Development of the Nervous System HS2017

BIO 344/376-1305-00

Neurodevelopmental Diseases

Esther Stoeckli

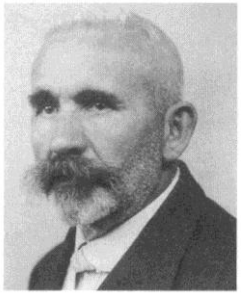
The prevalence of mental disorders in the US

Major depression	5.3 %
Posttraumatic stress disorder	3.6 %
OCD (obsessive, compulsive disorder)	2.4 %
Panic disorders	1.6%
Schizophrenia	1.3 %
Bipolar disorder	1.1 %
Autism Spectrum Disorders	0.1-0.2 %
Anorexia nervosa	0.1 %

Hyman, Neuron 28 (2000) 321-323

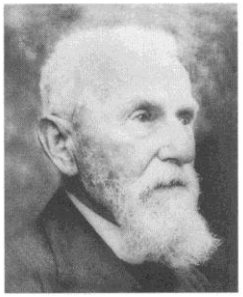
Schizophrenia

Emil Kraepelin
Dementia Praecox, 1919



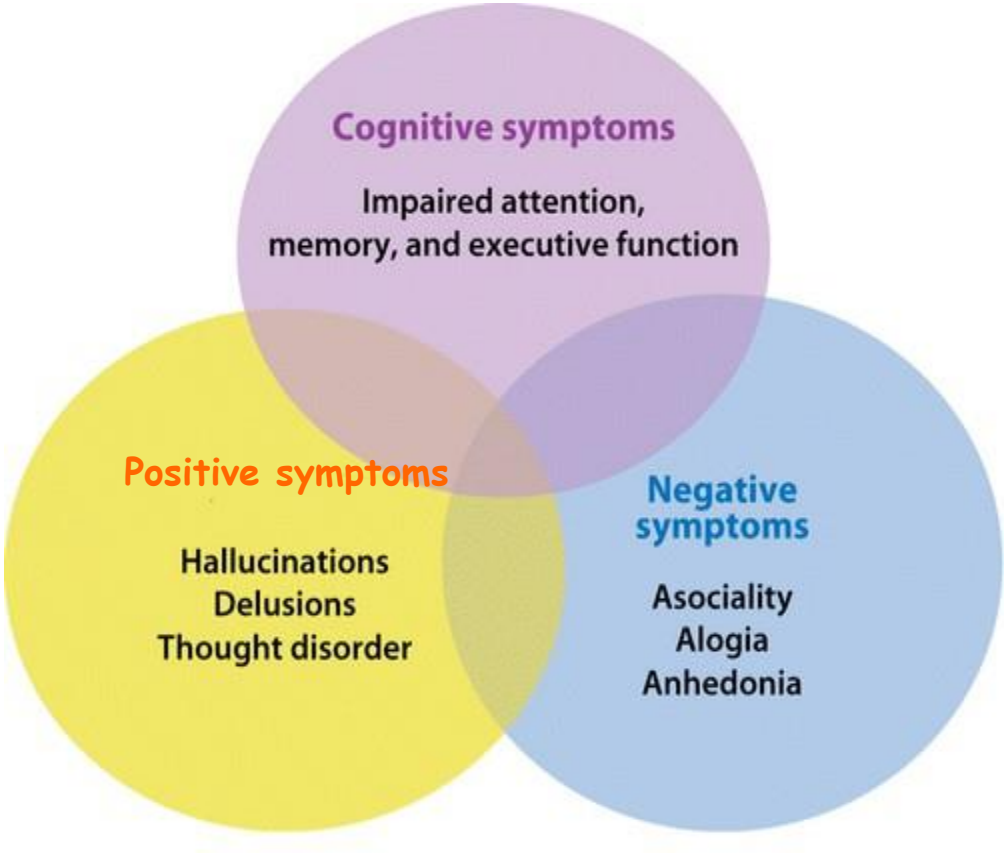
Emil Kraepelin
(1856–1926)

Eugen Bleuler
Schizophrenia, 1911



Eugen Bleuler
(1857–1939)

Schizophrenia is a brain disorder that is characterized by abnormal mental functions and (resulting) disturbed behavior



Ibrahim and Tamminga, Annu Rev Pharmacol Toxicol 51(2011)189-209

Disturbances in basic **cognitive functions**

attention
executive functions
specific forms of memory

deficits in memory, especially working memory

In addition many patients have concomitant mood symptoms including depression and anxiety

Vulnerability to schizophrenia is clearly related to genetic factors

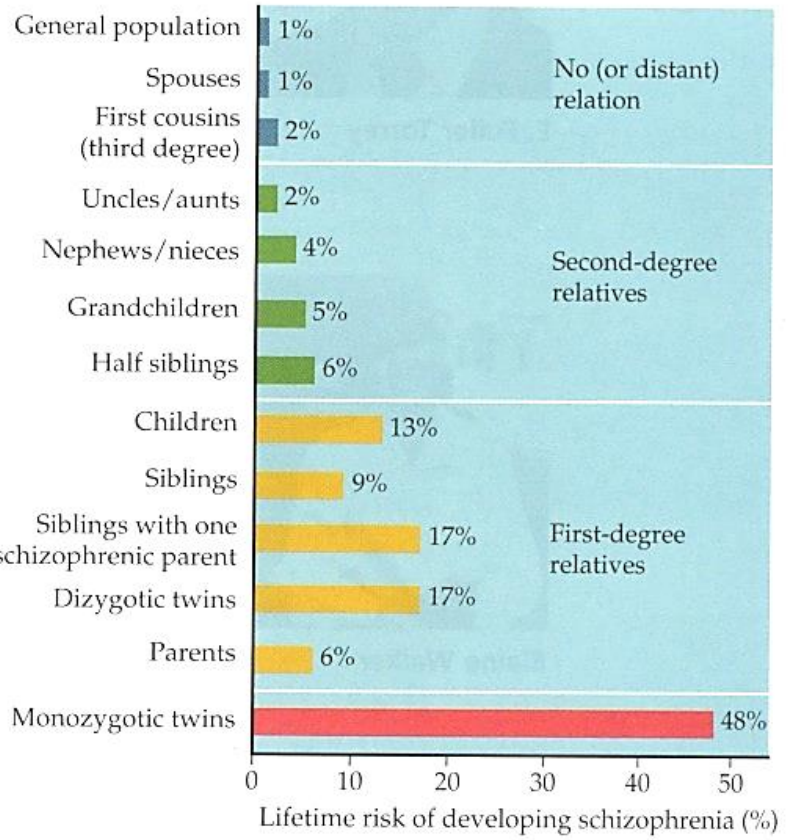
based on evidence from family, twin, and adoption studies

lifetime risk

1% in general population

50% in monozygotic twins
~17% in dizygotic twins

the closer one is genetically linked to someone, the higher the probability of also developing schizophrenia



from Rosenzweig, Breedlove, Watson, 2005

Genetics alone cannot explain the occurrence of schizophrenia, there must be 'environmental' factors!

identified 'environmental' risk factors:

environment already starts before born:

viral infection during fetal development

exposure to toxic, traumatic, or autoimmune insults

(genetic incompabilities of the immune systems or also effects severely affecting the mother)

poor maternal nutrition

(e.g. during a famine when food not abundant)

problems during gestation (e.g. problems during labor/birth)

schizophrenia is multigenetic and multifactorial - many things also foiund in the population but not all together

Schizophrenia can be associated with physical changes in the brain.

identified hallmarks:

- enlarged ventricles in schizophrenic sibling
  indicating shrinkage of the brain tissue

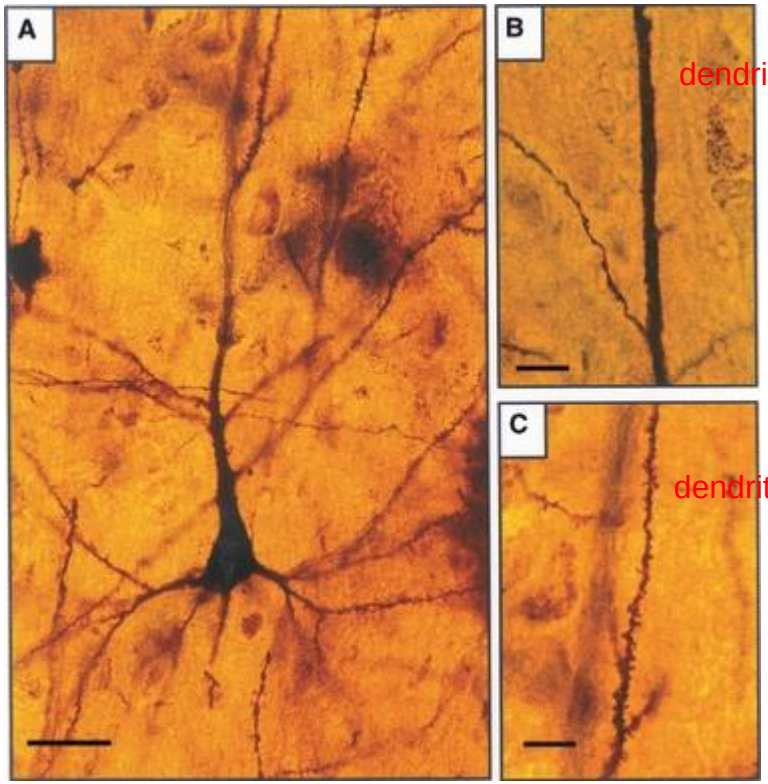
- reduced size of hippocampus and amygdala

- changes in fine structure and function of cortical connections
  dopamine and glutamate transmission

those things on their own are not sufficient to identify schizophrenia

but obviously they are not useful for diagnosis

Spine density on apical dendrites of pyramidal cells is reduced in schizophrenic patients



dendrite, anormal

SCZ patient

dendrite, normal

normal brain

control

Garey, J. Anatomy, 2006

too much dopamine leads to excitotoxicty, destroying the cell in the end

Dopamine hypothesis

Antipsychotic drugs that act on D_2 receptors are effective in some patients

consistent with the hypothesis that positive symptoms of schizophrenia are due to an excess of DA signaling in the striatal and/or mesolimbic areas of the brain

DA excess in D_1 receptors
DA deficit in D_2 receptors

however

negative symptoms are thought to be due to deficits in DA signaling in the prefrontal cortex probably mediated by D_1 receptors

In addition to the dopamine system, there is a lot of evidence for a contribution of the glutamate system

