Klinisk neuropsykologi: epilepsi och neurodegenerativa sjukdomar

Thomas Karlsson

Epilepsy

The Patient H.M.

Henry Molaison, aged 60 in 1986, sits for tests at MIT. By this point, he had been the subject of study for half his life. Photograph: Jenni Ogden from the book "Trouble In Mind: Stories from a Neuropsychologist's Casebook". See also: *http://www.newyorker.com/books/page-turner/the-man-who-forgot-everything*

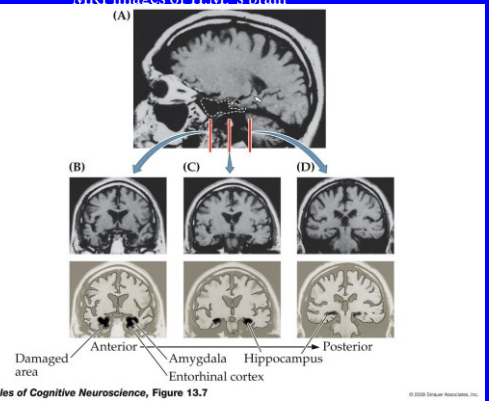
If We had the Whole Day: Brenda Milner

- https://www.youtube.com/watch?v=g4-6A8u8QBc (1 h interview about H.M., the right frontal cortex, and other interesting stuff)
- https://www.youtube.com/watch?v=JliczINA__Y (12 min summary)

The Patient H.M.

Henry Molaison, aged 60 in 1986, sits for tests at MIT. By this point, he had been the subject of study for half his life. Photograph: Jenni Ogden from the book "Trouble In Mind: Stories from a Neuropsychologist's Casebook". See also: *http://www.newyorker.com/books/page-turner/the-man-who-forgot-everything*

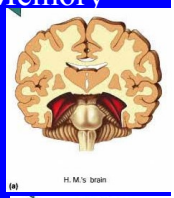
MRI images of H.M.'s brain

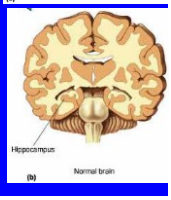


Principles of Cognitive Neuroscience, Figure 13.7

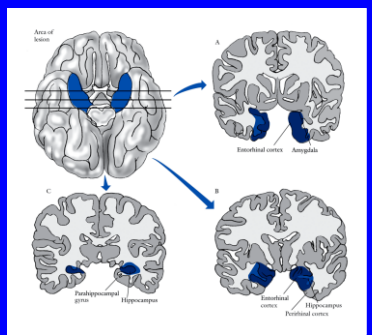
IV. Temporal Lobe & Memory

- B. H.M. (case study)
- 1. epilepsy surgery in 1953
- 2. bilateral medial temporal lobe removed (23.8)
- a. cortex
- b. amygdala
- c. hippocampus
- 3. partial retrograde amnesia
- 4. profound anterograde amnesia
- 5. long-term memories intact
- 6. short-term memory normal
- 7. procedural memory intact



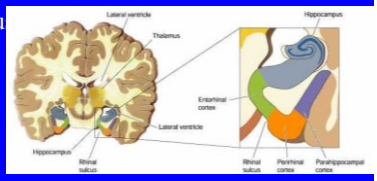


Brain structures removed during H.M.'s surgery.



Temporal Lobe & Memory

- C. Medial temporal lobe structures (23.9)
- 1. hippocampu
- 2. entorhinal
- cortex
- 3. perirhinal
- cortex
- 4. parahippocampal cortex



Compulsory Sterilization

- In Sweden, regulated by law 1934-2013
- From 1941, disability included

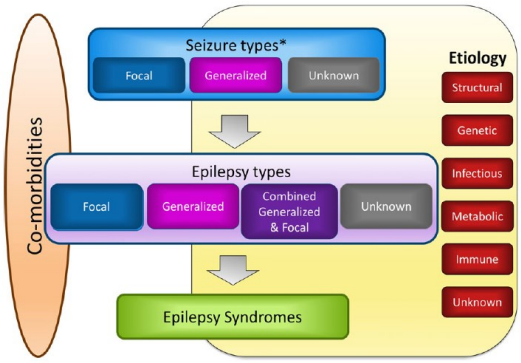
- Lifetime prevalence 5 %
- Point prevalence 5.5 per 1000 (Forsgren, 1992)
- Incidence 40-70 per 100000 (rich countries)
  100-190 per 100000 (poor countries
- Decreases among children, increases among the elderly

- Substantially decreases quality of life:
  - Threats to physical safety.
  - Generation of new epileptogenic foci (may ↑ seizure frequency/duration).
  - Epileptic encephalopathy or Sudden unexpected death in epilepsy (SUDEP).
- Medical treatment fails in 30% of cases.

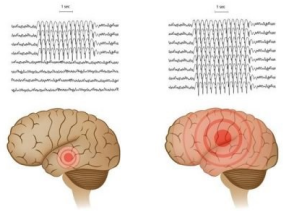
- Surgical management ↓ health care costs and ↑ quality of life.
  - Success rate is related to the *epileptogenic zone*.
- Epileptogenic Zone = Area of cortex indispensable for generation of seizures. Aimed to be completely resected/disconnected for control of seizures. May or may not be identifiable on imaging.

New Classification

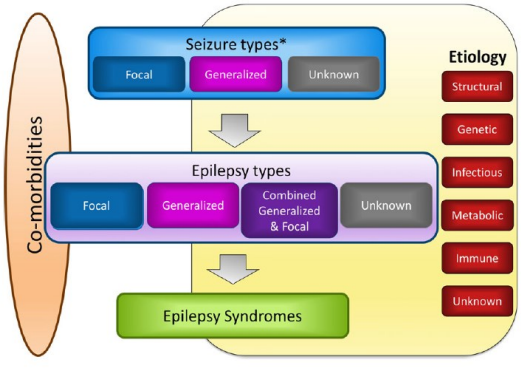
- The International League Against Epilepsy (ILAE) has approved a new way of organizing seizures that reflects recent advances in our understanding of the brain and seizures. This new system will make diagnosis and classification of seizures easier and more accurate.
- These terms don't change what occurs during a seizure, but offer a different way of naming seizures. More accurate ways of naming seizures can lead to more appropriate treatment.



Scheffer *et al*. *Epilepsia*, *58*(4):512–521, 2017 doi: 10.1111/epi.13709

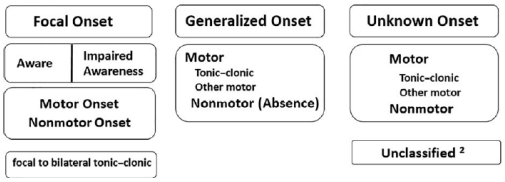


Focal seizure Generalized seizure



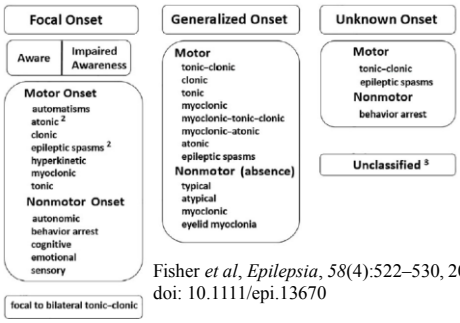
Scheffer *et al*. *Epilepsia*, *58*(4):512–521, 2017 doi: 10.1111/epi.13709

Seizure Types



Fisher *et al*, *Epilepsia*, *58*(4):522–530, 2017 doi: 10.1111/epi.13670

Seizure Types (Expanded)



Fisher *et al*, *Epilepsia*, *58*(4):522–530, 2017 doi: 10.1111/epi.13670

Generalized seizures (1' 15''):
http://www.youtube.com/watch?v=w5Jv0SZRwwk&feature=fvwrel

Focal (formerly partial) seizures:
http://www.youtube.com/watch?v=e10FSjHvV74&feature=relmfu

