Gene-environment interactions in psychiatry

Neurobiological basis of mental disorders

Psychopathology, Mental status examination

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Objectives of the lecture

By the end of the lecture you should

- Have a clear idea and an overview about the etiology of psychiatric disorders.
- Become familiar with the most important risk factors (genetic and environmental) for psychiatric disorders.
- Understand the general concept of gene-environment interactions.
- Understand the significance of the mental status examination and additional examinations in psychiatry

The fundamental questions

- What causes psychiatric disorders?

or

- Why some individuals have psychiatric disorders and others don’t?

Case presentation 1.

Source: Public Broadcasting Service (www.pbs.org)

Questions 1

- How do we call the condition described by Andrew?
- What is the most probable diagnosis?
- What other diagnoses should we think of?

Questions 1

- How do we call the condition described by Andrew?
    - Psychosis
- What is the most probable diagnosis?
    - Schizophrenia or schizoaffective disorder
- What other diagnoses should we think of?
    - Drug/medication-induced psychosis
    - Organic psychosyndrome (e.g. brain tumor, temporal lobe epilepsy, multiple sclerosis, encephalitis)
    - Mood disorder
    - Personality disorder

Case presentation 2.

- 23 year old female patient presents herself at the Department after a family debate.
- Chief complaints: „I am treated brutally by my family… I think people on the street mean bad to me…People are staring at me…People are hurting me.”
- Feels that things have changed several months ago. Sought ambulatory treatment and received antidepressant medication.
- Following examination: symptoms of anxiety, paranoid and religious delusions, acoustic hallucinations („I heard the voice of Jesus and my teacher talking to me.”)
- Positive family history: uncle diagnosed with schizophrenia

Questions 2

- What is the cause of her psychiatric problems according to the patient? (What was her explanation?)

- According to you?

Questions 2

- What is the cause of her psychiatric problems according to the patient? (What was her explanation?)
    - Family conflicts, psychological stress
- According to you?
    - Uncle diagnosed with schizophrenia, this means genetic/biological vulnerability.

- The fundamental question of etiology: What causes the disorder? Environmental or genetic factors? Or both?

Psychiatric disorders

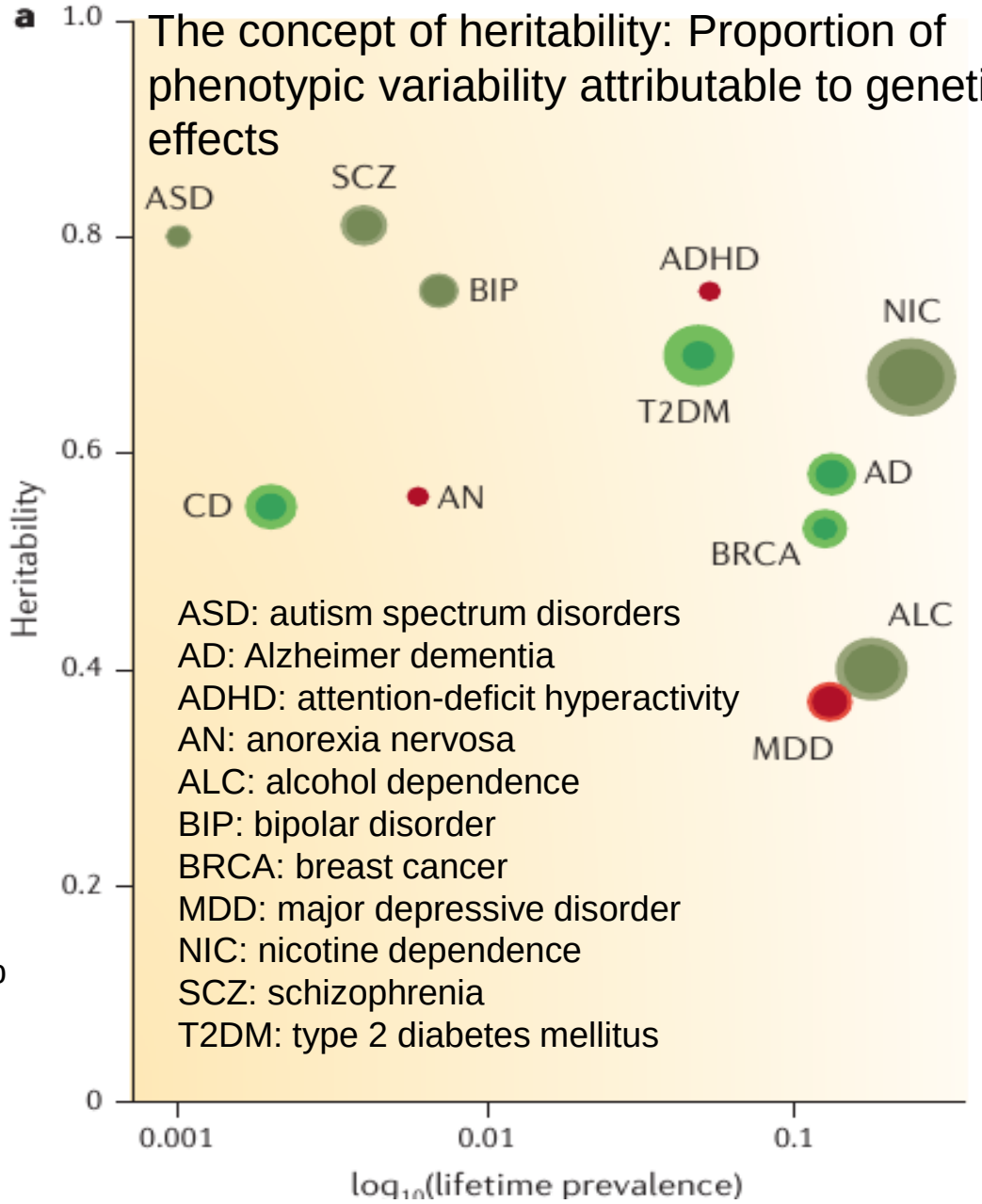
- Severe and prolonged impairment of affect, cognition, and behavior leading to social dysfunction.
- Diagnoses based on interview and behavioral assessment
- Fulfill official diagnostic criteria (time criterion, number of symptoms, dysfunction, exclusion of other etiologies)

  DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Text revision (1994, 2000)
  DSM-5: 2013

- Why do we think psychiatric disorders have anything to do with genes?

Most psychiatric disorders run in families

- Positive family history
- Risk for developing psychiatric disorders increases 5 to 20 times (according to disorder) in the presence of a first degree relative
- Twin studies offer a possibility to dissect genetic and environmental factors by examining concordance rates.
  - Schizophrenia: MZ:59%, DZ:15%,
  - Bipolar disorder: MZ:65%, DZ:14%
  - Unipolar depression: MZ:50%, DZ:18%
  - Alcohol-dependency: MZ:26%, DZ:12% (Kendler, 1986)

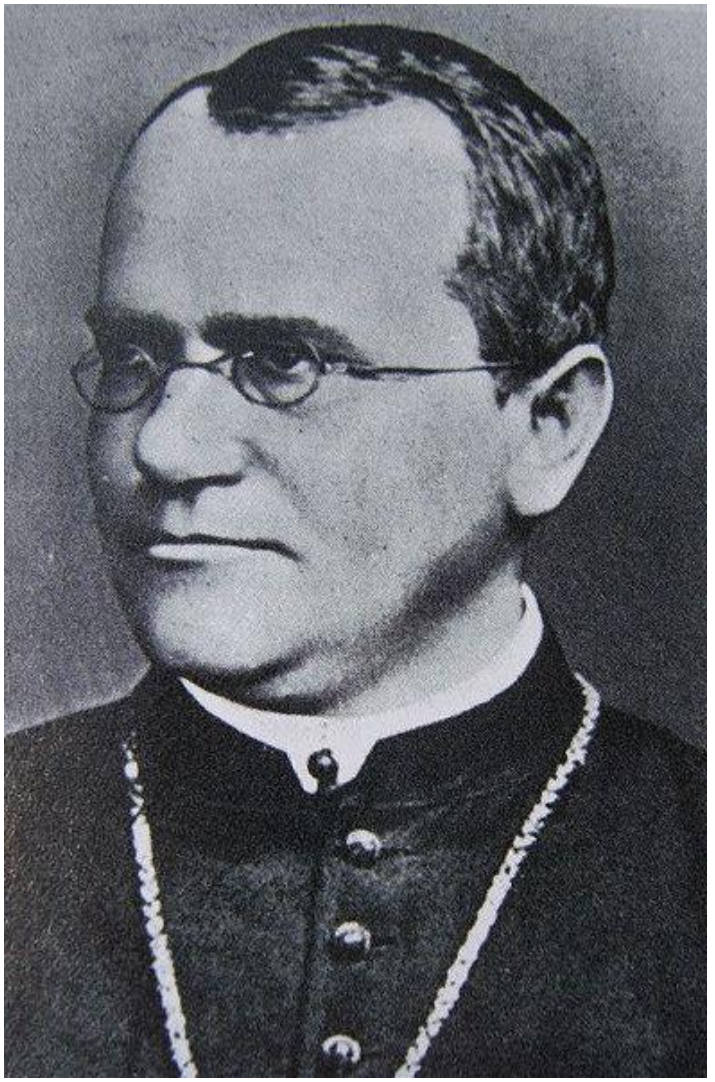


Source: Sullivan et al, 2012. *Nature*

Psychiatric disorders are not mendelian disorders

Question 3

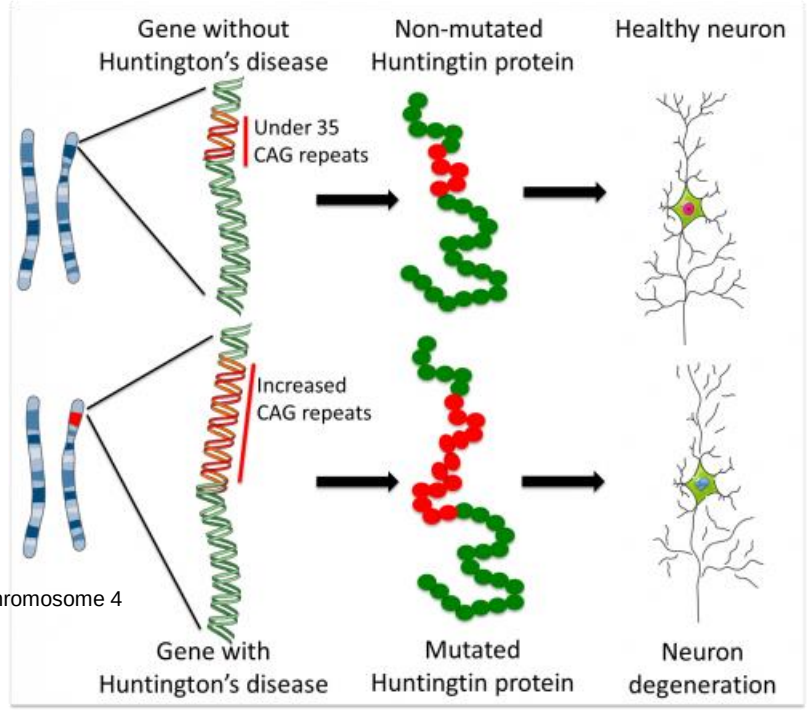
Can you name mendelian disorders?



Johann Gregor Mendel
(1822-1884)

Psychiatric disorders are not mendelian disorders

- Huntington's disease is a mendelian disorder
- Important for the differential diagnosis of depression



Source: Eurostemcell.org

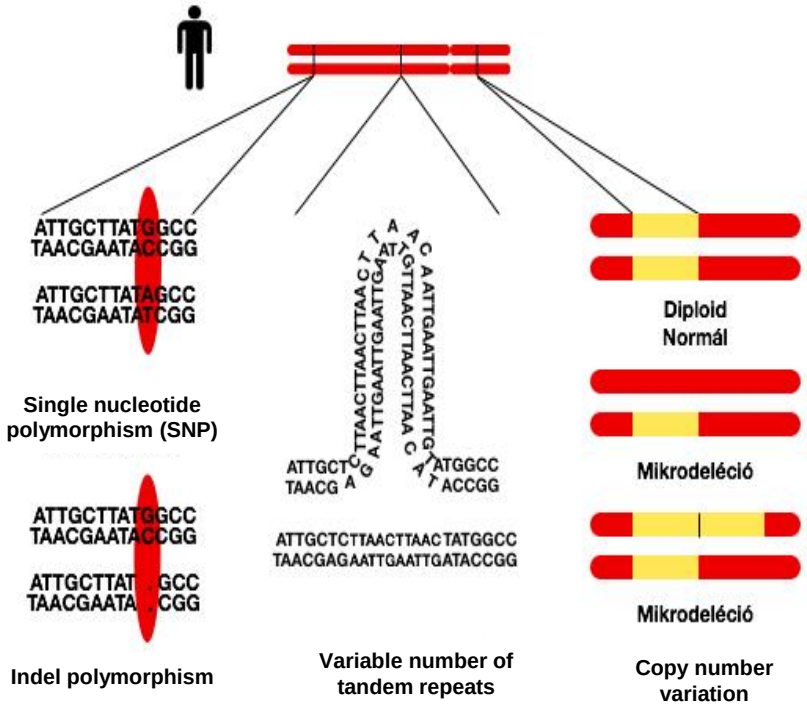
- Schizophrenia, mood disorders, anxiety, substance abuse are most probably polygenic disorders.
- One candidate gene can't explain phenotypic variance.

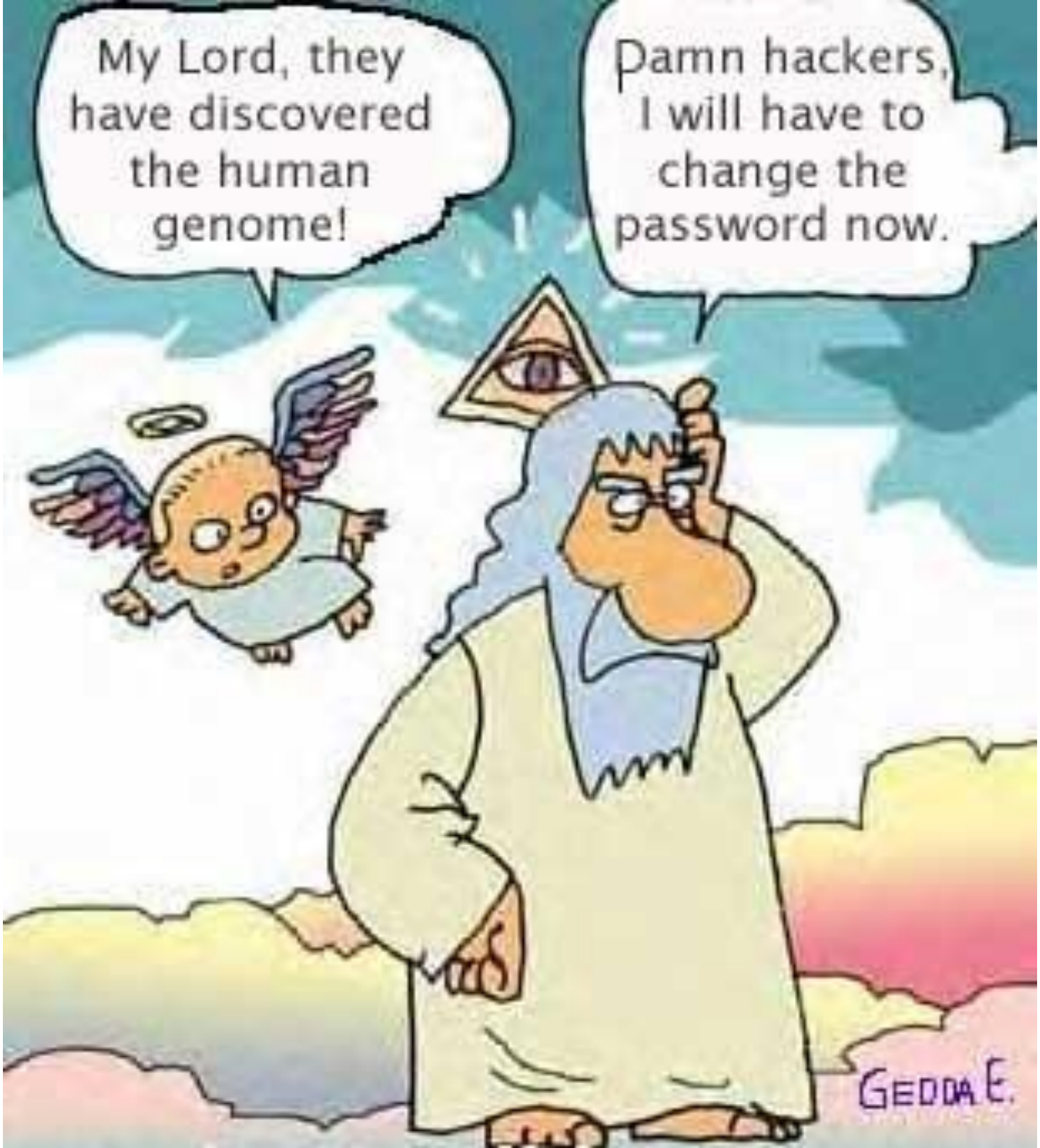
Psychiatric genetic studies: the hunt for candidate genes

