

الحمد لله
الرحمن الرحيم

IN THE NAME OF GOD

Psychoneuroimmunology and Psychiatry

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Professor of Psychiatry

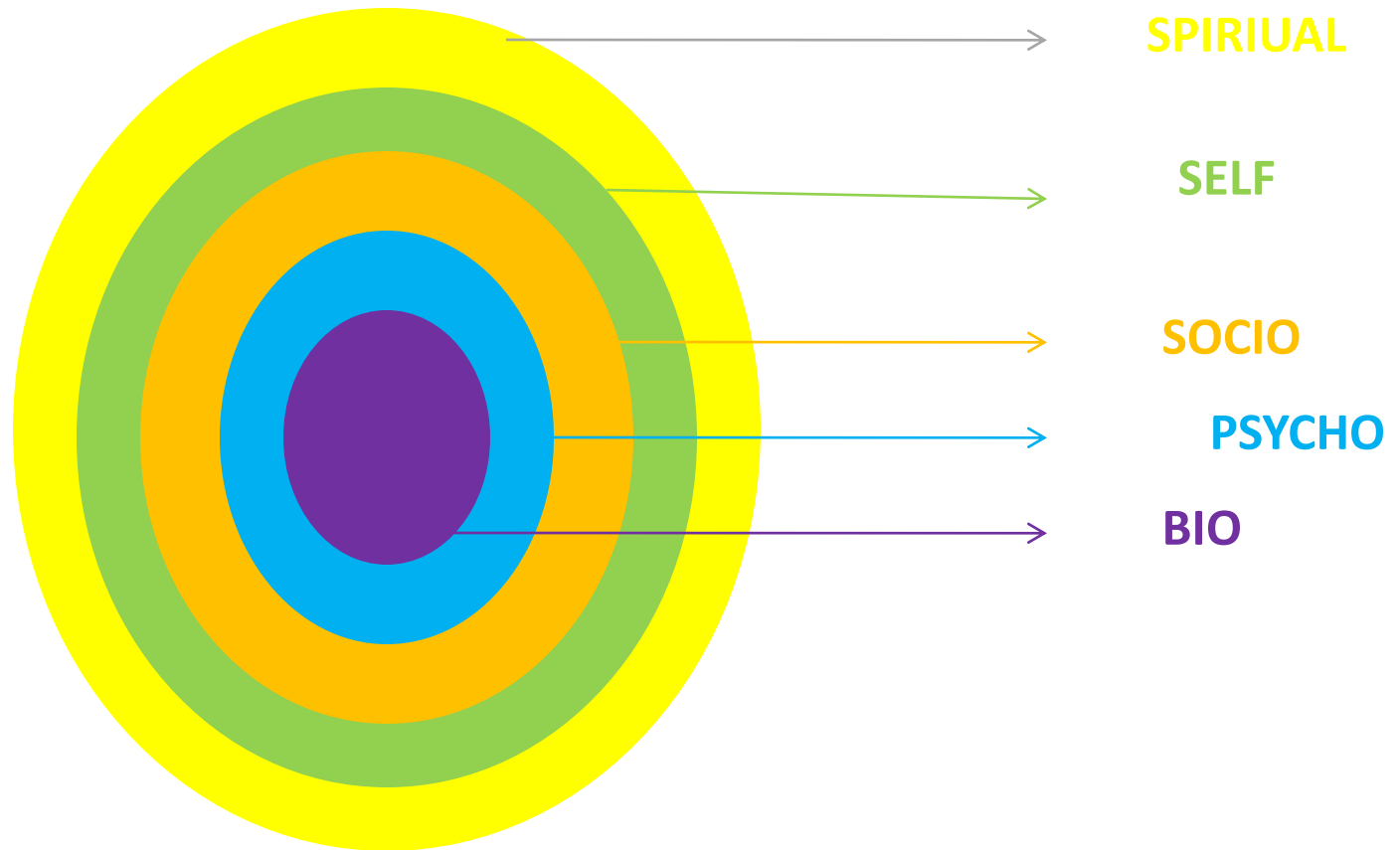
Tehran University of Medical Science

The Second Iranian Neuropsychiatry Congress

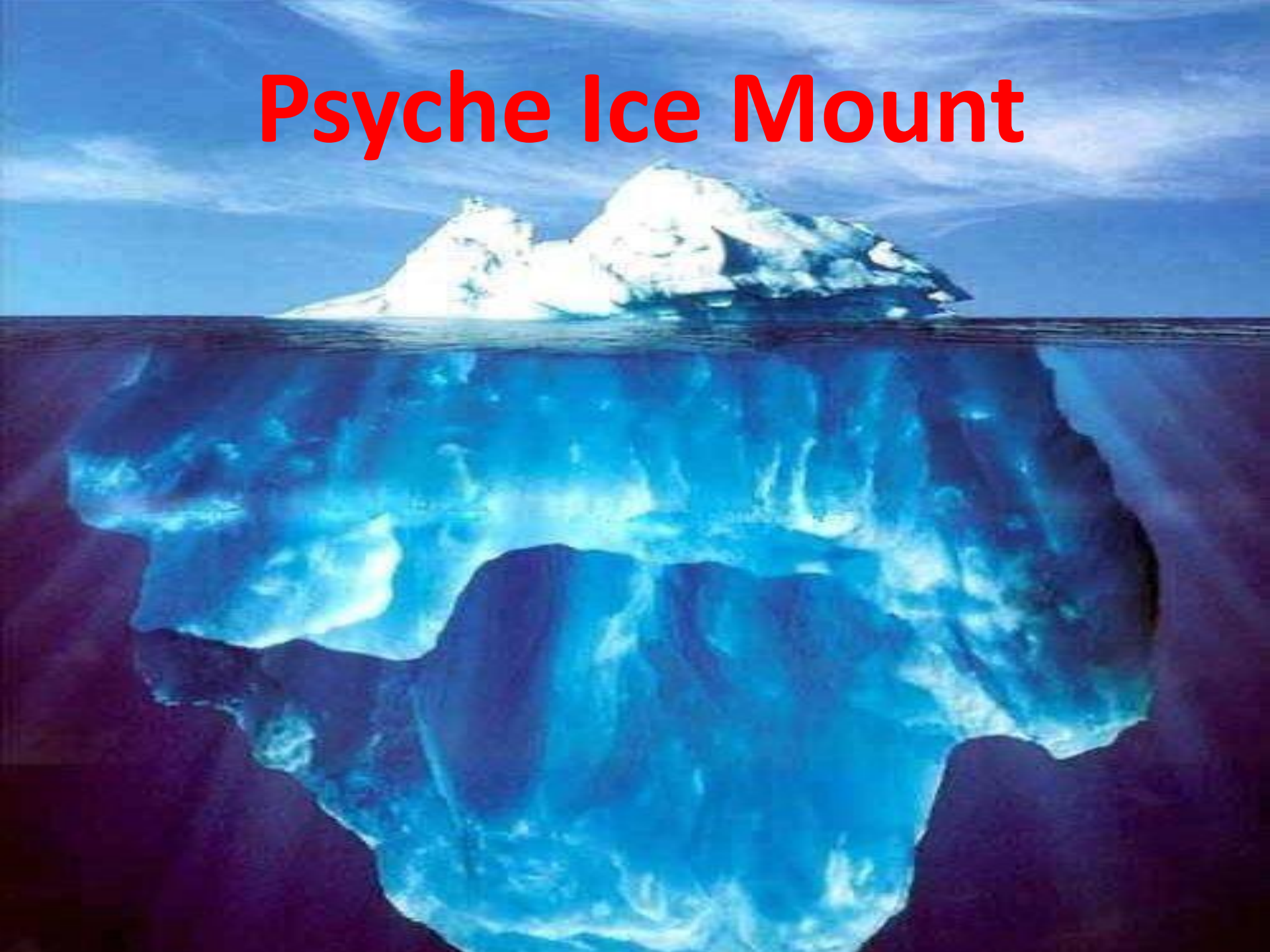
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Religion Human Diagram



