Autoimmunity and Psychiatry

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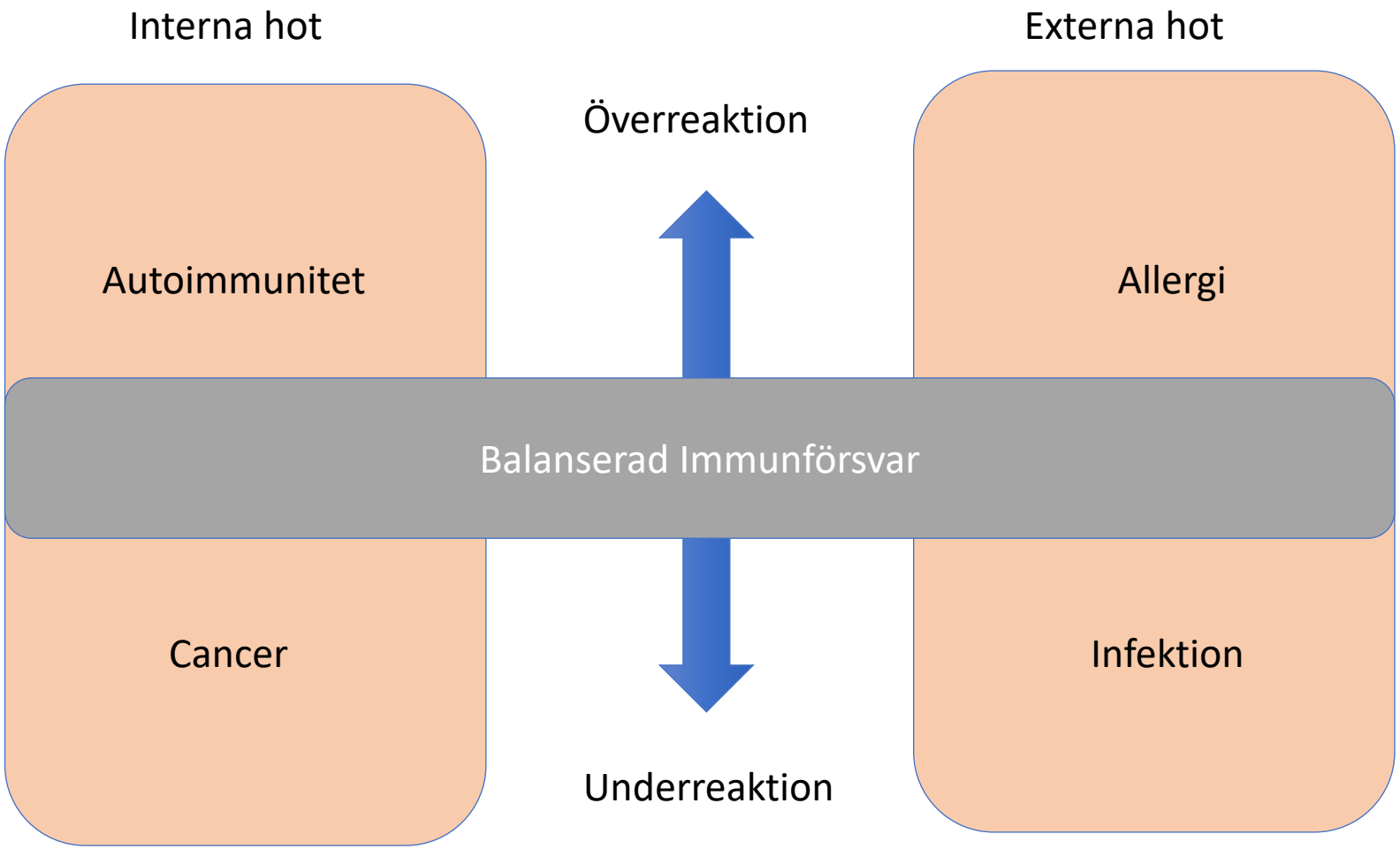
Layout

- Basic concepts of the immune system
- It is all connected
- The cutting edge
- What can be done today in the clinic

Balanserad immunförsvar



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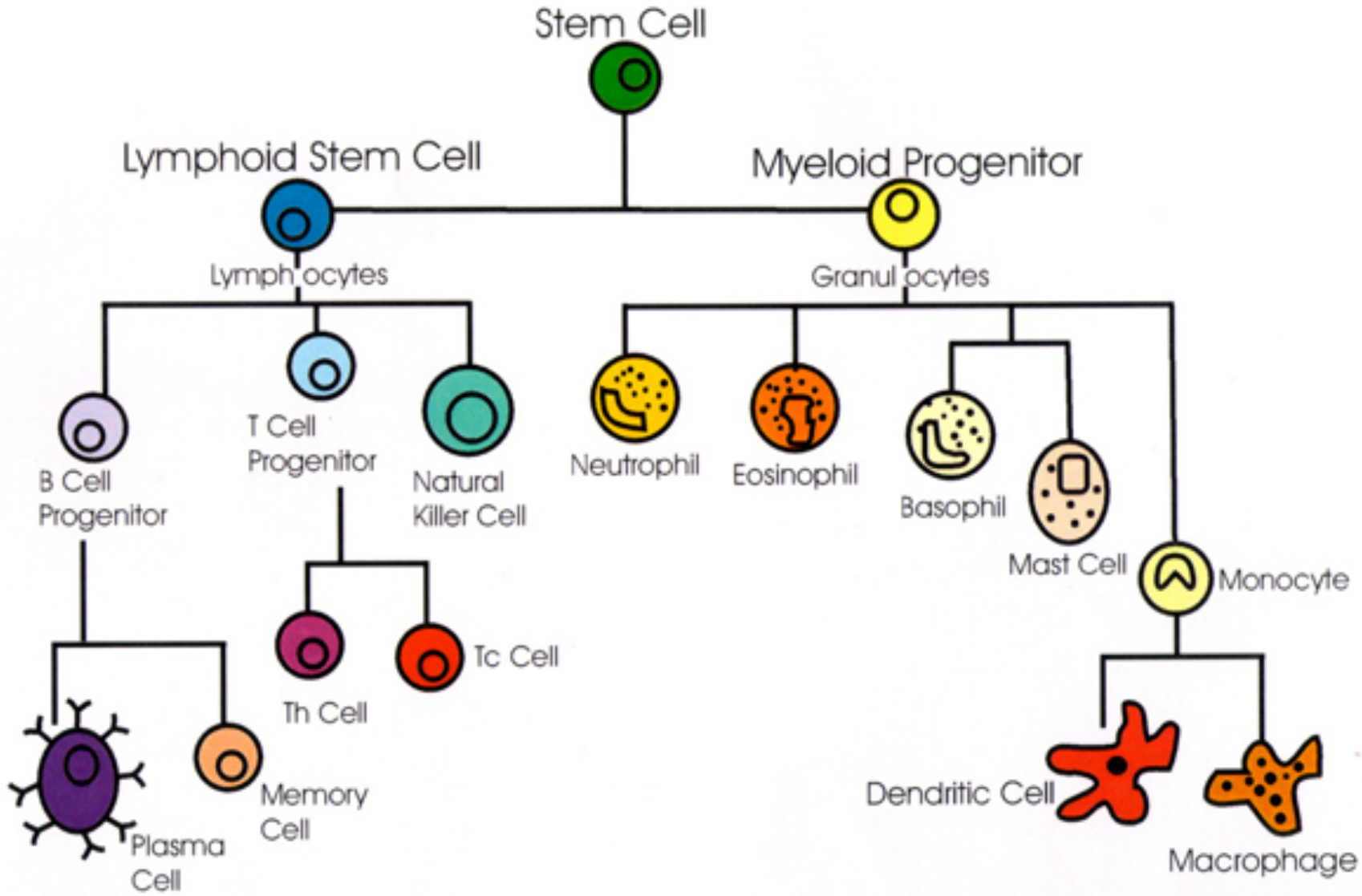
Cells of the Immune System



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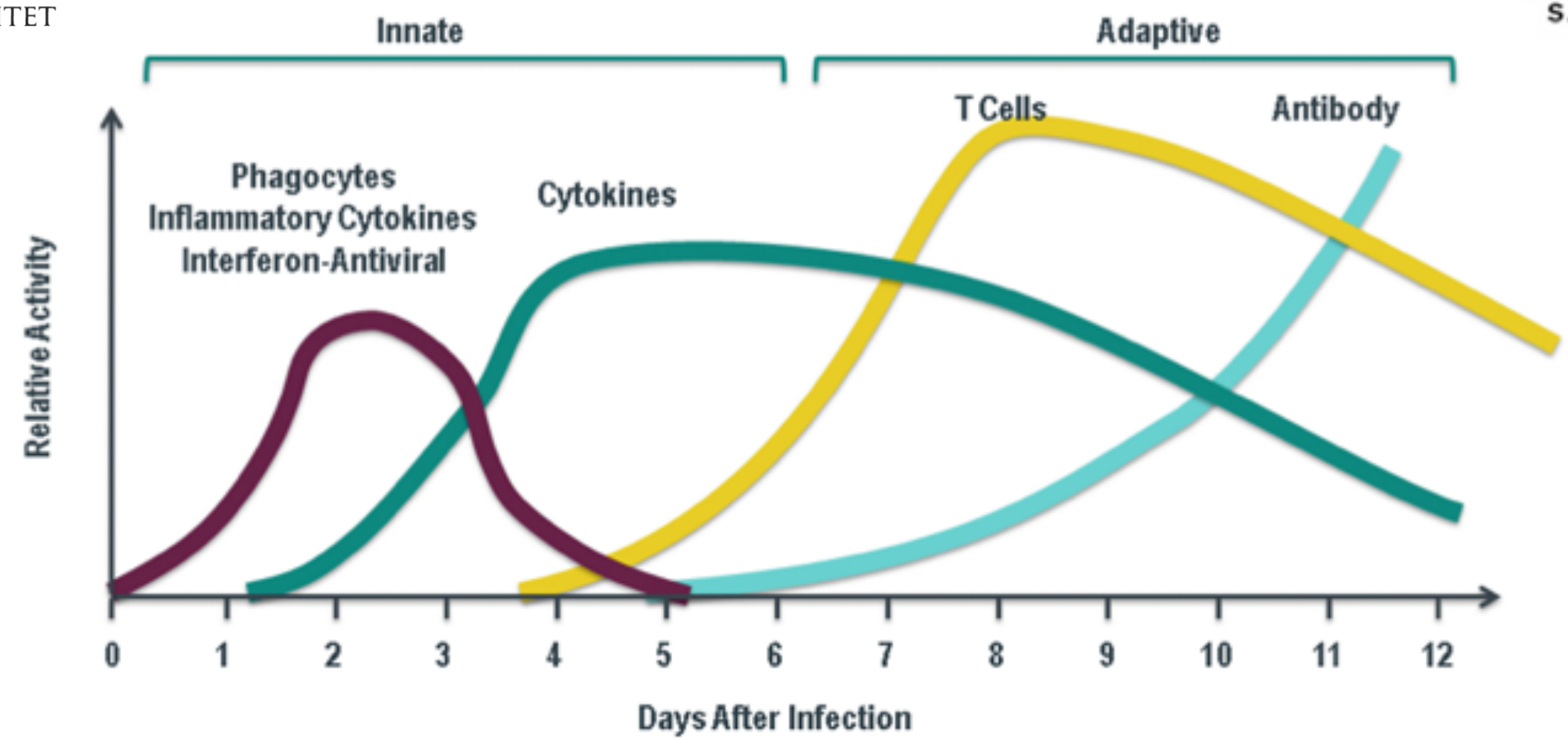
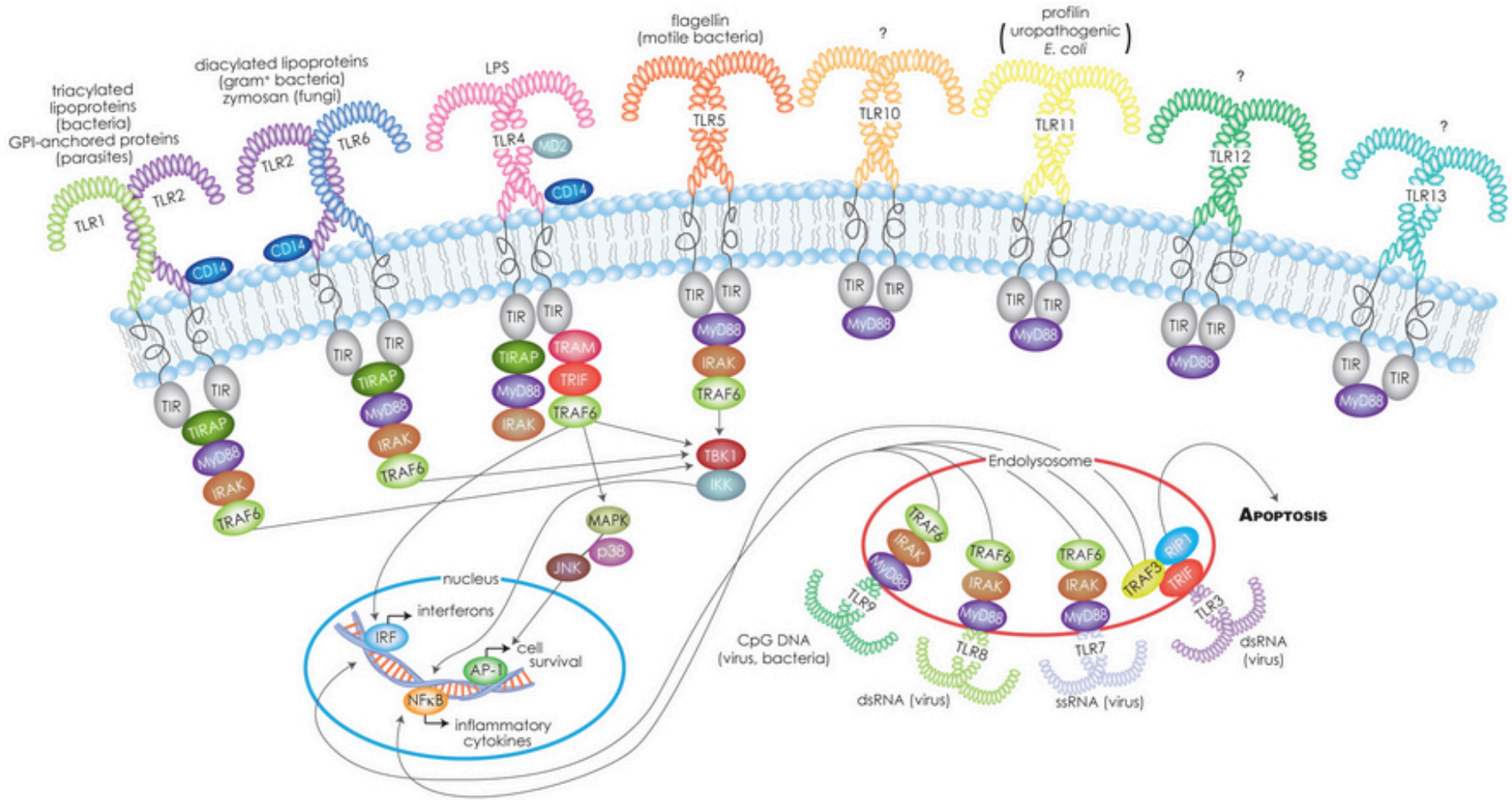