3 min

Table 1. Changes in seizure type classification from 1981 to 2017

1. Change of "partial" to "focal"
2. Certain seizure types can be either of focal, generalized, or unknown onset
3. Seizures of unknown onset may have features that can still be classified
4. Awareness is used as a classifier of focal seizures
5. The terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized were eliminated
6. New focal seizure types include automatisms, autonomic, behavior arrest, cognitive, emotional, hyperkinetic, sensory, and focal to bilateral tonic–clonic seizures. Atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be either focal or generalized
7. New generalized seizure types include absence with eyelid myoclonia, myoclonic absence, myoclonic–tonic–clonic, myoclonic–atonic, and epileptic spasms

Electroclinical syndromes arranged by age at onset[a]
- Neonatal period
  - Benign familial neonatal epilepsy (BFNE)
  - Early myoclonic encephalopathy (EME)
  - Ohtahara syndrome
- Infancy
  - Epilepsy of infancy with migrating focal seizures
  - West syndrome
  - Myoclonic epilepsy in infancy (MEI)
  - Benign infantile epilepsy
  - Benign familial infantile epilepsy
  - Dravet syndrome
  - Myoclonic encephalopathy in nonprogressive disorders
- Childhood
  - Febrile seizures plus (FS+) (can start in infancy)
  - Panayiotopoulos syndrome
  - Epilepsy with myoclonic atonic (previously astatic) seizures
  - Benign epilepsy with centrotemporal spikes (BECTS)
  - Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
  - Late onset childhood occipital epilepsy (Gastaut type)
  - Epilepsy with myoclonic absences
  - Lennox-Gastaut syndrome
  - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)[b]
  - Landau-Kleffner syndrome (LKS)
  - Childhood absence epilepsy (CAE)
- Adolescence – Adult
  - Juvenile absence epilepsy (JAE)
  - Juvenile myoclonic epilepsy (JME)
  - Epilepsy with generalized tonic–clonic seizures alone
  - Progressive myoclonus epilepsies (PME)
  - Autosomal dominant epilepsy with auditory features (ADEAF)
  - Other familial temporal lobe epilepsies
- Less specific age relationship
  - Familial focal epilepsy with variable foci (childhood to adult)
  - Reflex epilepsies

Distinctive constellations
- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy

Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)

Epilepsies attributed to and organized by structural-metabolic causes
- Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)
- Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
- Tumor
- Infection
- Trauma
- Angioma
- Perinatal insults
- Stroke
- Etc.

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
- Benign neonatal seizures (BNS)
- Febrile seizures (FS)

[a]The arrangement of electroclinical syndromes does not reflect etiology.
[b]Sometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).

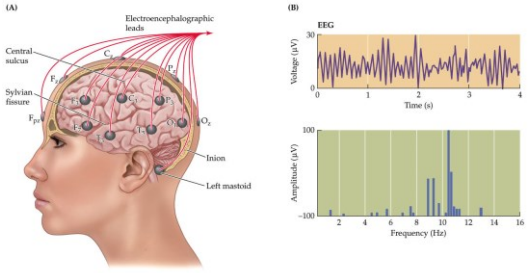
Electroclinical syndromes and other epilepsies

En neurofysiologisk diagnos

- 20 % av patienter som söker hos högspecialiserade centra (inriktade på terapiresistent epilepsi) har psykogena, icke-epileptiska anfall (men 30 % av dessa har också epilepsi); 5 % på vanlig neurologmottagning
- EEG

Studying The Brain's Electrical Activity
EEG Recordings

- Electroencephalogram (EEG)
  - Hans Berger in 1930s
- Electrodes are placed onto the skull
- Measures the summed graded potentials from many thousands of neurons, especially the neocortex



Studying The Brain's Electrical Activity
EEG Recordings

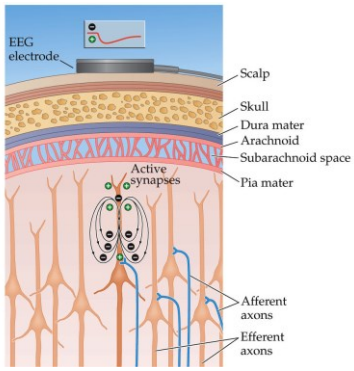
Three Important Features:

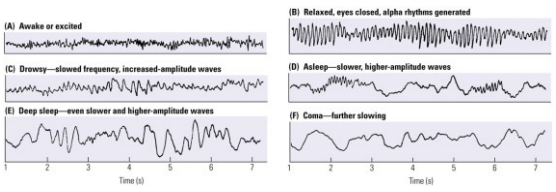
1. The living brain's electrical activity is <u>never</u> silent, even when a person is asleep or anesthetized
   - Amplitude (height of brain waves)
   - Frequency (number of brain waves per second)

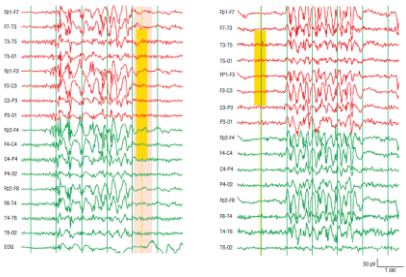
Studying The Brain's Electrical Activity

EEG Recordings

2. An EEG recorded from the cortex has a large number of patterns, some of which are rhythmic
   - Example: Alpha rhythm
     - Rhythmic EEG wave with a frequency of 11 cycles per second
3. The EEG changes as behavior changes
   - From alert to coma





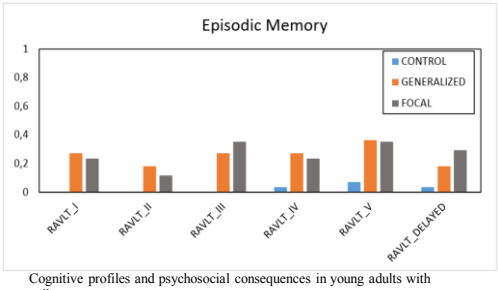


Classic 'slow-wave' discharges. Nguyen, *et al., Arch Neurol. 2006 ;63: 1321-1323.*

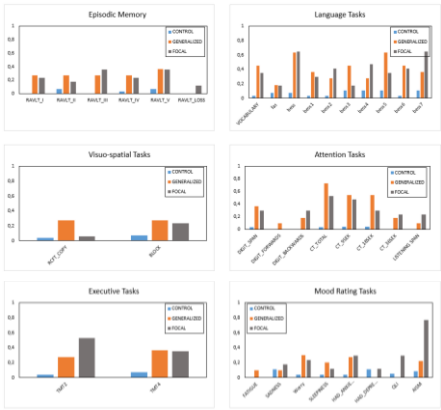
Tabell 8. Tabellen anger förekomsten av nio typer av kognitiva problem i samband med epilepsi.

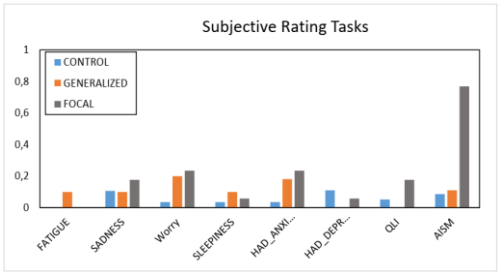
Domän	Förekomst	Antal personer/100 000	
		Lägsta	Högsta
Global	1,7	604	604
Uppmärksamhet	20,17	7 169	7 169
Minne	28,19	10 018	10 018
Exekutiv	18,67	6 633	6 633
Problemlösning	5,79	2 057	2 057
Arbetsminne	20,47	7 273	7 273
Språk	7,54	2 678	2 678
Visuospatial	9,77	3 472	3 472
Motor/praxis	18,55	6 590	6 590
Kognitiv hastighet	--	--	--
Någon	--	--	--

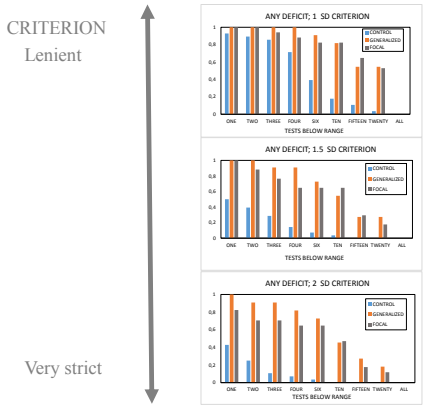
*Uppskattat antal personer i befolkningen med denna kognitiva funktionsnedsättning



Cognitive profiles and psychosocial consequences in young adults with epilepsy.
Helena Gauffin, Anne-Marie Landtblom, Daniel Ulrici, Anita Mc Allister, Helene Veenstra and Thomas Karlsson. *Manuscript in preparation*.