Psyche Ice Mount



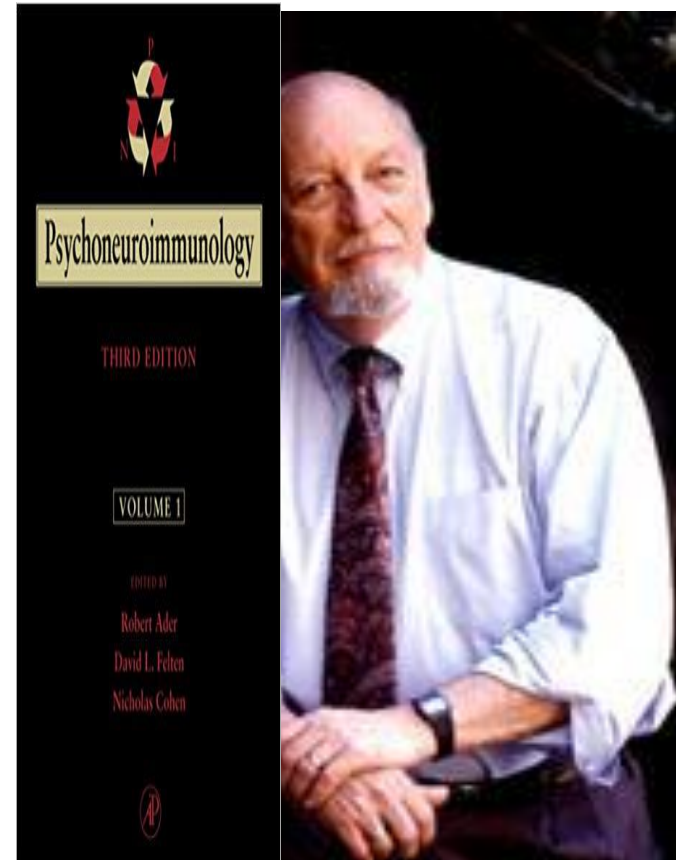
**Dr. Candace Pert (1946-2013)
has been called “The Mother of
Psychoneuroimmunology”,
and “The Goddess of
Neuroscience” by her many
fans.**



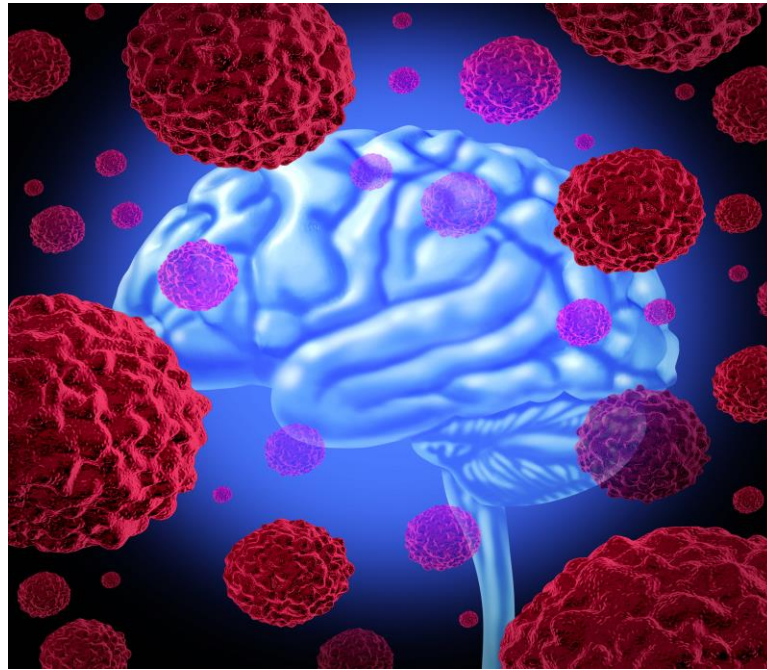
Robert Ader , 1974

the brain directly influences the immune system by using classical conditioning in rats.

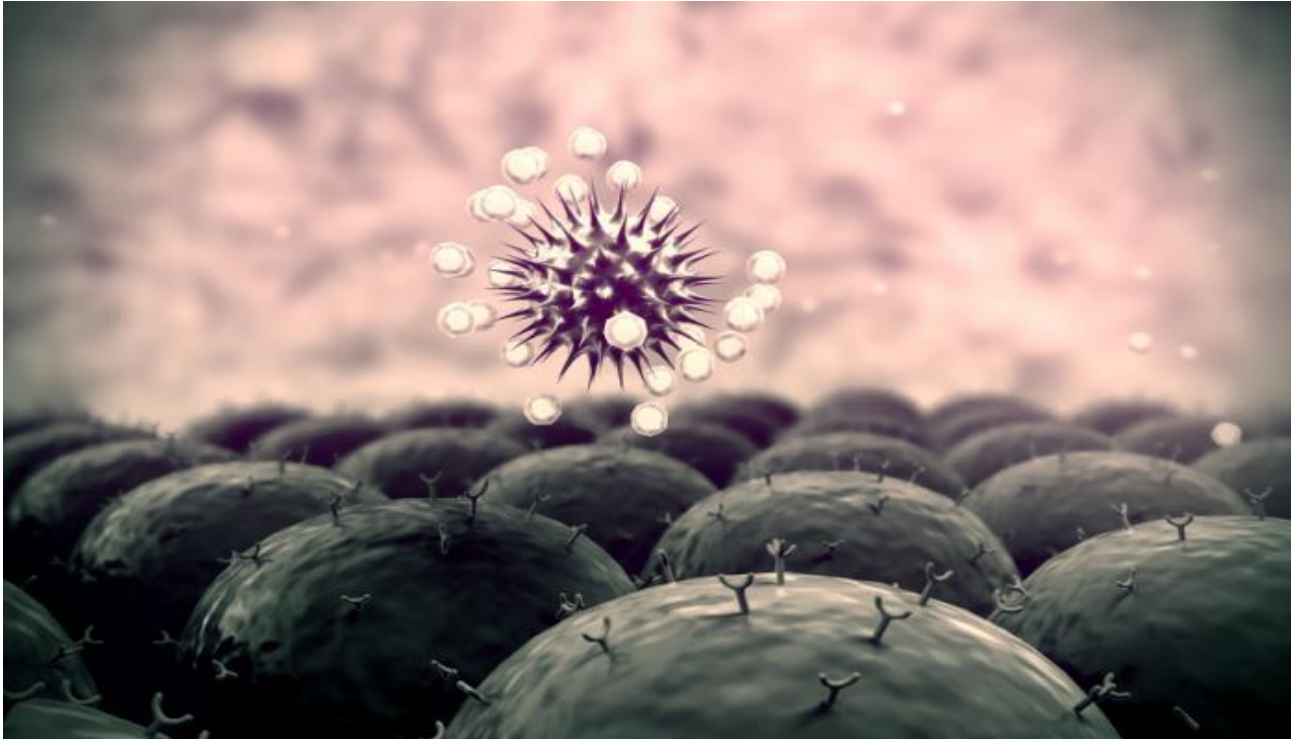
**(Placebo effect)
“The Father of
Psychoneuroimmunology”**



Psychoneuroimmunology = psychology, neuroscience, immunology, physiology, genetics, pharmacology, molecular biology, psychiatry, behavioral medicine, infectious diseases, endocrinology, and rheumatology,....



PsychoNeuroImmunology (PNI)
ImmunoNeuroPsychiatry(INP)
ImmunoPsychiatry(IP)
psychoendoneuroimmunology (PENI)



Definition of Psychoneuroimmunology

Robert Ader(2000):

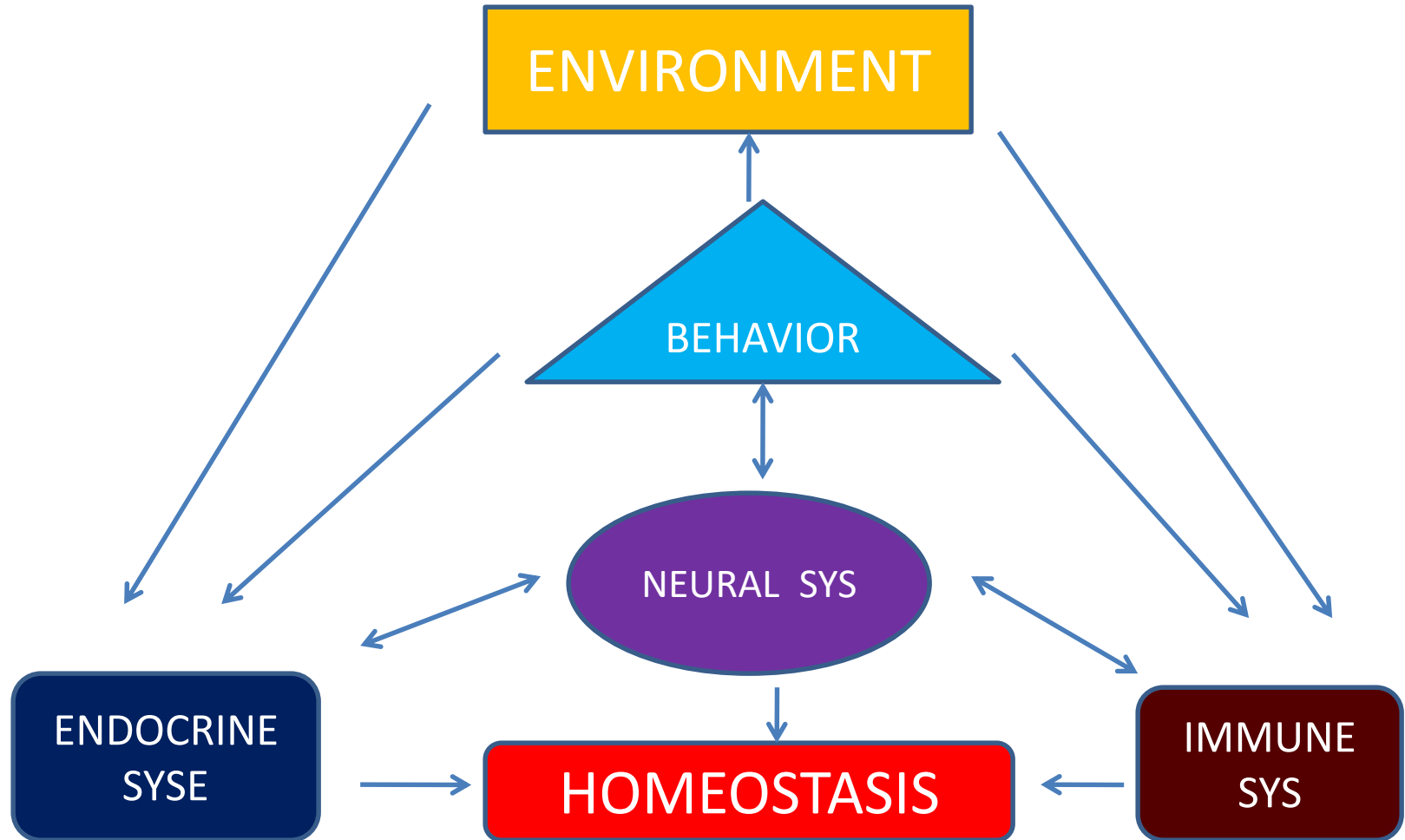
Psychoneuroimmunology is a convergence of disciplines- namely, **the behavioral sciences**, **the neurosciences**, **endocrinology**, and **immunology**- intended to achieve a more complete understanding of the way the interactions among these systems serve homeostatic ends and influence health and disease.

