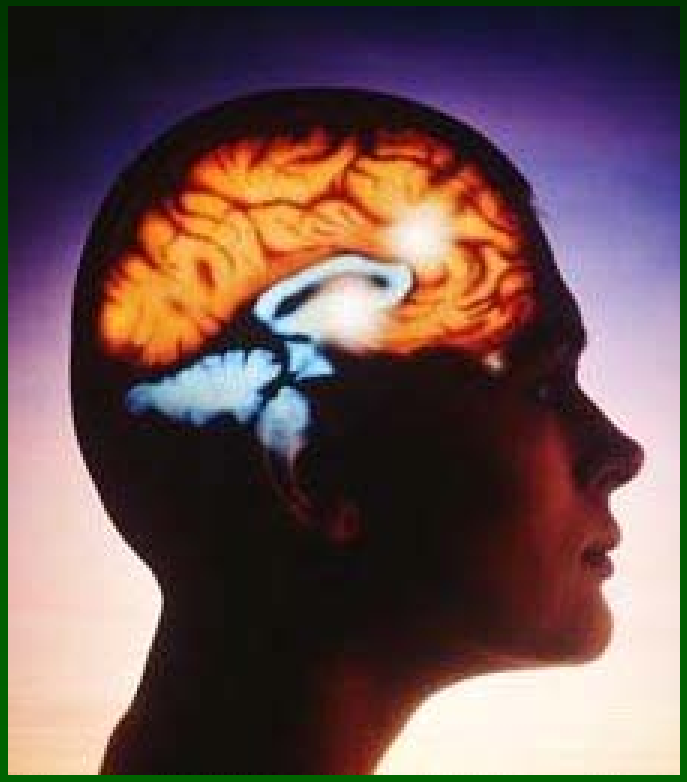
Brain complexity..... ..... and disease



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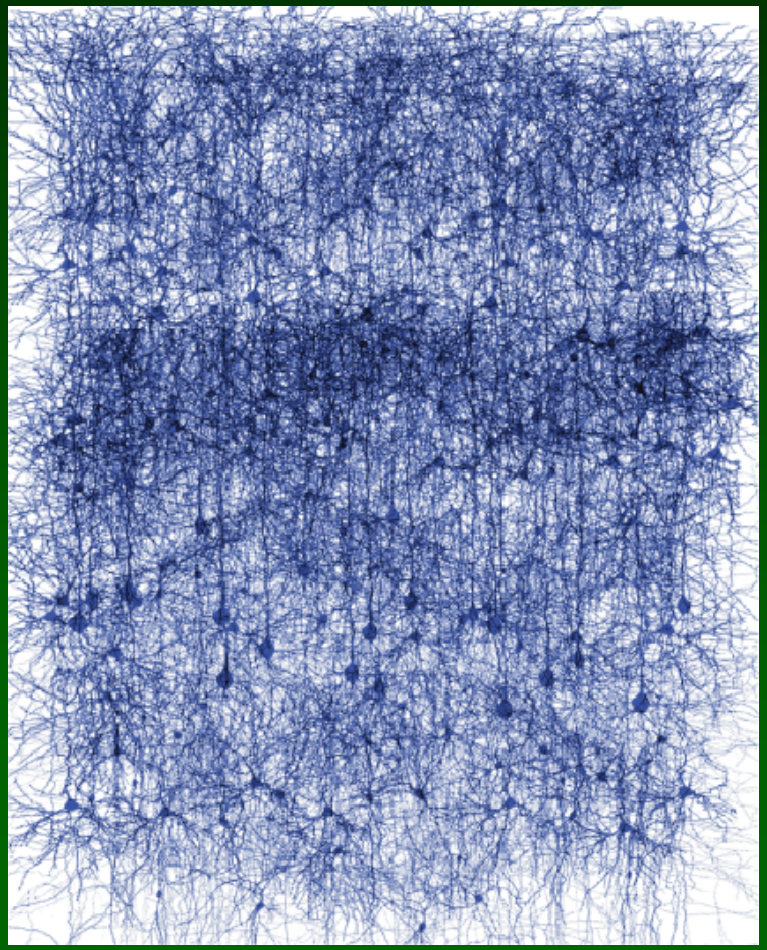
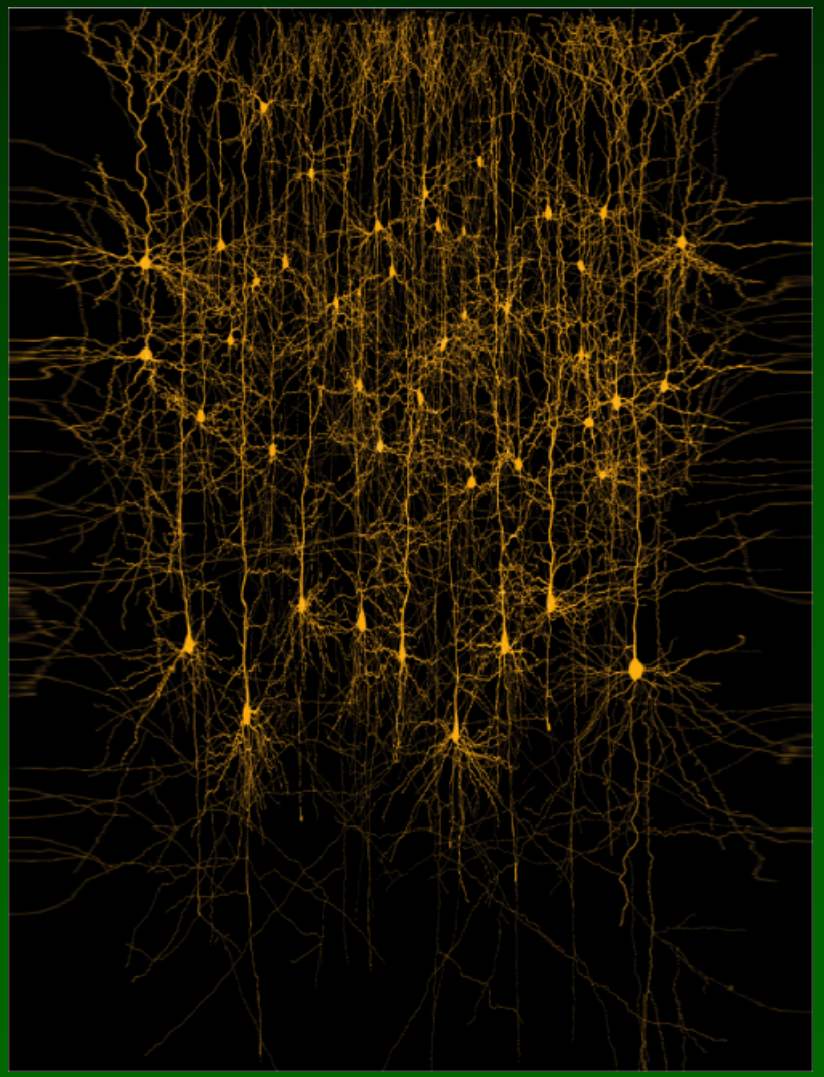
September 5, 2008

Dr. Stefan Maas, BioS Lehigh U.

Brain networks





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Brain Trivia

The average number of neurons in the brain =

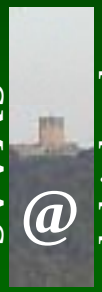
100 billion.

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.



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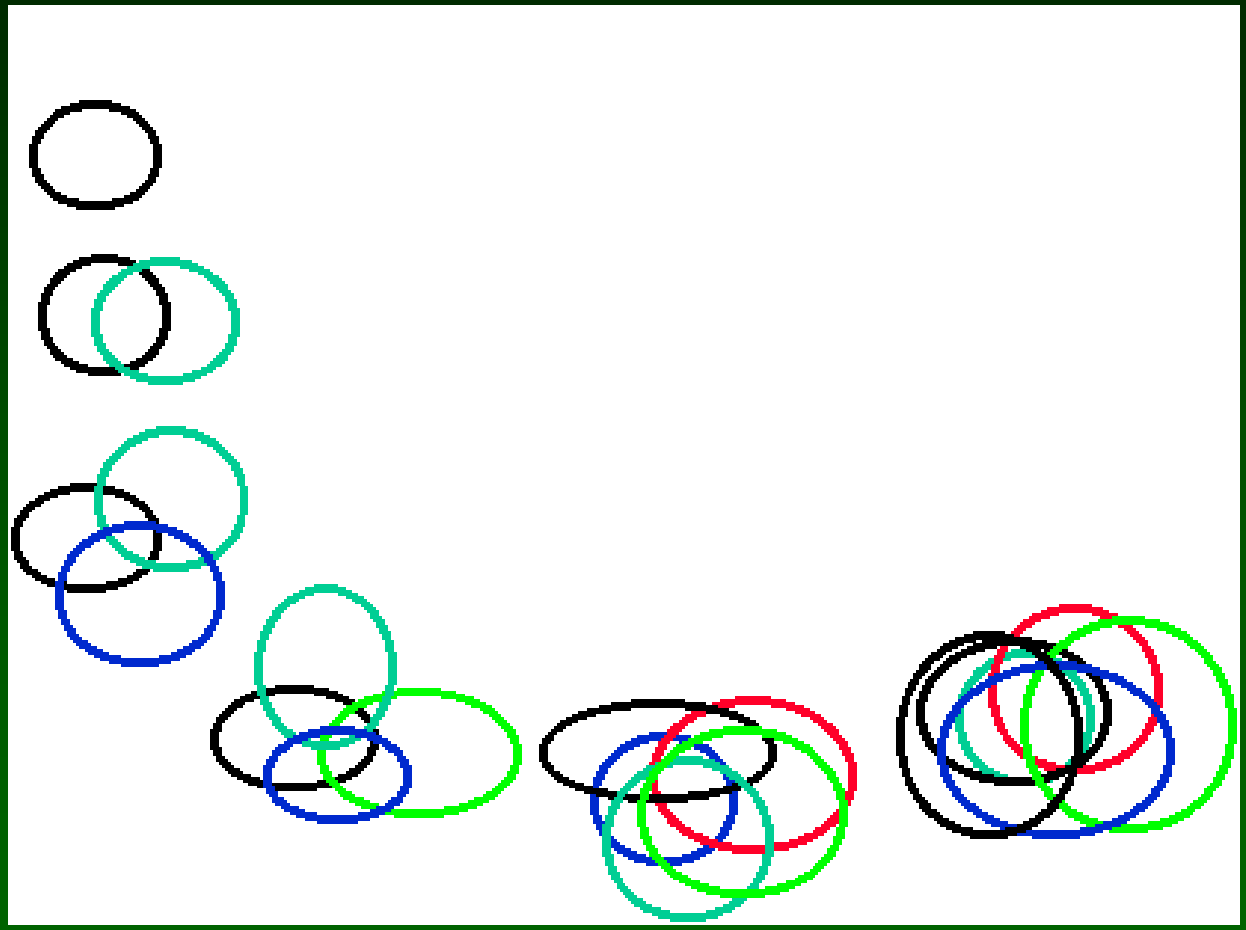
Complexity of the Brain

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"

