adhesion molecules
↑ Acute phase reactants

CNS

↑ CRH
↓ 5HT, DA
↓ Growth factors
↑ NFkB/p38 MAPK

Somatic comorbidity in depression mediated by neuroendocrine-immune mechanisms

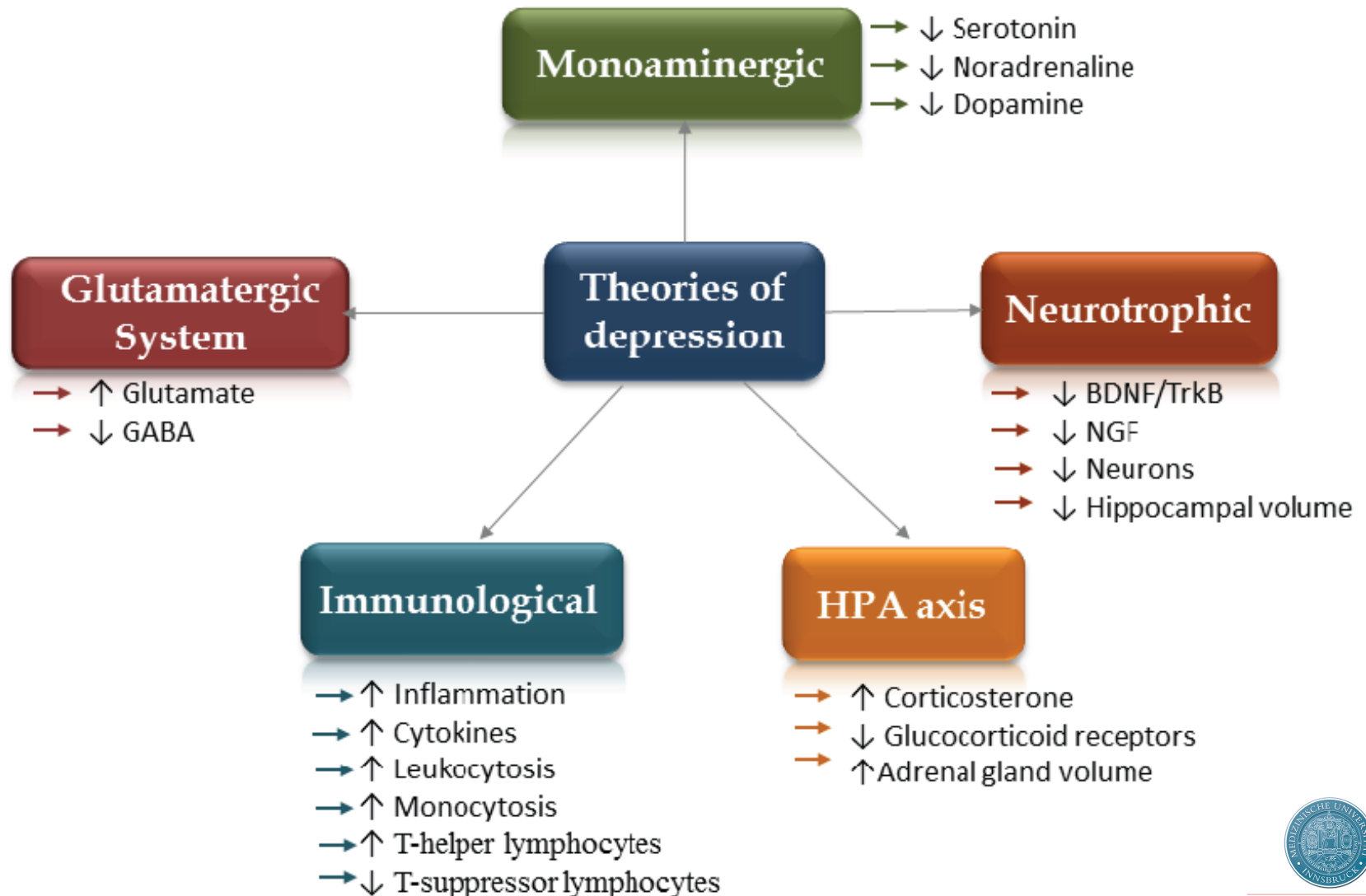


Contributing Factors in Chronic Non-Resolving Inflammation and Disease

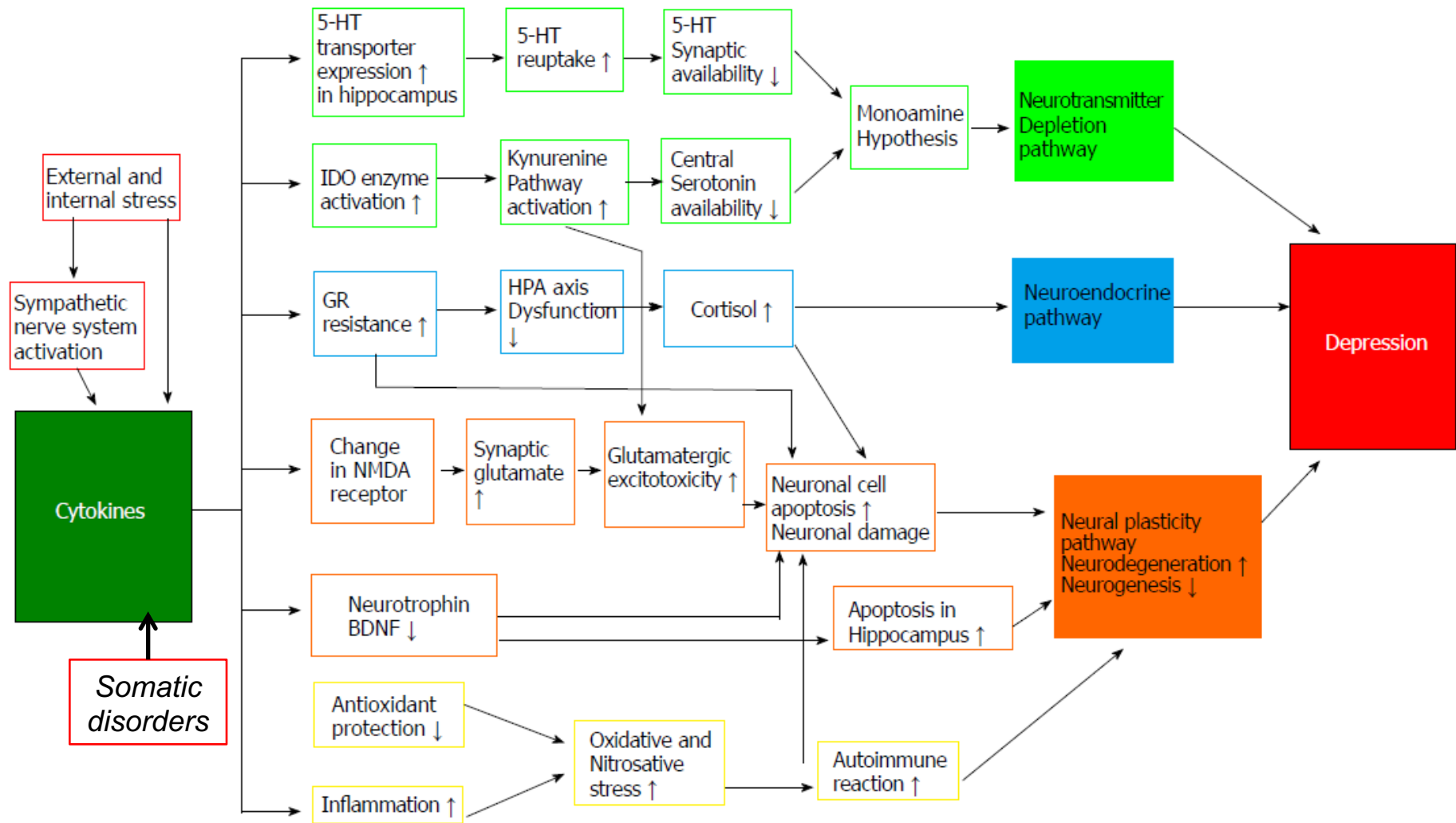
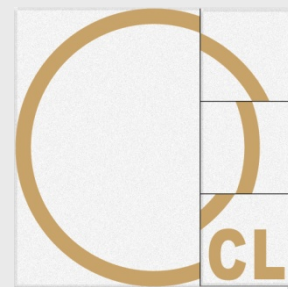


