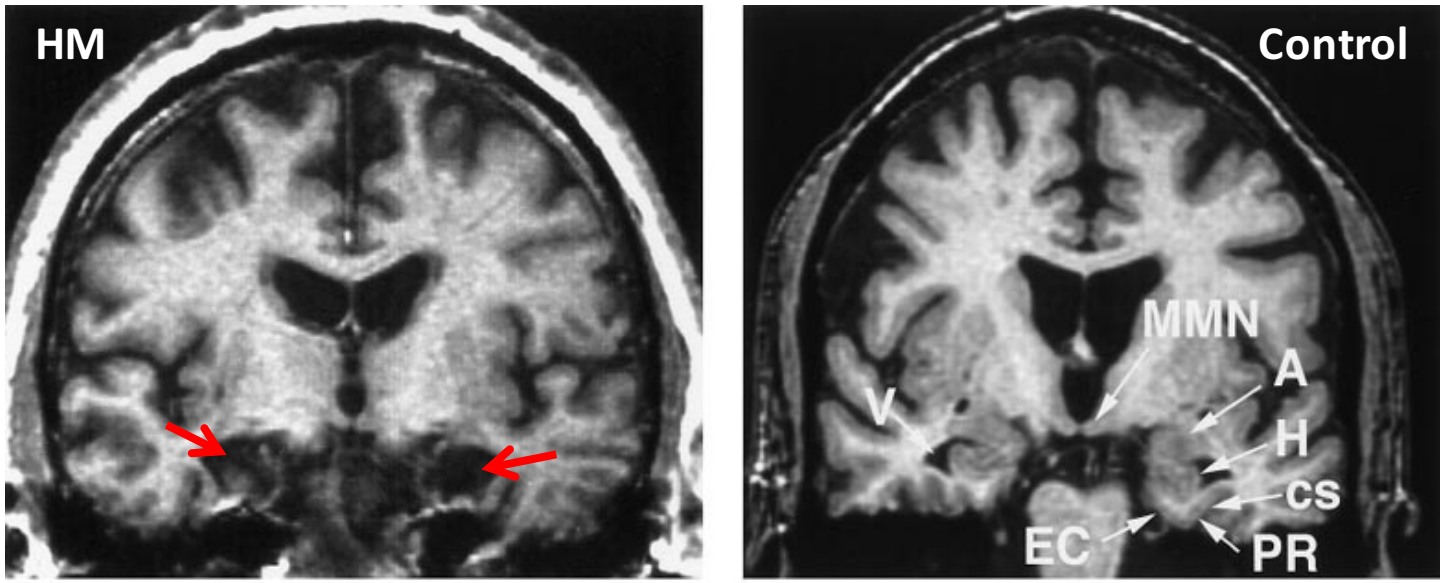
# Introduction to cognitive neuropsychiatry

Szabolcs Kéri

# *H.M.*: A man imprisoned in his past




**Anterograde amnesia**: impaired memory for new events, persons, concepts, and words

Spared:

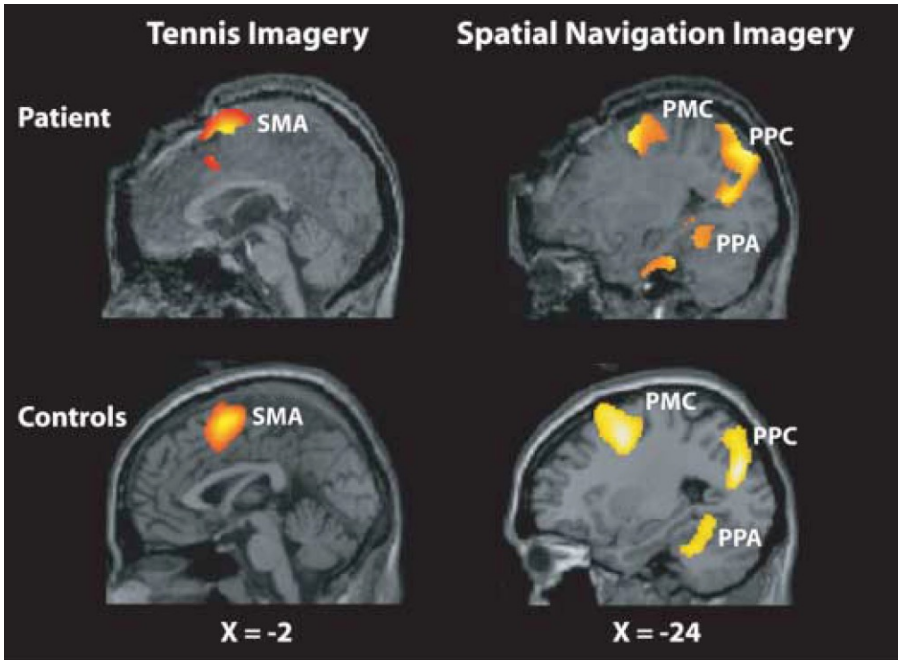
- -old memories
- -IQ
- -short-term memory
- -sensory and motor skills

**Medial temporal lobe:**

*H* – hippocampus
*EC* – entorhinal cortex
*PR* – perirhinal cortex
*A* - amygdala
*MMN* – mammilary bodies

# LOCKED-IN syndrome: a man imprisoned in his own body
## (maladie de l'emmuré vivant )

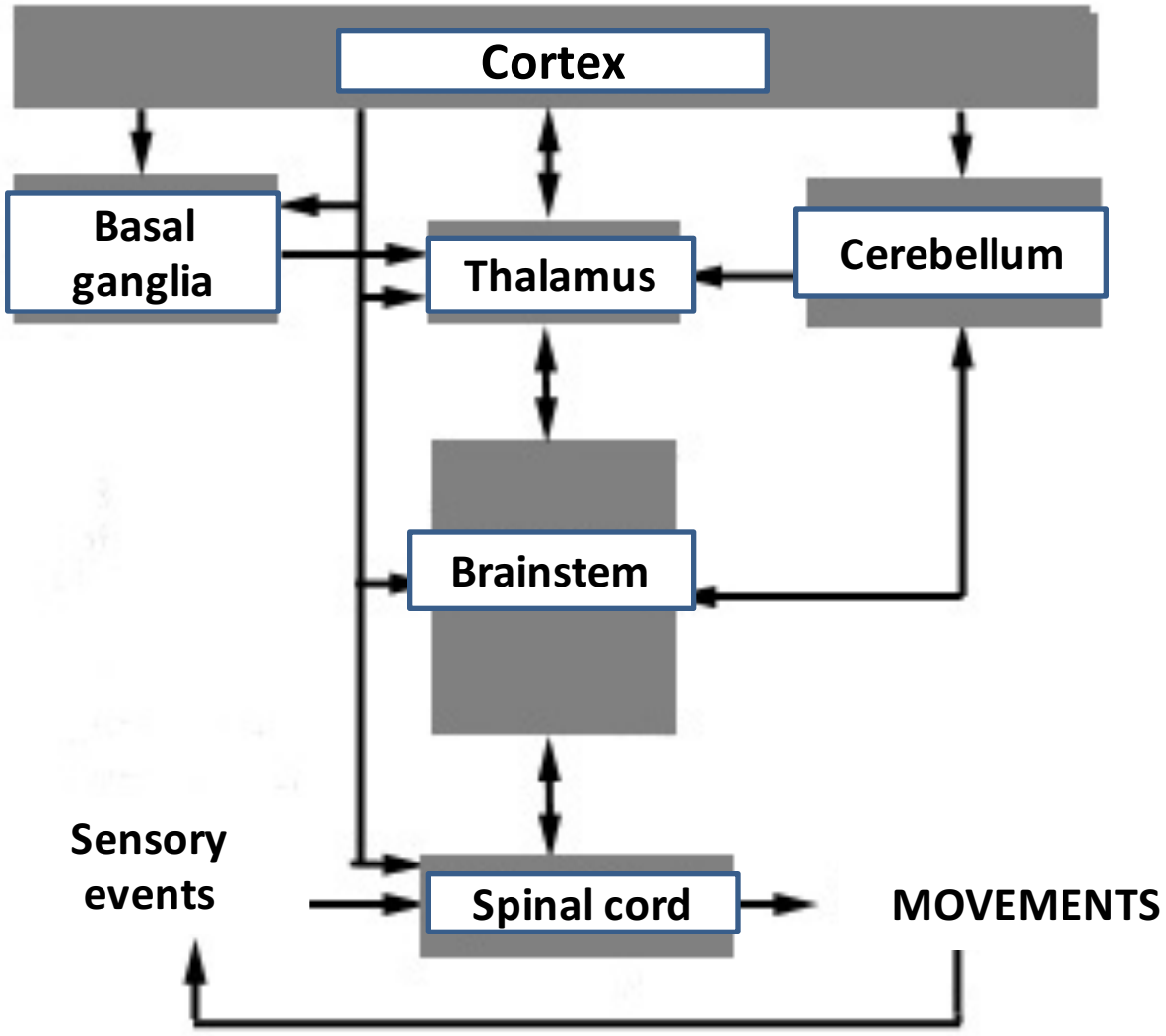
Brain activation during visual imagery in a patient who is not able to contact the world




**SMA** – supplementary motor area
**PMC** – premotor cortex
**PPC** – posterior parietal cortex
**PPA** – parahippocampal „place" area


„The Diving Bell and the Butterfly"
/Jean-Dominique Bauby/

Owen AM et al. Science 2006;313:1402.


Cortex
Basal ganglia
Thalamus
Cerebellum
Brainstem
Sensory events
Spinal cord
MOVEMENTS

# Definition and classification of learning and memory

**I. Learning** – acquisition of new information or altered behavior

**II. Memory** – storage of information

**II/a. Short-term**

**Iconic memory:** sensory cortex, high capacity, milliseconds

**Working memory:** frontal cortex, limited capacity, seconds

**II/b. Long-term**

**Declarative (explicit):** conscious recollection

**Non-declarative (implicit):** without conscious recollection

# Types of learning

1. **Sensitization** (increasing response after stimulus exposure, e.g. alarming)
2. **Habituation** (decreasing response along repeated stimulus exposure)
3. **Classical (Pavlovian) conditioning:**

Food (unconditioned stimulus) → salivation (unconditioned response)

Ringing bell (conditioned stimulus)


**Fear conditioning in humans**

**4. Operant conditioning:**

from an initially random behavior the rewarded pattern is strengthened

**5. Imitation** learning (using tools, role modeling)

**6. Episodic** learning:

Encoding events: objects, persons, actions in the context of place and time

**7. Semantic** transfer of knowledge: concepts and language symbols

# Working memory

- *Active* and *short-term* maintenance of information (e.g., a phone number before dialing)
- Connection with *attention* and *intentional encoding/retrieval* related to long-term memory

**Components:**

**Central executive**: maintaining, refreshing, inhibiting, and shifting information for planning, problem solving and decision making

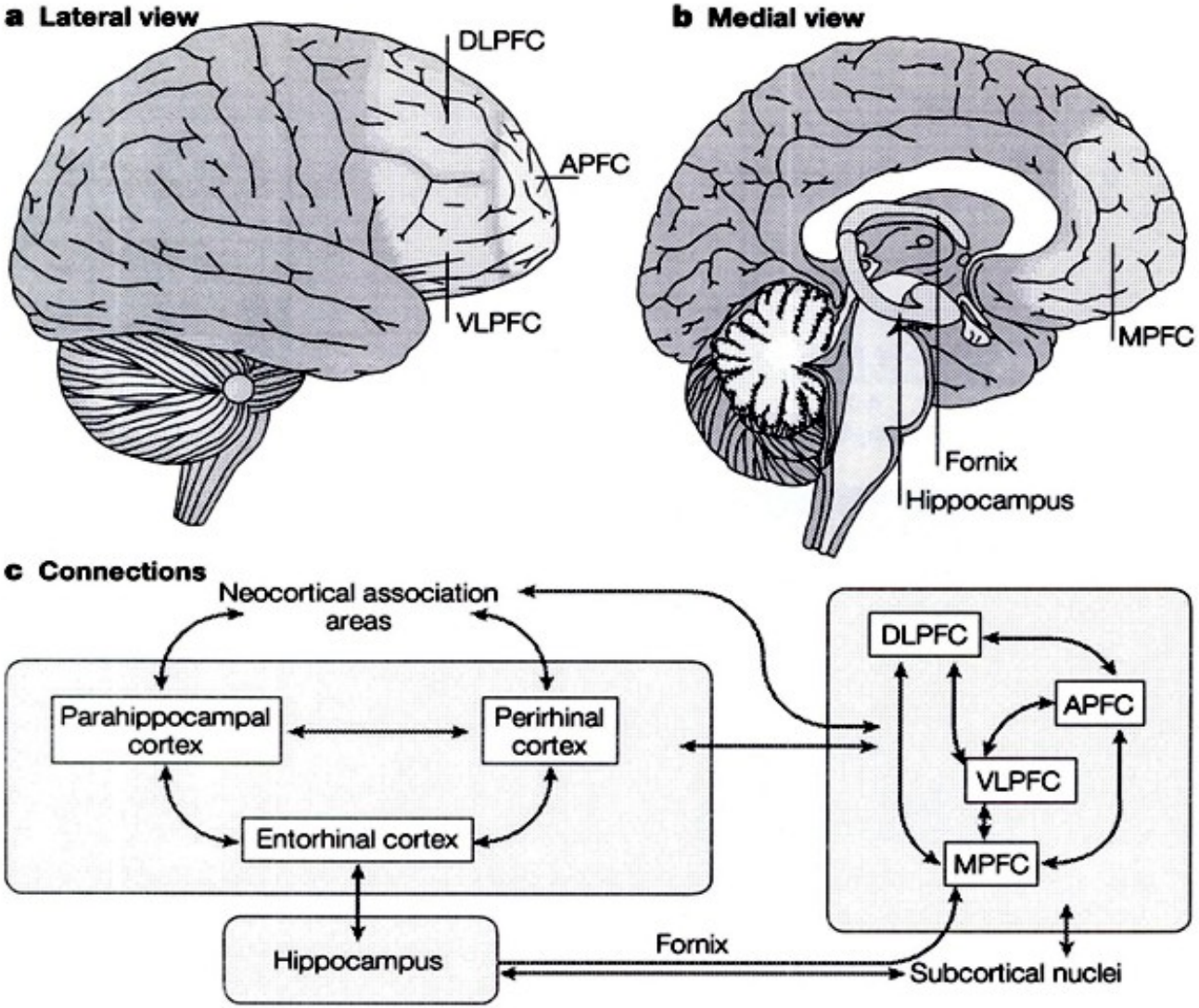
**Buffer systems**: storage (verbal and visual information)

**Neuronal substrates:**

Execution: **dorsolateral prefrontal cortex** (Brodmann 9, 46)

Storage: **parietal** and **temporal cortex**

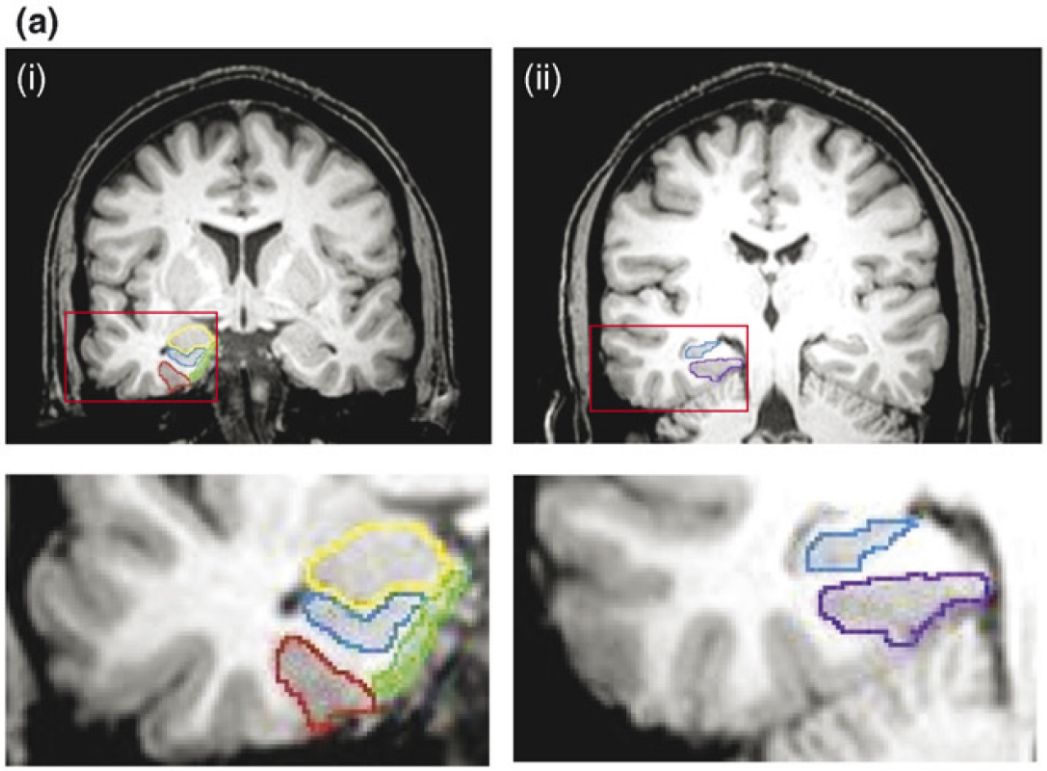
Selection: **basal ganglia** (dorsal caudate nucleus)