Definition of Psychoneuroimmunology

Jorge H. Daruna(2004):

Psychoneuroimmunology represents the most integrative scientific discipline capable of providing an understanding of health in all its complexity and, thus, guiding efforts to promote the health of individuals and communities.

Interaction between different systems and effect on Homeostasis



History of PNI

- The field of psychoneuroimmunology has come into existence in relatively more recent times.
- The term *psychoneuroimmunology* was first employed by Ader in 1980 to capture what had become growing evidence of the intercommunication between the brain and the immune system.
- Ader notes that interest in such a link can be traced back to early work by Russian investigators, who, based on Pavlov's work, hypothesized that immune responses could be conditioned and reported preliminary positive findings as early as 1926.

History of PNI

- Also, the studies of Hans Selye in the 1930s demonstrating that a variety of noxious conditions (stressors) caused endocrine effects and changes in immune tissues were important in the birth of this field.
- Ader has further traced the emergence of psychoneuroimmunology through the work of Rasmussen (1950s) on the effect of psychological stress on susceptibility to infection, and Solomon's work (1960s) exploring an autoimmune etiology for schizophrenia.

History of PNI

- In the **1970s**, well-designed conditioning studies, as well as a variety of **animal** and **human** studies documenting effects on the immune system by manipulations of the situation or the occurrence of **life events** affecting the individual's emotional state, further underscored that a link must exist between **brain activity** and the **cells of the immune system**

History of PNI

- Indeed, the fact that the immune system can affect the brain had already been discovered in the **1930s**, when it was observed that **vaccination against rabies** could cause massive inflammation of the **brain**.
- This was because the vaccine was prepared from central nervous system tissue, which led to an immune response against the individual's own brain.
- Moreover, in the **late 1950s and early 1960s**, investigators, including Fessel and Hirata-Hibi, Heath, and Solomon, made observations suggesting immune **abnormalities in schizophrenic patients**, including the possibility that schizophrenia could be an autoimmune disorder.

History of PNI

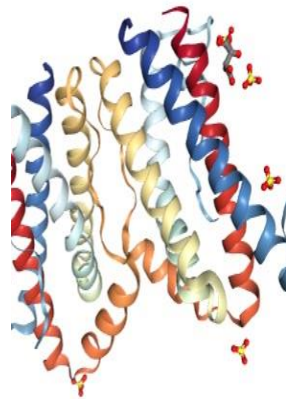
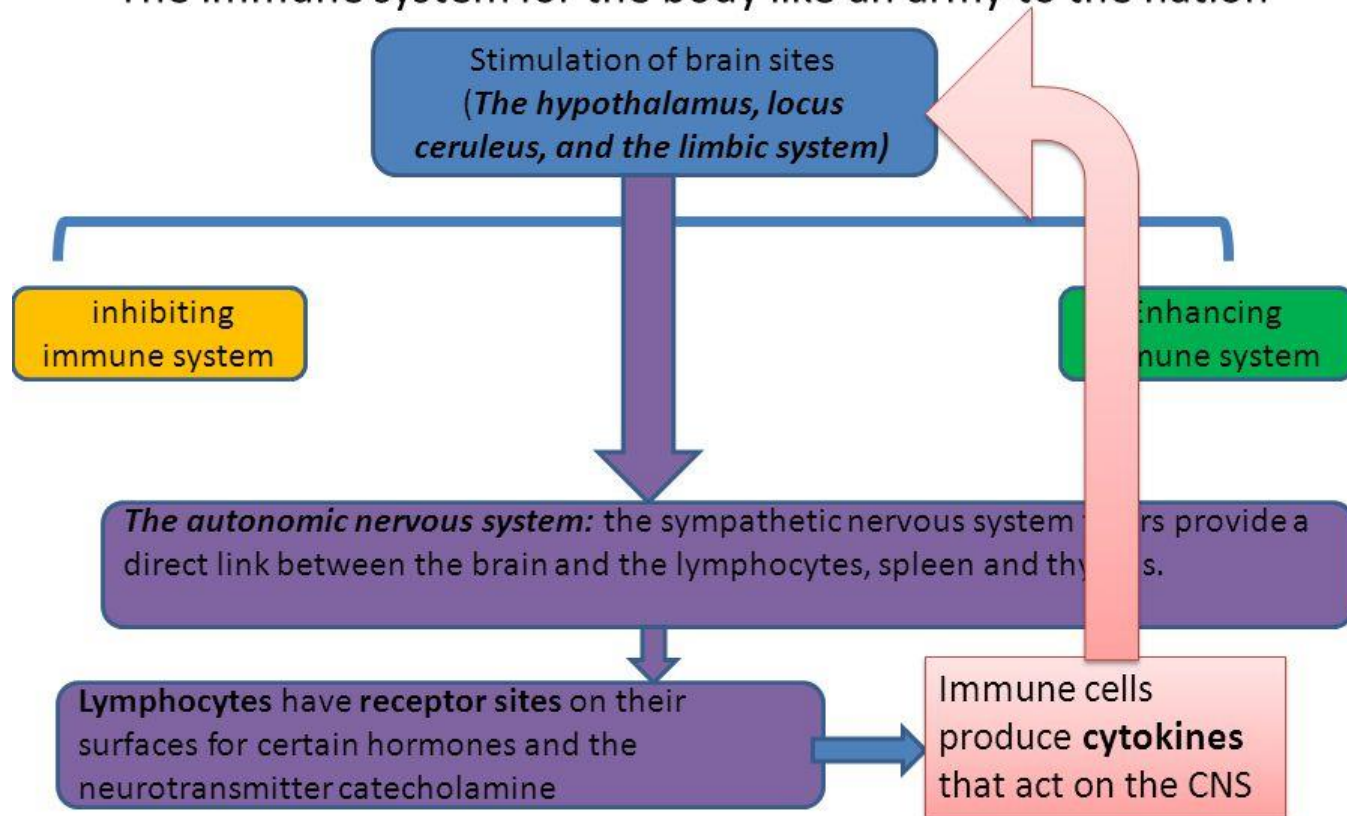
- The hypothesis that **major psychiatric disorders could result from misdirected immune activity** continued to receive attention.
- Misdirected immune activity has now been implicated in a number of disorders of the brain that affect behavior and mental processes (**e.g., childhood-onset obsessive-compulsive disorder**).