Episodic Memory
Language Tasks
Visuo-spatial Tasks
Attention Tasks
Executive Tasks
Mood Rating Tasks
CONTROL
GENERALIZED
FOCAL

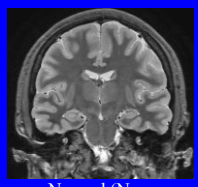

Subjective Rating Tasks
CONTROL
GENERALIZED
FOCAL
1
0,8
0,6
0,4
0,2
0
FATIGUE
SADNESS
Worry
SLEEPINESS
HAD_ANXI...
HAD_DEPR...
QLI
AISM


CRITERION
Lenient
Very strict
ANY DEFICIT; 1 SD CRITERION
ANY DEFICIT; 1.5 SD CRITERION
ANY DEFICIT; 2 SD CRITERION
CONTROL
GENERALIZED
FOCAL
ONE
TWO
THREE
FOUR
SIX
TEN
FIFTEEN
TWENTY
ALL
TESTS BELOW RANGE

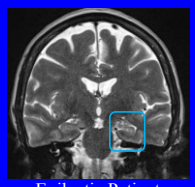
Hippocampal Sclerosis/Mesial Temporal Sclerosis

Hippocampal Sclerosis/Mesial Temporal Sclerosis

- Most common form of focal epilepsy, also with the highest surgical success rate.
- Coronal oblique images for evaluation of internal architecture of hippocampus (perpendicular to its main axis).
- Epileptic patient: Hippocampal asymmetry highlights abnormal T2 hyperintense signal, volume loss, and loss of internal architecture.

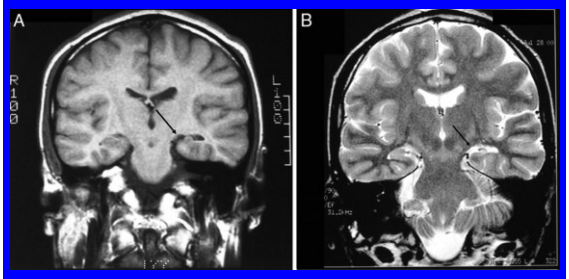


Normal (Non-Epileptic) Patient

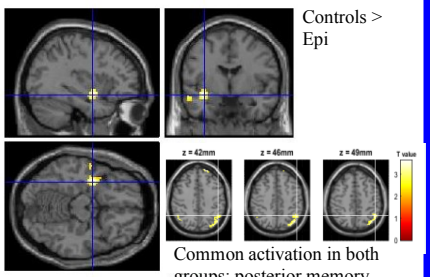


Epileptic Patient

Hippocampal Sclerosis/Mesial Temporal Sclerosis



HS: fMRI

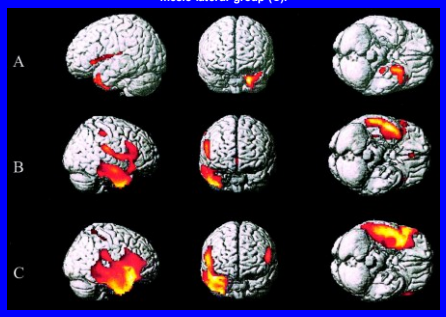


Controls > Epi

Common activation in both groups: posterior memory network

HS: Metabolism

Fig. 1 3D MRI representation of hypometabolic areas in MTLE patients (significant differences compared with 10 healthy volunteers using SPM99, threshold: P = 0.001, corrected for extent to 20 voxels) in the mesial group (A), the anterior mesial-lateral group (B) and the widespread mesio-lateral group (C).



Francine Chassoux et al. Brain 2004;127:164-174

HS: Neuropsychology

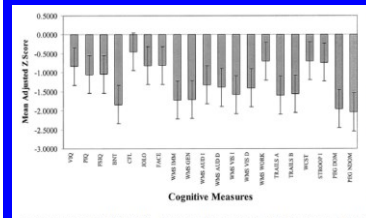
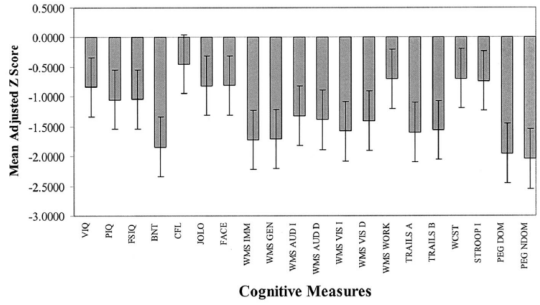


Figure 1. Mean adjusted (age, gender, education) z scores for patients with temporal lobe epilepsy compared with healthy control subjects. Epilepsy patients performed significantly worse across all test measures. VIQ = Verbal IQ; PIQ = Performance IQ; FSIQ = Full-Scale IQ; BNT = Boston Naming Test; CFL = Letter Fluency; JOLO = Judgment of Line Orientation; FACE = Facial Recognition; WMS IMM = Wechsler Memory Scale–III Immediate Memory; WMS GEN = Wechsler Memory Scale–III General Memory; WMS AUDI = Wechsler Memory Scale–III Auditory Immediate; WMS AUDD = Wechsler Memory Scale–III Auditory Delay; WMS VISI = Wechsler Memory Scale–III Visual Immediate; WMS VISD = Wechsler Memory Scale–III Visual Delay; WMS WORK = Wechsler Memory Scale–III Working Memory; TRAILS A = Trail Making Test A; TRAILS B = Trail Making Test B; WCST = WCST-64 Wisconsin Card Sorting Test–Preservative Responses; STROOP-I = Stroop Color–Word Interference; PEG DOM = Grooved Pegboard–Dominant Hand; PEG NDOM = Grooved Pegboard–Nondominant Hand.

HS: Neuropsychology



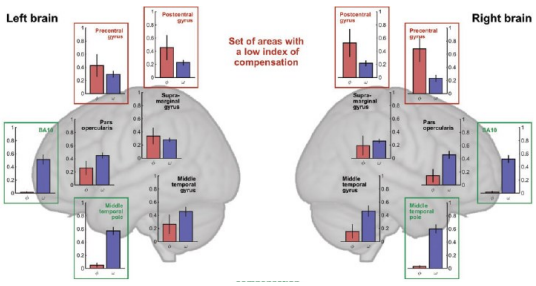
Epilepsy Surgery

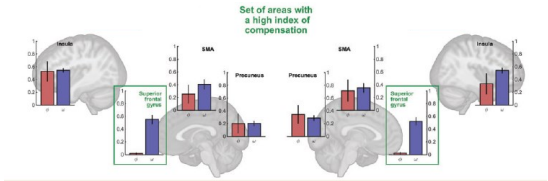
Epilepsy Surgery

- Preservation of function
- Keep the patient awake
  - EEG, fMRI, and other imaging modalities doesn't tell the whole story

Epilepsy Surgery

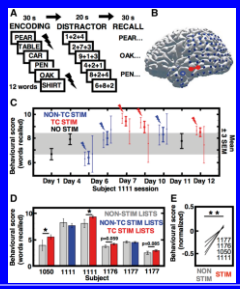
http://www.theguardian.com/world/video/2015/jun/04/man-plays-guitar-conscious-brain-surgery-video

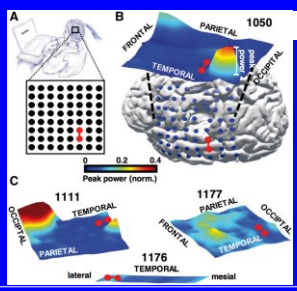




Treatment

- Stimulation of *lateral* temporal cortex



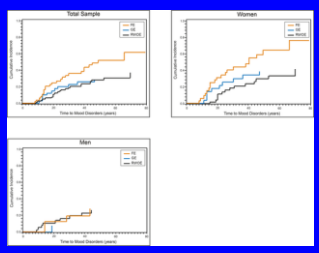


Gamma frequency: 32 – 100 Hz

Relation to Psychiatric Problems

- "Melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy."
- Hippocrates, ≈ 400 BC

