Differences between normal aging-related dementia and Alzheimers

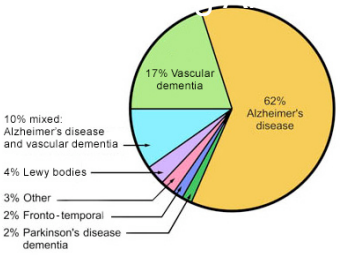
Dementia is a *broad category degenerative disorder* that refers to the loss of memory and other cognitive skills due to changes in the brain caused by age, disease or trauma. The changes can occur gradually or quickly. Memory loss alone is not always a sign of dementia, but memory loss along with other forms of cognitive impairment is an indicator.

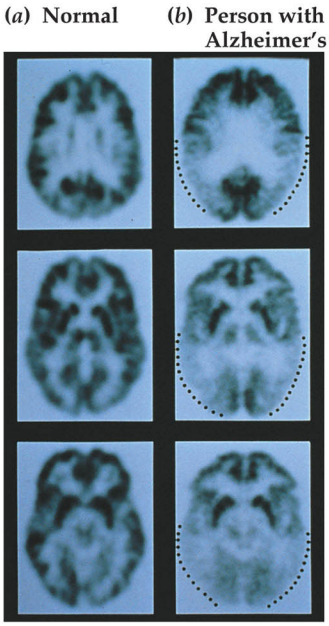
Repeatedly asks the same questions
Becomes lost or disoriented in familiar places
Cannot follow directions
Is disoriented as to the date or time of day
Doesn't recognize and is confused about familiar people
Has difficulty with routine tasks such as paying the billS
Neglects personal safety, hygiene, and nutrition

Alzheimer's Disease is a *sub-type of dementia*, and is a brain disease characterized by lesions that gradually destroy cells in the brain, starting in the *hippocampus*. As neurons die, affected areas *shrink* and become smaller. The areas of the brain that control memory, logical thinking, and personality are the most affected. As grey matter is reduced, *ventricles* in the brain containing CSF become enlarged.

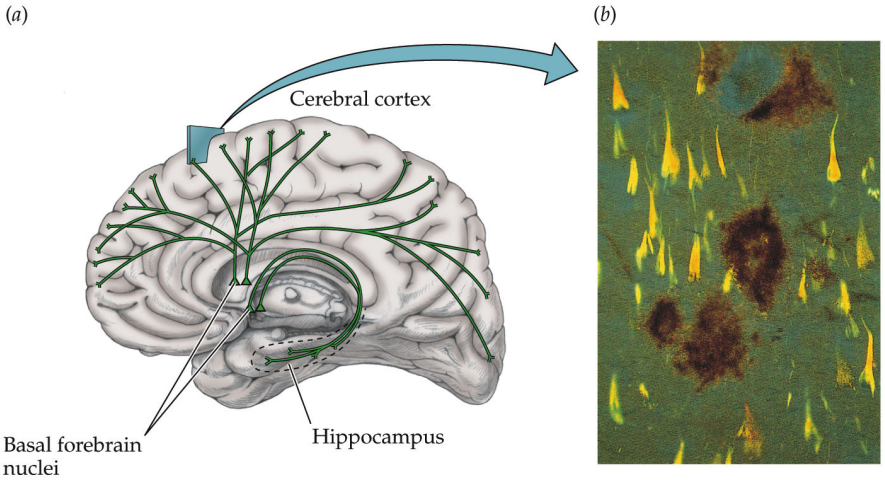
* Loss of recent memory
* Problems with language, calculation, abstract thinking, and judgment
* Depression, anxiety, and personality changes
* Unpredictable quirks or behaviors
* Late in the disease, delusions and hallucinations
* Trouble knowing time, date, or place