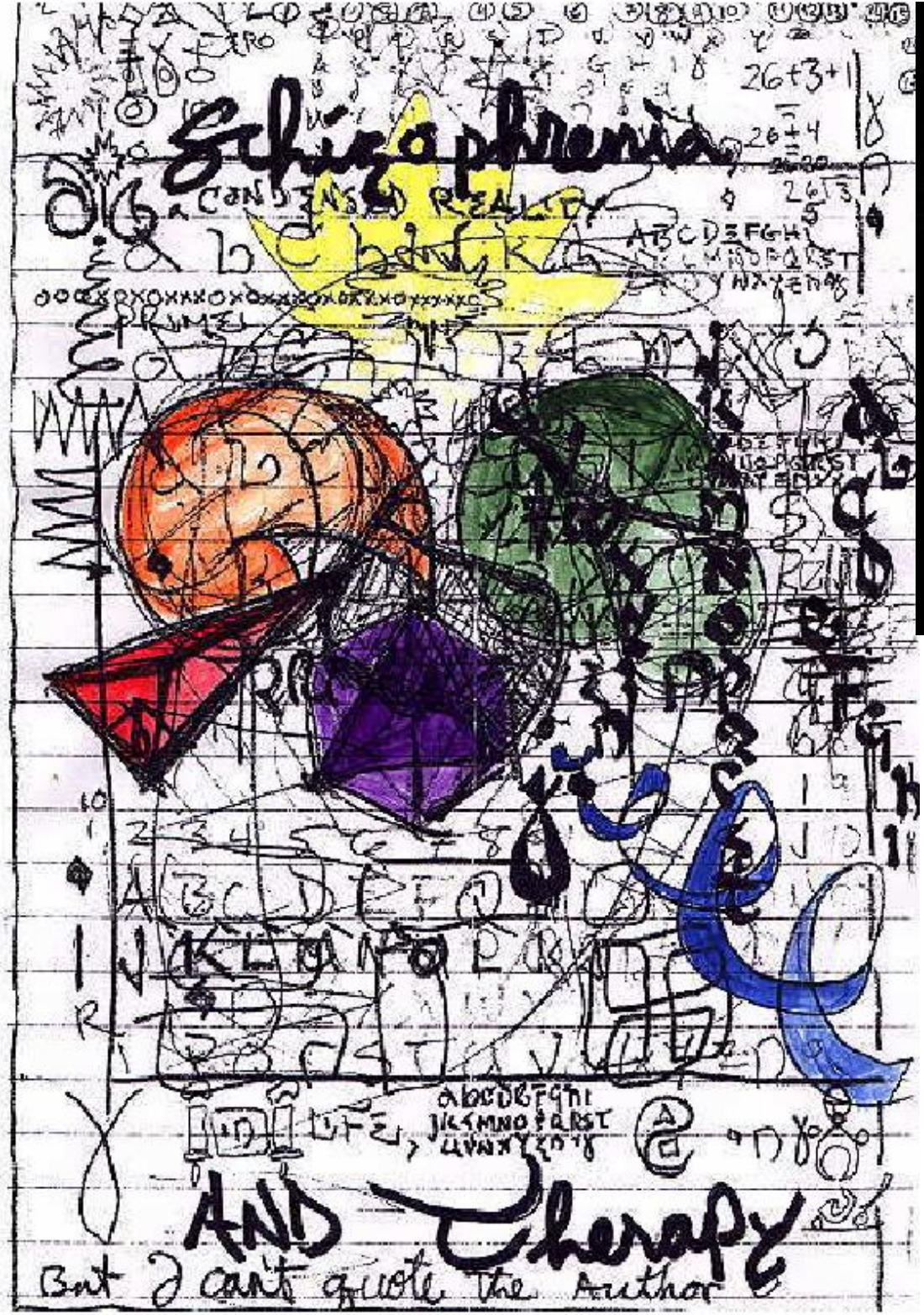
- Population genetics:
  - Family studies
  - Twin studies
  - Adoption studies
- Epidemiologic studies:
  - Genetic cohorts
- Molecular methods
  - Linkage studies
  - Association studies
  - Expression studies
  - Epigenetic analyses
- Stem cell models
- Animal models

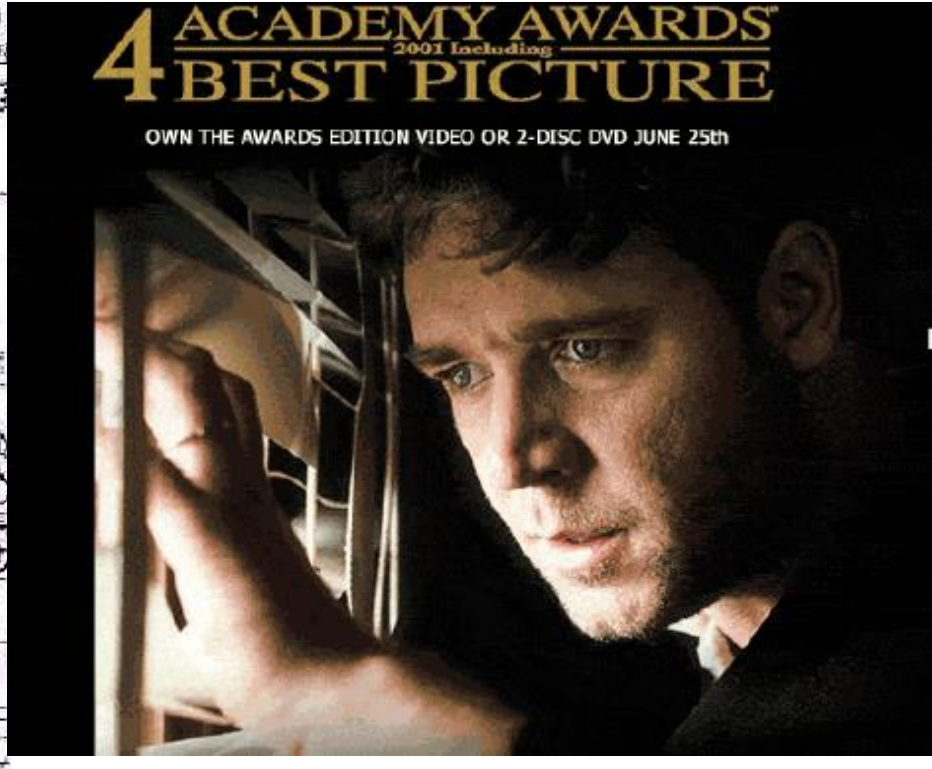
The Human Genome Project and its implications

- 2001: Publication of Human Genome Project: $3x10^9$ base-pairs, 20.000 coding genes, 15.000 non-coding genes, and 15.000 pseudogenes.
- „3000 books of 1000 pages, 1000 letters on each.”
- Polymorphic regions: 0,1% of DNA
- Types of polymorphisms: SNP (single nucleotide polymorphism), VNTR (variable number of tandem repeats), CNV (copy number variation, micrdeletions and microduplications)
- Junk DNA: repetitive elements mostly originating from retrotransposons
- „Island of genes” floating in the ocean of repetitive sequences




My Lord, they have discovered the human genome!
Damn hackers, I will have to change the password now.
GEDDA E.


Schizophrenia
AND Therapy
But I can't quote the Author


4 ACADEMY AWARDS
2001 Including
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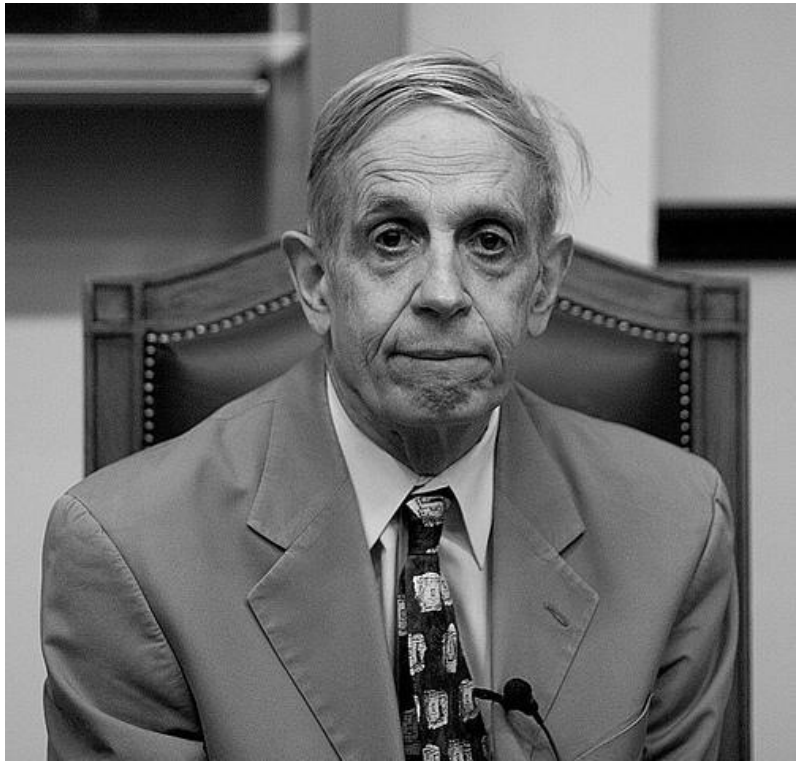
OWN THE AWARDS EDITION VIDEO OR 2-DISC DVD JUNE 25th



Schizophrenia

- Main symptoms: delusions, hallucinations, disorganized thoughts and behavior, negative symptoms.
- Familial transmission is straightforward (heritability: 0.8, MZ twins: 48-59%, DZ twins: 16% concordance)
- Referred to as the totally unsuccessful example of linkage and association studies
- GWAS studies did not replicate previously implicated candidate genes, and significant markers only explain 3% of the heritability -> “missing heritability”

Schizophrenia genetics

- Common variants associated with schizophrenia:
  - 6p21-23: Major Histocompatibility Complex (MHC) I region

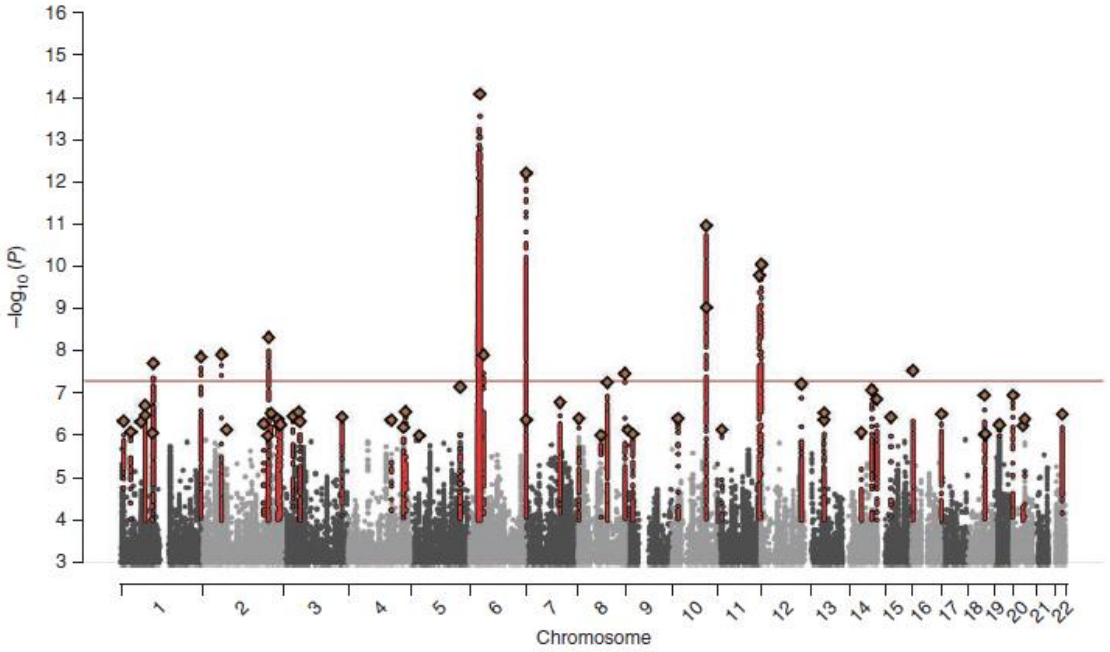
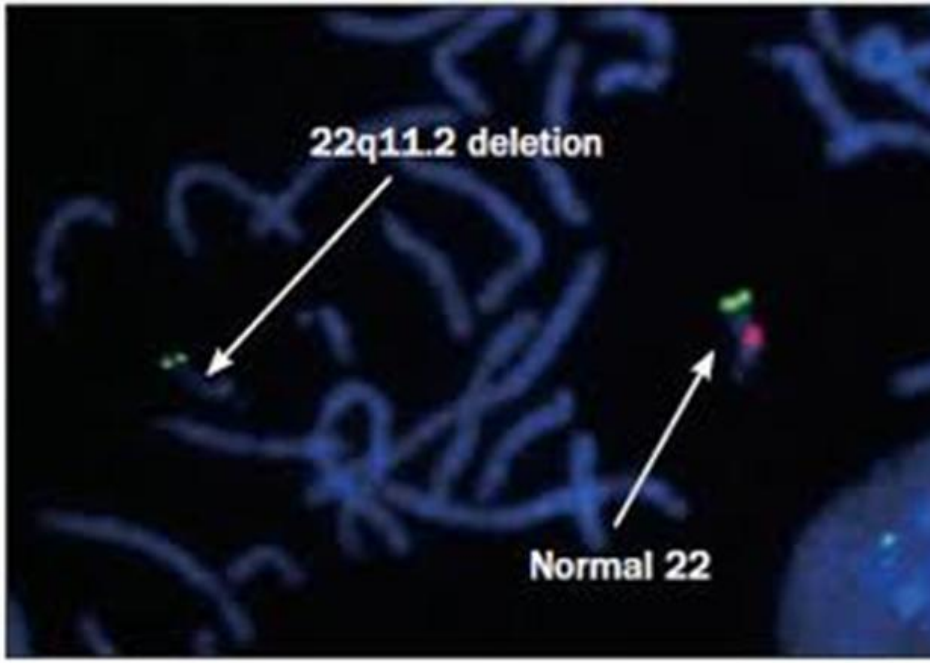


Figure 1 Manhattan plot of the Swedish and PGC schizophrenia meta-analysis results. The *x* axis shows chromosomal position, and the *y* axis shows $-\log_{10}(P)$. The red line is the genome-wide significance level (5×10^{-8}).

Source: Ripke et al, 2013. *Nature Genetics*

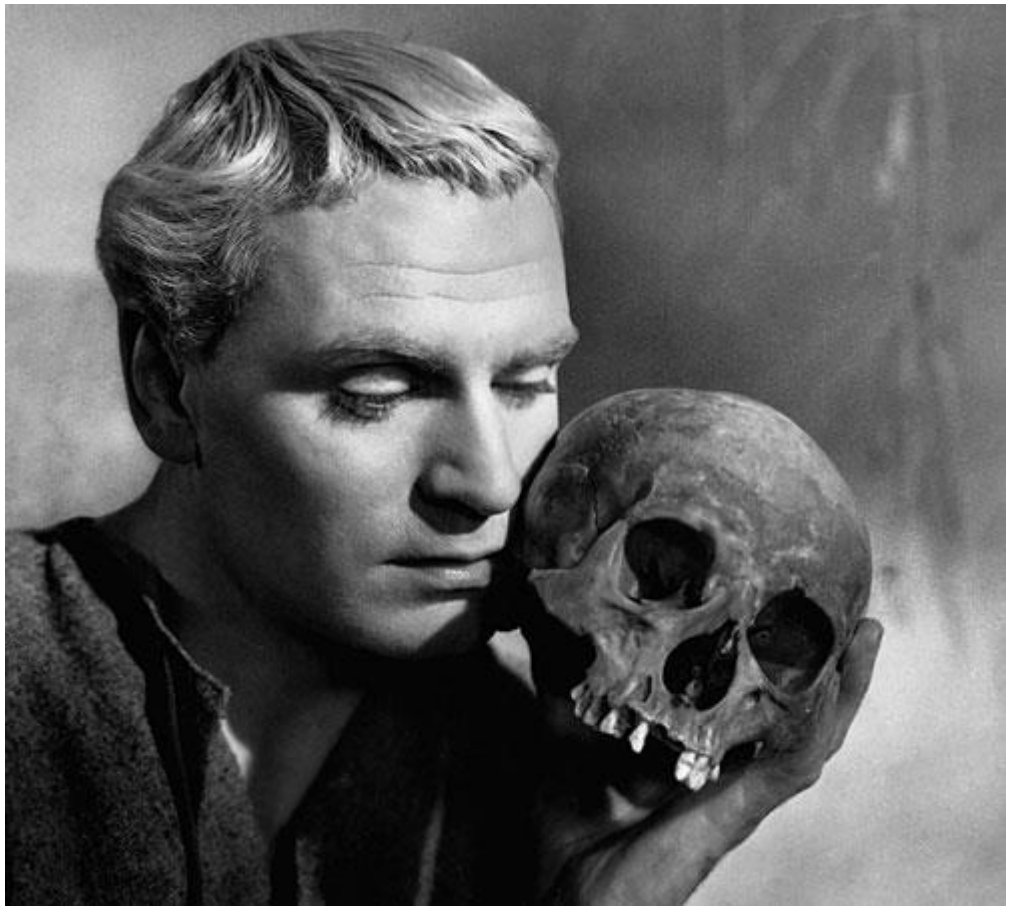
- Rare microdeletions and minroduplications are enriched in schizophrenia:
  - 22q11.2 deletion syndrome – velocardiofacial (VCFS) / DiGeorge syndrome



Source: Karayiorgou, 2010, Nature Neuroscience

Question 4

Which characters show symptoms similar to schizophrenia in William Shakespeare’s dramas?



Hamlet, Prince of Denmark

Talking to ghosts, saying the truth – actually not schizophrenic.