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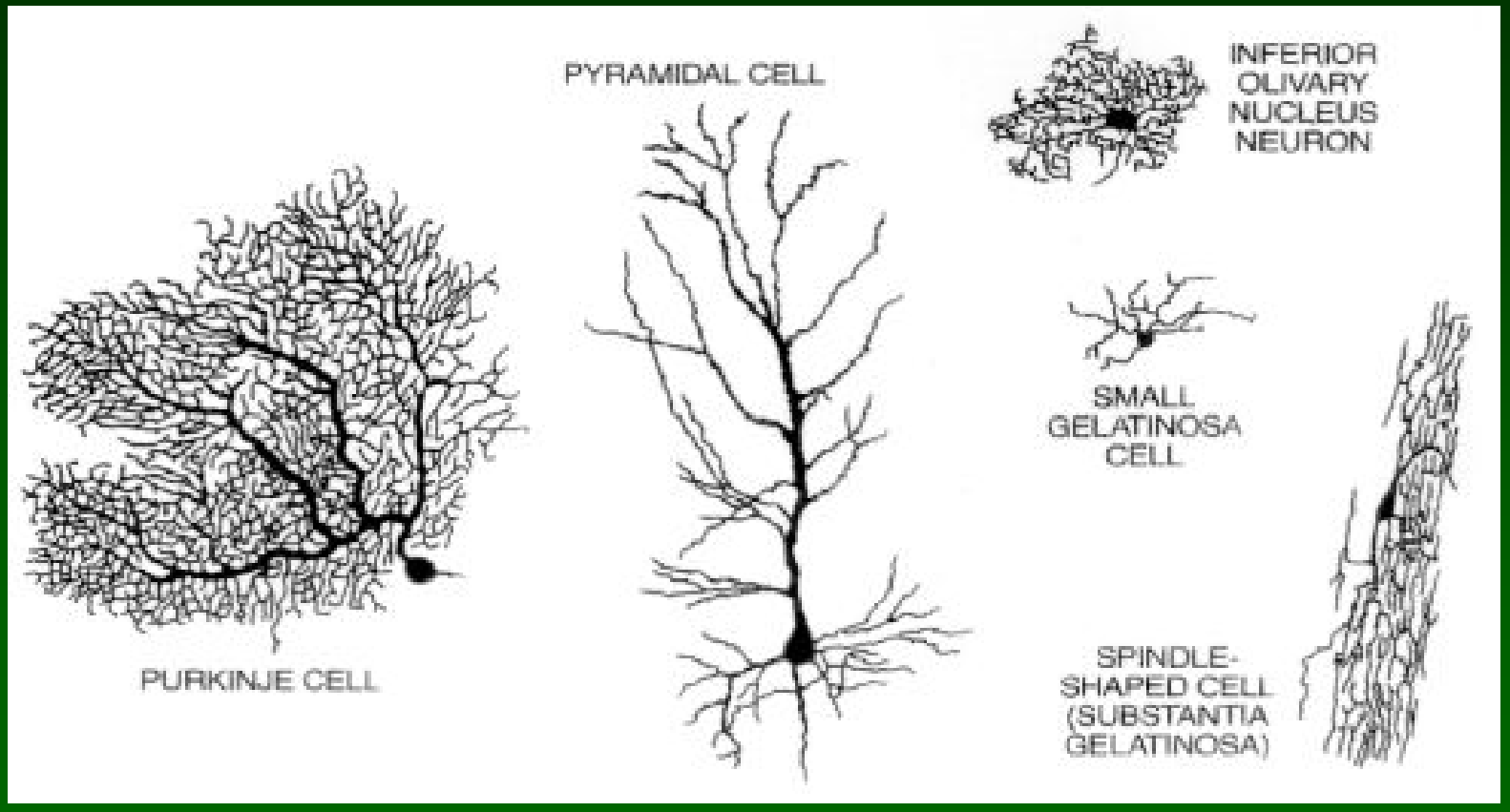
Complexity of the Brain



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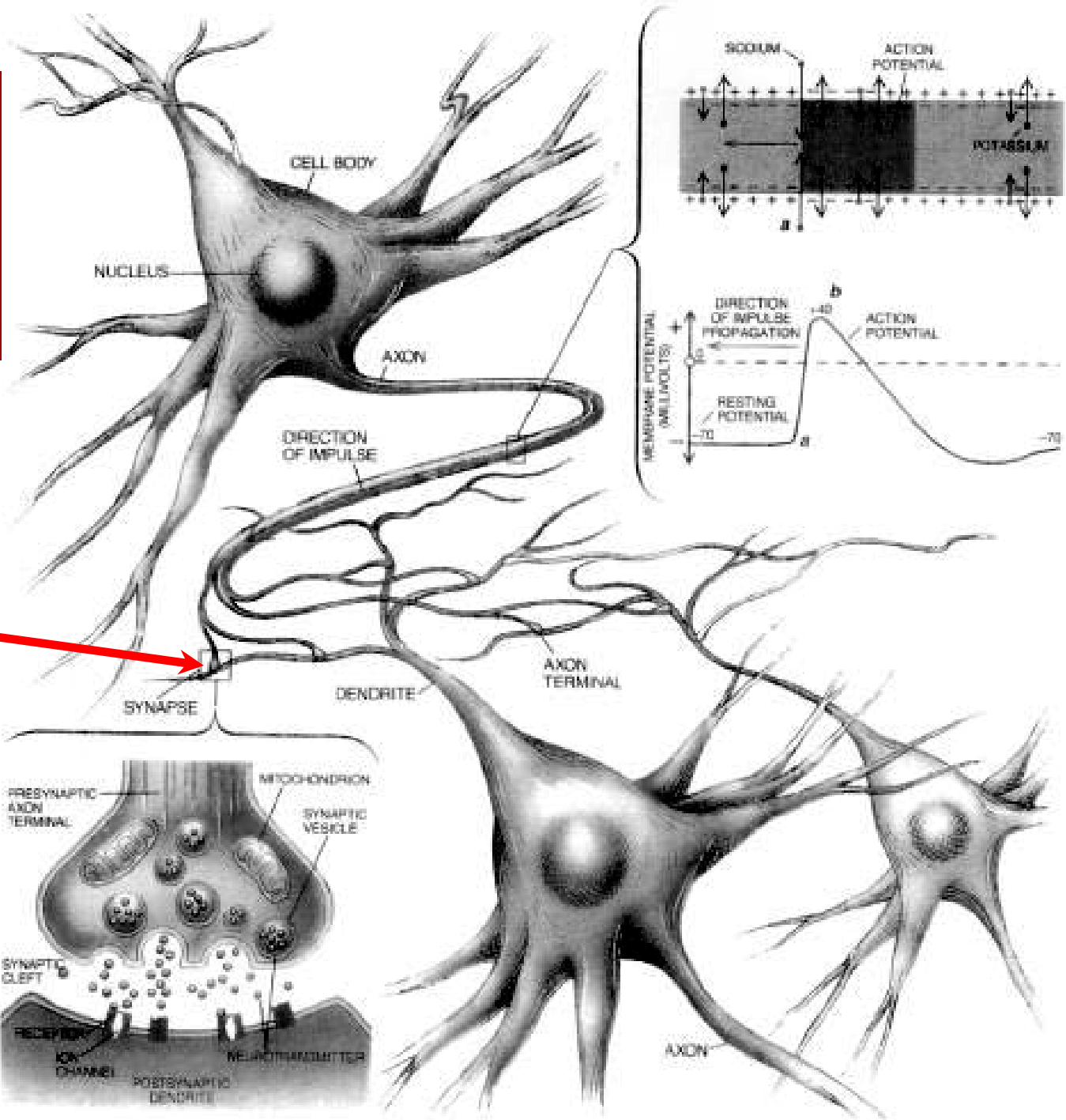
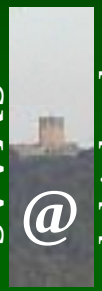
Nerve Cell Communi-cation

Synapse





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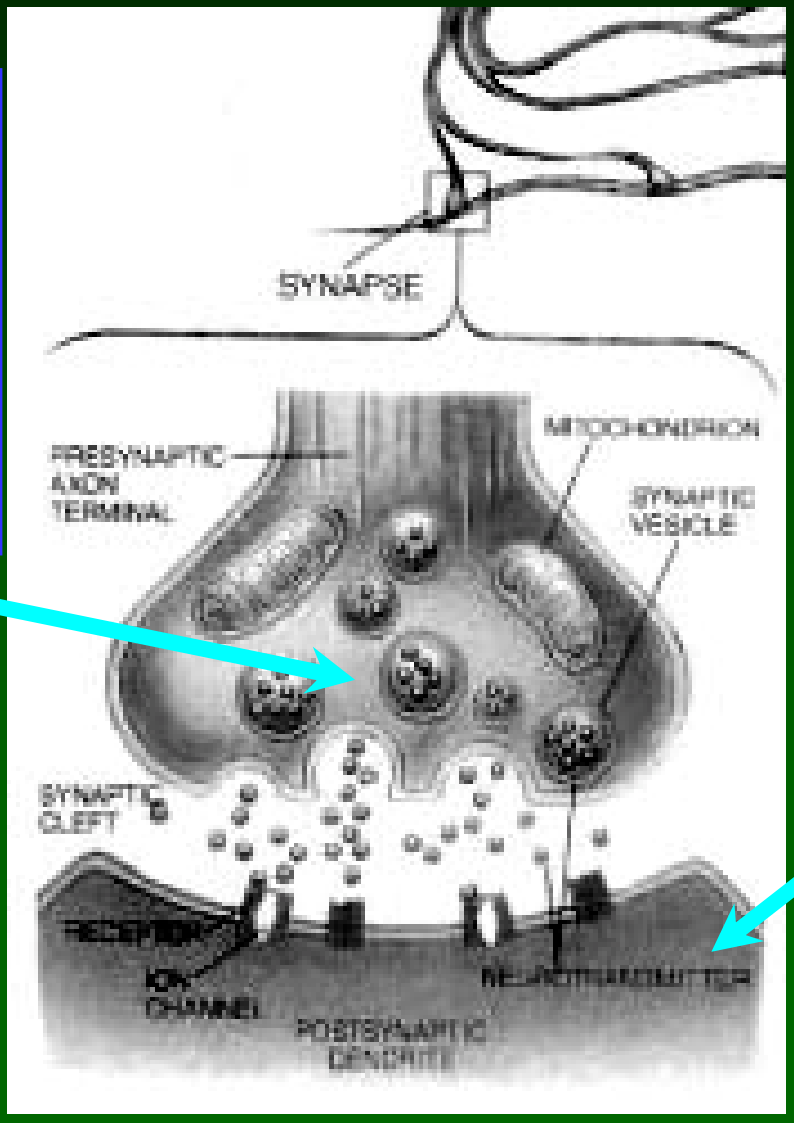
Complexity of the Brain

The synapse typically has two parts:

A presynaptic structure containing packets of neuro-transmitters



and a postsynaptic structure of the receiving neuron

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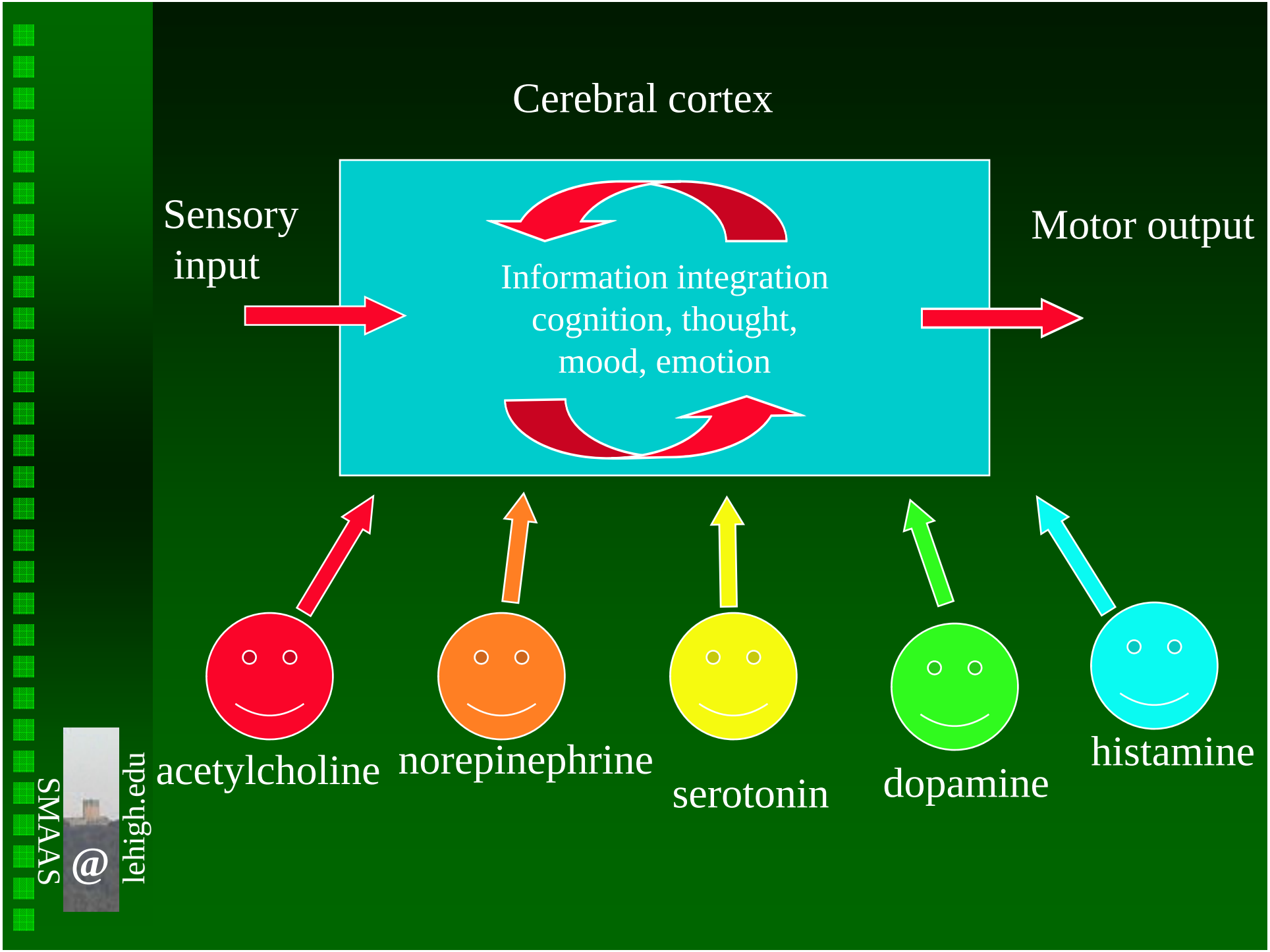
Cerebral cortex
Sensory input
Information integration
cognition, thought,
mood, emotion
Motor output
acetylcholine
norepinephrine
serotonin
dopamine
histamine
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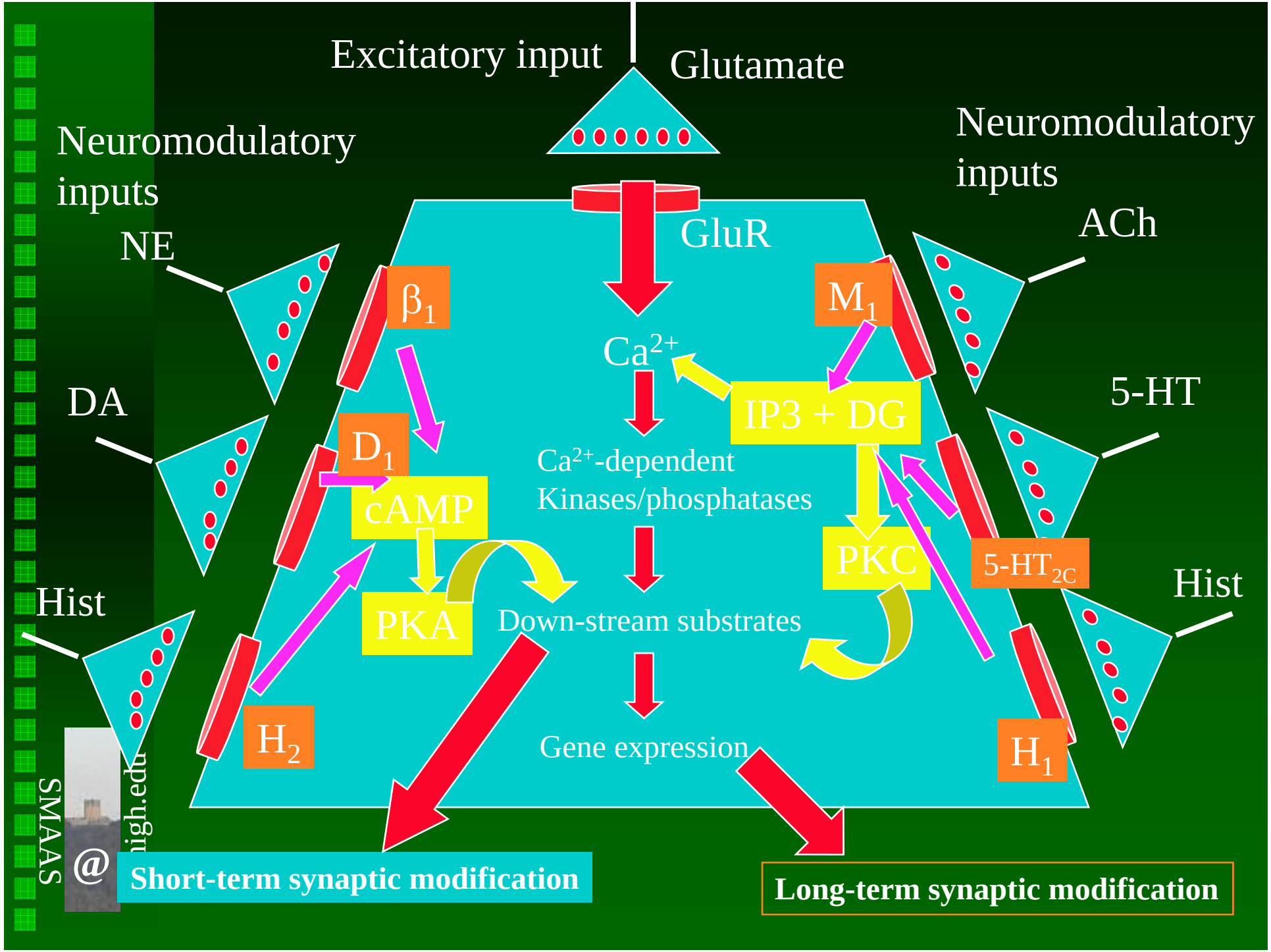
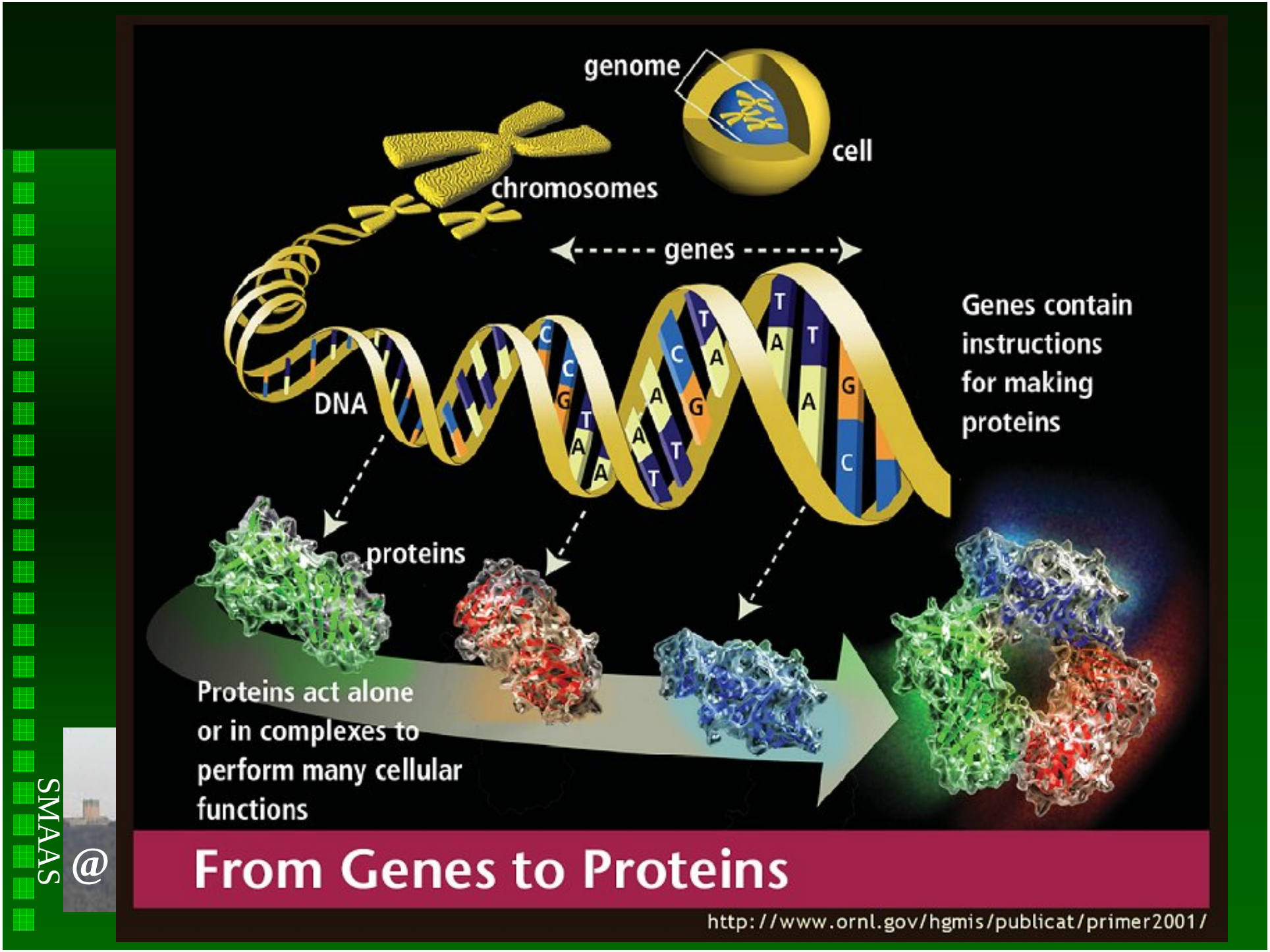

Excitatory input
Glutamate
Neuromodulatory inputs
NE
Neuromodulatory inputs
ACh
GluR
β1
M1
Ca2+
DA
IP3 + DG
5-HT
D1
Ca2+-dependent Kinases/phosphatases
cAMP
PKC
5-HT2C
Hist
PKA
Down-stream substrates
Hist
H2
Gene expression
H1
Short-term synaptic modification
Long-term synaptic modification


genome
cell
chromosomes
genes
DNA
Genes contain instructions for making proteins
proteins
Proteins act alone or in complexes to perform many cellular functions
From Genes to Proteins
http://www.ornl.gov/hgmis/publicat/primer2001/