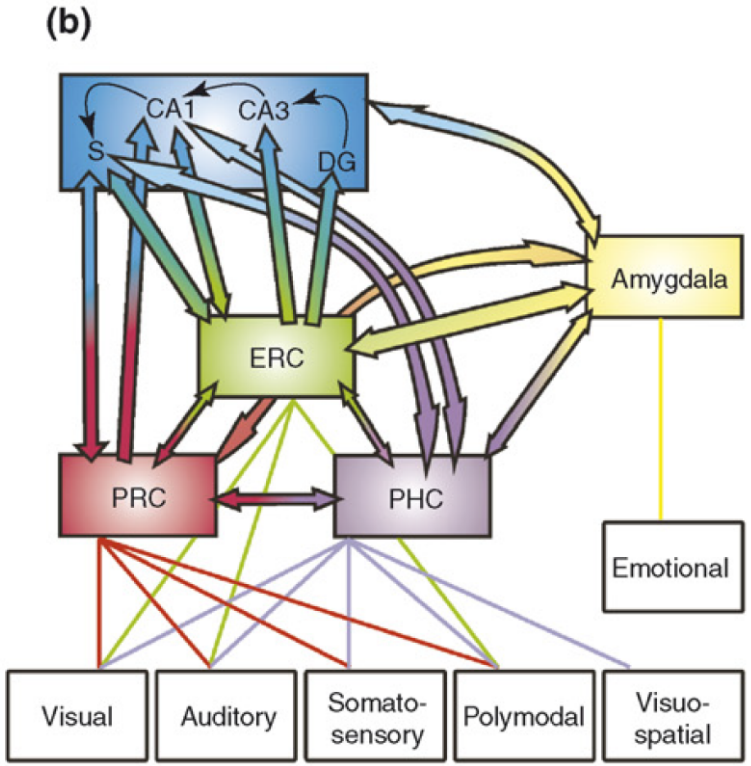



**Thalamo-mammilary tract**

**DLPFC** (dorsolateral prefrontal cortex) – manipulation of working memory content (planning, problem solving)
**VLPFC** (ventrolateral) – simple information maintenance
**APFC** (anterior) - multitasking
**MPFC** (medial-ventral) – conditioning, reward-punishment learning (with amygdala and ventral striatum)

# Neuronal structures for explicit memory



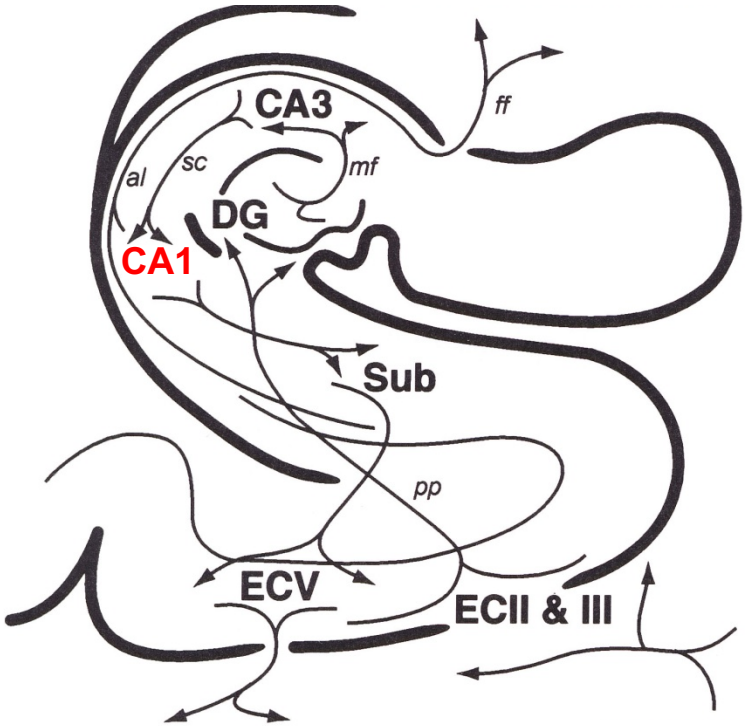



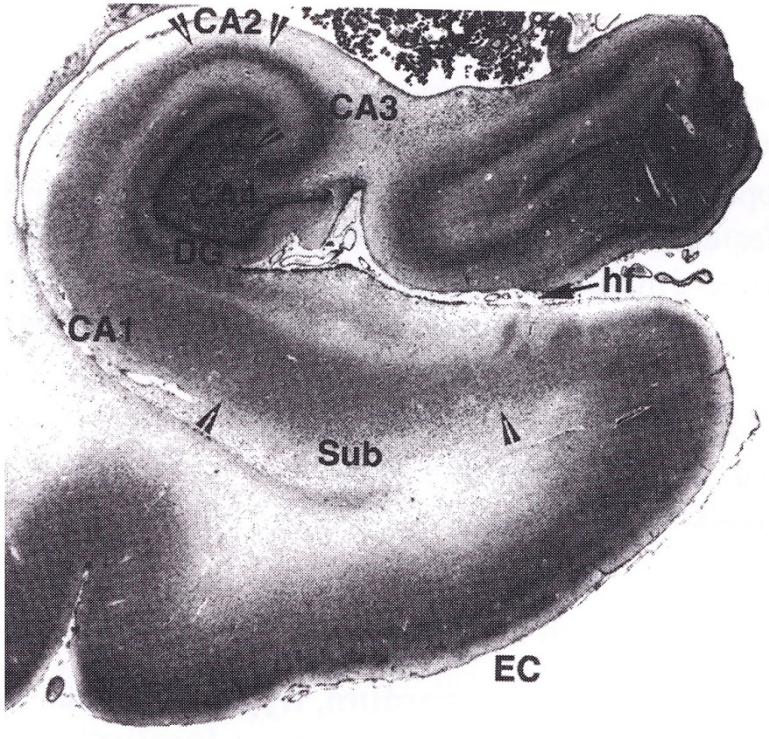

**Medial temporal lobe**

**ERC – entorhinal cortex**
**PRC – perirhinal cortex**
**PHC – parahippocampal cortex**
**DG – gyrus dentatus**
**S – subiculum**
**CA – Cornu Ammonis**

# Fine structure of the medial temporal lobe

**Septum, thalamus, hypothalamus (fimbria-fornix)**




**Multimodal association and sensory cortex**

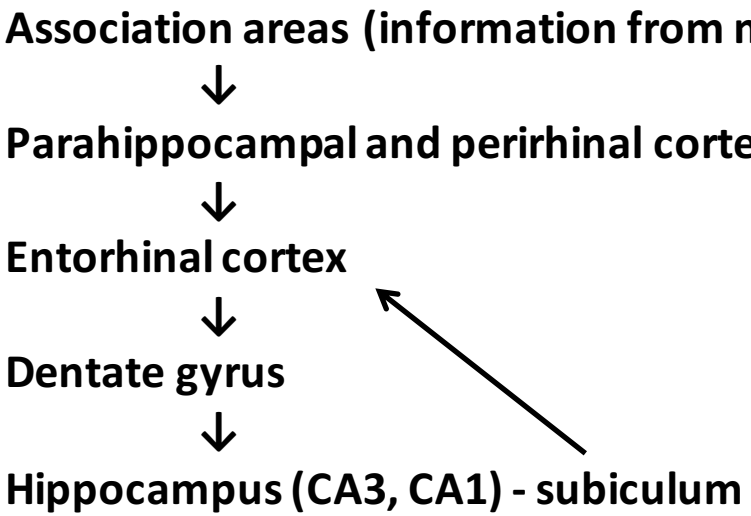
**EC** – entorhinal cortex
**DG** – dentate gyrus
**Sub** – subiculum
**CA** – Cornu Ammonis

**DG – CA3** – mossy fibers (mf)
**CA3 - CA1** – Schaffer's collaterals (sc)
**Perforant axons**: main input (pp)

# Explicit (declarative) memory

- Conscious recollection
- Content can be described verbally
- Storage even after a single exposure

**Episodic:** events
**Semantic:** facts, concepts, language symbols




**Medial temporal lobe**:

1. Synthesis of multimodal information and associations
2. Conscious recollection
3. Time and space context
4. „Corticalization”- consolidation

**1. CA3-CA1 Schaffer's collateral long-term potentiation (LTP)**

(collaboration of AMPA - NMDA glutamate receptors)

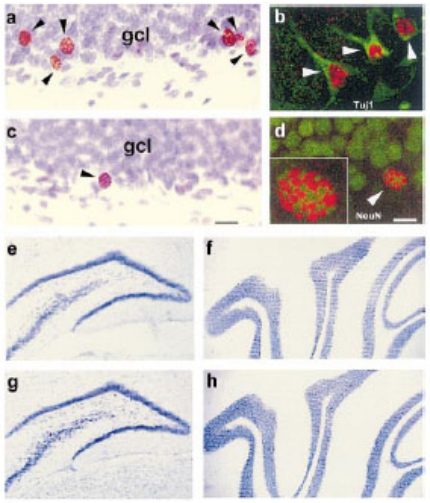
**2. Hebbian synapses**: strengthening of frequently used connections

(receptor and morphological changes, e.g. increased number of dendritic spines)

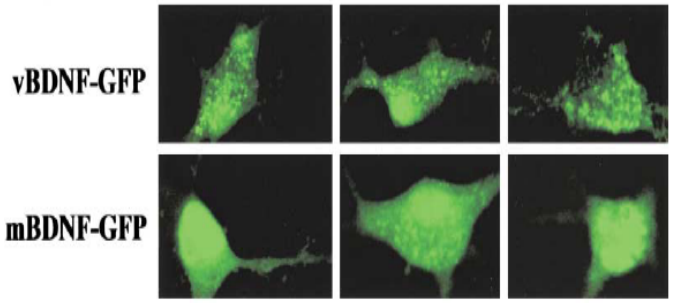
**3. Brain-Derived Neurotrophic Factor (BDNF)**

**4.** Cell division in dentate gyrus' **granular cells**

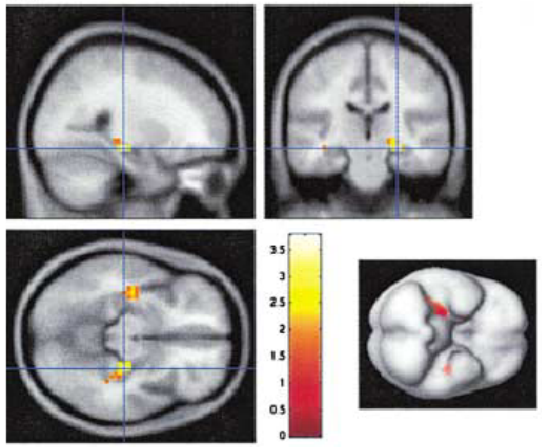
**Cell division**




**BDNF distribution in the hippocampal cells – effect of genetic variation**




**Effect of genetic variations of BDNF on hippocampal activity in humans**

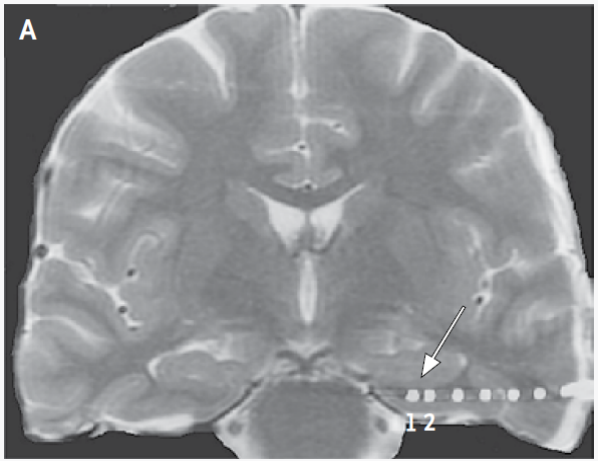



Gould E et al. Nat Neurosci 1999;2:260; Egan M et al. Cell 2003;112:257.

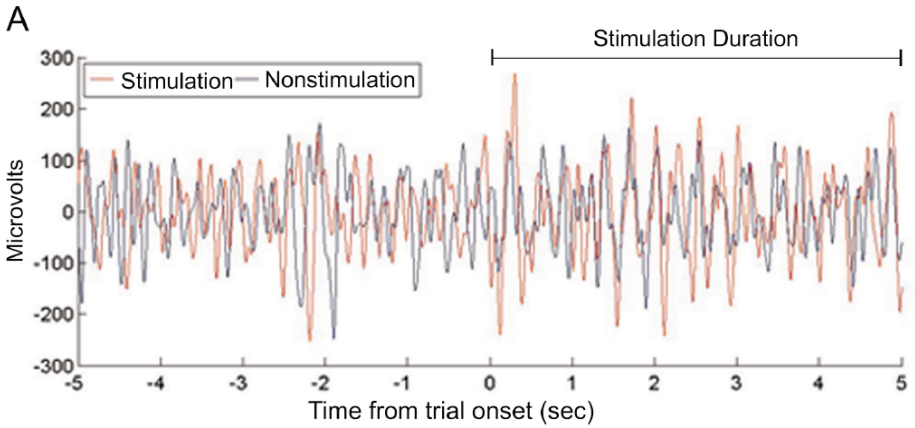
# Stimulation of the human entorhinal cortex during neurosurgery boosts spatial learning and modifies hippocampal activity

Task: to learn the pathway between two shops in a virtual town

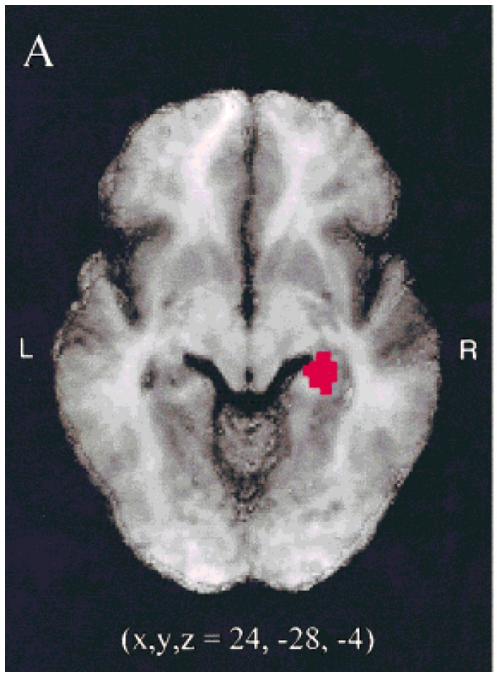

Stimulating electrode in the entorhinal cortex

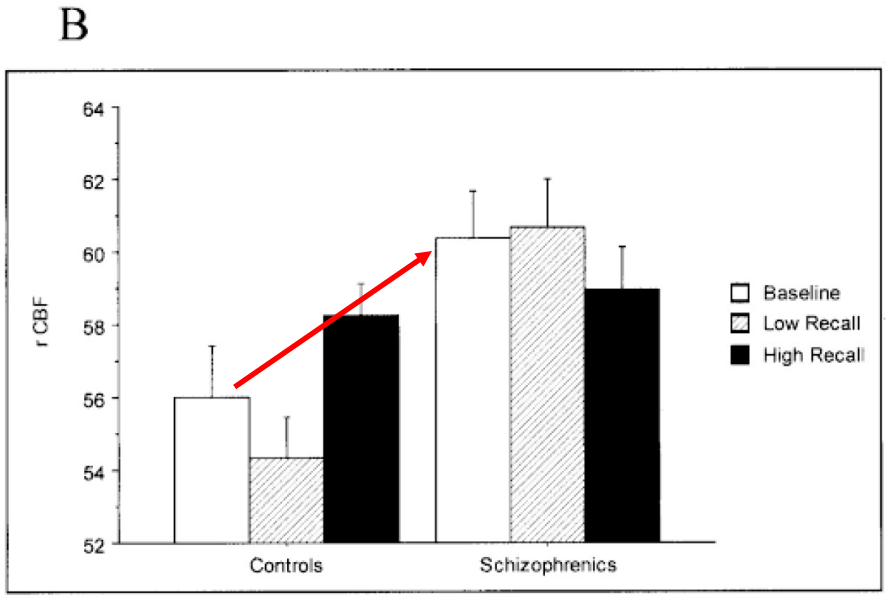


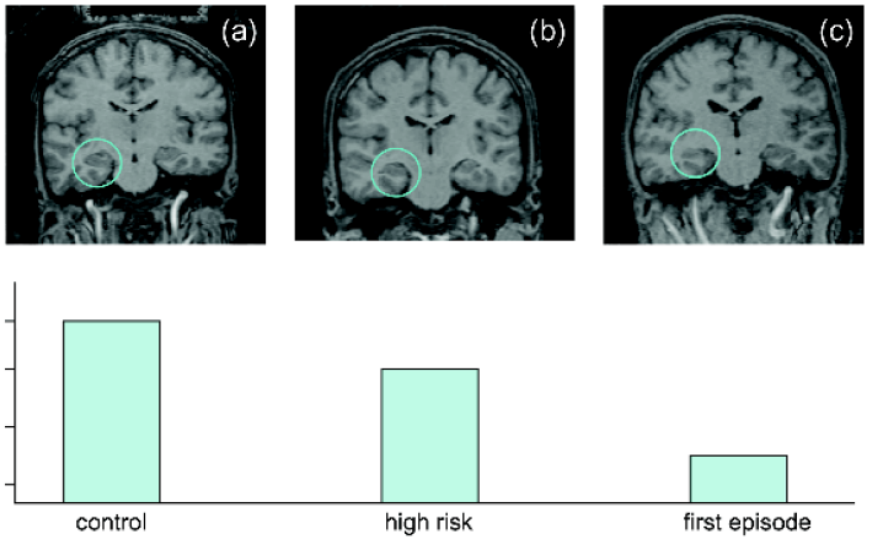

Change of theta activity in the hippocampus



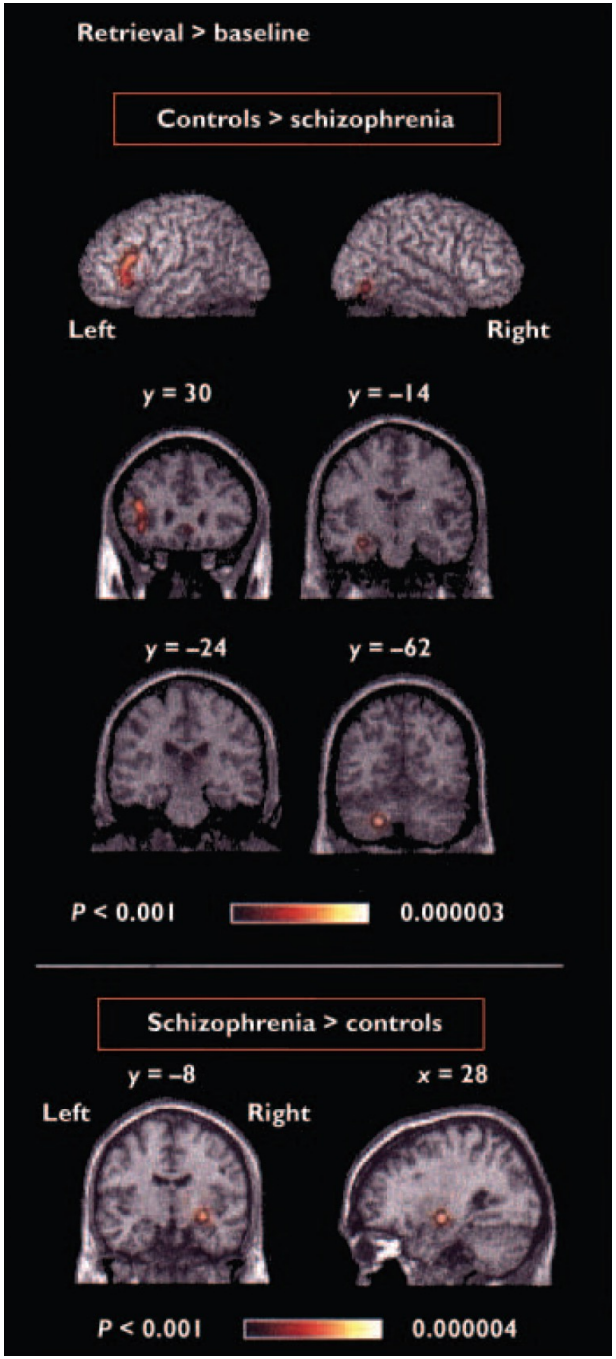

Suthana N et al. N Eng J Med 2012;366:502.