John William Waterhouse: Ophelia (Hamlet) – disorganized behavior

Macbeth and Lady Macbeth
– paranoid psychosis

Edgar - Tom O’Bedlam
(King Lear) – the madman,
chronic schizophrenia

Mood disorders: Major depression and bipolar disorder

Hallmark symptoms:

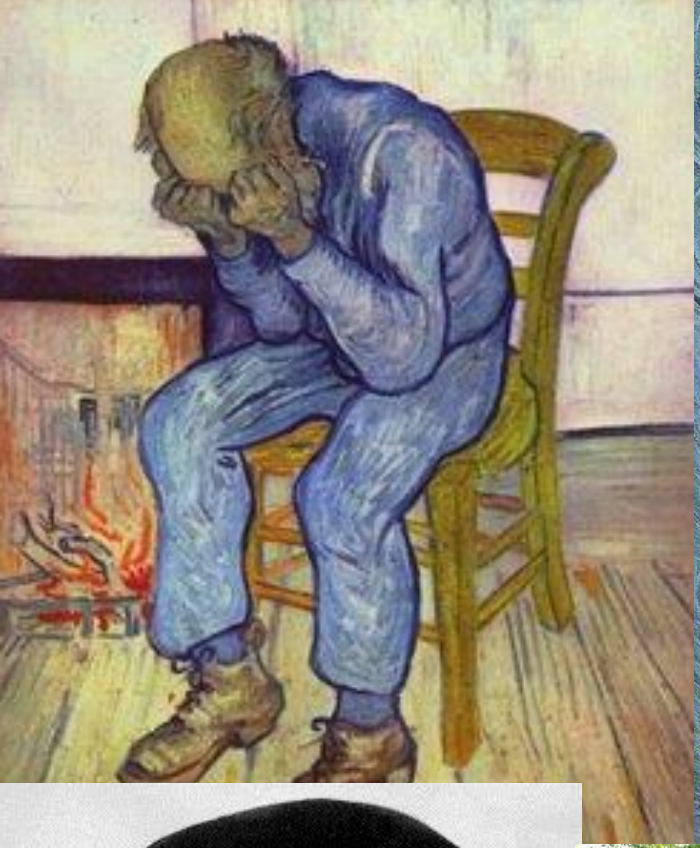
• Depression: depressed mood, anhedonia, problems with concentration, performance problems, somatic symptoms (loss of appetite, sleep problems)

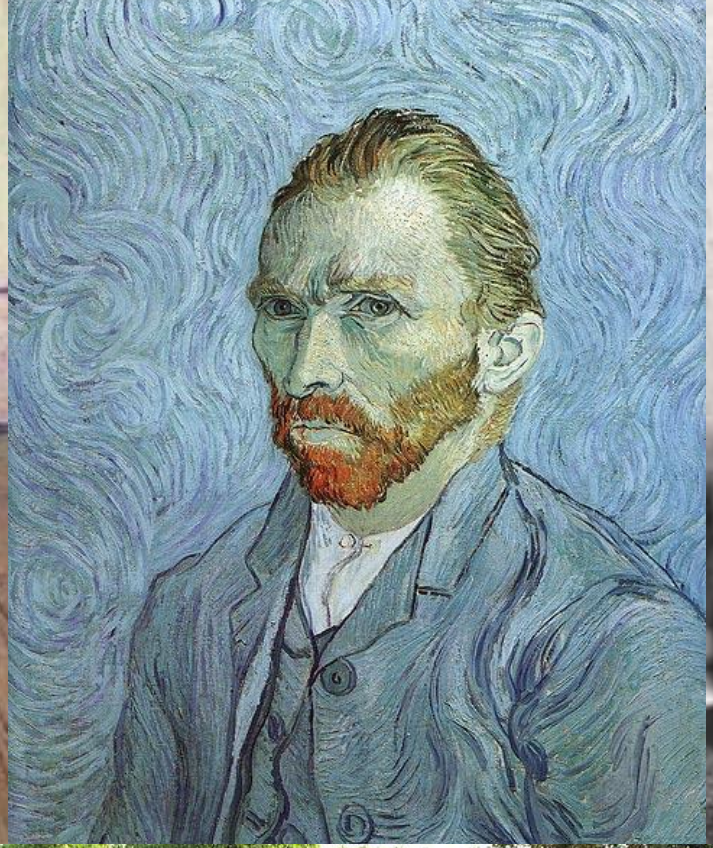
• Mania: elevated mood, flight of ideas, hyperactivity, decreased critical insight

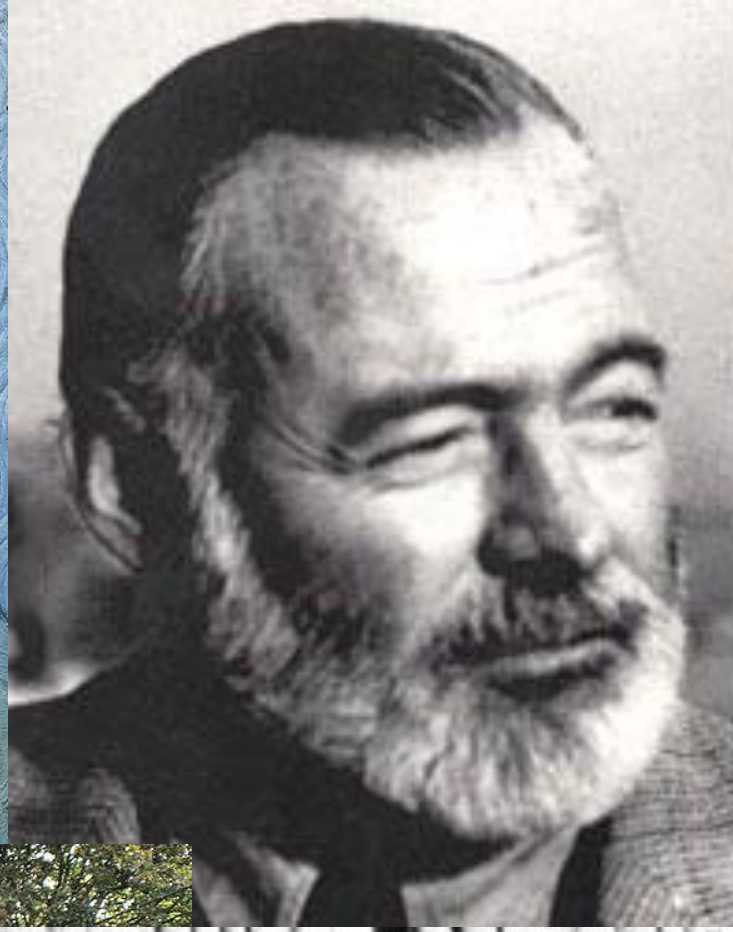
• Bipolar disorder: cycles of depression and mania

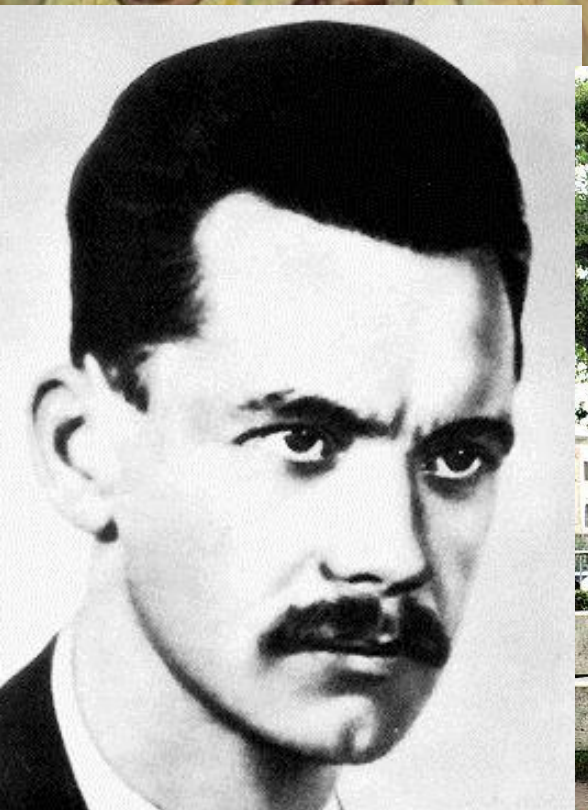
•Decreased social functioning, family problems

•High risk of suicide









Genetics of mood disorders

- Highly prevalent disorders (lifetime prevalence: MDD~15%, BD~3-5%)
- Familial transmission straightforward in BD (heritability: 0.8, MZ: 65%, DZ: 14%), moderate in MDD (heritability: 0.39, MZ:50%, DZ:18%)
- GWAS studies yielded a few significant markers in BD with only 1 gene in concert with linkage results (CACNA1C, OR=1.14), again explaining only 2% of phenotypic variance .
- No markers reached significance in MDD, and the main candidate gene (SLC6A4) association was dismissed by recent meta-analyses.

What is the explanation? Why can’t we find the genes for schizophrenia or depression?

- Although psychiatric disorders have a high heritability efforts to identify individual genes have been unsuccessful.

- Gene-gene interactions? Epistatic and other regulatory mechanisms?

- Is there any other factor that we should consider?

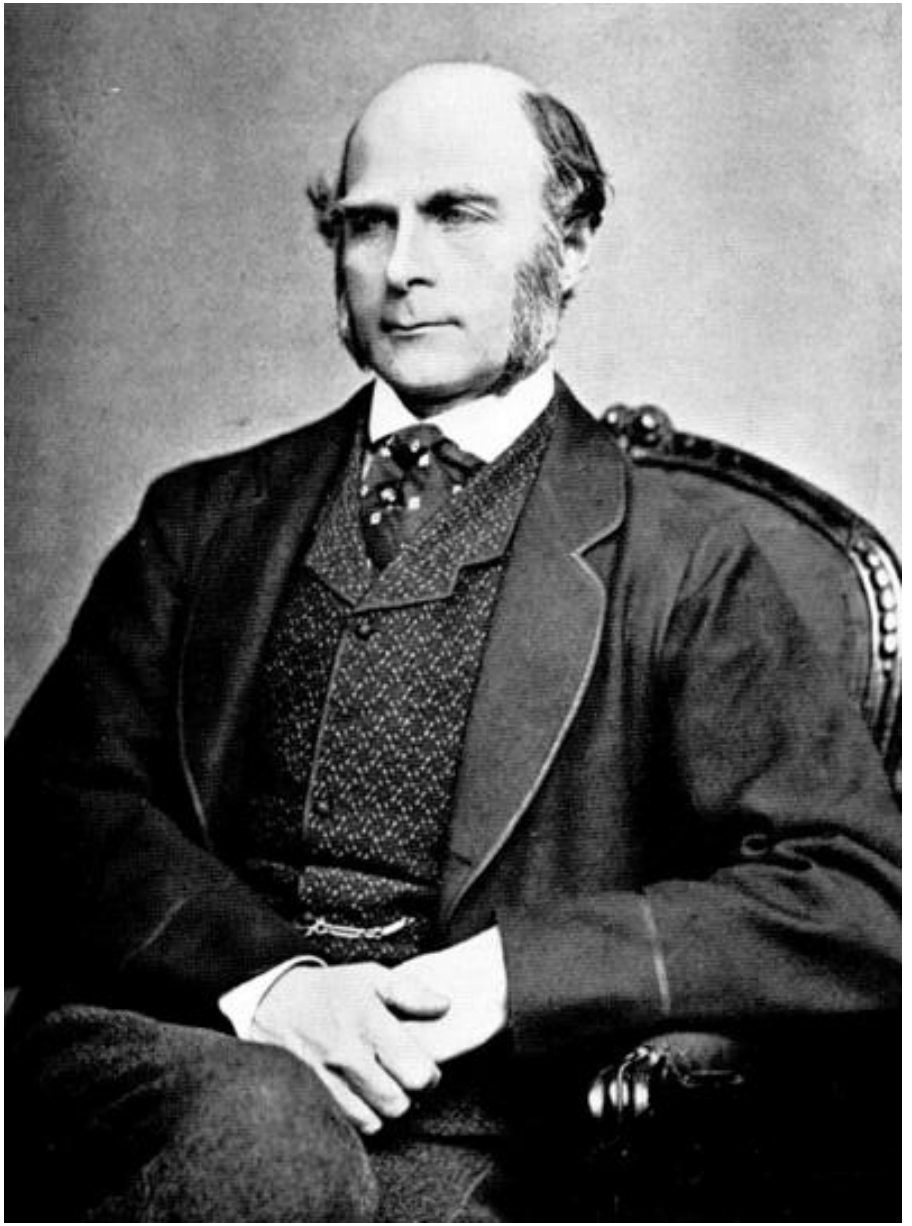
Gene-Environment (GxE) Interactions

- Refers to the phenomenon where genetic and environmental factors both play a role in the etiology of a disease and possibly strengthen each others effect.
- Especially important in chronic non-communicable diseases (cardiovascular medicine, endocrinology, psychiatry, etc).
- Elucidating GxE interactions can lead to better prevention and therapeutic measures.

Sir Francis Galton (1822-1911)

English Men of Science: Their Nature and Nurture (1874)

- Twin studies
- Behavioral genetics
- Psychometry
- (Cousin of Charles Darwin)



Gene-Environment (GxE) Interactions II. Psychiatry

- Alternative definition: Genetic control of vulnerability against the environment (Tsuang et al, 2004)

- „ The most interesting question of psychopathology: How does an environmental factor get in to the CNS of a human and how does it cause the symptoms of a disturbed mind.” (Caspi and Moffit, 2006)

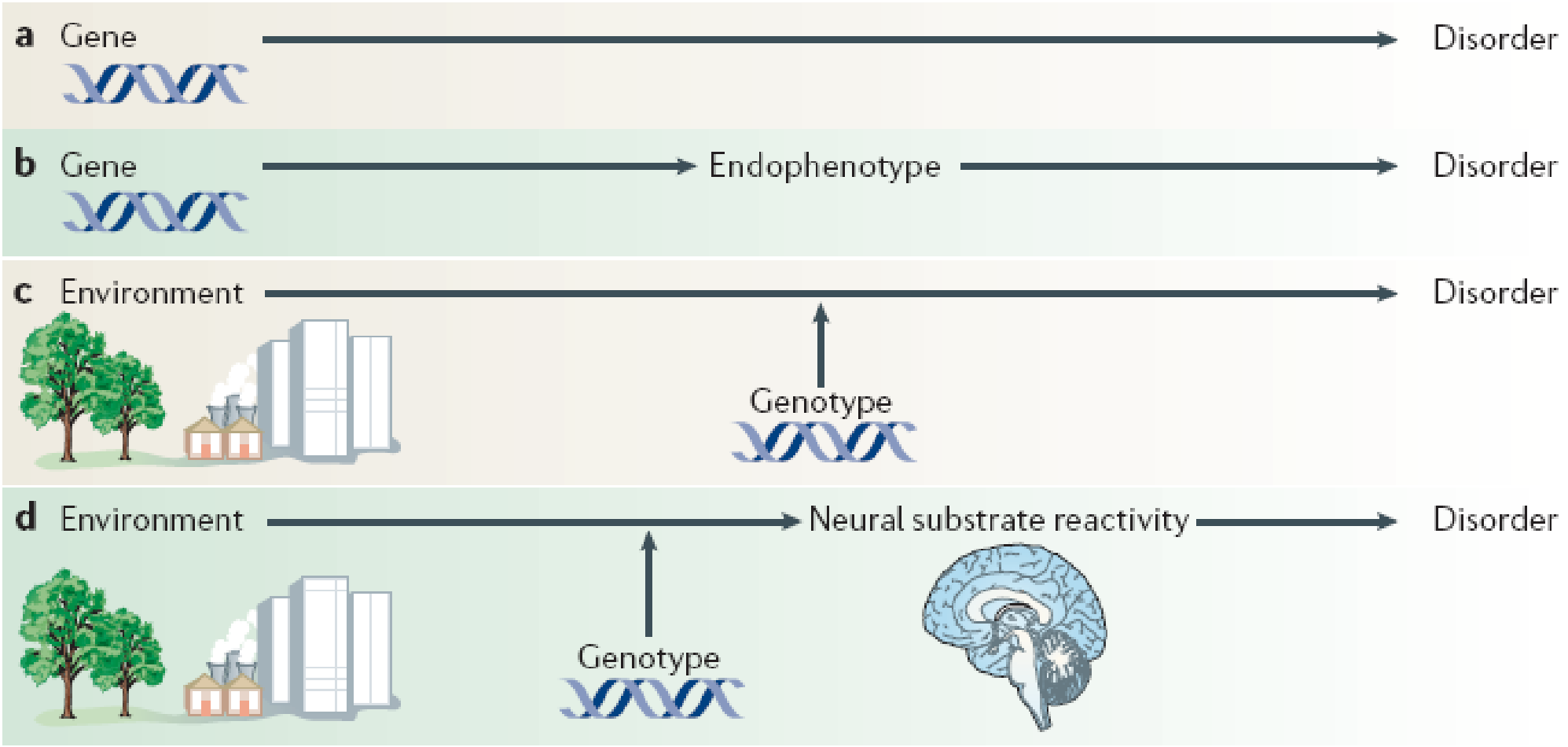
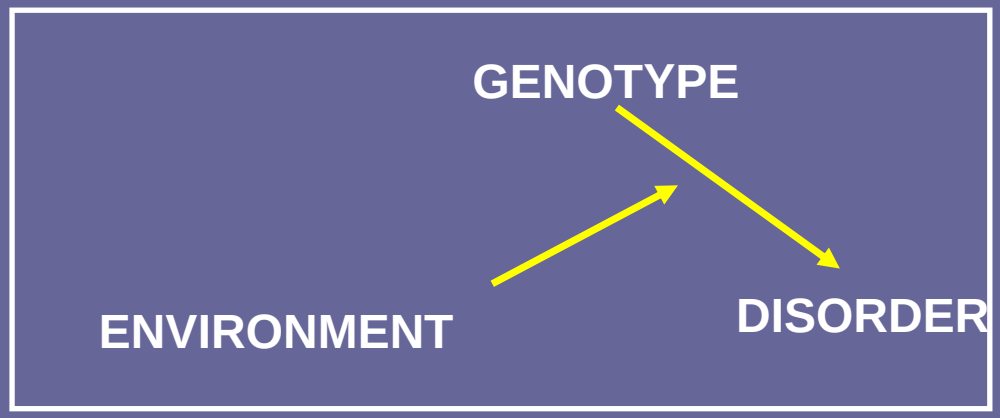
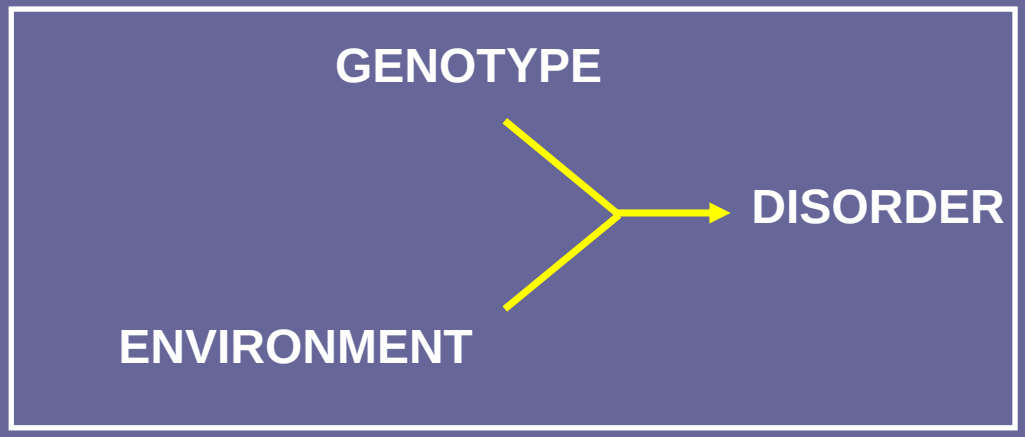
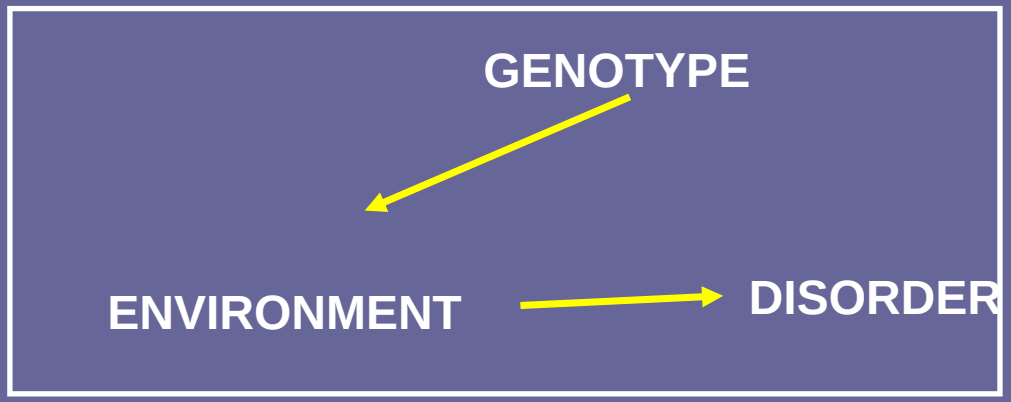


Figure 1 | **Approaches to psychiatric genetics research. a** | The gene-to-disorder approach assumes direct linear relations between genes and disorder. **b** | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. **c** | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. **d** | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.

