

Gender en psychiatrie

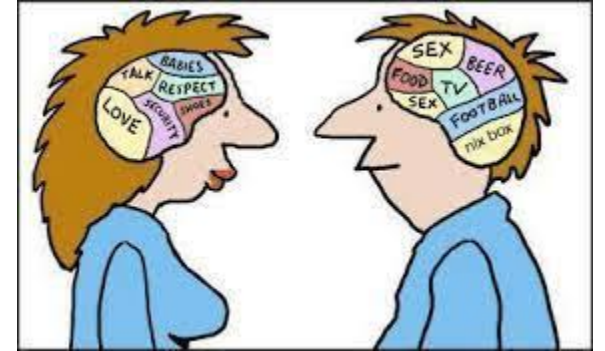
Prof. Dr. G. Heylens

Psychiater

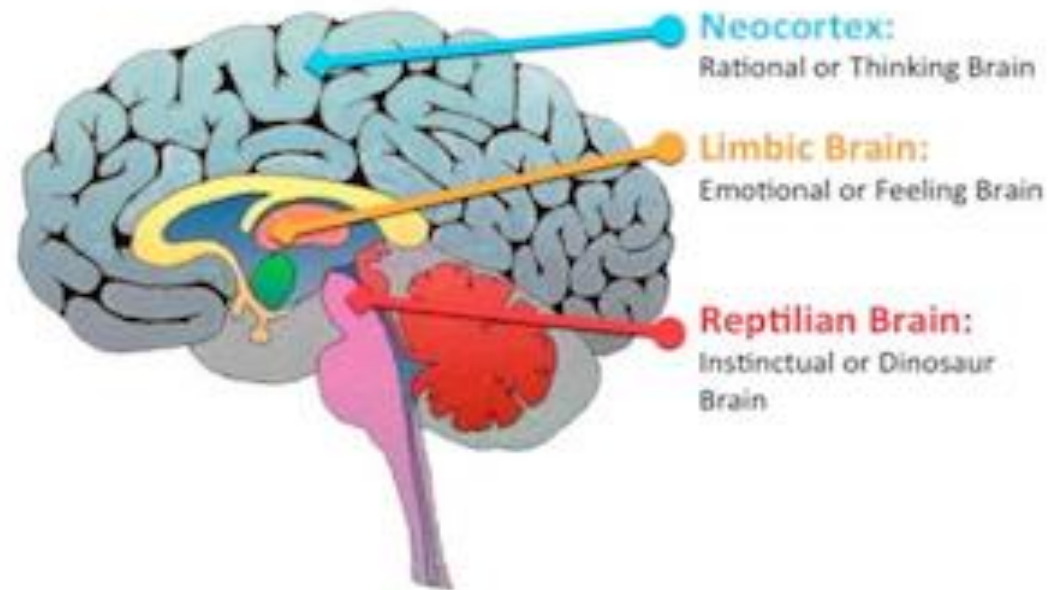
Centrum voor seksuologie en gender

Sekseverschillen in de hersenen (Ruigrok et al, 2014)