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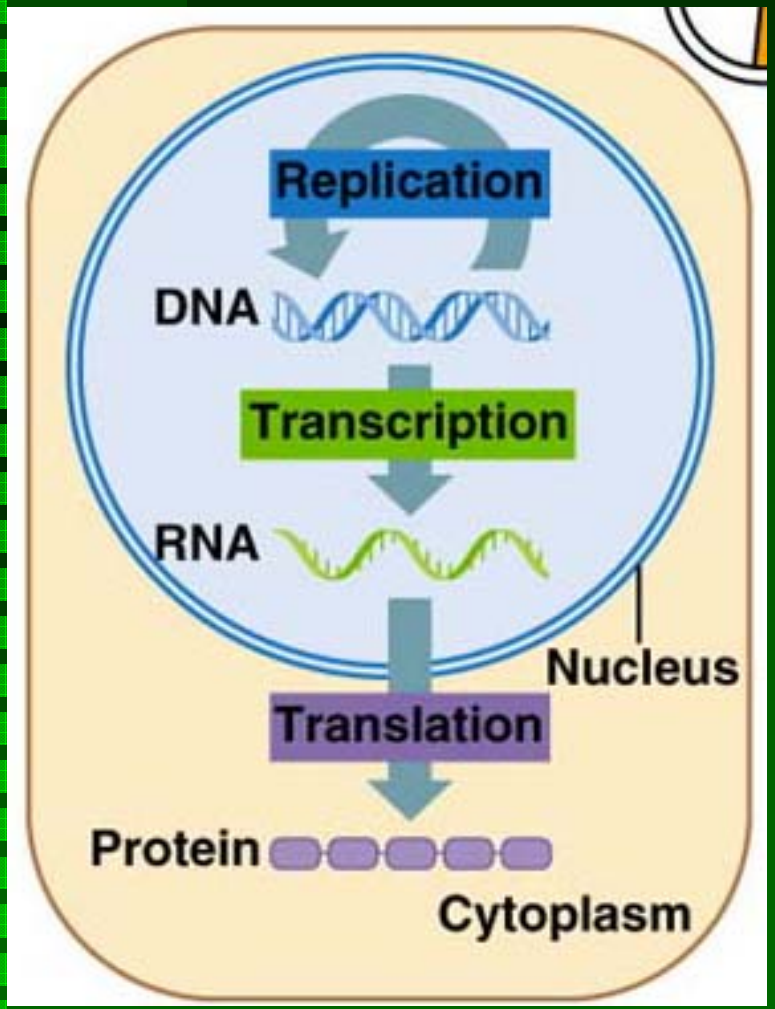
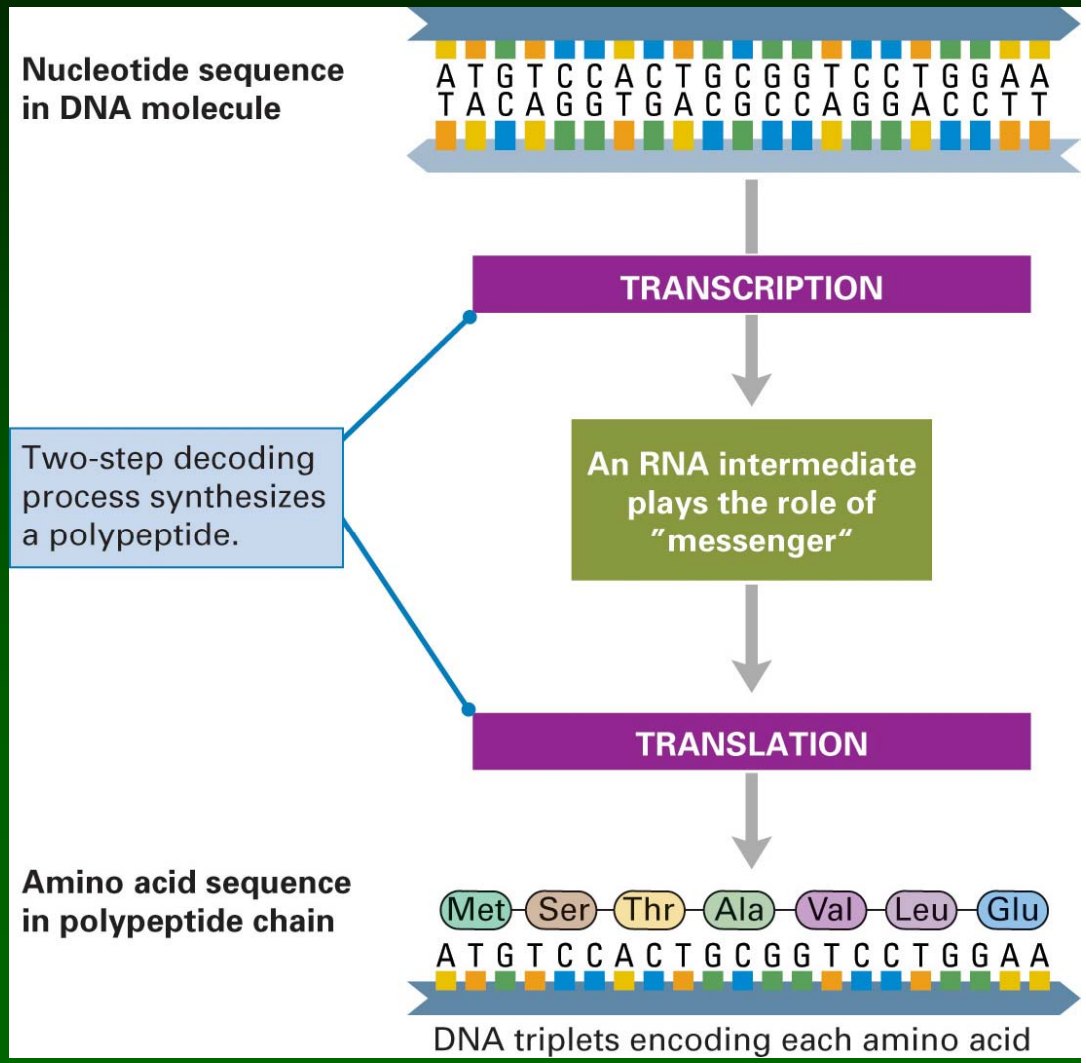
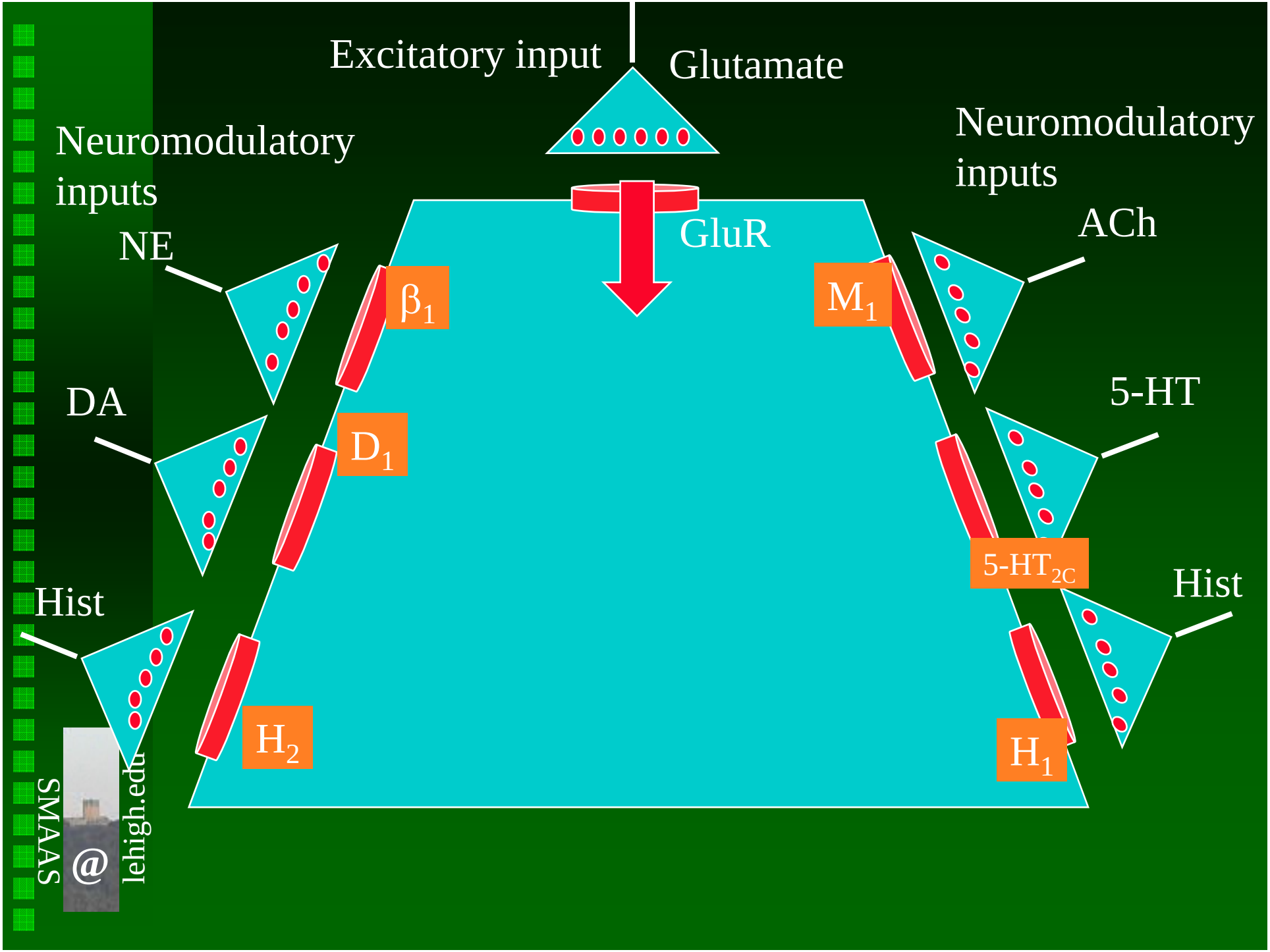
Genes code for Proteins with RNA as an intermediate






Excitatory input
Glutamate
Neuromodulatory inputs
NE
DA
Hist
Neuromodulatory inputs
ACh
5-HT
Hist
GluR
β1
D1
H2
M1
5-HT2C
H1
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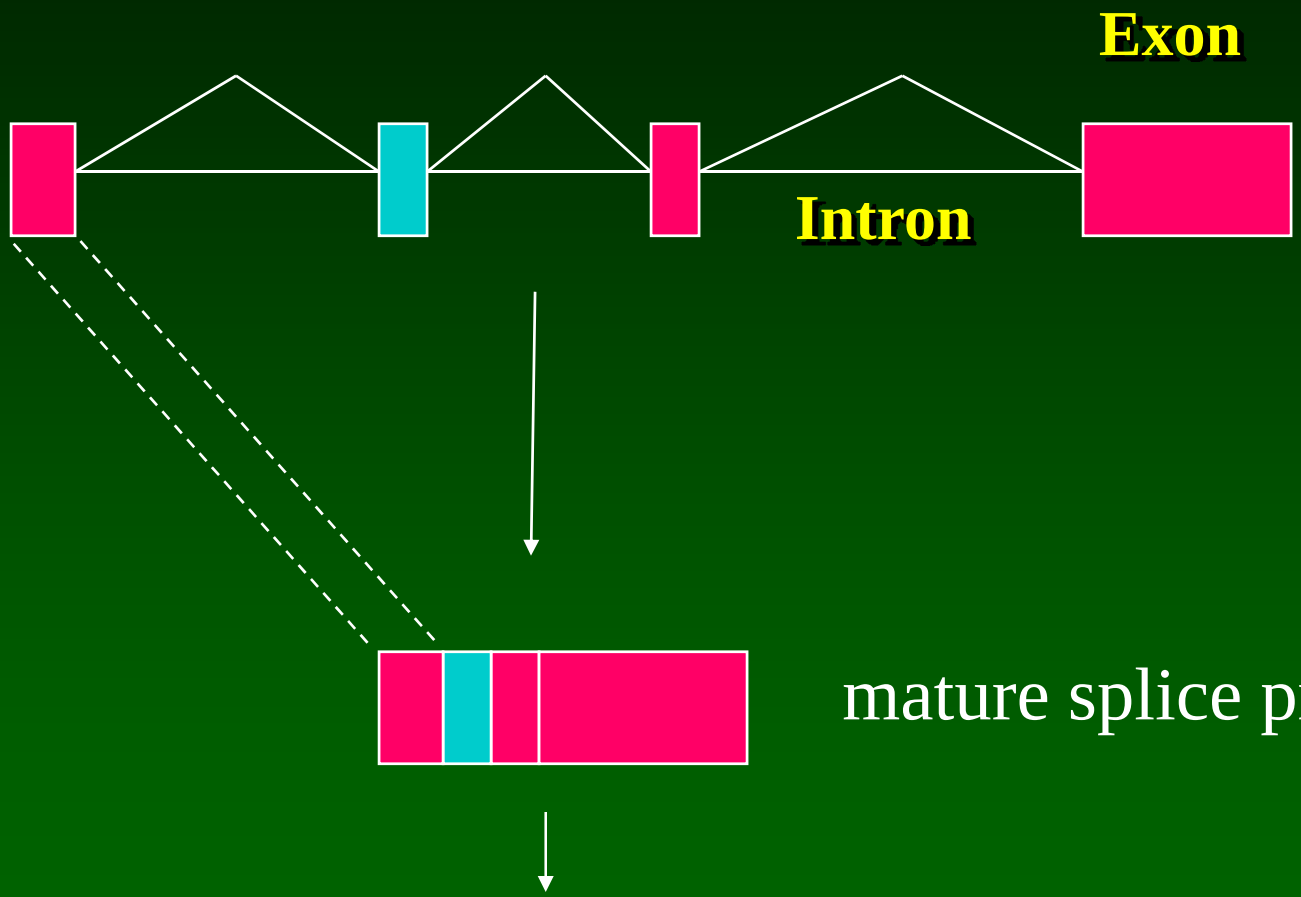
Gene splicing:
Removal of non-coding introns



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I A M T H E 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