Possible models of gene-environment interaction (GEI)

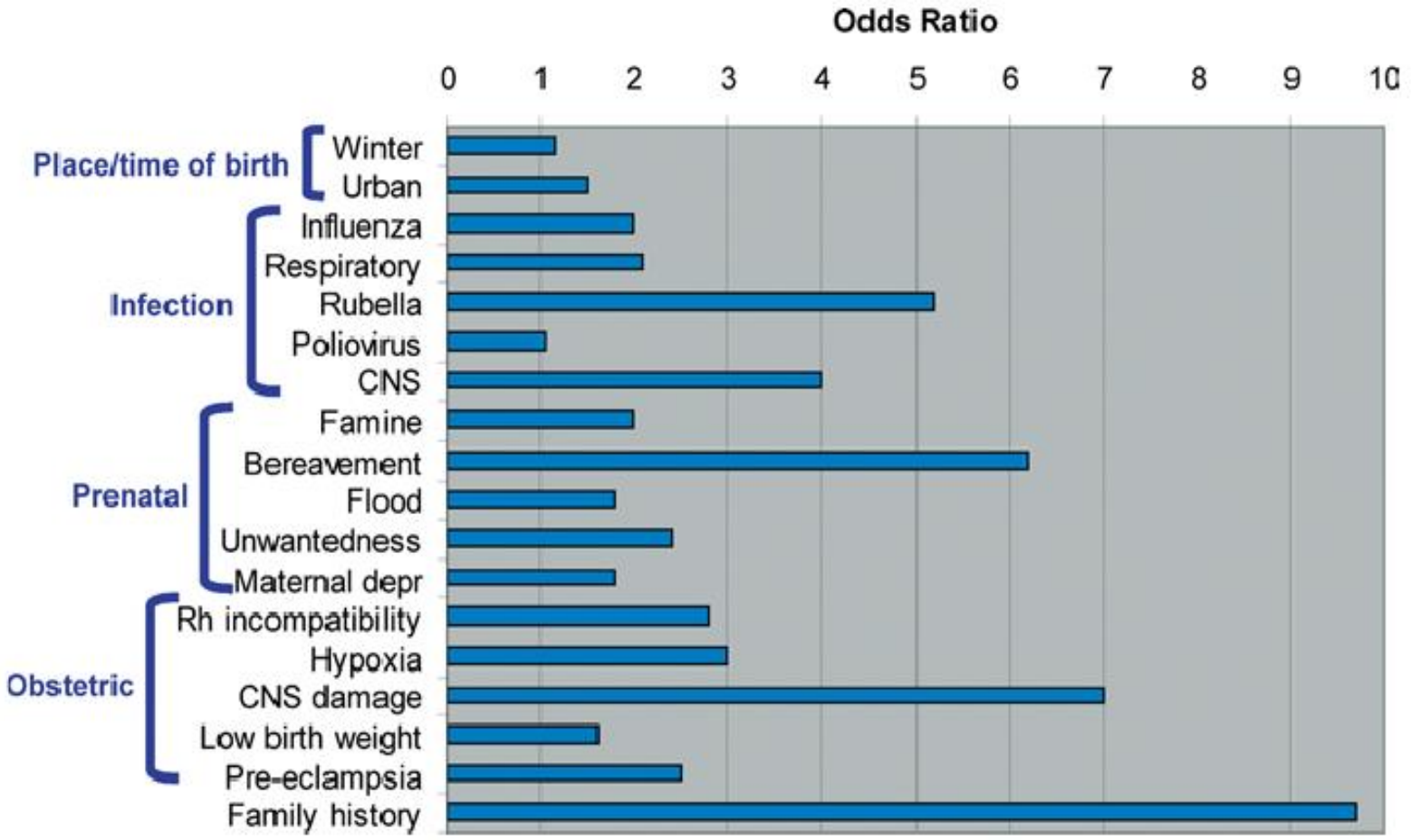






Ottmann, Nature Precedings, 2008.

Environmental risk factors in schizophrenia



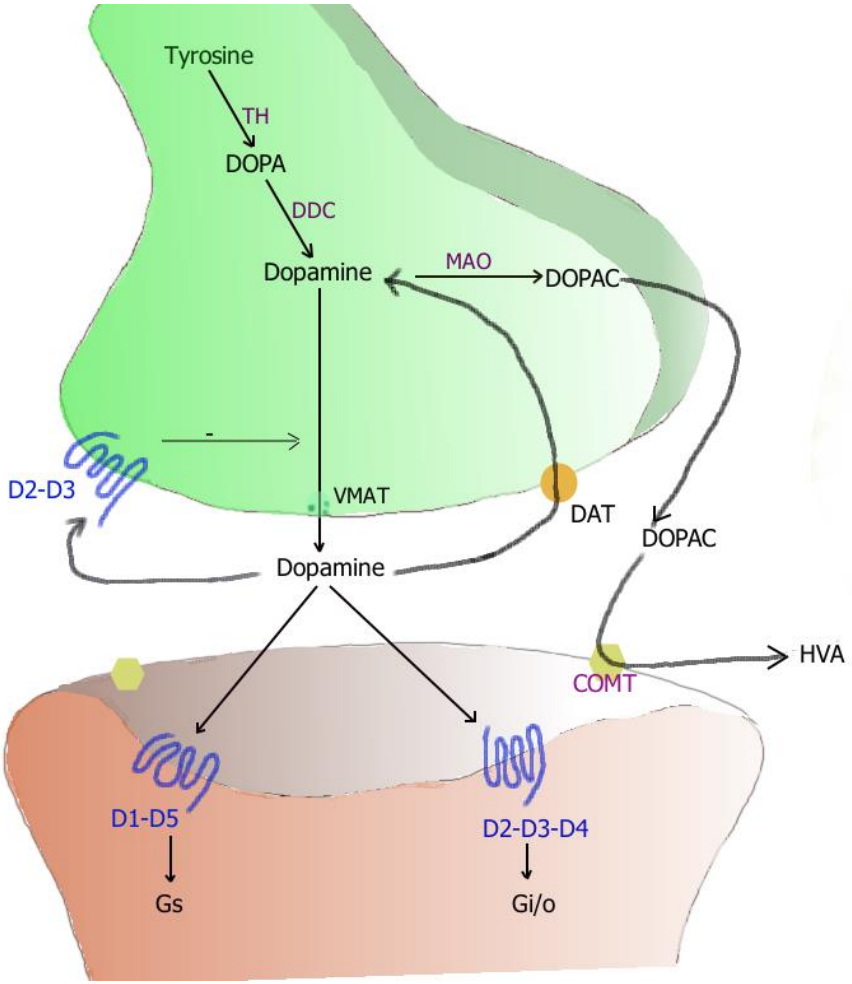
From: Sullivan, 2005. The Genetics of Schizophrenia. *PloS Medicine*

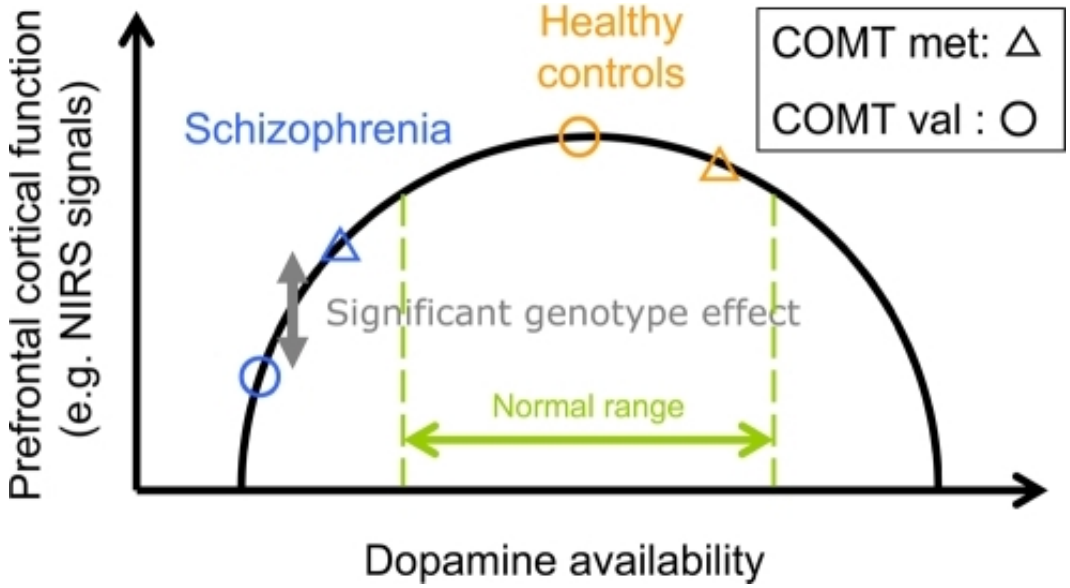
Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction

- Epidemiological cohort study: Dunedin (Southern island of New Zeland)
- Catechol-O-methyltransferase: role in the elimination of dopamine in the prefrontal cortex
- missense mutation that generates a valine (Val) to methionine (Met) substitution at codon 158 ($Val^{158}Met$),

Caspi et al, 2005

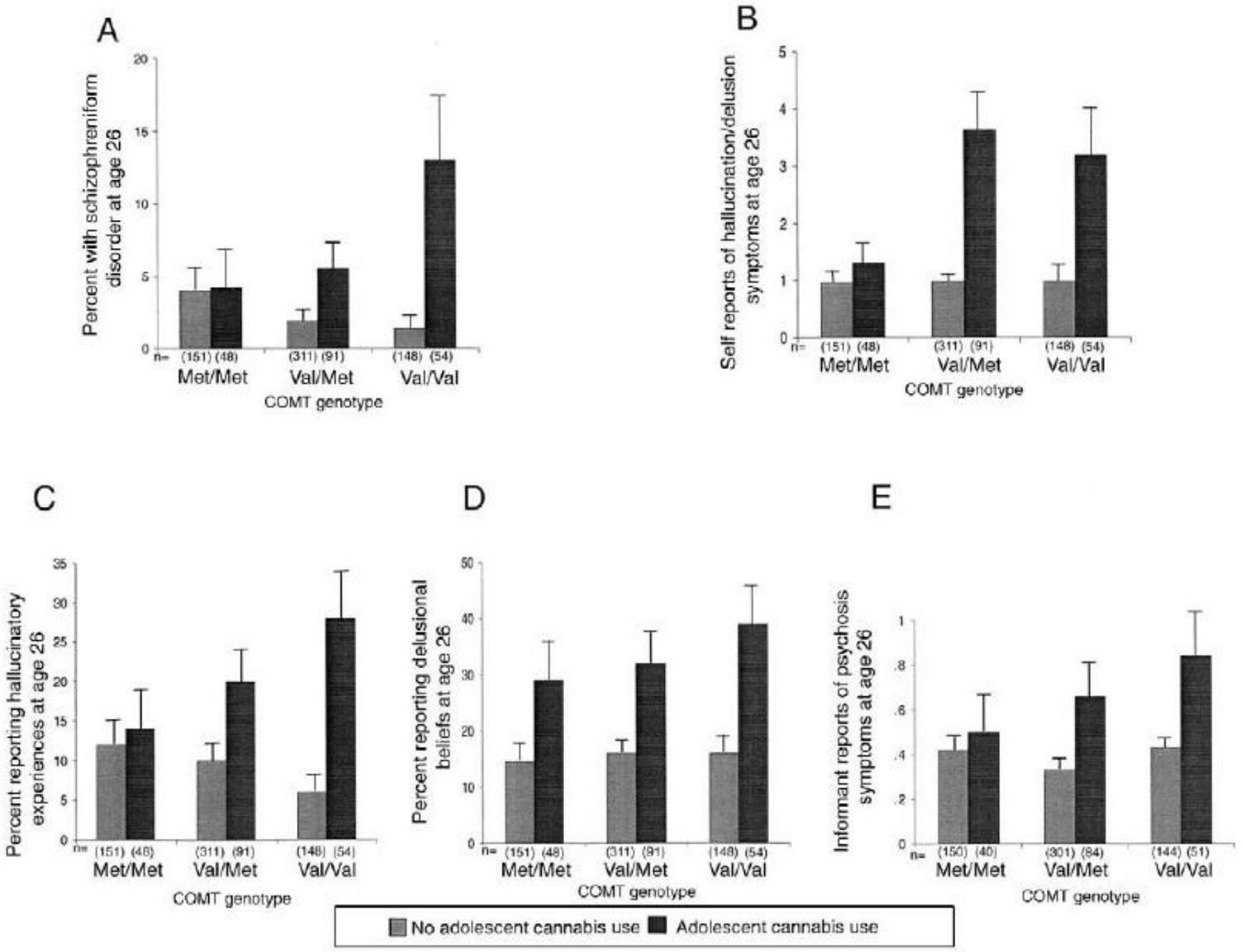
COMT eliminates dopamine from the synaptic cleft and modulates prefrontal cognitive function



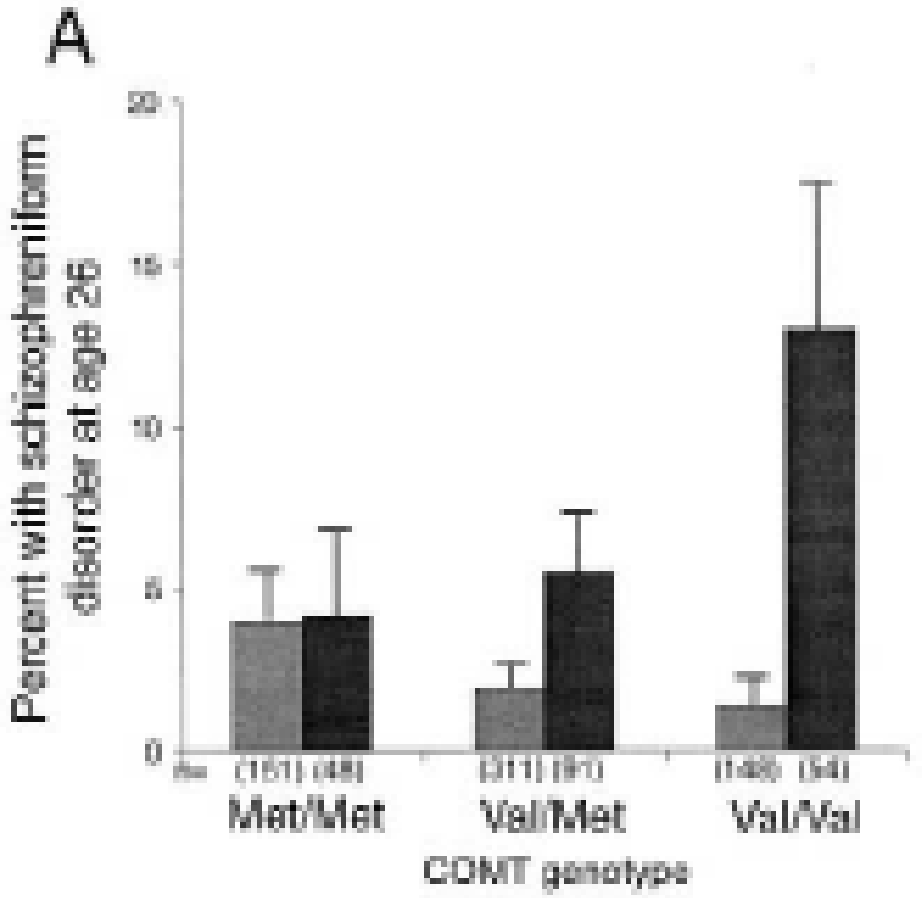


For review: Meyer-Lindenberg, Nature Neurosceince, 2006

The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene



Caspi et al, 2005.