Innate versus Adaptive immunity

	Innate	Adaptive
Receptors	Primitive and broad	Highly specific (T and B cell receptors)
Kinetics	Fast (hours-days)	Slow (days-wks)
Regulation	+/-	++++
Amplification	No (insignificant)	Yes
Self discrimination	-	++++
Duration	Short (days)	Long (months/yrs)
Memory	-	++++

Toll-Like Receptors

DAMPs= Damage associated Molecular paterens
PAMPs = Pathogen associated Molecular paterens
XAMPs =



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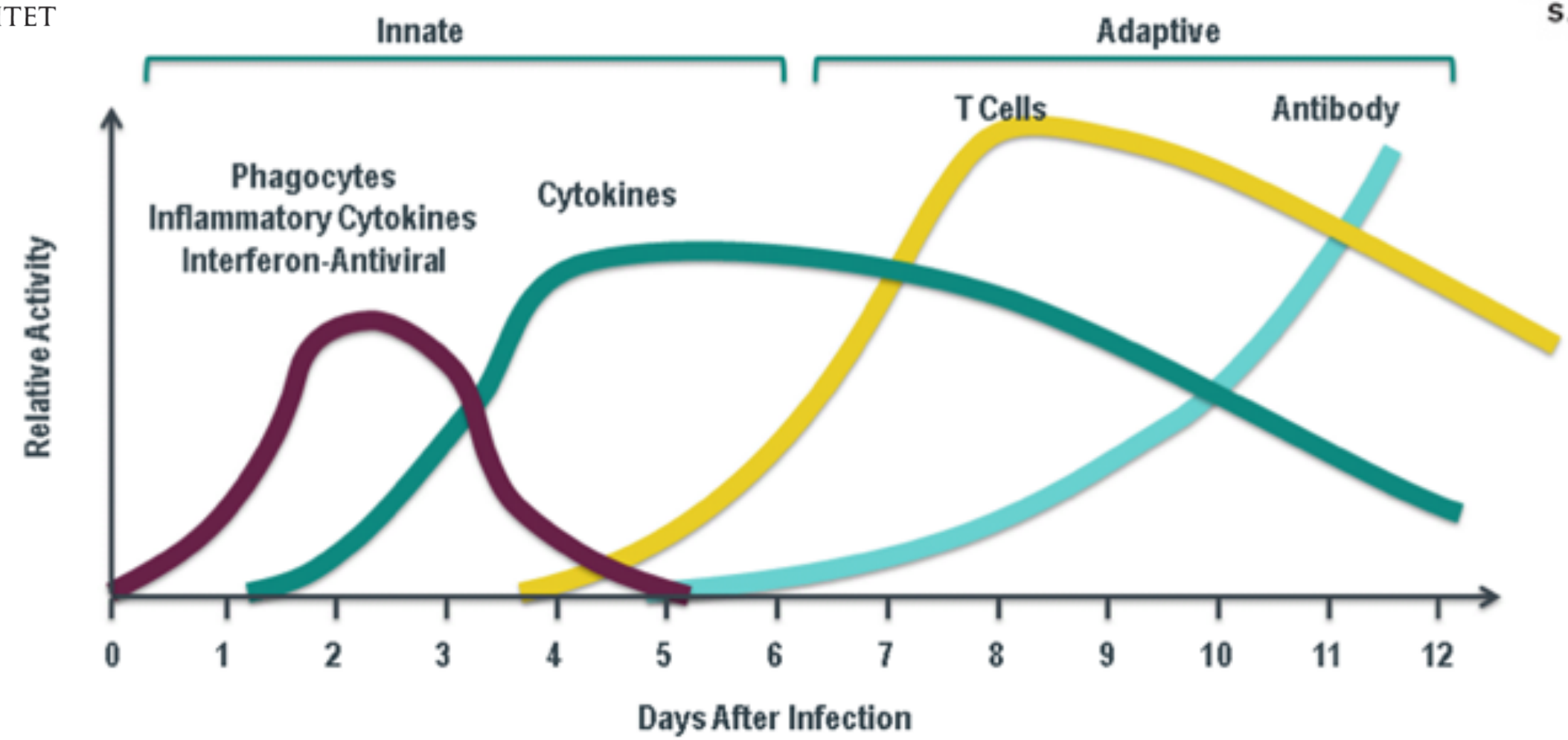


Gravida kvinnor med depression har svårt att aktivera anti-inflammatoriska processer

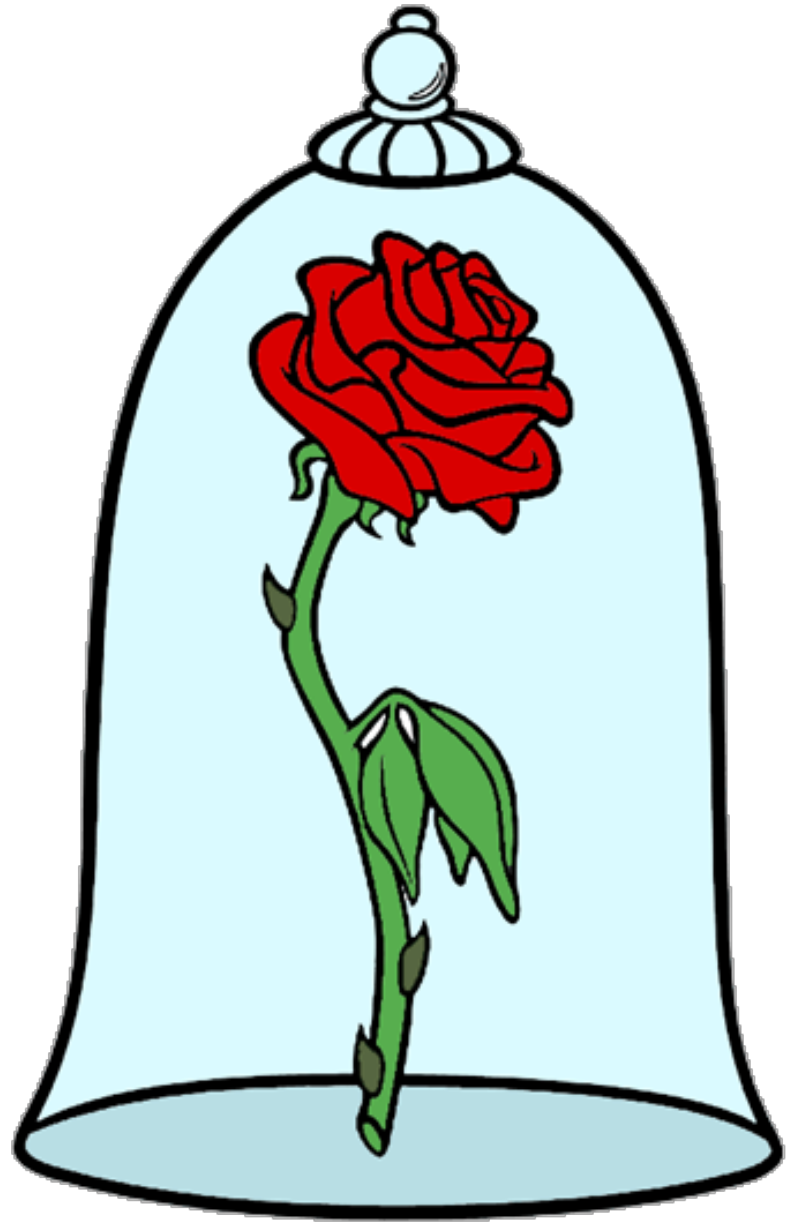
TRAIL (M2 makrofager)