Priciples of Alternative Splicing

n

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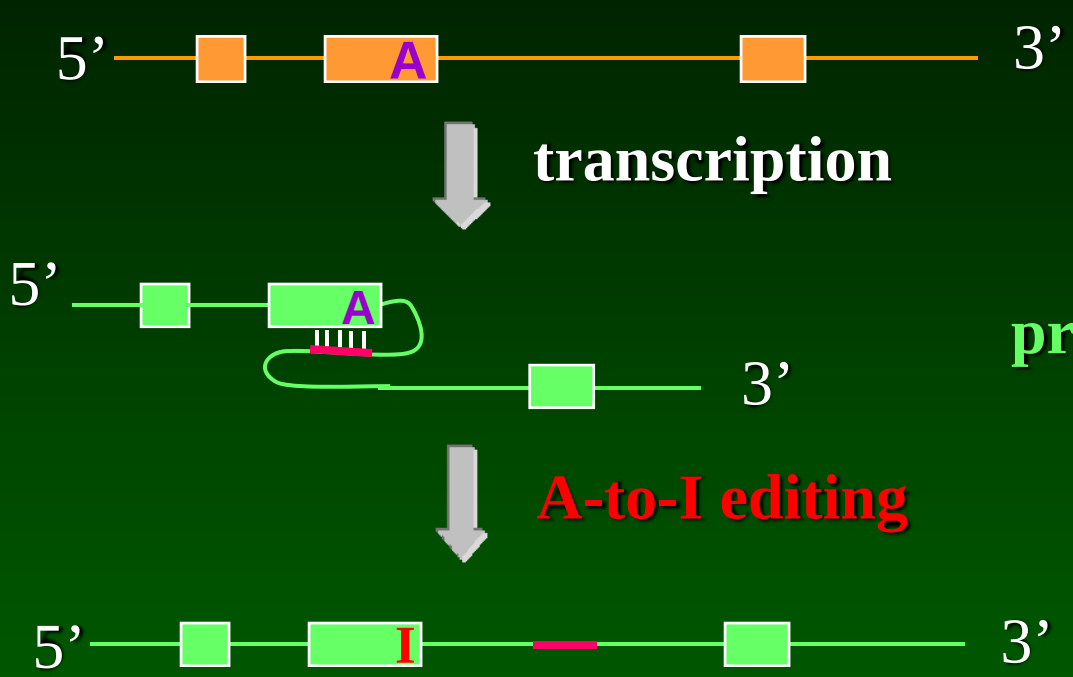
RNA editing



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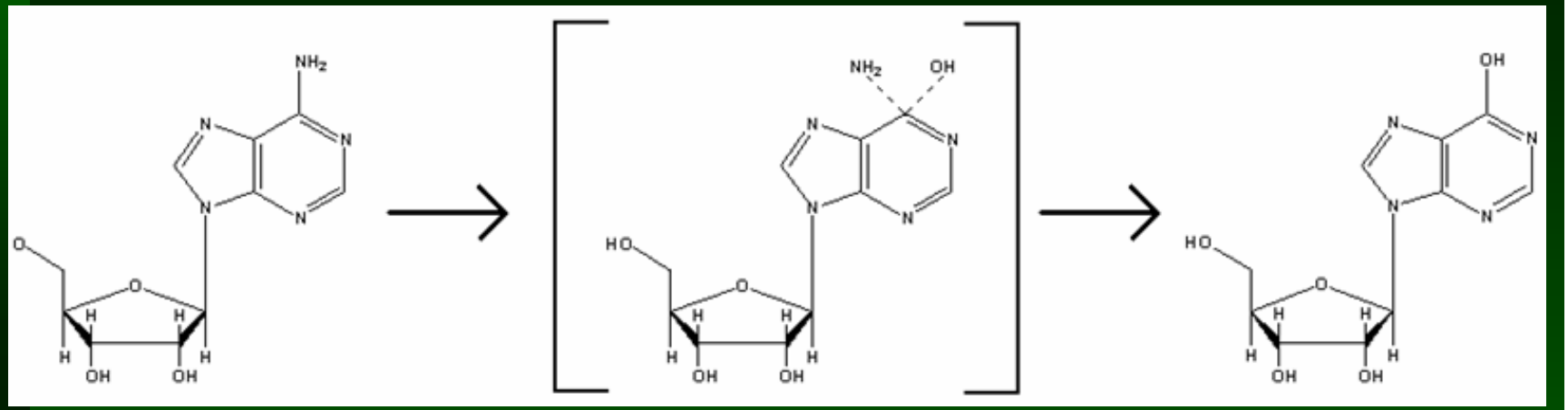

Adenosine

Inosine

- Adenosine converted to Inosine
- Interpreted as Guanosine
- Expand the proteome

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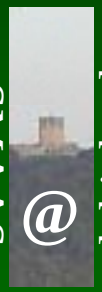
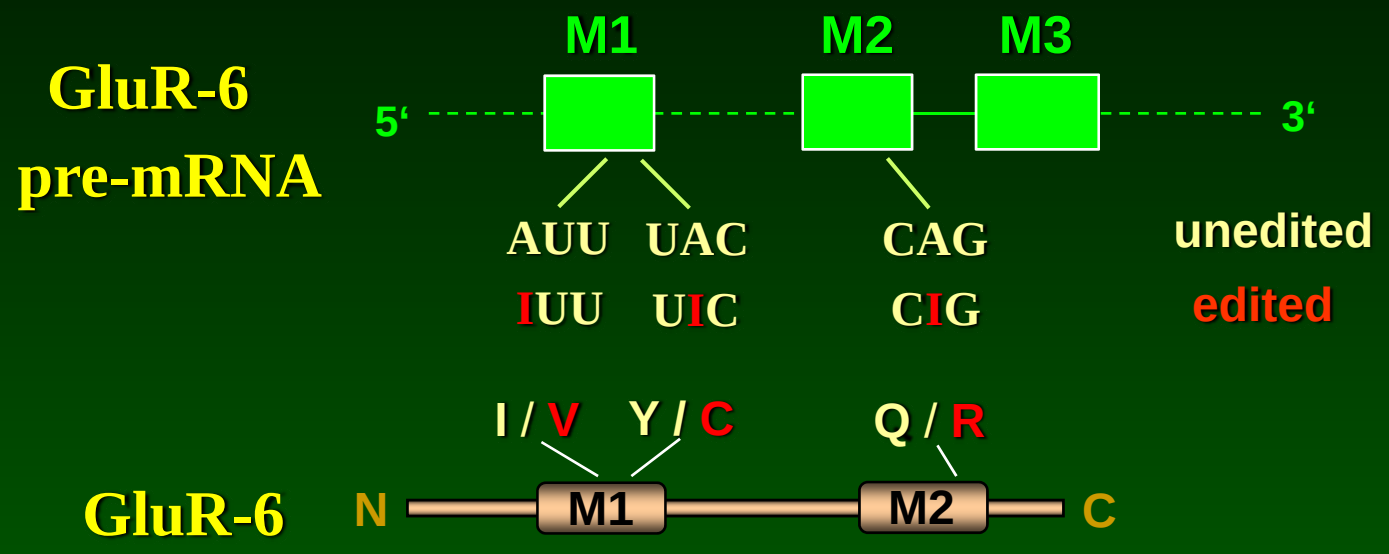
Mammalian substrates of A-to-I pre-mRNA editing

Gene	codon	amino acid	editing [%]
GluR-B	CAG/C**I**G	Q/**R**	**100**
GluR-B,-C,-D	AAG/A**I**G	R/**G**	**60-80**
GluR-5,-6	CAG/C**I**G	Q/**R**	**40-80**
GluR-6	AUU/**I**UU	I/**V**	**80**
	UAC/U**I**C	Y/**C**	**80**
5-HT_{2C} Serotonin-receptor	AUA/**I**UA	I/**V**	**40-90**
	AAU/A**I**U	N/**S**	**35-40**
	AUU/**I**UU	I/**V**	**45-75**



Diversity through RNA editing



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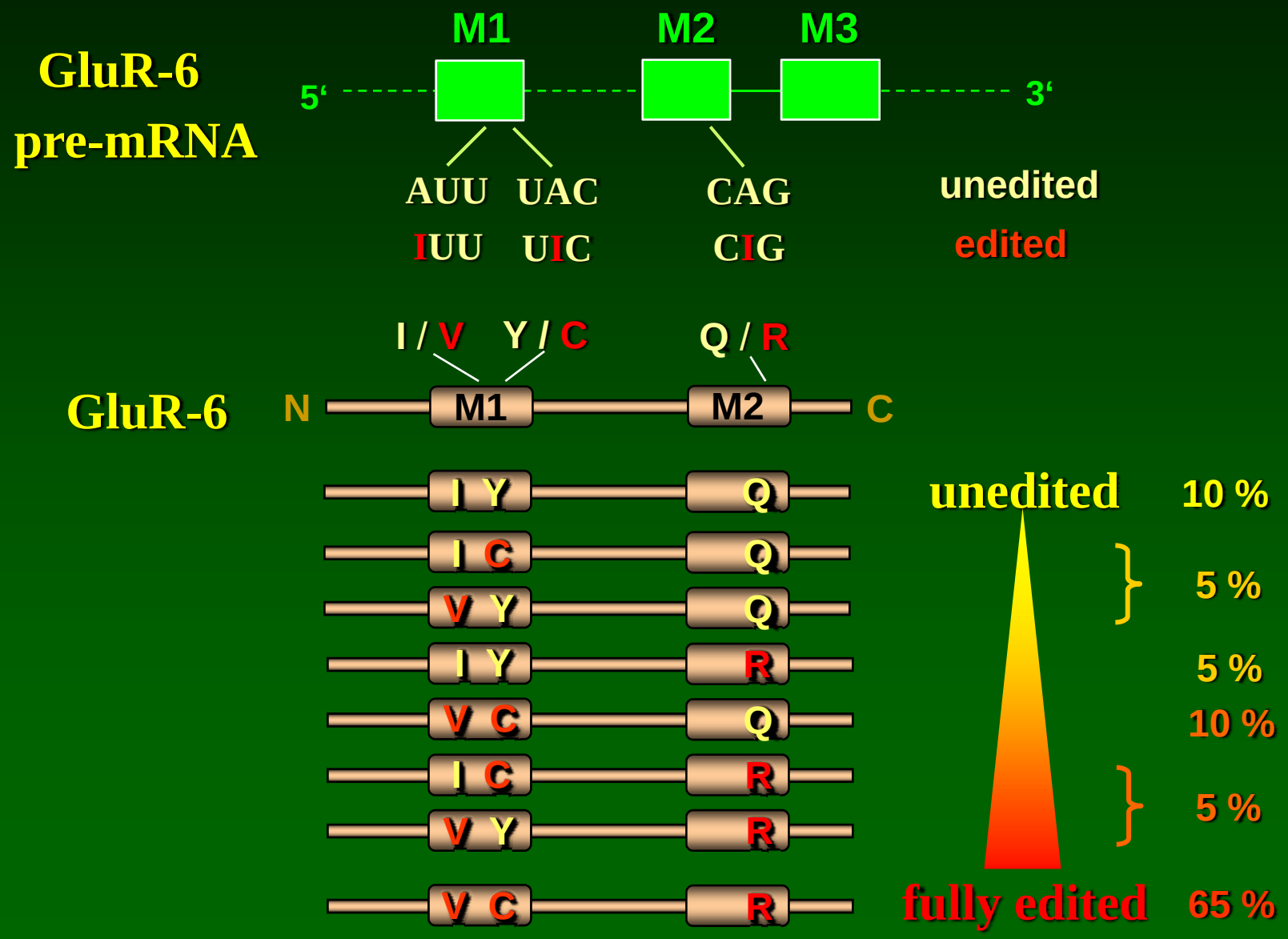
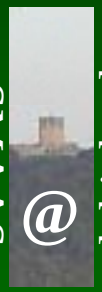
Diversity through RNA editing





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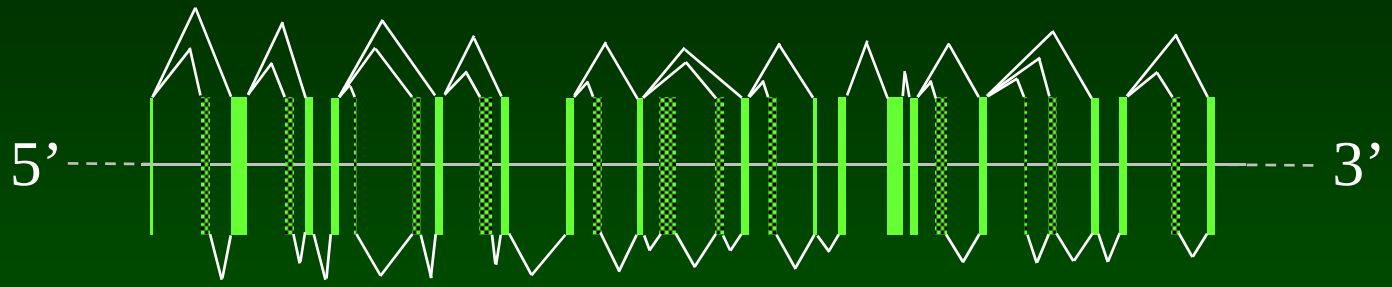
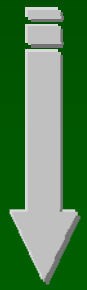
Even more diversity