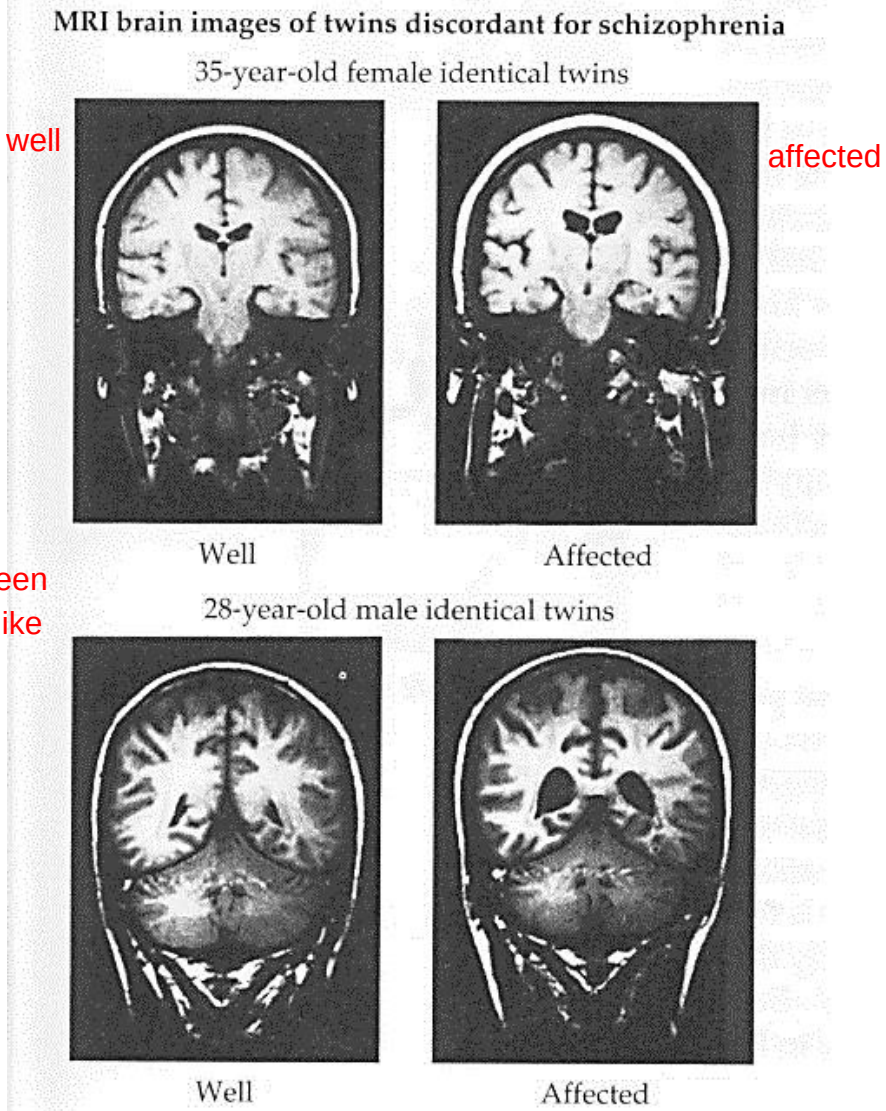
NMDAR hypofunction hypothesis

morphological changes in SCZ patients' brains

evidence that NMDA agonists/antagonists affect symptoms/cause symptoms in healthy subjects

well

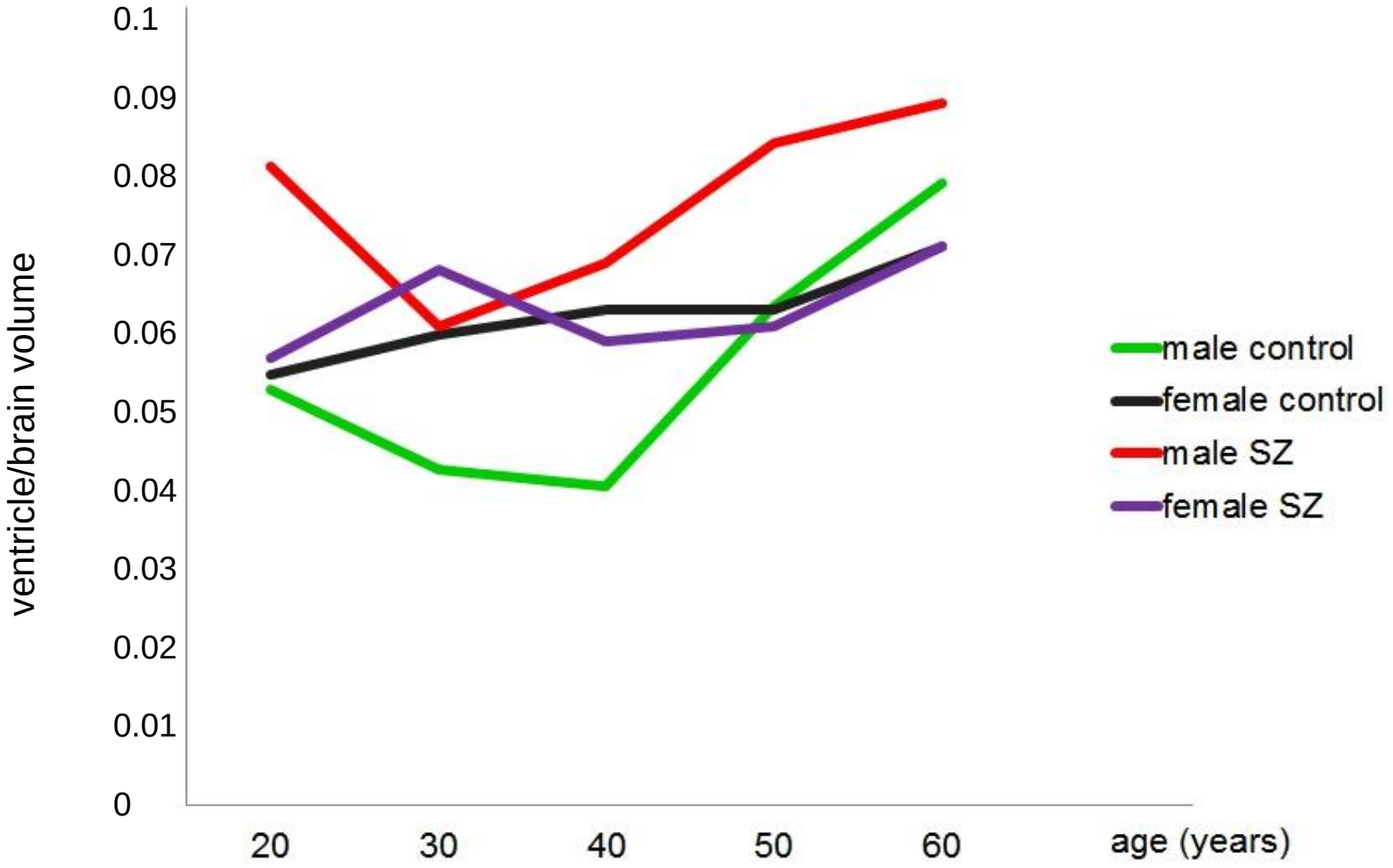
affected



ventricle size is very different between individuals and siblings as it looks like

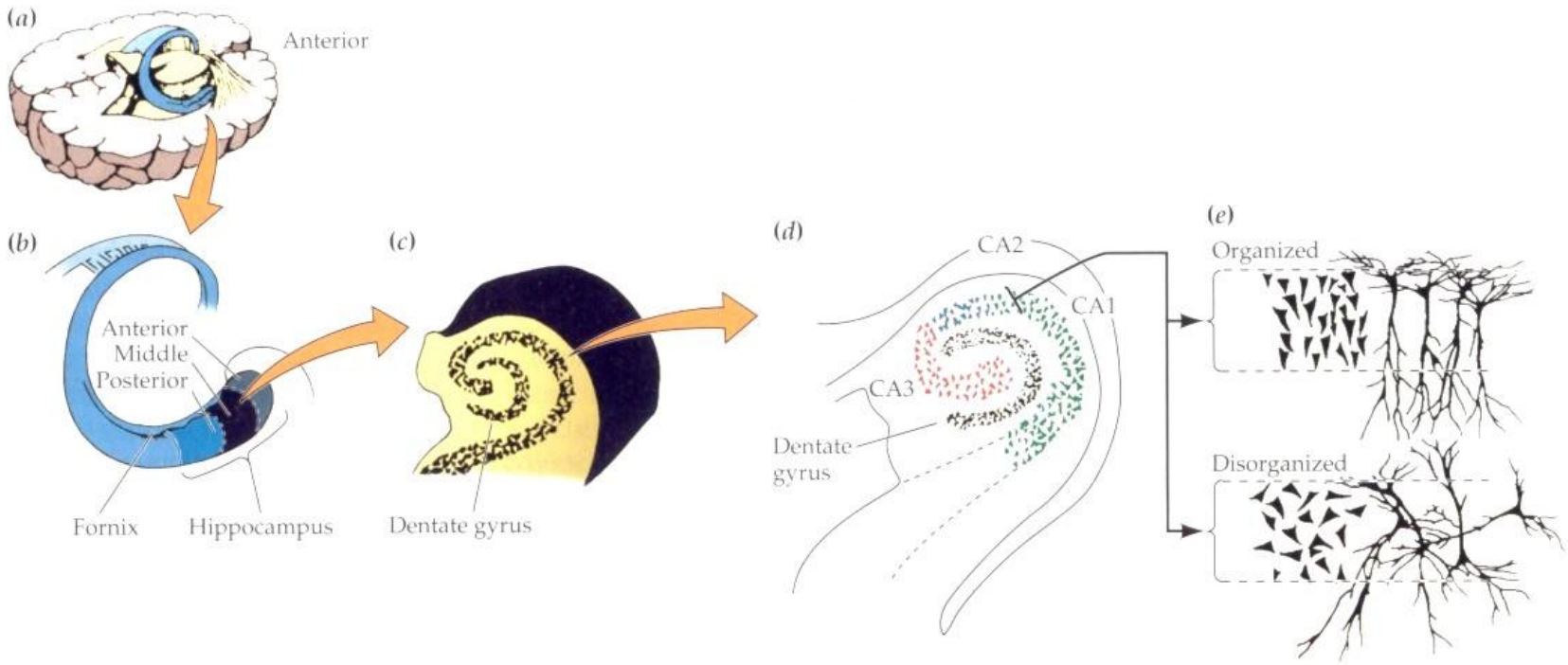
from Rosenzweig, Breedlove, Watson, 2005

Ventricle size varies with gender and age



from Rosenzweig, Breedlove, Watson, 2005

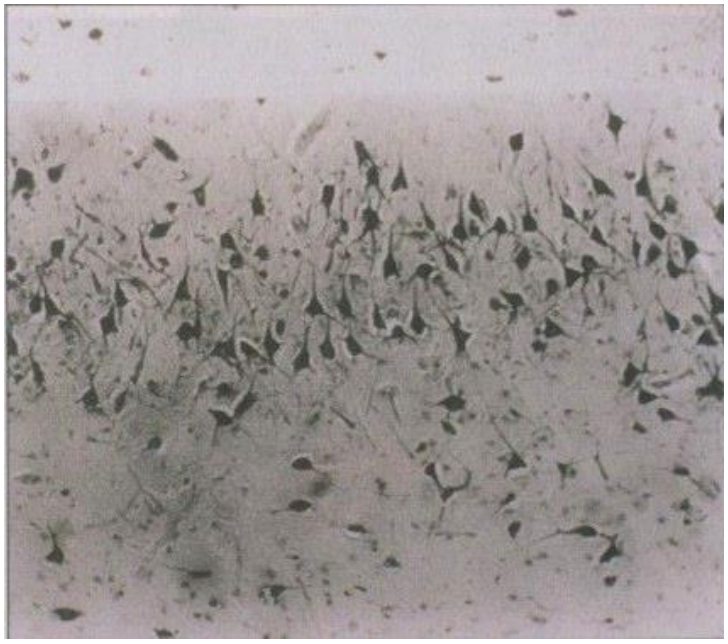
Cell polarity is disturbed in some brains of patients suffering from schizophrenia



from Rosenzweig, Breedlove, Watson, 2005

Cell polarity is disturbed in some brains of patients suffering from schizophrenia