History of PNI

- Thus, the picture that has begun to emerge is one wherein **life circumstances**, by affecting brain activity, **can alter immune function**, with the **potential to have health consequences**.
- Meanwhile, the immune system's response to pathogen stimulation **causes the release of substances that can affect brain activity and may even disrupt its functioning**

Communication between the brain and immune system

The immune system for the body like an army to the nation



General organization of immune defenses

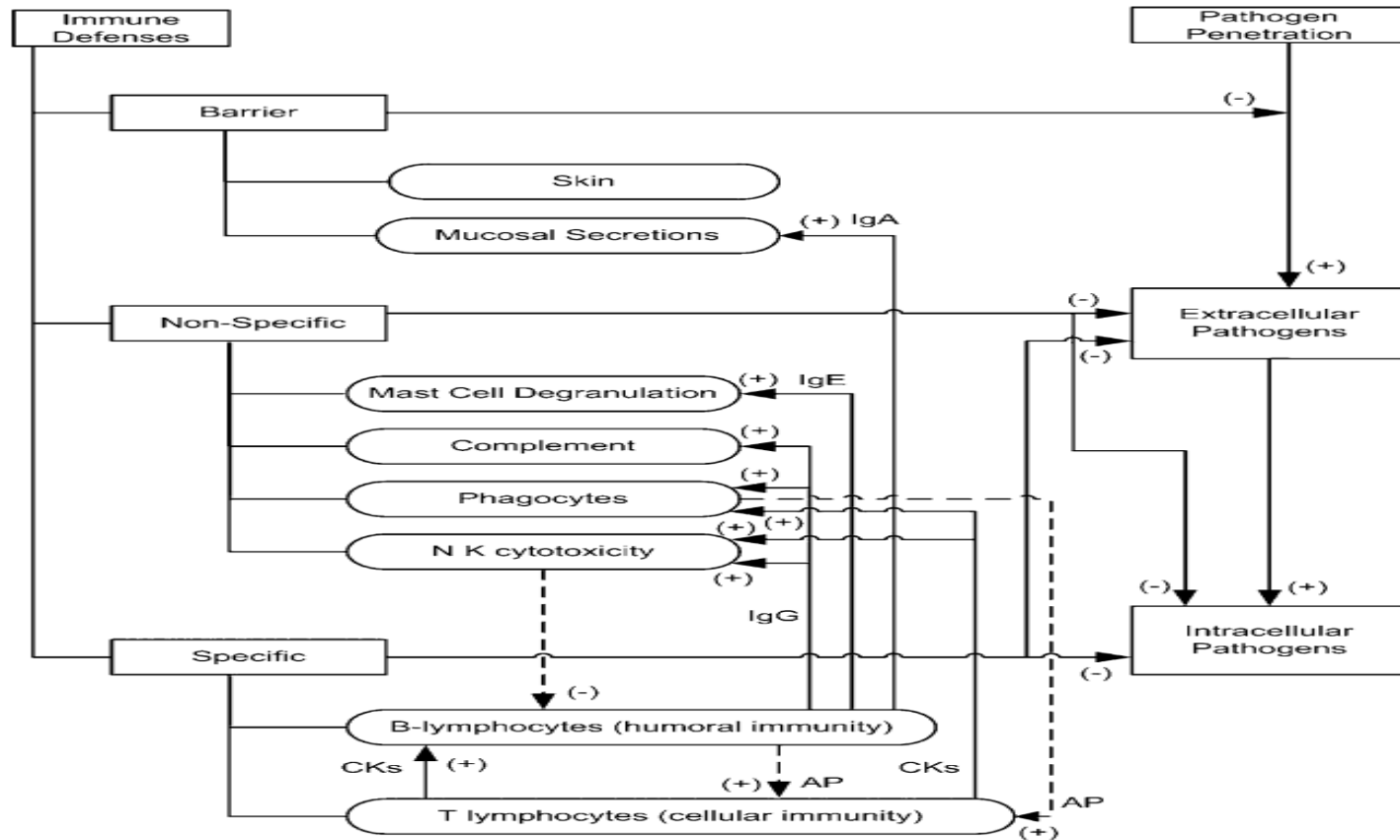


Figure 3.15 General organization of immune defenses. AP, antigen presentation; CKs, cytokines; IgG, immunoglobulin G; NK, natural killer.

Hypothalamic–pituitary–endocrine gland axes

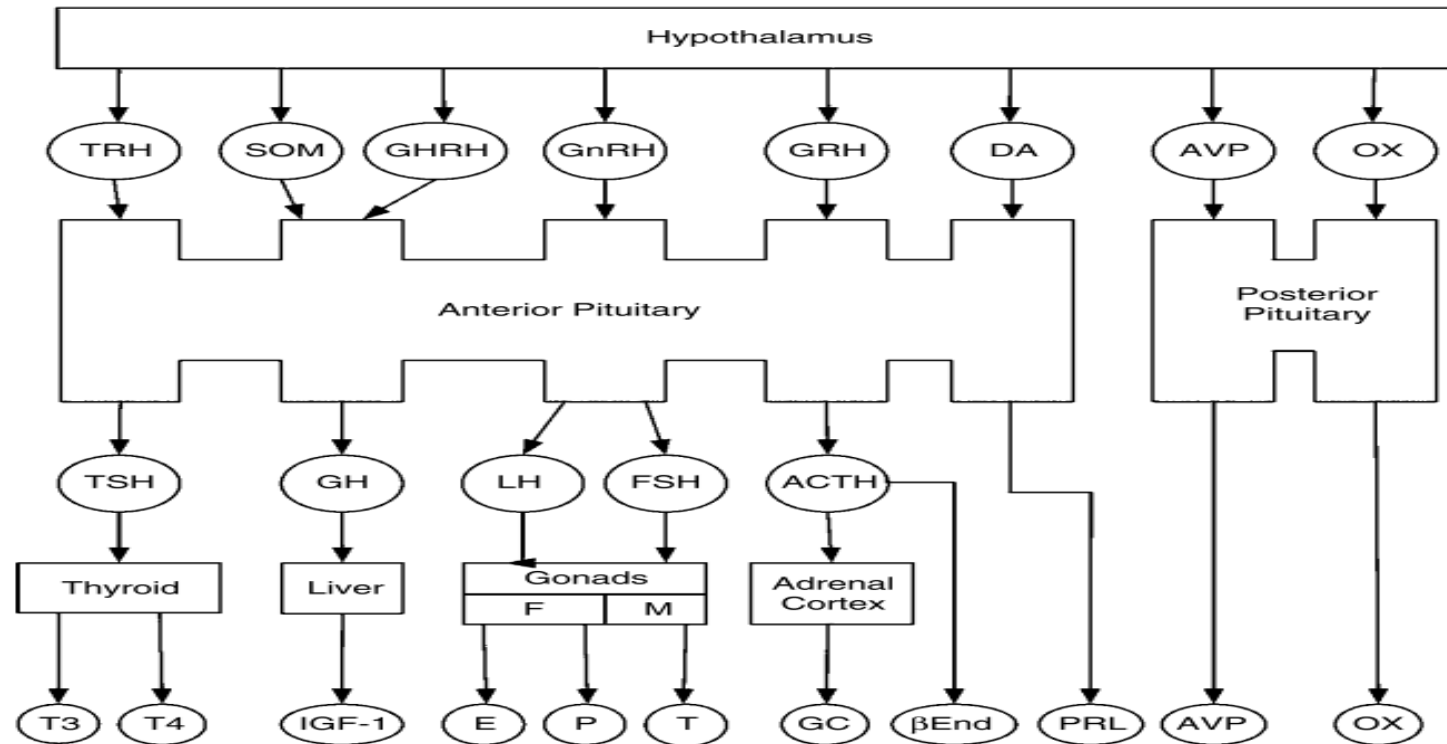


Figure 4.1 Hypothalamic–pituitary–endocrine gland axes. ACTH, adrenocorticotrophic hormone; AVP, arginine vasopressin; β-end, β-endorphin; CRH, corticotropin-releasing hormone; DA, dopamine; FSH, follicle-stimulating hormone; GC, glucocorticoids. GH, growth hormone; GH-RH, growth hormone–releasing hormone; GnRH, gonadotropin releasing hormone; IGF, insulin-like growth factor; LH, luteinizing hormone; OX, oxytocin; P, progesterone; PRL, prolactin; SS, somatostatin; T, testosterone; T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

Infection and Psychosocial Stress

- Psychosocial stress represents the facet of **contextual change** that may increase the **probability of disease or enhance its progression** and thereby produce additional stress.
- The available data lend some support to the role of psychosocial stress in infectious disease.
- Life change is at least a weak predictor of the onset of infectious disease.
- Studies focusing on family dynamics suggest that **disturbed relationships predict increased episodes of infectious disease.**

Infection and Psychosocial Stress

- Personality characteristics such as **introversion** and **chronic states of negative emotion** such as **depression** are associated with a higher probability of **clinical symptoms of infection** and a more rapid progression to disease in the case of HIV infection.
- **Well-controlled studies of upper respiratory tract infections further support the role of psychosocial variables as predictors of the response to experimentally induced viral infection.**