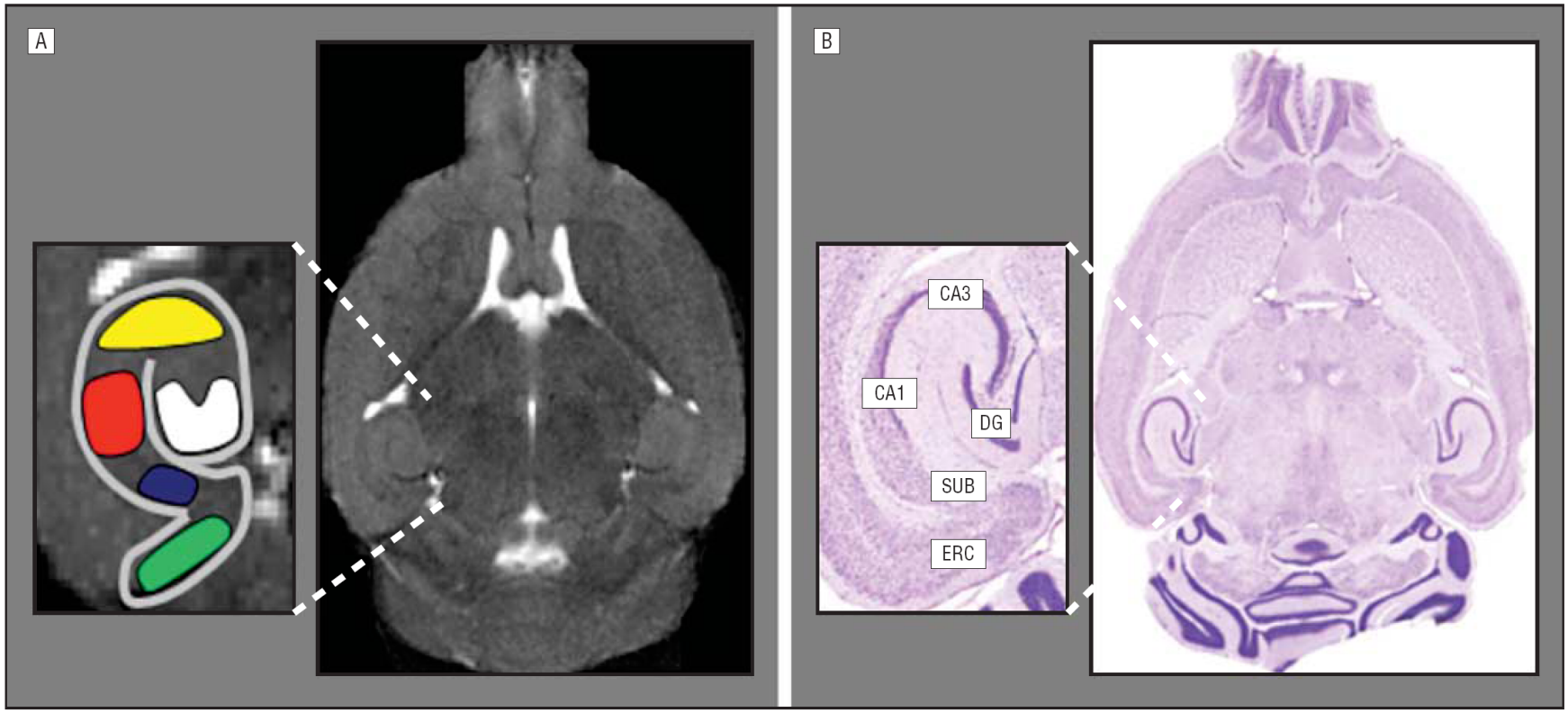



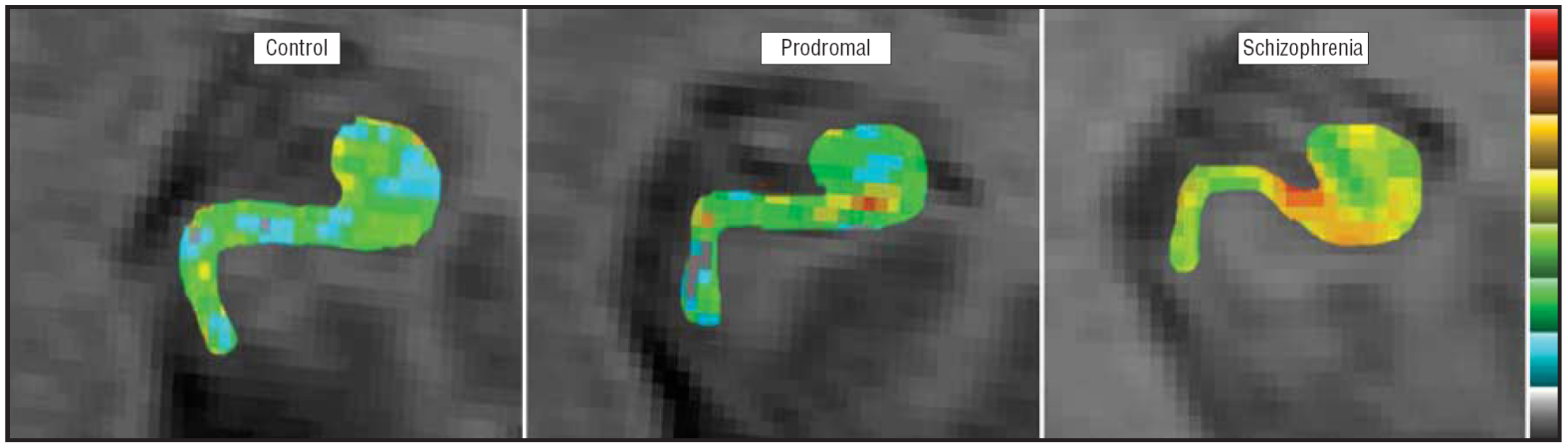

Heckers, 2001; Whalley , 2005

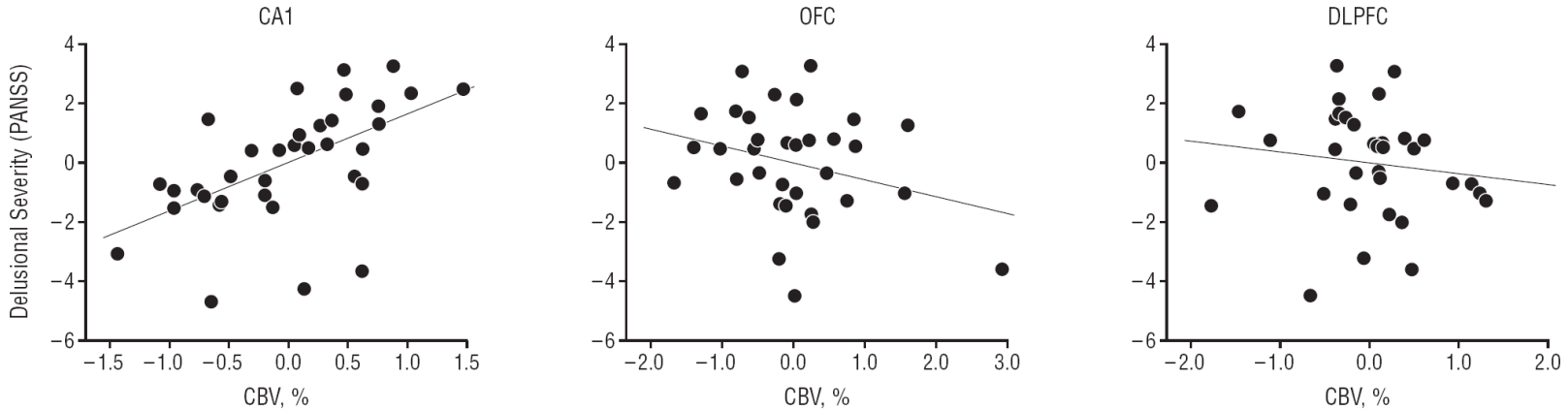

Retrieval > baseline
Controls > schizophrenia
Left
Right
y = 30
y = –14
y = –24
y = –62
P < 0.001
0.000003
Schizophrenia > controls
y = –8
x = 28
Left
Right
P < 0.001
0.000004