normal control



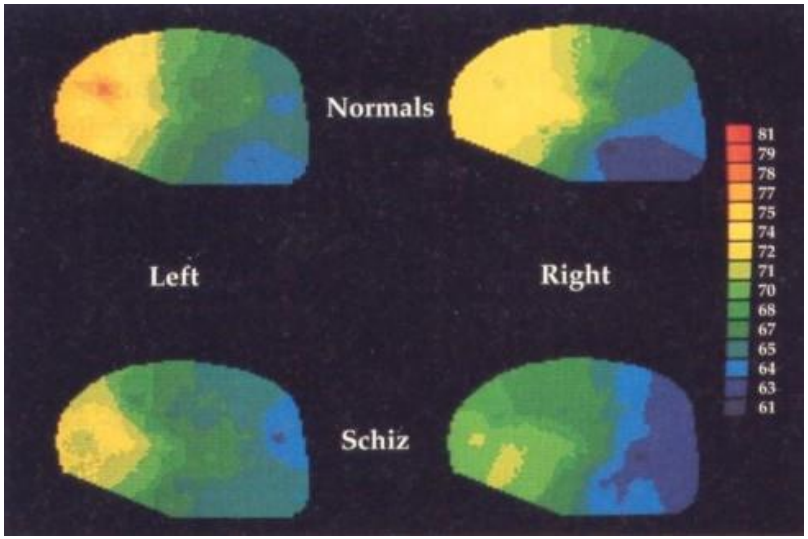
patient with schizophrenia

from Rosenzweig, Breedlove, Watson, 2005

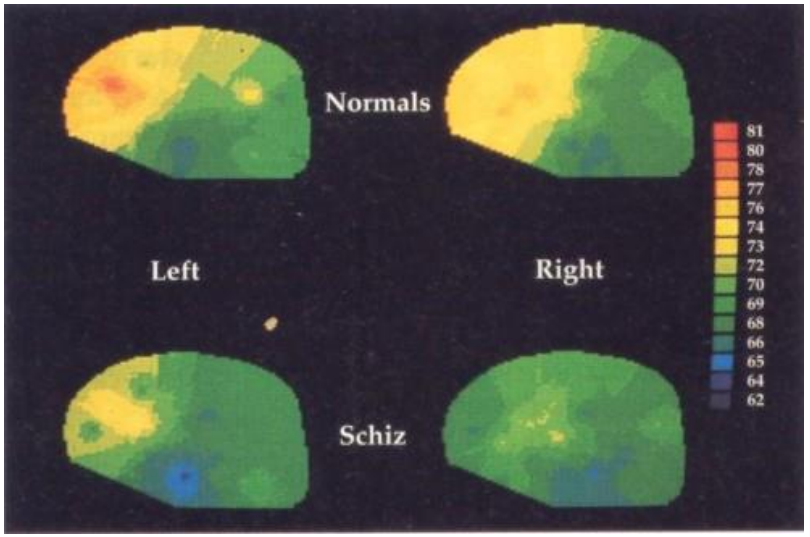
Schizophrenia can be associated with functional changes in the brain

reduced activity in the frontal cortex in patients compared to unaffected twin sibling

at rest



during task



from Rosenzweig, Breedlove, Watson, 2005

Manifestions supporting neurodevelopmental background of schizophrenia

maturational processes are perturbed, such as

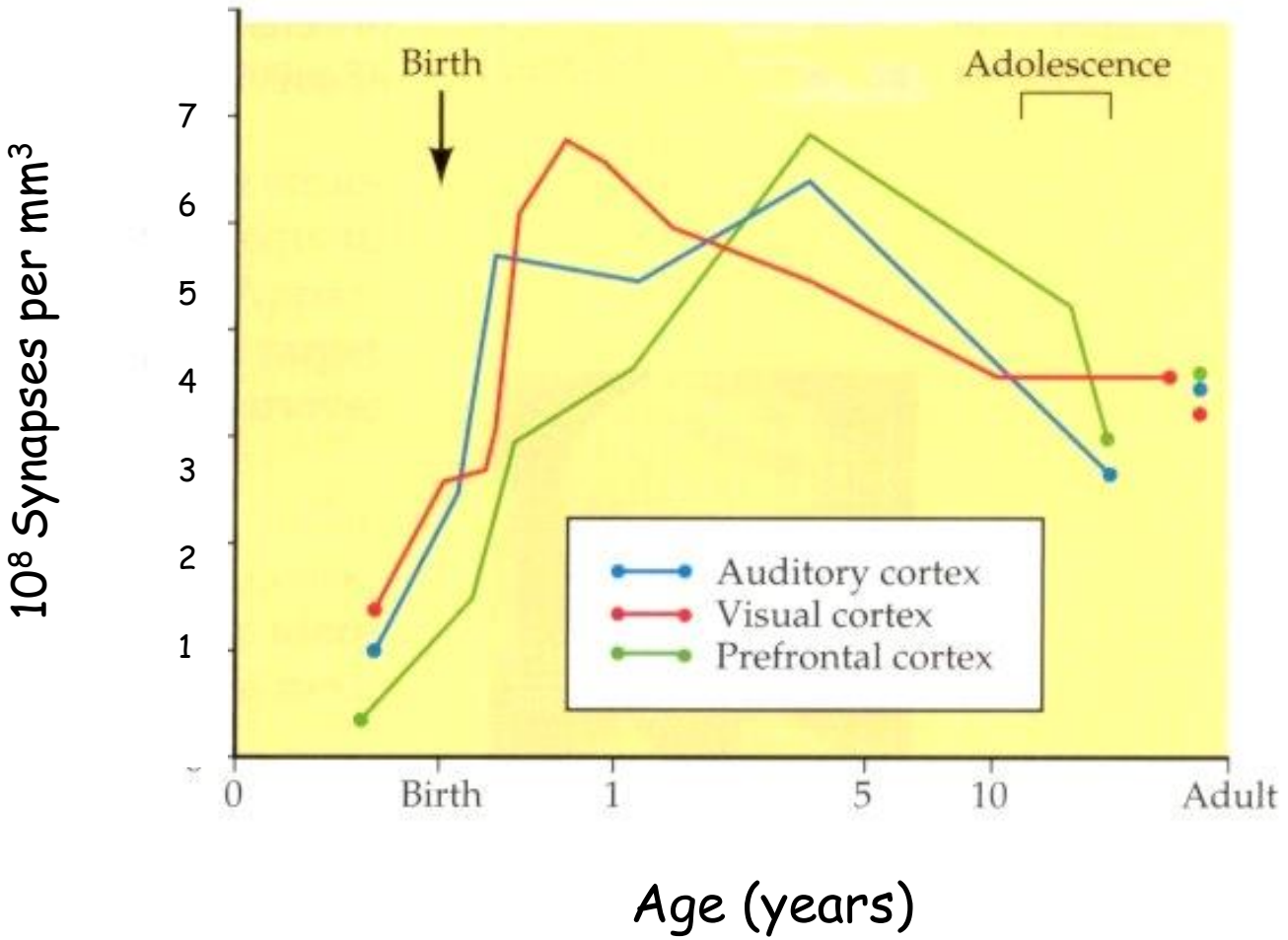
apoptosis

synaptic pruning

myelination

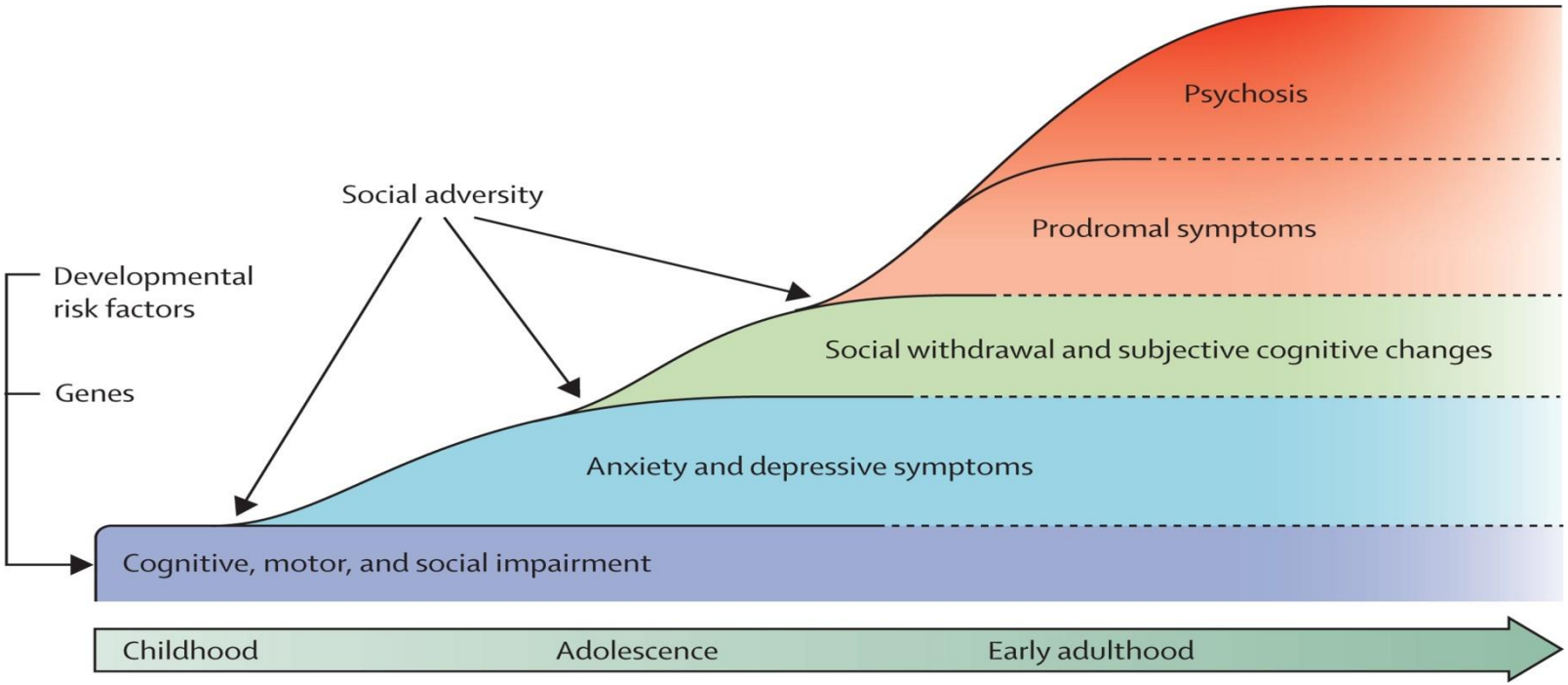
not the right number of synpases: too many or too few - connections are there that are not supposed to be there.
research: trying to explain cognitive symptoms that are linked to anormal numbers of synpases giving rise to these symptoms

Why does schizophrenia manifest itself during adolescence?



from Rosenzweig, Breedlove, Watson, 2005

The trajectory to schizophrenia showing the evolution of symptoms



Howes & Murray, Lancet 2014

Schizophrenic patients often revealed neurological deficits during childhood and adolescence

impaired cognitive skills
attention deficits
irritability
delayed gross motor development

similar neurological deficits are evident in the non-schizophrenic relatives of patients

Concept: etiology of schizophrenia involves multiple hits:

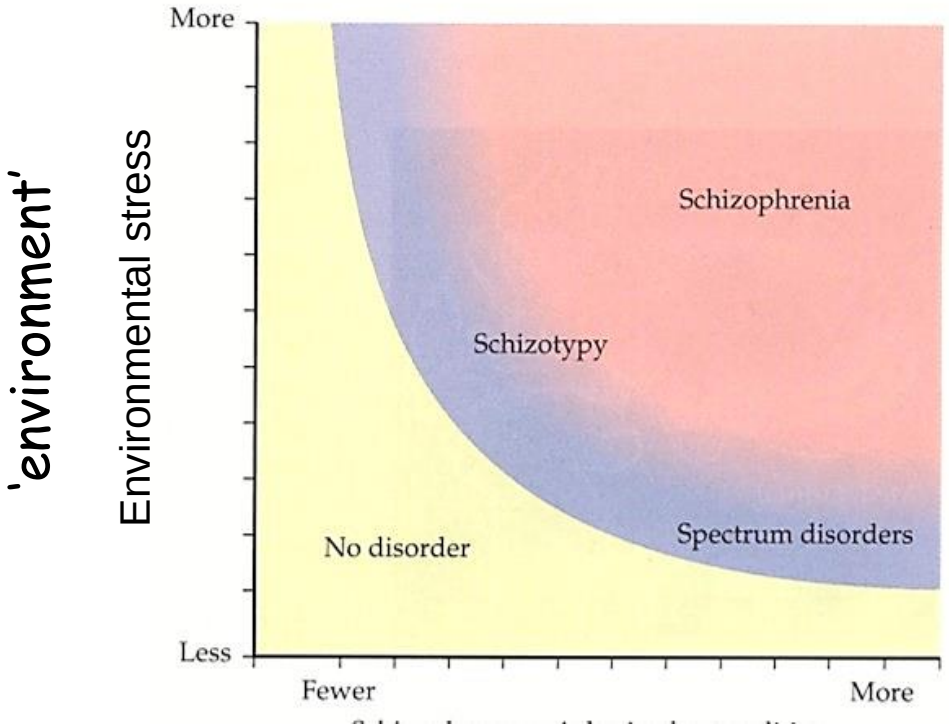
GENES X ENVIRONMENT

difference to other neurodevelopmental diseases:

manifestion not immediate but only
during second or third decade of life

Model by Mirsky and Duncan

Schizophrenia emerges when the combination of environmental stressors and brain abnormalities exceeds a threshold value.