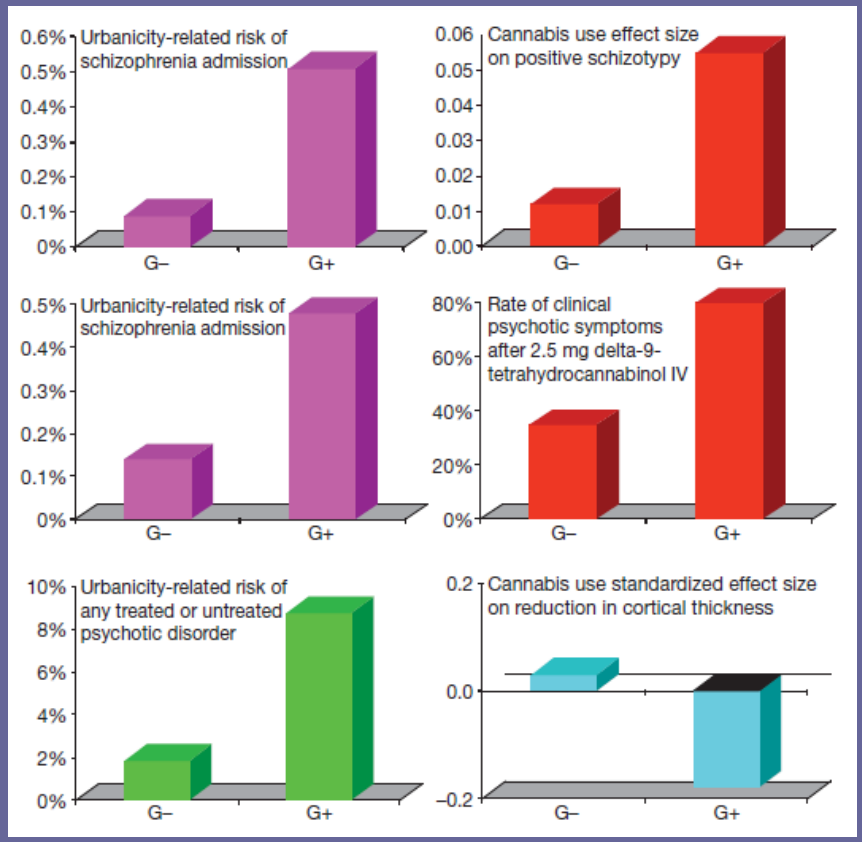


13% of individuals carrying the Val/Val genotype and using cannabis had schizophreniform disorder

Good idea to genotype yourself before flying to Amsterdam and „taking it easy”.

Other GxE mechanisms in schizophrenia”

- Prenatal infections and deprivation (Clarke et al., Am J Psychiatry, 2009.)
- Obstetric complications (Nicodemus et al., 2008. Molecular Psychiatry)
- Developmental trauma: abuse, bullying (Arsenault et al., Am J Psy, 2011)
- Urbanicity (Krabbendam and van Os, Sch Bull, 2005)
- Minority (immigrant) status (Pinto et al, 2008, Weiser et al, 2008)
- Cannabis and other psychotropic drugs
- Discrimination and stigma
- Family conflict – Expressed emotion (Kéri et al., Am J Med Gen 2008)



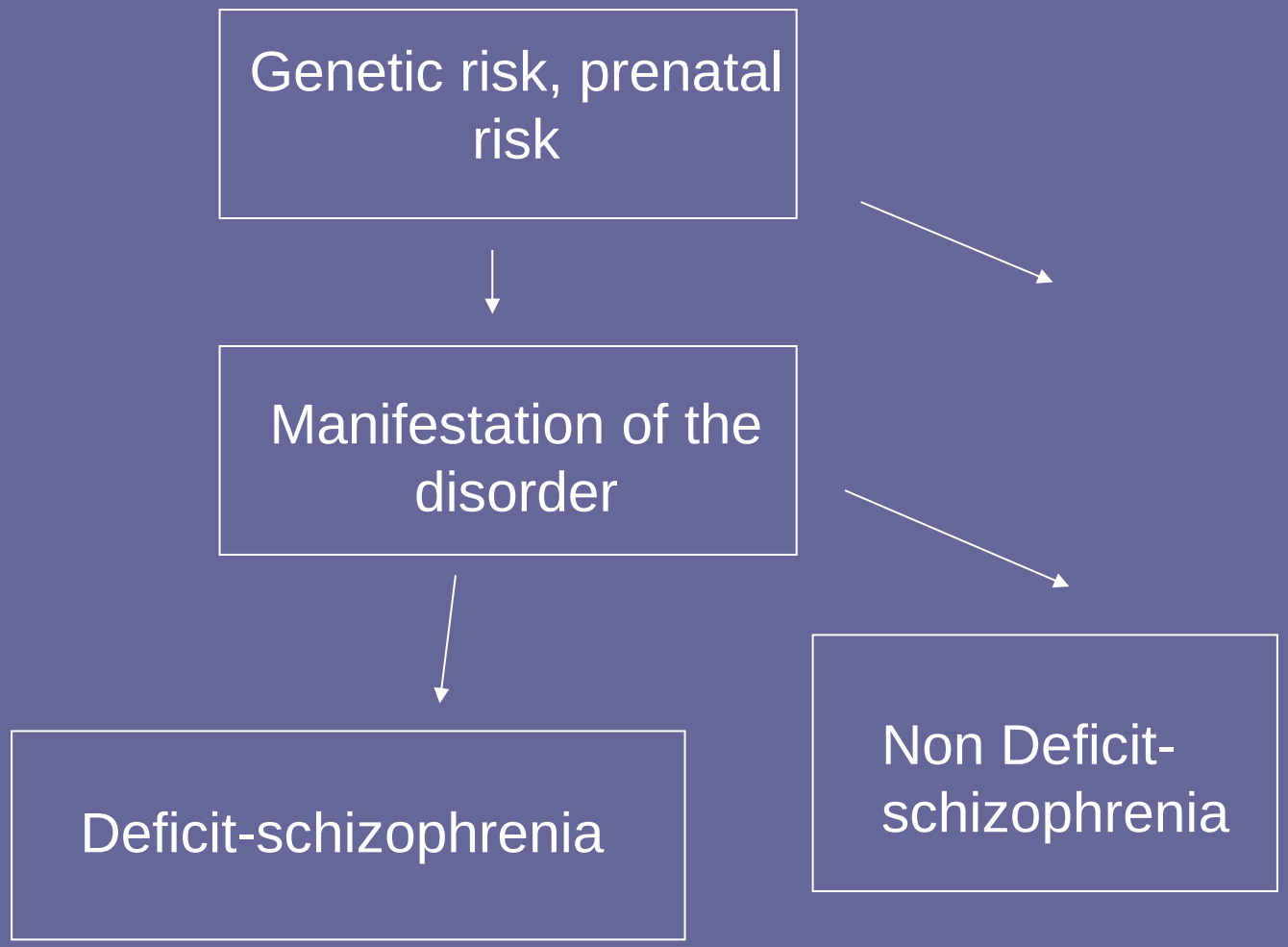
(van Os et al. Nature, 2010)

The „multiple-hit” neurobiological model of schizophrenia

„First hit”

„Second hit”

„Third hit”

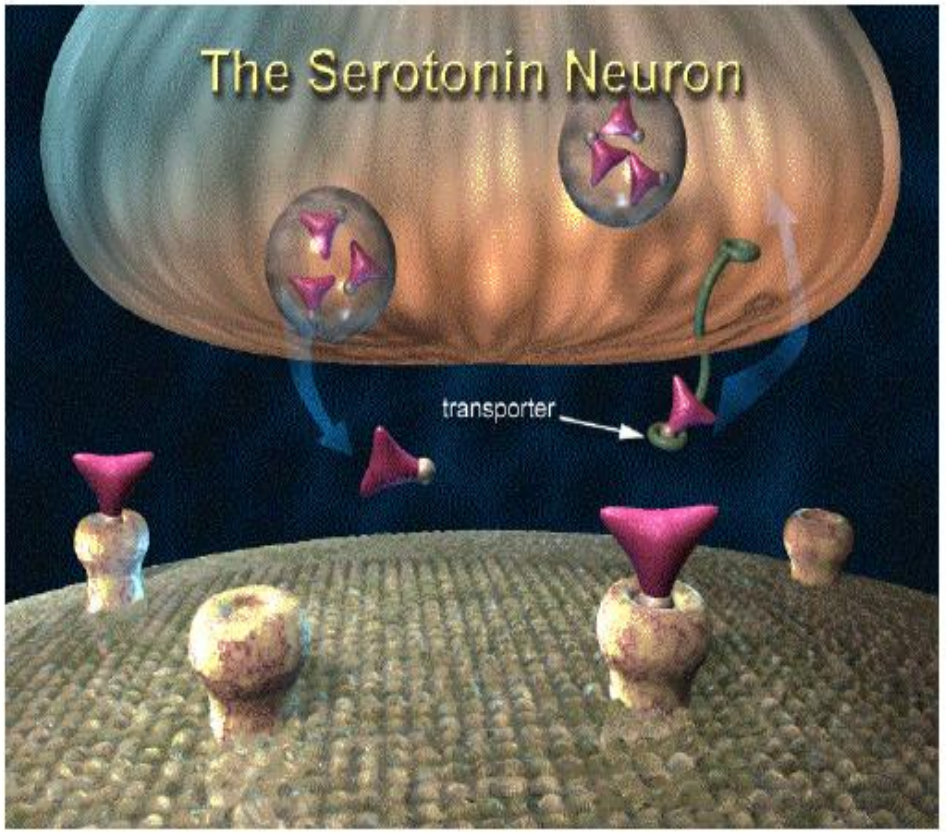


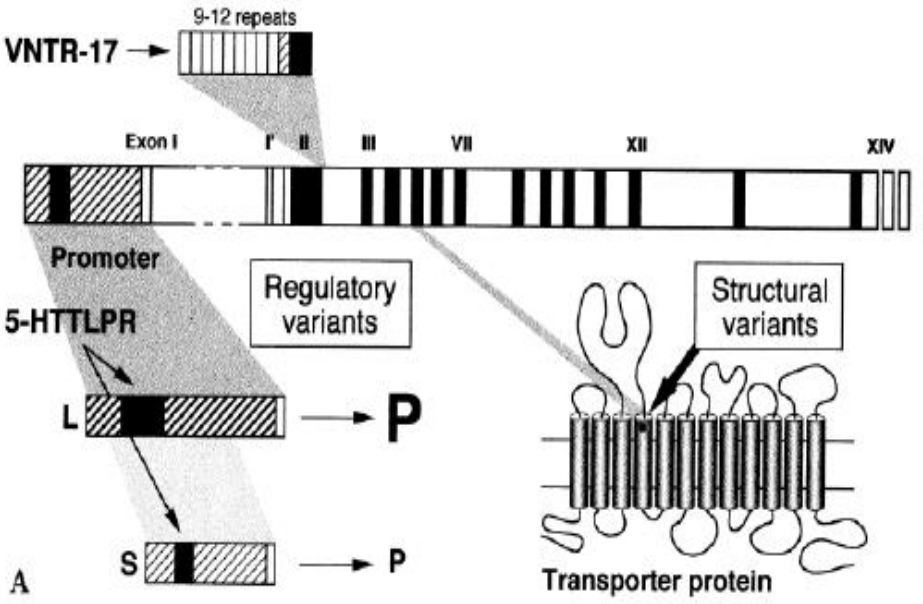
Risk factors for major depression (biological, psychological, environmental)

- Positive family history for mood disorders, anxiety, substance abuse, suicide
- Aging (elderly undertreated for depression!)
- Female gender (premenstrual changes, postpartum period, pre-menopause)
- Somatic disorders (cardiovascular disease, stroke, cancer, chronic pain, insomnia)
- Certain medications: corticosteroids, interferon treatment, cytostatics.
- Major life changes, transitions, stressful live events
- Childhood adversity, physical and sexual abuse, bullying
- Personality disorders, certain extreme personality traits (perfectionism, narcissism, generalized chronic anxiety)
- Lack of social support
- Low socioeconomic status

For review: Kopp and Réthelyi, 2004 and many others

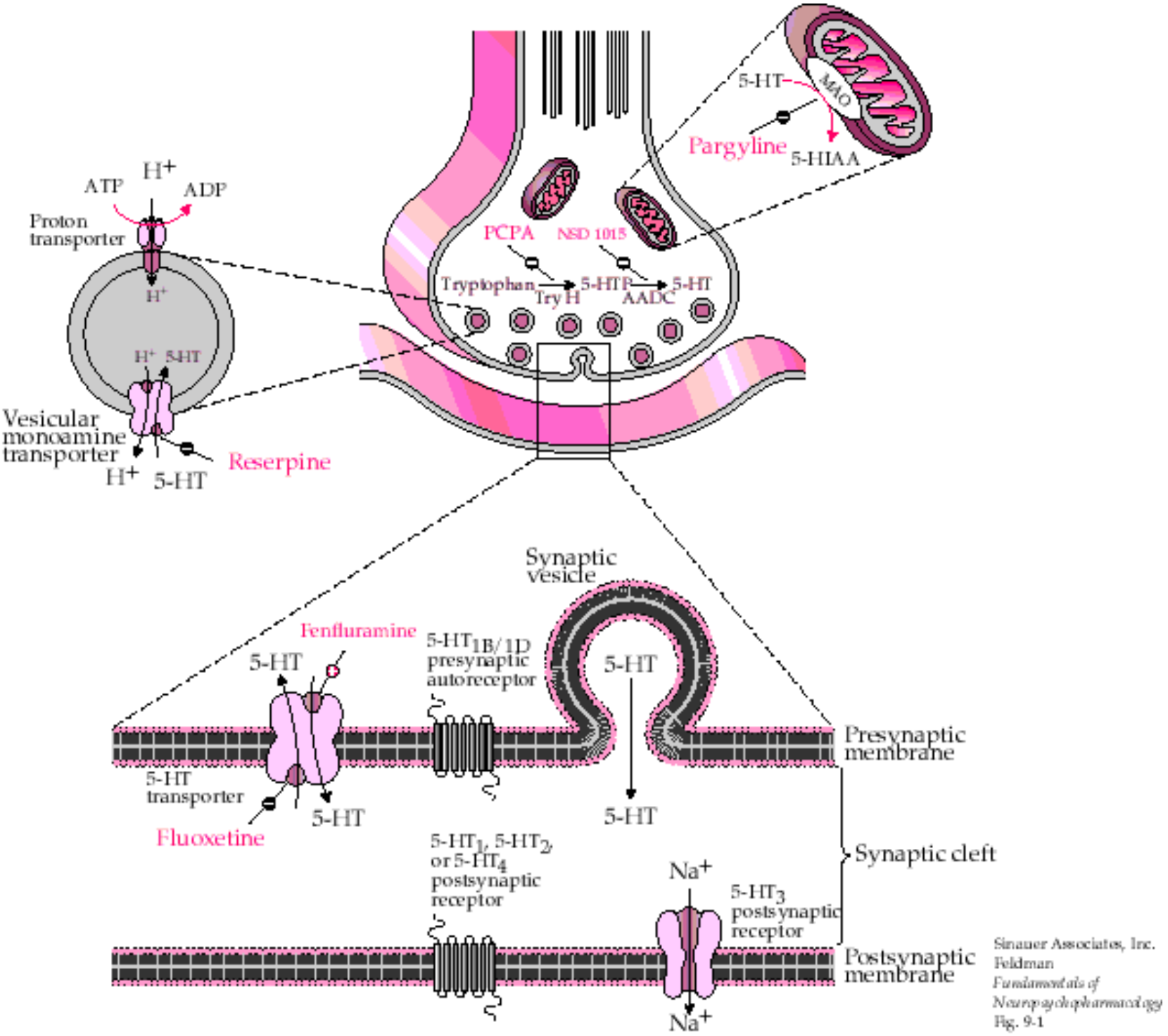
Serotonin transporter (SLC6A4, 5-HTT)





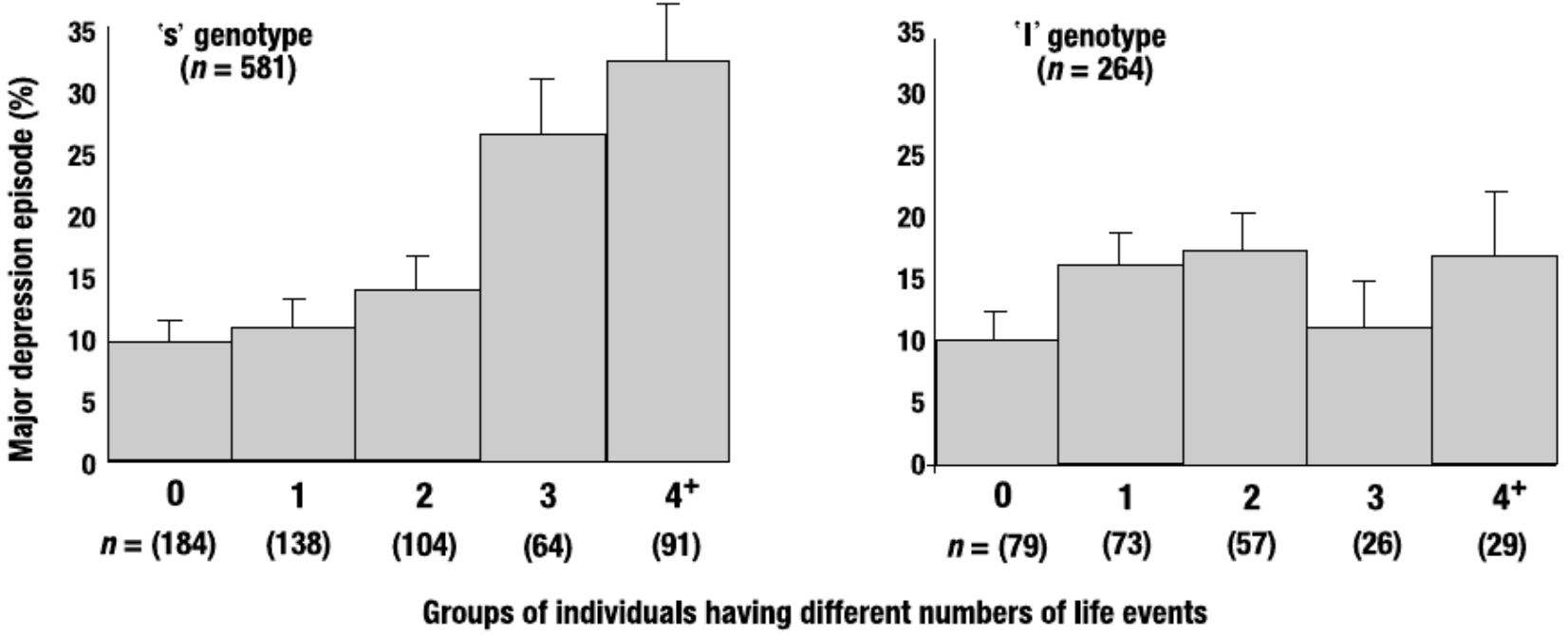
Lesch et al, 1998

- Location: 17q11.2
- Major regulatory element in the serotonin transmission and primary target of antidepressant (SSRI) medications
- 5-HTTLPR (5-HTT linked polymorphic region) – VNTR polymorphism
- S allele (14 repeats) -> reduced expression level and slower serotonin turnover
- L allele (16 repeats) -> normal expression level and serotonin turnover