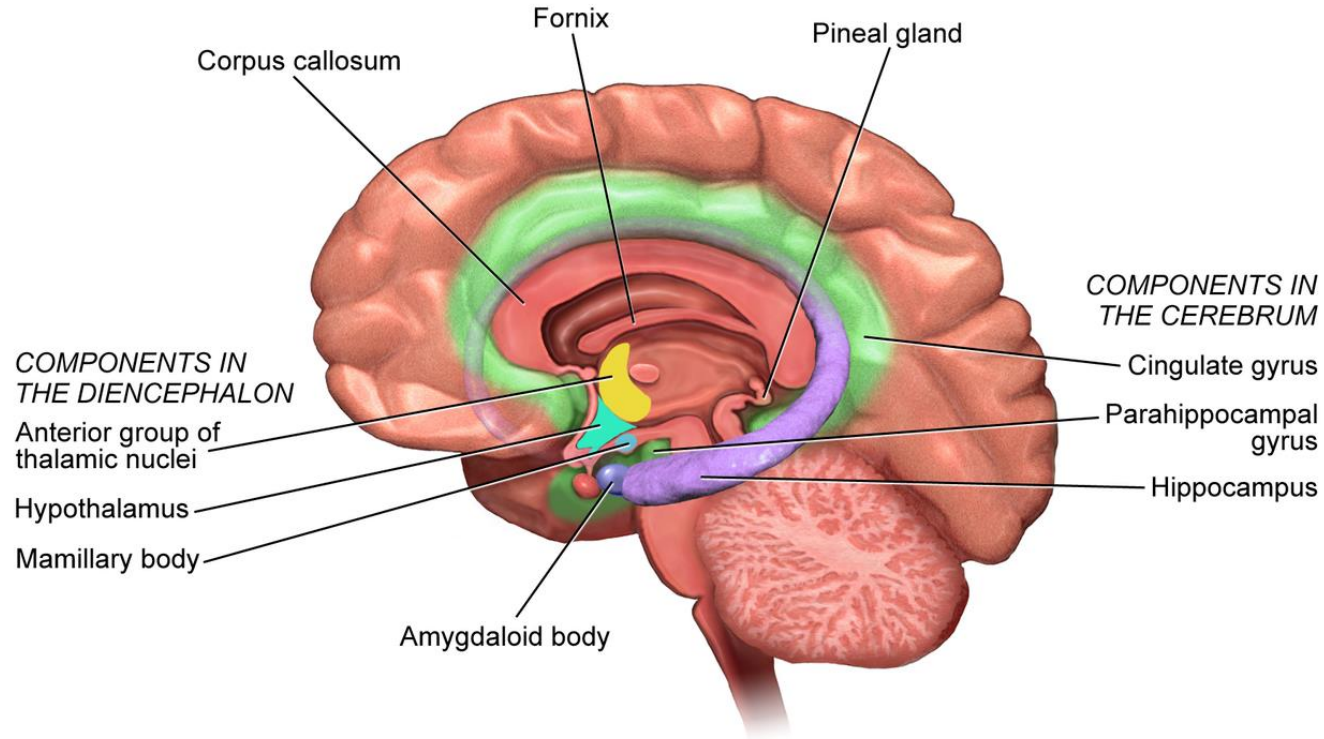
- Mannen 8-13% groter absoluut **volume**: nagenoeg alle regio's/bestanddelen (cerebrum, cerebellum, witte en grijze stof, CSF)
- Ook verschillen **weefseldensiteit**
- Verschillen vastgesteld over alle leeftijdscategorieën
- Verschillen veel kleiner dan gelijkenissen!
- Limbisch systeem!



De hersenen: overzicht



The Limbic System



Functies Limbisch systeem

Emotie (gyrus cinguli, insula)

Emotieregulatie (amygdala)

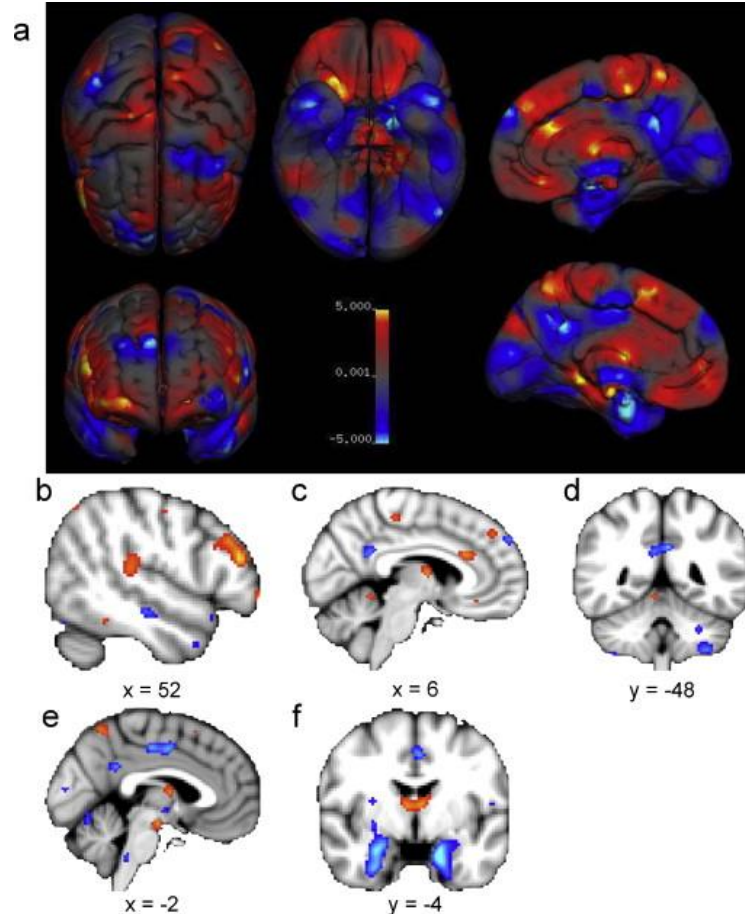
Emotioneel geheugen (amygdala, hippocampus)