*E.Haroon et al Neuropsychopharmacology
Rev2011modified*

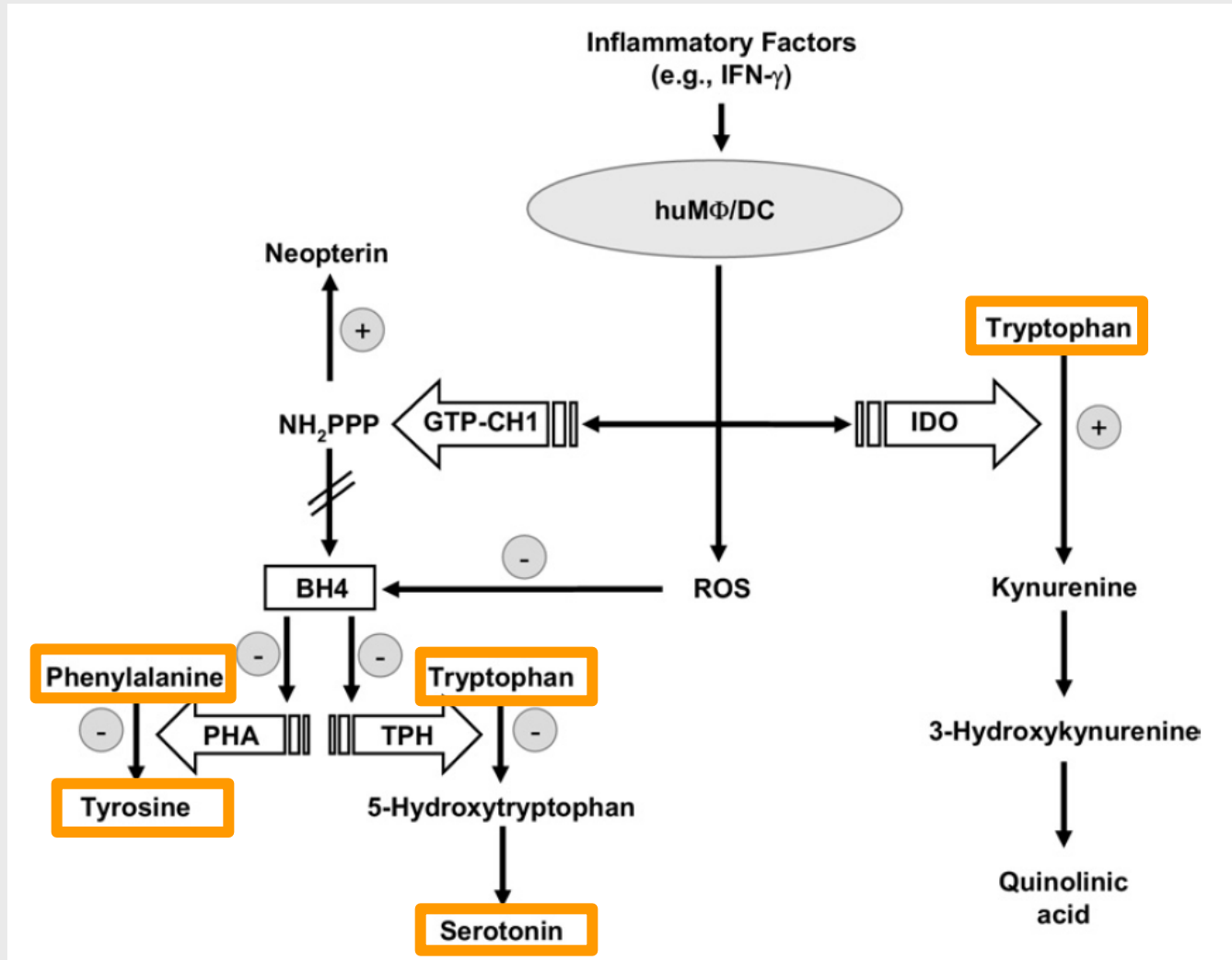
Hypotheses of Depression



Neuroinflammatory pathways in the pathogenesis of depression



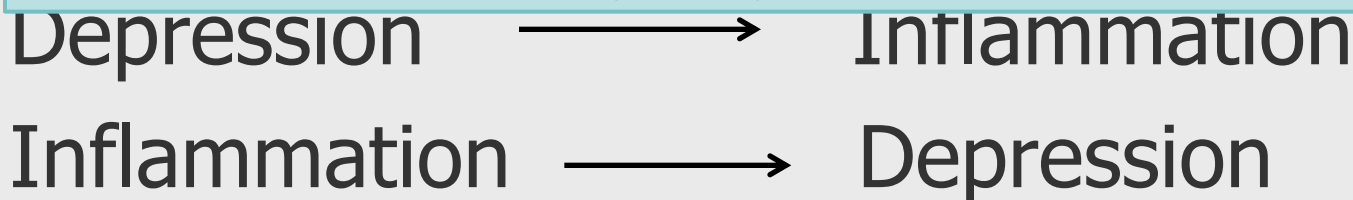
Inflammatory-induced metabolic pathway changes



Increase of CRP: Association with Depression

- CRP –increase: independent risk factor with predictive value
CRP, IL-1, IL-6 –increase associated with depression in
clinical and community – based samples (review Howren 2009)
- BMI: mediating and modifying factor
 - medication reduces the influence