Achim, 2005

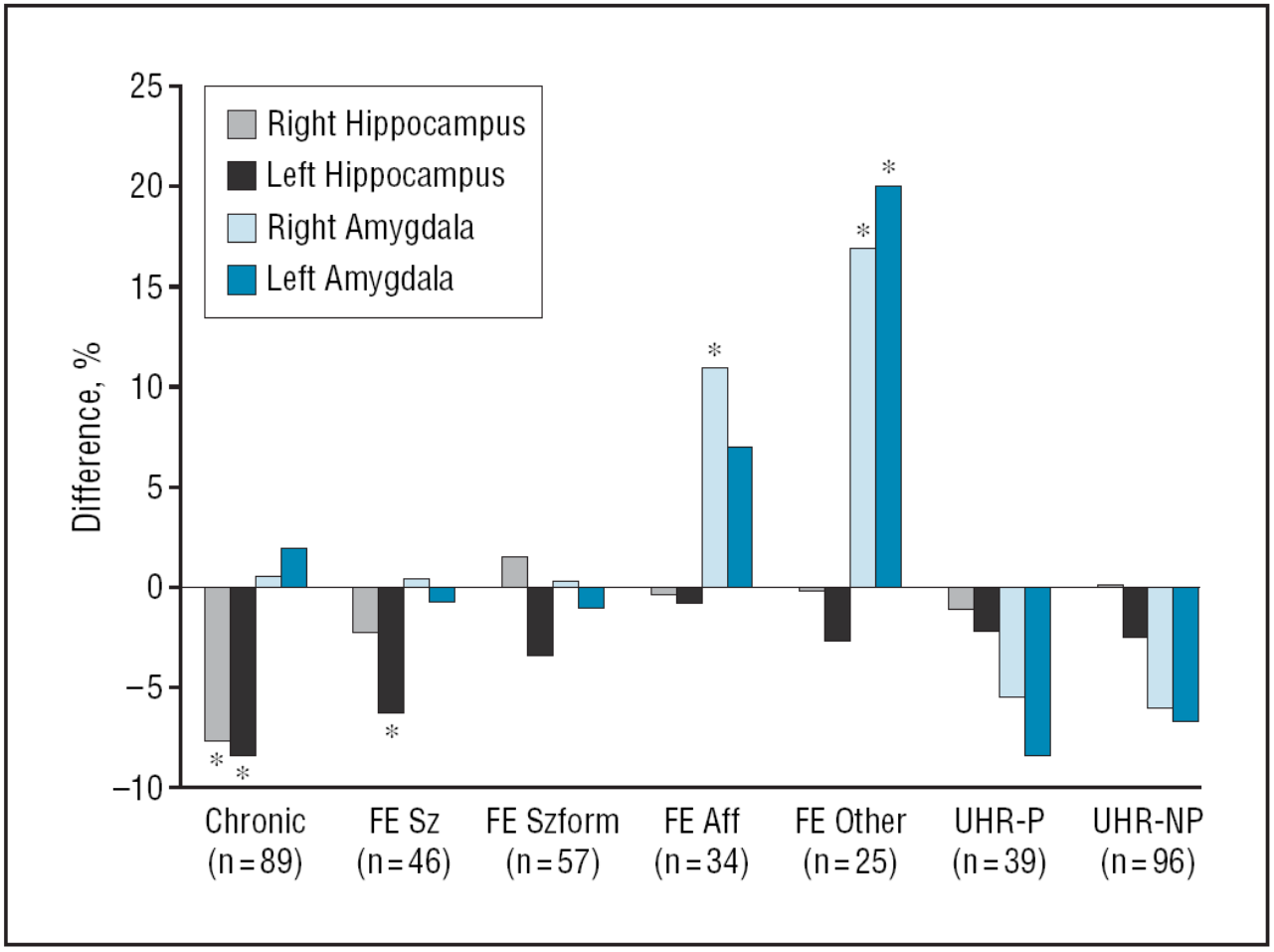



Schobel, 2009

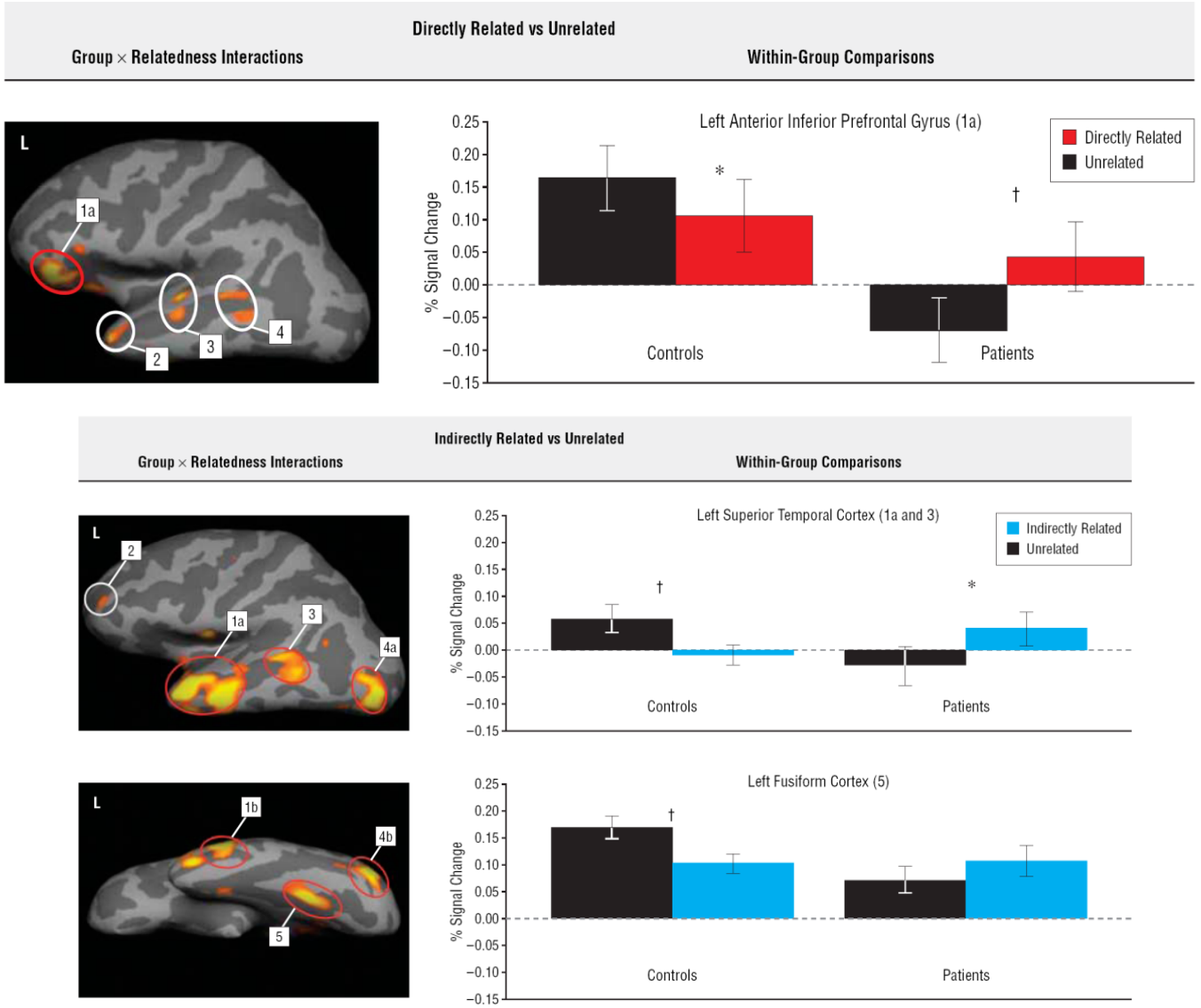



Schobel, 2009

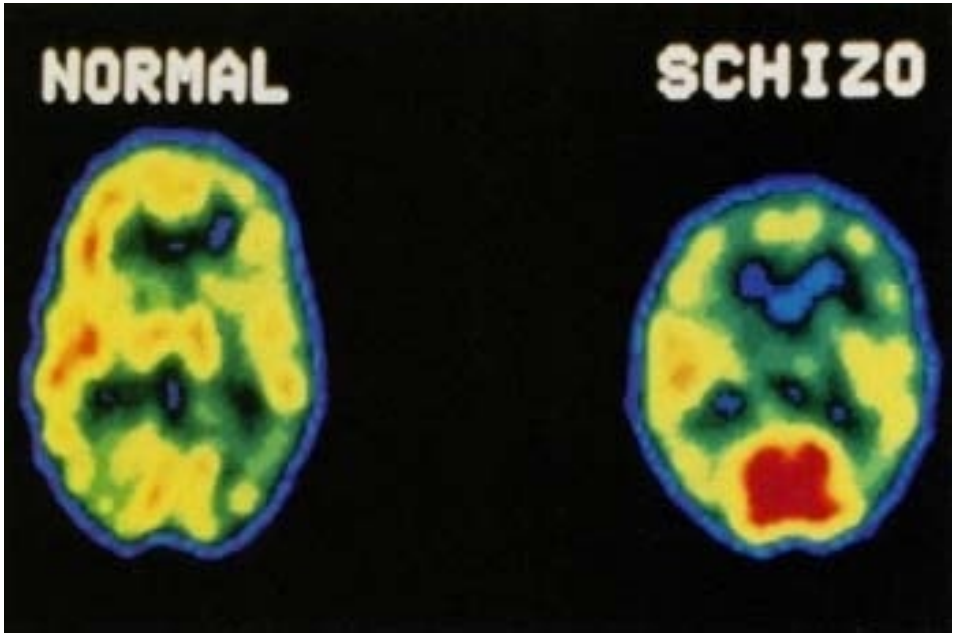



Velakoulis , 2006

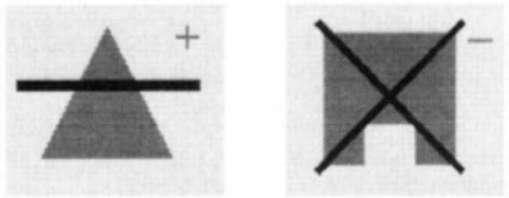



Kuperberg, 2007

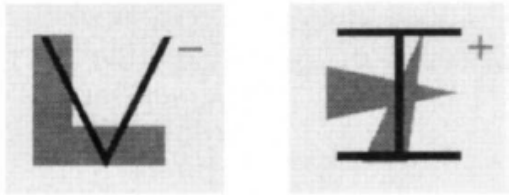
Daniel Weinberger



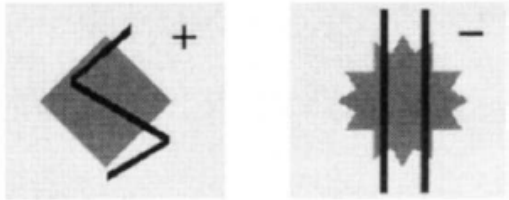
*a* Compound discrimination



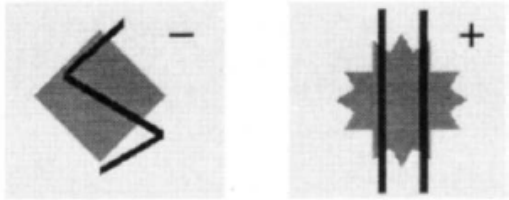

*b* Intra-dimensional shift

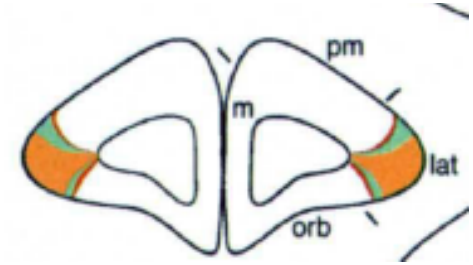


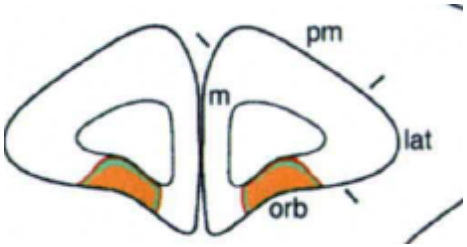

*c* Extra-dimensional shift



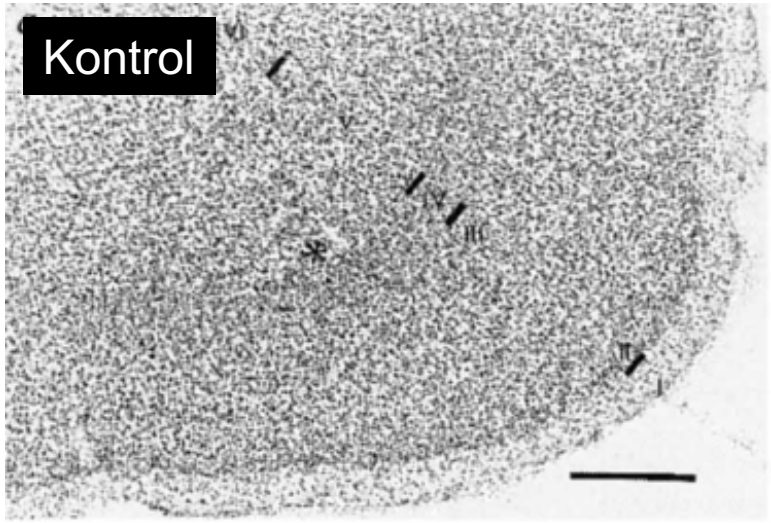

*d* Reversal

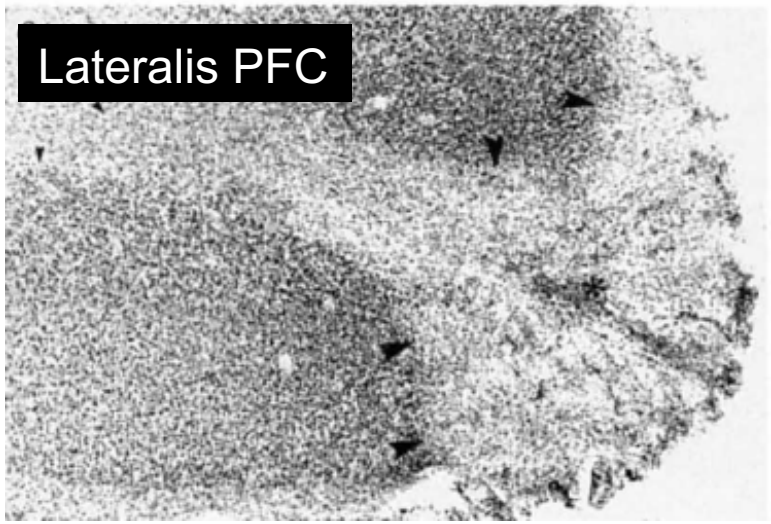


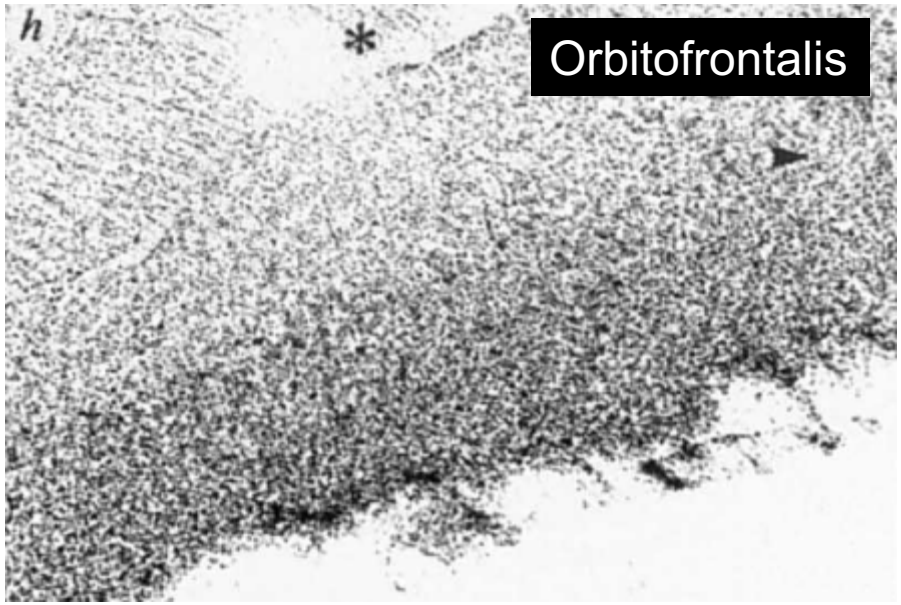



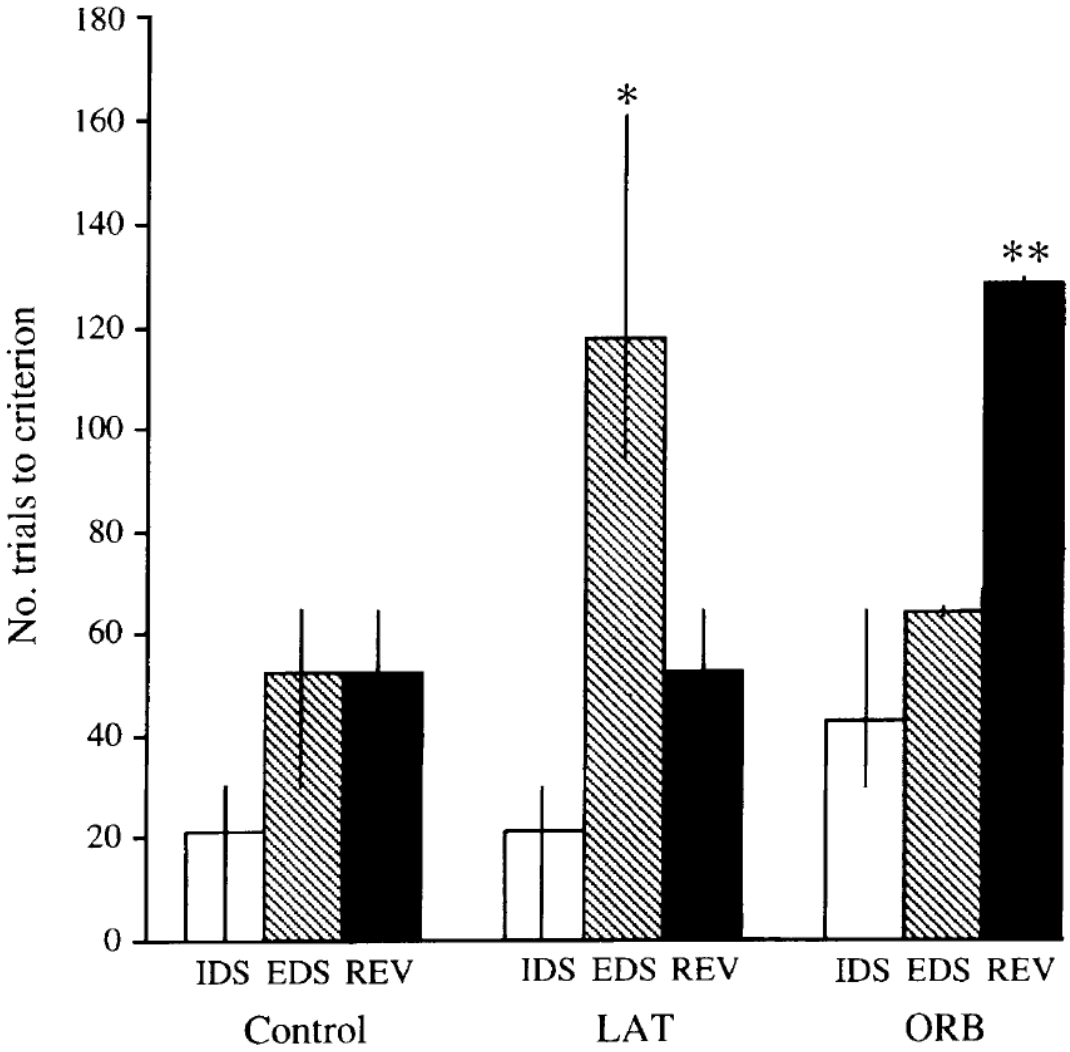




Dias, 1996


Kontrol


Lateralis PFC


Orbitofrontalis

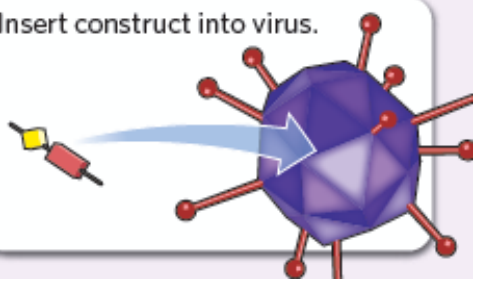

180
160
140
120
100
80
60
40
20
0
No. trials to criterion
*
**
IDS EDS REV
IDS EDS REV
IDS EDS REV
Control
LAT
ORB

**STEP 1**

Piece together genetic construct.

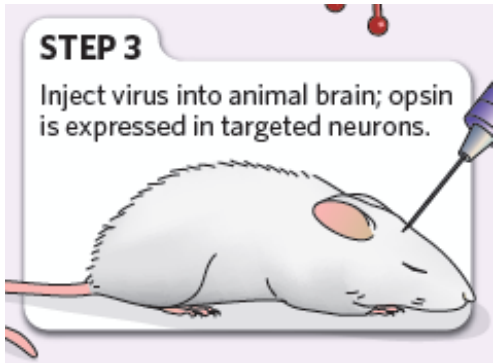

**STEP 2**

Insert construct into virus.



**STEP 3**

Inject virus into animal brain; opsin is expressed in targeted neurons.

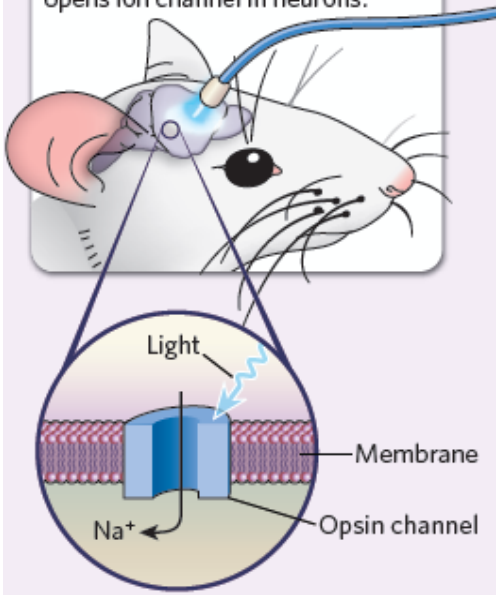


**STEP 4**

Insert 'optrode', fibre-optic cable plus electrode.

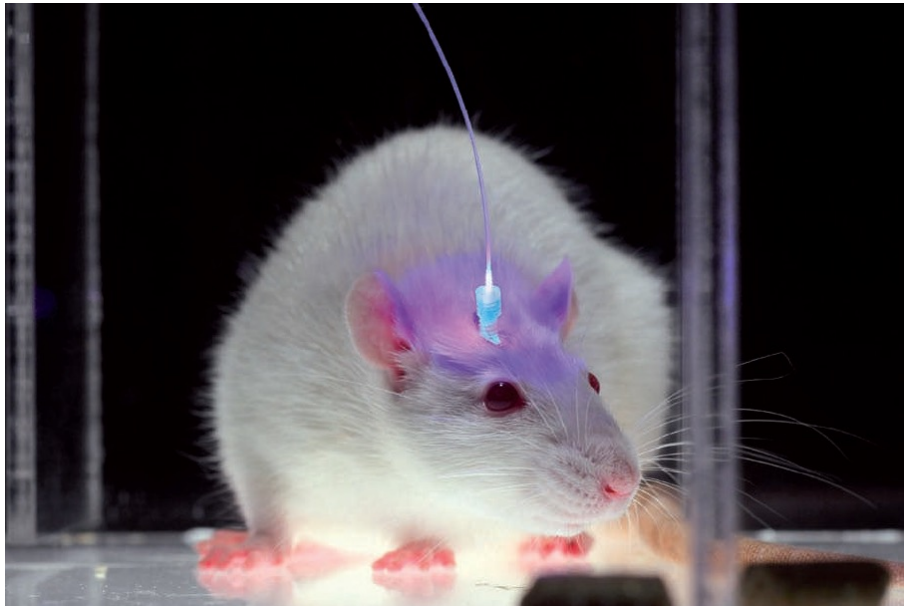
**STEP 5**

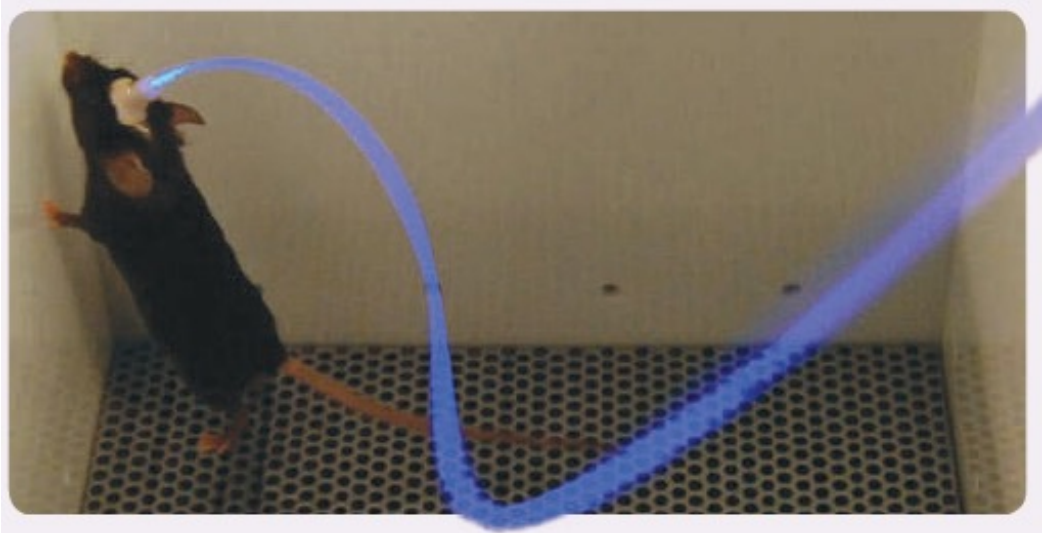
Laser light of specific wavelength opens ion channel in neurons.