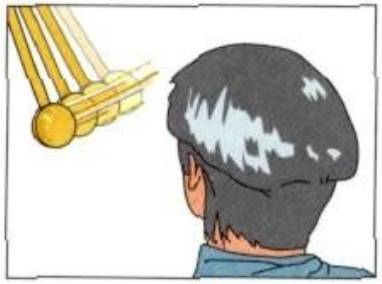


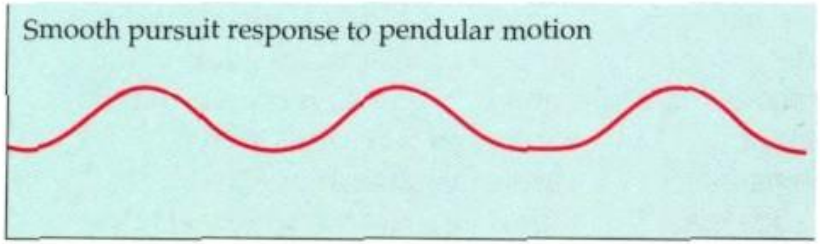
from Rosenzweig, Breedlove, Watson, 2005

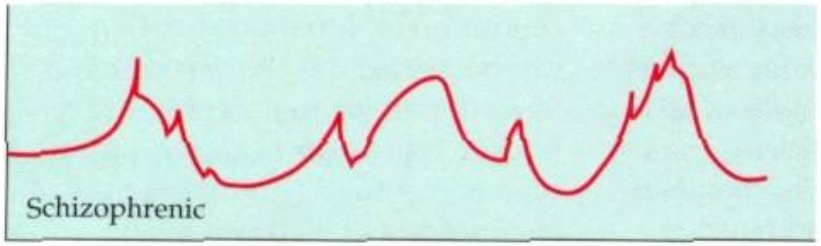
Neuropsychological characteristics differ between schizophrenics and non-affected twin siblings

e.g. eye tracking

schizophrenic patients are unable to follow the movements of a pendulum smoothly







About 25% of all patients recover completely and show no obvious signs of having had the disease.

More than half of the remainder substantially improve but nevertheless show some residual signs, such as occasional memory or sleep problems, not feeling exactly ‚right' or just not being able to tolerate tension and stress.

About 75% of those that do improve do so within the first 3 years of diagnosis.

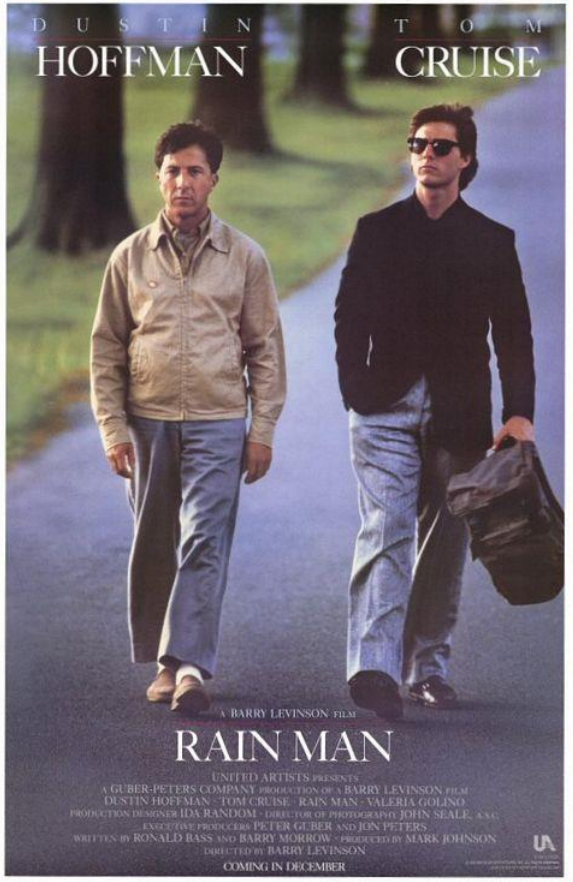
Suggested reading on Schizophrenia:

Lewis, D.A. and Levitt, P. (2002)
Schizophrenia as a disorder of neurodevelopment
Annu Rev Neurosci 25:409-432

Howes, O.D. and Murray, R.M. (2014)
Schizophrenia: an integrated sociodevelopmental-cognitive model
Lancet 383:1677-1687

Autism

first described by Leo Kanner, 1943



Autism is a neurodevelopmental disorder that is defined by deficits in social interaction, impaired communication, and by unusual restricted, repetitive behaviors.

Autism begins in infancy, before three years of age

Often diagnosis of autism is preceeded by observations of ‚abnormal' behavior of a child, e.g.
parents are concerned because child does not interact or communicate

Young children with autism often do not interact with peers, do not share happiness, do not interact with parents

Repetitive behaviors begin to develop in preschool years.

Signs of sensory overload, avoidance of novel stimuli

Diagnostic criteria for autistic disorder:

Social interaction: Qualitative impairment in social interactions, as manifested by at least two of the following:

a) marked impairment in the use of multiple nonverbal behaviors, e.g. eye-to-eye gaze

b) failure to develop peer relationships

c) lack of spontaneous seeking to share enjoyment with other people

d) lack of social or emotional reciprocity

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV, 1994

DSM-V today

Communication: Qualitative impairments of communication,
as manifested by at least one of the following

a) delay in, or total lack of, the development of spoken language

b) marked impairment in initiating or sustaining a conversation with others

c) stererotyped and repetitive use of language

d) lack of varied, spontaneous make-believe or imitative play

make-believe play: typical for children - they pretend they are cooking on a chair or being soldiers in the sandbox for example

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV, 1994

Behavior: Restricted, repetitive, and stereotyped patterns of behavior, as manifested by at least one of the following

a) preoccupation with one or more stereotyped or restricted patterns of interest

b) adherence to nonfunctional routines or rituals

c) stereotyped and repetitive motor mannerisms

d) persistent preoccupation with parts of objects

behaving has to be analyzed in an age-dependent manner

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV, 1994

https://www.youtube.com/watch?v=YtvP5A5OHpU

Autistic children

avoid eye contact with parents when held

push away from close contact

severely impaired language acquisition

automatic acts (incessant rocking)

may or may not be mentally retarded

up to a third of individuals with ASD report epilepsy

comorbidity: epilepsy

mental retardation is not always the case; some can be very smart - also referred to as asperger's syndrome sometimes

Conceptualization of a spectrum of autism-related disorders:

Childhood Disintegrative Disorder kids seem to do fine in first two years, then halt in development and development regresses then: mutation in gene on X chr, lethal for boys, but girls live and survice

Asperger's Disorder normal speech, but difficulties in social interactions, very smart and highly functional

Pervasive Developmental Disorder-Not otherwise specified (PDD-NOS) group where all kids are put in when they fit in no other groups, neither cognitively nor genetically

common theme:

qualitative deficits in social behavior and communication

sibling recurrence risk is approx. 4.5%

population incidence 3-6/1000 (for full spectrum of autistic disorders)

concordance rate for monozygotic twins: ~60%
for classical autism, up to 92% for full spectrum
(autism is the most heritable psychiatric disorder)

concordance rate for dizygotic twins: ~3-10%

autism is 4-5 times more prevalent among males

Genome-wide linkage studies with large patient cohorts have provided large data sets

many genes are linked to synaptogenesis and axon guidance

Autism as an ‚under-connectivity' syndrome

not a single mutation is enough for autism

'environmental' stressors

another drug/medics
thalidomide use

certain viral infections (rubella, influenza, cytomegalovirus)

maternal anticonvulsants
drugs against epilepsy

problems to be solved:

definition of brain regions that are most severely affected

types of alterations (structural versus neurochemical)

biochemical tools for diagnosis

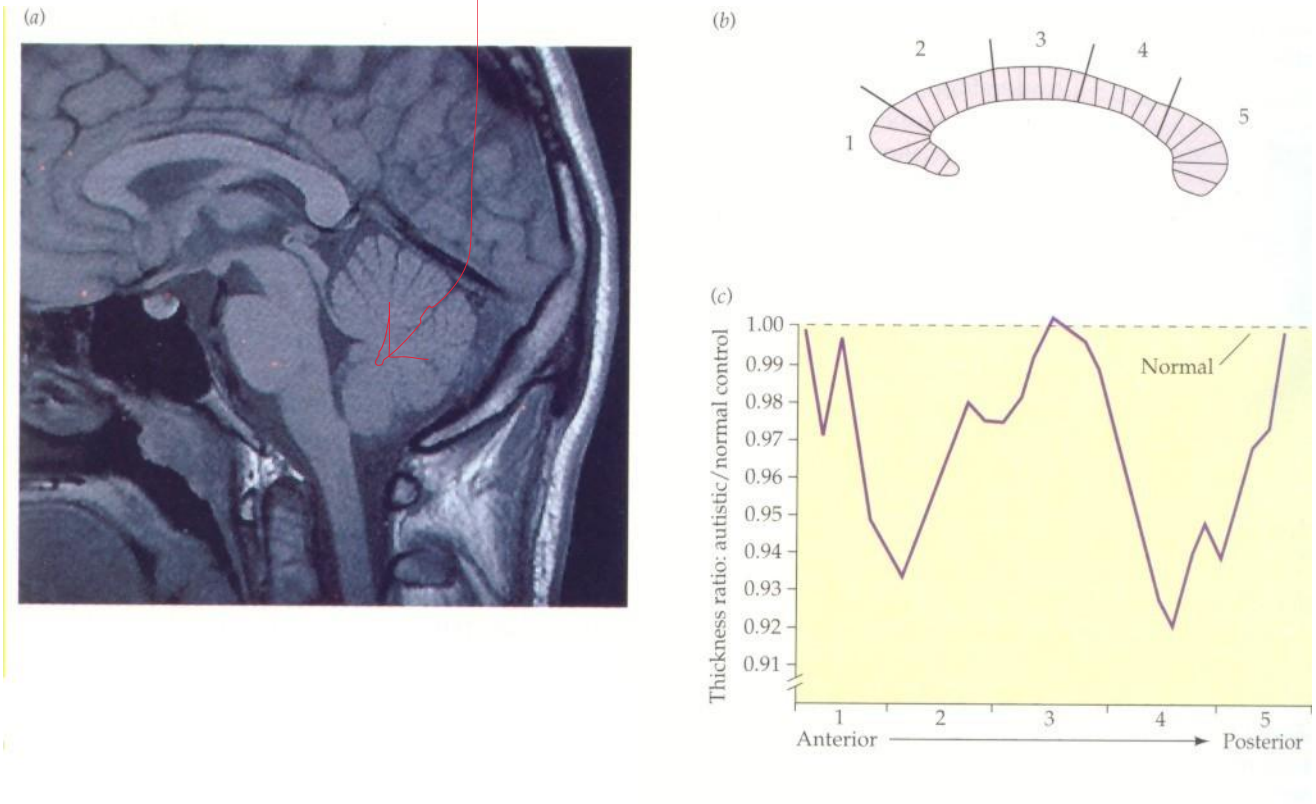
overcome problems with diagnosis due to heterogeneity