***Cumulative Depressive Episodes Predict Later
C-Reactive Protein Levels: A Prospective Analysis***
Copeland WE et al.: Biol Psychiatry 2012;71:15-21



Increased Markers of Inflammation in Depression

- Increased activation markers: complement proteins, pos. APPs, (CRP), neopterin, prostaglandin E2, HLA-DR+,
- **Elevation of cytokines: IL-6, TNF- α , TNF- β , IL-1, IL-1ra**
- significant associations to severity
- treatment response /resistance

Zorilla 2001

Dowlati 2010

Meyers 2005,

Miller 2009

Sluzewska 1996, 97

"Macrophage theory of depression"

"Activated IRS"

Smith 1991

Maes 1993

Maes 1995

.....

Results of a recent study on the topic Cancer - Inflammation - Depression



Psychoneuroendocrinology (2015) xxx, xxx–xxx



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Levels in neurotransmitter precursor amino acids correlate with mental health in patients with breast cancer

Hüfner K^{a,*}, Oberguggenberger A^a, Kohl C^a, Geisler S^b,
Gamper E^a, Meraner V^a, Egeter J^a, Hubalek M^c,
Beer B^d, Fuchs D^b, Sperner-Unterwieser B^a



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Methods

- 154 subjects included in the study (DPR^{+/-}, BCA^{+/-}):
- Patients with breast cancer (BCA): no signs of active disease, in aftercare program
- Patients with depression (DPR): HADS ≥ 8 pts or therapy with AD or ICD-10 diagnosis of F32, F33, F43
- Sociodemographic parameters, severity of depressive symptoms and anxiety (ANX) at time of study were recorded
- Neopterin measured by enzyme-linked immunosorbent assay
- Kynurenine/tryptophan and phenylalanine/tyrosine ratios analysed by HPLC
- Two-way ANCOVA (adjusted for age, BMI and smoking), main effects “physical health” (BCA+ vs. BCA-) and “mental health” (DPR+ vs. DPR- or ANX+ vs ANX-) ($p < 0.05$)