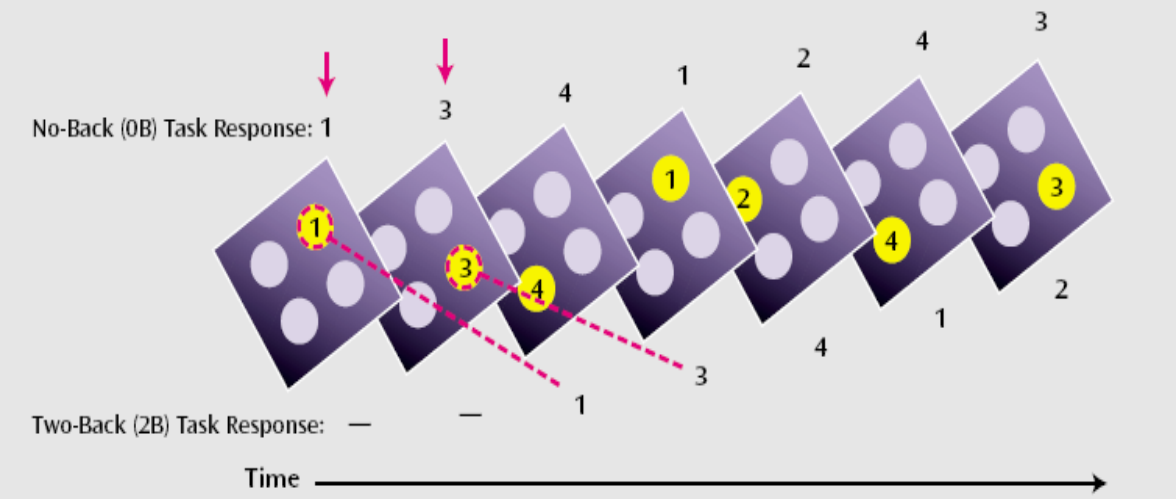


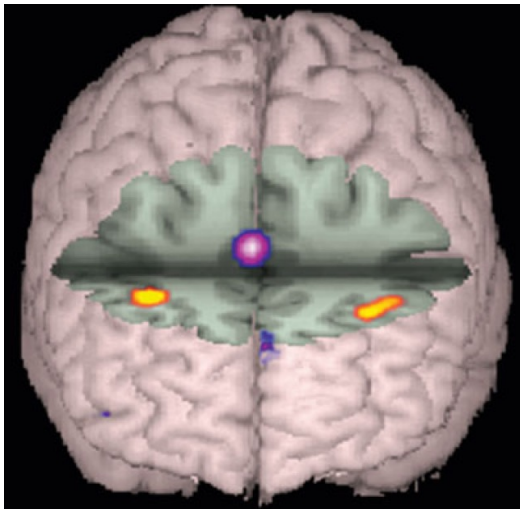

**STEP 6**

Record electrophysiological and behavioural results.

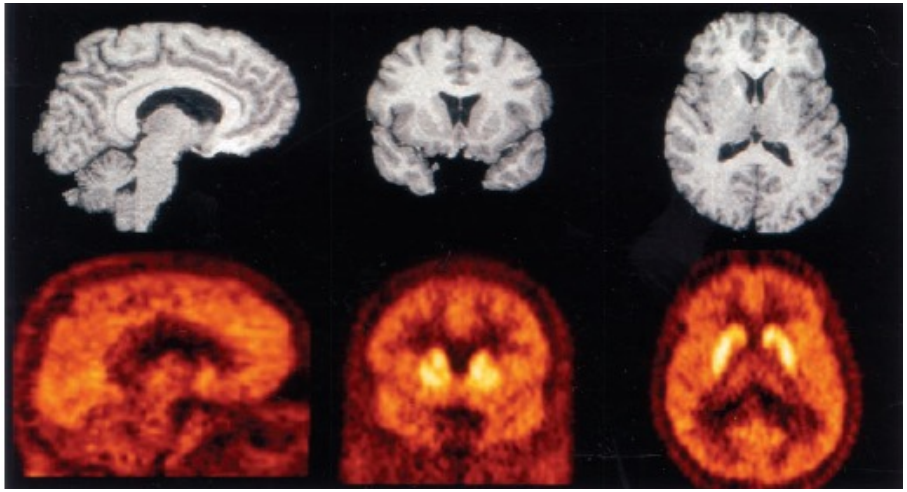


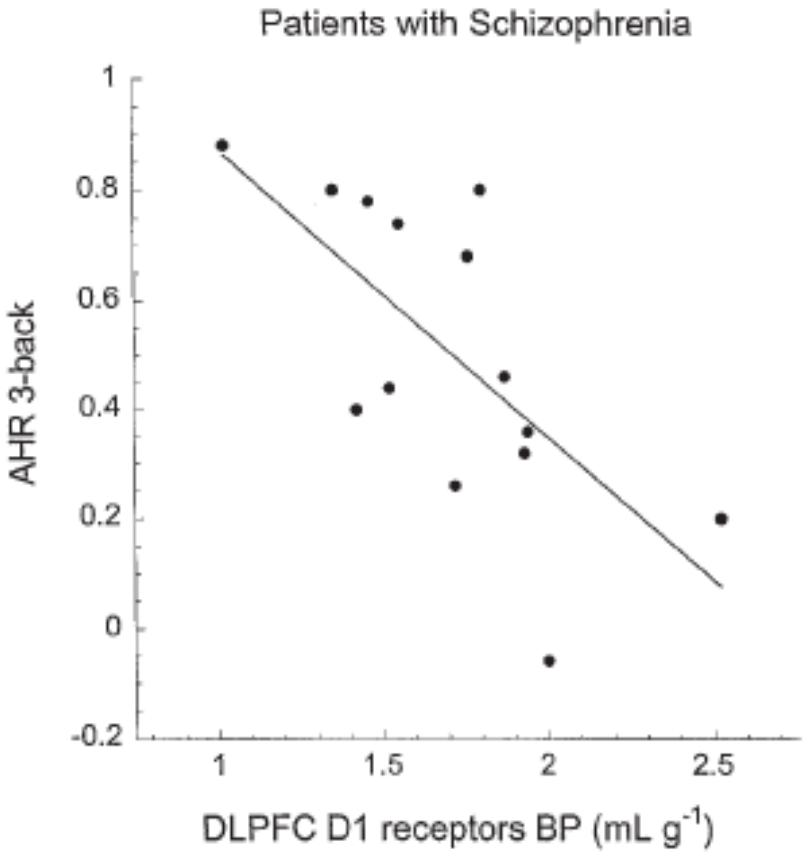



No-Back (0B) Task Response: 1
3
4
1
2
4
3
1
3
4
1
2
3
4
1
2
4
1
3
Two-Back (2B) Task Response: —
—
Time

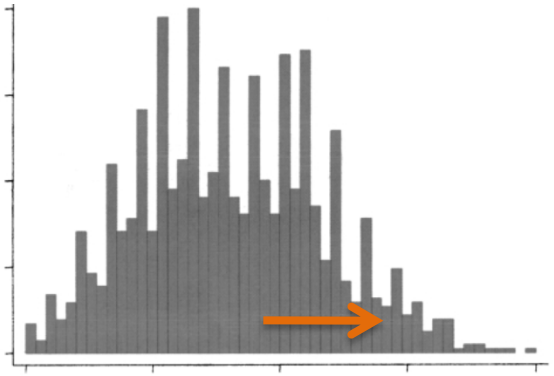


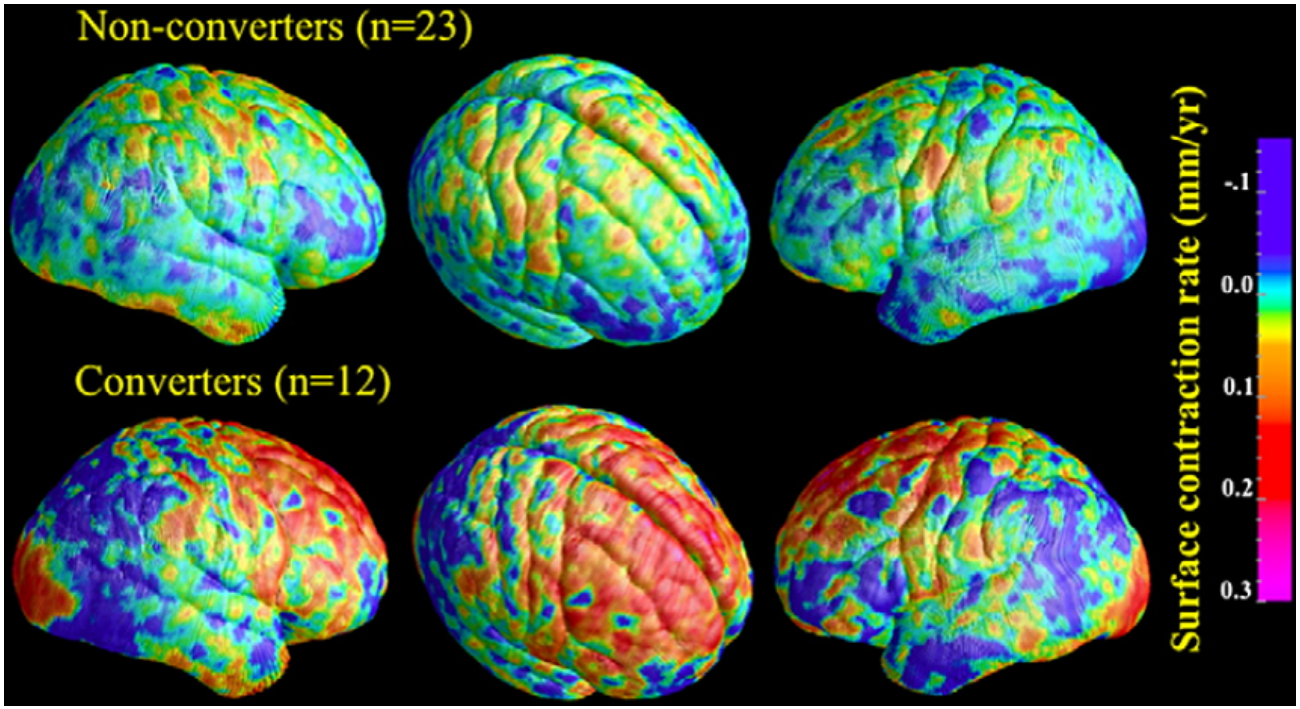
Glahn , 2005






Abi-Dargham, 2003






Sun D et al. Schizophr Res, in press

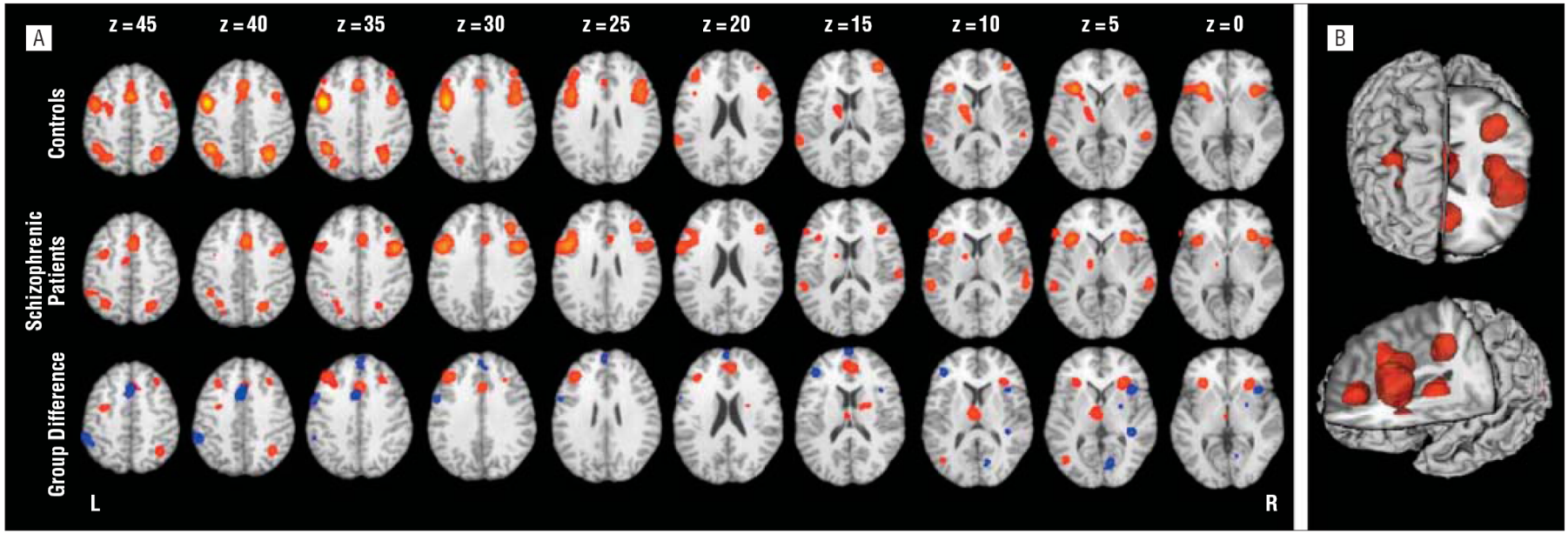
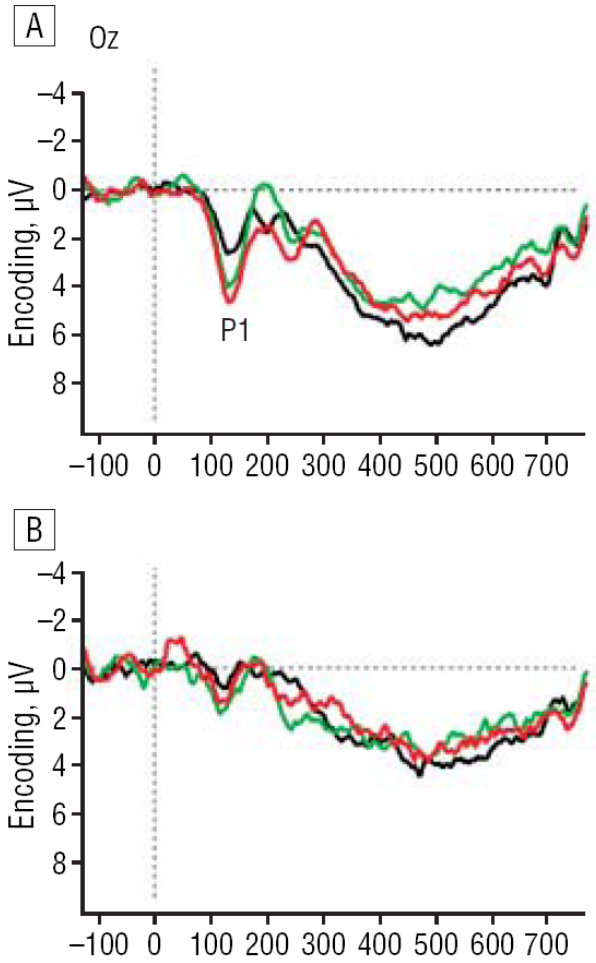
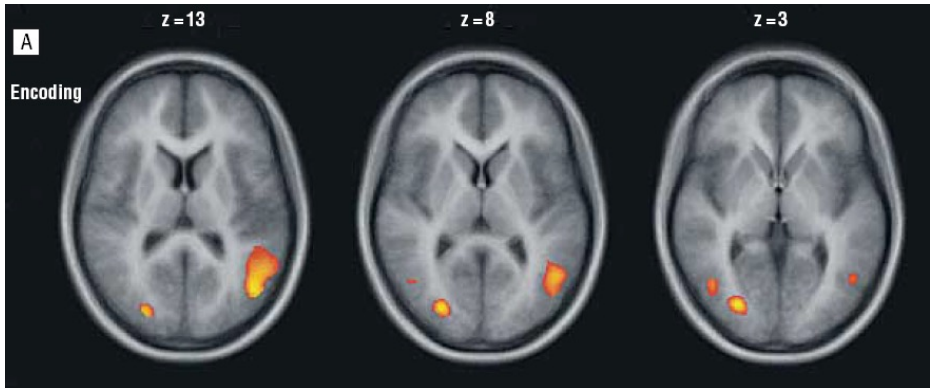



**Figure 1.** Global analysis of executive function studies in schizophrenia. A, Brain regions with significant activation across executive function task types. In the bottom row, clusters in which controls showed more activation than schizophrenic patients are in red and clusters in which schizophrenic patients showed more activation than controls are in blue. B, Three-dimensional rendering of areas with more activation in controls than in schizophrenic patients across task types (global). L indicates left; R, right.