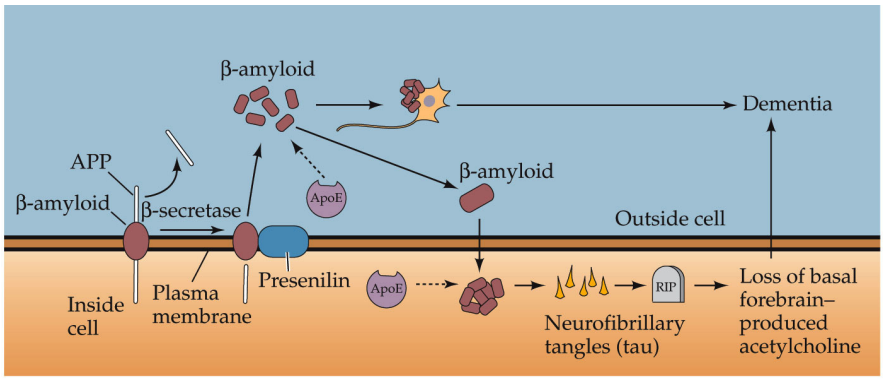
Clinical features	Vascular Dementia	Alzheimer's Disease
History of atherosclerotic diseases	Transient ischemic attack, strokes, atherosclerotic risk factors e.g., diabetes mellitus, hypertension	Less common
Onset	Sudden or gradual	Gradual
Progression	Slow or stepwise progression	Slow, progressive decline
Neurological examination	Neurological deficits	Normal
Gait	Often disturbed early	Usually normal
Memory	Mild impairment in early phase	Prominent in early phase
Executive function	Marked impairment and early	Impaired later





BIOLOGICAL PSYCHOLOGY, Fourth Edition, Figure 7.27





β-amyloid protein is formed after sequential cleavage of the amyloid precursor protein (APP) -- a trans-membrane glycoprotein of undetermined function.

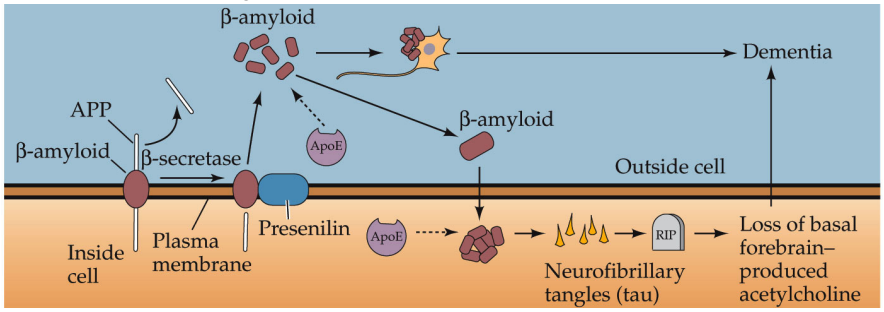
Amyloid plaques are composed of a tangle of normally ordered fibrillar aggregates called *amyloid fibers* -- a protein fold shared by other peptides such as prions associated with protein misfolding diseases (e.g., mad cow).

Mouse models of Alzheimer's disease☆

Alicia M. Hall, Erik D. Roberson*

Center for Neurodegeneration and Experimental Therapeutics, Departments of Neurology and Neurobiology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

AD is *not* associated with one single gene, but there are three gene mutations associated with a rare autosomal dominant for of AD -- **APP, PSEN1, PSEN2** (amyloid precursor protein, Presenillin)---- all of which alter production of **B-amyloid protein**. Though low incidence, these provide the main AD mouse models. Also are risk genes, such as **ApoE**, (apolipoprotein) for which the E4 allele increases risk 4X (9-15X if homo recessive). Additional mutations affect **tau**, which causes the neurofibrillary component, and this mutation has been added (double transgenic) to the above.



Tg line	Gene/isoform	Mutation	Promoter	Plaques (mo)	Cognitive deficits (mo)
hAPP models					
PDAPP	hAPP695 < 751,770[a]	Ind	PDGF-B	6–9	6
J20	hAPP695 < 751,770[a]	Swe, Ind	PDGF-B	6	4
Tg2576	hAPP695	Swe	HamPrP	9	10
APP23	hAPP751	Swe	Thy1	6 CAA: 12	3
TgCRND8	hAPP695	Swe, Ind	HamPrP	3 CAA: 11	3
TASD-41	hAPP751	Swe, Lon	Thy1	3 CAA: 7	6
R1.40	hAPP YAC[b]	Swe	hAPP	14–15	16–17
Aβ Models					
BRI-Aβ42A	BRI-Aβ42	n.a.	MoPrP	3	?
hAPP/PS1 models					
PSAPP	hAPP695	Swe	HamPrP	6	4
(Tg2576xPS1)	PSEN1	M146L	PDGF-B		
APPswe/PS1ΔE9	m/hAPP695[c]	Swe	MoPrP	6	6
	PSEN1	ΔE9	MoPrP		
5xFAD	hAPP695	Swe, Lon, Flo	Thy1	2	6
	PSEN1	M146L, L28V	Thy1		
2xKI	m/hAPP[c]	Swe	mAPP	6	9–12
	PSEN1	P264L	mPS1		
Models with hTau					
TAPP	hAPP695	Swe	HamPrP	8–15	Motor deficits
(Tg2576xJNPL3)	hTau-4R0 N	P301L	MoPrP		
	hAPP695	Swe	Thy1		
3xTg	hTau-4R0 N	P301L	Thy1	6	4.5
	PSEN1	M146V	mPS1		
vhtau	hTau PAC[d]	Wild-type	hTau	–	12