Motivatie

Planning (OFC)

Genot (nucleus accumbens)

A meta-analysis of sex differences in human brain structure: brain volume (Ruigrok et al, 2014)

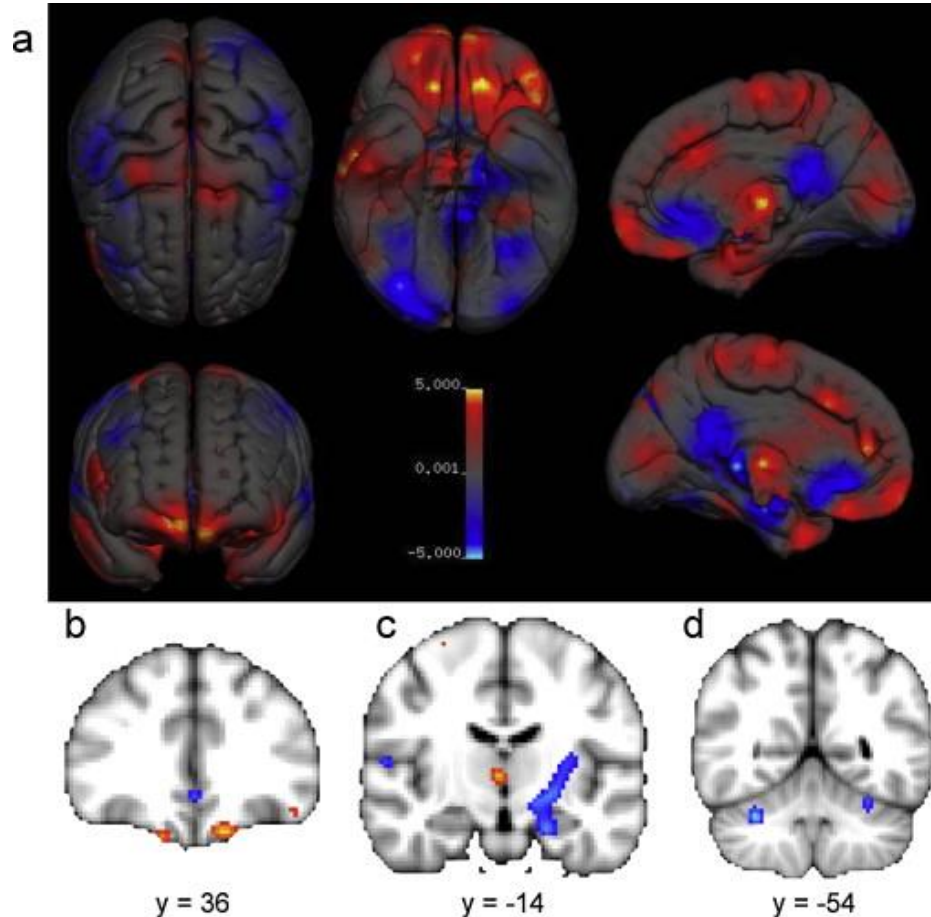


The [amygdala](#), [hippocampus](#), [planum temporale](#) and [insula](#) display sex differences.

- On average, males have larger brain volumes than females.

Panels b–f display areas of larger volume in females (red) including (b) the right inferior and middle frontal gyri, pars triangularis and planum temporale; (c) thalamus and right anterior cingulate gyrus; and (f) left and right thalamus; and areas of larger volume in males (blue), including (c) the anterior cingulate gyrus; (d) bilateral posterior cingulate gyrus and precuneus and left cerebellum; (e) anterior and posterior cingulate gyri; and (f) left and right amygdalae, hippocampi and parahippocampal gyri.