no biomarkers to say for sure that this person suffers from ASD

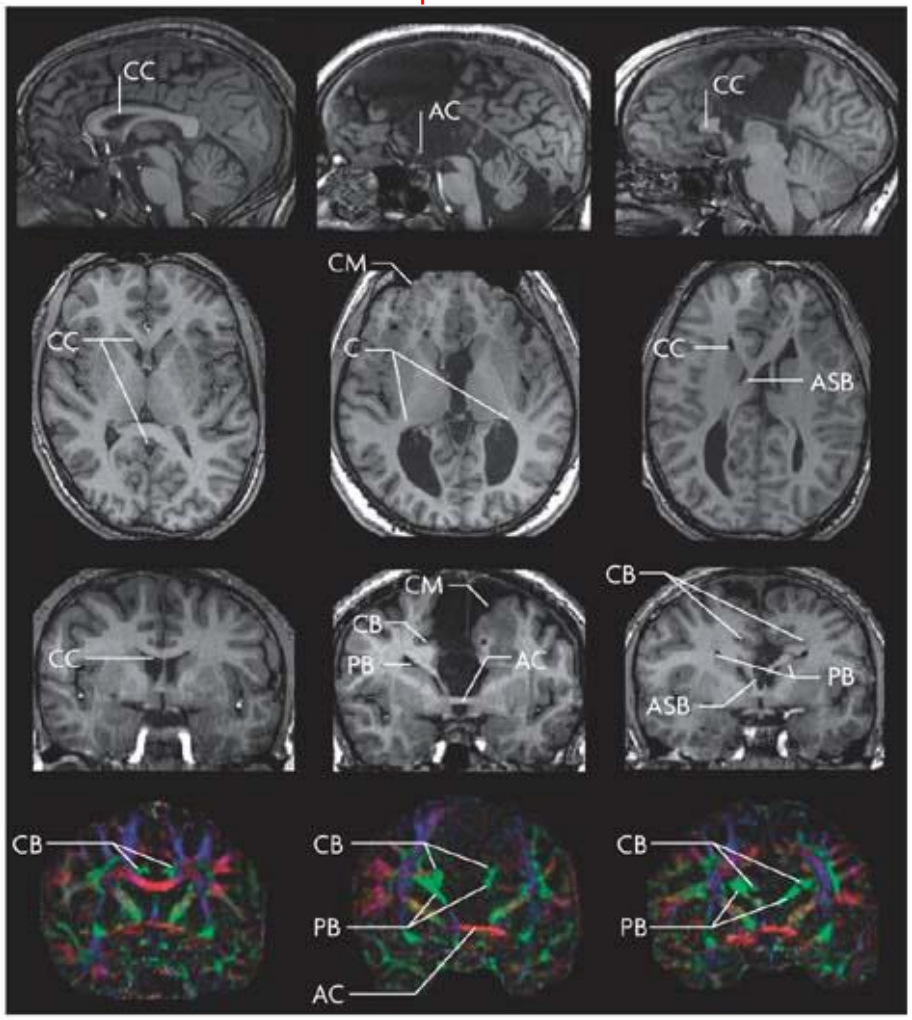
Most prevalent abnormalities found in autistic brains

reduced corpus callosum & changes in cerebellar structure

smaller corpus callosum and changes in cerebellar structure



Complete or partial agenesis of the corpus callosum



no corpus callosum

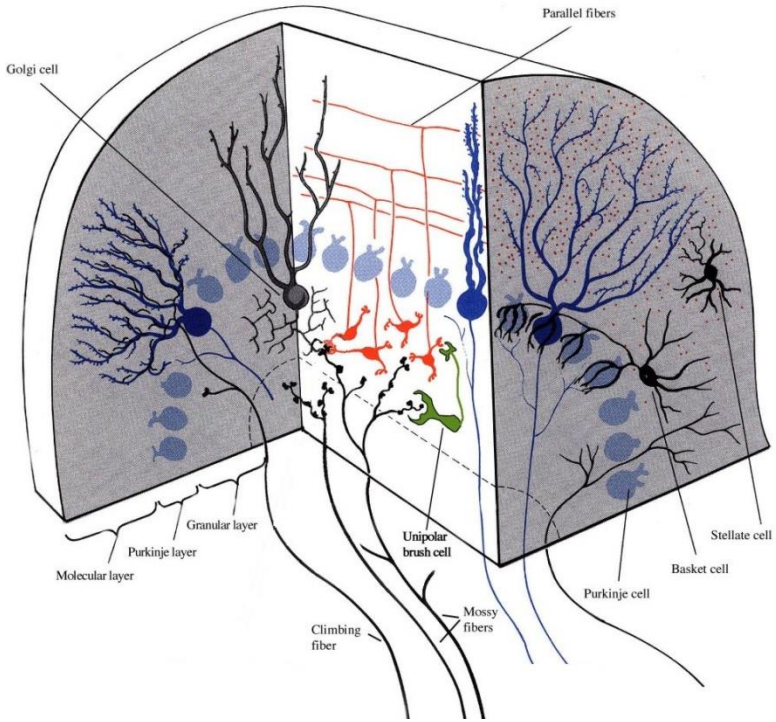
thiining of cc

cc := corpus callosum

Paul et al., Nature Rev Neurosci. 2007

Loss of Purkinje cells has been commonly found in several studies.

Loss of cells in deep cerebellar nuclei in some studies.



additional anatomical/morphological findings

(changes in numbers)

changes in synapse formation and elimination

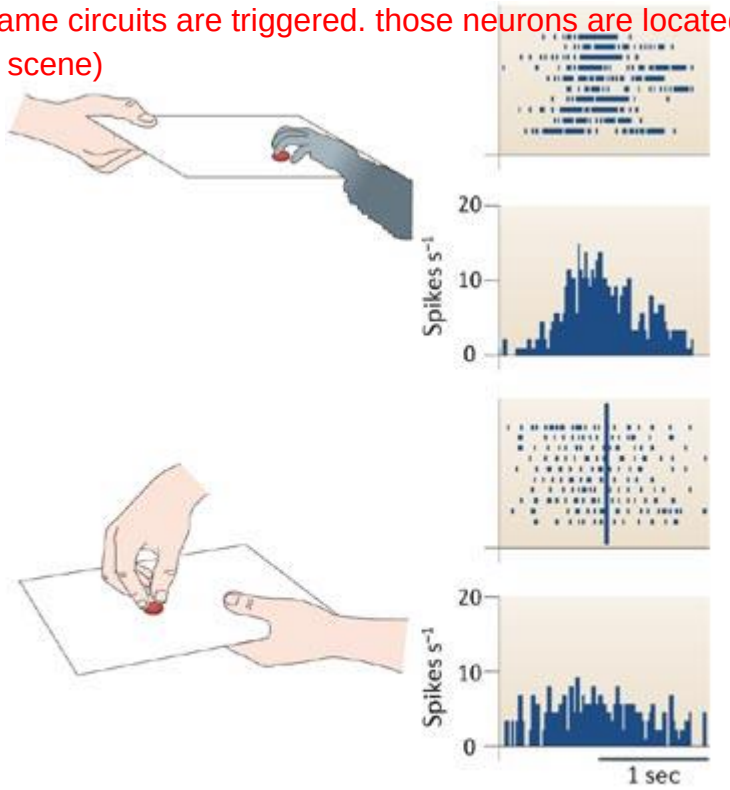
cells more densely packed, smaller cells

reduced complexity of dendritic arbors

However!!
Formal reports of autopsy studies during the last 25 years involved only about 30 brains!

Disturbance of the Mirror Neuron System in patients with autism

mirror neuron system: when specific scene observed, when food item presented and taken, then neural activity. when someone observes this scene, then some of the same circuits are triggered. those neurons are located e.g. in the temporal lobe (as if one was doing it himself instead of just looking at scene)



Iacoboni and Dapretto, *Nature Reviews Neuroscience* **7 (2006)**, 942–951

The MNS helps to understand intentions

a setting up a table

cleaning the table

Iacoboni and Dapretto, *Nature Reviews Neuroscience* **7 (2006)**, 942–951

Common to all autism spectrum disorders:

disturbance of normal social behavior

ranging from subtle abnormalities in social reciprocity, particularly with peers, to much more obvious difficulties in the use of eye contact, facial expression, and social motivation.

Interpretation of facial expressions are markedly impaired in autistic subjects.

Iacoboni and Dapretto, *Nature Reviews Neuroscience* **7 (2006)**, 942–951

Additional reading:

Chen et al., Annu Rev Pathol Mech Dis 10(2015)111-144

Geschwind and Levitt, Curr Opin Neurobiol 17(2007)103-111

lec: wont ask this slide for exam

Mental Retardation

significantly sub-average intellectual functioning

IQ < 70

profound:	IQ < 20
severe:	IQ 20 -35
moderate:	IQ 35-50
mild:	IQ 50-70
borderline:	IQ 70-85

Mental Retardation

sinificantly sub-average intellectual functioning

significant limitations in adaptive functioning in at least two of the following skill areas:

communication, self-care, ability to live independently, social and interpersonal skills, work, leisure, health and safety

onset before the age of 18 years

syndromic and non-syndromic forms

boys more affected than females because X-linked - some forms, not all, are X-linked

~0.4% of the general population are mentally retarded

Male to female ratio for moderate to severe ID/MR (IQ<50) is 1.4 and 1.9 for mild ID/MR (IQ 50-70)

XLMR accounts for 10-16 % of all severely retarded patients
20-25 % of all levels of ID/MR

XLMR is 6-8 times more prevalent than expected when compared to the ~3% of gene contribution by the X chr.

~40% of the 885 protein-coding genes identified on X are expressed in the brain!

that's why we have an overrepresantation of X-linked chromosome linked mental retardation cases

~ 100 genes associated with XLMR have been described so far

2/3 of XLMR are non-syndromic

Novel *GDI1* mutation in a large family with nonsyndromic X-linked intellectual disability

non syndromic forms - cannot be seen by mere eye as in down sydrome

mice model has shown: LTP: mental retardation was obvious when LTP was reduced compared to controls. also mice are non-primates so it's difficult.

American Journal of Medical Genetics Part A
Volume 155, Issue 12, pages 3067-3070, 14 OCT 2011 DOI: 10.1002/ajmg.a.34291
http://onlinelibrary.wiley.com/doi/10.1002/ajmg.a.34291/full#fig2

Syndromic mental retardation: Down syndrome

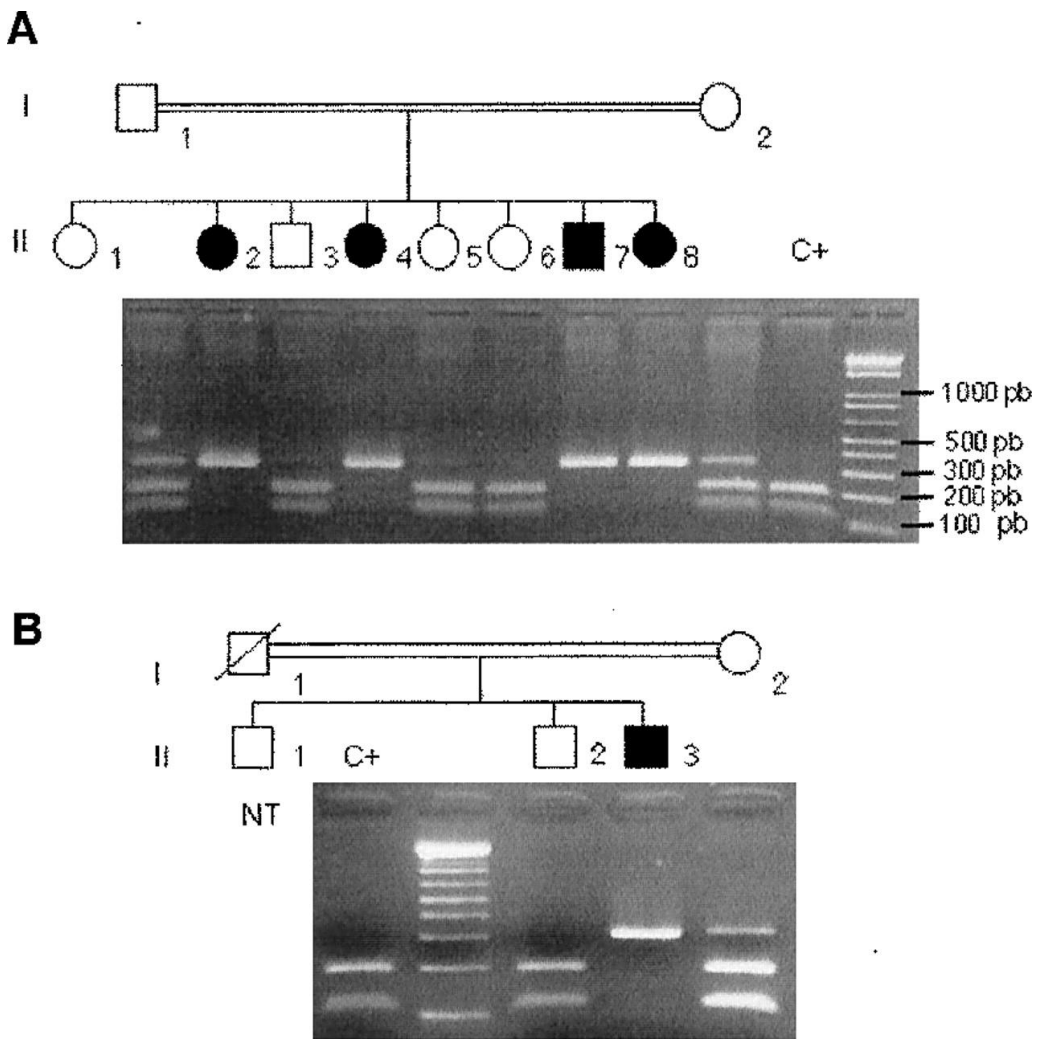
this is syndromic

nonsyndromic

NS-autosomal MR is much more difficult to study; first gene Neurotrypsin, identified in 2002