"It is important to emphasize that no existing mouse model exhibits all features of AD. The ideal model of AD would develop the full range of clinical and pathological features of AD, including cognitive and behavioral deficits, amyloid plaques and neurofibrillary tangles, gliosis, synapse loss, axonopathy, neuron loss and neurodegeneration. Different mouse lines develop these phenotypes to varying degrees and in different combinations."

Note that, unlike some of the other disorders we have addressed to date, **AD has a well defined pathological AND behavioral profile**. Animal models can therefore use either neuropathology and/OR behavior as an outcome measure. This will affect model validity, and could show different results in drug tests.

Experimental models of vascular dementia and vascular cognitive impairment: a systematic review

Nadim S. Jiwa, Peter Garrard and Atticus H. Hainsworth

Clinical Neuroscience, Division of Clinical Sciences, St George's University of London, London, UK

Vascular cognitive impairment (VCI) is the next leading cause of dementia after AD.

Table 1 Neuropathological causes of clinical VCI

Cerebral small vessel disease: subcortical vascular dementia (including Binswanger's disease, lacunar state)
Large vessel disease: multi-infarct dementia (cortical)
Strategic infarct (e.g. thalamic)
Severe hypoperfusion state
Angiopathy (e.g. CAA)
Haemorrhage/microbleed
Hereditary vasculopathy (e.g. CADASIL)

VCI, vascular cognitive impairment; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

Human VCI conditions and symptoms.

Mechanism and disease state	Cognitive profile	Clinical confounds
Global hypoperfusion – chronic		
Low output cardiac failure	No detailed studies; reduced MMSE found in chronic cardiac failure	Aging; neurodegeneration; focal embolic lesions; variable neuroanatomical location
Large AVM		
Bilateral carotid stenosis/occlusion		
Chronic anaemia		
Global hypoperfusion – transient		
Cardiac arrest	Impaired long-term verbal and spatial memory; normal short-term memory	Variable duration; pre-existing chronic hypoperfusion
Carbon monoxide poisoning		
Focal hypoperfusion		
Small AVM	Depends on lesion size and location	Variable neuroanatomical location
Embolic occlusion		
Focal large vessel stenosis	Few detailed studies, mostly based on MMSE or small test batteries	Depression; anatomical variability
Cardiomyopathy		
Post-perfusion syndrome (post-cardiopulmonary bypass; multiple emboli)	Cognitive slowing; impaired attention and working memory	Anatomical variability; possibility of more than one mechanism
Hypercoagulable states	Unknown	Variable clinical expression
Hypertensive		
Primary hypertension	Visuospatial deficits; executive dysfunction	Age; hypercholesterolaemia
Secondary hypertension		Renal failure; diabetes
Vasculopathy		
CADASIL	Cognitive slowing; executive dysfunction	None
CAA	Episodic memory disturbance	Lobar haemorrhage; neurodegeneration
Diabetes mellitus types 1 and 2	Cognitive slowing; executive dysfunction	Variable clinical expression; variable neurological involvement

VCI, vascular cognitive impairment; AVM, arteriovenous malformation; MMSE, mini mental state examination; CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy.