A meta-analysis of sex differences in human brain structure: tissue density (Ruigrok et al, 2014)



Voxel-based regional sex differences in grey matter density. Female > Male in red, and Male > Female is in blue. Panel a, rendered overview of uncorrected regional sex differences in grey matter concentration. All other panels are thresholded at FDR $q < 0.05$. Panels b–c display areas of larger volume in females (red) in (b) frontal pole and (c) right thalamus; and in males (blue) including (c) left amygdala, hippocampus, insular cortex and putamen; (d) right and left cerebellum VI lobe.

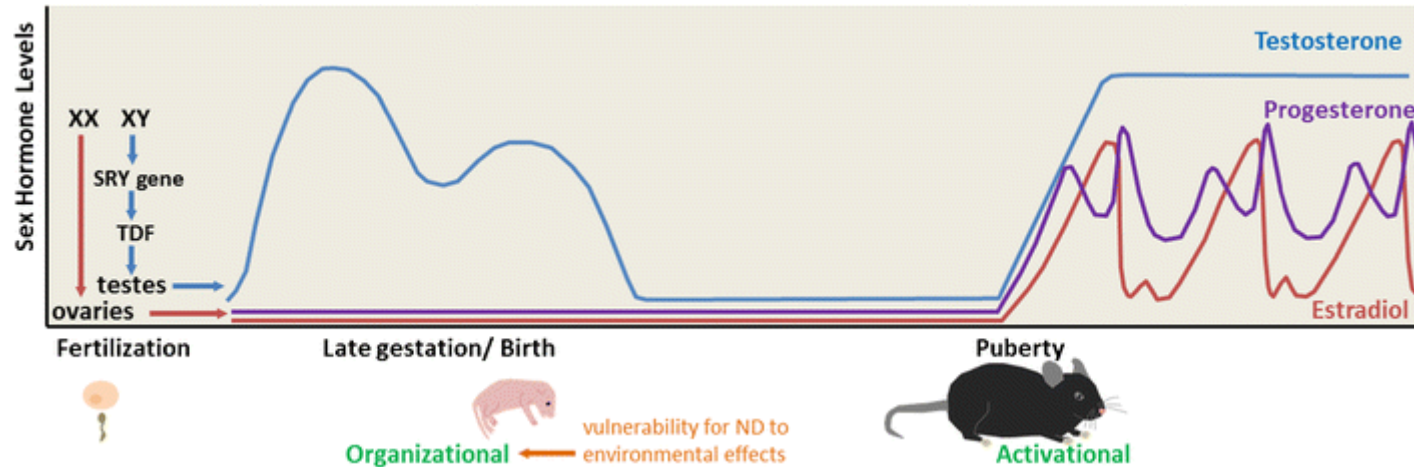
Verklaring sekseverschillen hersenen (McCarthy et al, 2015; McEwen & Milner, 2017))

- Zowel prenataal als postnataal differentiatie structuur en functie: genetisch, omgeving, epigenetisch
- Initieel “tunnelvisie”: verschillen gelimiteerd tot hersenengebieden betrokken bij reproductie (hypothalamus/hypofyse)
- Naderhand bredere invloed van hormonen op hersenstructuren (bv hippocampus)
- Op heden evidentie invloed hormonen op diverse hersenstructuren (frontale cortex, sensorimotorische cortex, ...)
- Sekseverschillen met betrekking tot reactie op stress (hippocampus): vrouwen meer responsief voor acute stress, en minder adaptatie tov chronische stress (neuro-immunologisch)

Sekseverschillen psychiatrische aandoeningen

- Male bias: autisme, ADHD, schizofrenie (Neurodevelopmental disorders, ND)
- Female bias: angst en depressie

Invloed geslachtshormonen Neurodevelopmental disorders (ND)(Ferri et al, 2018)



Many of the genes associated with autism encode proteins involved in synapse formation or maintenance, cell adhesion, and scaffolding. These molecules may be targets of hormones during the organizational period of development, resulting in the male preponderance observed in ND

Hypotheses sekseverschillen ND (Ferri, 2018)