Mood disorders in familial epilepsy: A test of shared etiology



Mood disorders in familial epilepsy: A test of shared etiology, Epilepsia, *59* (2), 431-439, First published: 10 January 2018, DOI: (10.1111/epi.13985)

Mood disorders in familial epilepsy: A test of shared etiology

- Increased risk in women with focal, idiopathic epilepsy
- Slight increase in relatives

Mood disorders in familial epilepsy: A test of shared etiology, Epilepsia, *59* (2), 431-439, First published: 10 January 2018, DOI: (10.1111/epi.13985)

Affektiva störningar--ED

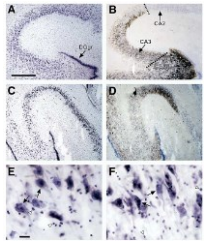


Figure 1. Brightfield photomicrographs of coronal sections of the postmortem human hippocampal formation. (**A**) Cresyl violet–stained section from a 70-year-old male control subject (postmortem interval = 29 hours) and (**B**) an adjacent section processed by Timm staining. Note the intensely stained granule cell layer of the dentate gyrus (DGgr) in (**A**) and (**B**), and the clear demarcation in (**B**) between hippocampal subfields CA2 and CA3 afforded by the Timm staining. A dashed line identifies the border between CA2 and CA3, and the second dashed line shows the border between CA3 inserted within the dentate gyrus (DG) and CA3 external to the dentate gyrus. (**C**) Cresyl violet–stained section from a depressed 77-year-old man (postmortem interval = 26 hours) and (**D**) an adjacent section processed by Timm staining. Pyramidal neurons and glial nuclei of CA3 are highlighted (**E**, Control; **F**, MDD) with large black arrows and white arrowheads, respectively. The scale bars in (**A**) and (**E**) are 730 μm and 25 μm, respectively.

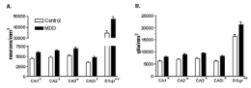
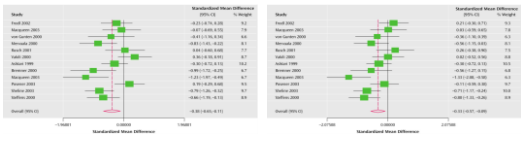


Figure 3. Neuronal (**A**) and glial (**B**) density in the hippocampus of control subjects and subjects with major depressive disorder (MDD). Pyramidal neurons were quantified in hippocampal fields CA1–CA3, and granule cells were quantified in the granule cell layer of the dentate gyrus (DGgr) of 21 control subjects and CA3 and dentate gyrus (DGgr) from 19 depressed subjects. Data in CA1 and CA2 are presented from 18 depressed subjects. Values are least squares adjusted means ± SE. (**A**) There is a significant effect of diagnosis on pyramidal neuron density in all CA subfields (*$p < .0001$) and granule cell density in the dentate gyrus (**$p = .0004$). Pyramidal neuron density is increased by 35%–36% in CA subfields, and granule cell density is increased in the dentate gyrus by 37%. (**B**) There is a significant effect of diagnosis on glial cell density in all CA pyramidal neuron subfields (*$p < .0001$) and glial cell density in the granule cell layer of the dentate gyrus (**$p = .0007$). Glial cell density is increased by 28%–31% in the CA pyramidal neuron subfields and glial cell density is increased in the granule cell layer of the dentate gyrus by 30%.

Hippocampus



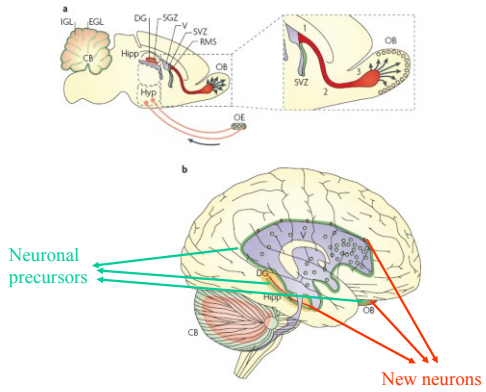
Left Right

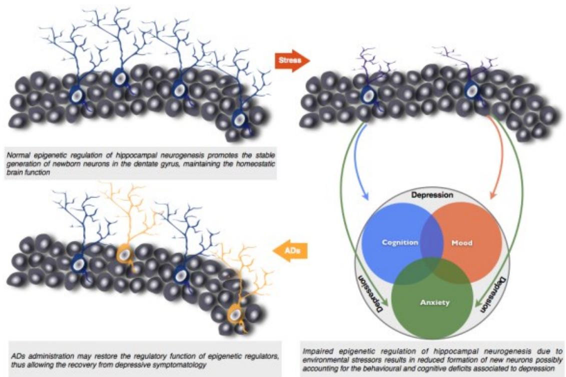
Stamceller

- Embryonala stamceller
- Neuronala stamceller

Stamceller

- Däggdjur och fåglar utnyttjar olika strategier
- Påtaglig neurogenes i hörselkortex hos fåglar i samb med häckning och apoptos vid flyttning
- Däggdjur har ingen liknande känd neuronal strategi!





Mateus-Pinheiro *et al. Clinical Epigenetics* 2011 **3**:5 doi:10.1186/1868-7083-3-5

TABLE 1. Studies of Hippocampal Volume in Patients With Unipolar Depression

Study and Year	Magnet Strength (T)	Slice Thickness (mm)	Patients: N	Age (years) Mean	Age (years) SD	Male (%)	Left Volume (mm³) Mean	Left Volume SD	Right Volume (mm³) Mean	Right Volume SD	RECUR[a]	Comparison Subjects: N	Age (years) Mean	Age (years) SD	Male (%)	Left Volume (mm³) Mean	Left Volume SD	Right Volume (mm³) Mean	Right Volume SD	Hippocampal Volume: Between-Group Differences and Clinical Correlations
Posener et al. (28), 2003	1.5	1.0	27	33.0	10.7	44	2546.8	382.7	2948.4	446.7	3	42	33.2	10.8	45	2475.0	359.4	2993.9	414.2	No significant between-group difference. No correlation with number of episodes or accumulated duration of disease.
MacQueen et al. (20)[b], 2003	1.5	1.2	20	28.4	11.8	35	2738.8	301.1	2793.0	303.8	1	20	28.4	11.5	35	2761.0	368.4	2784.8	342.2	No significant between-group difference.
MacQueen et al. (20)[b], 2003	1.5	1.2	17	35.9	11.1	35	2381.8	275.5	2392.0	256.7	3	17	36.2	11.9	35	2703.0	249.0	2692.8	190.1	Bilateral hippocampal volume deficits in patients relative to comparison subjects. Correlation between bilateral hippocampal volume deficits and length of illness.
Frodl et al. (29), 2002	1.5	1.0	30	40.3	12.6	43	3681.8	395.0	3847.0	400.0	1	30	40.6	12.5	43	3772.0	397.0	3763.8	411.0	No significant between-group difference.
Rusch et al. (30), 2001	1.5	1.2	25	33.2	9.5	44	1770.8	230.0	1870.0	240.0	2	15	37.4	14.4	40	1768.0	250.0	1810.8	210.0	No significant between-group difference.
Mervaala et al. (25), 2000	1.5	3.0	34	42.2	12.2	47	3104.8	391.0	3462.0	405.0	3	17	42.1	14.6	35	3441.0	436.0	3700.8	467.0	Significantly lower left hippocampal volume in patients relative to comparison subjects.
Vakili et al. (32), 2000	1.5	3.0	38	38.5	10.8	45	2640.8	550.0	2610.0	580.0	2	20	40.3	10.4	45	2460.0	380.0	2600.8	510.0	No significant between-group difference. Correlation between smaller right hippocampal volume and poor antidepressant response in women.
von Gunten et al. (31), 2000	1.5	1.5	14	57.6		42	2498.6	294.8	2597.9	244.8	1	14	58.1		42	2644.4	489.4	2699.5	321.7	No significant between-group difference.
Steffens et al. (24), 2000	1.5	3.0	66	71.7	8.4	23	2820.8	360.0	2900.0	390.0	3	18	67.1	5.0	50	3170.0	440.0	3300.8	440.0	Significantly lower right hippocampal volume in patients relative to comparison subjects. Negative correlation between hippocampal volume and age at onset (older onset age associated with smaller hippocampus).
Bremner et al. (26), 2000	1.5	—[c]	16	43.0	8.8	63	948.0	288.0	982.0	269.0	3	16	45.0	10.0	63	1166.0	248.0	1113.8	194.0	Significantly lower left hippocampal volume in patients relative to comparison subjects. No correlation with number of episodes.
Ashtari et al. (33), 1999	1.0	3.1	40	74.3	6.8	29	1745.8	380.0	1742.0	345.0	3	46	71.4	8.3	40	1853.0	340.0	1843.8	337.0	No significant between-group difference. No correlation with number of episodes or age at onset.
Sheline et al. (50), 2003	1.5	1.3	24	50.8	17.1	0	2171.8	316.0	2203.0	315.0	3	24	52.8	17.8	0	2421.0	318.0	2429.8	326.0	Bilateral hippocampal volume deficits in patients relative to comparison subjects. Correlation between total hippocampus volume and days of untreated depression.