Table 3 Cognitive impairment in experimental models

Model	Sensorimotor or other confounding features	Cognitive profile
Global hypoperfusion – chronic		
Rat BCCAo	No major motor deficit. Some optic nerve damage. No/mild hippocampal damage (initially)	Impaired working memory and reference memory (MWM, Radial maze; NORT; TMSAT) (Pappas *et al.* 1996; Ohta *et al.* 1997; Sarti *et al.* 2002; Storozheva *et al.* 2008)
Gerbil bilateral carotid stenosis	Normal locomotor activity	Impaired learning ability at 6–12 weeks (PAT) (Kudo *et al.* 1990, 1993)
Mouse bilateral carotid stenosis	Motor deficits from 3 months (rotarod, hotplate, Posholt forced swim test). Optic nerve damage	Impaired working memory but not reference memory at 30 days; both impaired at 5 months (Radial maze; Barnes maze) (Shibata *et al.* 2007; Nishio *et al.* 2010)
Mouse UCCAo	None seen (normal locomotion)	Impaired memory in NORT but not TMSAT (Yoshizaki *et al.* 2008)
Global hypoperfusion – transient		
Rat 4-VO	Reduced locomotor activity	Impaired working and reference memory (Radial maze; PAT) (Chung *et al.* 2002)
Gerbil 2-VO	No gross abnormalities; increased locomotor activity (Andersen and Sams-Dodd 1998)	Reduced working and reference memory (PAT, TMSAT, MWM) (Wiard *et al.* 1995; Andersen and Sams-Dodd 1998; Carboni *et al.* 2008)
Mouse 2-VO	No effect on motor activity (Matsuoka *et al.* 1995)	Impaired learning (PAT, TMSAT) (Yamamoto *et al.* 2009)
Focal hypoperfusion		
MCAo (rats, mice)	Contra-lateral forepaw dysfunction	Prolonged learning and memory deficits. See text
ET-1 injection	Contra-lateral sensorimotor deficit (Whitehead *et al.* 2005a; Lecrux *et al.* 2008)	Not specifically tested (see Whitehead *et al.* 2005a,b)
Embolic occlusion		
Injected emboli	Impaired paw use (staircase test)	Impaired working and reference memory (TMSAT, Barnes maze) (Rasmussen *et al.* 2006; Rapp *et al.* 2008)
Photo-activated thrombo-emboli	Forelimb dysfunction and incoordination	Impaired learning (MWM) (Alexis *et al.* 1995; Fukatsu *et al.* 2002)
Hypertensive		
Hypertensive monkeys	Some retinopathy	Impaired attention, short-term memory and executive function at 12 months (CSST, DRST) (Kemper *et al.* 2001; Moore *et al.* 2002; Moss and Jonak 2007)
SHRSP	No major neurological deficit prior to stroke event	Impaired learning and memory (TMSAT, PAT) (Yamaguchi *et al.* 1994; Togashi *et al.* 1996; Minami *et al.* 1997; Kimura *et al.* 2000; Ueno *et al.* 2002)
Vasculopathy		
Hyperhomocysteine	Normal motor function (rotarod)	Impaired spatial learning and reference memory but not working memory (MWM, DNMTP) (Bernardo *et al.* 2007; Troen *et al.* 2008)
Notch3 transgenic mice	No impairment reported	None reported
MR5−/− mice	Normal locomotor activity/ coordination	Impaired learning (NORT, TMSAT) (Araya *et al.* 2006; Kitamura *et al.* 2009)
Diabetic rats/mice	Obesity. No visual or motor dysfunction detected	Impaired learning and memory (MWM, PAT) (Kuhad and Chopra 2007; Tsukuda *et al.* 2007; Takeda *et al.* 2010)

BCCAo, bilateral carotid artery occlusion; UCCAo, unilateral common carotid occlusion; VO, vessel occlusion; MCAo, middle cerebral artery occlusion; ET-1, endothelin-1; DNMTP, delayed non-matching to position task; MWM, Morris water maze; NORT, novel object recognition test; PAT, passive avoidance task; TMSAT, T-maze spontaneous alternation test; CSST, conceptual set-shifting task; DRST, delayed recognition span task; SHRSP, stroke-prone spontaneously hypertensive rat.

Outcome measures include pathology AND behavior.

Behavioral tasks typically used:

- Morris maze/Barnes maze (spatial)
- Radial arm maze 8-arm (spatial working memory)
- Novel object task
- Passive avoidance tests
- Spontaneous alternation in T or Y maze
- Motor tasks

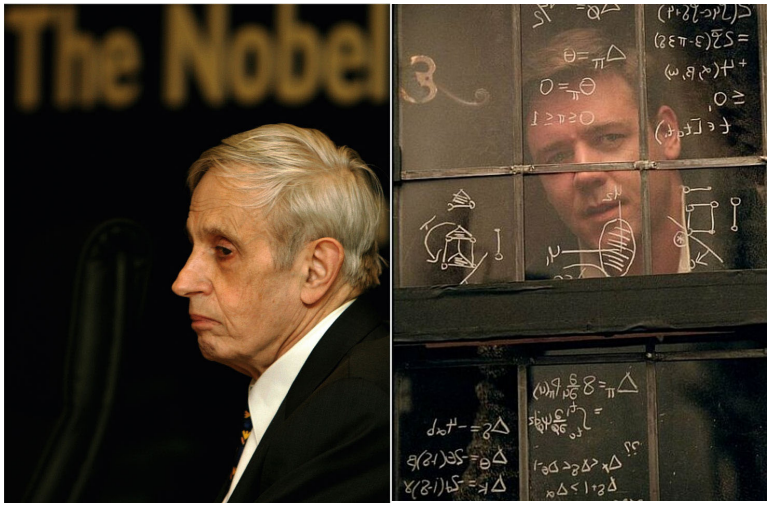
Schizophrenia -- a psychiatric diagnosis that describes a mental illness characterized by distortions in the perception or expression of reality -- most commonly including auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking. Onset of symptoms usually occurs in early 20's for males and early 30's for females, with about 0.4–0.6% of the population affected. Studies suggest that genetics, prenatal factors (stress, teratogens), neurobiology, and environment (e.g., rate is double in urban versus rural environments, probably due to stimulation and stress) are important factors. Pregnancy can trigger symptoms in women.