CSF-1 (M-CSF) → M2 makrofager

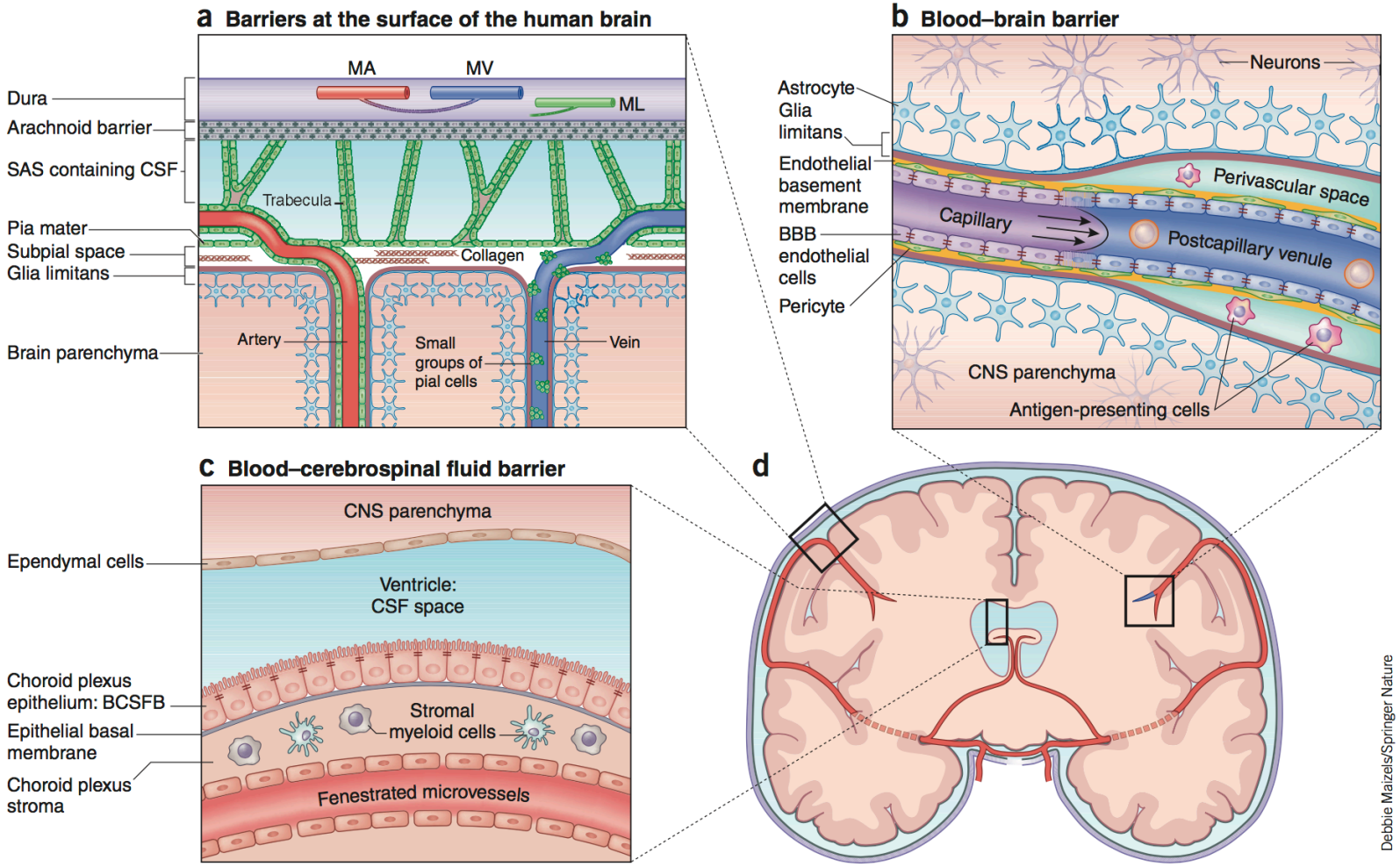
CX3CL1 (Fraktaline) inducerar M2 polarizering

VEGF-A associerad till TGF beta och M2 makrofager

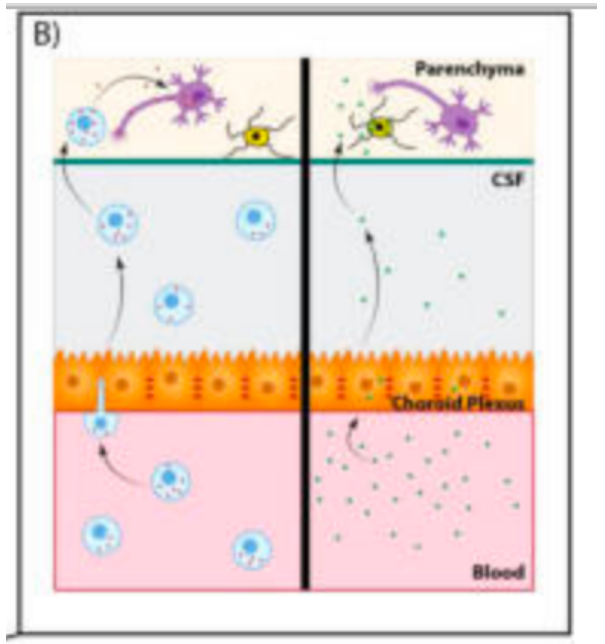
Edvinsson et al, Psychoneunoendocrinology 2017



The choroid plexus is the weak link in the BBB

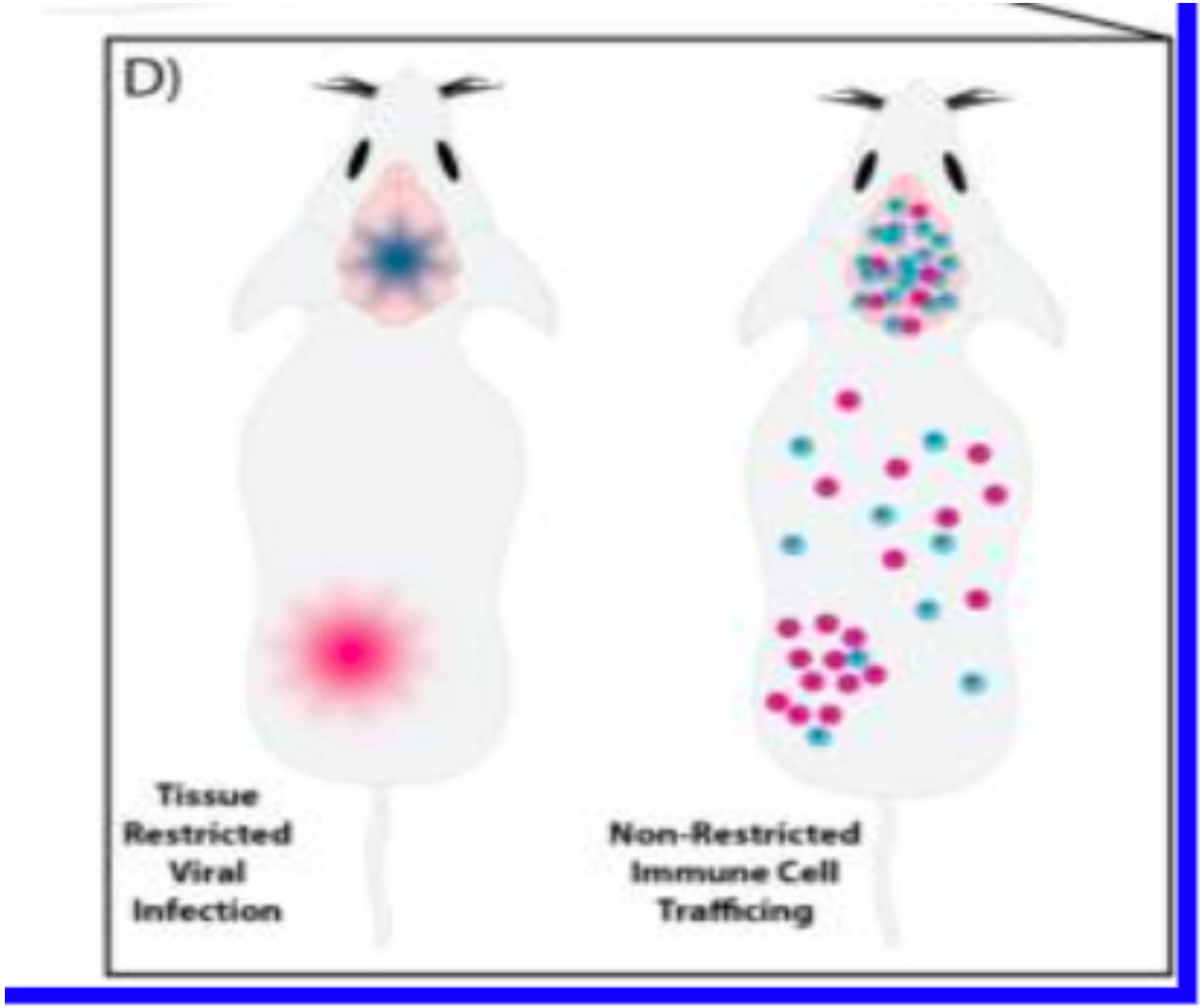


Neurotropic viruses include:
Rabies
Polio
Herpesviruses
Influenza
West Nile virus,
Measles virus
SARS-COV2