Minzenberg, 2009




Haenschel , 2007

# Implicit (non-declarative) memory 1.

- Not requires conscious awareness and intentionality
- Poor verbal description
- Requires long training
- BUT: *Close interaction with explicit memory*

## 1. Sensitization, habituation, conditioning

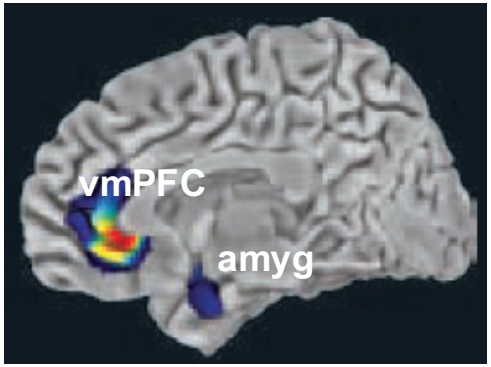
**a. Amygdala** [amyg]

**Lateral part: sensory input even from thalamic level**

**Central part: output**

- **Periaqueductal grey matter:** behavioral response (approach or avoidance)
- **Lateral hypothalamus:** vegetative changes
- **Paraventricular nucleus (hypothalamus):** endocrinological changes

**b. Ventromedial prefrontal cortex** [vmPFC]: amygdala regulation



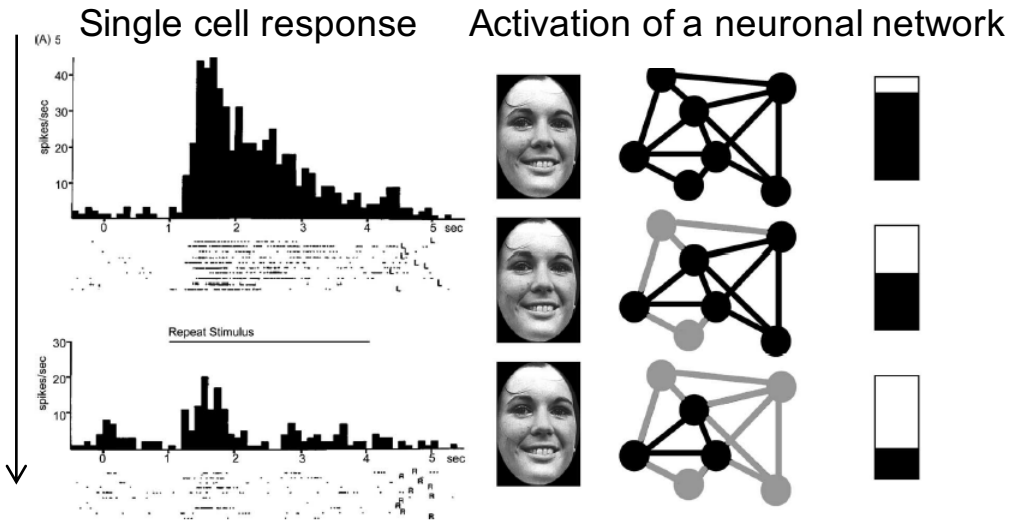
# Implicit (non-declarative) memory 2.

**2. Learning of skills and habits** (e.g., playing on violin, repetitive behaviors)

**Basal ganglia, cerebellum**:
Selection of motor and cognitive patterns, reinforcement (reward), timing

**3. Priming**

Mere observation of a repetitive stimulus enhances the effectiveness of behavior or its probability (e.g., recognition of a face, spontaneous retrieval of a word)




**Take a look at the list!**

**Window**
**Clothes**
**Hairdresser**
**Flower**
**…**

**Complete the words!**

**Ha…**
**Fl…**
**To…**
**Ma…**

# Levels of language organization

1. **Phonological** and **orthographic** level (organization of sound and written symbols)

2. **Lexical** level (words)

3. **Semantic** level (concepts, meanings)

4. **Grammatical** level (assembly of words to sentences)

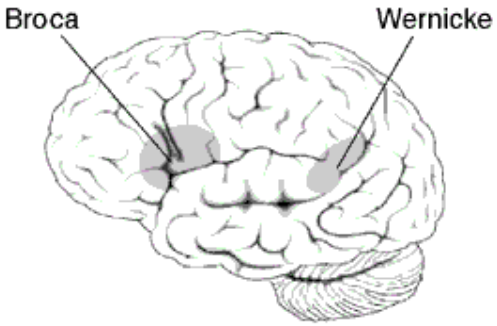
5. **Pragmatic** level (imagining the thoughts and intentions of other people during conversation, social and situational rules)

# Neuronal substrates of speech

**1. Broca's area** (Brodmann 45, posterior inferior frontal gyrus)
- Motor center of speech (telling words and sentences)
- Lesion – **motor aphasia**:
  poverty of speech output – total loss of speech
  agrammatism
  spared understanding

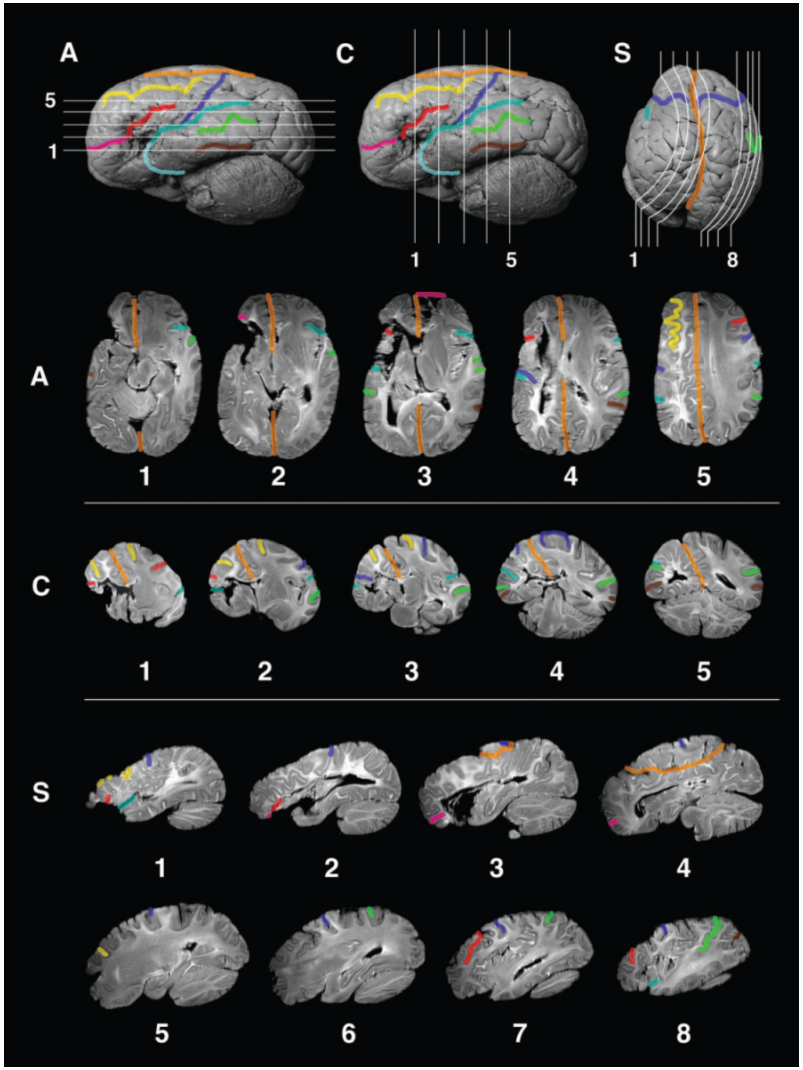
**2. Wernicke's area** (Brodmann 22, posterior superior temporal gyrus)
- Understanding speech
- Lesion – **sensory aphasia**:
  meaningless speech (word salad)
  impaired understanding

**3. Arcuate fasciculus**
- Connection between Broca and Wernicke
- Lesion - **conduction aphasia**:
  impaired repetition of heard words



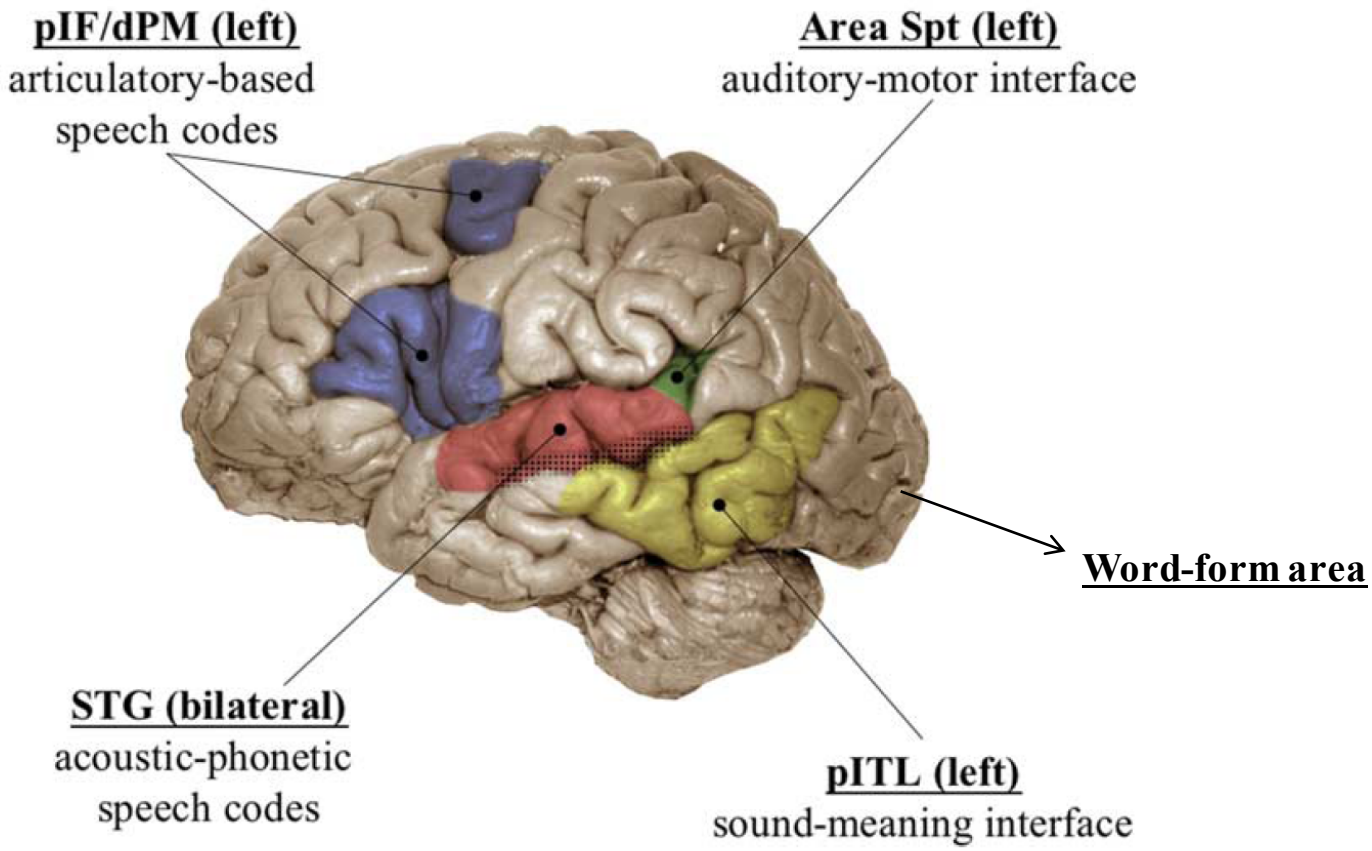

**Leborgne's („Tan") brain, Paul Broca (1861)**

# Broca revisited: visualization of Tan's lesion using high-resolution imaging techniques




Dronkers NF et al. Brain 2007;130:1432.

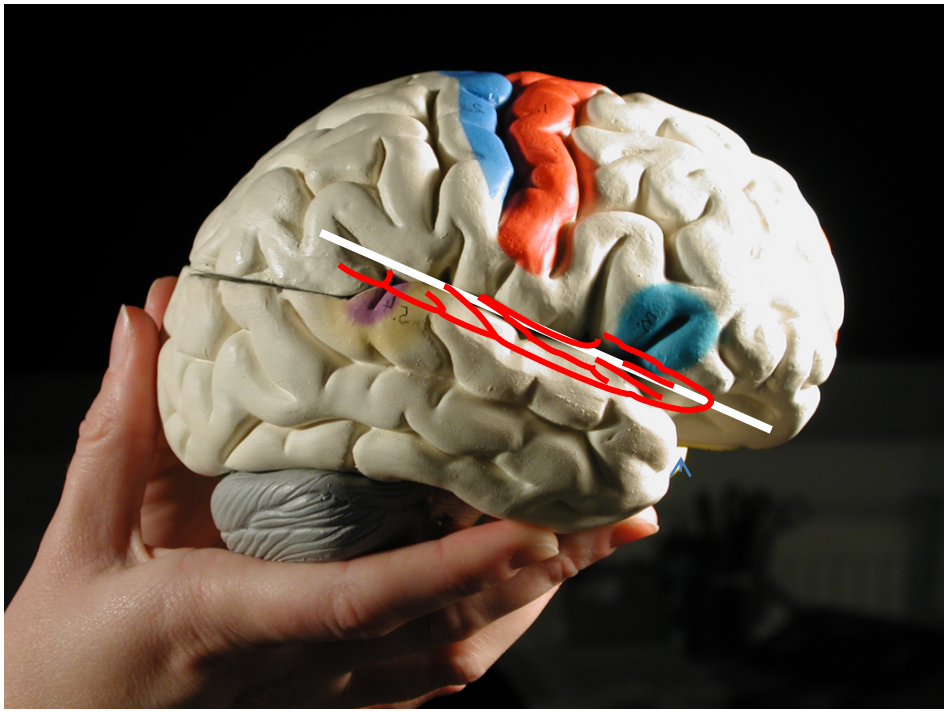
# An alternative model for language organization

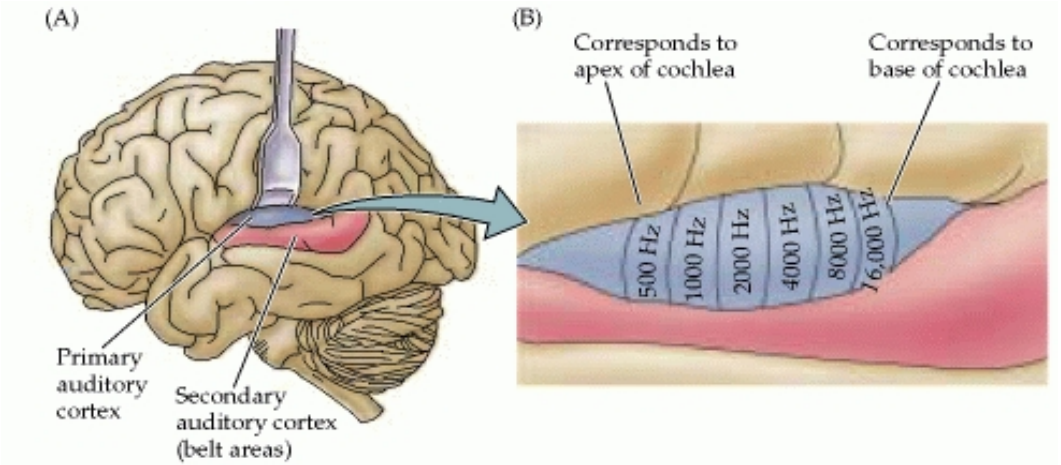


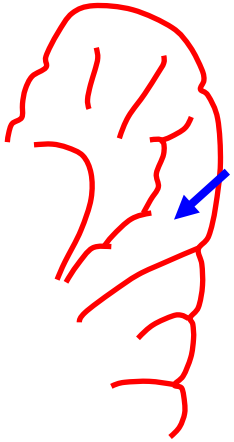

Hickok G & Poepel D. Cognition 2004;92:67.

**STG** – superior temporal gyrus, **pIF** – posterior inferior frontal, **dPM** – dorsal premotor, **Spt** – superior-posterior temporal, **pIT** – posterior inferior temporal

Hickok G & Poeppel D. Cognition 2004;92:67.





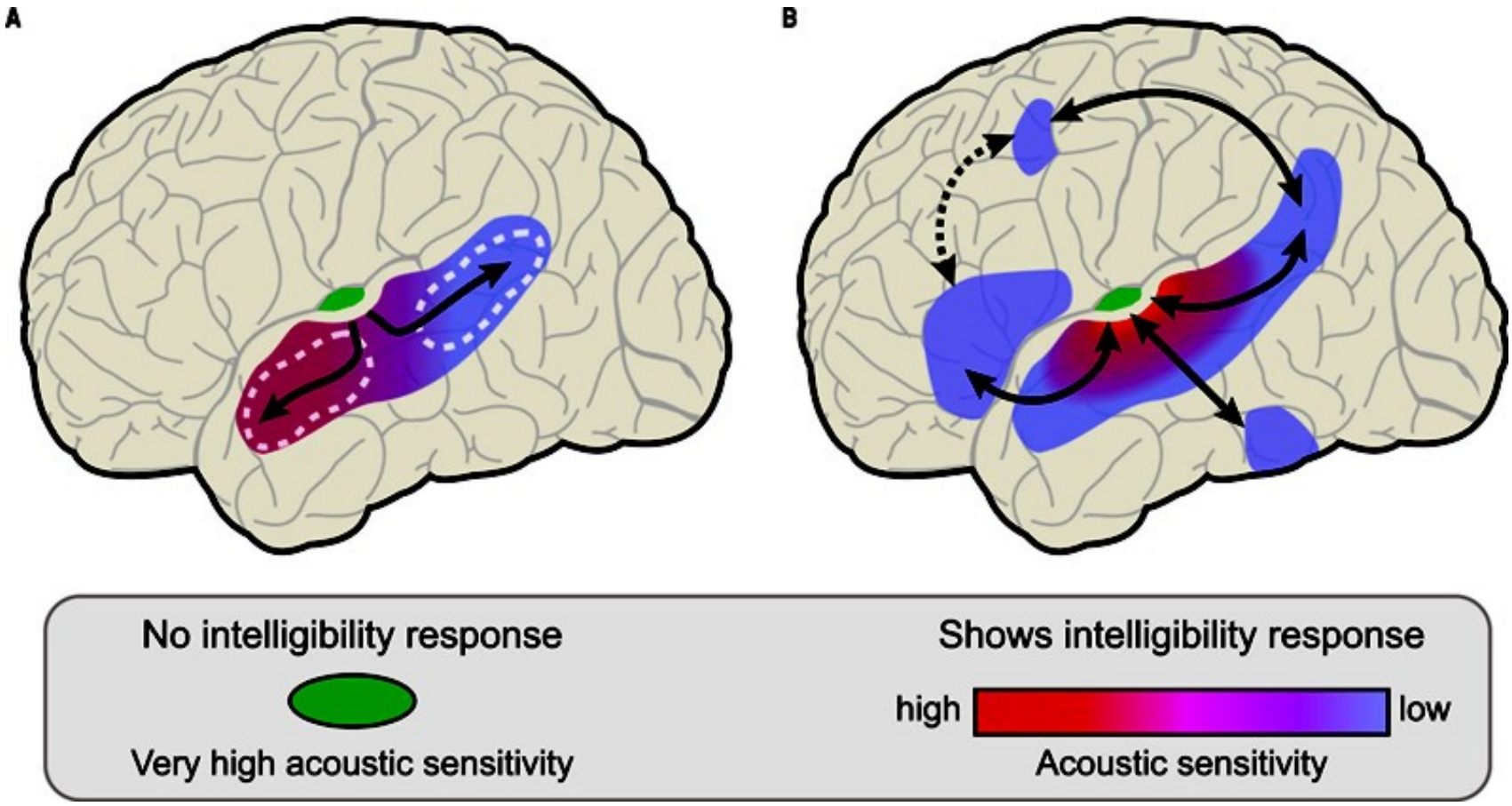



Planum frontale

Heschl gyrus
(primary auditory cortex
Brodmann 41)