Diagnosis is based on the patient's self-reported experiences and observed behavior, as well as duration of symptoms. Slightly more common in men.

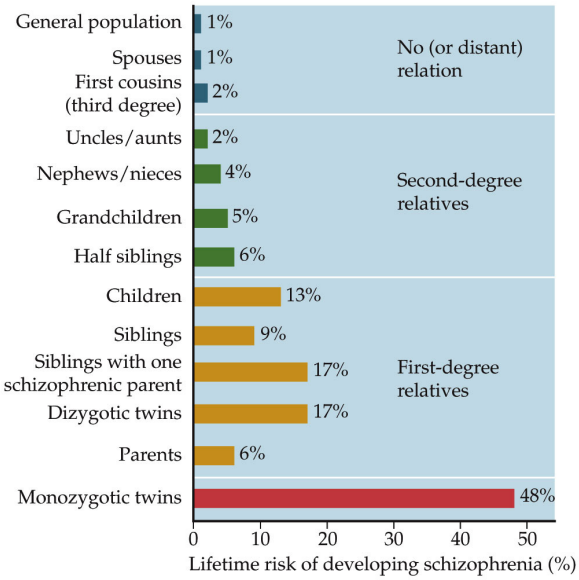
No laboratory test for schizophrenia exists.

TABLE 16.2 Symptoms of Schizophrenia

Positive symptoms	Negative symptoms
Hallucinations, most often auditory	Social withdrawal
Delusions of grandeur, persecution, etc.	Flat affect (blunted emotional responses)
Disordered thought processes	Anhedonia (loss of pleasurable feelings)
Bizarre behaviors	Reduced motivation, poor focus on tasks
	Alogia (reduced speech output)
	Catatonia (reduced movement)



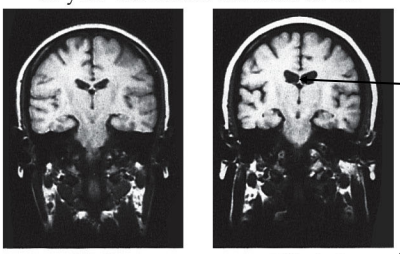
John Nash, a Nobel-prize winning mathematician, experienced auditory hallucinations that fueled his paranoia, portrayed in the movie *"A Beautiful Mind."*



Strong heritability component in schizophrenia, but not 100%.

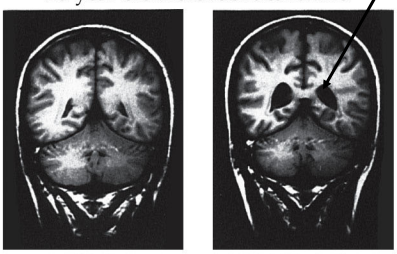
MRI brain images of twins discordant for schizophrenia