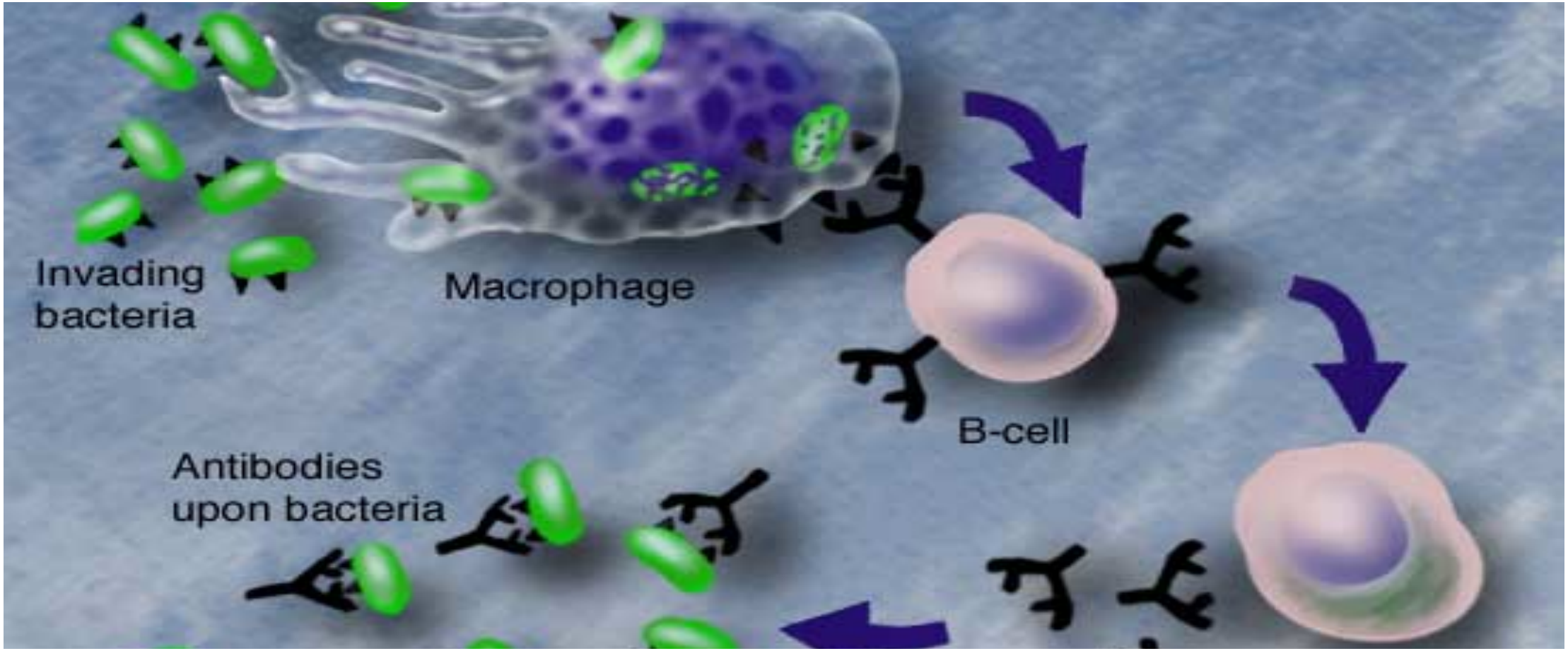


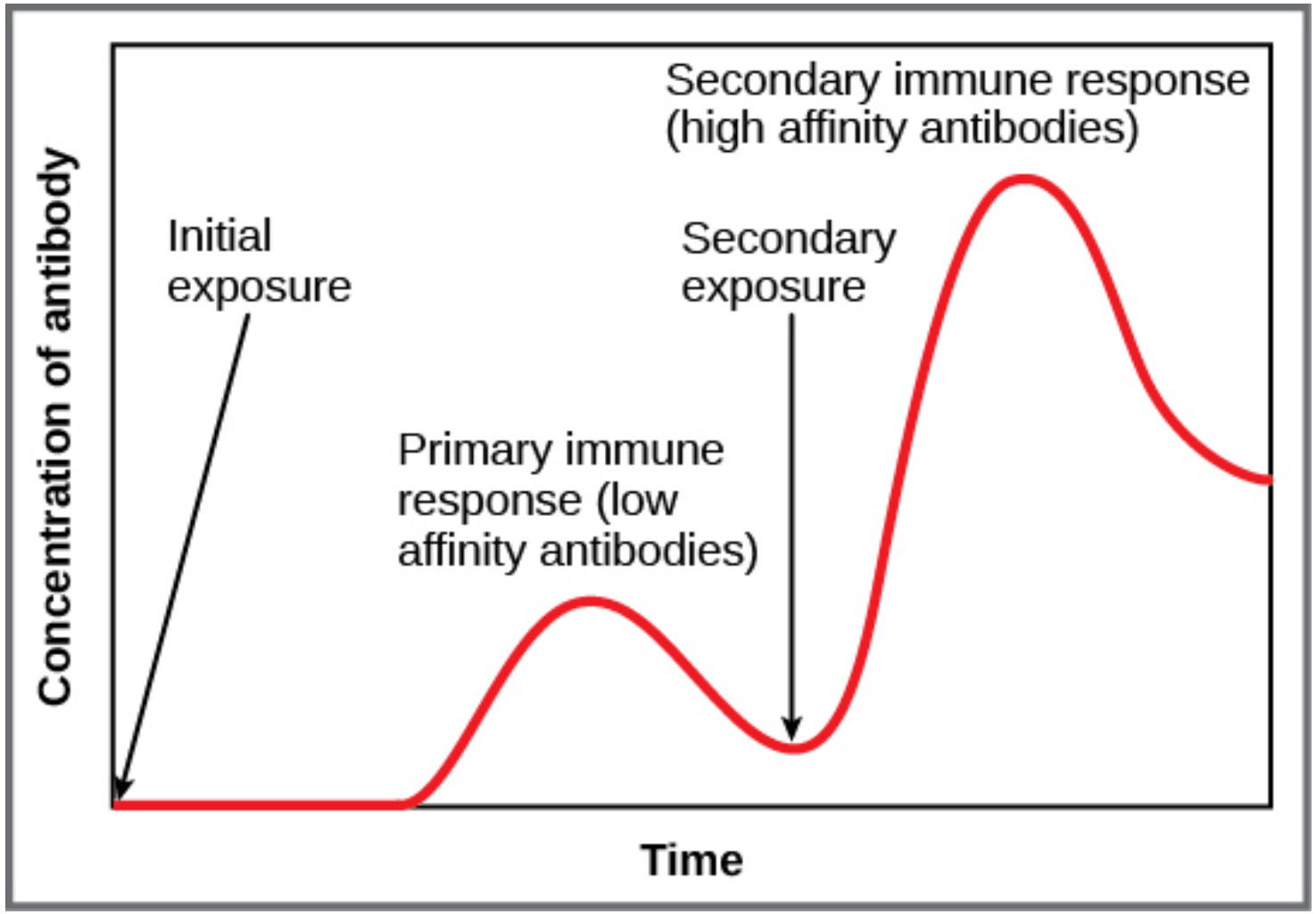
The choroid plexus stroma harbors dendritic cells and macrophages but no blood brain barrier; instead the epithelial cells of the choroid plexus are connected by unique parallel running tight junctions and express efflux pumps.

Measles plus enterococci = Encephalitis



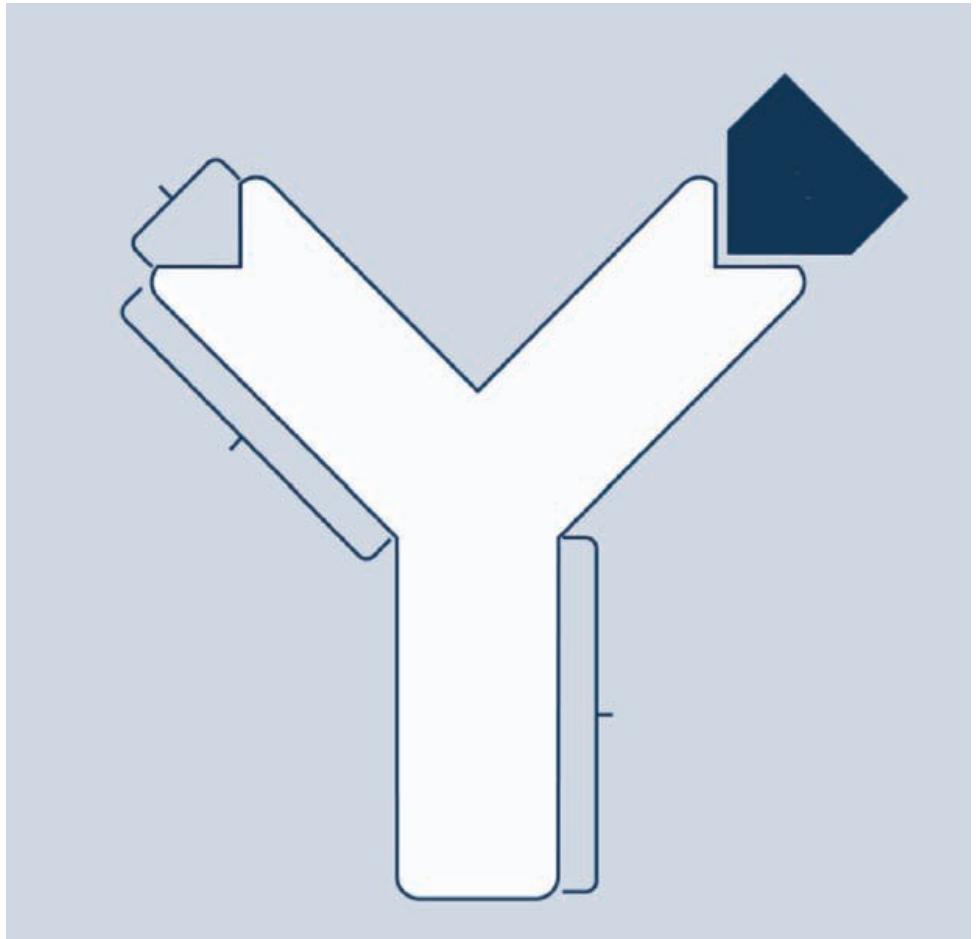
B-cells


Invading
bacteria
Macrophage
B-cell
Antibodies
upon bacteria

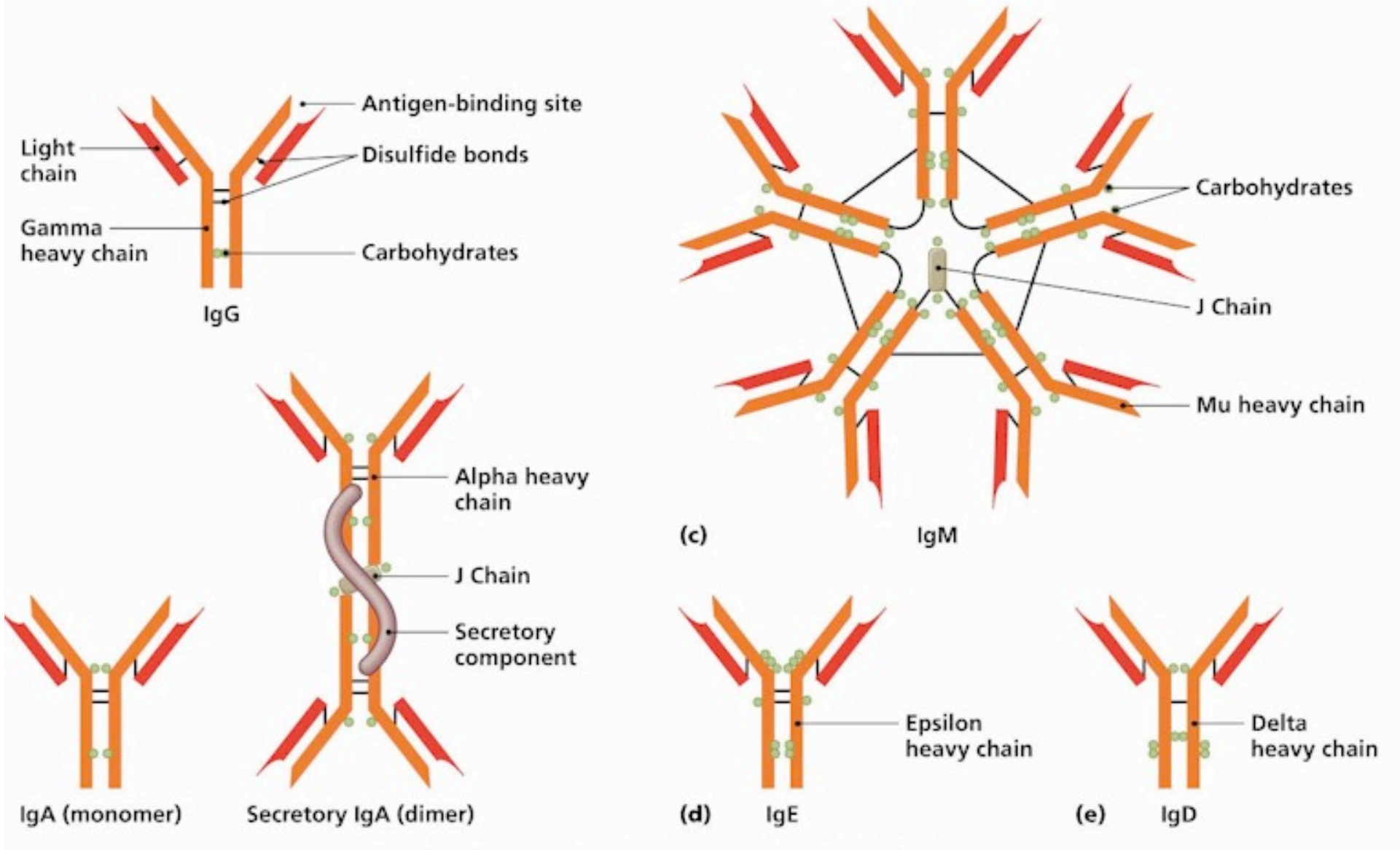

Secondary immune response
(high affinity antibodies)
Initial
exposure
Secondary
exposure
Primary immune
response (low
affinity antibodies)
Concentration of antibody
Time