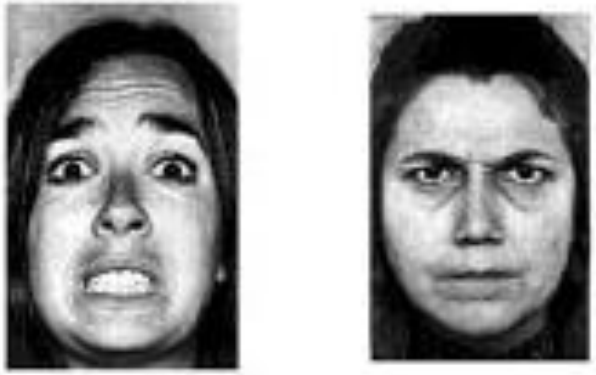
Sinauer Associates, Inc.
Feldman
Fundamentals of Neuropsychopharmacology
Fig. 9-1

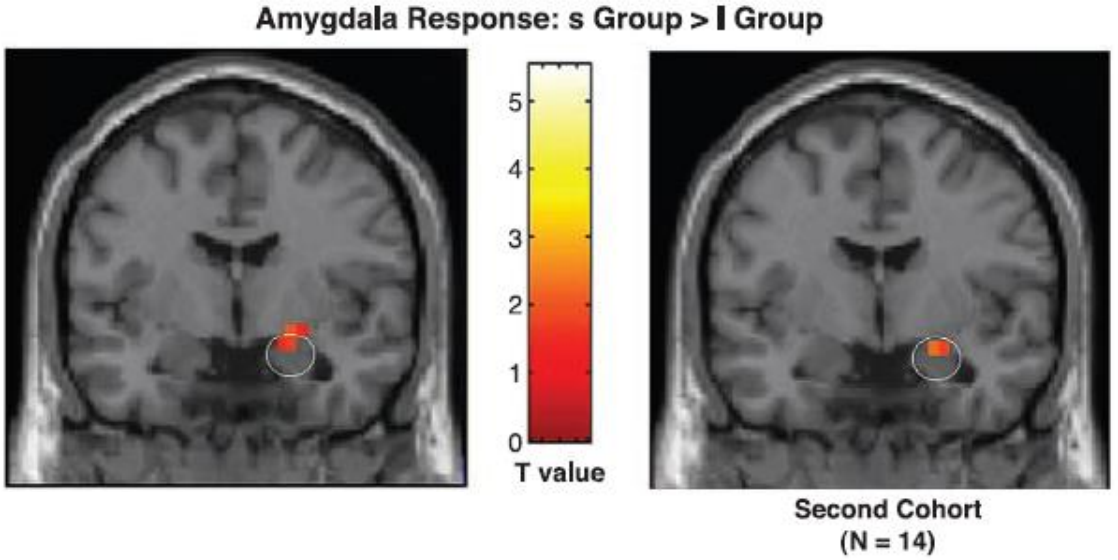
Influence of Life Stress on Depression: Moderation by 5-HTTLPR

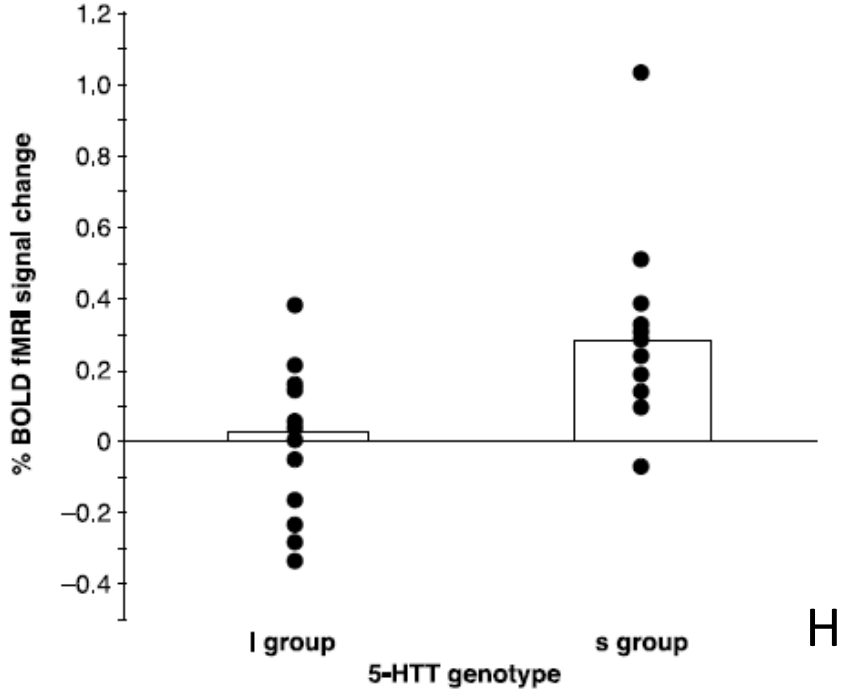


From: Caspi et al, 2003. Science

5HTTLPR genotype influences amygdala activation in response to fearful facial images



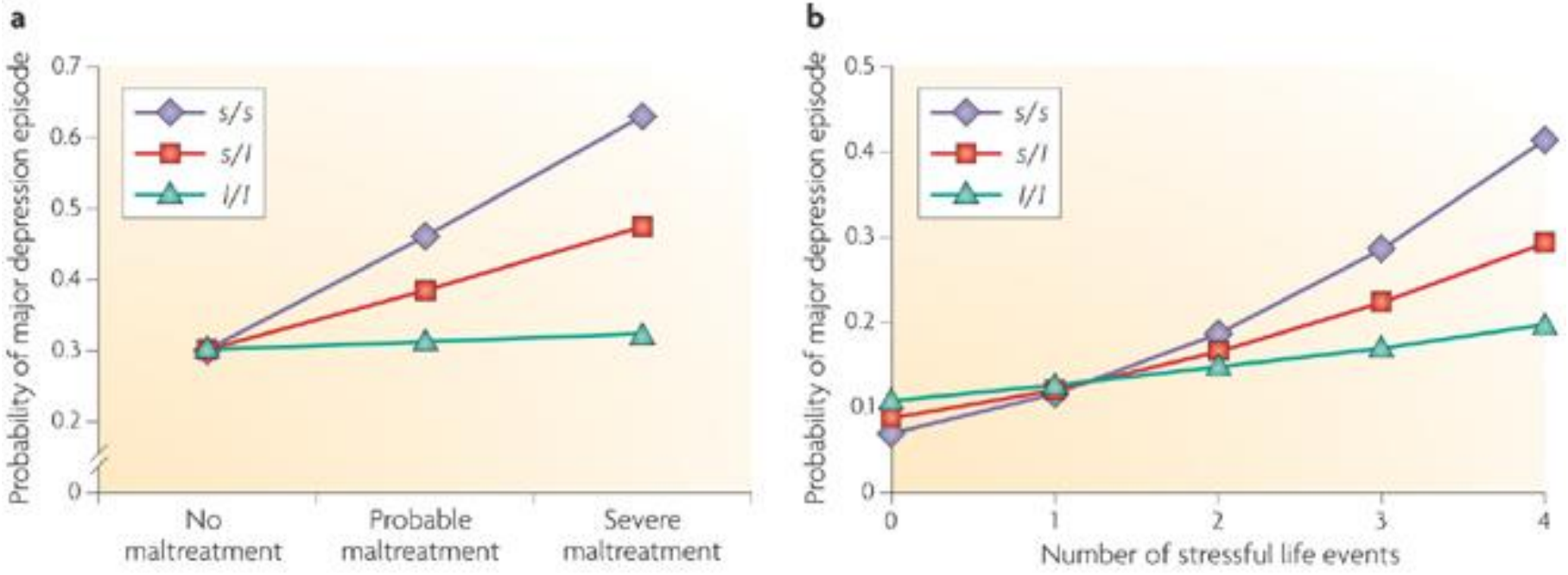




Hariri et al, Science, 2002.

Sounds good so far, but…

- Reanalysis of the original data, and new data from the 30 year follow-up study (Dunedin cohort)(Fergusson et al, 2012, Munafò et al., 2009, Risch et al, 2009) don't support the original interaction between 5-HTTLPR and stressful life events.
- The association remain significant in the case of childhood adversities.
- Never mind, this is the problem of researchers…

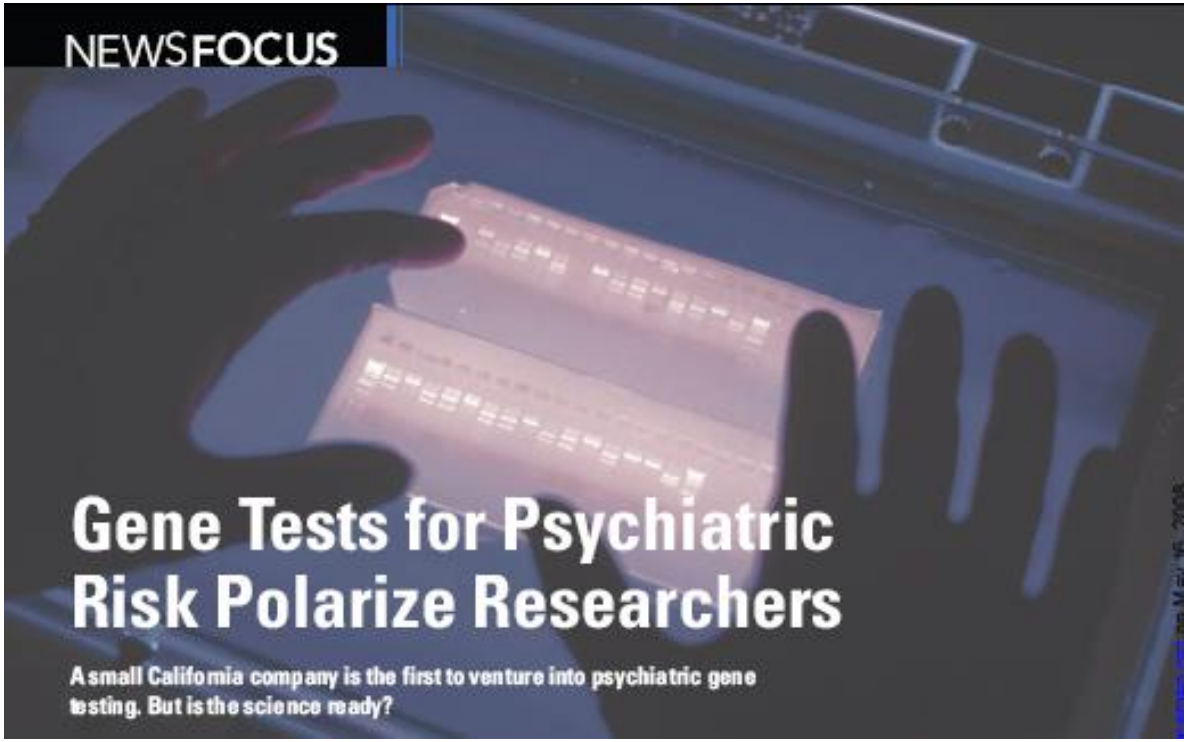


For review: Burmeister et al, 2008.

Nature Reviews | Genetics

Take-home messages

- Genetic and environmental factors are both extremely important in the etiology of psychiatric disorders.
- Schizophrenia: high heritability, demonstrated gene-environment interactions for urban upbringing, minority status and cannabis use.
- Major depression: moderate level of heritability, demonstrated interactions between 5-HTTLPR and stressful life events.
- Understanding gene-environment interactions is important for diagnostics and successful treatment.



SCIENCE VOL 319 18 JANUARY 2008

Critics of the scientific community: Current results don't support the use of genetical testing for diagnostic purposes.

Ethical problems!

Players in the Psychiatric Gene-Testing Business

Company	Test available	Disease	Type of test	Number of genes
NeuroMark	mid–2008	Major depression	Risk of suicidality from antidepressants	4
Psynomics	now	Bipolar disorder	Diagnosis and response to antidepressants	2*
SureGene	mid–2009	Schizophrenia	Risk of psychosis and response to antipsychotics	6

* Psynomics plans to add five more genes early this year.

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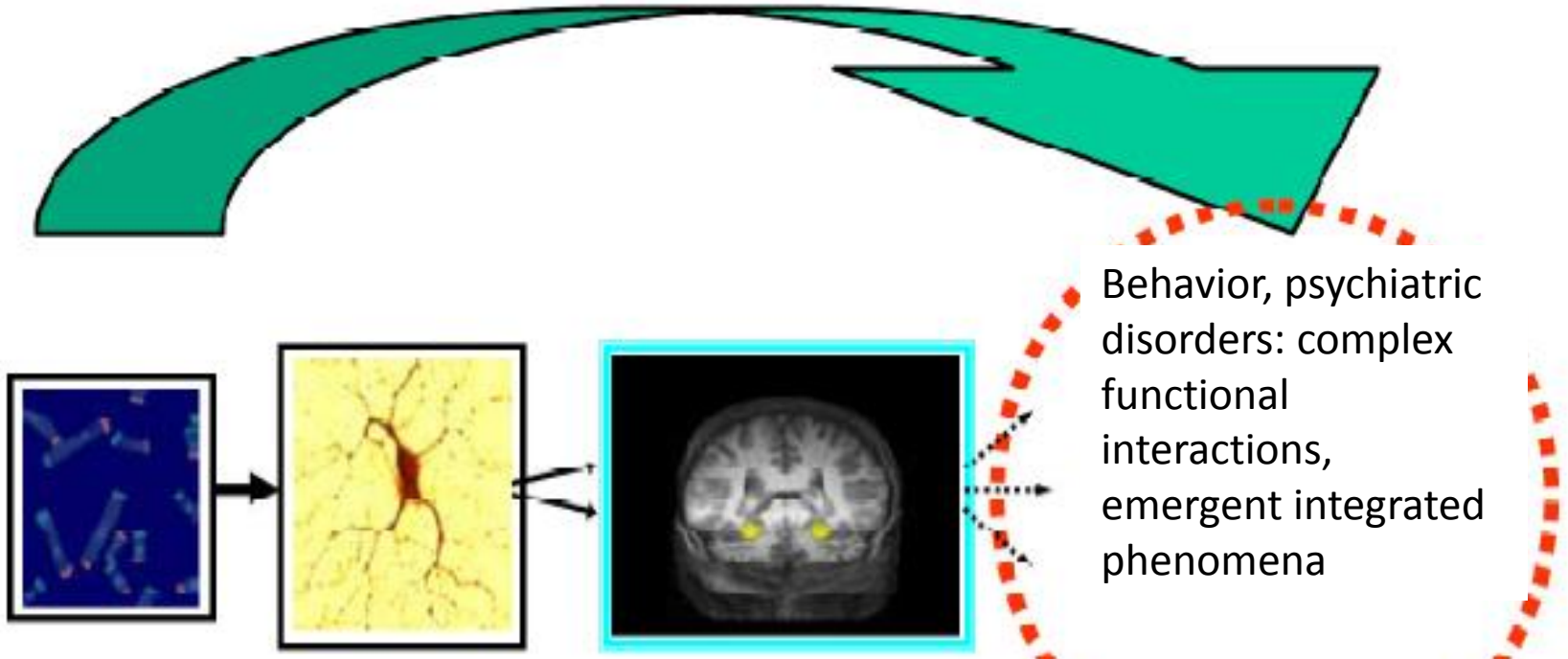
Scientific Resources and Principles

Physician Resources

Biological mechanisms giving rise to mental disorders



Behavior, psychiatric disorders: complex functional interactions, emergent integrated phenomena

Genes: many SNPs with small effect (polygenes) or rare variants (CNVs)

Neurons and neuronal circuitry: subtle structural and molecular alterations (gene expression)

Brain networks: reaction to internal and external stimuli

modified after Hariri et al, 2006.

