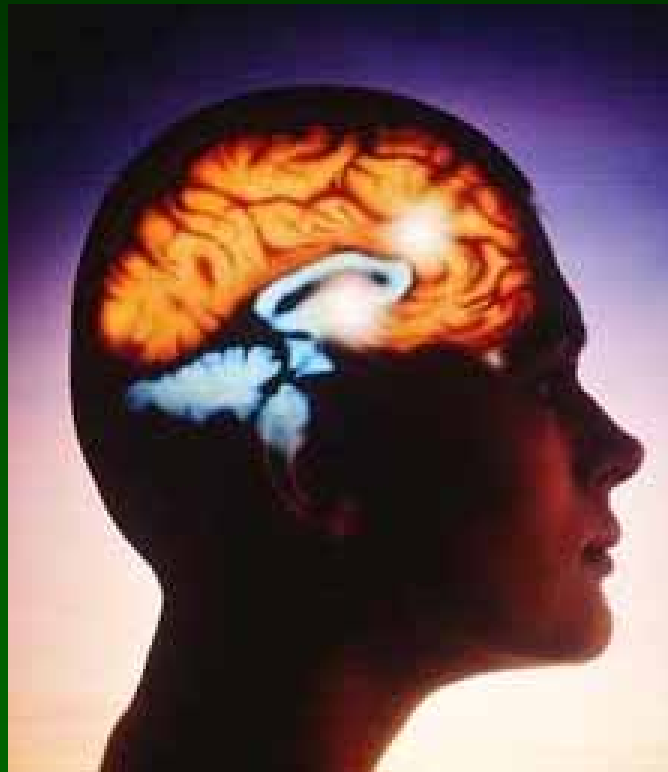


# Brain complexity..... ..... and disease



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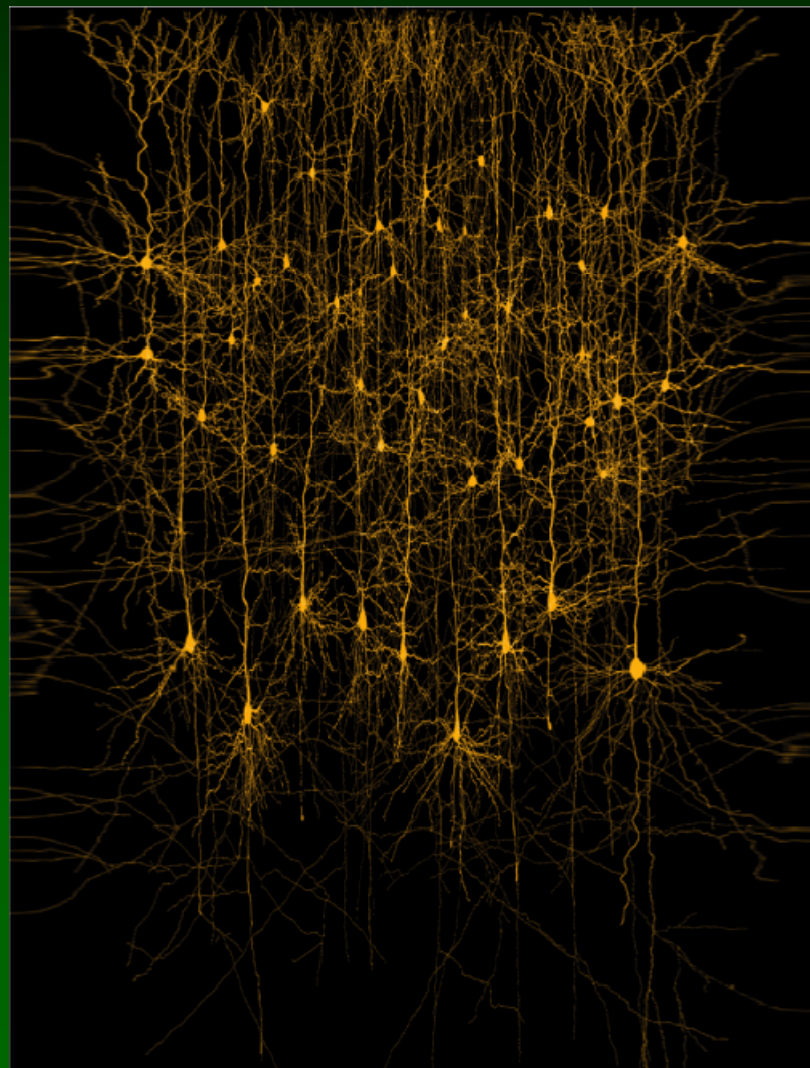
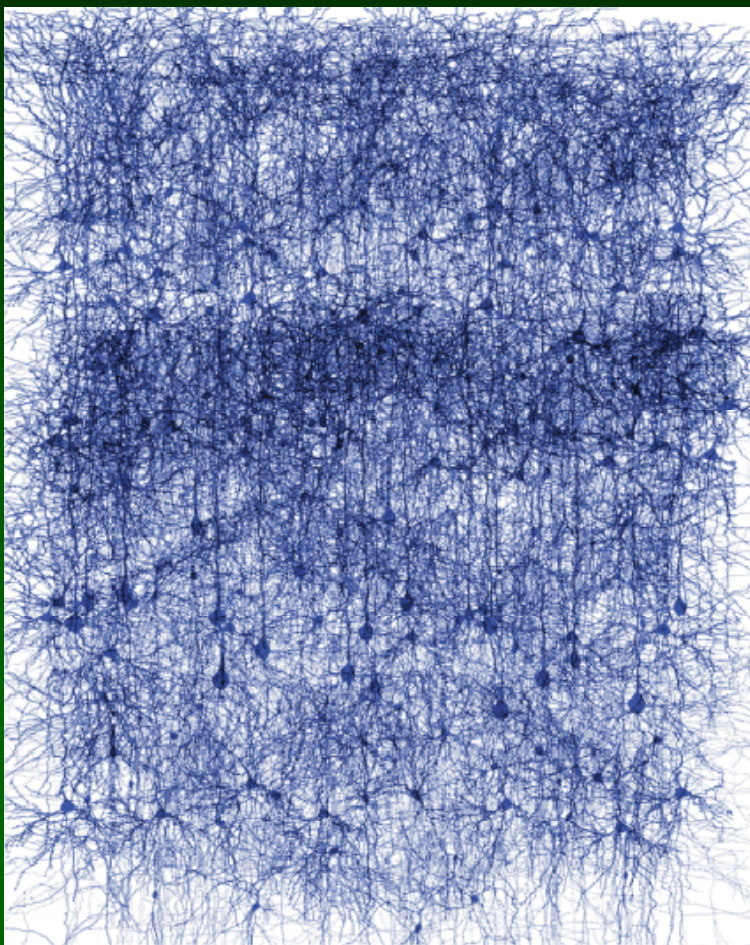
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*September 9, 2009*

*Dr. Stefan Maas, BioS Lehigh U.*

# Brain networks



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# Brain Trivia

The average number of neurons in the brain = *100 billion.*

more than *100,000* kilometers of inter-connections

The adult brain weighs *about 3* pounds.

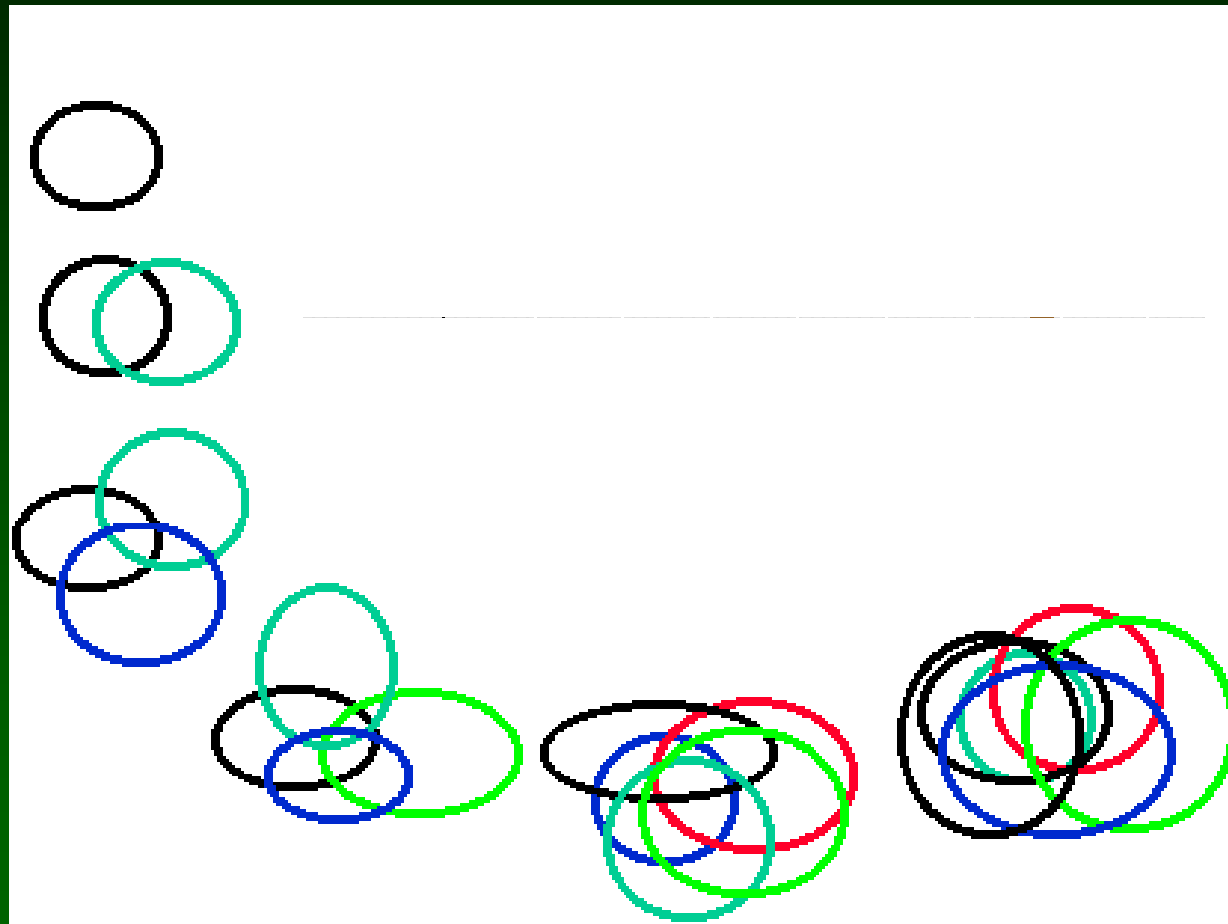
The average number of glial cells in the brain = *10-50 times the number of neurons.*

# Complexity of the Brain

**100 billion** neurons plus  
**>1 trillion** glia cells connected by  
**100 Trillion** synapses  
in a single human brain  
organized into exquisitely  
complex circuits...