Antibodies

In any individual, 10^6 to 10^7 different antibody molecules



IGG vs IGM and IGA



Types of autoimmune responses

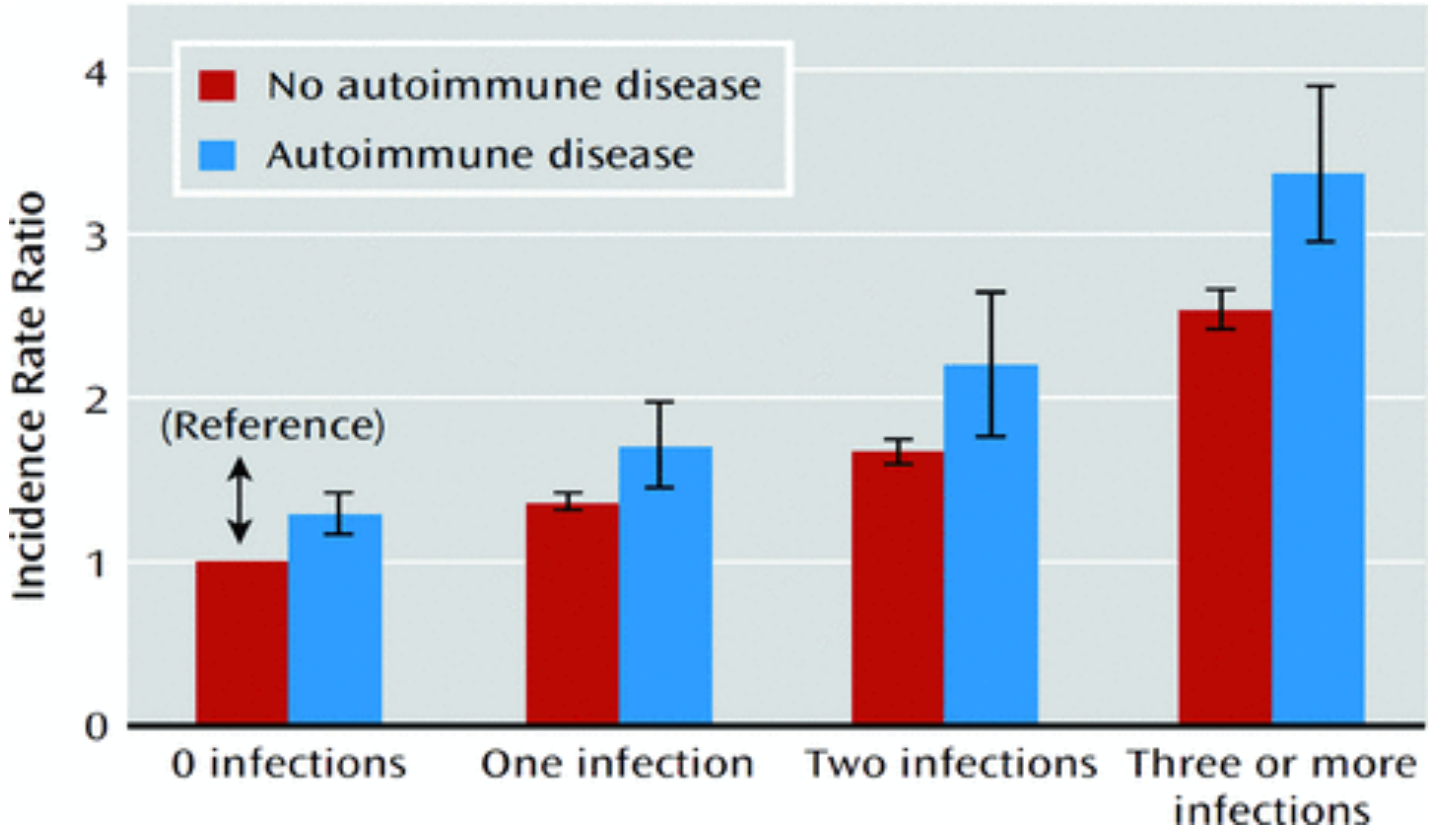
- **Destructive:**
  - a)cytotoxic T-cell mediated (ie diabetes type 1)
  - b) antibody-mediated tissue damage via compliment activation (ie heamolytic anemia, Goodpastures)
- **Autoreactive:**
  - Autoantibodies that modulate biological functions (ie Graves, myestinia gravis)
- **Complex:**
  - multiple autoantibodies and organ targets, immunecomplex damage, large clinical variation (SLE)

Autoimmune diseases with higher prevalence rates among patients with schizophrenia and their relatives

- Thyrotoxicosis
- Celiac disease
- Acquired hemolytic anemia
- Interstitial cystitis
- Sjögren’s syndrome
- Psoriasis
- Autoimmune hepatitis
- Type 1 diabetes
- Multiple Sclerosis

Eaton 2006 and 2010

Autoimmune diseases and infections as risk factors for schizophrenia



Benros 2012

Immune system aberrations in ASD

- Elevated risk for autoimmune disorders (OR 1.33)
- A common genetic variant related to autoimmunity was found in both patients with RA and ASD (HLA − DR B1*04 alleles)
- Decreased immunoglobulin levels, particularly IgG (recently IgD levels were shown to be 58% lower in ASD serum)
- Elevated risk for circulating autoantibodies: anti-brain antibodies, anti-endothelial cell antibodies, anti-nuclear antibodies, and anti-folate receptor antibodies
- Altered cellular immunity -> Abnormalities in T cell responses
- Biomarker studies identified significant dysregulation on immune function and inflammation

Family history of Autoimmunity is a risk for AST

- A Danish registry found that mothers with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and type 1 diabetes were more likely to bear children with ASD (about 30% increased risk)
- association between family history of autoimmune disease including hypothyroidism, type 1 diabetes, rheumatoid arthritis, as well as psoriasis and a higher risk of ASD

Autoimmunity and cerebral folate deficiency in AST

- Cerebral folate deficiency in over 20% of AST
- Antibodies against glutathione and folate receptor-α autoantibody (FRAA) elevated in AST (>40%)
- High dose folate (50mg) improves symptoms is AST with FRAA
- Mothers with FRAA have higher risk for children with FRAA

ADHD and autoimmunity

- Although the comorbidity of autoimmune diseases with ADHD was low, ADHD patients had a significantly greater prevalence of **ankylosing spondylitis** (OR = 2.78), **ulcerative colitis** (OR = 2.31), and **autoimmune thyroid disease** (OR = 2.53) than the controls. In females with psoriasis and with Chrons Disease.
- Children whose mothers had any autoimmune disease, type 1 diabetes, hyperthyroidism, rheumatic fever or rheumatic carditis, or psoriasis were significantly more likely to be diagnosed with ADHD.

GAS infections and neuopsychiatric symptoms

- Large cohort studies, (Taiwan and Denmark) -> higher odds ratio of developing OCD, tics, and ‘mental disorders’ following streptococcal pharyngitis or other respiratory tract infections.
- Higher ADHD symptoms in children with chronic tic disorders (90% Tourette’s syndrome) (neurology 2021)
- Fluctuations in serum cytokines during exacerbations in children with Tourette’s syndrome/tics were present in one study (15)
- Patients with ADHD might be more prone to infections during childhood and subclinical streptococcal infections during adulthood. Moreover, they seem to have an increased risk for basal ganglia autoimmunity in adulthood

Limbic encephalitis

”Tänk dig att du på kort tid blir totalt personlighetsförändrad, får en rad skrämmande psykiska och fysiska symtom och blir allt sämre – och att ingen förstår varför. […] Läkarna trodde att Susannah Cahalan hade drabbats av schizofreni eller bipolär sjukdom. Men hon hade fått en ovanlig autoimmun reaktion som angrep hjärnan.” DN 2013

Autoimmun limbisk encefalit

- antikroppar mot *neuronala ytantigen* (ofta synaptiska)
- många av dessa patienter utan bakomliggande malignitet
- **I**bland EEG och/eller MRI-avvikelser i temporallober
- liquor visar **inbland** lätt pleiocytos
- **ibland** polyklonala band, förhöjd proteinmängd och förhöjt IgG-index
- normalt glukos

Autoimmunitet mot följande strukturer i hjärnan är associerade med psykotiska symptom

Antigen	Kön	Symptom	Associerade tillstånd
NMDAR	80% kvinnor	Personlighetsförändringar, psykos, katatoni, epileptiska anfall, dyskinesi, mutism	Teratom, mykoplasma pneumoniae, Guillam-Barré
LGl1	65% män	Amnesi, epileptiska anfall, psykos, hyponatremi	Neuroektodermala tumör, tymom
Caspr2	85% män	Morvan's syndrom*, neuromyotoni,	Tymom
AMPAR	90% kvinnor	Ataxi, nystagmus, amnesi, epileptiska anfall, personlighetsförändringar, psykos	SCLC, tymom, bröstcancer
$GABA_BR$	50% kvinnor	Epileptiska anfall, konfusion, psykos, insomni, agitation	SCLC
DPPX	50% män	Agitation, myokloni, tremor, epileptiska anfall, diarré	
D2R, D1R	55% män	Dystoni, korea, motoriska tics, agitation, depression, psykos, tvång, ångest	Post streptokock infektion, Sydenhams korea, Tourettes
lyso-GM1			
Gangliosid		Migrän, epileptiska anfall, depression, psykos, stroke	SLE
Rib-P		Psykos, depression	SLE

AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; D1R och D2R, Dopamin receptor 1 och 2; GABAbR, γ-aminobutyric acid B receptor; LGI1, leucine-rich gliomainactivated 1; lyso-GM1, lyso-ganglioside GM1; NMDAR, N-methyl-D-aspartate receptor; Rib-P, *ribosomal* P protein; SCLC, small cell lung carcinom; SLE, Systemisk lupus erythematosus; *Myokloni, insomni, hallucinatoriskt beteende ** Minnesförlust, depression och hallucinatoriskt beteende

Några viktiga skillnader

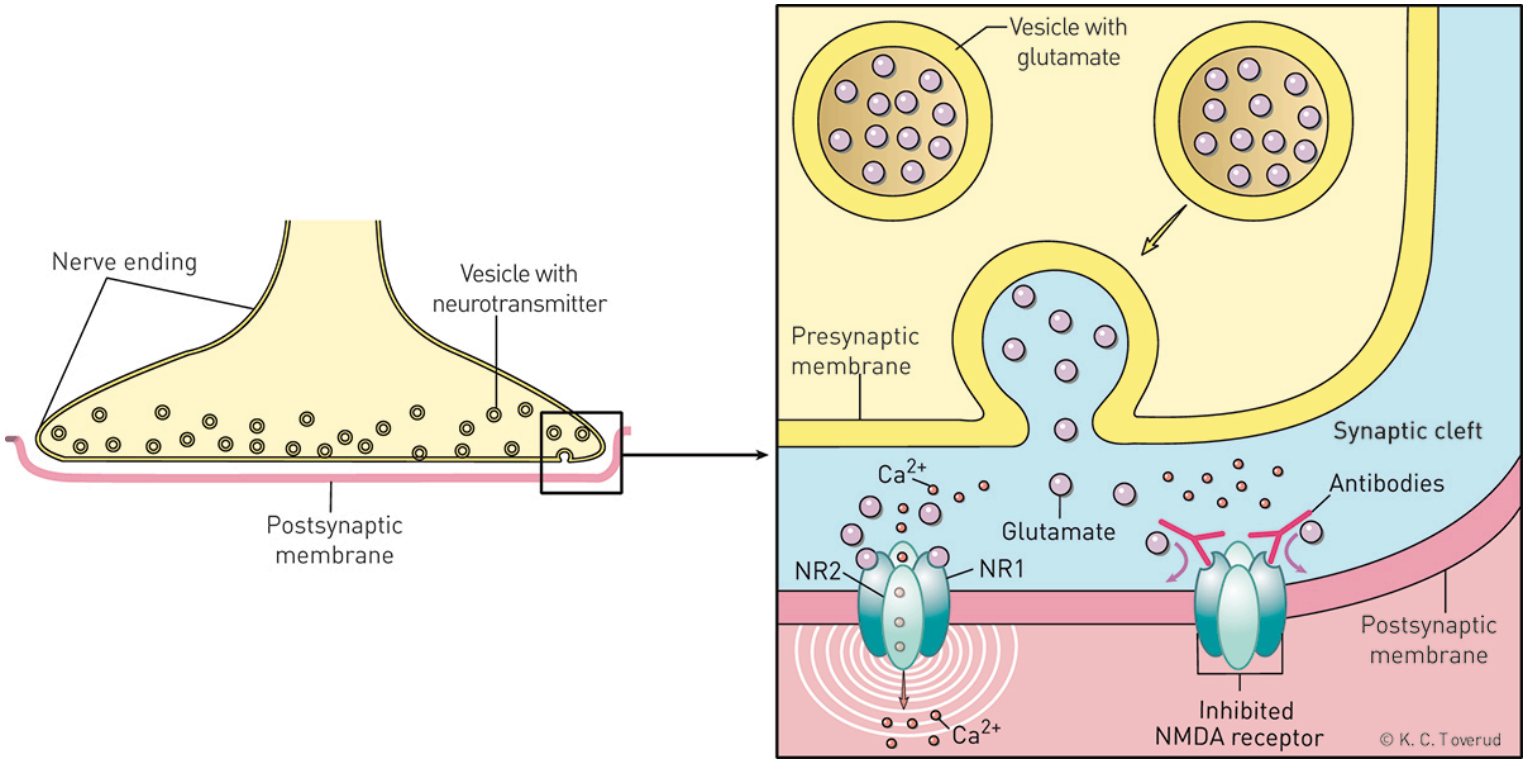
Intracellulära antigen

- stark association till cancer
- antikropparna är inte direkt patogena
- sannolikt en T-cellsmedierad sjukdom
- dålig prognos

Membranbundna antigen

- i varierande grad associerad till cancer (t ex NMDAR-encefalit 38 %)
- vanligare hos barn
- antikropparna är i regel patogena
- förhållandevis god prognos