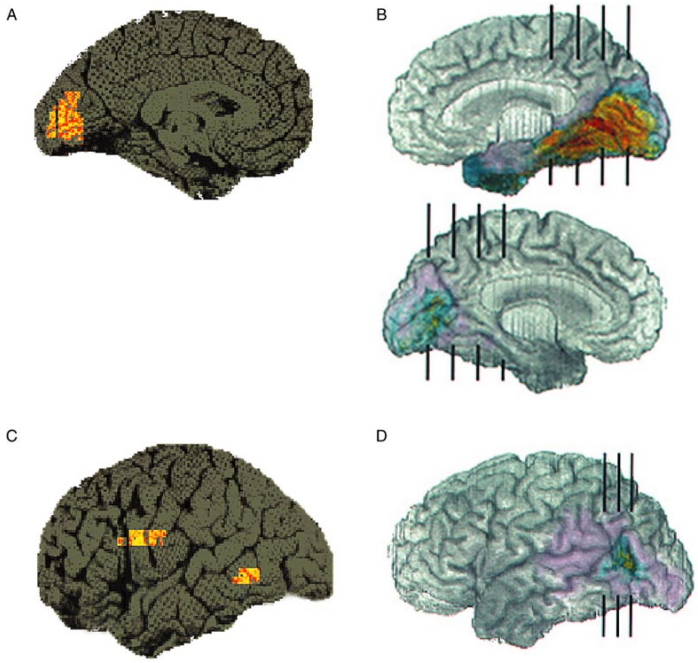
Planum temporale

# Intelligibility of response: sensitivity to conceptual content and meaning of stimuli




Peelle JE et al. Front Hum Neurosci 2010;4;51. doi: 10.3389/fnhum.2010.00051

**Agnosia**: inability to recognize objects, persons, words;
loss of meaning (semantic disorder)




Impaired recognition of living beings

Impaired recognition of objects and tools

**Gerstmann's syndrome:**
Lesion of left angular and supramarginal gyrus
***Alexia*** (reading)
***Agraphia*** (writing)
***Acalculia*** (counting)

# Hemispheric specialization

**Right handed:** *>90%* left hemisphere language localization
**Left handed:** *70%* - left
*15%* - right
*15%* - bilateral

**Wada's test:** injection of sedatives (sodium amobarbital) into the internal carotid artery during speech – selective inhibition of one hemisphere

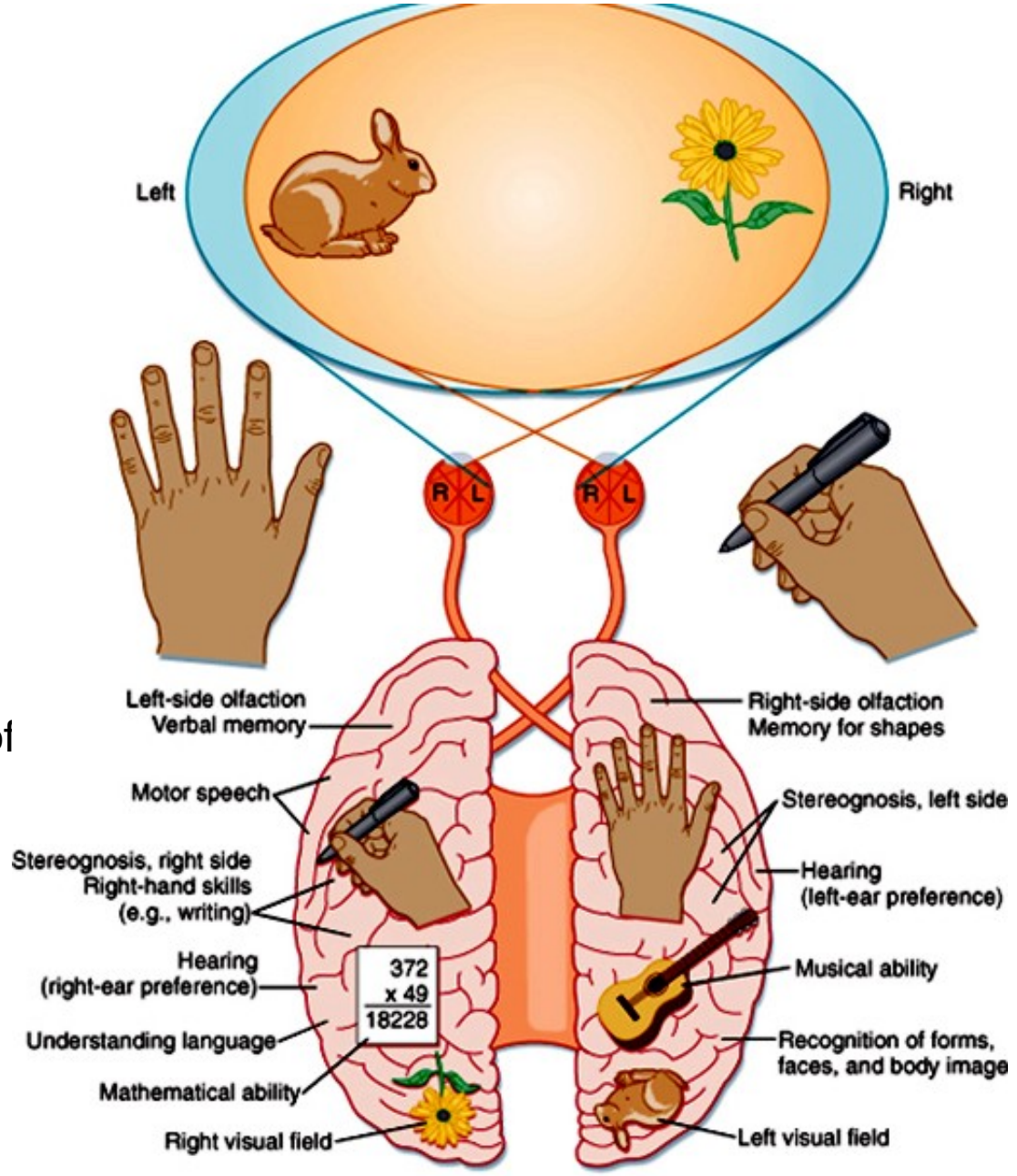
**Split-brain**
- Surgical dissection of the corpus callosum
- Images projecting to left hemisphere can be named, those projecting to right hemisphere can be recognized but not named

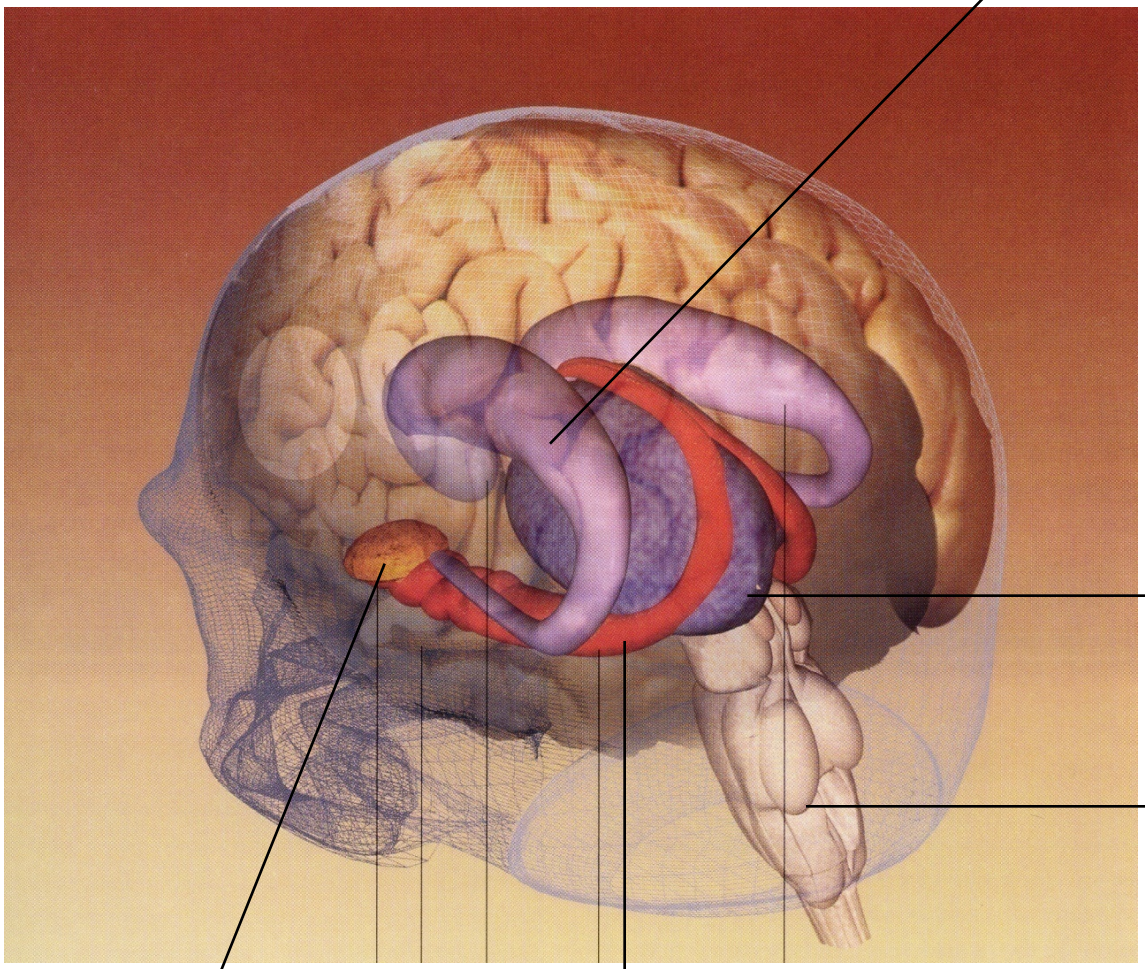
**Left:**

- Written and spoken language
- Mathematical skills
- Rational thinking
- Detailed, step-by-step analysis of information

**Right:**

- Expressive aspects of language (**prosody** = pace and intonation of speech to express emotions)
- Processing of complex visual images and faces
- Spatial relationships
- Synthesis of information



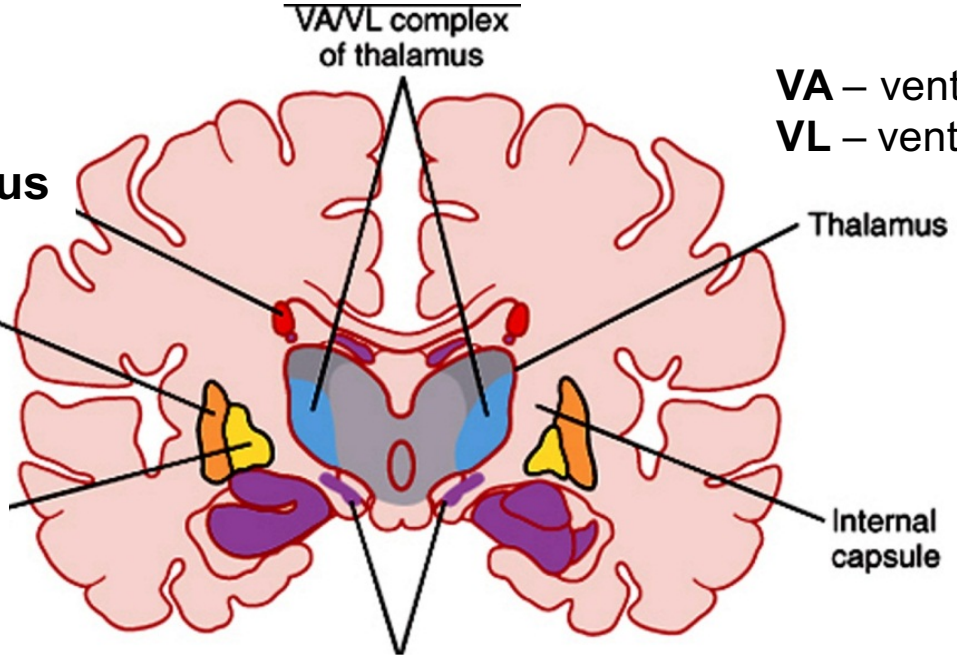

n. caudatus
thalamus
brainstem
amygdala
hippocampus

**NEOSTRIATUM**

- **n. caudatus**
- **putamen**

**PALLIDUM**

- **globus pallidus**

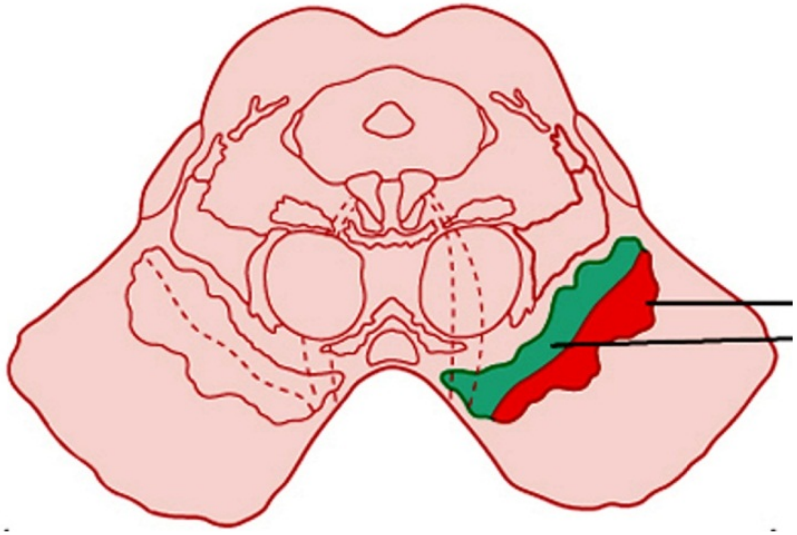



**VA** – ventralis anterior
**VL** – ventralis lateralis

**n. subthalamicus (Luys)**

**ARCHISTRIATUM**
**ventral striatum (n. accumbens)**

- **Amygdala central and medial nucleus**
- **Claustrum**



**substanita nigra**
**pars compacta**
**pars reticularis**

**Main cell types of neostriatum:**

**Medium spiny neurons**

- receiving cortical tracts

Types:

**a. GABA** + substance P/dynorphin

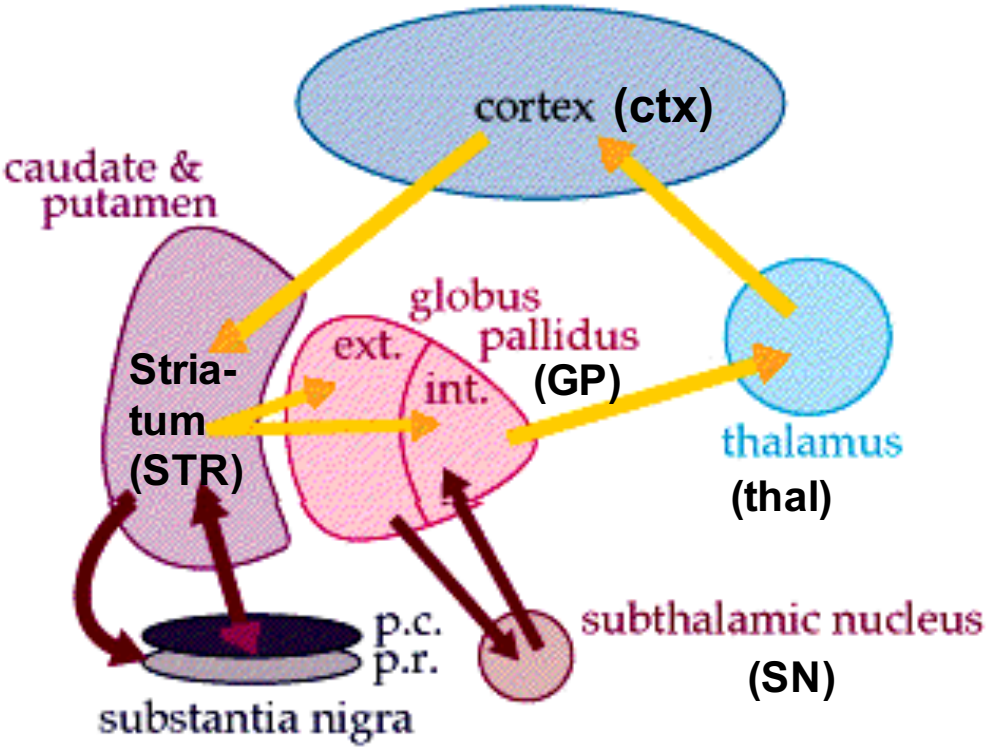
**D1** dopamine receptor

**b. GABA** + encephalin

**D2** dopamine receptor

**Cholinergic interneurons**

(~10%, no spines)




**p.c**. = **pars compacta** – **dopamine – nigrostriatal pathway**

p.r. = pars reticularis, ext. = external, int. = internal

1. **Direct** *(„go")* path (D1): ctx → +STR → -GPint → -thal → +ctx
2. **Indirect** *(„no-go")* path (D2): ctx → +STR → -GPext → -SN → +GPint → -thal →+ctx
3. **Hyperdirect** path: ctx →+SN → +GPint → -thal → +ctx

+: excitatory (glutamate)