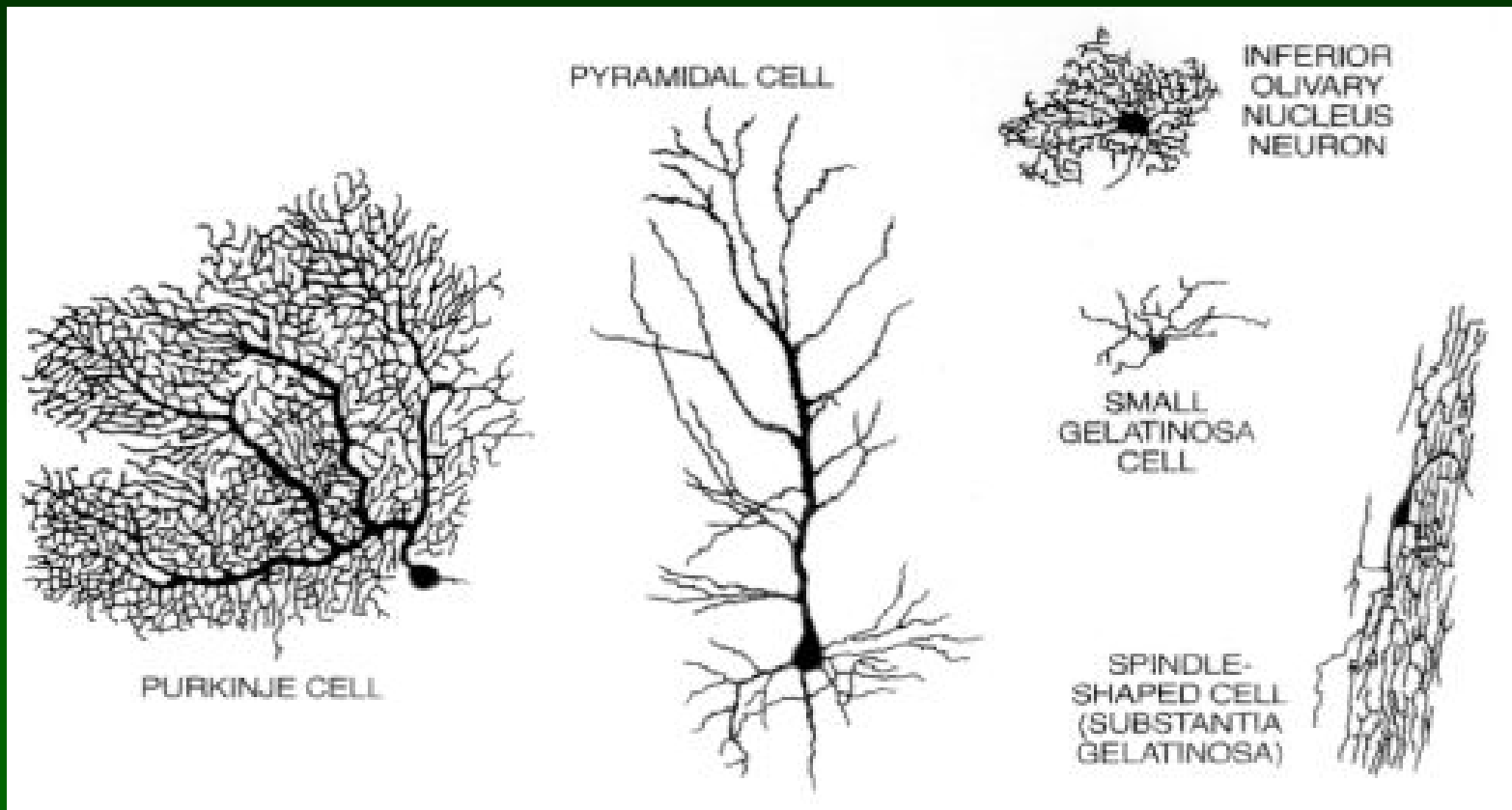
responding to experience, drugs,  
disease, and injury...

# Generation of Complexity



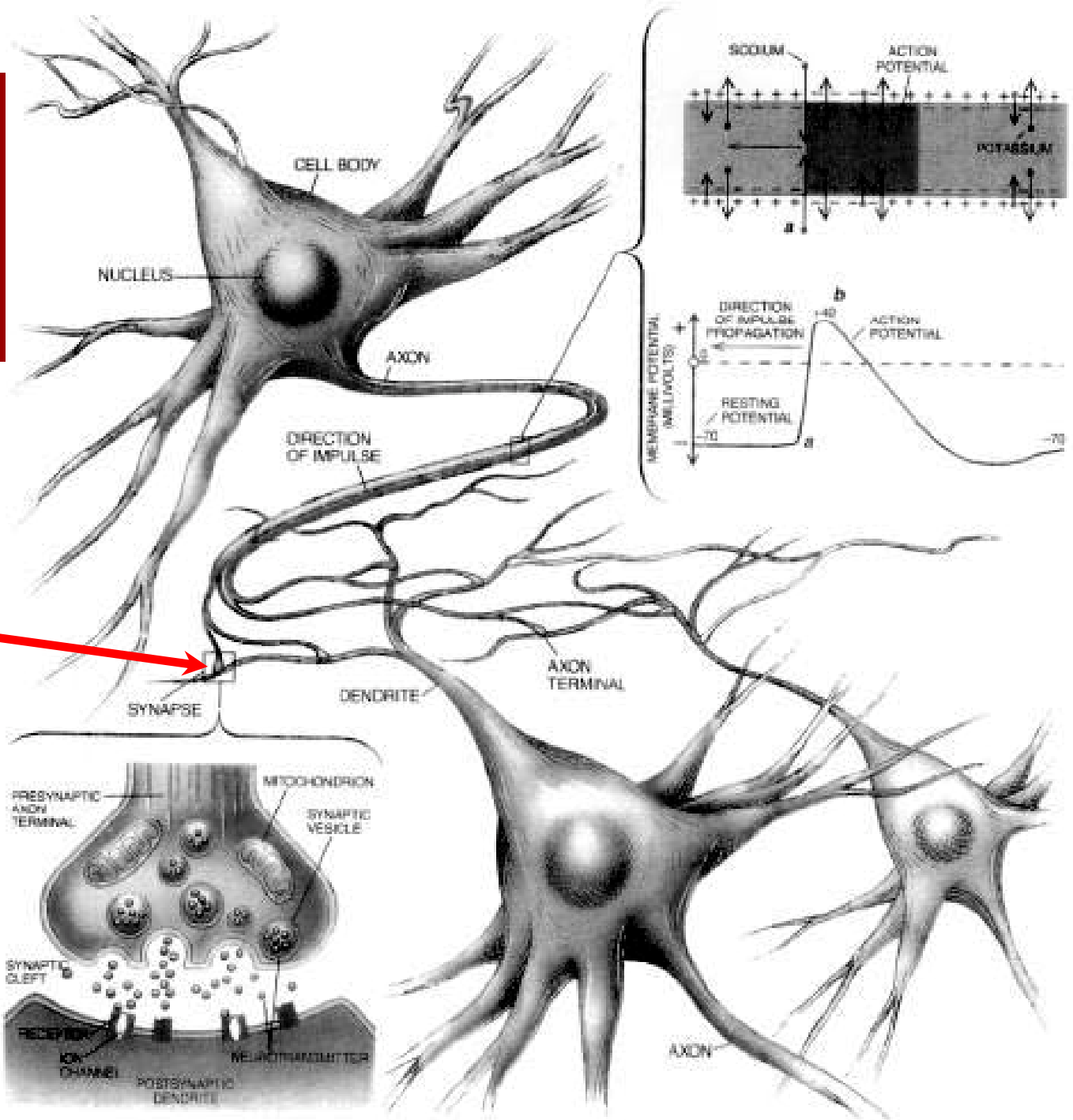
Areas generated =  $2^n - 1$  where  $n$  is the number of "things"

# Complexity of the Brain



# Nerve Cell Communication

## Synapse

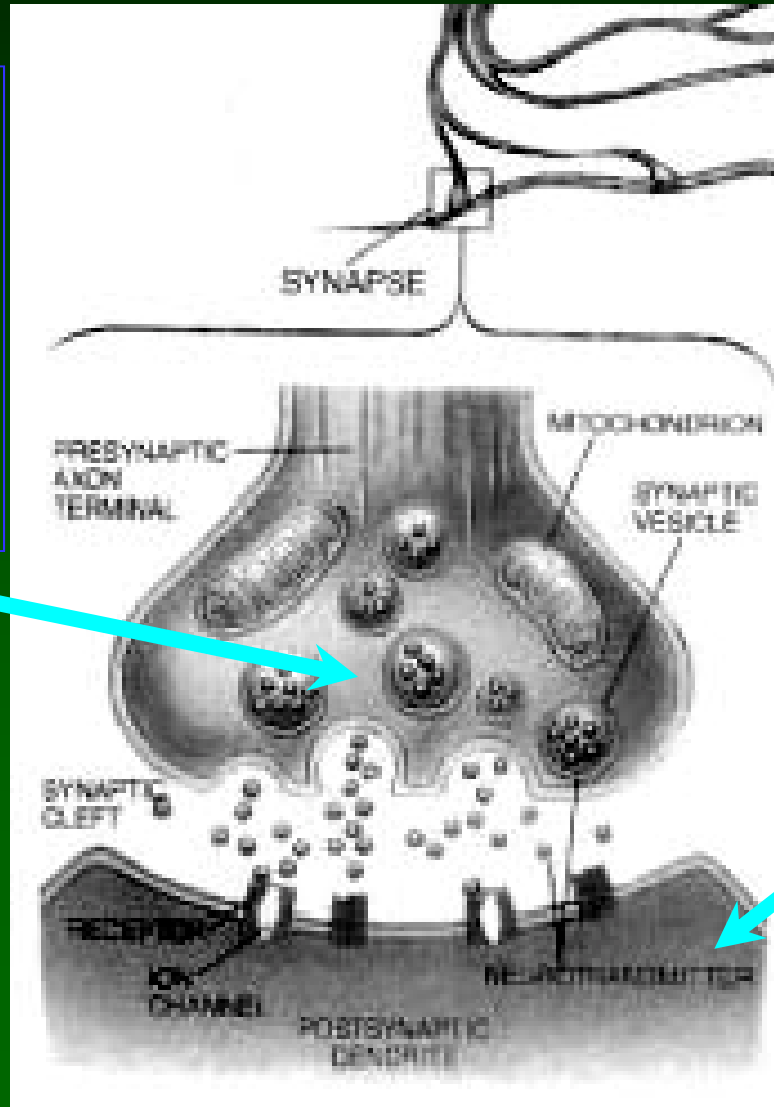




# Complexity of the Brain

The synapse typically has two parts:

A presynaptic structure containing packets of neurotransmitters

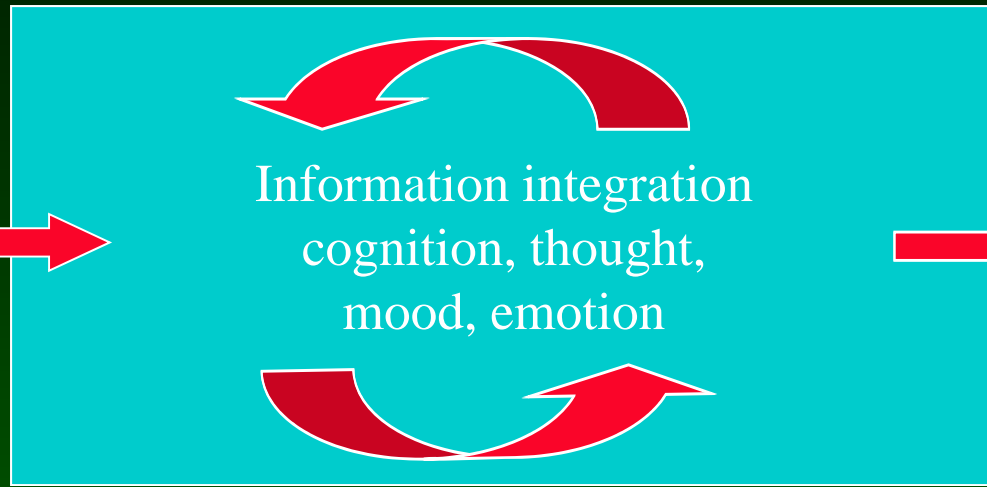


and a postsynaptic structure of the receiving neuron

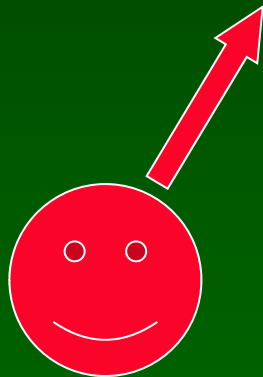


# Cerebral cortex

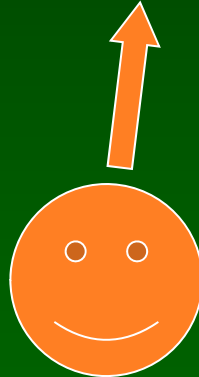
Sensory input



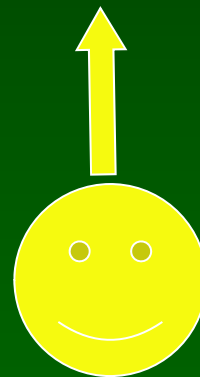
Motor output



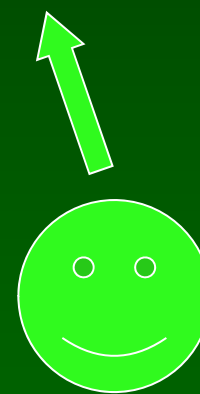
acetylcholine



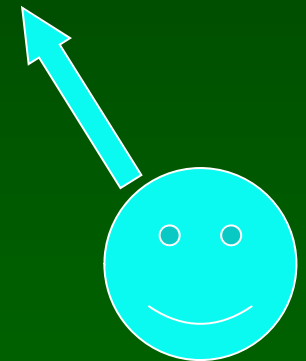
norepinephrine



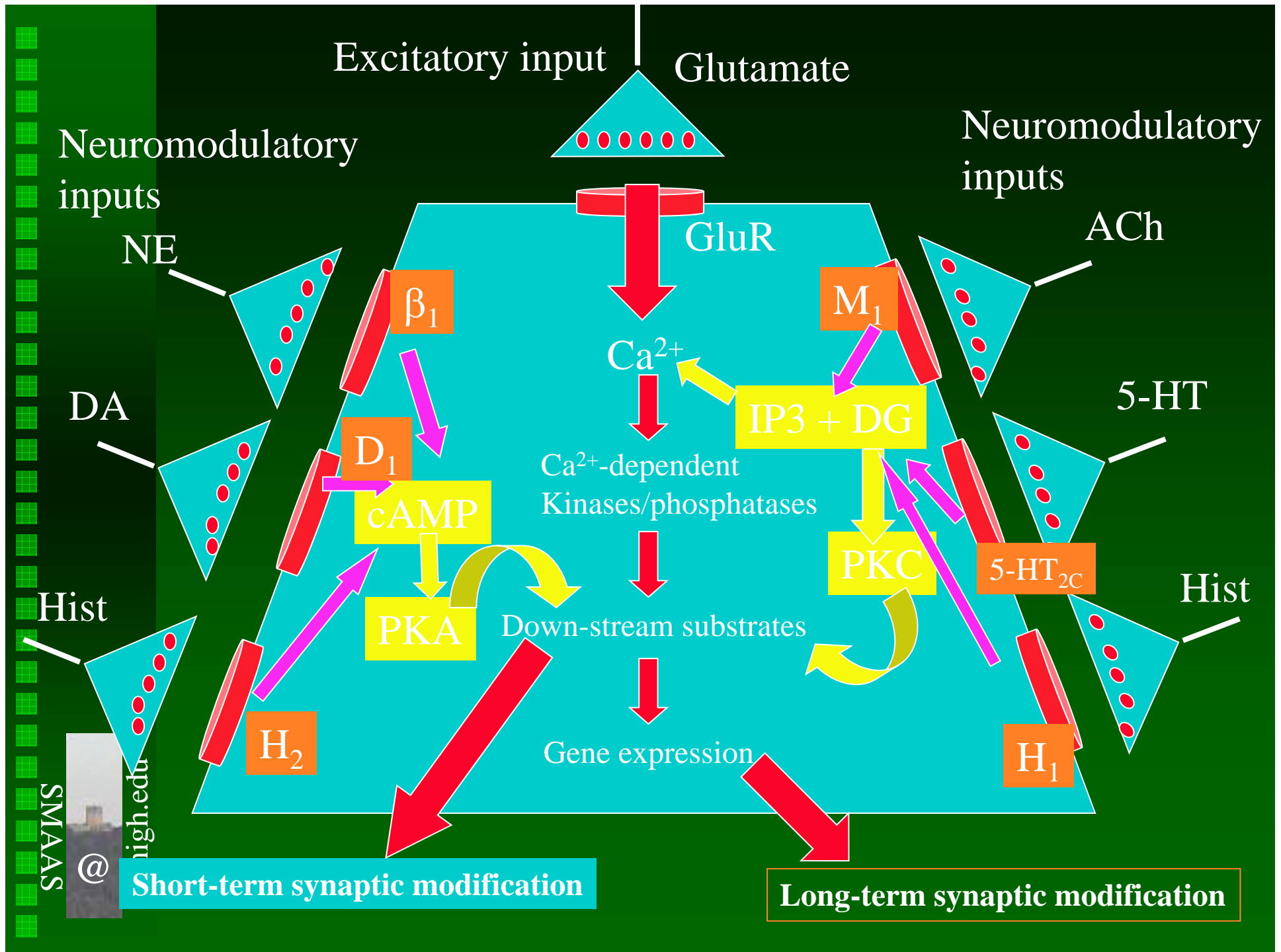
serotonin

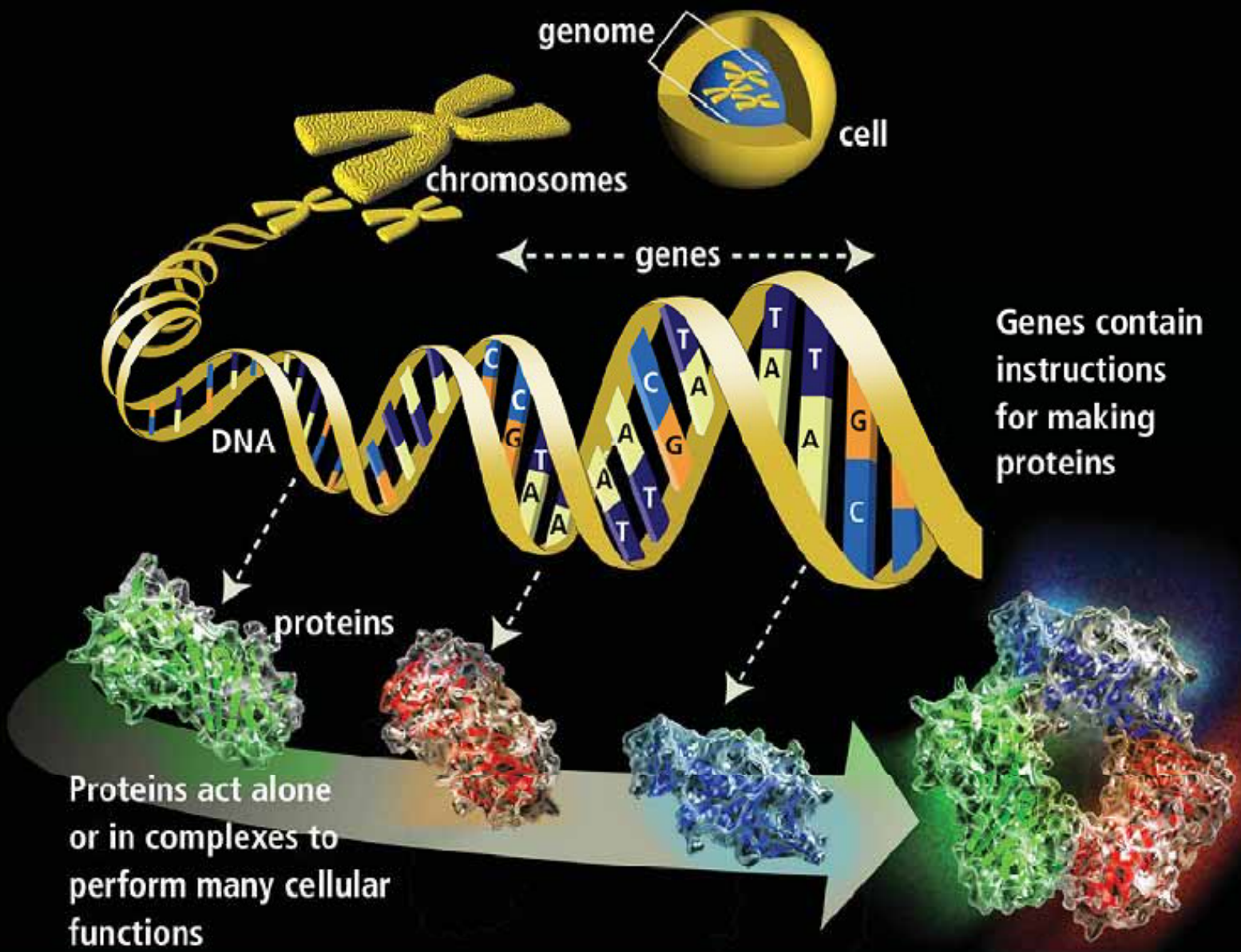


dopamine



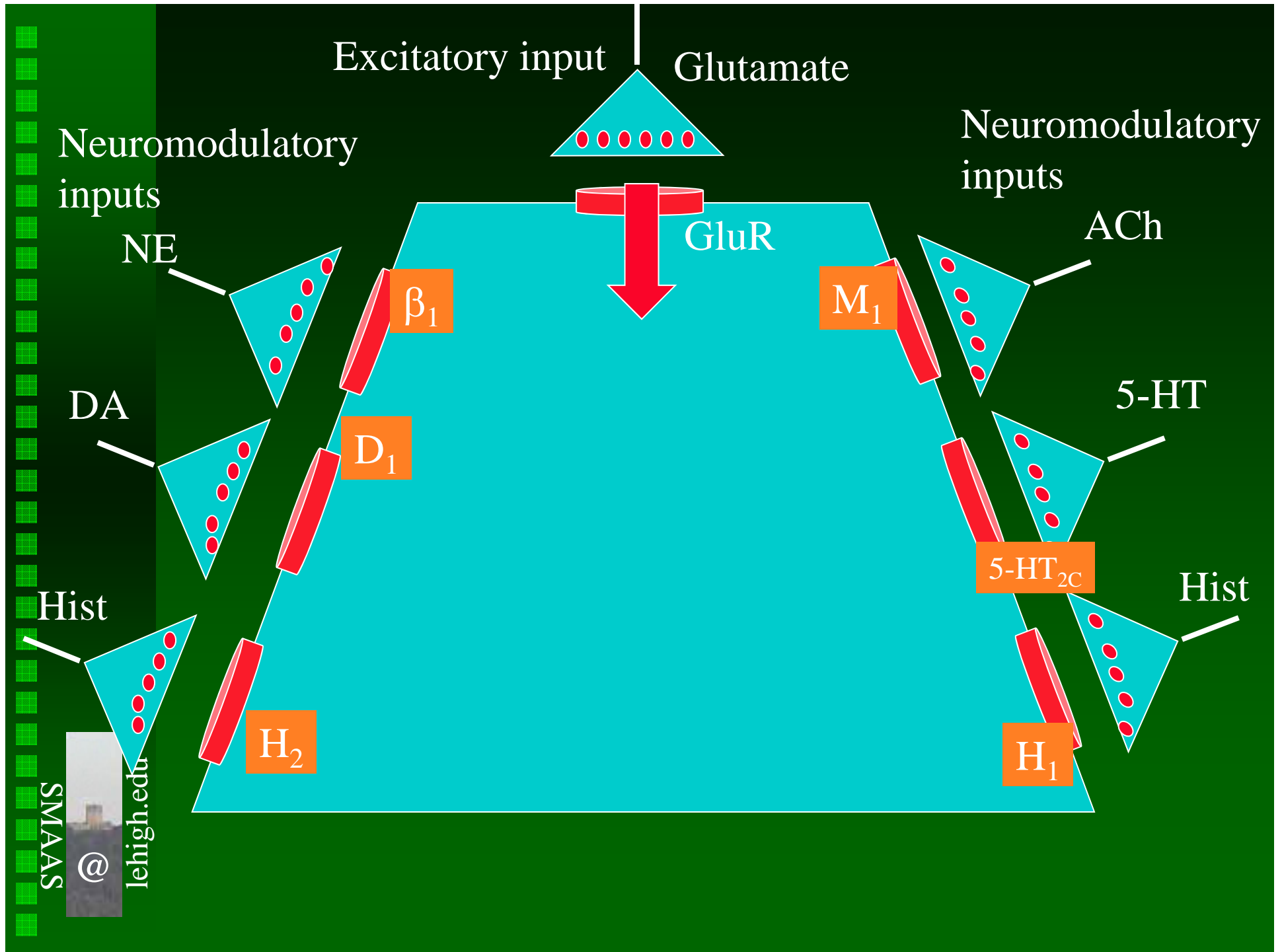
histamine



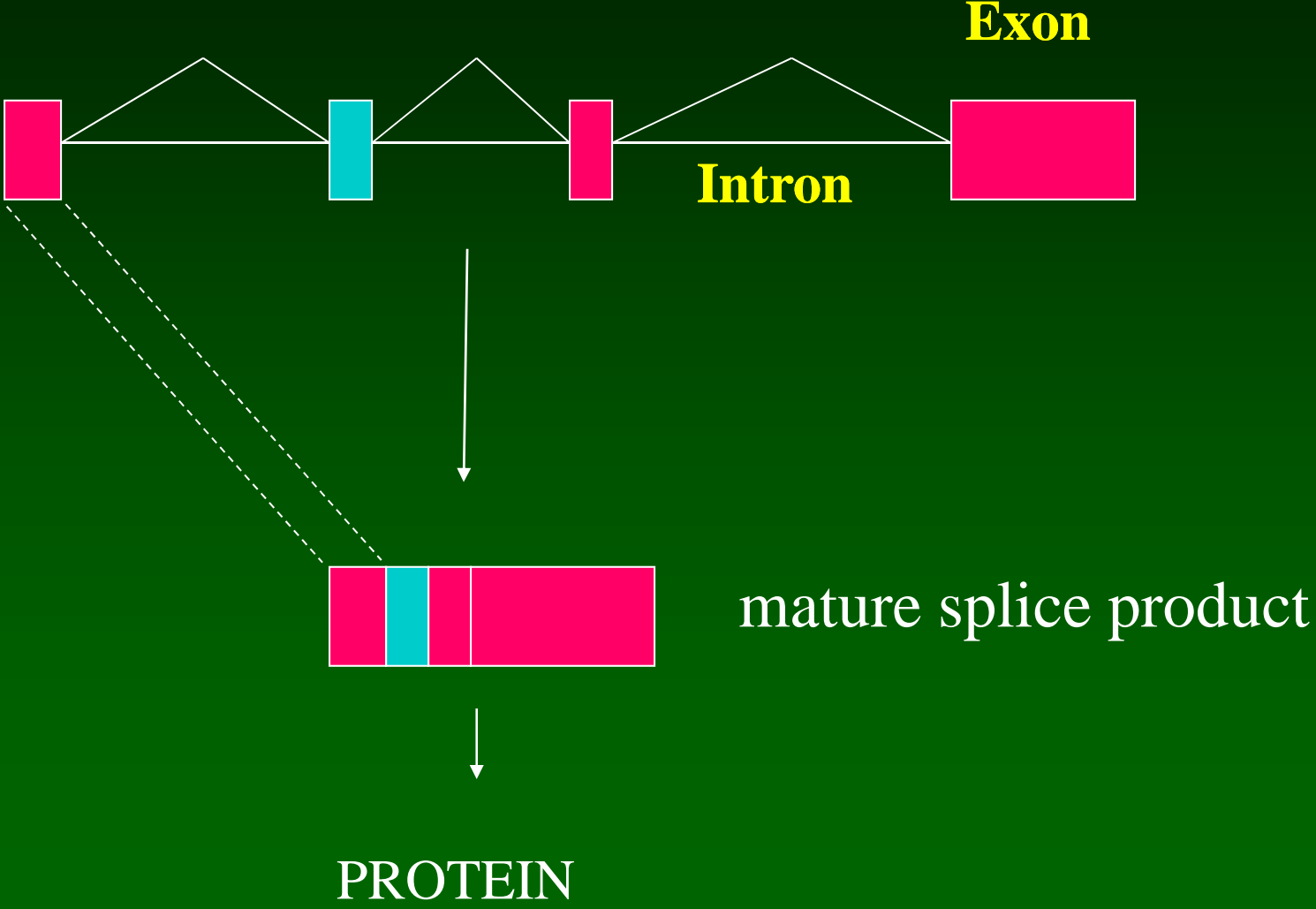


# From Genes to Proteins

<http://www.ornl.gov/hgmis/publicat/primer2001/>