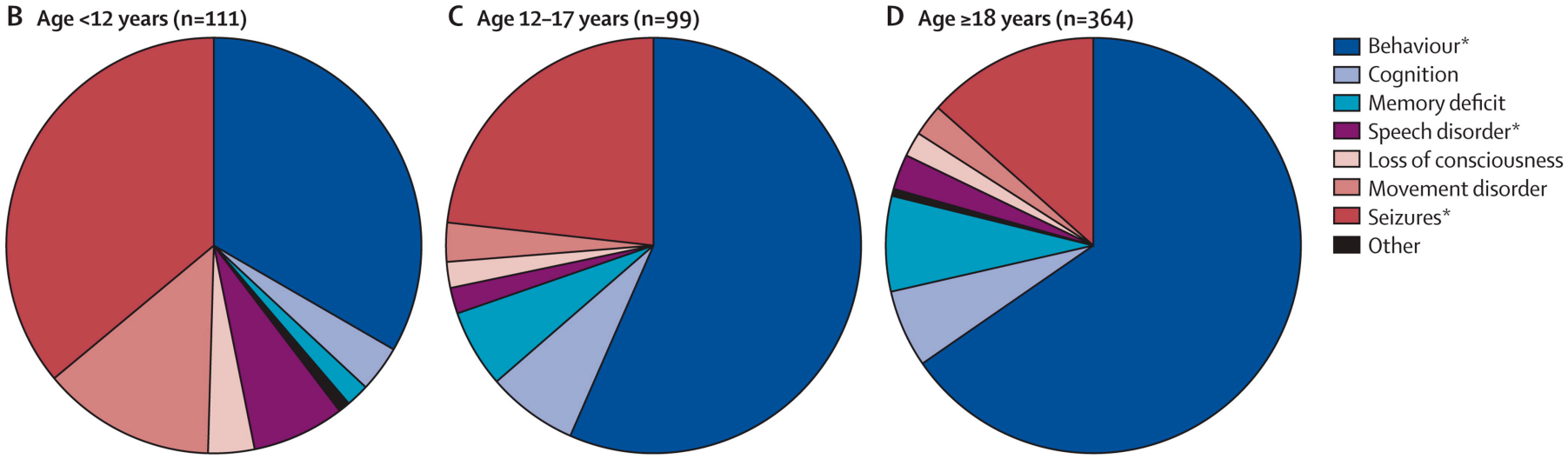
Mechanism?


Nerve ending
Vesicle with neurotransmitter
Postsynaptic membrane
Vesicle with glutamate
Presynaptic membrane
Synaptic cleft
Ca2+
Glutamate
Antibodies
NR2
NR1
Postsynaptic membrane
Ca2+
Inhibited NMDA receptor
© K. C. Toverud

Initial signs and symptoms	All patients (100)	NMDAR (53)	Non-NMDAR (24)	Intracellular antigens (23)
Psychiatric				
Acute behavioral changes	56 (56%)	46 (87%)	7 (29%)	3 (13%)
Hallucinations (visual, auditory)	25 (25%)	23 (43%)	1 (4%)	
Memory deficits (retro- and anterograde amnesia)	22 (22%)	11 (21%)	8 (33%)	4 (17%)
Confusion/aggression	18 (18%)	11 (21%)	6 (25%)	1 (4%)
Paranoid delusions	17 (17%)	13 (26%)	2 (8%)	1 (4%)
Depressed mood	13 (13%)	10 (19%)	4 (16%)	1 (4%)
Catatonia	10 (10%)	10 (19%)		
Mutism	8 (8%)	8 (15%)		
Anorexia	1 (1%)	1 (2%)		
Any of the above symptoms	65 (65%)	53 (100%)	14 (58%)	7 (30%)
Neurological				
Sensorimotor deficits	30 (30%)	8 (15%)	7 (29%)	13 (57%)
Seizures		10 (19%)	2 (8%)	5
Generalized tonic-clonic	13 (13%)	9 (17%)	1 (4%)	3 (13%)
Focal	4 (4%)	1 (2%)	1 (4%)	2 (9%)
Faciobrachial dystonic seizures	7 (7%)		7 (29%)	
Speech dysfunction (pressured speech, verbal reduction)	15 (15%)	10 (19%)	4 (16%)	
Movement disorders	11 (11%)	7 (13%)	1 (4%)	3 (13%)
Headache	12 (12%)	9 (17%)	1 (4%)	2 (9%)
Reduced levels of consciousness	7 (7%)	5 (9%)	2 (8%)	
Paralysis	7 (7%)	4 (8%)	1 (4%)	2 (9%)
Cerebellar ataxia	10 (10%)	1 (2%)	3 (12%)	7 (30%)
Diplopia	7 (7%)	3 (6%)		4 (17%)
Any of the above symptoms	67 (67%)	39 (74%)	20 (83%)	20 (87%)

Herkin 2017

Age differences in debut symptoms

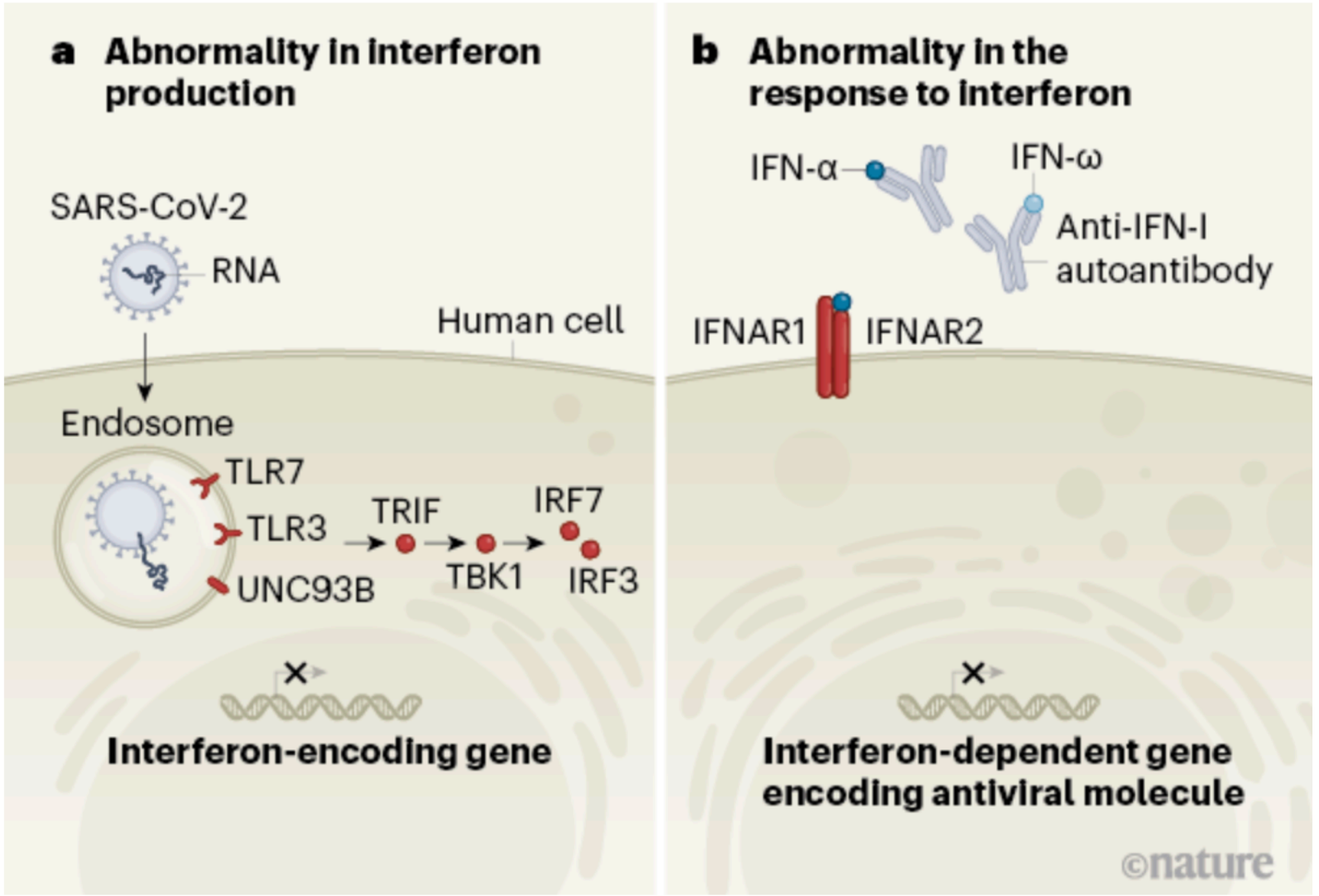


Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet neurology*. 2013; 12: 157-65.

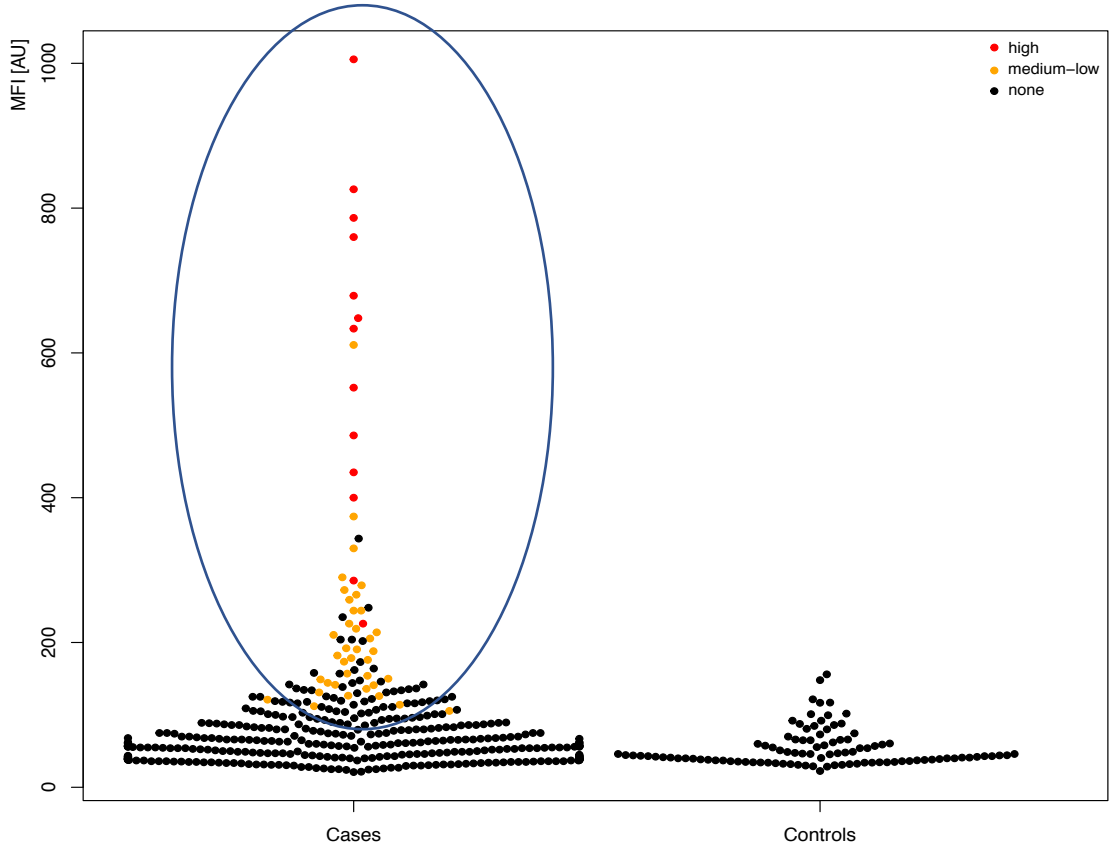
Higher prevelance of NMDArAB after:

- Influenza A (Males)
- Influenza B (Males)
- Vaccination (influenza)
- Measles
- Herpes encephalitis (6 weeks after in children)

Autoimmunity that regulates the Immune system?