		Female Protective Effect	Both/Either	Male Vulnerability
Multi-Hit Hypothesis	Genes	Females require higher genetic and symptomatic burden	Sex-specific SNPs, CNVs, SNPs	Genes over-represented genes in male brains implicated in ASD
		Relatives of affected females more likely to be affected	Risk genes interact with sex-specific pathways	Y chromosome haplotypes may increase ASD risk
		X-inactivation genes protective		
Epigenetics	Females need higher epigenetic dysregulation for diagnosis	Sex-specific transcriptome	Male rats show decreased MeCP2 after VPA	
Environment	Females have lower fT	←	Sex differences in neurotransmitters, neuropeptides increase risk	fT affects ASD-related pathways, proteins, processes
			Sex differences in immune function affect males and females differently	Increased immune activation affects males more
			Diagnosis based on male research; females under-represented	

Summary of theories and phenomena that contribute to the male bias of ASD and ND. *fT* fetal testosterone, *SNP* single nucleotide polymorphism, *SNV* single nucleotide variant, *CNV* copy number variant, *MeCP2* methyl-CpG-binding protein 2, *VPA* valproic acid

Autisme

- M/F ratio: 3-4: 1 (hoger bij normaal IQ, lager bij IQ < 70)
- Onderschatting bij meisjes/vrouwen!

ADHD

- M>F kinderleeftijd en adolescentie
- M = F volwassenleeftijd? (wisselende resultaten)
- referral bias, M meer externaliserend, F meer internaliserend

ADHD (Rucklidge, 2010)

Variable	Boys vs Girls	Men vs Women
Hyperactivity/impulsivity	M>F	M>F
Inattention	F>M	F>M
Tactile defensiveness (sensory processing)	F>M	?
Low self-esteem	F>M	F = M?
Poorer coping skills	F>M	F = M
Deficit in IQ	F>M	?
Deficit in executive functioning	F = M ^a	F = M
Motor function deficits	M>F	?
Anxiety	F>M (SAD only?)	=
Depression	F>M?	=