# Gene splicing: Removal of non-coding introns



I AM THE Q S R T V F I R S T Q P B A S R T V S E C O N D Q A B D E C T V A L T E R N A T I V E

# Principles of Alternative Splicing

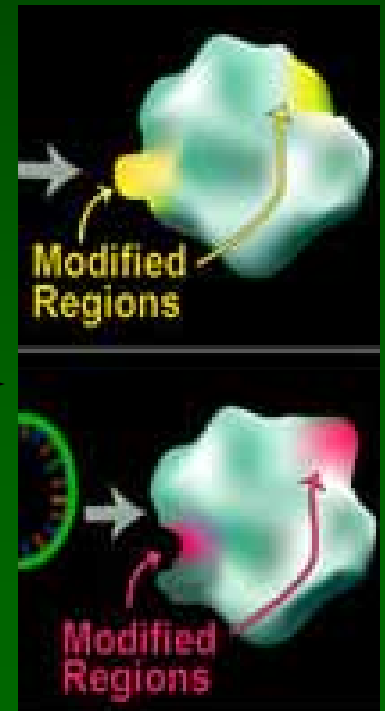
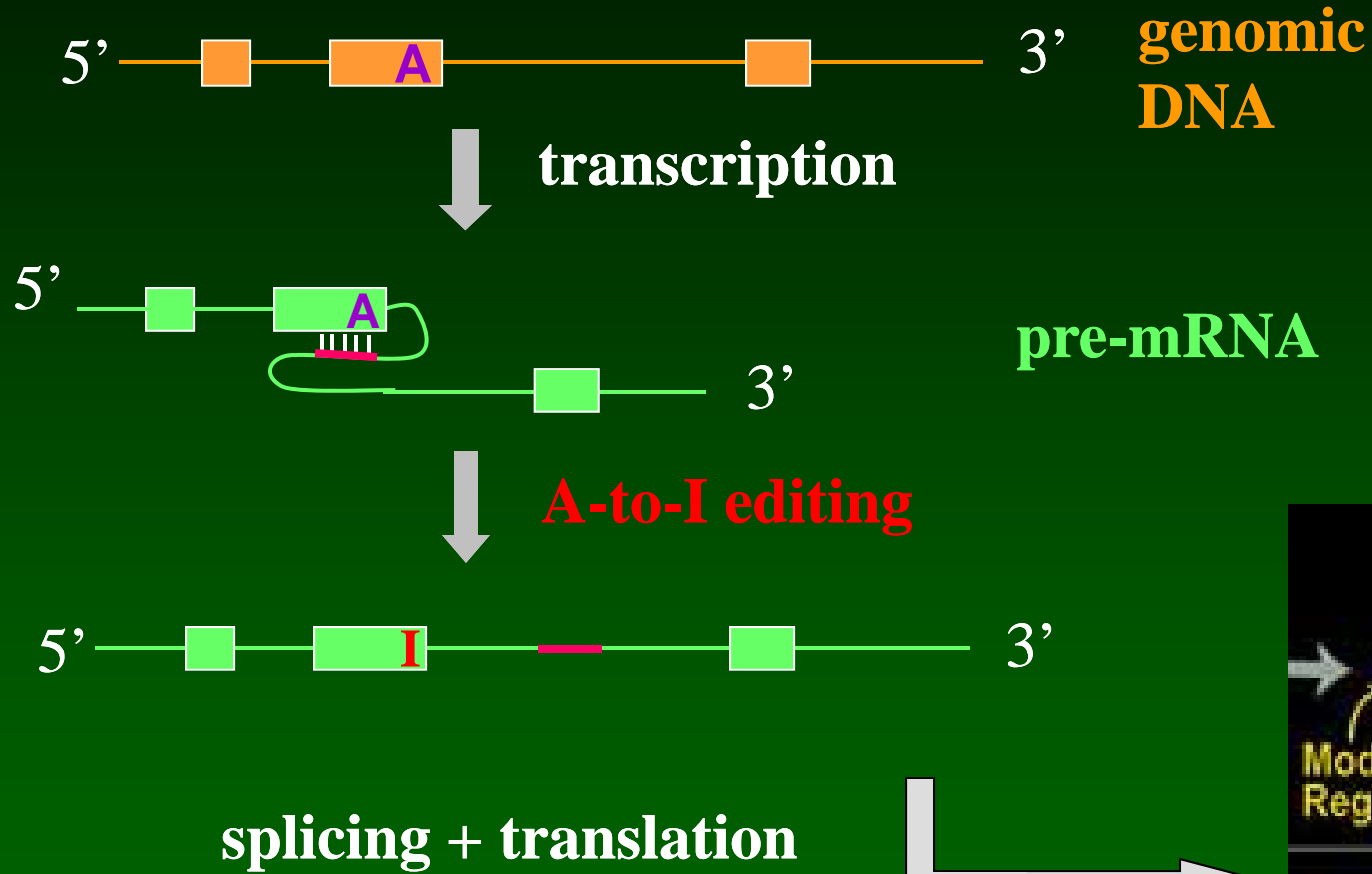
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# RNA editing





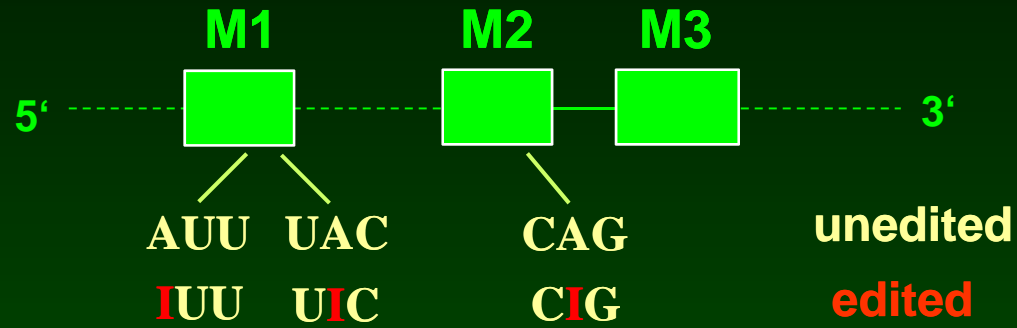
# Mammalian substrates of A-to-I pre-mRNA editing

Gene	codon	amino acid	editing [%]
GluR-B	CAG/CIG	Q/R	100
GluR-B,-C,-D	AAG/AIG	R/G	60-80
GluR-5,-6	CAG/CIG	Q/R	40-80
GluR-6	AUU/IUU	I/V	80
	UAC/UIC	Y/C	80
5-HT <sub>2C</sub> Serotonin- receptor	AUA/IUA	I/V	40-90
	AAU/AIU	N/S	35-40
	AUU/IUU	I/V	45-75