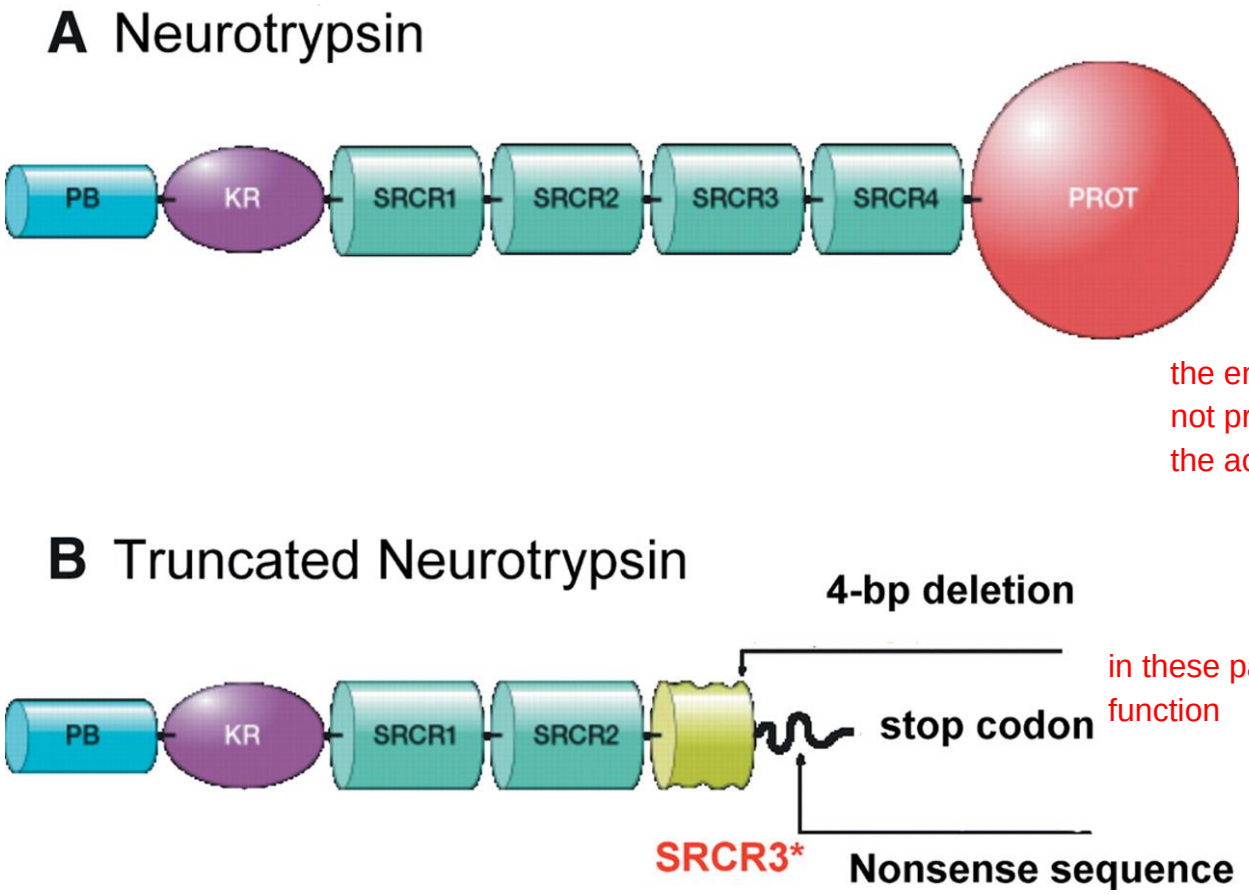
not X-linked

Mutational analysis of neurotrypsin – a gene linked to NS-autosomal ID



F Molinari et al. Science 2002;298:1779-1781

A 4bp-deletion induces a premature stop codon resulting in a truncated version of Neurotrypsin



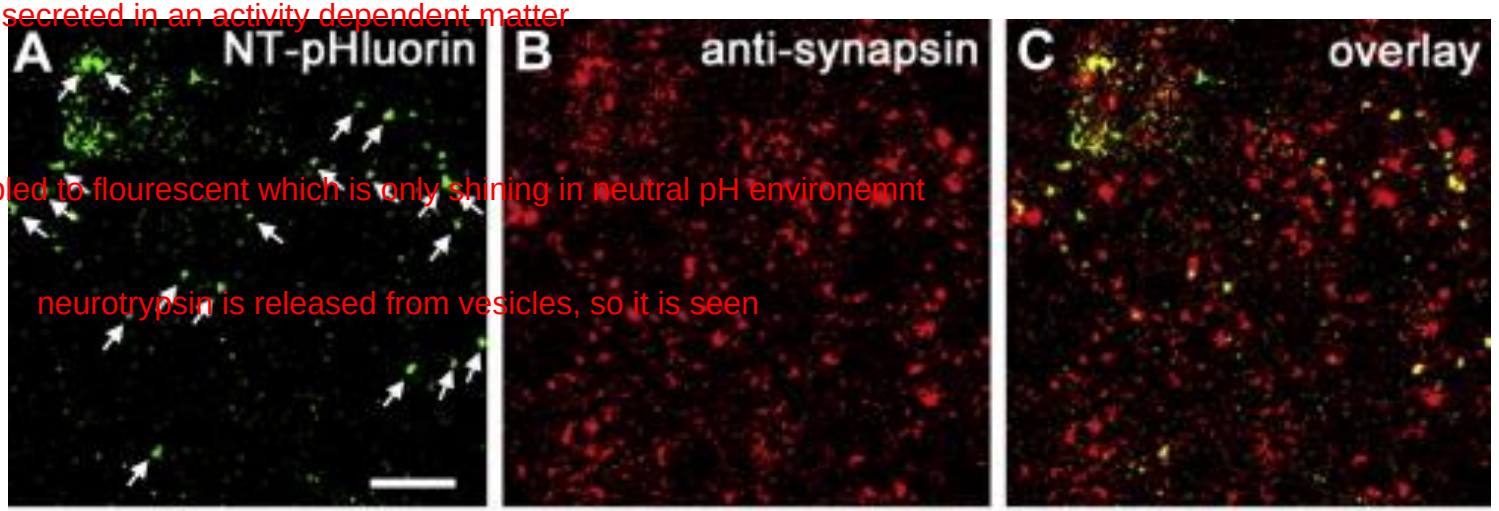
the entire C-terminal part was not present; the red domain is the active domain

in these patients, there was no function

Molinari F et al. Hum. Mol. Genet. 2003;12:R195-R200

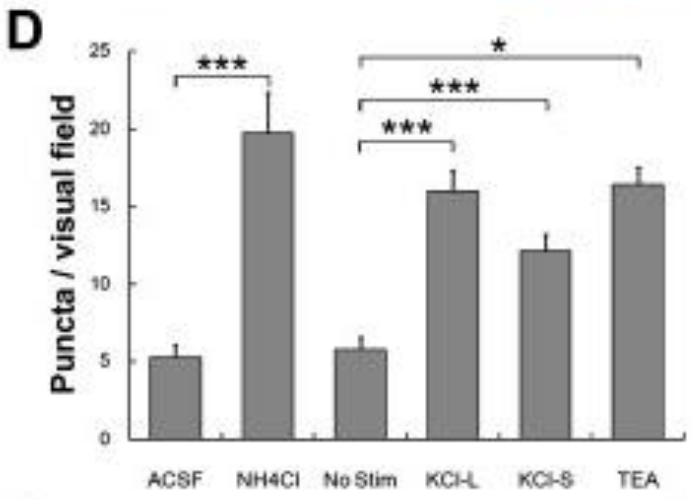
Neurotrypsin release depends on synaptic activity

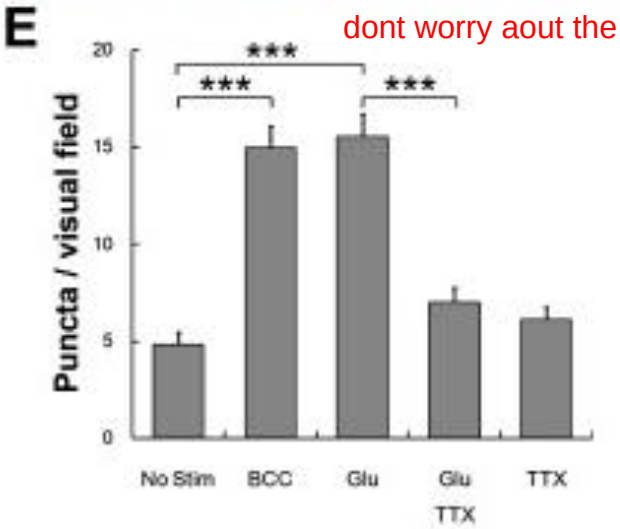
neurotrypsin is secreted in an activity dependent matter



neurotrypsin coupled to flourescent which is only shining in neutral pH environemnt

neurotrypsin is released from vesicles, so it is seen





dont worry aout the details

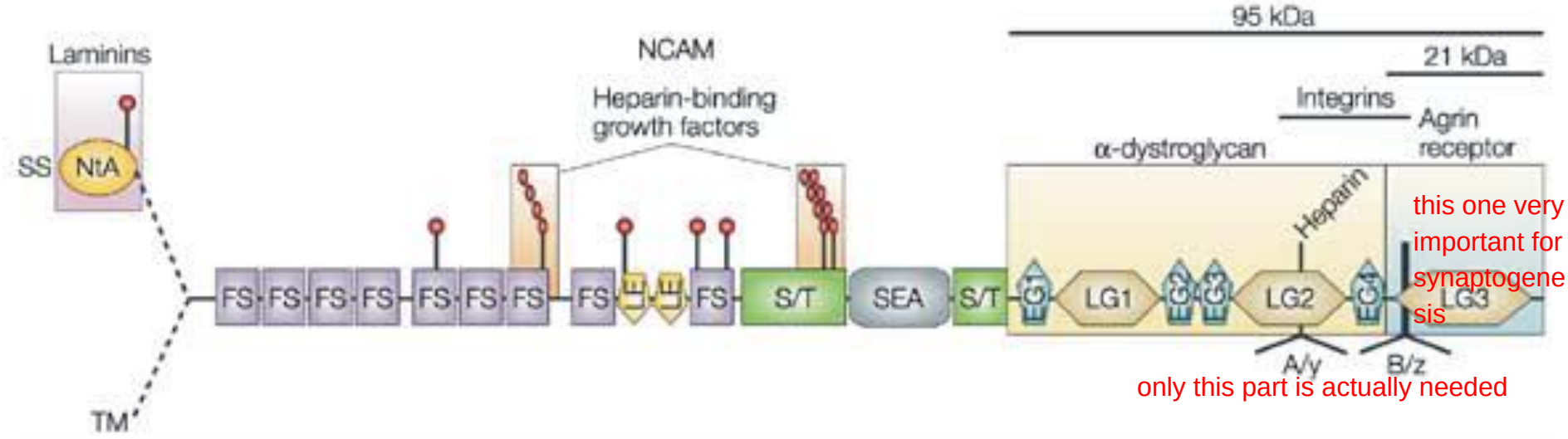
ACSF: artificial cerebrospinal fluid

in any case, we need synaptic activity such that there is neurotrypsin release

Matsumoto-Miyai et al., Cell 2009

agrin induces NMJ

Agrin -
A motorneuron-derived organizer of the NMJ
and involved in CNS synaptogenesis