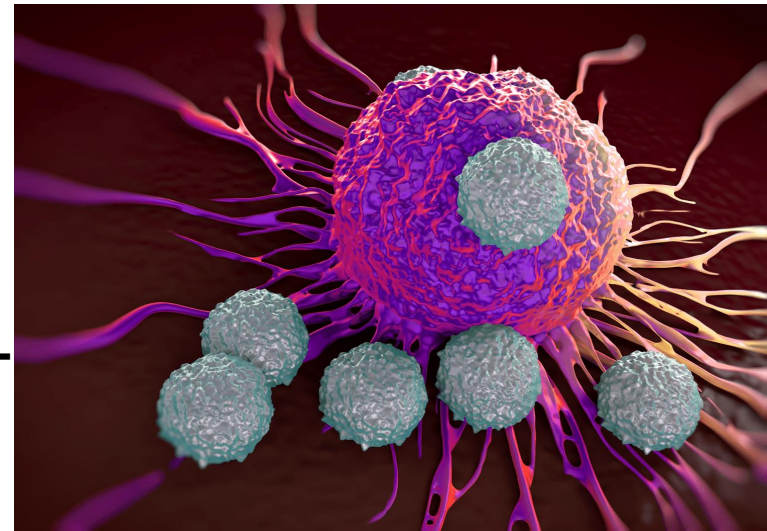
Infection and Psychosocial Stress

- The role of infection is now recognized in **cardiovascular disease**, **peptic ulcers**, and even **psychiatric disorders**.
- However, recognition of the role of pathogens in such diseases should not eclipse awareness of the influence of psychosocial stress.
- Psychosocial stress is a factor whose contribution may be obscured because it is not always necessary or sufficient to cause disease.
- Moreover, psychosocial stress may have diametrically opposed effects across individuals and diseases.

inflammatory-mood pathway

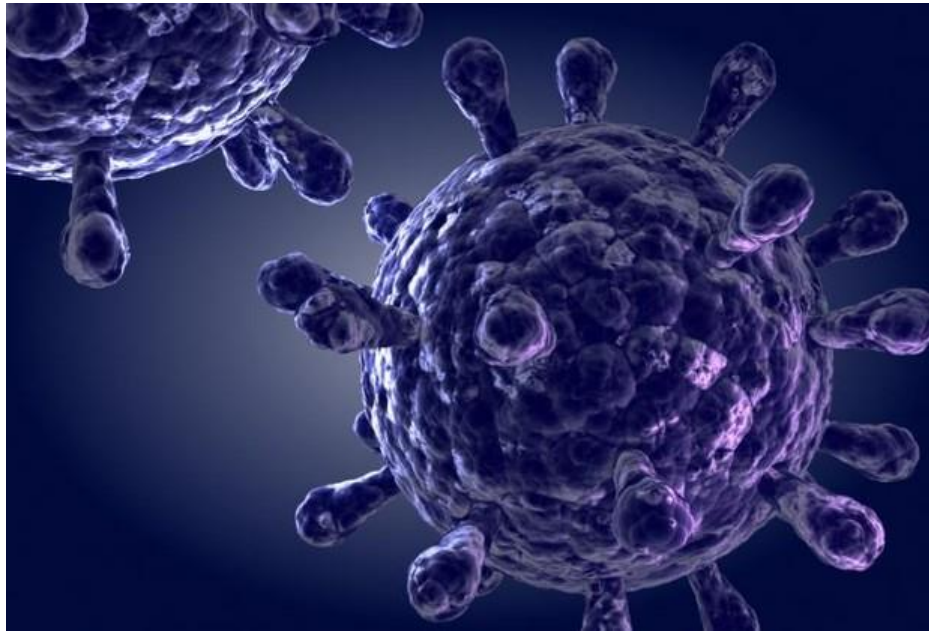
bidirectional relationship between BD and immune dysfunction. Key mechanisms include:

- cytokine-induced monoamine changes,
- increased oxidative stress,
- pathological microglial over-activation,
- hypothalamic-pituitary-adrenal (HPA) axis over-activation, alterations of the microbiome-gut-brain axis
- sleep-related immune changes



Cytokines induced sickness behavior

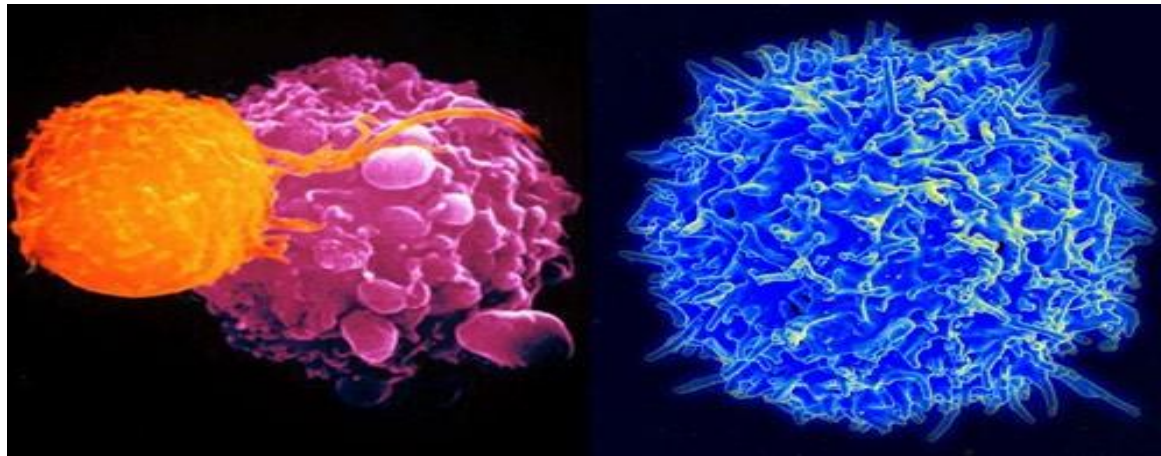
Up to 50% of patients with autoimmune diseases show an impairment of health-related quality of life and exhibit depression-like symptoms.



Cytokines induced sickness behavior

Healthy animals injected with pro-inflammatory IL-1 β and tumor necrosis factor alpha (TNF- α) cytokines demonstrate **social withdrawal** .

administration of the proinflammatory cytokine **IFN- α** is associated with **reduced levels of serotonin** in the prefrontal cortex .



Depressive Disorders and PNI

- Aspects of depression, such as anorexia and general lack of interest, resemble features of sickness behavior and again raise the possibility of at least a partial failure to terminate the **sickness response**.
- In fact, there is some evidence that after episodes of viral infection, individuals describe themselves as more depressed.
- Also consistent with this line of reasoning is that administration of cytokines (e.g., IFN- α) to humans can induce depression.

Depressive Disorders and PNI

- Moreover, depressed individuals have been found to have higher levels of acute-phase proteins, proinflammatory cytokines (e.g., IL-6), and soluble IL-2 receptor, as well as higher white blood cell counts, as is often seen in the early response to infection.
- Essentially, depression appears to be associated with **activation of some aspects of nonspecific immunity.**
- However, antidepressant treatment does not necessarily normalize cytokine profiles even when effective at ameliorating the depression.

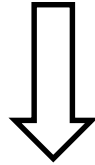
Depressive Disorders and PNI

- In addition, depressed individuals may be more heavy users of alcohol and tobacco.
- These are substances that independently have been shown to affect measures of immune function.
- Thus, until more carefully conducted studies sort-out the influence of such confounding variables, the notion that immune changes in depression resemble those evident during sickness behavior must remain tentative.

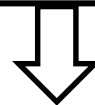
Depressive Disorders and PNI

- The situation is more complicated because there is also evidence that depressed patients are immunologically less reactive than controls.
- They have lower proliferative responses to mitogens and lower NK cell activity.
- In addition, although depressed patients have some of the features characteristic of sickness behavior including hypersomnia (e.g., in atypical depression), **most depressed patients have difficulty sleeping. Insomnia affects the immune system;** particularly, cytokine production is affected and NK cell activity is decreased as a result of sleep deprivation.