# Diversity through RNA editing

**GluR-6  
pre-mRNA**



**GluR-6**



unedited 10 %

5 %

5 %

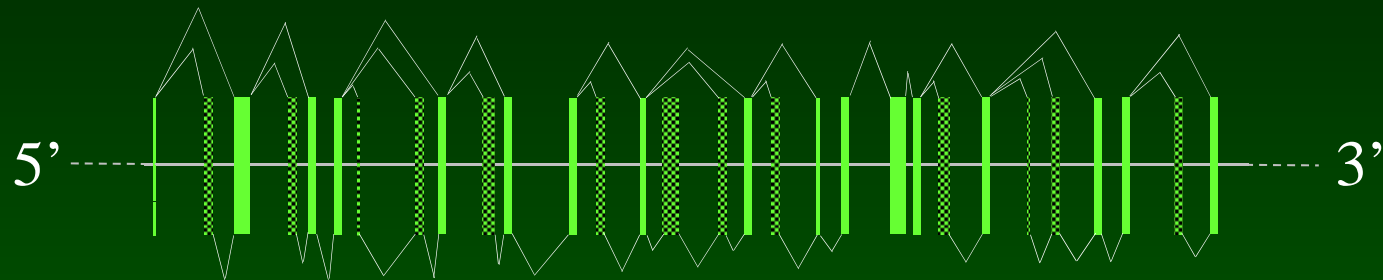
10 %

5 %

fully edited 65 %

# Even more diversity

*paralytic pre-mRNA*



**alternative  
splicing**

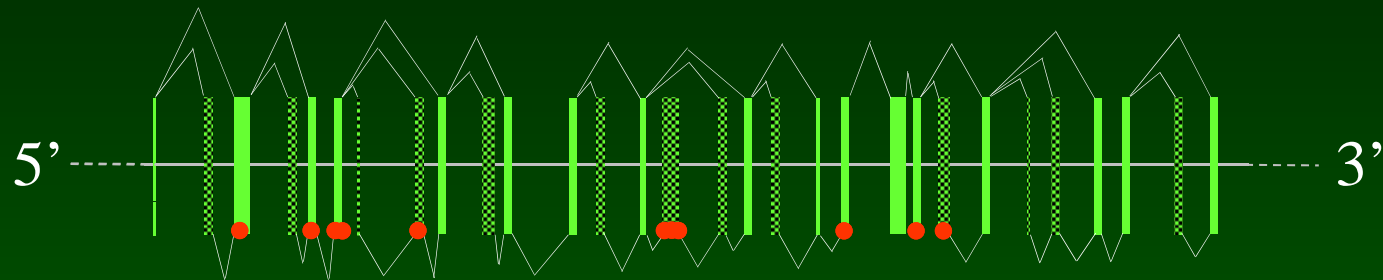


—■— constitutive exon  
—■— alternative exon

**1 536 variants**

# Even more diversity

*paralytic pre-mRNA*



alternative  
splicing

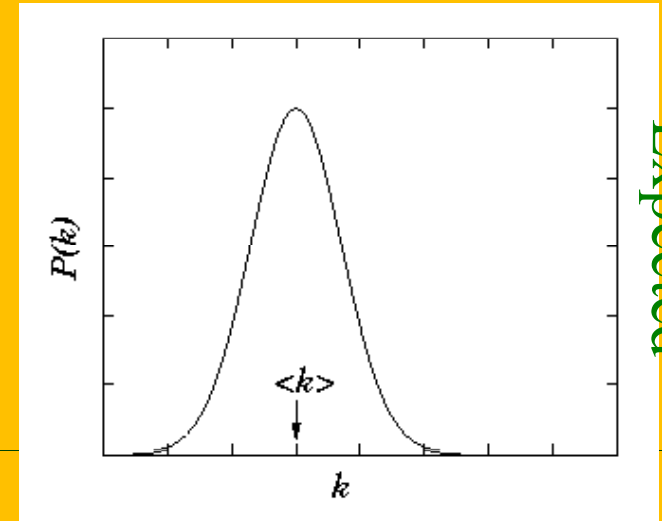
**RNA  
editing**

- constitutive exon
- ▨ alternative exon
- editing site