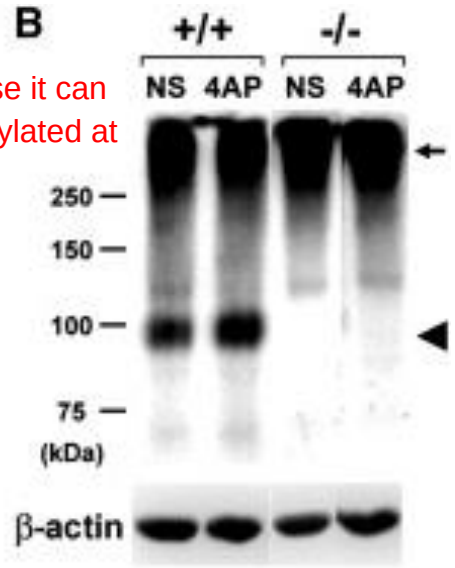
this one very important for synaptogenesis

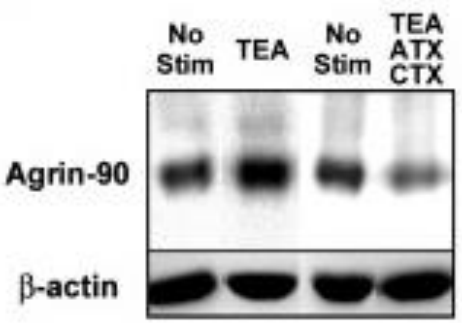
only this part is actually needed

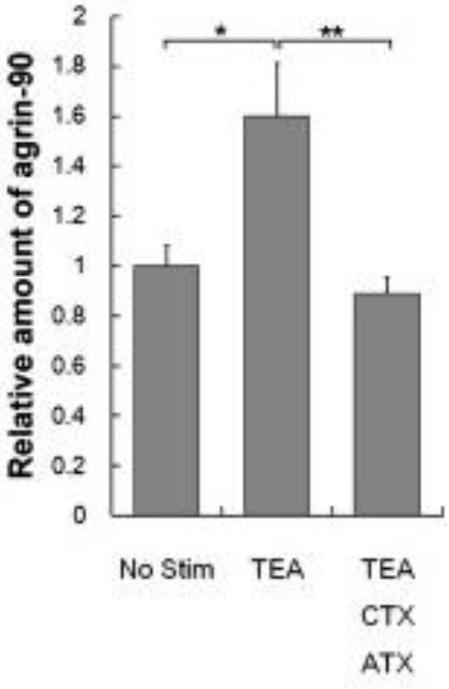
neurotrypsin cleaves agrin

Agrin cleavage depends on the presence of Neurotrypsin and is stimulated by synaptic activity

smear: because it can also be glycosylated at different levels



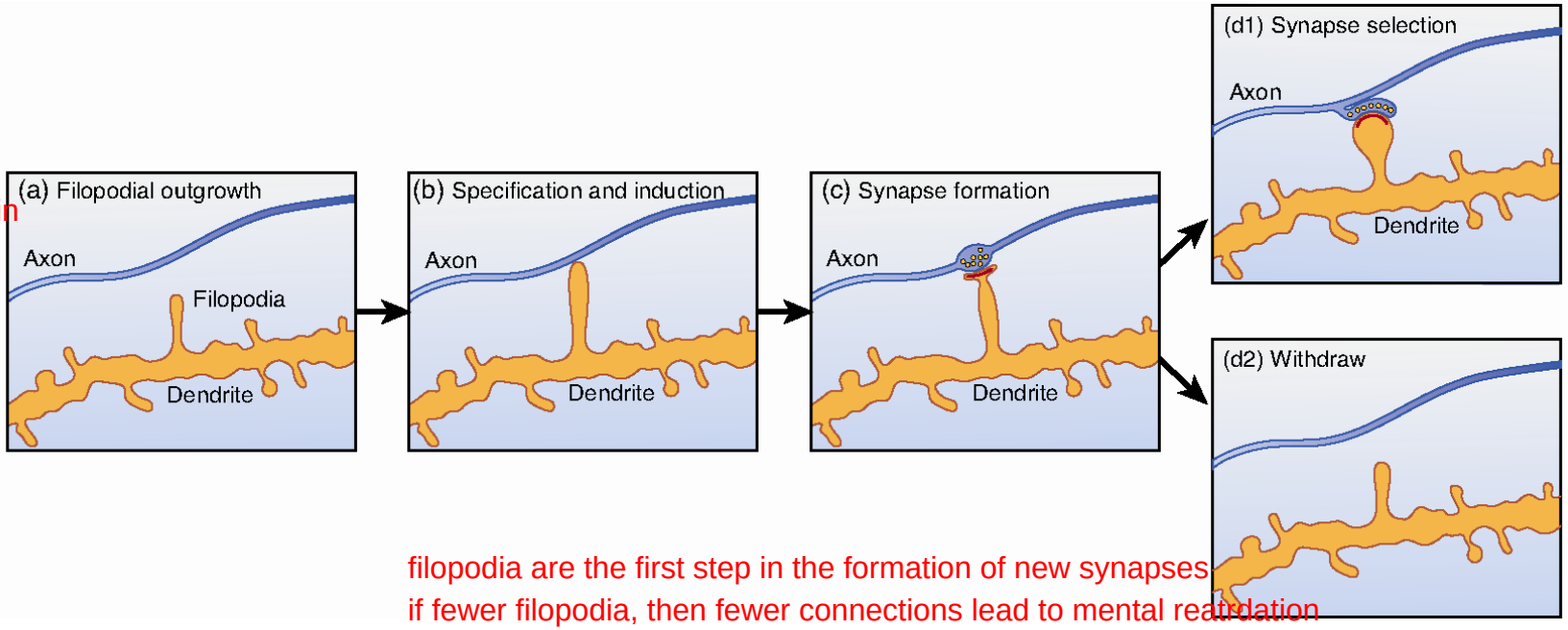




Matsumoto-Miyai et al., Cell 2009

Dendritic filopodia are precursors of synapses

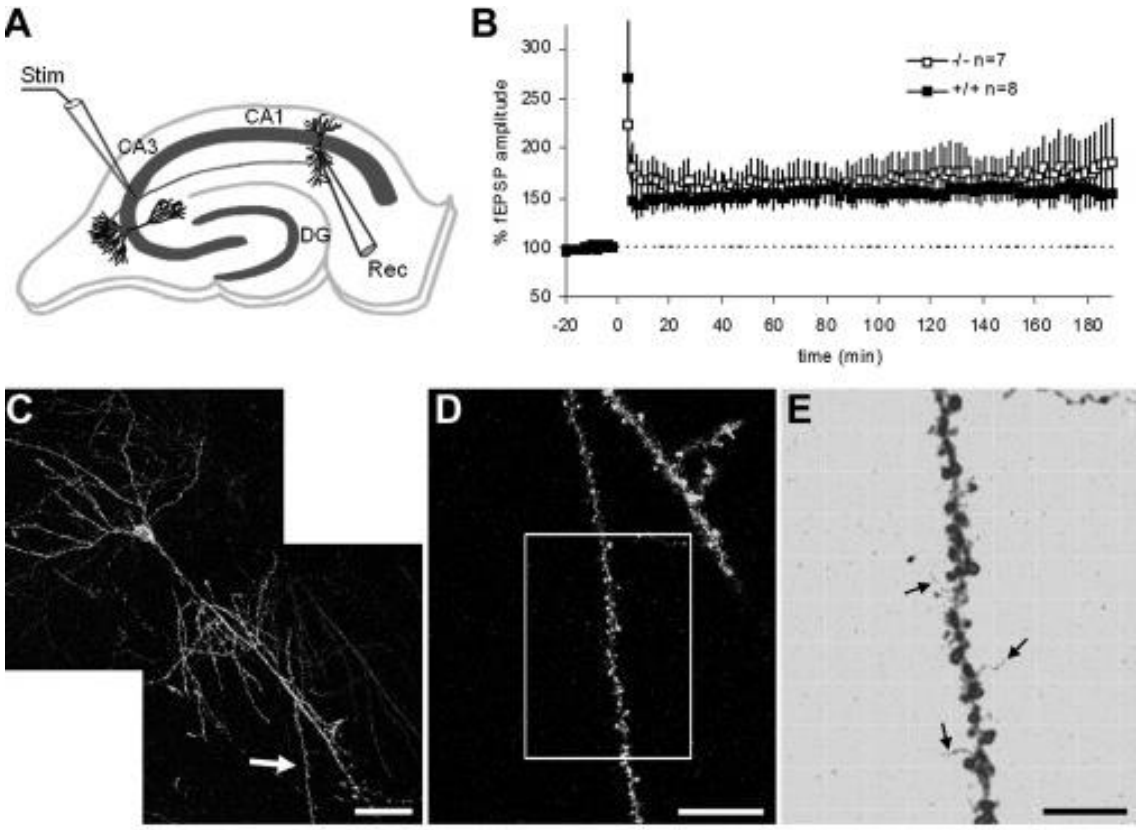
hat's what agrin
hen does

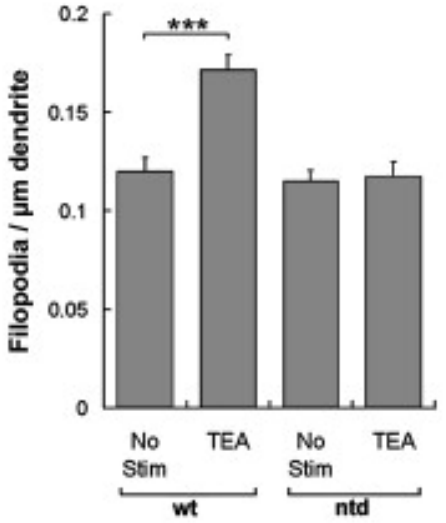


filopodia are the first step in the formation of new synapses
if fewer filopodia, then fewer connections lead to mental retardation
this is the identified cause. not a 0% of forming synapses (they were alive after all), but there was a severe decrease in filopodia formation and synapses formation in these individuals. so mental retardation: fewer synapses due to lacking agrin which can't induce synpase formation due to loss of neurotrypsin that cleaves agrin

LTP is intact, but LTP-associated formation of filopodia is abolished in Neurotrypsin-deficient mice