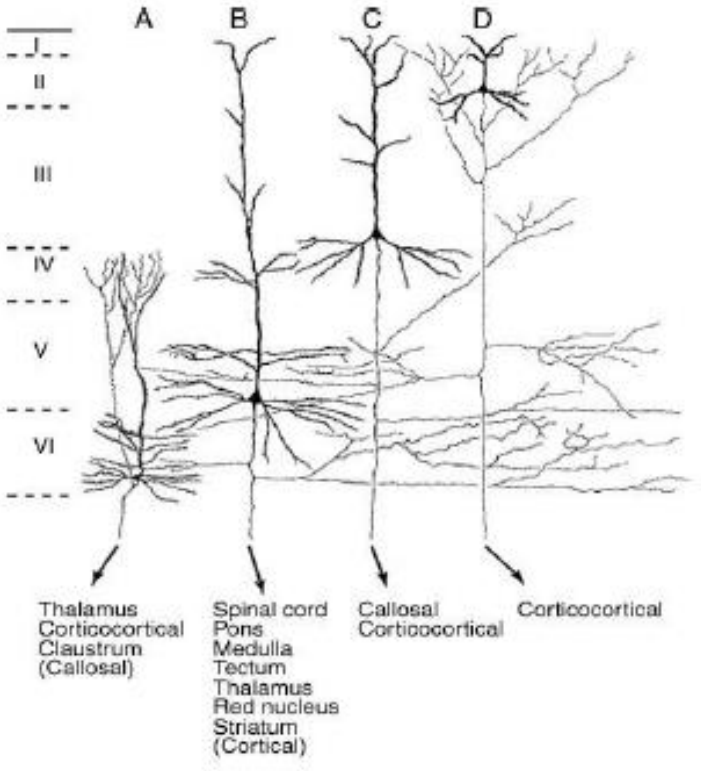
Basic neuroanatomy and neurophysiology

- Lobus, sulcus, gyrus

-Neuron, dendrite, synapse

-Neurotransmitter and receptor

-Postsynaptic and action potential



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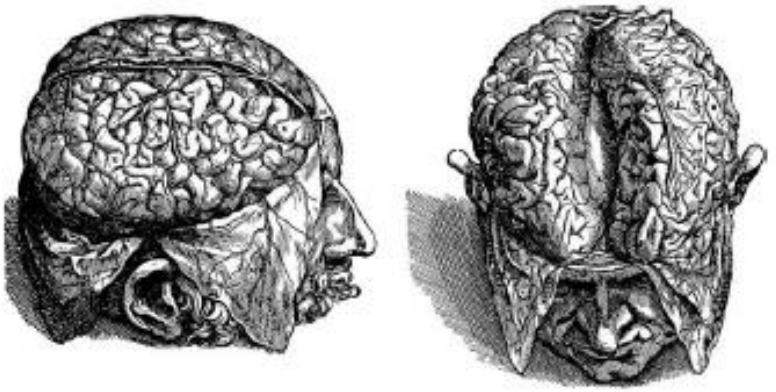

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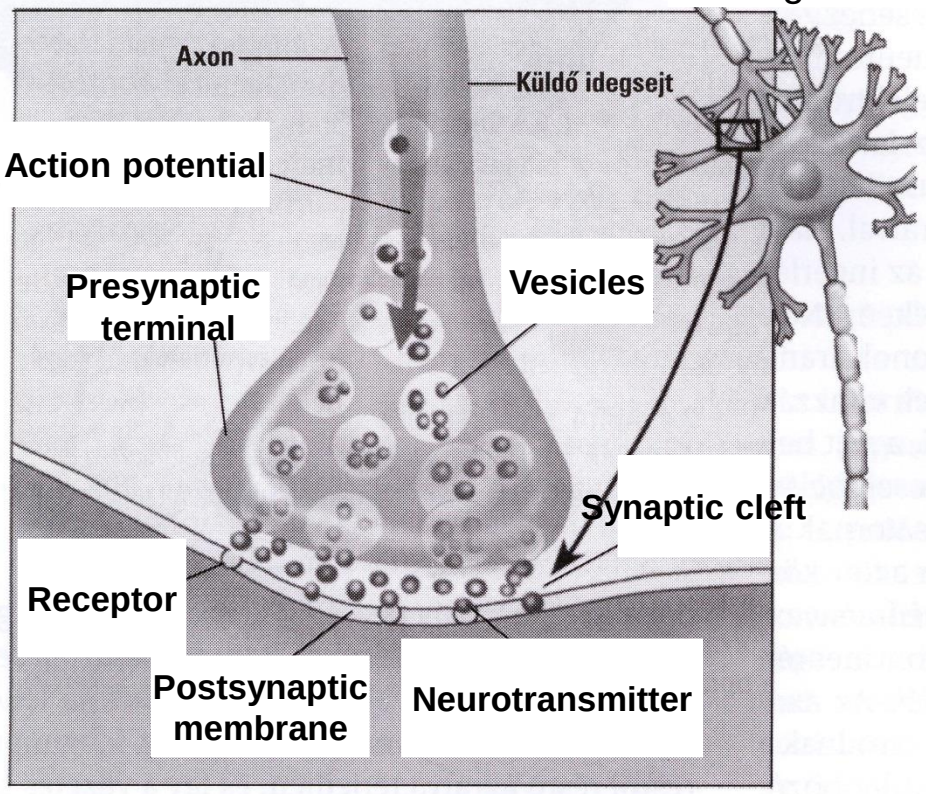
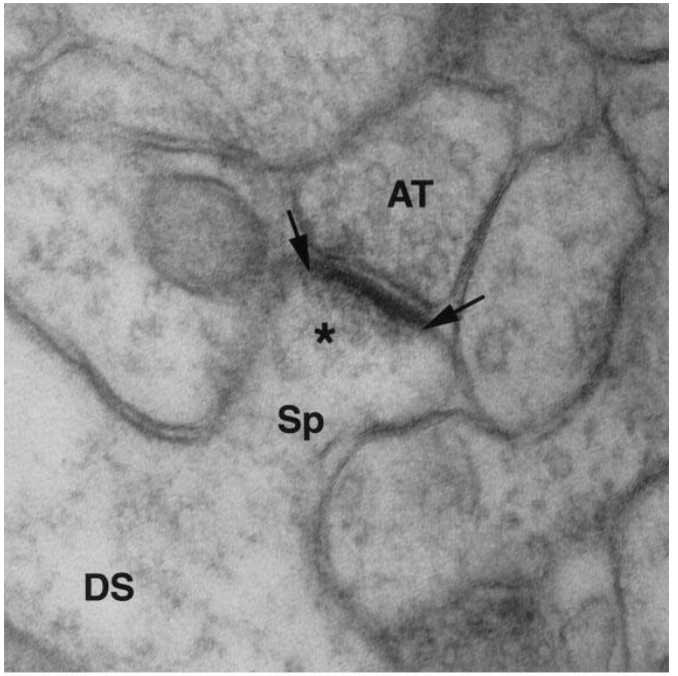
Sending neuron

Receiving neuron





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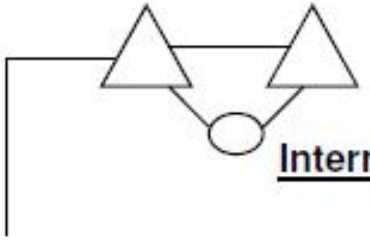
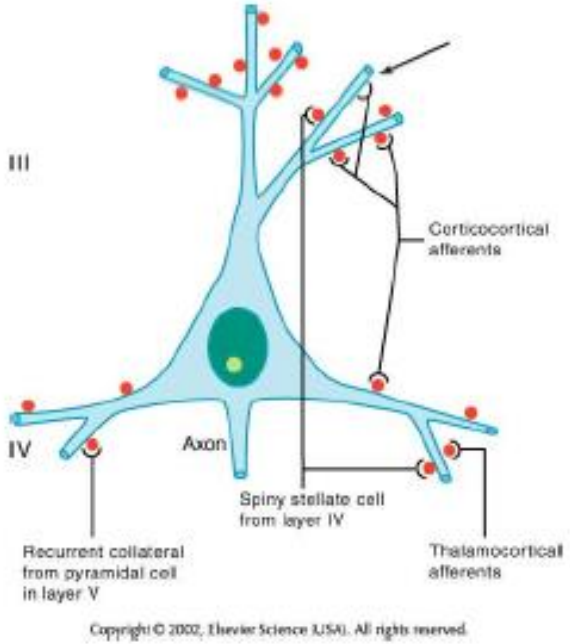
Basics of neurotransmission



Pyramidal neuron: glutamate, (excitatory)

Interneuron: Gamma-aminobutyricacid (GABA), (inhibitory)

Modulatory pathways from the brain-stem: dopamine, serotonin (5-HT), noradrenalin, from the basal forbrain: acetyl-cholin



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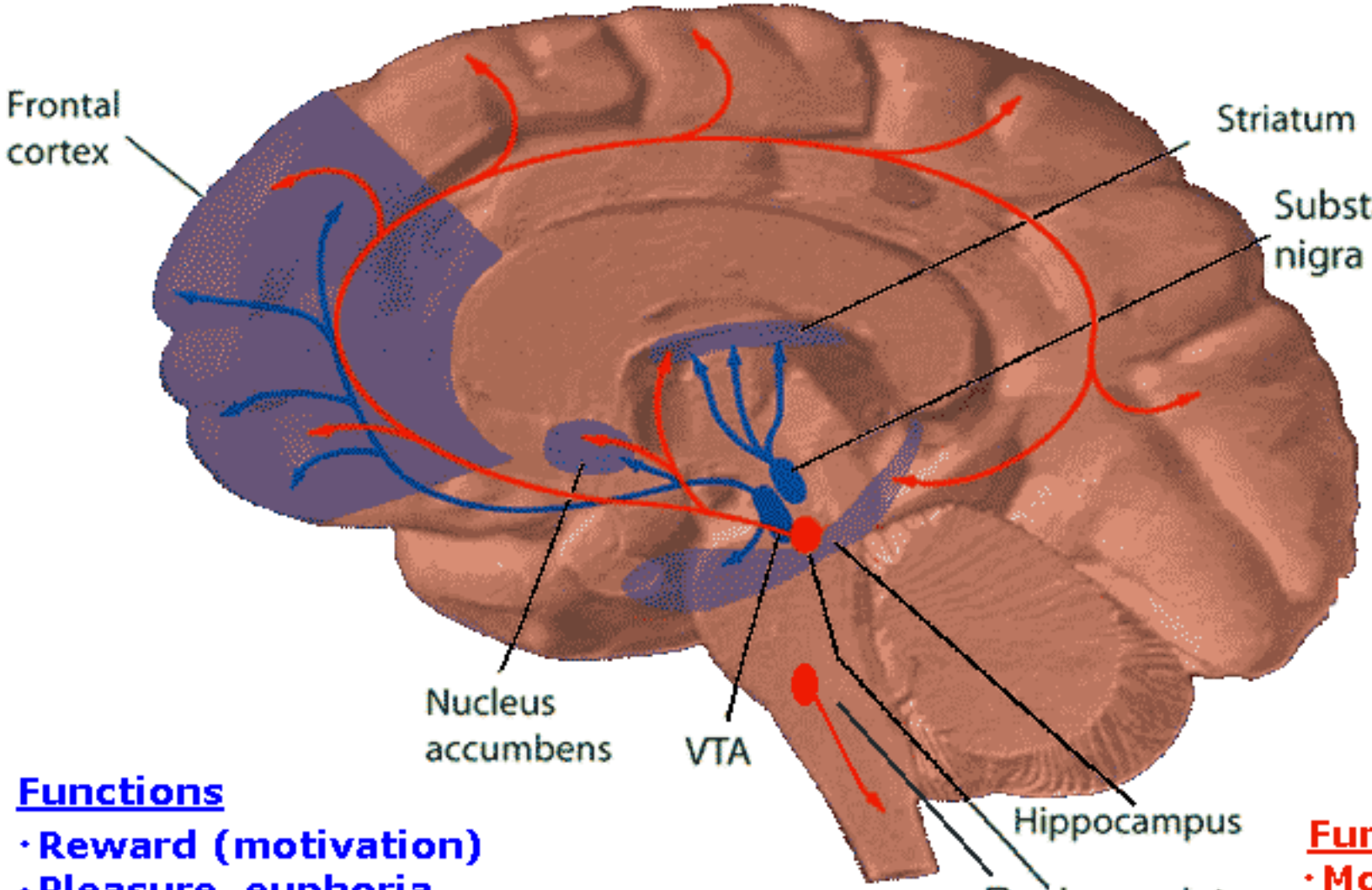
Chandelier neuron:
synchronisation of pyramidal neurons, GAD67 (glutamate decarboxylase), GABA synthesis