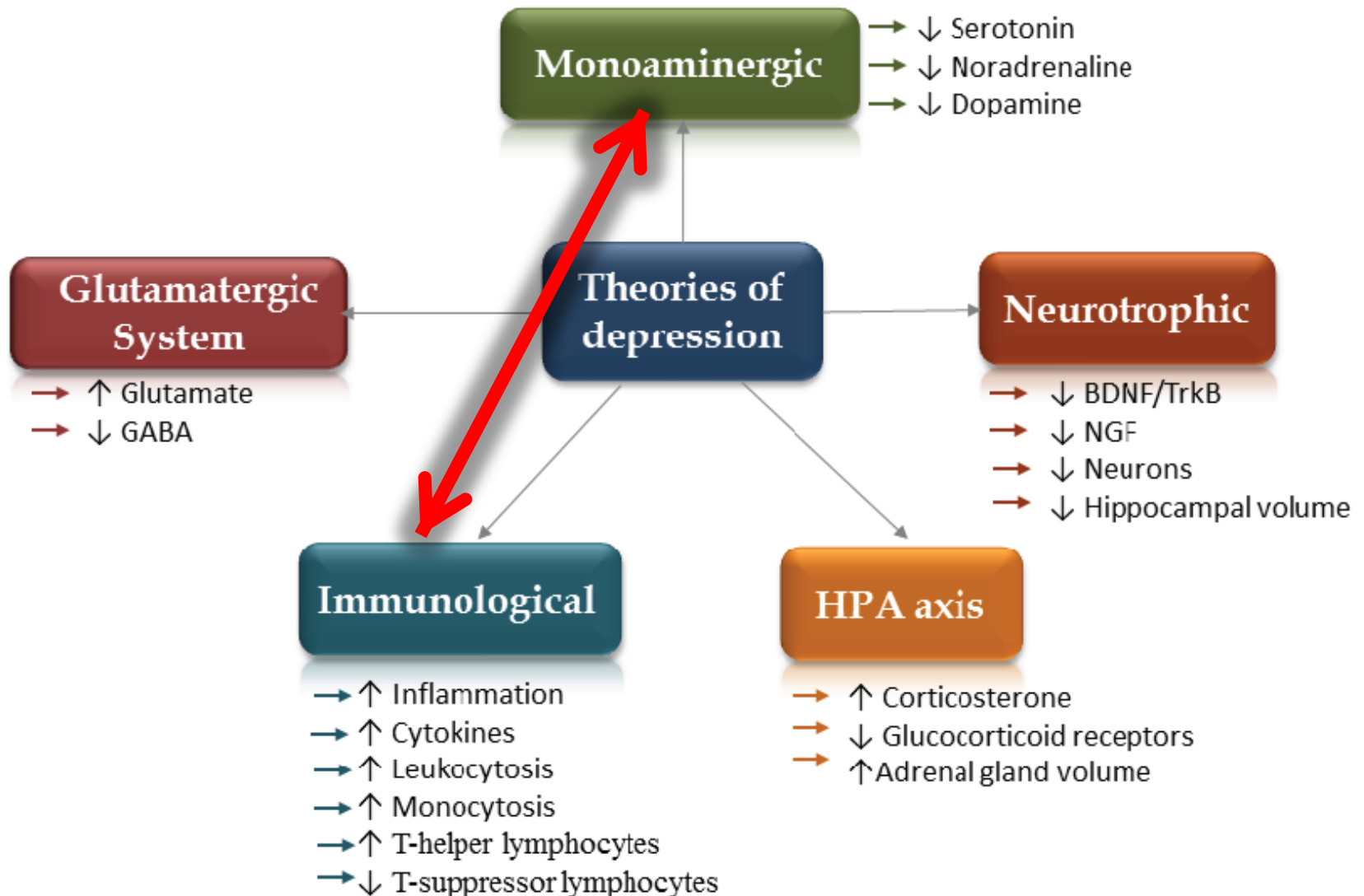
Conclusion

- Higher neopterin levels in patients with mental disease (DPR⁺ or ANX⁺)
- The differences in neurotransmitter precursor amino acid ratios were most evident in patients with physical and mental comorbidity
 - > PHE/TYR increased in depression
 - > KYN/TRP increased in state anxiety
- Changes in serotonin and catecholamine pathways could be important in linking breast cancer and psychological distress
- Possible hypothesis :
 - > in BCA⁺DPR⁺ SNRI could be tried first line
 - > in BCA⁺ANX⁺ SSRI might be more promising

Hypotheses of Depression



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Factors that have a positive impact on the therapy of depression



- Information of patients and families about the disorder and treatment options
- Good therapeutic relationship
- Individual planning of therapy concepts
- Evaluation of diagnosis (including additional diagnostic procedures)
- Evaluation of therapeutic process



Treatment options for depression:

- Antidepressant drugs
- Psychotherapy (cognitive-behavioral)
- Exercise
- Light therapy (predominantly for SAD)
- Sleep deprivation
- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (rTMS)
- Vagus nerve stimulation (?)

Which patients with depression should receive psychopharmacological medication?



Guidelines APA, NICE,
S3-Guidelines of DGPPN 2012

Which psychopharmacological medication is used?

- Antidepressants
- „mood stabilizer“
- Antipsychotic medication
- Benzodiazepines



Long-term therapy of recurrent depression

- Aim: to avoid a new depressive episode or a relapse
- Long-term therapy should be recommended:
 - > 3 episodes of depression, or
 - > 2 episodes +:
 - Family history of affective disorders
 - Rapid onset of the next depressive episode
 - Young age at the first episode
 - Severe episodes
- After good response - continue with the same dose of the same antidepressant
- For at least 2 episode-cycles (4-5 years?) at min. 2 years
- discontinuation should be planned and done slowly

Psychotherapeutic aspects in the treatment of depression:

- Supportive
- Often recommended in combination with medication
- Effective in the acute phase of the disorder as well as prophylactically
- Most study results in CBT
- Aims: e.g.: changing dysfunctional thinking, increasing self esteem, training of social behaviour

Future aspects

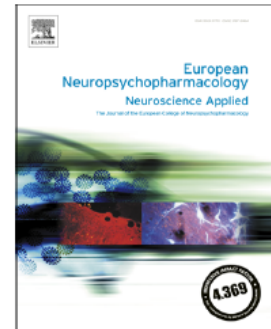
- **„biomarker profiling“:**
 - diagnostic tool
 - therapeutic tool (personalized medicine)
- **therapeutic options:**
 - different antidepressant medication
 - mood stabilizers
 - cytokines (e.g. TNF- α antagonist)
 - cytokine-signaling pathways (e.g. COX-inhibitors)
 - metabolic pathways (e.g. IDO-inhibitors, Kyn-modulators)
 - others: omega-3 fatty acids, curcumin
 - nutrition/diet
 - exercise/sport
 - relaxation

European Neuropsychopharmacology (2017) 27, 554-559



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Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation

Carmine M. Pariante