Autoantibodies towards protein LBP



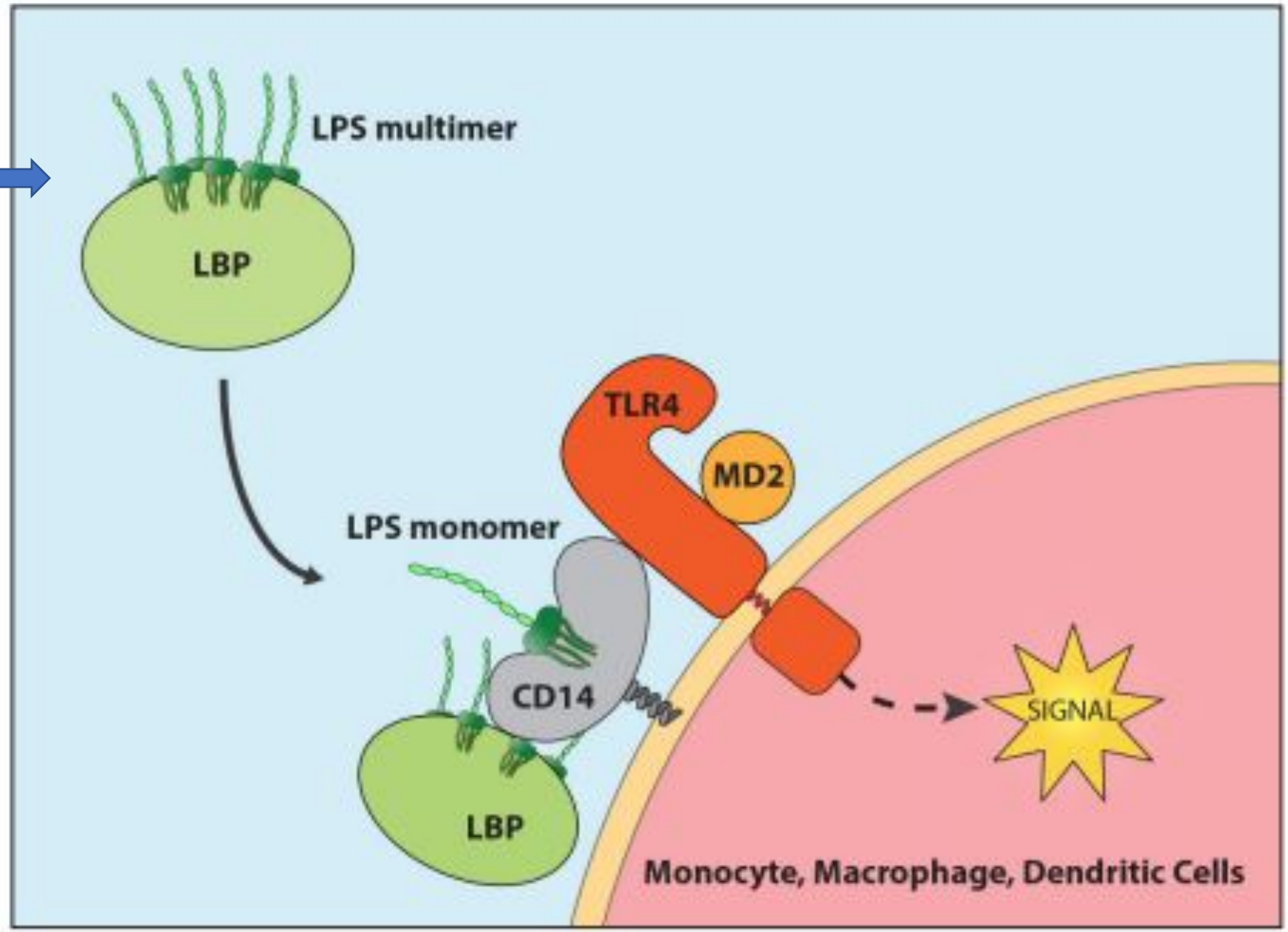
Colored are patients with high (red), medium-low (orange) reactivity towards protein lipopolysacharide bindning protein.

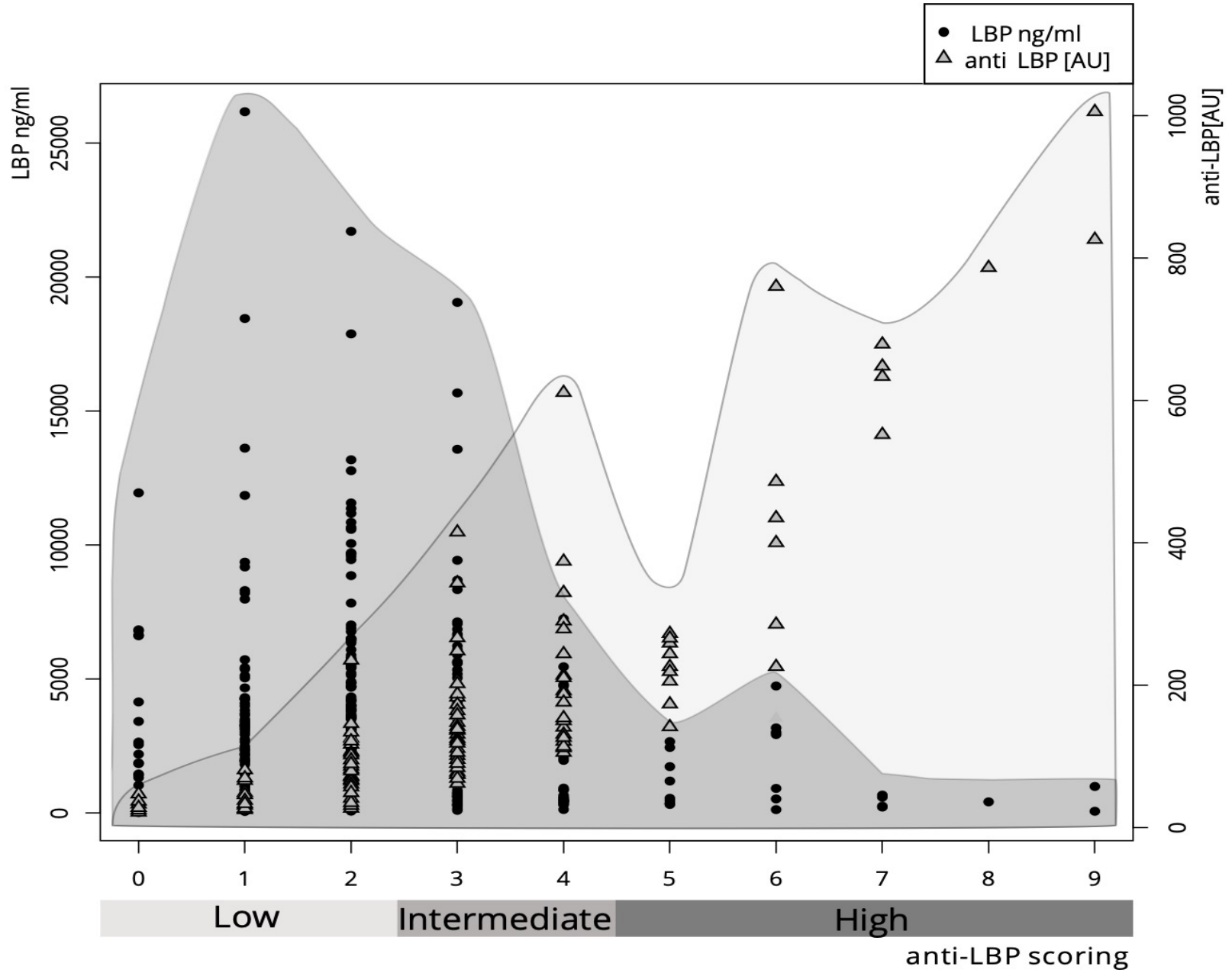
David Just
Post-Doc

Just et al. Psychoneuroendocrinology, 2021

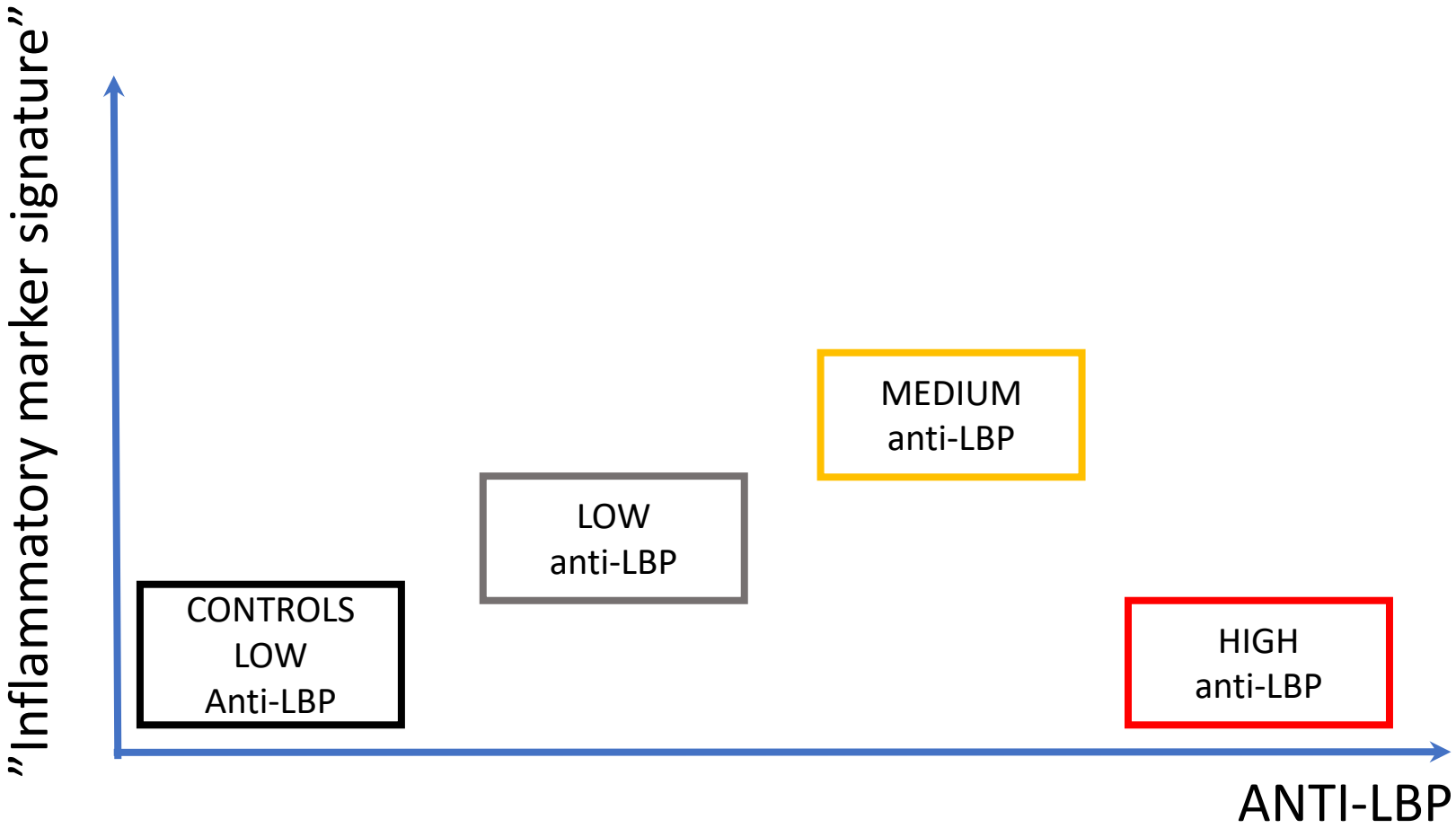
Parts of E-coli in the blood trigger the Innate immune system via TLR4

Chronic stress can activate the same pathway = Sterile inflammation

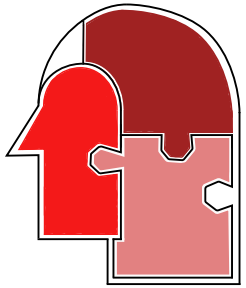




Just et al. Psychoneuroendocrinology, 2021



Just et al. Psychoneuroendocrinology, 2021



Is this due to primary or secondary immunodeficiencies?

Particular types of infectious agents?

Microbiome alterations?

Other factors?