Dopamine Pathways

Serotonin Pathways



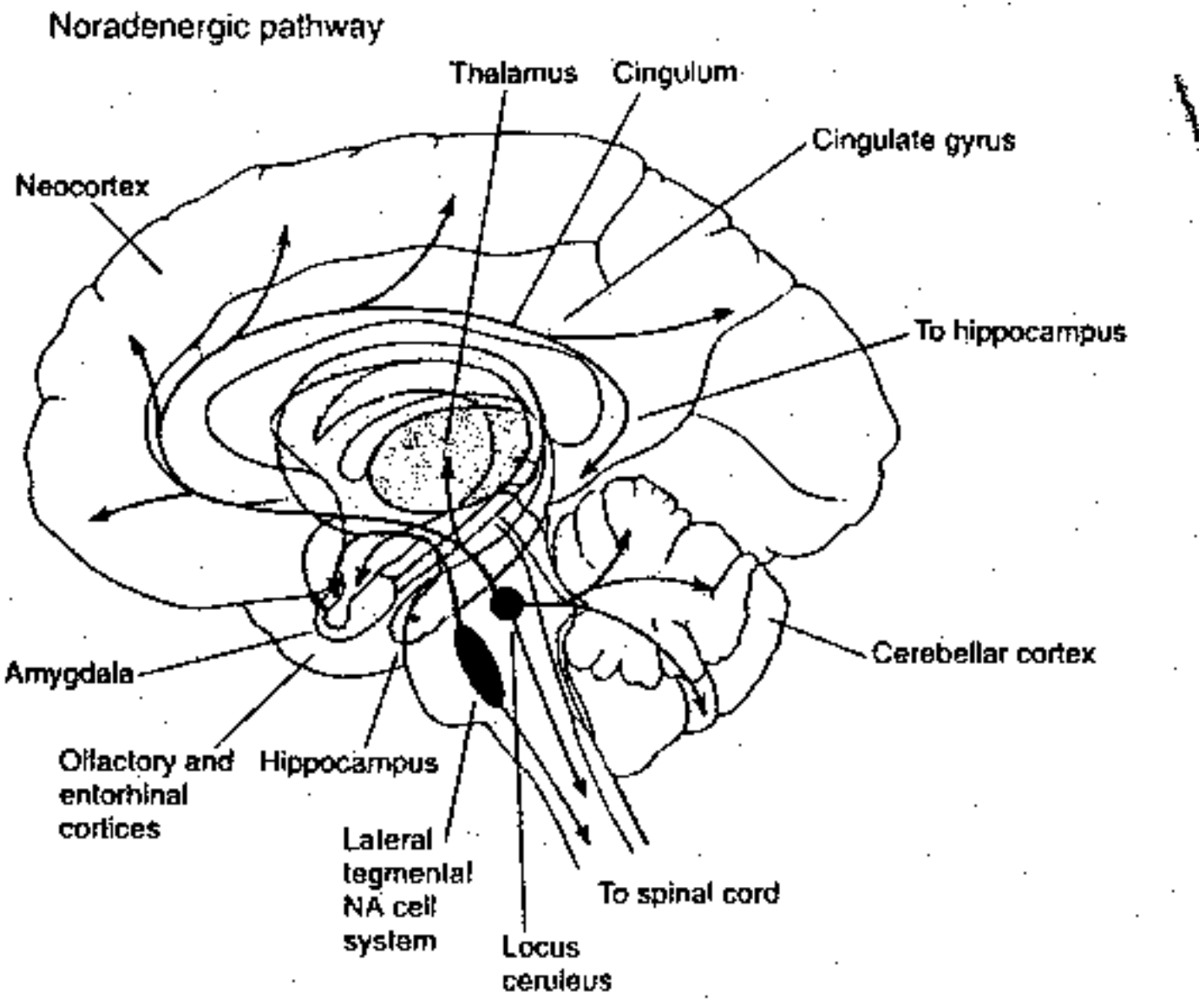
Functions

- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

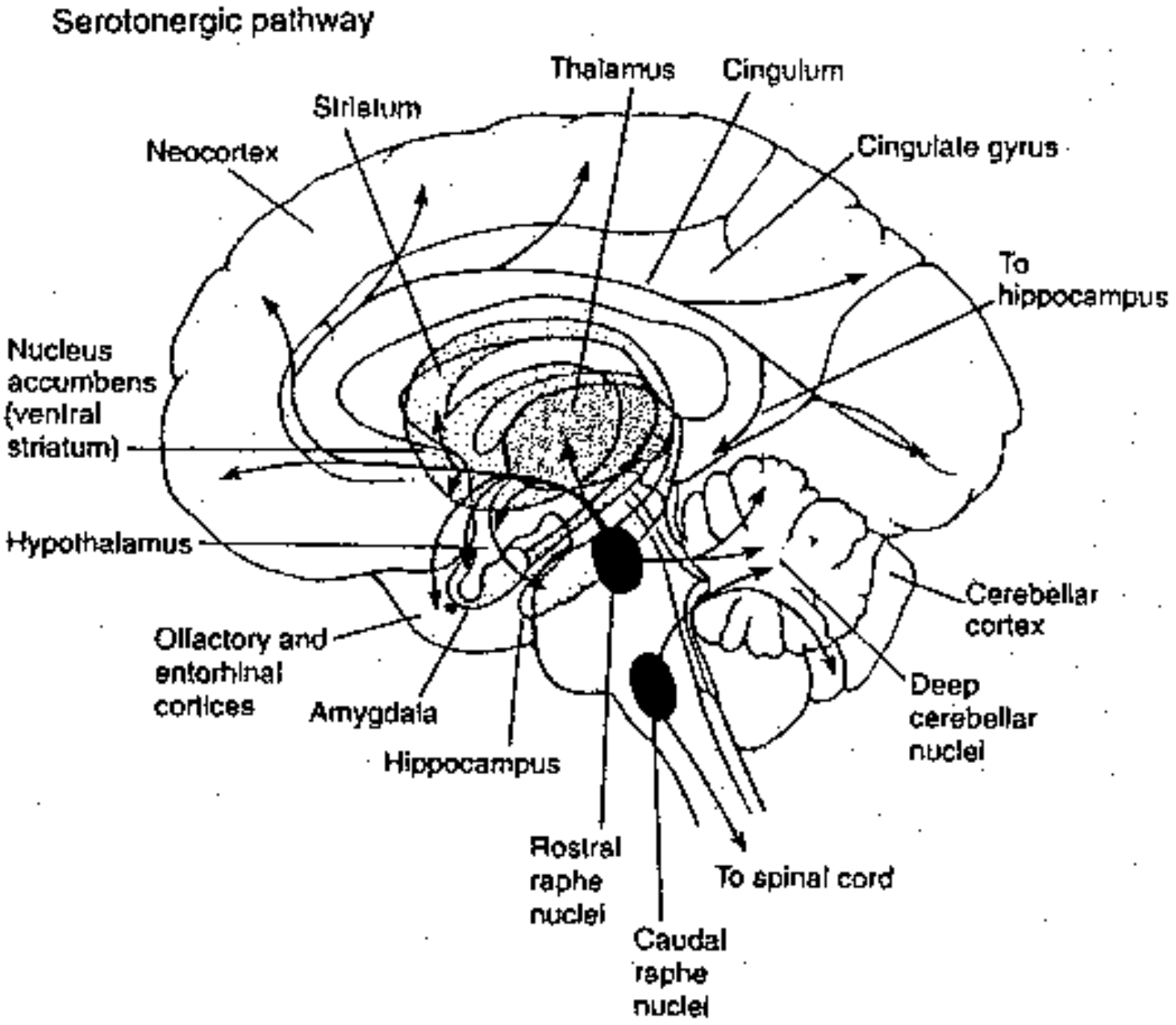
Functions

- Mood
- Memory processing
- Sleep
- Cognition

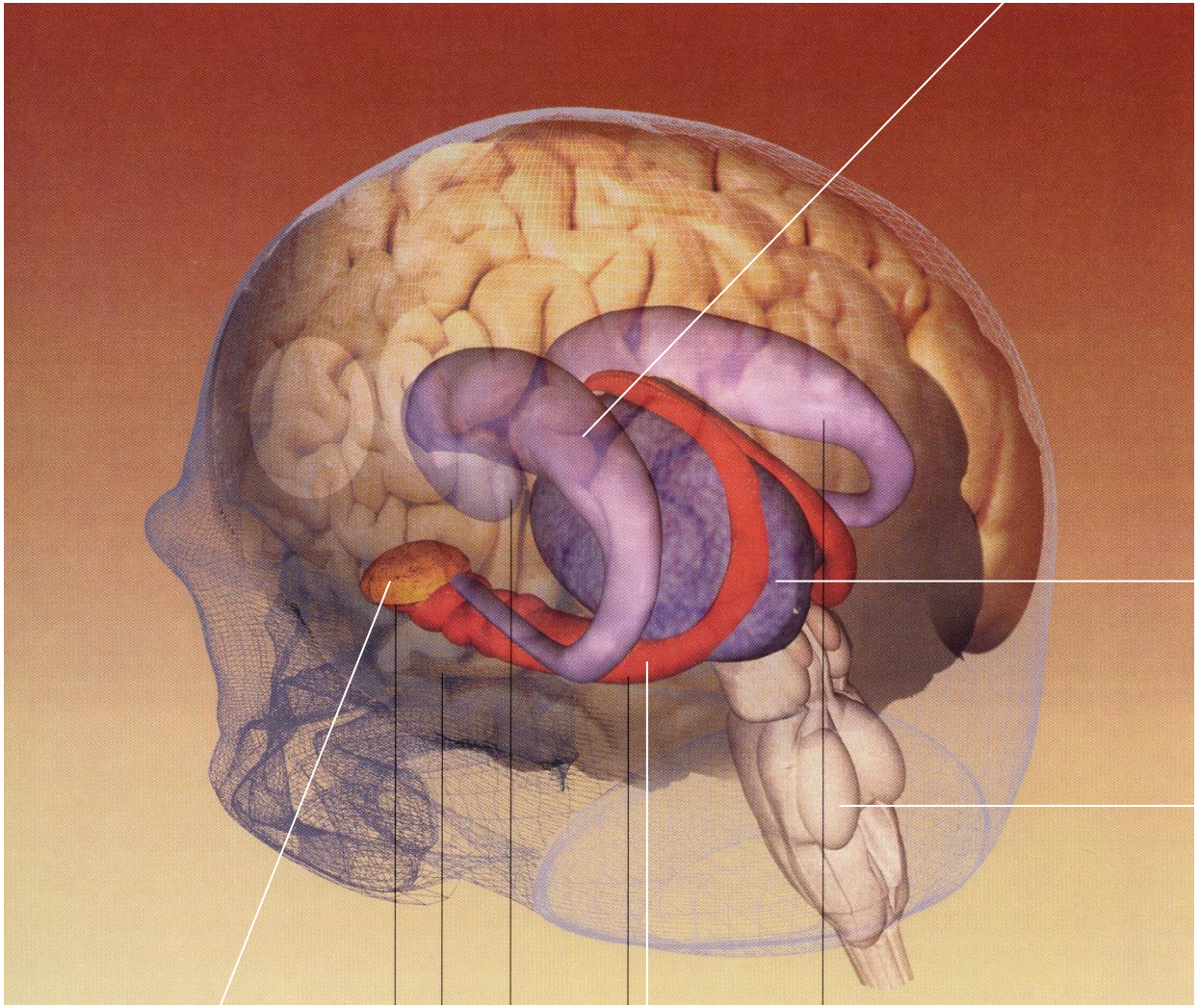
Noradrenergic pathways



Serotonergic pathways



basal ganglia



thalamus

brainstem

amygdala

hippocampus

Limbic system

Frontal lobe:

- Dorsolateral part: higher cognition, working memory, executive function
- Ventromedial part: emotional and social functions
- Cingular cortex: cognitive and affective integration
- **Schizophrenia, affective disorders**

Basal ganglia:

- Movement regulation
- Skill and habit learning (feedback and reward)
- Ventral striatum (n. accumbens) – reward (dopamine)
- **Parkinson`s disease, addictions**

Amygdala:

- Emotion, fear, anxiety
- **Depression, anxiety disorders**

Hippocampus:

- Remembering facts and events (explicit memory), spatial information, synthesis of information
- **Alzheimer`s disease, depression, schizophrenia**

Psychiatric examination (Mental status examination)

- Medical discussion
- Exploration: Aimed questions, psychopathological assessment and evaluation of behavior
- Establishment of patient-doctor relationship (psychotherapy)
- Syndromatolgical diagnosis

- Additional information: Internal medicine and neurological examination, heteroanamnesis, laboratory tests, other examinations (X-ray, EEG, brain imaging), psychological tests
- Nosological diagnosis – differential diagnosis

Elements of the mental status examination

- Circumstances of admission (complaints, symptoms, with whom, police, ambulance, voluntary or involuntary)
- Cross-sectional psychopathological symptoms
- Longitudinal course of symptoms
- Previous psychiatric treatment: ambulatory / hospitalization
- Suicide and aggression risk assessment
- Pharmacological history
- Somatic history
- Family history
- Addictions (alcohol, drug, behavior)
- Premorbid personality

Domains of the Mental state and most important symptoms

- Consciousness: drowsy, sopor, coma, integrated, delirious
- Orientation: oriented vs. disoriented in place and time
- Attention and concentration: focused, hypo- and hypervigility
- Perception: Hallucinations (acoustic, visual, olfactory, tactile, imperative, commenting, Ekbom-syndrome)
- Memory: short term memory impairment, Korsakoff-syndrome
- Intellectual capabilities: IQ, menta retardation
- Formal thought disorder: derailment, flight of ideas, pressured speech
- Delusion, obsessions, phobias: paranoid, grandiosity, delusion of reference
- Mood: euthymic, dysthymia, irritated, hyperthymic, elation
- Motivations, psychomotor functions: hypo- or hyperbulia
- Suicidal risk
- Insight and cooperation

Psychiatric evaluation, file, case report

1. Personal data
2. Circumstances of admission, present complaints
3. History: somatic, psychiatric, family, pharmacological, addictions
4. Biographical information, education, work, life circumstances
5. Exploration
6. Status: internal, neurologic, psychiatric
7. Diagnosis: ICD and DSM-IV (or DSM-5)
8. Differential diagnosis
9. Summary
10. Plan of examination and therapy

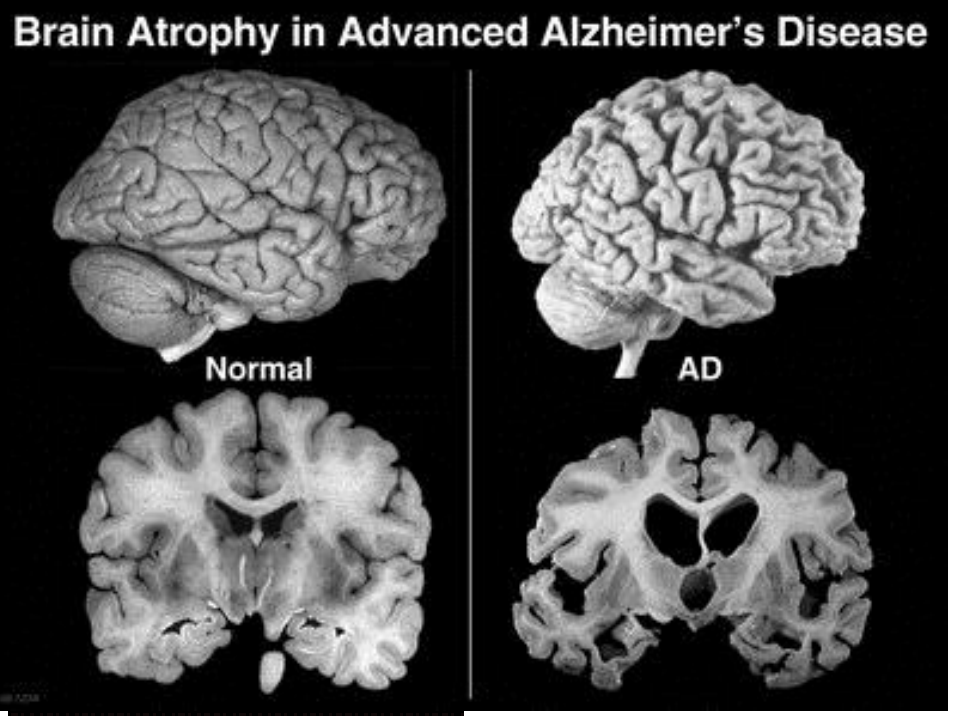
Laboratory examinations

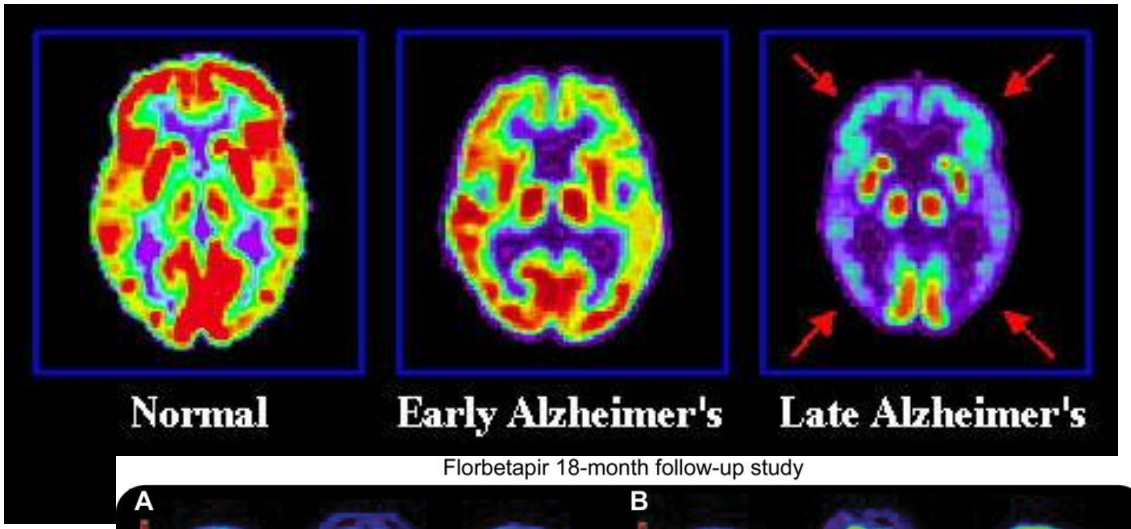
1. Routine laboratory examinations
2. Endocrinological examinations (thyroid function, prolactin)
3. Ammonia – in case of hepatic encephalopathy
4. Psychoactive drug test: urine analysis
5. Intravenous drug users: Hepatitis (HbsAg, HCV), HIV
6. Young women of childbearing age: Pregnancy test
7. Patients with dementia: neurosyphilis examination (LP), Vit. B12 vit., TSH.
8. Serum levels of psychopharmacons: lithium, valproic acid, carbamazepin
9. Side effects of psychopharmacons: clozapin – agranulocytosis, atypical antipsychotics – metabolic parameters.
10. Autoimmune encephalitis: anti-NMDA-receptor antibodies.
11. Genetic examinations: Huntington-chorea, familial Alzheimer disorders, Creutzfeld-Jakob (Prion Protein Gene), Fragile-X syndrome, Wilson-disease (coeruloplasmin!).

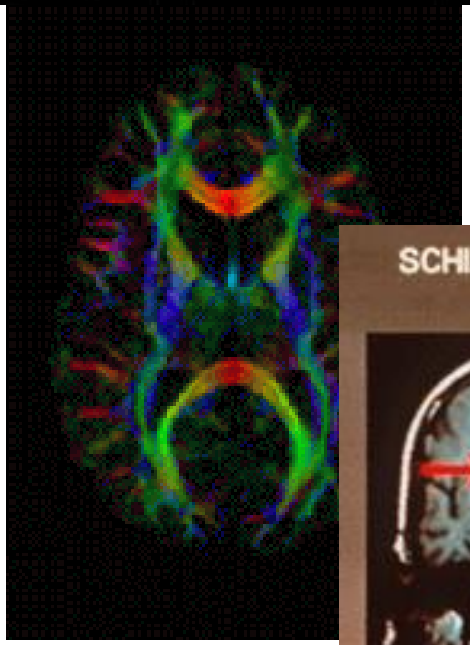
Brain imaging techniques

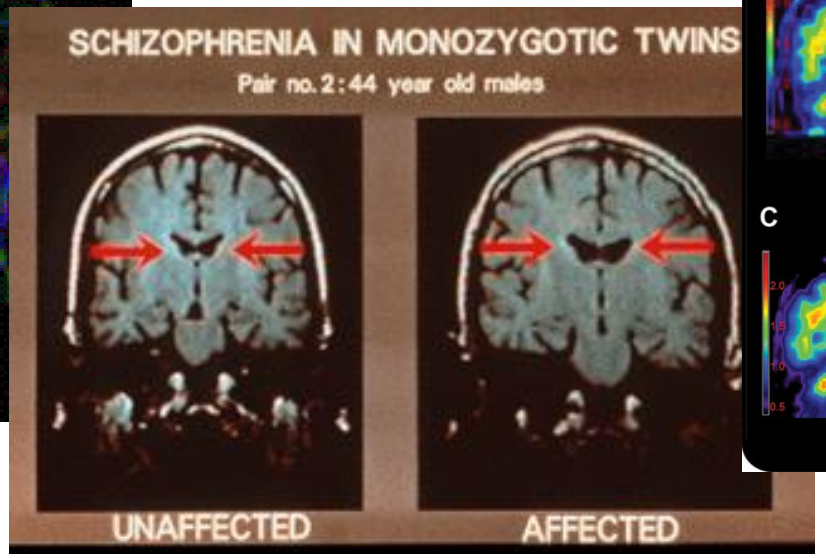
- Structural brain imaging:
  - Computer tomography (CT): first examination in acute conditions like delirium, catatonic stupor, exclusion of acute stroke and brain tumors. Should be done in all cases of first episode psychosis, and mood disorders above age 50.
  - Magnetic Resonance Imaging (MRI): subcortical dementias, brain stem lesions, demyelinisation

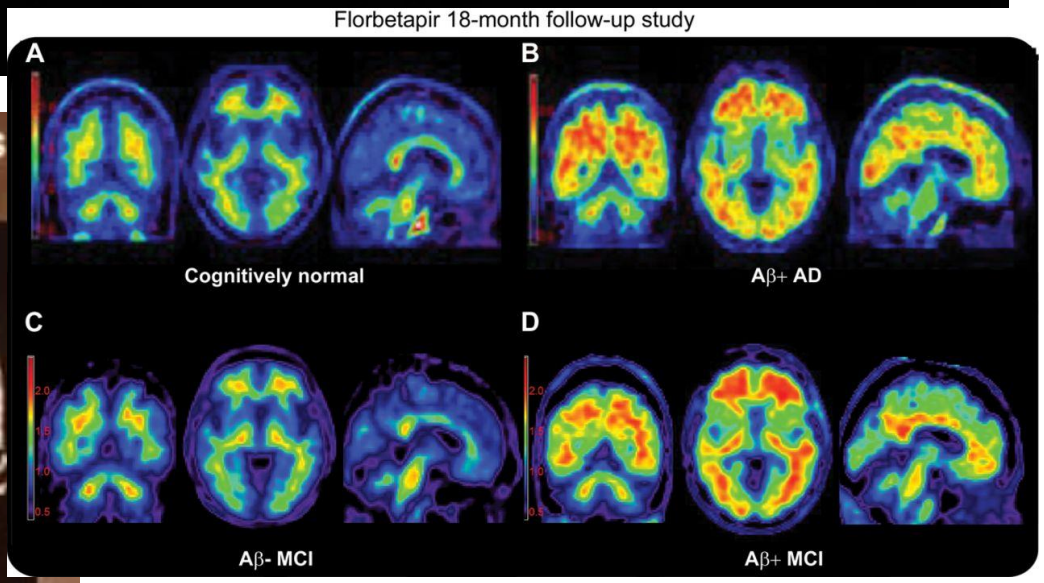
- Functional brain imaging: - predominantly research purposes
  - PET (Positron Emission Tomography): Metabolic processes (glucose uptake), receptor binding using radioligands
  - fMRI: blood-flow (BOLD signal), resting state and task-related haemodynamic changes
  - DTI: Diffusion Tensor Imaging – white matter connectivity.











Források: www.nia.nih.gov, www.neurology.org, www.allinfodir.com

Thank you for your attention!

Questions?

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