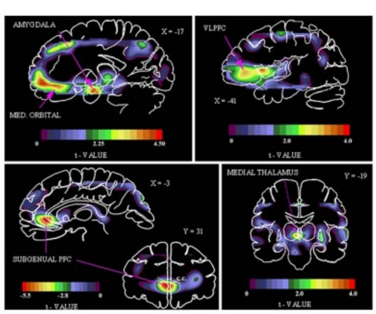
[a] 1=first-episode patients, 2=mixed group, 3=patients with recurrent depression.
[b] Data on first time depression and recurrent depression presented separately in this table.
[c] Data not given.

TABLE 2. Studies of Hippocampal Volume in Patients With Bipolar Depression

Study and Year	Magnet Strength (T)	Slice Thickness (mm)	Patients: N	Age (years) Mean	Age (years) SD	Male (%)	Left Volume (mm³) Mean	Left Volume SD	Right Volume (mm³) Mean	Right Volume SD	Comparison Subjects: N	Age (years) Mean	Age (years) SD	Male (%)	Left Volume (mm³) Mean	Left Volume SD	Right Volume (mm³) Mean	Right Volume SD	Hippocampal Volume: Between-Group Differences and Clinical Correlations
Brambilla et al. (40), 2003	1.5	1.5	24	35.0	10.0	63	3930.0	600.0	3910.8	710.0	36	37.0	10.0	63	4040.0	600.0	3850.8	540.0	No significant between-group difference. No correlation between hippocampal volume and age at onset, accumulated duration of disease, number of episodes, or lithium treatment.
Hauser et al. (41), 2000	0.5	5.0	25	41.8	10.5	48	6.8[a]	1.1[a]	6.4[a]	0.8[a]	19	35.2	7.1	53	6.6[a]	0.6[a]	6.4[a]	0.7[a]	No significant between-group difference.
Strakowski et al. (42), 1999	1.5	1.0	24	27.0	6.0	71	4380.0	600.0	4300.8	600	22	28.0	6.0	59	4200.0	400.0	4280.8	400.0	No significant between-group difference. No correlation between hippocampal volume and accumulated duration of disease, number of episodes, or treatment.
Altshuler et al. (38), 1998	1.5	1.4	12	50.8	13.3	100	2386.0	406.0	2462.8	412.0	18	53.4	11.1	100	2898.0	324.0	2222.8	388.0	No significant between-group difference.
Pearlson et al. (37)[b], 1997	1.5	5.0	11	34.9	8.6	0	399.8	145.0	304.8	45.0	17	31.6	8.0	0	376.0	100.0	420.0	131.0	No significant between-group difference.
Pearlson et al. (37)[b], 1997	1.5	5.0	16	34.9	8.6	100	400.8	76.0	414.8	77.0	43	31.6	8.0	100	385.0	87.0	416.8	105.0	No significant between-group difference.
Swayze et al. (36), 1992	0.5	10.0	48	33.9	—[c]	60	1340.0	388.0	1310.8	388.0	47	—[c]	—[c]	60	1440.0	410.0	1470.8	368.0	Significant lower right hippocampal volume in patients relative to comparison subjects.

[a] Unit of measurement not stated in paper.
[b] Data on male and female subjects given separately.
[c] Data not given.

Dissociation EG—BIP?



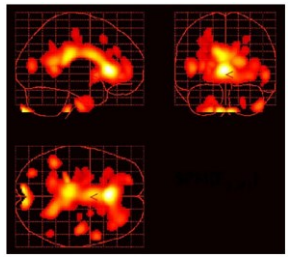
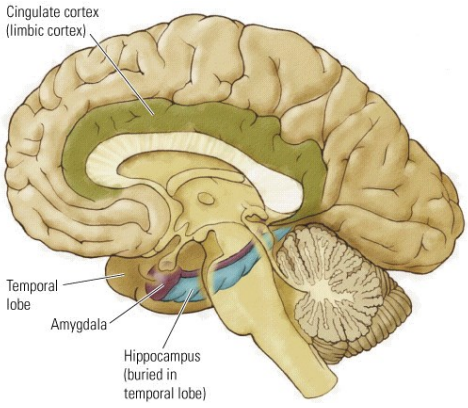
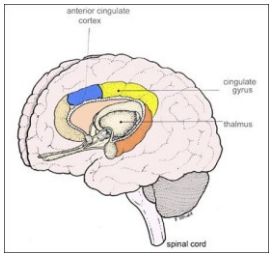


Fig. 4 Reduced muscarinic type 2 (M2) receptor binding in the cingulate cortex in depressed subjects with bipolar disorder relative to healthy controls. The statistical parametric map shows voxel t values corresponding to areas where the uptake of [^{18}F]FP-TZTP, a PET radioligand which selectively binds M2 receptors, was significantly reduced (at $P < 0.005$) in bipolar depressives relative to healthy controls. The areas of maximal difference between groups were located in the anterior cingulate cortex. Reproduced from Camus et al. (2006a)





Anterior cingulate

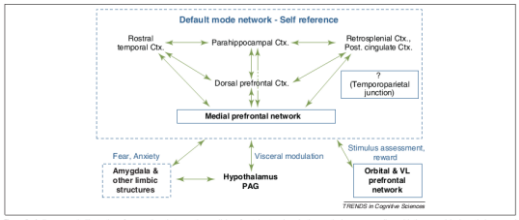
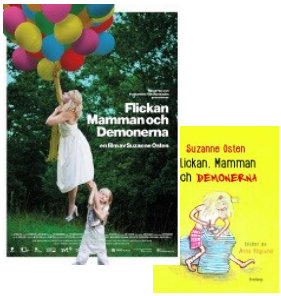


Figure 2. A diagrammatic illustration of connections between the medial prefrontal network and other cortical areas, as well as with the amygdala, hypothalamus and periaqueductal gray (PAG). Note that the medial network is part of the system that has been defined in humans as the 'default mode network' (DMN) and that connections have been defined in monkeys between all the components of the DMN, except the temporoparietal junction.

Schizophrenia



Schizophrenia

- **Schizophrenia** is a pattern of extremely disturbed thinking, emotion, perception, and behavior
  - Ability to communicate and relate to others is severely impaired
  - Most aspects of daily functioning are disrupted
- One of the most severe and disabling of all mental disorders

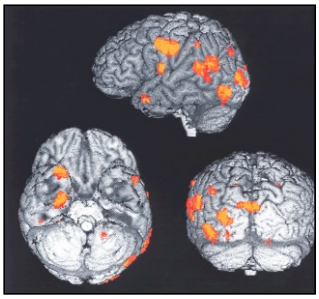
Symptoms of Schizophrenia

- Thought and language are often disorganized
  - Neologisms; loose associations; clang associations; word salads
- Content of thinking is often disturbed
  - Types of delusions include ideas of reference, thought broadcasting, thought blocking or withdrawal, and thought insertion
- Difficulty in focusing attention
  - May feel overwhelmed as they try to attend to everything at once

Symptoms of Schizophrenia (cont.)