Inflammation:



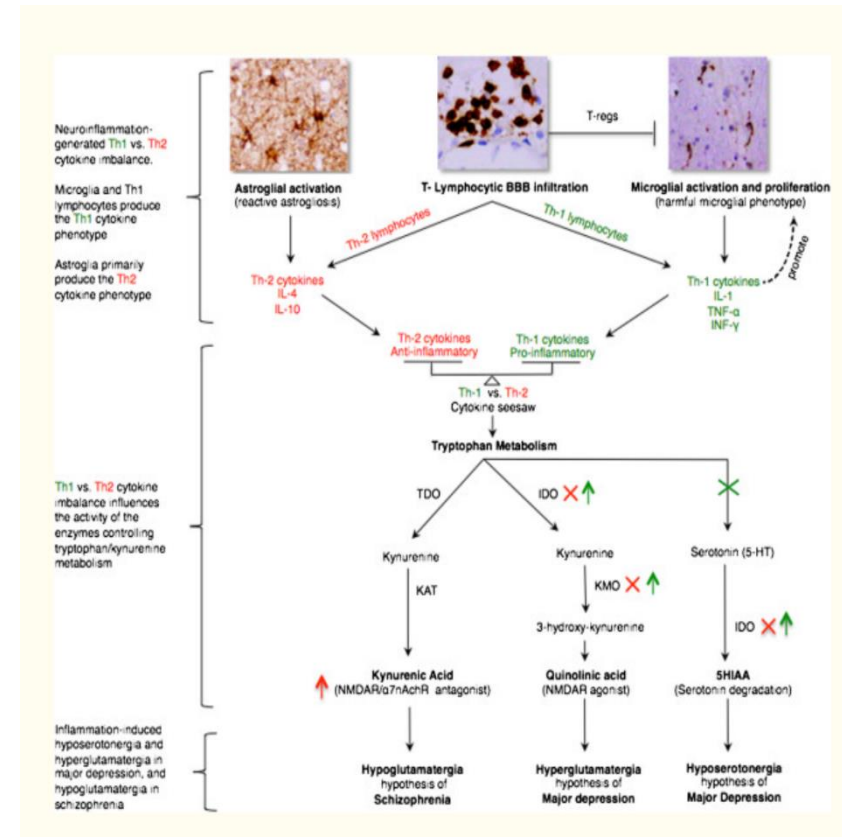
low-level neuroinflammation



**Alterations of
dopaminergic, serotonergic,
noradrenergic and
glutamatergic
neurotransmission**



Affective symptoms

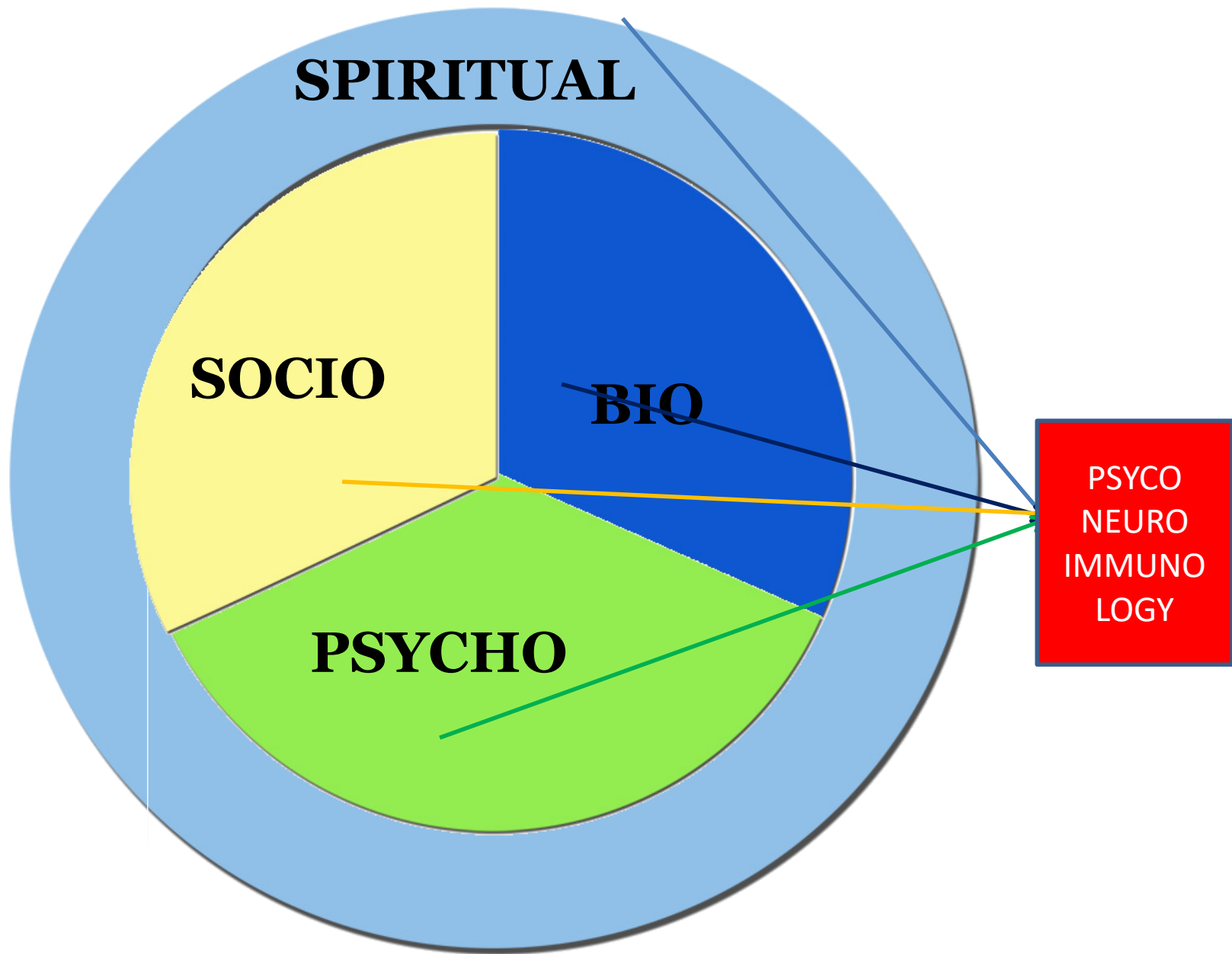


Schizophrenia and PNI

- Solomon in 1981 underscored the possibility that the brain condition known as schizophrenia may be the cause of the immune abnormalities.
- Yolken and Torrey (1995) have pointed out the complexity in this area of research. Infection may operate in **utero** or in early postnatal life and then be undetectable.
- One or several common infectious agents may need to interact with genetic vulnerability in a way that is also affected by the timing and the precise cerebral location of the infection, or the **infection may trigger an autoimmune process.**

Schizophrenia and PNI

- In conclusion, they note, “There are no studies that provide a definite link between an infectious agent and these diseases” [schizophrenia and bipolar disorder].
- In this respect, [they] are similar to Multiple sclerosis or Parkinson’s disease, both of which are suspected of having a viral etiology, but definite proof is still lacking”



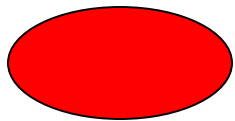
Normal Human Diagram By PNI

Psychoneuroimmunology studies in Iran

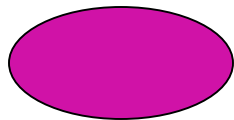
- Noorbala, A.A., Nasehi, A.A.,Vojgani M., (1999):
- “Comparison of cellular immunity in Major Depressive Disorder patients and Normal group, before and after treatment”:
- Participants: 21 MDD inpatients & 21 Normal group,
- Assessment: LTT, CD_3^+ , CD_4^+ , CD_8^+ , CD_{56}^+ & CD_4/CD_8 before and after 8 weeks treatment
- Treatment with Amitryptylin (150mg/daily)
- Conclusion: No significant finding with patients (Before, After treatment) and Normal group

Psychoneuroimmunology studies in Iran

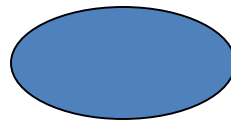
- Noorbala A.A., Alipour A., Motieian(2000), Study of Relation between Mood states and Function of Immune system,(No: 100):
- Participants: 20 Inpatients MDD, 20 Inpatients BMD, 20 Normal group (Happiness), 20 Normal group (sadness), 20 Normal group (Norm),



Mania



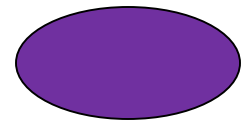
Happiness



Normal



Sadness



Depressed

- Assessment: LTT, CD_3^+ , CD_4^+ , CD_8^+ , CD_{56}^+
- Conclusion: LTT Criteria was significant between Happiness group and other group. Higher in Happiness group.