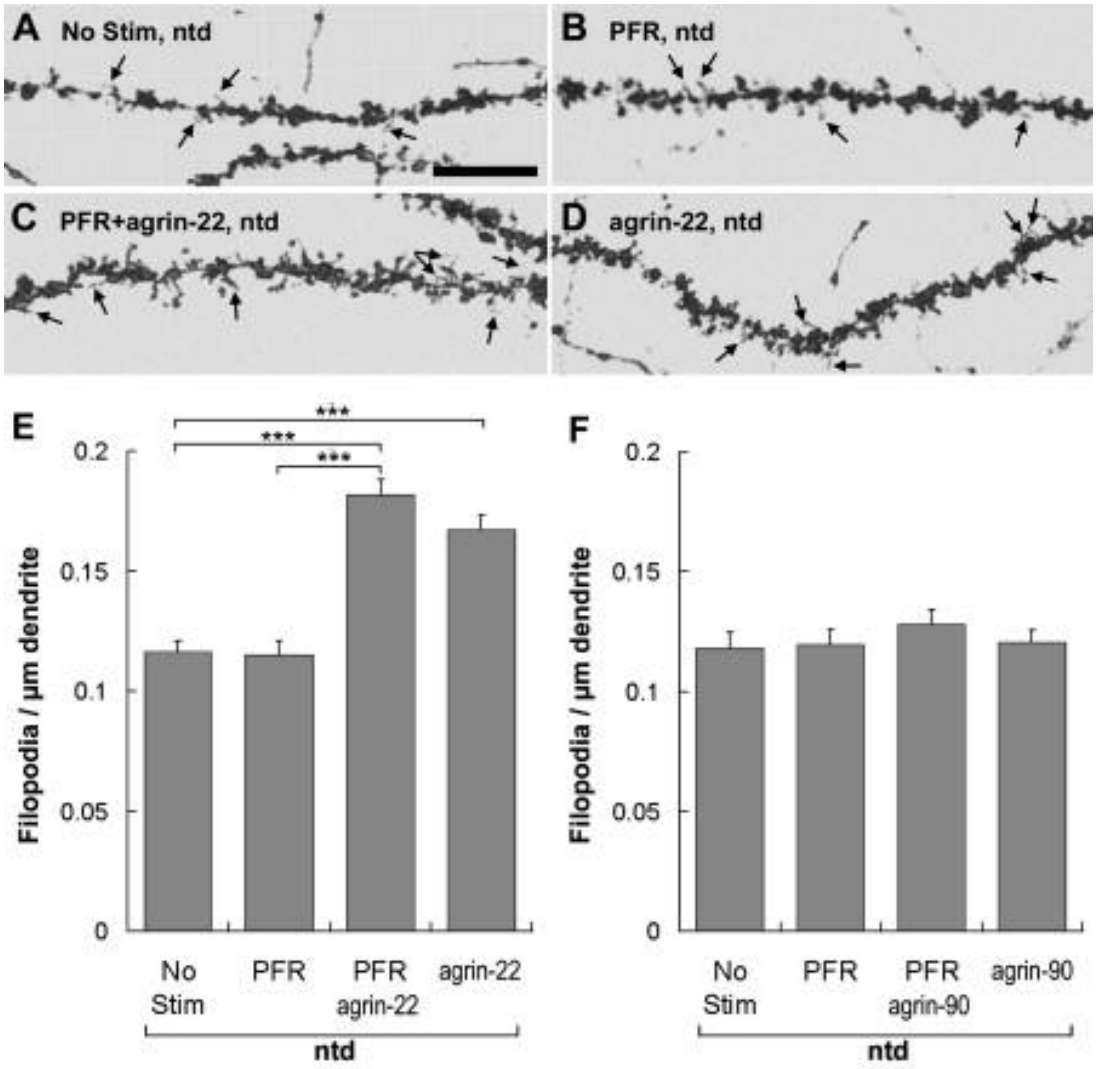
the synapses who were there were strengthened, but the possibility to form new filopodia + new synapses was severely impaired





Matsumoto-Miyai et al., Cell 2009

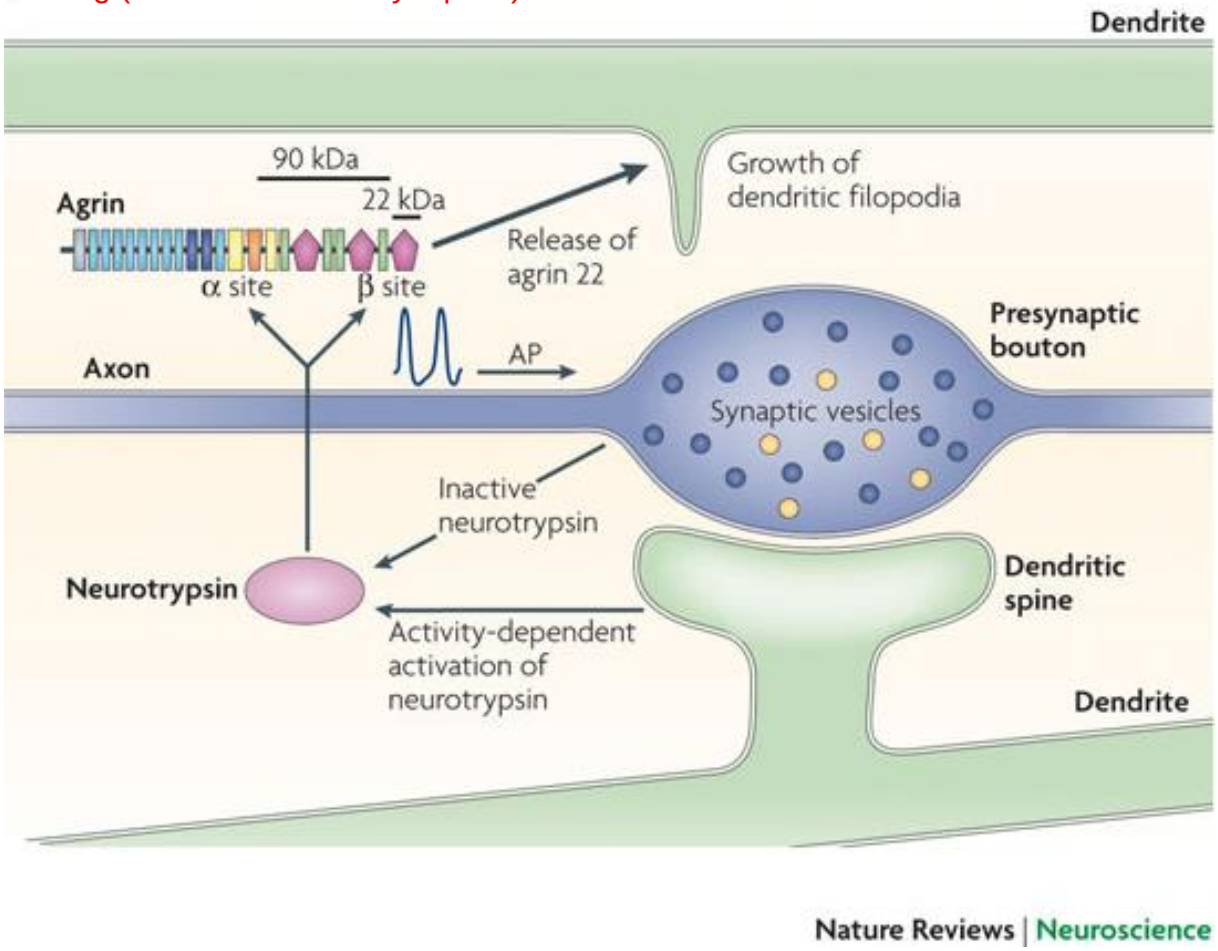
The Neurotrypsin-dependent Agrin cleavage product, agrin-22, rescues filopodia induction in Neurotrypsin KO mice



Matsumoto-Miyai et al., Cell 2009

Neurotrypsin is a coincidence detector

this means: neurotrypsin only actived when deactivation of dendrite - this releases something (still unknown) which activates neurotrypsin - this can then cleave agrin and produce the 21-22kD fragment. this induces learning (formation of new synapses)



The dual role of the extracellular matrix in synaptic plasticity and homeostasis. Dityatev A, Schachner M, Sonderegger P., Nat. Rev. Neurosci. 11(2010)735-746

Many of the genes implicated in MR are involved in

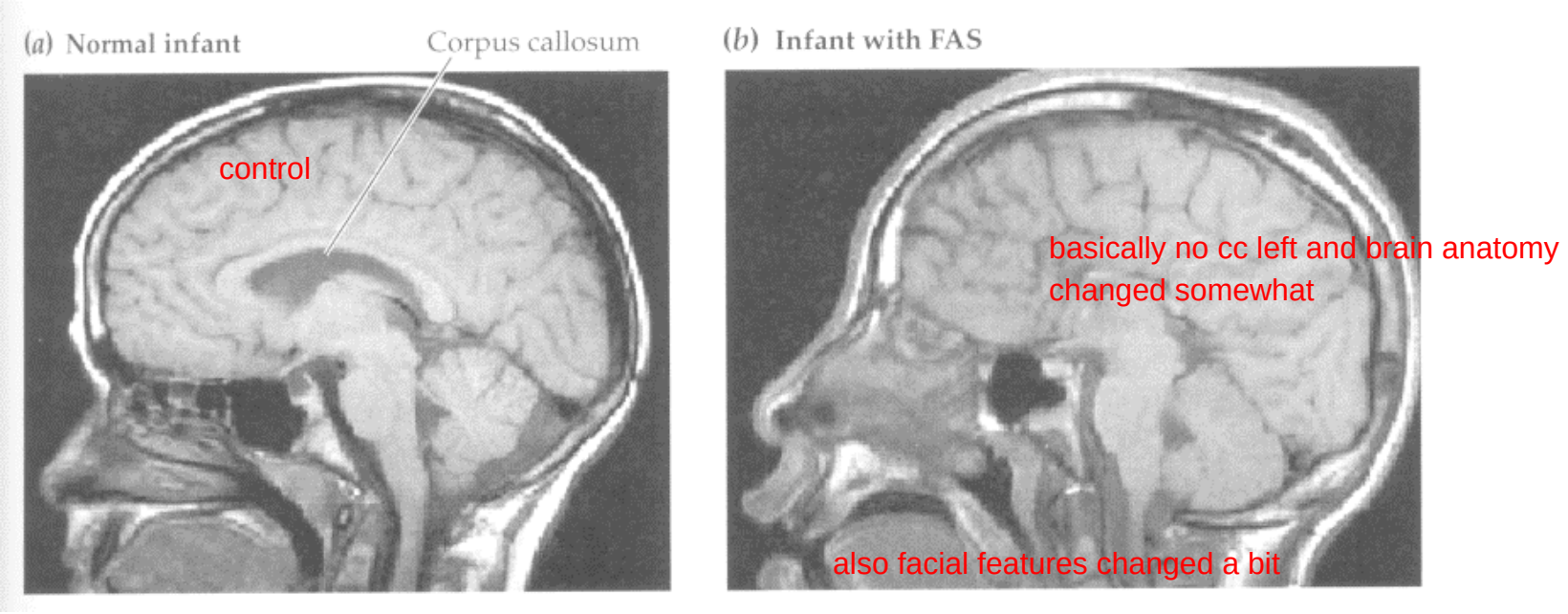
- neurite outgrowth (regulation of actin cytoskeleton)
- axon guidance
- synapse formation and plasticity
- neurotransmitter release

MR/ID can be caused by exposure to drugs during pregnancy

about 40% of children born to alcoholic mothers show a distinctive profile of anatomical, physiological, and behavioral impairments known as

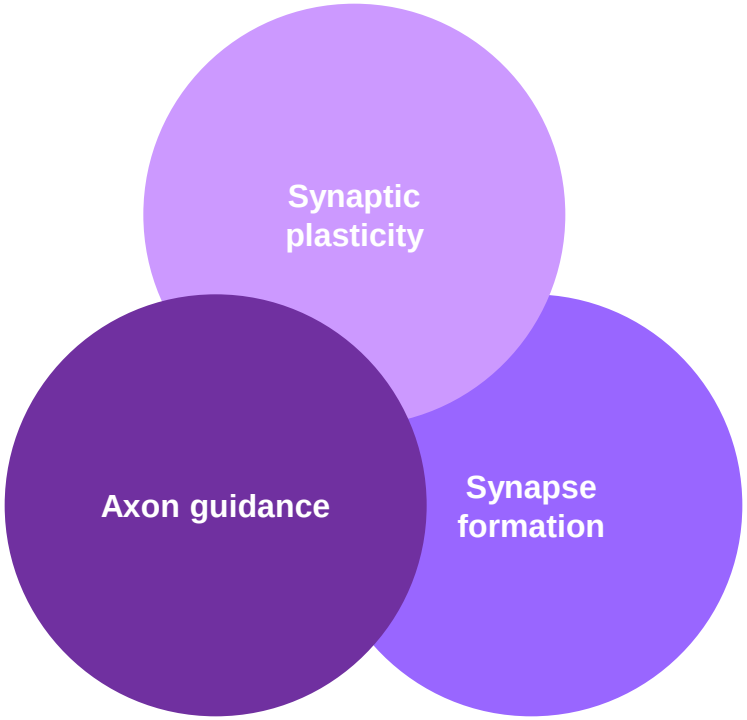
Fetal Alcohol Syndrome (FAS) or Fetal Alcohol Spectrum Disorders (FASD)

Brain anatomy can be affected at the macroscopic level in children born with FAS



from Rosenzweig, Breedlove, Watson, 2005

Genes associated with neurodevelopmental diseases affect more than one step in neural circuit formation



Stoeckli, EJN 2012, 35:1811-1817