- Perceptual disorders such as **hallucinations**
- Emotional expression is often muted (flat affect)
  - Expressions that are displayed are often exaggerated or inappropriate
- Lack of motivation and poor social skills
- Deteriorating personal hygiene
- Inability to function on a daily basis

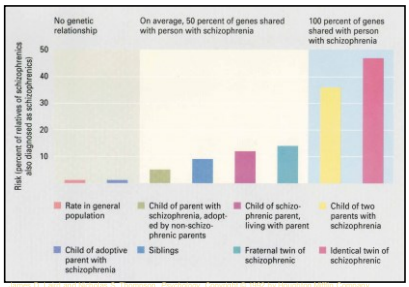
PET: Areas
of the Brain Activated During Hallucinations

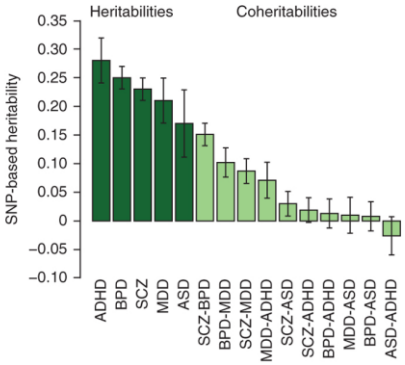


Categorizing Schizophrenia

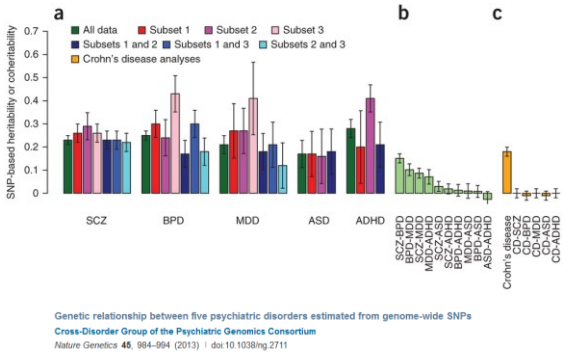
- DSM-IV subtypes
  - Paranoid
  - Disorganized
  - Catatonic
  - Undifferentiated
  - Residual
- Positive versus negative symptom dimension

Genetics and the Risk of Schizophrenia





Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs
Cross-Disorder Group of the Psychiatric Genomics Consortium
Nature Genetics **45**, 984–994 (2013) | doi:10.1038/ng.2711



Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs
Cross-Disorder Group of the Psychiatric Genomics Consortium
Nature Genetics **45**, 984–994 (2013) | doi:10.1038/ng.2711

Environmental Origins

- Malnutrition
  - More common following famine
- Viral infections in mothers
  - Influenza
  - Herpes Simplex?
- Early cannabis use

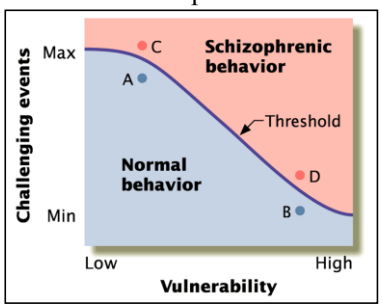
Other Biological Factors for Schizophrenia

- Possible abnormalities in brain chemistry, especially in neurotransmitter systems that use dopamine
- Possible neurodevelopmental abnormalities
  - Disruptions in brain development from before birth through childhood, when brain is growing and maturing

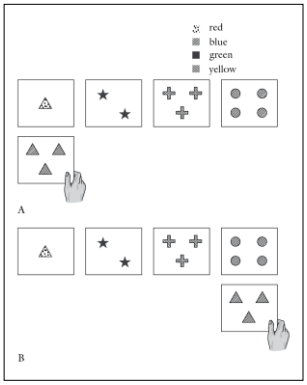
Psychological Factors

- Psychological factors alone are no longer considered to be primary causes of schizophrenia
- But psychological processes and social influences can contribute to appearance of schizophrenia and influence its course
  - e.g., maladaptive learning experiences
  - e.g., stressful family communication patterns

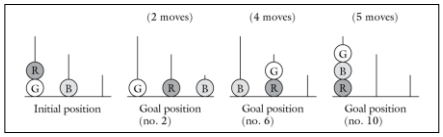
Figure 15.6 The Vulnerability Theory of Schizophrenia



Two examples of sorting behavior on the Wisconsin Card Sorting Test (WCST).



An example of three problems in the Tower of London task.



Fokus på prodromalfas

Neuropsykologi

Tabell 16. Tabellen anger förekomsten av elva typer av kognitiva problem i samband med psykossjukdomar (schizofreni och bipolär sjukdom). Effekten uttrycks som effektstorlek (Cohens *d*).

Domän	*d*	
	Schizofreni	Bipolär sjukdom
Global	--	--
Uppmärksamhet*	-1,02	-0,57
Minne*	-1,83	-0,78
Exekutiv	-1,10	-0,76
Problemlösning*	-0,83	-0,19
Arbetsminne	-0,67	-0,47
Språk	-0,99	0,04§§
Visuospatial	-0,56	-0,48§§
Motor/praxis	-0,41	-0,68§§
Kognitiv hastighet	-0,99	--
Taktil transfer**	-1,90	--
Någon‡	-1,43	--

*Avser icke-hospitaliserade personer. **Taktil bimanuell igenkänning av objekt. ‡Baserat på $\chi^2(1)=48{,}02$, $p<0{,}001$; data från Weickert et al. (2000). §§Data från Seidman et al. (2002).

BRITISH JOURNAL OF PSYCHIATRY (2003), 181 (suppl. 43), s30–s37

Subjective and objective neuropsychological abnormalities in a psychosis prodrome clinic*

MARTIN HAMBRECHT, MICHAEL LAMMERTINK, JOACHIM KLOSTERKÖTTER, EVELINE MATUSCHEK and RALF PUKROP

Table 1 Prevalence of self-perceived disturbances at the initial interview (rated as definitely present)

BSABS item no.	Self-perceived disturbance	% (n=51)
C.1.5	Difficulties concentrating	66.7
A.8.2+B.1.3	Impaired tolerance to certain social situations of everyday life that are primarily emotionally neutral	58.8
At least one of 15 symptoms (C.2.1d to C.2.3d2)	Visual perceptual disturbances†	52.9
A.8.1+B.1.2	Impaired tolerance to unusual, unexpected or specific novel demands	49.0
A.6.4	Decrease in the need for contact with others	47.1
C.1.3	Thought pressure†	43.1
At least one of four symptoms (C.2.4d to C.2.5s2)	Acoustic perceptual disturbances†	43.1
A.8.3+B.1.4	Impaired tolerance to working under pressure of time or rapidly changing different demands	37.3
C.1.7	Disturbance of expressive language	35.3
A.7.1	Decrease in the ability to maintain or initiate social contacts	35.3
C.2.8	Feeling overwhelmed by stimuli, hyperdistractability	33.3
C.1.1	Thought interference†	33.3
A.6.1	Change in mood and emotional responsiveness	31.4

Table 2 Observed psychopathology on Positive and Negative Symptom Scale (PANSS) and self-rated schizotypal traits at initial assessment in patients with and without transition (mean (s.d.))

	Transition $n=4$	No transition $n=40$	Total $n=44$
PANSS, positive score	14.0 (5.6)	11.1 (2.7)	11.2 (2.9)
PANSS, negative score	16.0 (3.5)	13.4 (5.0)	13.6 (4.9)
PANSS, general score	32.0 (6.2)	29.8 (4.2)	30.0 (4.4)
PANSS, total score	62.0 (11.5)	54.2 (8.8)	54.8 (9.1)
Magical ideation[1]	7.75 (6.4)	2.93 (2.7)	3.36 (3.4)
Physical anhedonia	5.25 (3.1)	4.15 (4.2)	4.25 (4.1)
Perceptual aberration	15.25 (7.8)	13.30 (8.1)	13.48 (8.0)

1. Mann–Whitney test: $P<0.10$ (transition v. no transition). Missing data for 7 patients (1 in the transition group, 6 in the no transition group).

Table 4 Differences in neurocognitive functions between prodromal patients (P), patients with schizophrenia (S), and normal controls (C); Mann–Whitney *U*-tests (mean (s.d.))