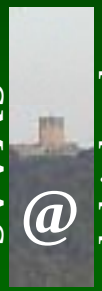
***paralytic* pre-mRNA**



alternative splicing



1 536 variants



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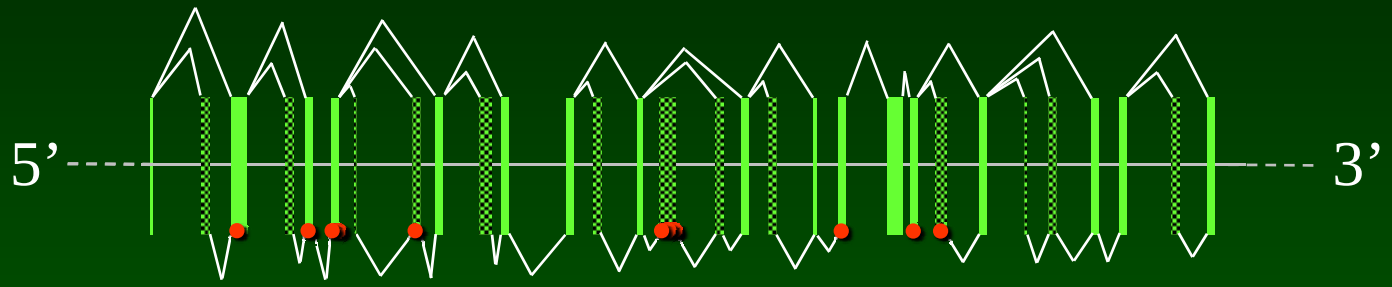
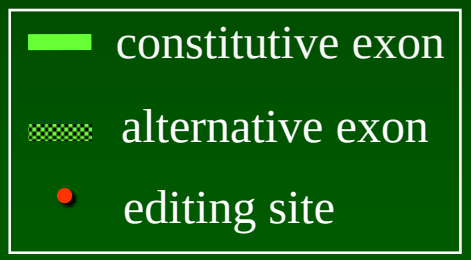
Even more diversity

***paralytic* pre-mRNA**





alternative splicing

RNA editing

1 032 192 variants

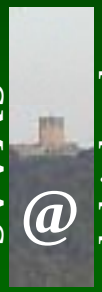


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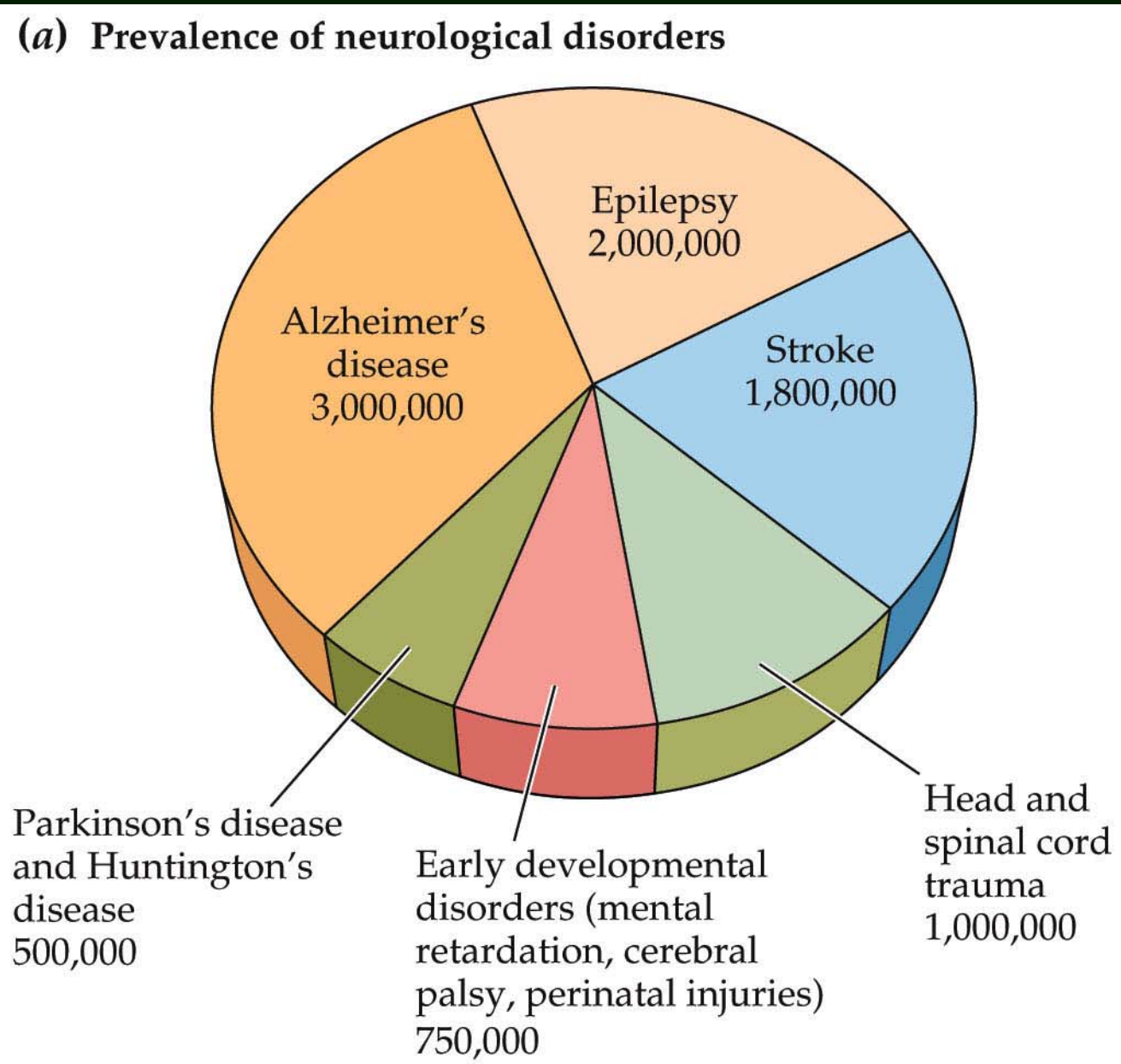
Figure 1.7 The Toll of Brain Disorders (Part 1)



***Biological Psychology 5e*, Figure 1.7 (Part 1)**

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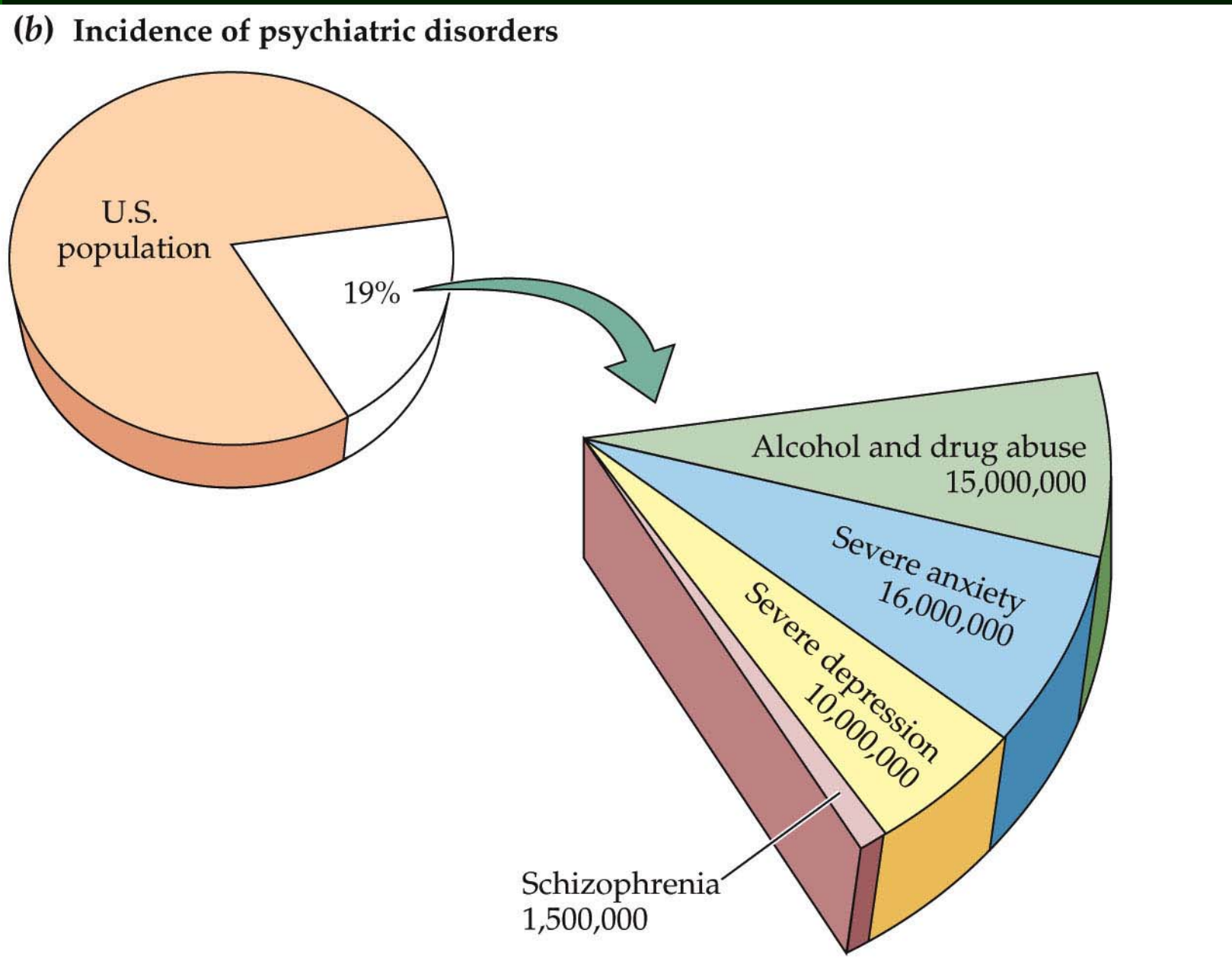
Figure 1.7 The Toll of Brain Disorders (Part 2)



***Biological Psychology 5e*, Figure 1.7 (Part 2)**

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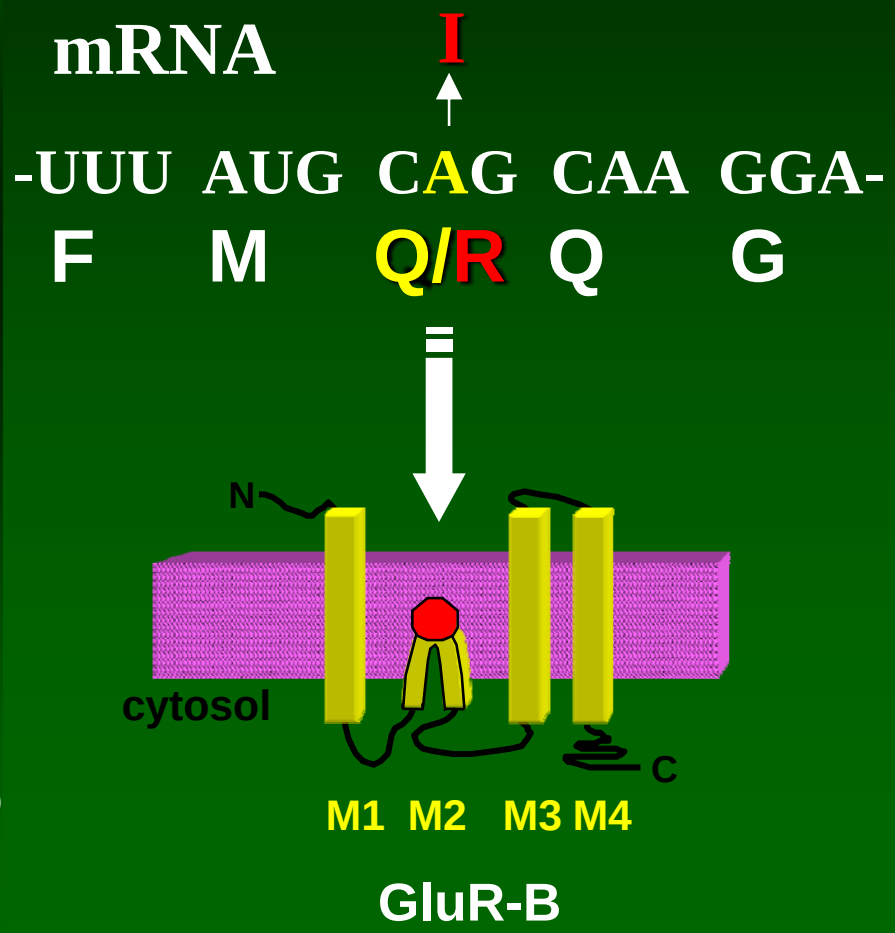
Q/R-site editing of glutamate receptor subunit GluR-B