**1 032 192 variants**

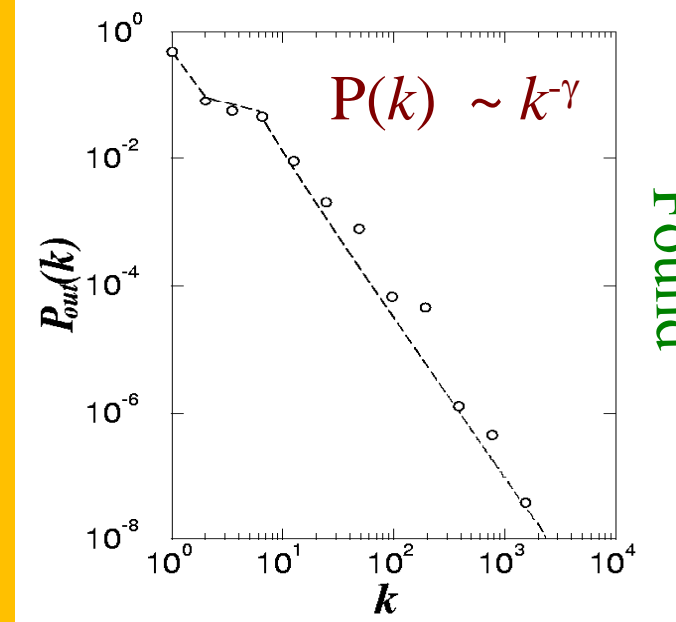
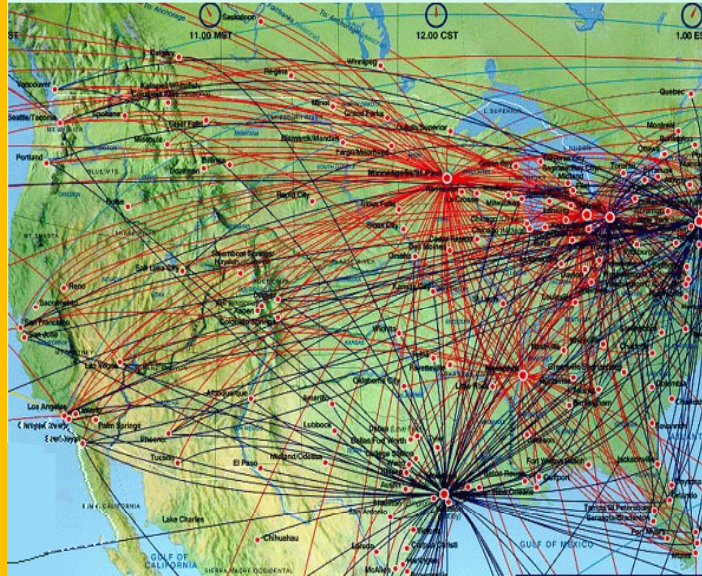
# World Wide Web

Exponential Network



Expected

Scale-free Network



Found

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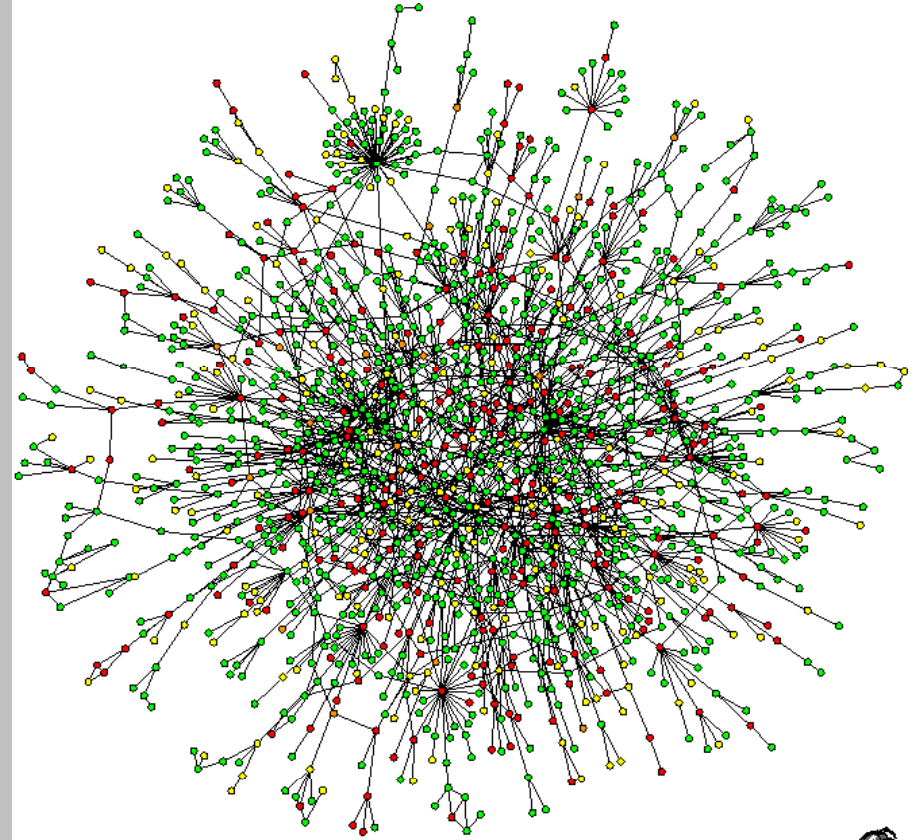
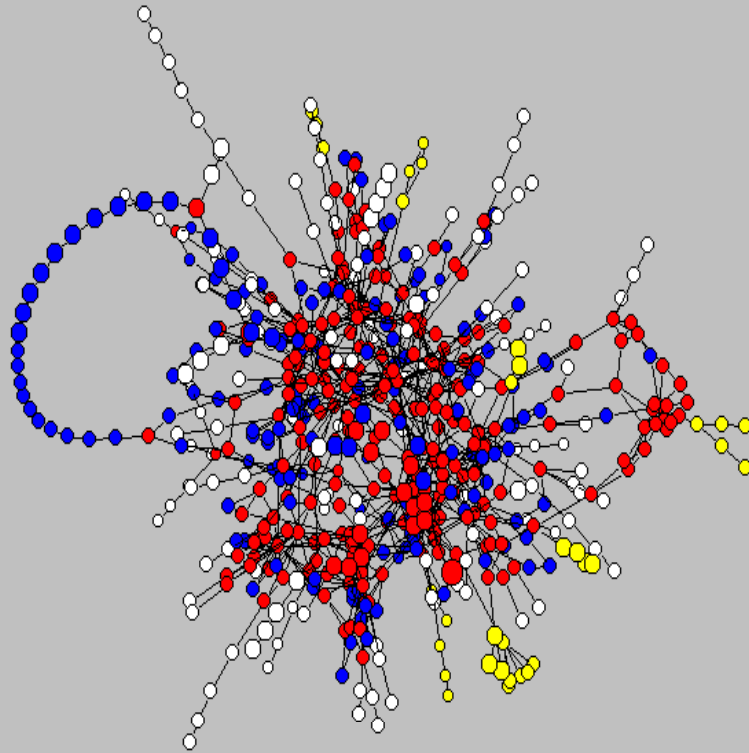
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R. Albert, H. Jeong, A-L Barabasi, *Nature*, 401 130 (1999).

# Metabolic Network

# Protein Interactions





# Internet-Map

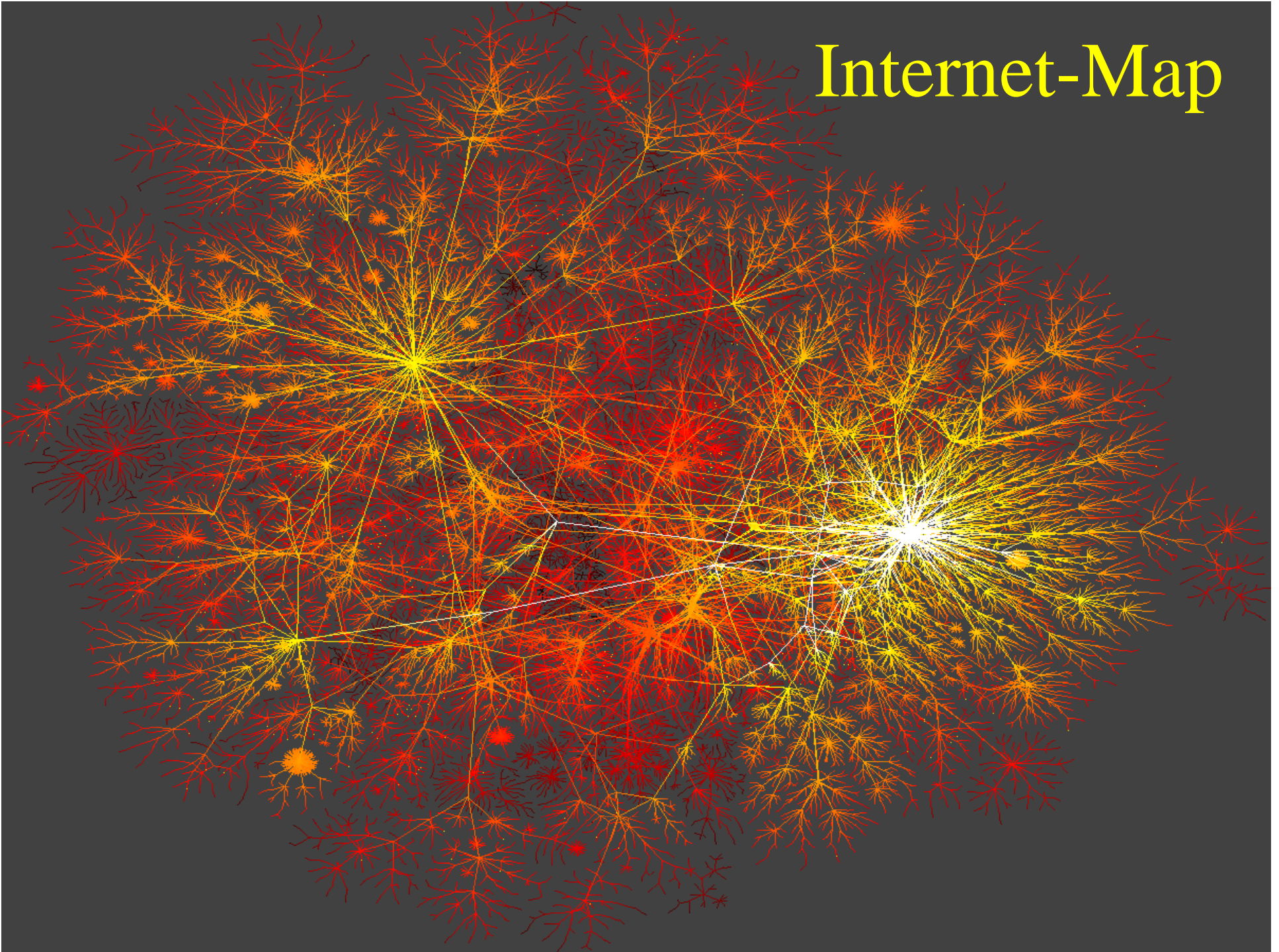


Figure 1.7 The Toll of Brain Disorders (Part 1)