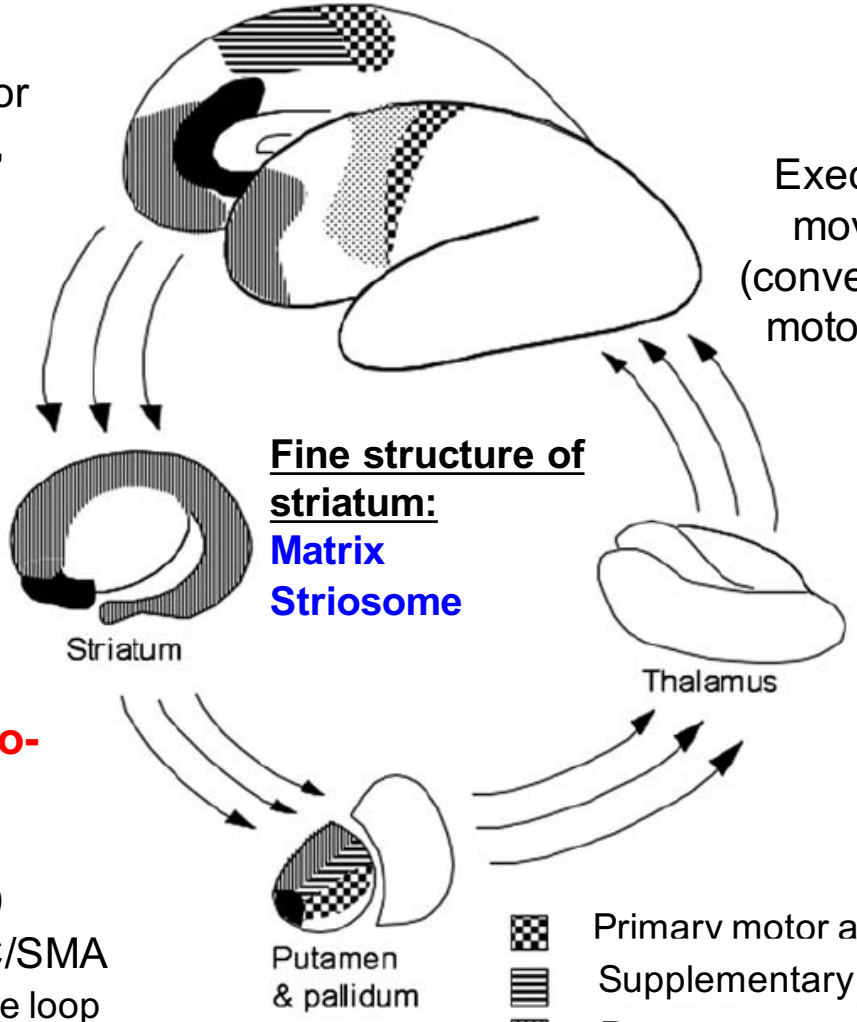
-: inhibitory (GABA)

# The cortico – striato – thalamo - cortical system

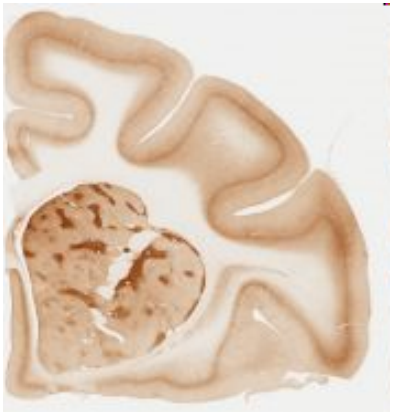
Plans, motor programs, affective impulses

Execution of movement (convergence to motor cortex)

Pattern selection, motivation and reinforcement (archistriatum, dopamine)




**Fine structure of striatum:**
**Matrix**
**Striosome**



**Fronto – striato - pallido-thalamic circuits**:

- **Cognitive** (*plan*, dorsal PFC – dorsal neostriatum)
- **Motor** (*movement*, PMC/SMA – putamen, matrix, separate loop for eye movements)
- **Affective** (*emotion-motivation*, ventral cingulum – archistriatum, striosome)

Primary motor area
Supplementary motor area (SMA)
Premotor area (PMC)
Prefrontal cortex (PFC)
Cingulum

# Disordered functioning of the basal ganglia

**I. Hypokinesia with increased muscle tone**

e.g. **Parkinson's disease** (*alfa-synuclein* protein accumulation, loss of dopamine producing cells in substantia nigra pars compacta)

**II. Hyperkinesia with decreased muscle tone**

e.g. **Huntington chorea** (abnormal *huntingtin* protein, loss of GABAergic neurons in striatum, 4. chromosome CAG triplet↑)

# Parkinson's disease

1. Reduced and slow movements *(hypo- and bradykinesia)*
2. Muscle tone↑ *(cogwheel rigidity)*
3. Resting *tremor* with low frequency
4. Disturbances of gait and posture
5. Blunted affect (mask-like face)
6. Disorder of planning and problem solving, slow thinking

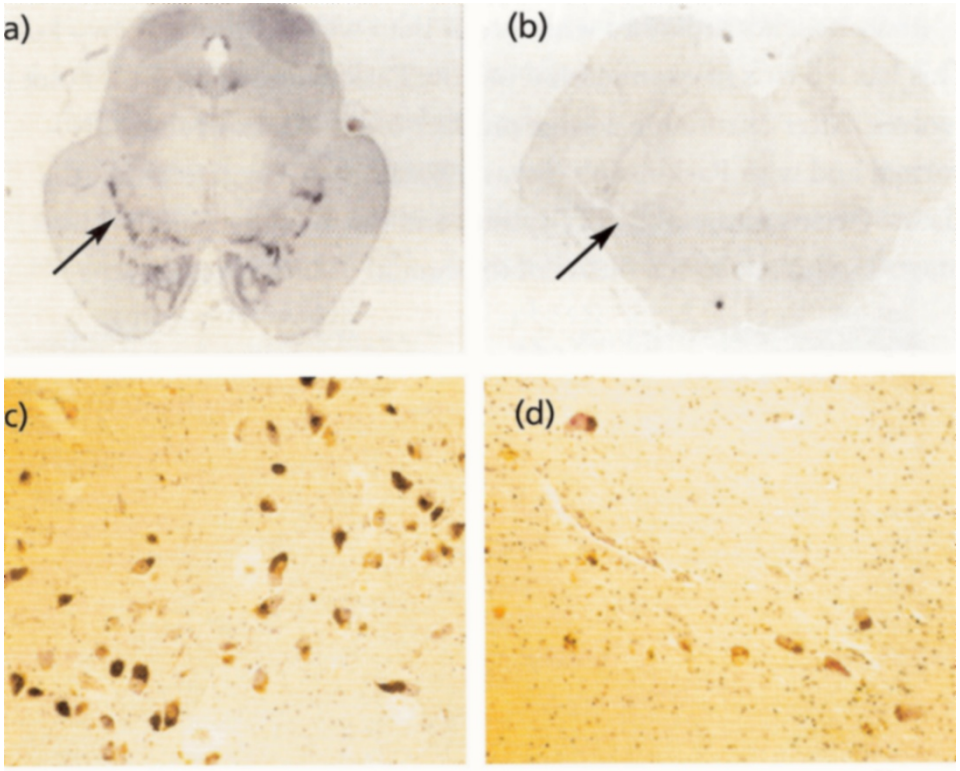
**Pathogenesis:** dopaminergic cell loss in substantia nigra pars compacta

**Treatment:**

- L-DOPA (dopamine's progenitor)
- Dopamine receptor agonists
- Deep brain stimulation

Gowers, 1886

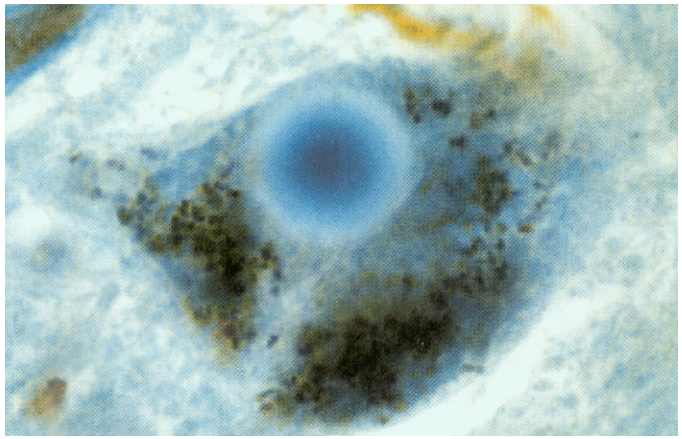
**Normal substantia nigra** **Parkinson's**



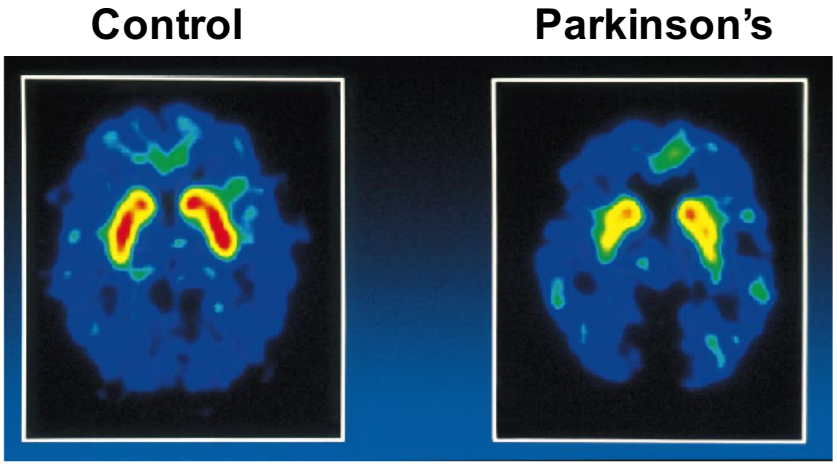

**Neuromelanine containing dopaminergic cells**

**Reduced number of dopaminergic cells**

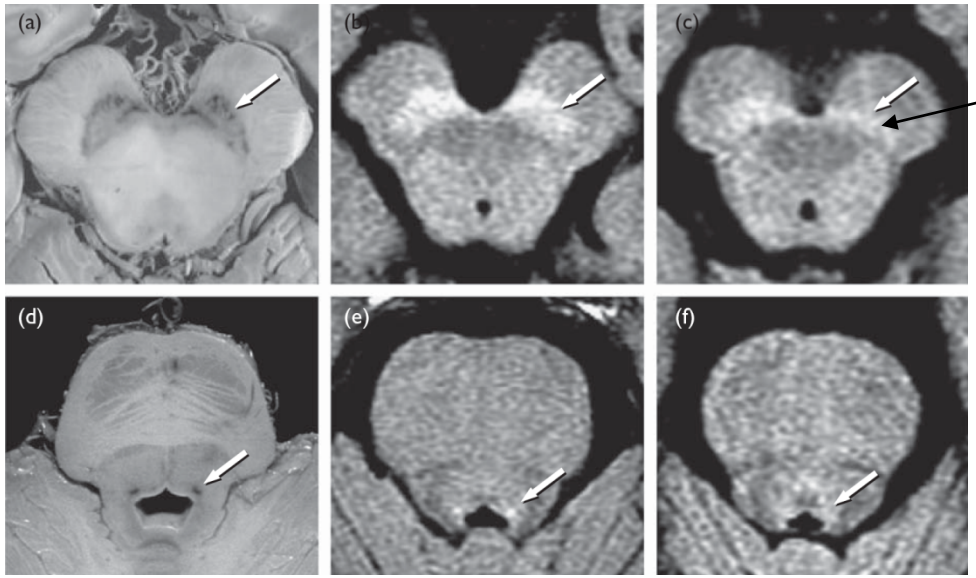
***Lewy-body:*** **aggregated alpha-synuclein and other proteins**



## Disorder of dopaminergic transmission: positron emission tomography (PET)




## Neuromelanine-sensitive magnetic resonance imaging (MRI)

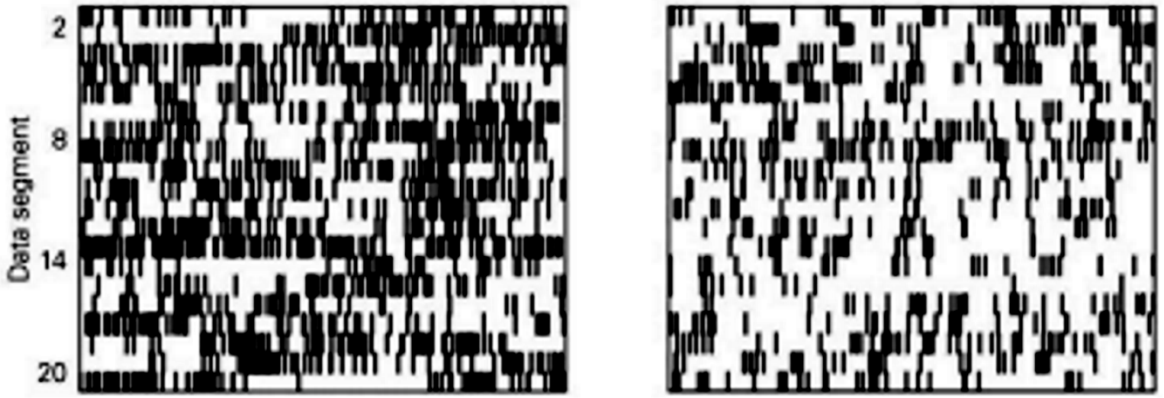



Decreased intensity in Parkinson's substantia nigra

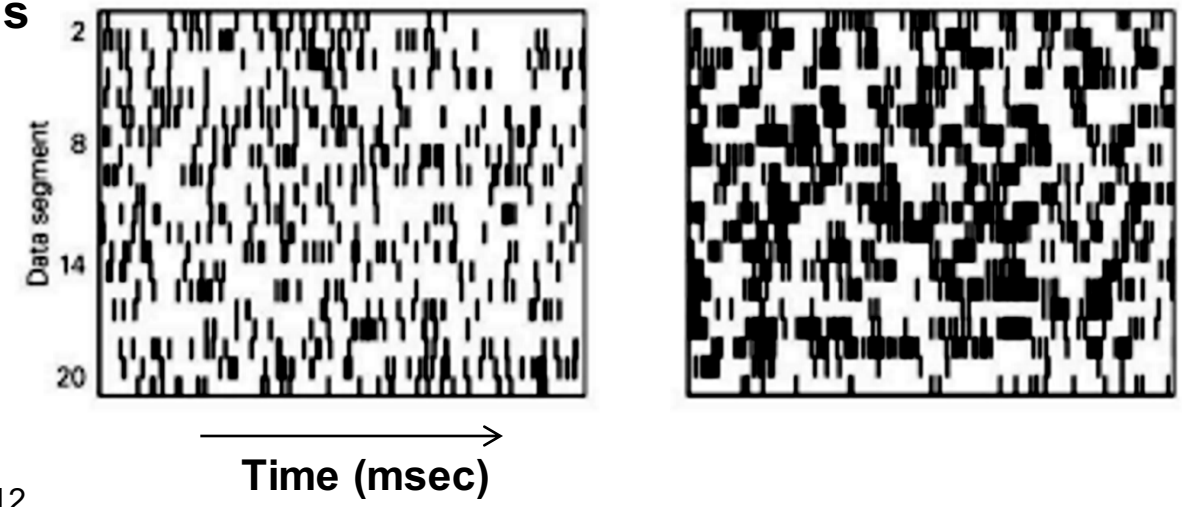
# Neuronal activity in Parkinson's disease

**Normal** **Parkinson**

**External pallidum**

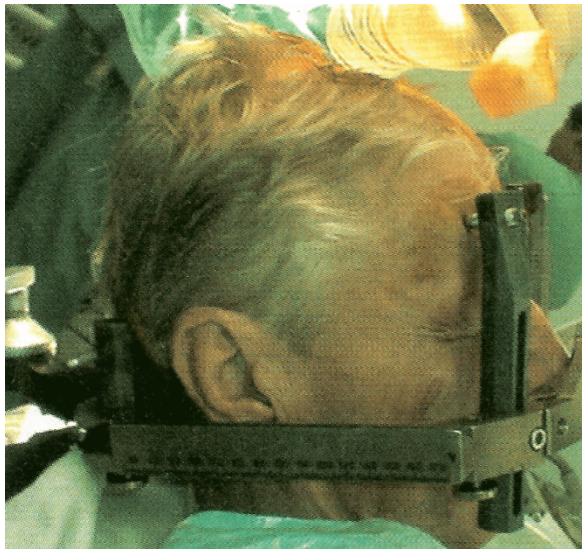


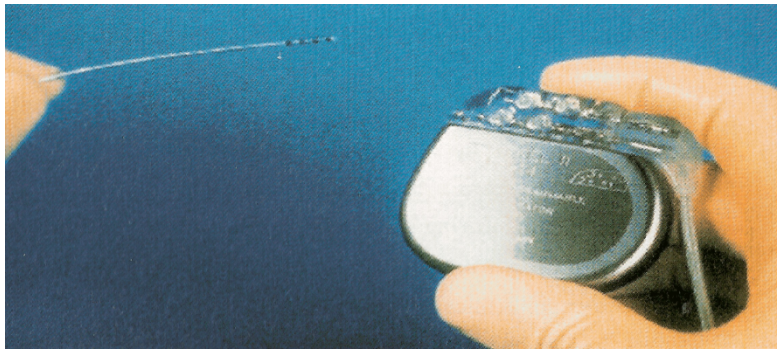

**Subthalamic nucleus**




Kandel & Schwartz et al., 2012

# Deep brain stimulation (DBS) in Parkinson's disease





# Disorders of the basal ganglia
## (formerly together with Parkinson's: *extrapyramidal symptoms*)

**Chorea**: large amplitude „dancing" movements of extremities

**Ballism**: involuntary flinging, swinging, and jerking movements of proximal extremities (n. subthalamicus lesion)

**Athetosis**: slow, sinuous, writhing movements (putamen lesion)

**Tic**: repetitive, non-rhythmic, movement or vocalization (e.g. eye blinking, throat clearing), **Tourette's disease**

**Dystonia**: tone↑ in circumscribed muscles (e.g. torticollis)
dopamine antagonist drugs may induce **tardive dyskinesia** [grimacing, tongue protrusion, lip smacking]