Neurocognitive function	Controls, $n=29$	Prodrome, $n=29$	Schizophrenia, $n=29$	*P* for P v. C	*P* for P v. S
Visual backward masking (% hits)	86.93 (5.82)	84.71 (14.04)	75.19 (14.72)	0.680	<0.001
Attention (% hits)	81.47 (10.37)	72.66 (18.26)	53.52 (20.23)	0.044	0.001
Spatial working memory (pixel distance to target)	55.73 (11.54)	55.79 (18.24)	86.51 (39.96)	0.529	<0.001
Verbal memory (no. of words)					
Free recall (trials 1–5)	12.11 (1.50)	11.21 (1.69)	9.46 (2.41)	0.044	0.004
Recognition	14.14 (1.36)	13.97 (1.45)	12.00 (2.82)	0.426	0.006
Verbal fluency (no. of words)	21.64 (4.74)	17.57 (4.94)	14.75 (5.44)	0.002	0.039
Visual memory (copy minus delay; standard score 0–36)	8.85 (5.13)	12.36 (5.51)	17.48 (7.32)	0.014	0.006
Wisconsin Card Sorting Test (% perseverative errors)	10.78 (5.95)	11.36 (5.16)	15.21 (7.52)	0.380	0.023

Slutsatser

- Förändringar beträffande framplockning i episodiska och semantiska minnesuppgifter
- Övriga domäner intakta
- Förekomst av en rad fynd senare i sjukdomen antyder neurodegenerativ process

Mekanism?

Retrieval induces adaptive forgetting of competing memories via cortical pattern suppression

Maria Wimber[1,2], Arjen Alink[2], Ian Charest[2], Nikolaus Kriegeskorte[2] & Michael C Anderson[2,3]

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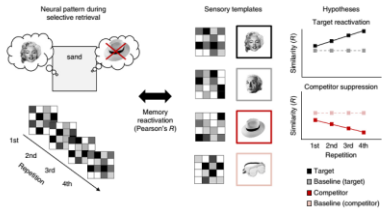
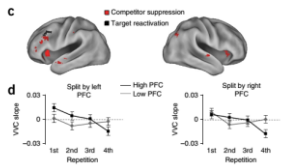




Neuroradiologi

BRITISH JOURNAL OF PSYCHIATRY (2002), 181 (suppl. 43), s58–s65

Structural magnetic resonance imaging in patients with first-episode schizophrenia, psychotic and severe non-psychotic depression and healthy controls

Results of the Schizophrenia and Affective Psychoses (SAP) project*

R. K. R. SALOKANGAS, T. CANNON, T. VAN ERP, T. ILONEN, T. TAIMINEN, H. KARLSSON, H. LAUERMA, K.-M. LEINONEN, E. WALLENIUS, A. KALJONEN, E. SYVÄLAHTI, H. VILKMAN, A. ALANEN and J. HIETALA

Grey matter

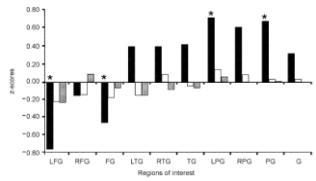


Fig. 1 Regional grey matter volumes in diagnostic groups in relation to healthy controls (L, left; R, right; F, frontal; T, temporal; P, posterior; G, grey matter). ■, schizophrenia; □, psychotic depression; ▨ non-psychotic depression. *denotes significant values.

White matter

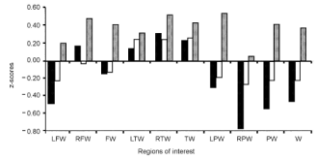


Fig. 2 Regional white matter volumes in diagnostic groups in relation to healthy controls (L, left; R, right; F, frontal; T, temporal; P, posterior; W, white matter). ■, schizophrenia; □, psychotic depression; ▨, non-psychotic depression.

Ventricular volume

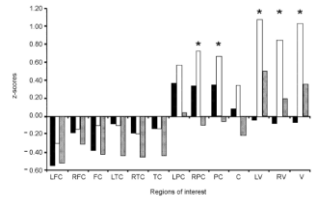
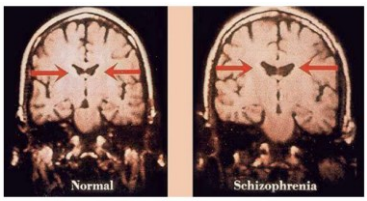


Fig. 3 Regional sulcal and ventricular cerebrospinal fluid (CSF) volumes in diagnostic groups in relation to healthy controls (L, left; R, right; F, frontal; T, temporal; P, posterior; C, sulcal CSF; V, ventricle CSF). ■, schizophrenia; □, psychotic depression; ▨, non-psychotic depression. *denotes significant values.

Note ventricular enlargement in PD, specifically; but not in schizophrenia.



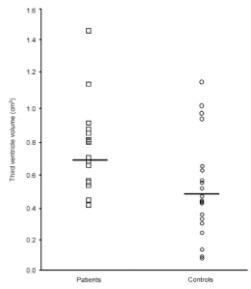
BRITISH JOURNAL OF PSYCHIATRY (2002), 181 (suppl. 43), s44–s52

Brain morphology in antipsychotic-naïve schizophrenia: a study of multiple brain structures

W. CAHN, H. E. HULSHOFF POL, M. BONGERS, H. G. SCHNACK, R. C. W. MANDL, N. E. M. VAN HAREN, S. DURSTON, H. KONING, J. A. VAN DER LINDEN and R. S. KAHN

Region	Patients with schizophrenia (n=20)	Comparison subjects (n=20)	Effect size	Observed power
Cranium	1463.25 (130.71)	1538.87 (164.37)	0.06	0.35
Total brain	1281.57 (118.70)	1353.94 (138.96)	0.08	0.41
Grey matter	669.87 (58.66)	691.93 (54.92)	0.04	0.22
White matter	455.19 (66.27)	499.47 (90.85)	0.08	0.40
Frontal lobe	280.99 (30.69)	299.64 (32.39)	0.08	0.45
Cerebellum	142.78 (14.71)	148.52 (13.03)	0.04	0.25
Caudate	9.22 (1.08)	9.19 (1.24)	0.00	0.05
Thalamus	14.37 (1.31)	14.97 (2.09)	0.03	0.18
Hippocampus	8.01 (0.77)	8.36 (0.80)	0.05	0.28
Parahippocampus	4.93 (0.94)	5.63 (1.14)	0.11	0.55
Lateral ventricles	13.18 (6.90)	14.82 (12.21)	0.01	0.08
Third ventricle*	0.85 (0.32)	0.62 (0.36)	0.11	0.54

Values are mean (s.d.). Effect size measured by the eta-squared based on the raw data.
*P<0.05.



Slutsatser, MRI

- Ventrikelförstoring inte vanligt under prodrom eller direkt efter insjuknandet
- Förekomst av dylika fynd (samt np fynd) indikerar neurodegenerativ process
- Frontalkortex samt Thalamus påverkade initialt

Functional neuroimaging

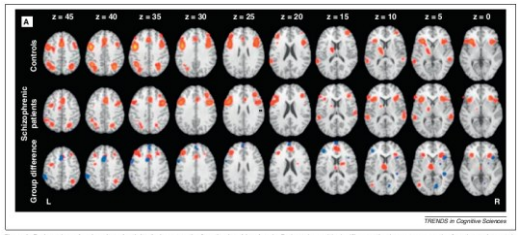


Figure 1. Brain regions showing altered activity during executive function in schizophrenia. Brain regions with significant activation across executive function task types. In the bottom row, clusters in which controls showed more activation than schizophrenic patients are in red and clusters in which schizophrenic patients showed more activation than controls are in blue. Reproduced, with permission, from [18].

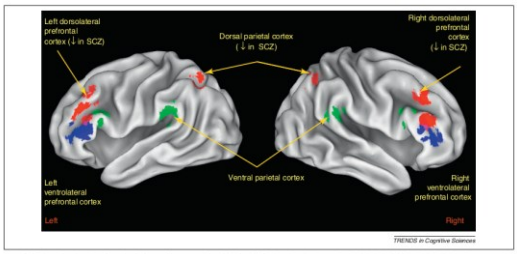


Figure 2. Regions showing altered activity during working memory in schizophrenia. Regions in red show reduced activity in individuals with schizophrenia compared to controls in a comparison of working memory performance to a control task in [46]. Regions in blue and green on the left hemisphere show greater activity for verbal and than non-verbal working memory in both healthy controls and individuals with schizophrenia. Regions in blue and green on the right hemisphere are homologous regions to those on the left hemisphere. Reproduced, with permission, from [46].