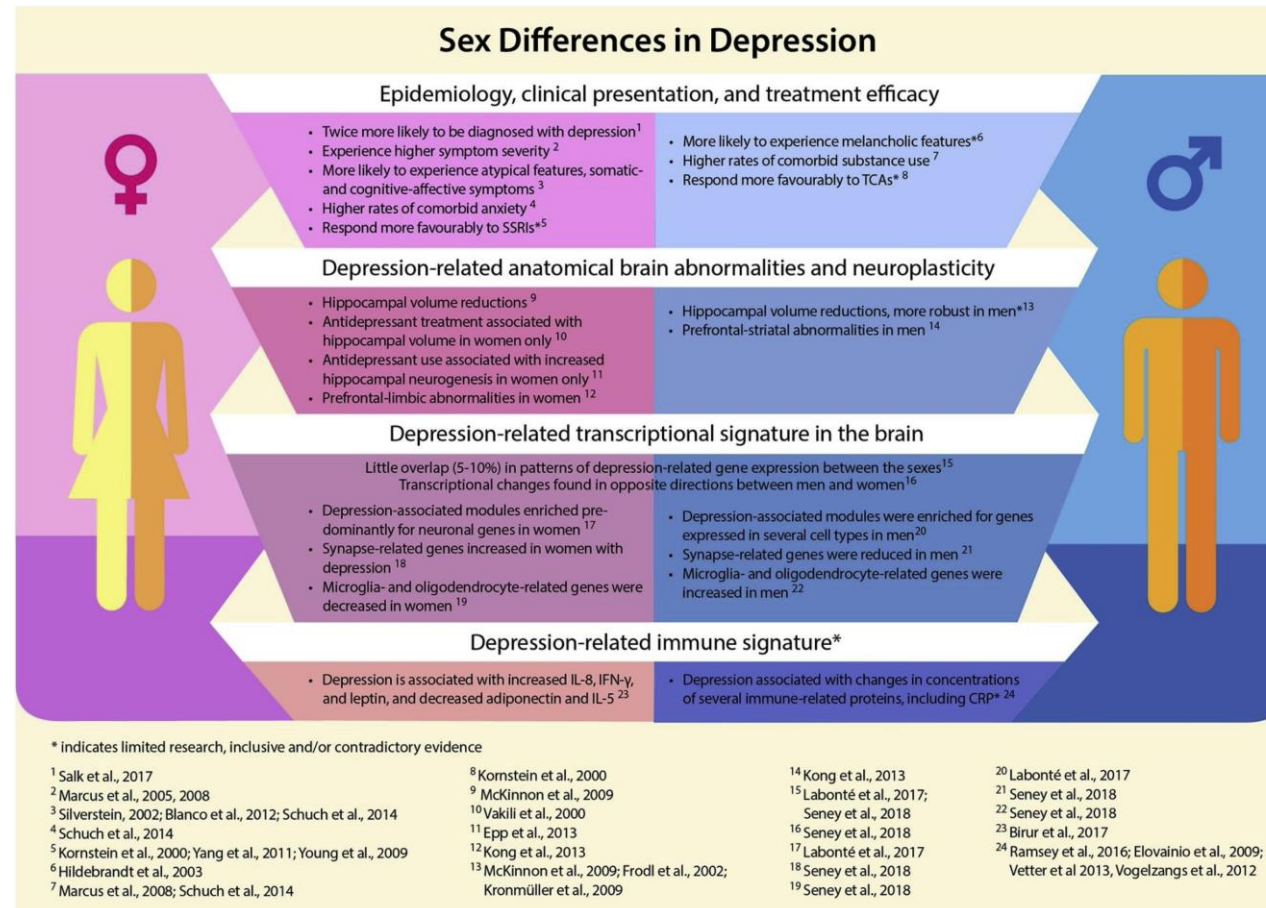
Schizofrenie

- M: vroegere onset dan F
- F: 2^e piek post-menopauze
- Prevalentie vergelijkbaar, andere incidentie.
- Beschermend effect oestrogenen?

Depressie

- Ratio M/F= 1:2
- F= meer atypische symptomen (hypersomnie, vermoeidheid,...)
- F = meer suïcidaal gedrag
- F= meer comorbiditeit angst en somatische symptomen
- Peripartum: verhoogd risico
- M = betere respons TCA, F = SSRI's (vooral premenopauze)

Depressie (Eid et al, 2019)



Angst (Bekker & van Mens-Verhulst, 2007)

Table 1. Prevalence of anxiety disorder subtypes and ratios of women versus men in *DSM-IV-TR*.^{3,5}

Anxiety Disorder Subtypes	Lifetime and Community-Based Prevalence, %	Women:Men
Agoraphobia	1.6 [*]	4:1 [†]
Panic disorder without agoraphobia	1-2	2:1
Panic disorder with agoraphobia	1-2	3:1
Specific phobia	7.2-11.3	2:1 [‡]
Social phobia	3-13	1:1 [§]
Obsessive-compulsive disorder	2.5	1:1
Posttraumatic stress disorder	8	2:1 [¶]
Acute stress disorder	14-33 [#]	Unknown
Generalized anxiety disorder	5	3:1

Middelengebruiksstoornis (Mc Hugh et al, 2018)

- M > F, maar gap wordt nauwer!
- Illegale middelen: M>F, medicatie M=F
- F = latere onset, mogelijk snellere progressie
- F = meer psychiatrische comorbiditeit (negatief effect prognose)
- Effect behandeling vergelijkbaar, mits targeted ifv co-morbiditeit

Sekseverschillen effect psychotropica (Duffy & Epperson, 2021)

- BEPERKT BESTUDEERD!
- Verschillen effecten en ongewenste effecten
- Vrouwen vaker psychotropica voorgeschreven (zelfs voor aandoeningen die meer bij mannen voorkomen)
- Bias op niveau studies: vrouwen vaak ondervertegenwoordigd
- Zelden differentiatie qua behandeling in functie van sekse!
- Zwangerschap en lactatie!

Sekseverschillen effect psychotropica

- In conclusion, women compared to men, tend to have a greater bioavailability and slower elimination of drugs leading to higher concentrations of free circulating drugs in serum and causing more side effects and adverse reactions to the psychotropic medication than men do. In general, women require lower doses of antidepressants, antipsychotics and benzodiazepines than men.