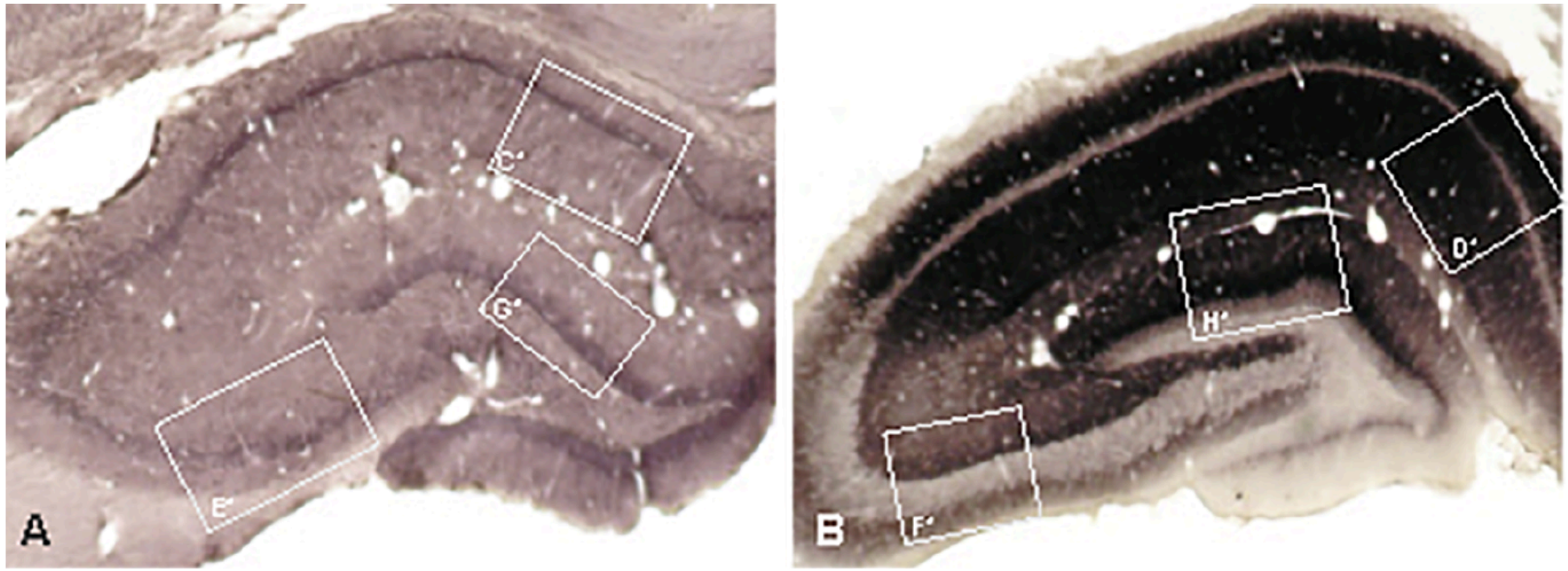
All of the above?

Commercial Tests for NMDAr-Abs have very low sensitivity

	Positive	Weak positive	Total
Live CBA (serum) *Lab A*	8	6	14
Live CBA (serum) *Lab B*	5	4	9
Fixed CBA (serum) *Lab C*	1	1	2
Live CBA (purif. IgG) *Lab A*	5	3	8

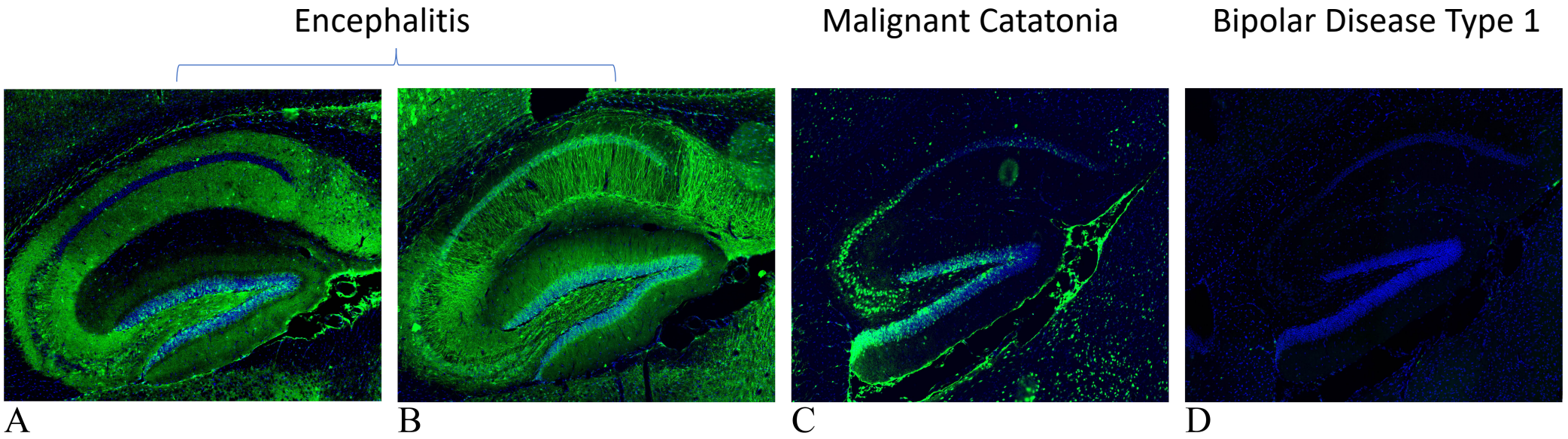
http://dx.doi.org/10.1016/j.biopsych.2017.06.015

Post-synaptic vs pre-synaptic NMDAR-Abs



Wagner, 2020, Brain Research

Antibodies against hippocampus in patient CSF after COVID-19



1) Mulder et al Brain Behaviour and Immunity, In Press, 2021, **2)** Mulder J, et al **,** Autoimmune Encephalitis Presenting with Malignant Catatonia in a 40-Year-Old Male Patient with Covid-19. Am J of Psychiatry, 2020, In press (in press), **3)** Virhammar J, et al Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in CSF. Neurology 2020;95(10):445-9.

Look for the following on Physical exam:

PANS/PANDAS/Sydenham chorea patients (at least 2 of the following signs:

- poor grip, Weakness in arms (cannot maintain arms overhead)
- milkmaid sign,
- positive glabellar sign,
- Findings on standing and sitting rhomberg (truncal instability, arm waivering/chorea (not twitches), leg movements, piano playing finger movements),
- hung-up reflexes
- overflow dystonia, etc.

Look for the following on Physical exam cont..

ALSO LOOK FOR:

Enthesitis, arthritis

Palatal petechiae. Prominent blood vessels in ear canals, over TMs, nasal septum and Palatal petechiae are common in acute cases (most likely post strep)

Levido reticularis, fingernail anomalies. (Chronic cases)

Ask about morning stiffness or pain

Evaluating autoimmunity in psychiatric pat.

Blood work: monocytosis (seen in PANS), **cytopenias** and **thrombocytopenia** (seen in lupus and other systemic autoimmune disease), and thrombocytosis (seen in vasculitis)
If elevated **Creatinine**, do full connective tissue disease work up. If elevated **liver enzymes** do Wilson's work-up and autoimmune hepatitis work-up

- **Thyroid antibodies** (TPO and TG antibodies)- to r/o SREAT (get these even if thyroid hormone is normal)
- **Antinuclear Antibody** (ANA, Immunoflourescence)- screen for lupus
- **AntiPhospholipid (APL) antibodies-** screen for APL syndrome and lupus which can be associated with prominent neuropsych symptoms (get full APL panel: beta 2 GP 1 ab, DRVVT, Lupus anticoagulant, anticardiolipin antibodies)
- **C3 and C4** (often low in lupus, low C4 predisposes autoimmunity). WE also see low C3 and C4 in strep triggered inflammatory disease (i.e. post-strep glomerlunephritis).

If suspected infection: ASO, DNASE B, mycoplasma IgM IgG

Urine analysis to look for hematuria, proteinuria, or casts which can be a a sign of a systemic autoimmune disease including lupus. If the patient has 1+ protein or greater (and spec grav is normal) obtain first morning protein to creatinine level.

If fevers, joint pain, rashes, etc * CRP, ESR

Other:

- If psychosis consider Ribosomal P antibodies, AE panel, Wilson's work-up
- If dry eyes or dry mouth consider SSA and SSB antibodies, rheumatology consultation

MRI: vasculitis, demyelinating lesions? (consider work up for NMO, MS, etc if present). Look for sinusitis and if present, consider treating.

Consider **FDG PET** (brain and whole body) in severe cases. We often se high signal if it is a new acute disease. In longer standing disease we often see area of hypometabolism.

EEG: PANS patients can have non-specific slowing (about 50%). A few have seizures. This EEG should capture transition from wake to sleep since this can bring out certain patterns that would alert the possibility of electrical status epilepticus in sleep (ESES) syndrome is characterized by a near-continuous spike-and-wave discharges during sleep with marked developmental regression. ESES can present as behavior/mood changes and more typically loss of understanding spoken language followed by loss of speech... but it has also been described in typical PANS presentations.

Lab: LP and CSF studies:

CSF: IgG synthesis index (CSF Protein & Immunofix Electrophoresis) ** Don't forget serum draw for IgG as well. CSF glucose, cell count, proteinNeuro damage markers (NFL, GFAL, TAU)

If neurodevelopmental issues, psychosis:
Neurotransmitters, CSF Amino Acids, CSF 5 Methyltetrahydrofolate

If multiple infections: Immunodeficiency work-up (IgA, IgE, IgG, IgM; immunology **testing**, vaccine titers)

If suspect ongoing infection: Bacterial/virus identification by sequencing.

Other CSF studies to consider:
Cytokines, CSF (IL-6)
Neuromyelitis Optica (NMO)/ anti-aquaporin NMO/AQP4-IgG plus MOG

Consider referral to ENT if large tonsils or sinusitis.

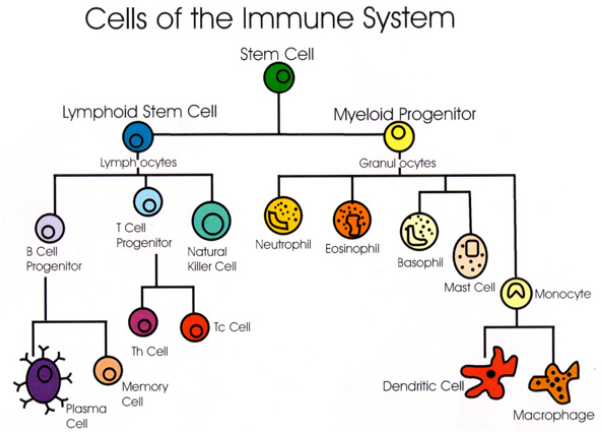
Then what?

- Treat mental health symptoms
- Treat ongoing verified infections, (in some cases prophylactically)
- Treat a suspected inflammation. However, note that if clinical work-up reveals significant CNS inflammation, differential diagnoses should be considered and expanded diagnostic work-up.

Treatment options

- Antibiotics
- NSAIDs
- Steroids
- IVIG
- Plasmapheresis, cytostatic and immunomodulatory drugs

Take home message



Psychiatric disorders are COMPLEX!!

Current psychiatric diagnoses are valid and reliable tools to sort patients for symptom based treatment strategies.

Psychiatric diagnosis are NOT valid biological groupings

When treatment fails or atypical /red flag features are present, maladaptive immunological features may be present.

The immune system can malfunction in many ways and give uprise to a plethora of symptoms resembling ”regular” psychiatric disease.

“I feel all jumbled up inside.

Like I’ve been taken apart and put back together by someone who really isn’t very good at puzzles”

Boy, age 9, UK, PANDAS

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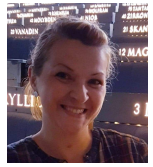

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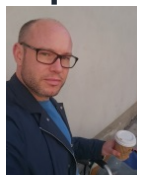

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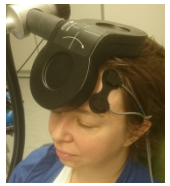

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M och N Nasvells stiftelse

Bissen Brainwalk
Till förmån för forskningen som räddade mitt liv

Svenska Läkaresällskapet

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