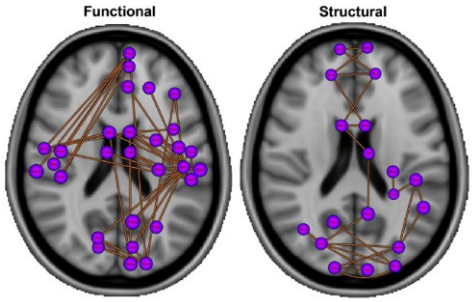


Fig. 6. Sub-networks of interconnected edges showing reduced resting-state functional (left) and structural (right) connectivity in two independent studies of people with schizophrenia. Data reproduced from Zalesky et al. (2010a, 2010b) and Zalesky et al. (2011a). Purple circles correspond to distinct brain regions defined using the same anatomical parcellation. Amy = amygdala; Cak = calcarine; CgG = anterior cingulate gyrus; CgG = mid anterior cingulate gyrus; Cune = cuneus; Fac = fusiform gyrus; FroO = medial orbital frontal gyrus; Fro1 = superior frontal gyrus; Fro8 = inferior orbital frontal gyrus; Fro9 = superior medial frontal gyrus; Hesc = heschl's gyrus; Hipp = hippocampus; Ins = insula; Lng = lingual gyrus; Occ1 = superior occipital gyrus; Occ2 = mid occipital gyrus; Par1 = superior parietal cortex; PCun = precuneus; PreC = precentral gyrus; PstC = postcentral gyrus; Rola = rolandic gyrus; SMA = supplementary motor area; Tem = superior temporal gyrus; Tem2 = middle temporal gyrus; Tem3 = inferior temporal gyrus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

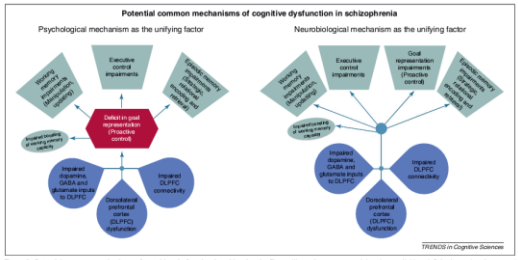
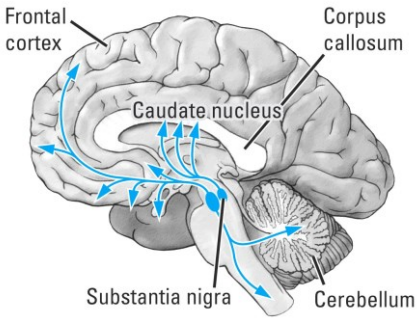
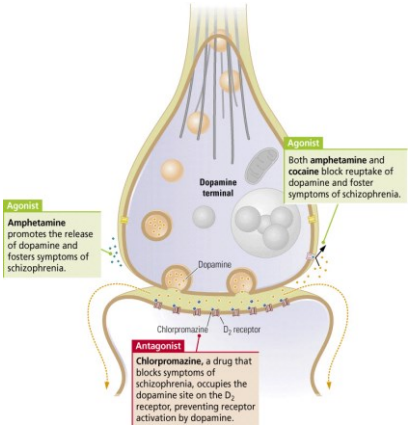


Figure 3. Potential common mechanisms of cognitive dysfunction in schizophrenia. Figure illustrating two potential pathways linking deficits in goal maintenance/proactive control, DLPFC function, and other cognitive impairments in schizophrenia. The panel on the left illustrates a pathway in which the influence of DLPFC dysfunction on deficits in cognitive domains, such as executive control, working memory and episodic memory in schizophrenia is mediated by an impairment in proactive control, which leads to impairments in these other domains. The figure on the right illustrates a pathway by which DLPFC function directly influences cognitive function in many domains in schizophrenia (including proactive control), but in which deficits in other cognitive domains are not mediated through proactive control impairments.

Brain histology & neurochemistry

Dopaminergic system





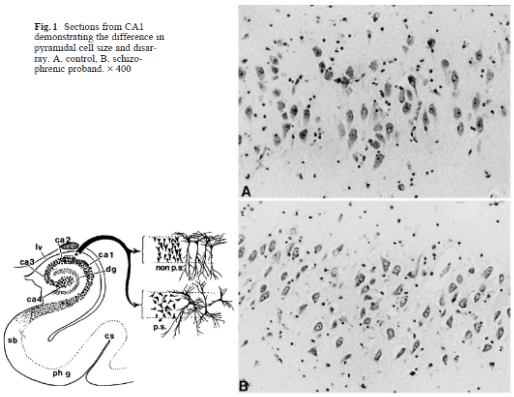
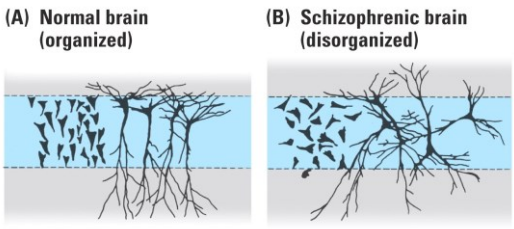
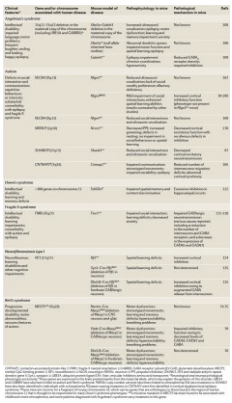


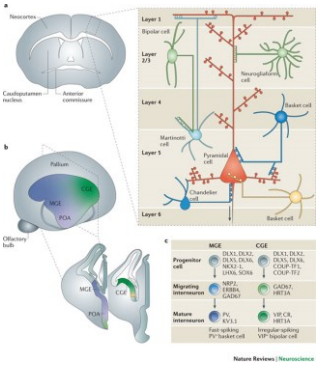
Fig. 1 Sections from CA1 demonstrating the difference in pyramidal cell size and disarray. A. control, B. schizophrenic proband. × 400



Interneuron deficiency

- ≈ 80 % of cortical neurons excitatory, glutamatergic pyramidal cells
- ≈ 20 % of cortical neurons inhibitory, GABA interneurons




a
Neocortex
Caudoputamen nucleus
Anterior commissure
Layer 1
Bipolar cell
Layer 2/3
Neurogliaform cell
Layer 4
Basket cell
Martinotti cell
Layer 5
Pyramidal cell
Chandelier cell
Layer 6
Basket cell
b
Pallium
LGE
MGE
POA
Olfactory bulb
MGE
CGE
POA
c
MGE
CGE
Progenitor cell
DLX1, DLX2, DLX5, DLX6, MASH1, LHX6, SOX6
DLX1, DLX2, DLX5, DLX6, COUP-TF1, COUP-TF2
Migrating interneuron
NRP2, ERBB4, GAD67
GAD67, HRT1A
Mature interneuron
PV, KV3.1
VIP, CR, HRT1A
Fast-spiking PV+ basket cell
Irregular-spiking VIP+ bipolar cell
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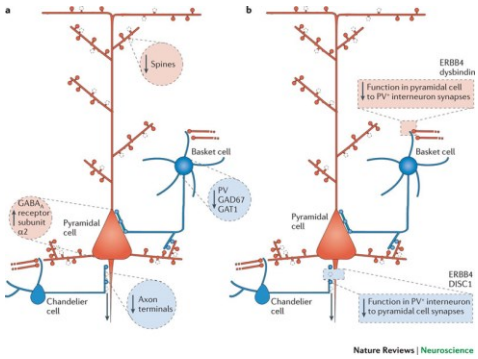
a
Spines
Basket cell
PV
GAD67
GAT1
GABA
receptor
subunit
α2
Pyramidal cell
Chandelier cell
Axon terminals
b
ERBB4
dysbindin
Function in pyramidal cell
to PV+ interneuron synapses
Basket cell
Pyramidal cell
ERBB4
DISC1
Chandelier cell
Function in PV+ interneuron
to pyramidal cell synapses
Nature Reviews | Neuroscience

- GABA-deficiency hypothesis replacing traditional dopamine hypothesis?