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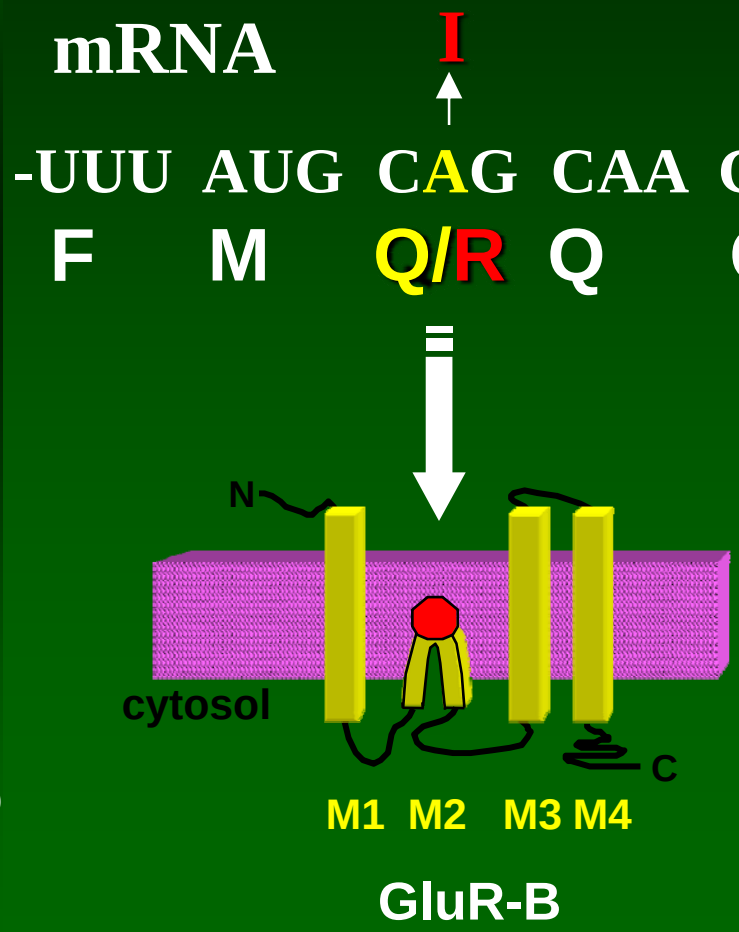
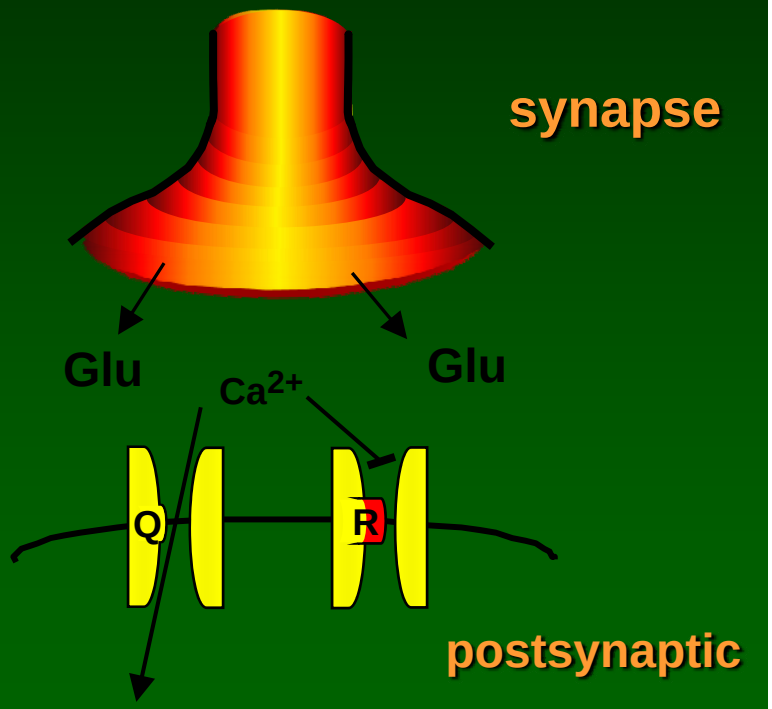
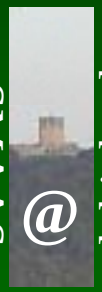
Q/R-site editing of glutamate receptor subunit GluR-B





>99.9% R



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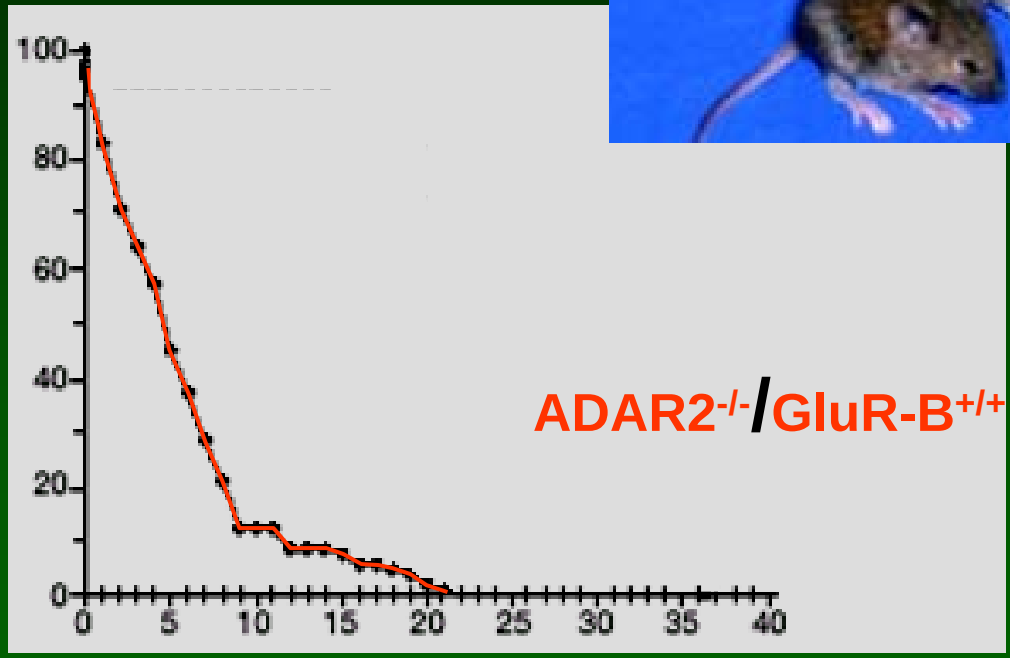
RNA editing enzyme deficient mice



(Higuchi, Maas, Single, Hartner et al., 2000, *Nature* 406, 78-81)

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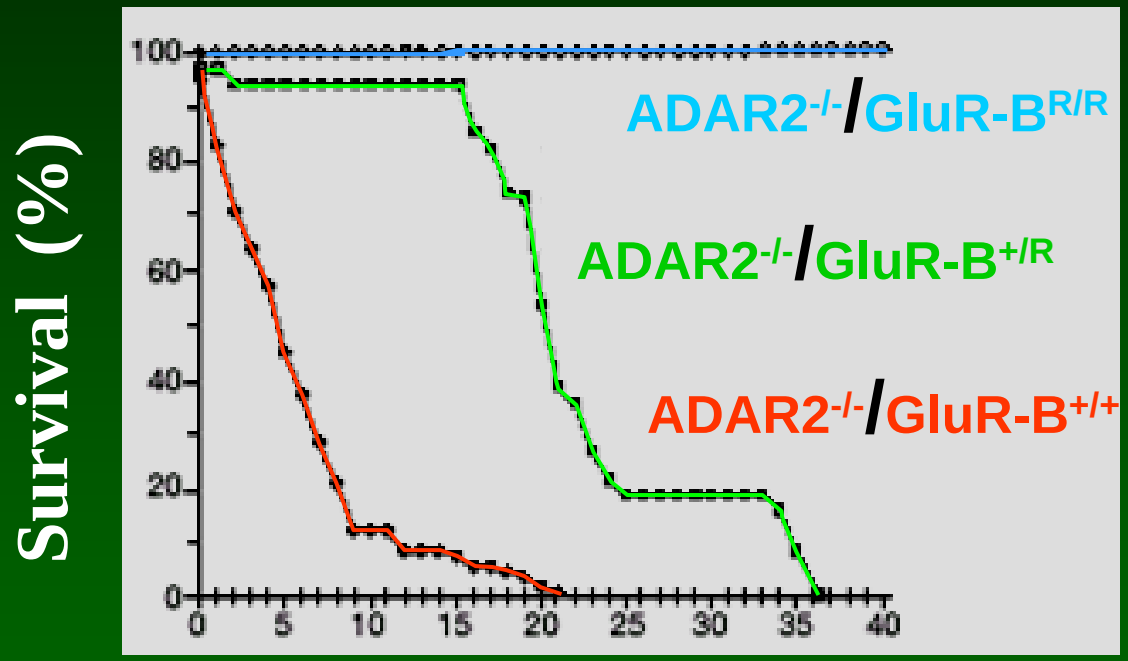
RNA editing enzyme deficient mice: Rescue by GluR-B point mutation



(Higuchi, Maas, Single, Hartner et al., 2000, *Nature* 406, 78-81)

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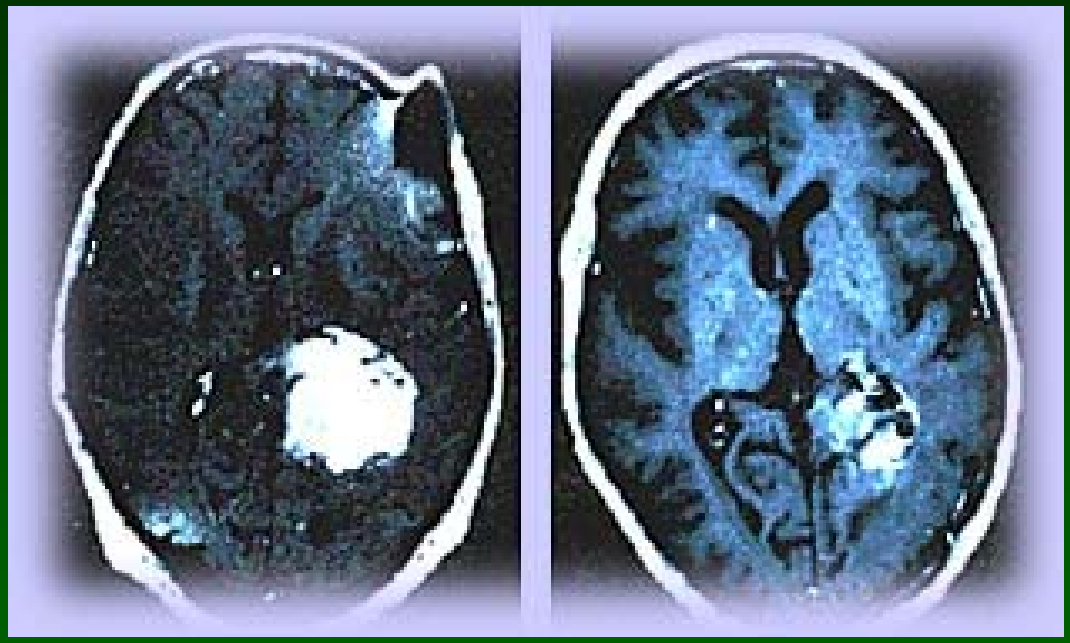
Glioblastoma multiforme (GBM)