Noorbala A.A, Alipour A. Motieian(2000),
Study of Relation between Mood states and Function of Immune system:

جدول ۱-۲ آماره‌های توصیفی متغیرها

حجم نمونه	انحراف معیار	میانگین	گروه‌ها	شاخصها
۲۰	۶/۲۸	۷۱/۵	افسرده	CD3 total-T cell
۲۰	۵/۳۶	۶۶/۳۹	غمگین	
۲۰	۸/۳۴	۶۸/۳۴	کنترل	
۲۰	۵/۱۸	۶۶/۰۴	شاد	
۲۰	۶/۴۴	۶۹/۱۳	مانیا	
۱۰۰	۶/۵۵	۶۸/۱۹	مجموع	
۲۰	۷/۵۵	۴۲/۱۱	افسرده	CD4 T-cell Helper
۲۰	۵/۲۰	۳۹/۴۵	غمگین	
۲۰	۷/۱۰	۳۹/۱۰	کنترل	
۲۰	۴/۸۳	۳۸/۵۰	شاد	
۲۰	۷/۳۸	۴۱/۳۹	مانیا	
۱۰۰	۶/۵۳	۴۰/۱۱	مجموع	
۲۰	۶/۶۹	۲۶/۴۲	افسرده	CD8 T-cell-suppressor
۲۰	۴/۷۱	۲۴/۱۵	غمگین	
۲۰	۷/۶۲	۲۴/۹۳	کنترل	
۲۰	۵/۸۸	۲۴/۱۲	شاد	
۲۰	۵/۶۵	۲۳/۶۷	مانیا	
۱۰۰	۶/۱۴	۲۴/۶۶	مجموع	
۲۰	۲/۴۸	۴/۲۷	افسرده	CD56 N.K.C
۲۰	۲/۵۷	۴/۵۱	غمگین	
۲۰	۲/۰۹	۳/۷۷	کنترل	
۲۰	۵/۰۴	۶/۹۹	شاد	
۲۰	۴/۶۰	۵/۵۹	مانیا	
۱۰۰	۳/۶۸	۵/۰۲	مجموع	

جدول ۱-۲ آماره‌های توصیفی متغیرها

حجم نمونه	انحراف معیار	میانگین	گروه‌ها	شاخصها
۲۰	۰/۸۵	۱/۹۴	افسرده	LTT Lymphocyte transformation test
۲۰	۱/۱۶	۲/۶۳	غمگین	
۲۰	۱/۵۷	۲/۵۷	کنترل	
۲۰	۳/۰۳	۴/۰۷	شاد	
۲۰	۰/۹۹	۱/۸۸	مانیا	
۱۰۰	۱/۸۶	۲/۶۲	مجموع	

Psychoneuroimmunology studies in Iran

- Noorbala A.A., Hamidi Kenari.H., Vojgani M., (2001): “Comparison of cellular immunity in manic phase patients (Bipolar I) with Normal subject.”
- Participants: 24 MDD inpatients & 26 Normal group,
- Assessment: LTT, CD_3^+ , CD_4^+ , CD_8^+ , CD_{56}^+ & CD_4/CD_8 before and after 8 weeks treatment
- Conclusion:
- LTT criteria before and after treatment(8weeks) by lithium drug was significant. Lower in patients

Psychoneuroimmunology studies in Iran

- **Vojgani M. , Nasehi A.A, Matloobi H, (2005):**
- **“Comparison of cell mediated immunity in Schizophrenic patients and Normal people” :**
- **Participants: 30 Schizo inpatients & 42 Normal group,**
- **Assessment: LTT, NK, ANA(Antinuclear Antibody), ACA(Anticytoplasmic Antibody), CIC(Circulatory Immune Complex)**
- **Conclusion: Decreased of LTT Schizophrenic patients in comparison with Normal people was significant, Increased NK in Schizo, No significant ANA & CIC and ACA was seen in only schizo**

Psychoneuroimmunology studies in Iran

- Noorbala A.A., Ghanei M, Arefnasab Z., (2013): Effectiveness of stress management techniques on psychoimmunological and respiratory factors in chemically injured veterans “
- Participants: 42 chemically injured veterans,(1-Mindfulness- Based Stress Reduction 2- Emotional Freedom Technique 3- Control)
- Assessment: GHQ-28,SF36,Spirometry test, Immunity tests
- before and after 8 weeks treatment
- Conclusion:
- MBSR & EFT improved Mental Health, Quality of life, Health-related quality of life and immunity variables (Increased Lymphocyte proliferation, prevent excessive increase of IL-17, No changes in CD4, CD8, and increased NK-cell in control group)

Evaluation of Inflammatory Markers in Patients With Depressed episode in Major Depressive Disorder and Bipolar Disorder Before and After Treatment

Laya Kafami¹, Sara Assadiasl², Sara Hashempour^{1,3}, Mohammad Hossein Niknam², Nami Mohammadian Khanssari⁴, Bahareh Mohebbi², Amin Hashemnezhad⁴, Bita Ansaripour⁵, Arash Mirabzadeh^{6, 7}, Banafsheh Mosharmovahed⁸, Fatemeh Fazeli², Mahshid Saleh⁹,
Ahmad Ali Noorbala^{1,3}

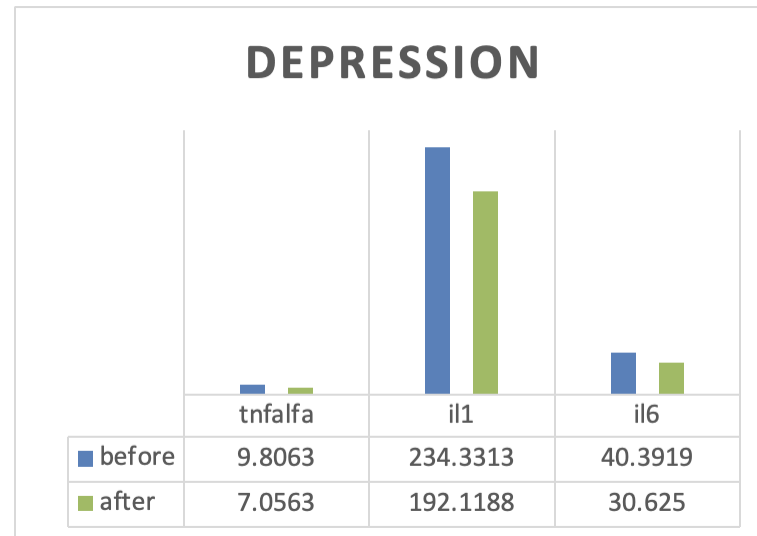
- 24 subjects (eight with bipolar disorder in the depressive phase and 16 with major depression) completed the six-month intervention period
- **Hamilton depression rating scale** was completed for each patient to assess the severity of depression before the intervention, two- and six-month follow-ups
- level of proinflammatory cytokines (**TNF- α , IL-1, IL-6**) was also measured in the same time points
- Participants with major depressive disorder was on **Fluoxetine** with different dosage according to their symptoms, and patients with depression episode of bipolar disorder were on **lithium** in therapeutic dosage.
- The main limitation of the study was the small sample size imposed by the COVID-19 pandemic restrictions and the loss of patients to follow-up

Evaluation of Inflammatory Markers in Patients With Depressed episode in Major Depressive Disorder and Bipolar Disorder Before and After Treatment

Major depressive disorder	6 month later
Hamilton depressive scale	P = 0.04
TNF- α	Decreased
IL-1	Decreased(P = 0.04)
IL-6	Decreased

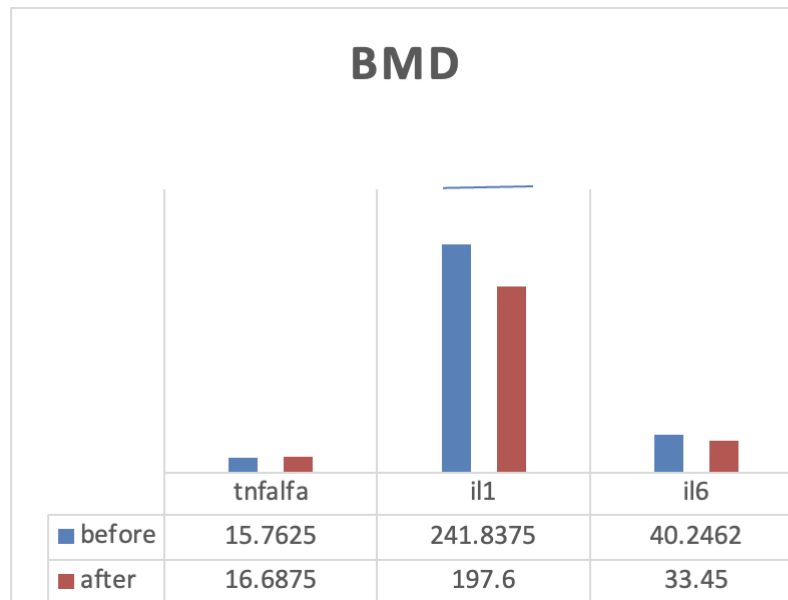
Bipolar disorder	6 month later
Hamilton depressive scale	P = 0.04
TNF- α	Inceased
IL-1	Decreased (P = 0.04)
IL-6	Decreased

Evaluation of Inflammatory Markers in Patients With Depressed episode in Major Depressive Disorder and Bipolar Disorder Before and After Treatment



Mean distribution of proinflammatory cytokines, IL-1, IL-6, and TNF- α , in patients with major depression before and after the intervention. The difference in the serum level of these cytokines before and after the intervention was insignificant.