35-year-old female identical twins



Well Affected

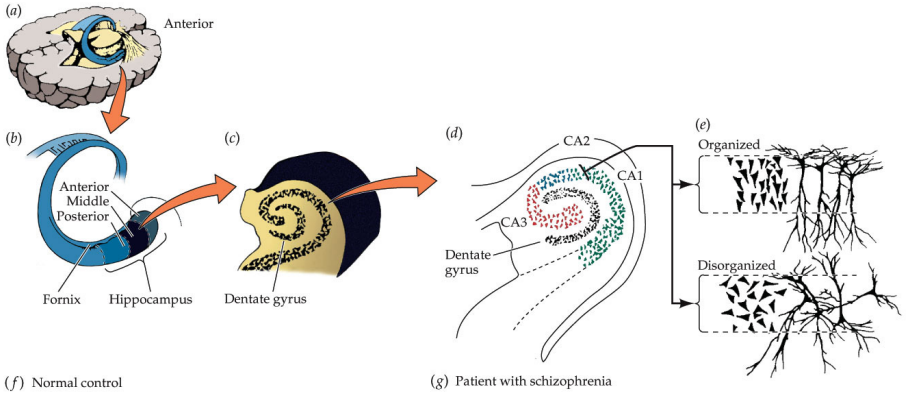
28-year-old male identical twins



Well Affected

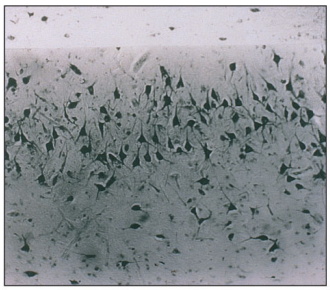
Schizophrenics have *enlarged ventricles*, which is consistent with other evidence of brain abnormalities (e.g., excess pruning in teen years).

Reductions in *hippocampu* size, & tissue abnormalitie are also seen in schizophrenics.



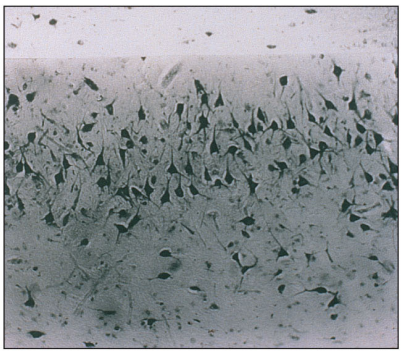
(f) Normal control

(g) Patient with schizophrenia



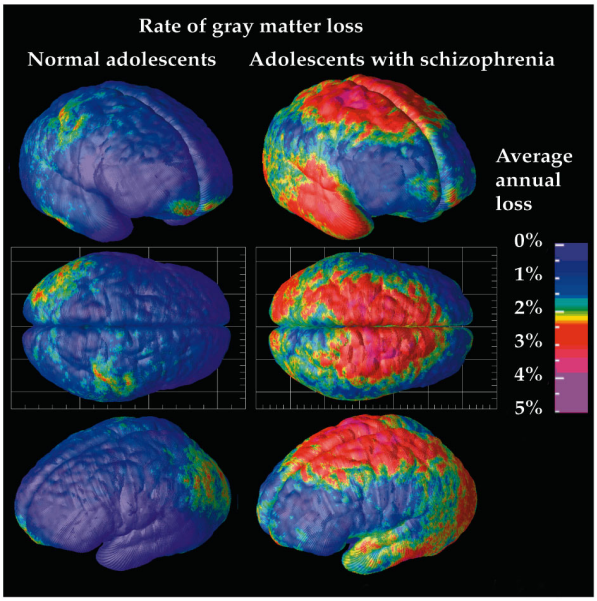
(*f*) Normal control

(*g*) Patient with schizophrenia

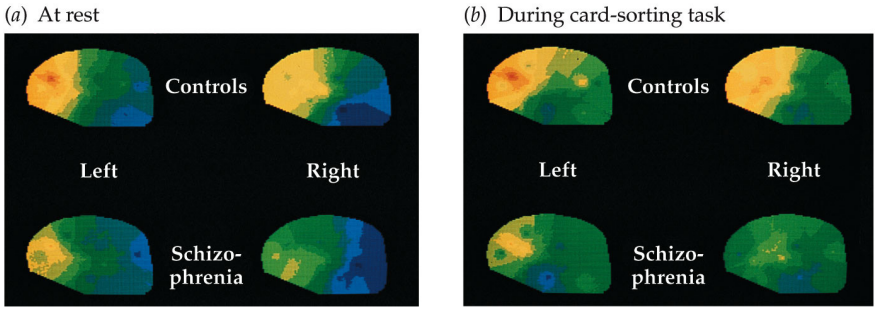


These neural anomalies probably arise during early development, when *neuromigration* is taking place (last trimester). This probably means that "schizophrenia" is present at birth – yet because it is not usually expressed until adulthood, it is NOT called a developmental disability. (Childhood schizophrenia is a rare exception).
We do *not* know what triggers the first "psychotic break" in young adults (hormones? stress? Pregnancy raises risk of "first break" in women).

Abnormal rate of grey matter loss in schizophrenic teens (***too much*** pruning).



Reduced frontal lobe function in schizophrenia.



This is consistent with impairments in frontal cortical tasks such as maintaining attention, or making “executive” decisions (e.g., what is appropriate to say in a given situation).

(The card-sorting task used here is also an Executive task).