(a) Prevalence of neurological disorders

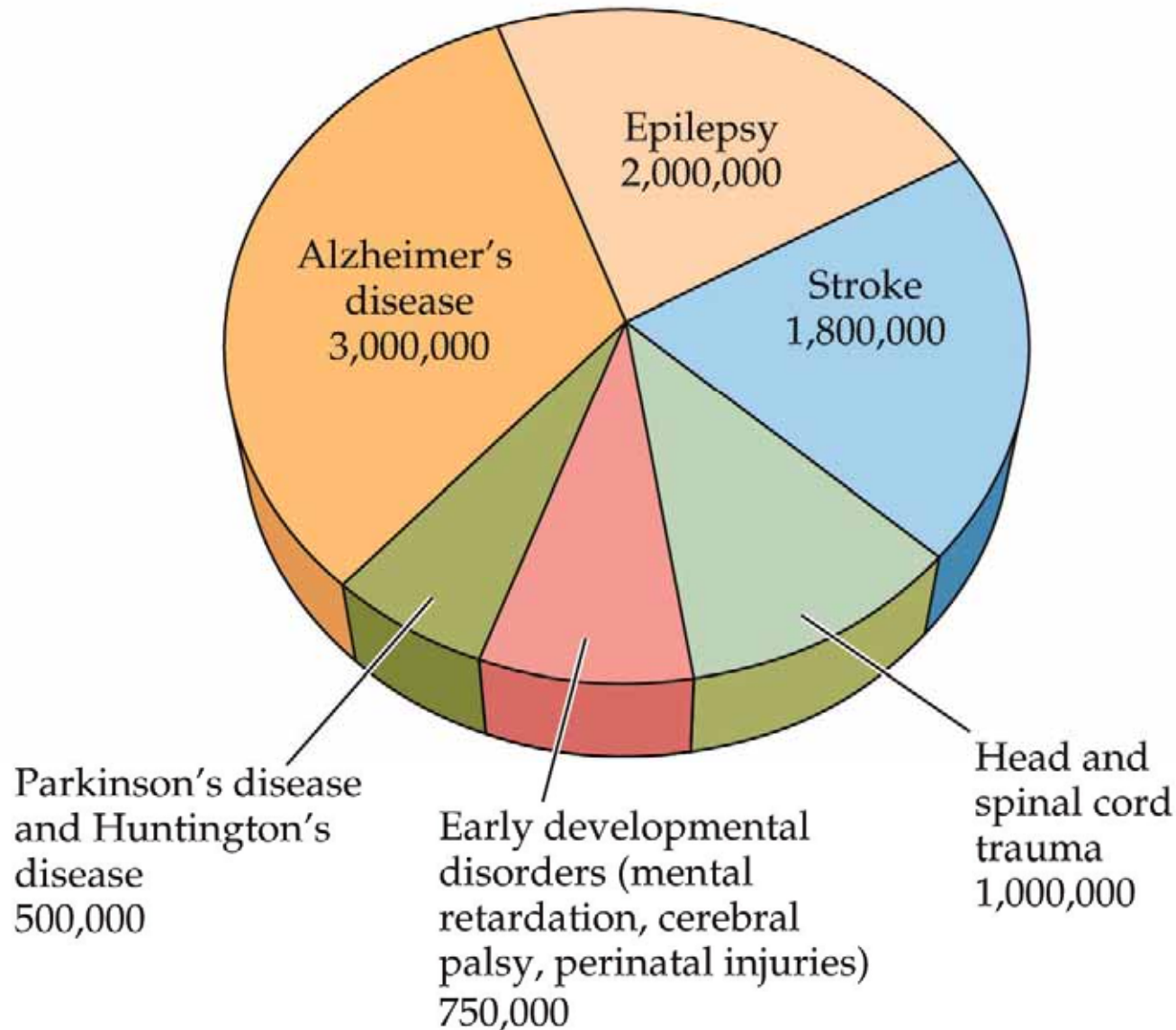
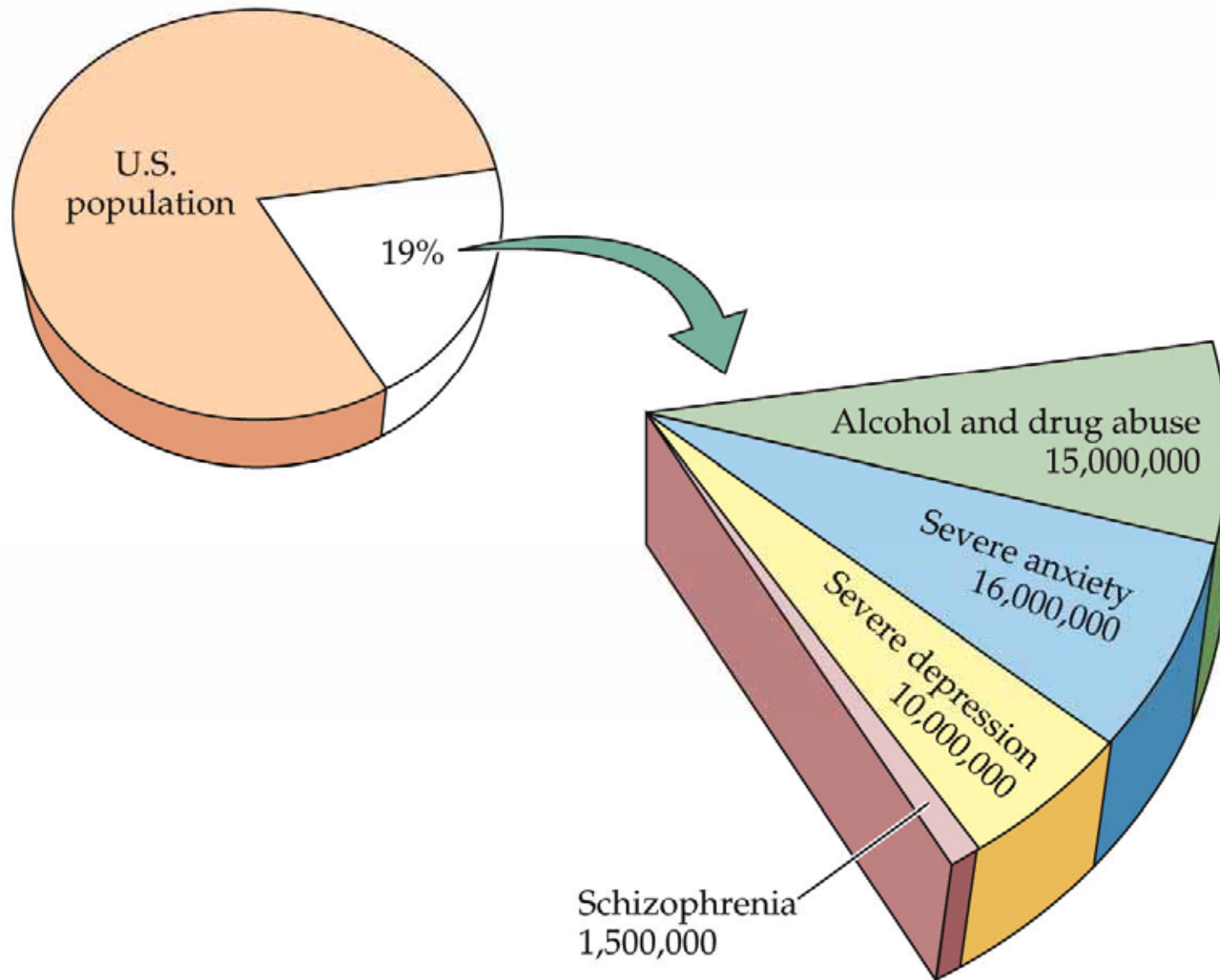


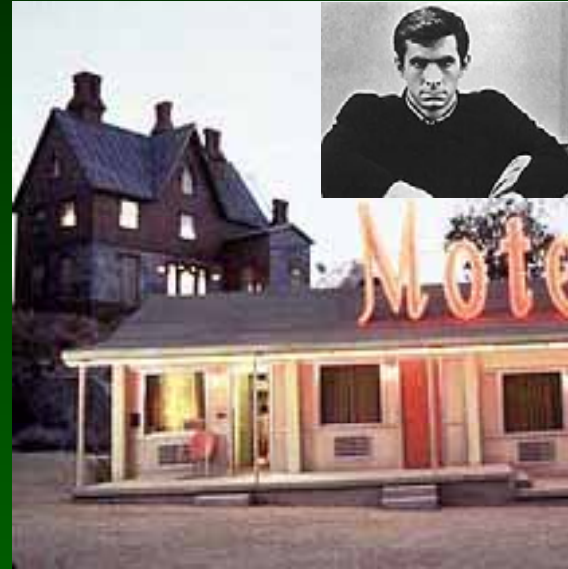


Figure 1.7 The Toll of Brain Disorders (Part 2)

(b) Incidence of psychiatric disorders



# Schizophrenia



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# True or False ?