Evaluation of Inflammatory Markers in Patients With Depressed episode in Major Depressive Disorder and Bipolar Disorder Before and After Treatment

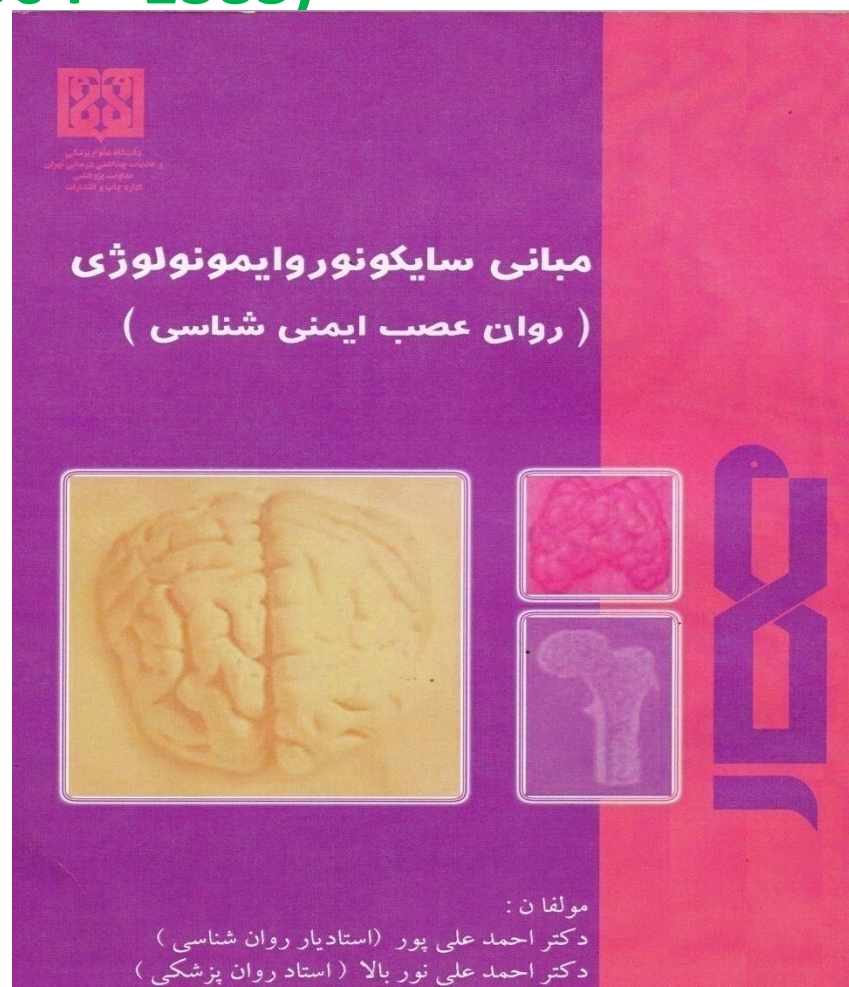
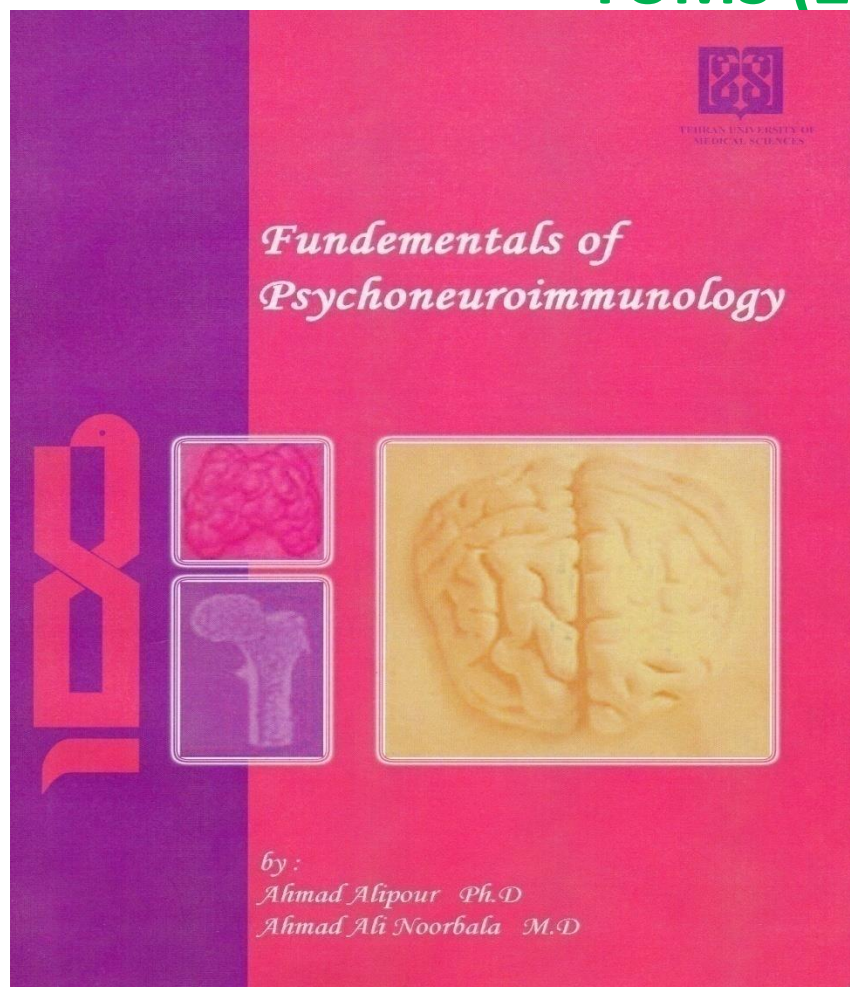


Mean distribution of proinflammatory cytokines, IL-1, IL-6, and TNF- α , in patients with bipolar disorder in depressed the depression episode before and after the intervention. The IL-1 serum level decreased significantly after the intervention (*). However, other changes (a decrease in IL-6 and an increase in TNF- α) were insignificant.

The first published book in the field of PNI in Iran

Fundamentals of Psychoneuroimmunology

TUMS (2004 =1383)



Fundamentals of Psychoneuroimmunology

Second Edition, 2020=1399

مبانی سایکونوروایمونولوژی

ویراست دوم

Fundamentals of Psychoneuroimmunology

Second Edition



مبانی
سایکونوروایمونولوژی

دانش سایکونوروایمونولوژی (Psychoneuroimmunology=PNI)، به شکلی نسبتاً جامع در نیمه دوم سال ۱۹۹۰ میلادی، توسط "آدر" و همکارانش به جامعه علمی معرفی و ترویج شد تا نگرش جدید شناختی نسبت به ابعاد آنمی و نیز تاثیر و تبادل متقابل این ابعاد بر یکدیگر و البته نگرش کامل تری در مورد سلامت و بیماری را به وجود آورد.

سایکونوروایمونولوژی، با بهره گیری پیوستاری از علوم پایه، علوم بالینی، شرایط محیطی و اجتماعی و نیز حالات معنوی، برای شناخت بیشتر از تغییرات سلامت و بیماری و بالین، تشخیص و درمان بیماری ها، تلاش می کند. سیستم ایمنی بدن در حکم نظام دفاعی انسان است که نه تنها، در برابر باکتری، ویروس، اجسام خارجی و بیگانه، واکنش نشان می دهد، بلکه در برابر حوادث ناخوشایند درونی و بیرونی و نیز تنش های آگاهانه و ناآگاهانه، هم پاسخی در خور تأمل در عضو آسیب پذیر به منصف ظهور می رساند. با بهره گیری از دانش روان، عصب، ایمنی شناسی (سایکونوروایمونولوژی)، پاسخ تغییرات بیولوژیک ناشی از تأثیرات عوامل روانی، اجتماعی و معنوی را می توان نشان داد.

By:

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توپیستدگان:

- دکتر احمد علی نوربالا (استاد روان پزشکی دانشگاه علوم پزشکی تهران)
- دکتر احمد علی پور (استاد روان شناسی سلامت دانشگاه پیام نور)
- دکتر لایا کفعمی (پسادکترای سایکونوروایمونولوژی)
- دکتر مرضیه حاجی یابایی (دکترای روان شناسی)
- دکتر سارا هاشم پور (متخصص روان پزشکی، فلوشیپ سایکوسوماتیک)

دکتر احمد علی نوربالا



Vision of Psychoneuroimmunology

Schleifer, S. J.(1999):

**Psychoneuroimmunology
is the connection ring
between **Physic** and
Metaphysic**

Conclusion

Psychoneuroimmunology is the connection ring between Basic Medical Sciences , Clinical Medical Sciences , Social Determinants of Health and Spiritual items through the Psychosomatic and Neuropsychiatry fields.

Conclusion

- **Psychoneuroimmunology** and research about it, is in the **early stages** in Iran like other regions of world.
- Findings of these researches are **controversial** like other regions.
- It needs **close cooperation** between Iranian Immunologists, Endocrinologists, and **Psychiatrists** to achieve advanced findings in **PNI field**.

THANK YOU

FOR YOUR ATTENTION



A GIFT FOR

ALL OF YOU