http://www.thejohnphilpthompsonfoundation.org/GlioblastomaMultiforme_1_.jpg

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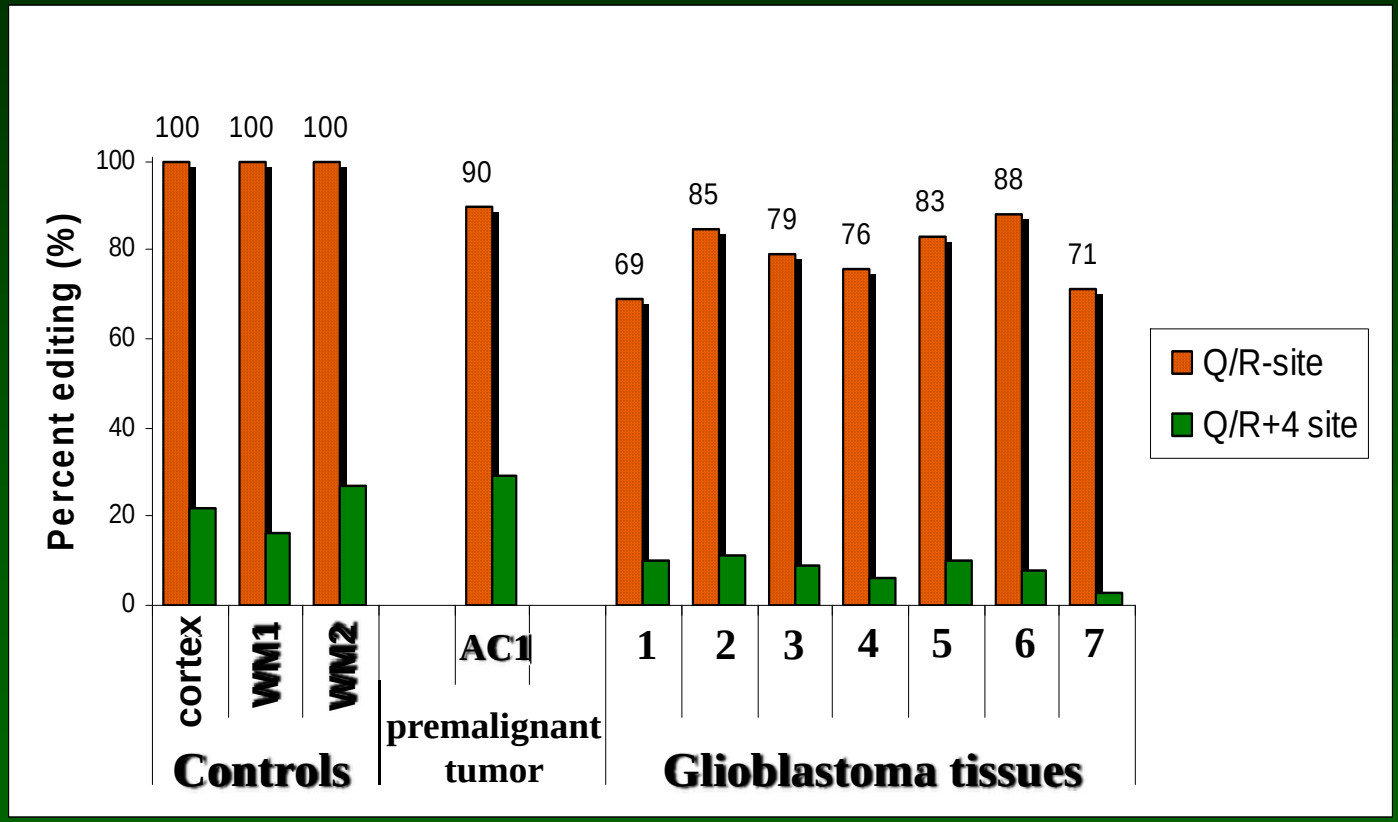
Q/R site editing in normal human brain and gliomas



(Maas et al., 2001, *PNAS* 98, 14687-92)

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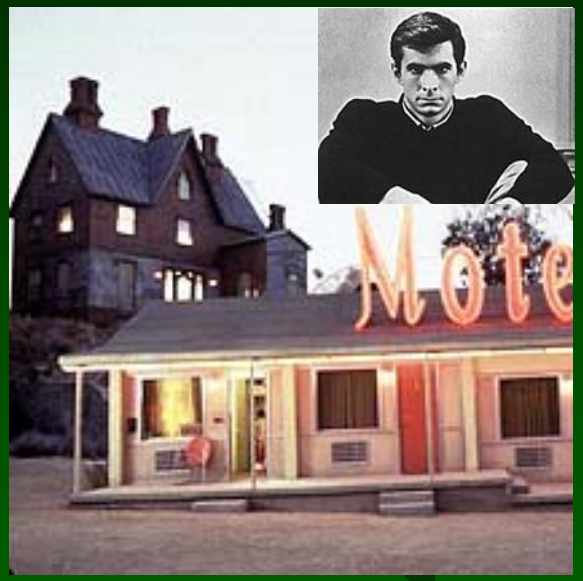
Schizophrenia



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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

- <u>cause unknown</u>

  => 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**

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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

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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

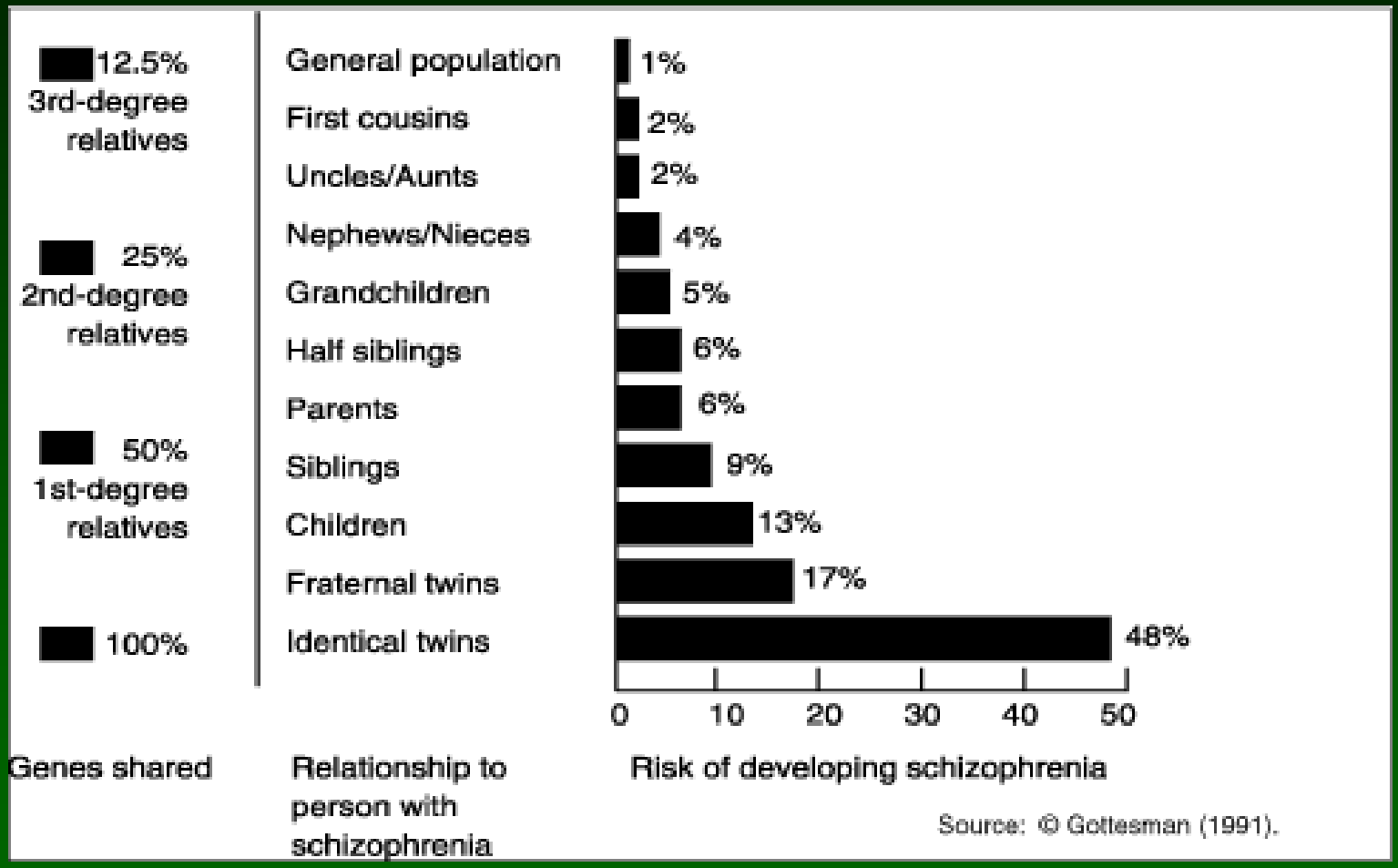
➢ Cognitive and Social Impairment

> Occur second

- Attention and Concentration deficits
- Problems with Learning and Memory
- Deficiency in executive Function

  abstract thinking, problem solving

Genetic factor



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

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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

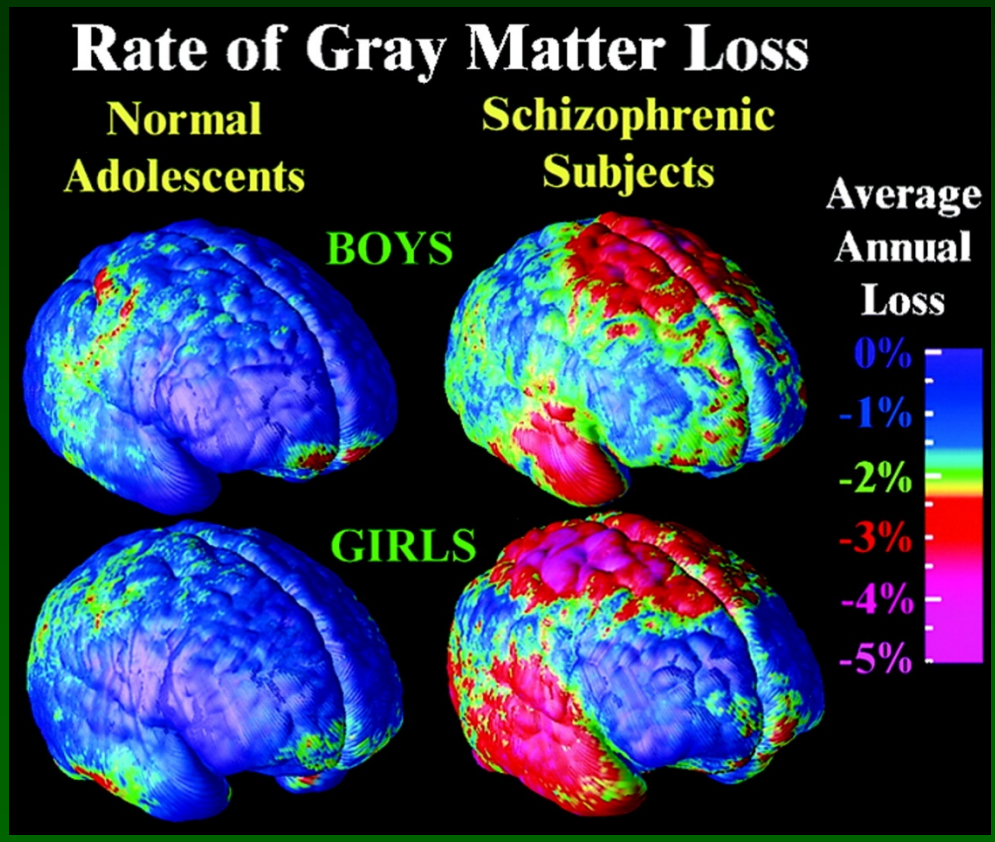
Stressful environmental conditions

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

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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

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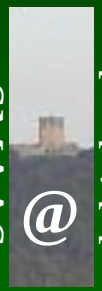
Therapy - Management

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



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Therapy - Management

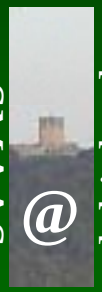
Major problem: non-compliance

ca. 50% (and higher soon after onset of disorder)

⇒ injectible depot

⇒ simplifications of regimen

⇒ direct delivery..



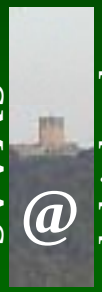
Therapy - Management

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

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