1. Schizophrenia is a rare illness
2. Schizophrenia generally strikes older people
3. People with Schizophrenia have multiple or split personalities
4. More hospital beds are occupied by people with Schizophrenia than any other medical illness

# Schizophrenia

- Mental illness
- One of the top ten causes of long term disability
- currently ca. 1% of population affected across countries and cultures
- same in developed and developing countries
- incidence of 0.2-0.4 per 1000  
=> lifetime risk of 1% for women and men

# Schizophrenia

- develops between ages 15 and 25 and mostly persists throughout the patient's lifetime
- cause unknown
  - > genetic factors
  - => early environmental influences
  - => social factors



# Symptoms and Disease Progression

Three broad types of Symptoms:

- **Positive (psychotic) Symptoms**
- **Negative (depressive) Symptoms**
- **Cognitive and Social Impairment**

# Symptoms and Disease Progression

## ➤ Positive (psychotic) Symptoms

- > Occur last, after several years of onset
- > Most apparent and often lead to first psychiatric contact, tend to be episodic
- ❑ Loss of contact with reality
- ❑ Delusions (false beliefs)  
*for example:* persecutory delusions, delusions of control, grandiose delusions and somatic delusions
- ❑ Hallucinations (auditory, visual, olfactory, tactile)  
Auditory hallucinations most common

# Symptoms and Disease Progression

## ➤ Negative (depressive) Symptoms

> Occur first

> Less dramatic but more pervasive  
and fluctuate less over time

### ❑ Blunted affect

eg, immobile facial expression, monotonous voice tone

### ❑ Anhedonia (lack of pleasure)

### ❑ Apathy

diminished ability to initiate and follow through on plans

### ❑ Alogia

reduced quantity of speech

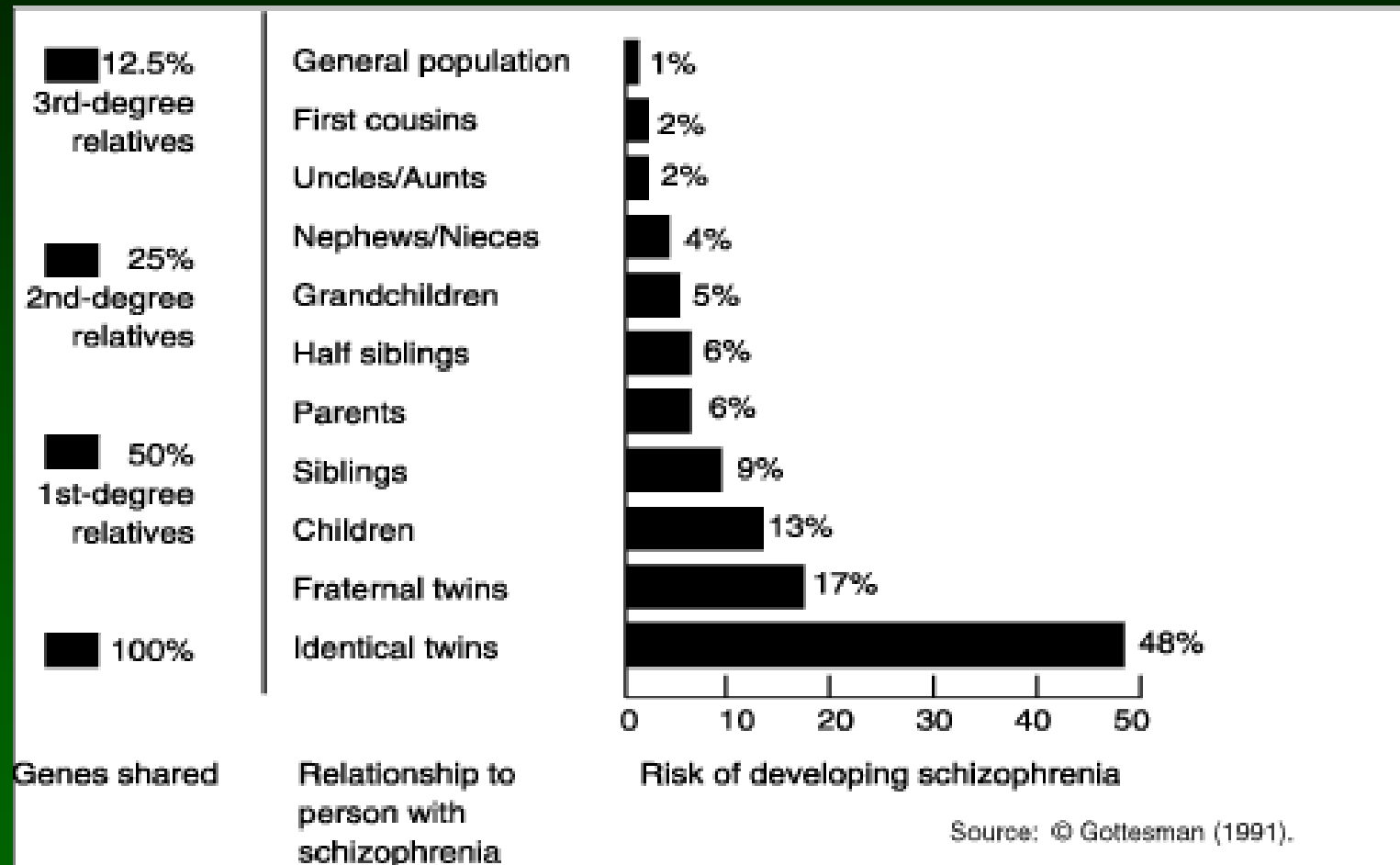
# Symptoms and Disease Progression

## ➤ Cognitive and Social Impairment

> Occur second

- ❑ Attention and Concentration deficits
- ❑ Problems with Learning and Memory
- ❑ Deficiency in executive Function  
abstract thinking, problem solving

# Genetic factor



# Genetic factors

Genetic transmission does not follow simple Mendelian single-gene inheritance patterns

→ Multiple susceptibility genes, each with small effect and acting in concert with environmental factors

Several genes shown to be linked with schizophrenia

Gene	Locus	Populations studied
<i>NRG1</i>	8p12-p21	Icelandic
<i>DTNBP1</i>	6p22	Irish
<i>G72</i>	13q34	French Canadian, Russian
<i>DAAO</i>	12q24	French Canadian
<i>RGS4</i>	1q21-22	USA ×2, Indian
<i>COMT</i>	22q11	USA, Israel, Chinese
<i>PRODH</i>	22q11	USA

# Environmental factors

## Biological:

Prenatal events or birth complications

Infections, hypoxia, winter birth, maternal malnutrition or use of psychoactive drugs

## Psychosocial:

Poverty and lower social class

Stressful environmental conditions

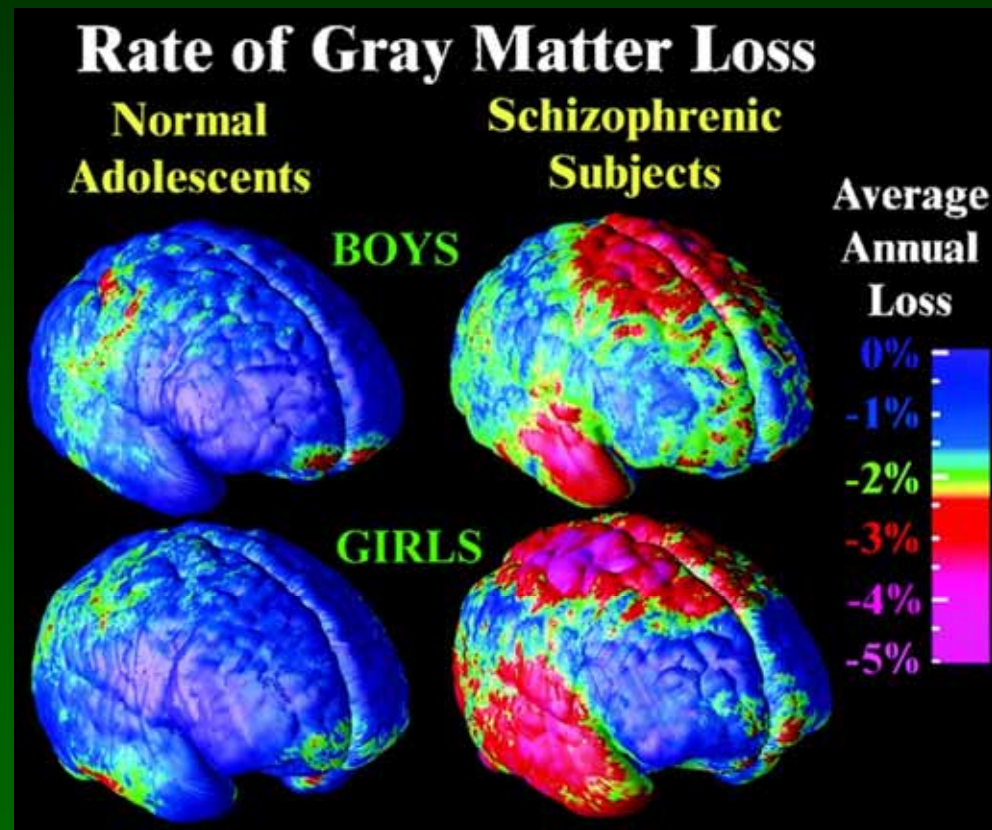
Urban versus rural background



# Pathophysiology

- Enlargement of the ventricular system
- Accompanied by overall reduction in brain volume and cortical grey matter

*MRI*



Changes are not directly linked to illness progression

# Pathophysiology

## Is Schizophrenia a demyelinating disorder?

- Some symptoms (psychosis, cognitive impairments) are similar to MS symptoms
- Time of onset is similar

## Is Schizophrenia a neurodevelopmental disorder?

- prevailing pathogenic model for Schizophrenia
- anatomical changes due to abnormal early brain development (visible *before* first episode)
- No sign of repair or degenerative processes (glial reactions, plaques)
- indications of defect in neuronal migration

Late onset related to processes during adolescence and early adulthood (excessive synaptic pruning?)

# Therapy - Management



# Therapy - Management

Neurotransmitter	Drug	Mechanism of action	SZ symptom
Dopamine	Neuroleptics	Antagonists of D2 receptor	↓
	Amphetamine	Increase dopamine in synaptic cleft	↑
Glutamate	Phencyclidine	Antagonist of NMDA receptor	↑
	D-serine, D-cycloserine, glycine	Agonist of NMDA receptor	↓
Serotonin	Atypical antipsychotics (clozapine)	Binding to 5-HT2 receptor	↓

Also: antidepressants, mood stabilizers, benzodiazepines

Combination therapy (**polypharmacy**) common

# Therapy - Management

Major problem: **non-compliance**  
ca. 50% (and higher soon after onset of disorder)

- ⇒ injectible depot
- ⇒ simplifications of regimen
- ⇒ direct delivery..

# Therapy - Management

## Early intervention

- prolonged untreated psychosis requires extended treatment
- Clinical symptoms worsen over the first several years
- worse prognosis after prolonged social isolation

Increased efforts to detect first-episode schizophrenia  
Even better: before major symptoms appear

# True or False ?

1. Schizophrenia is a rare illness

False: world-wide rate is 1:100

2. Schizophrenia generally strikes older people

False: age of onset is 15-25

3. People with Schizophrenia have multiple or split personalities

False: they are split from reality

4. More hospital beds are occupied by people with Schizophrenia than any other medical illness

True 8% of hospital beds