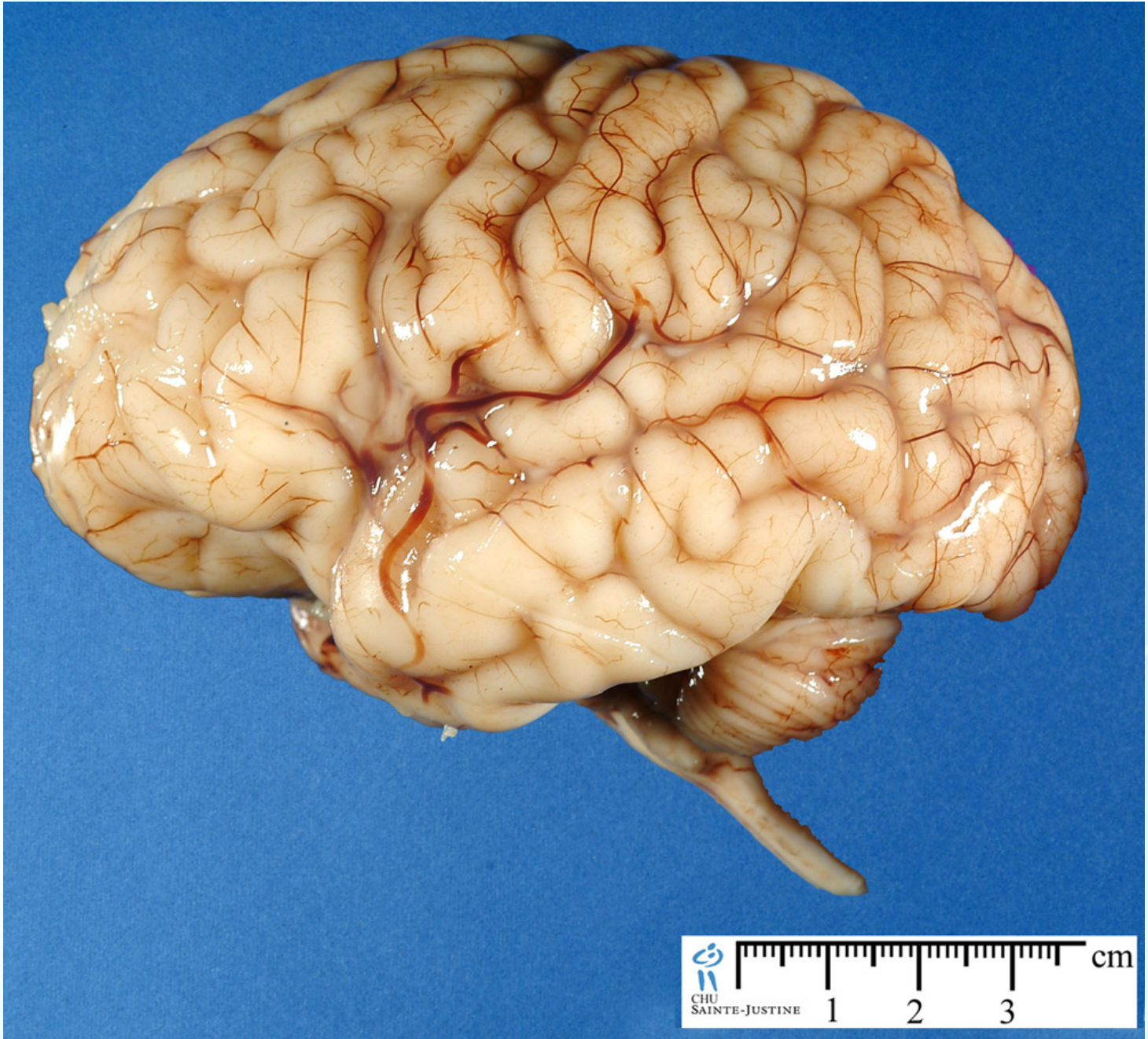


# Every head has its own headache

*(Arab proverb)*

Verner Anttila  
March 6<sup>th</sup>, 2012



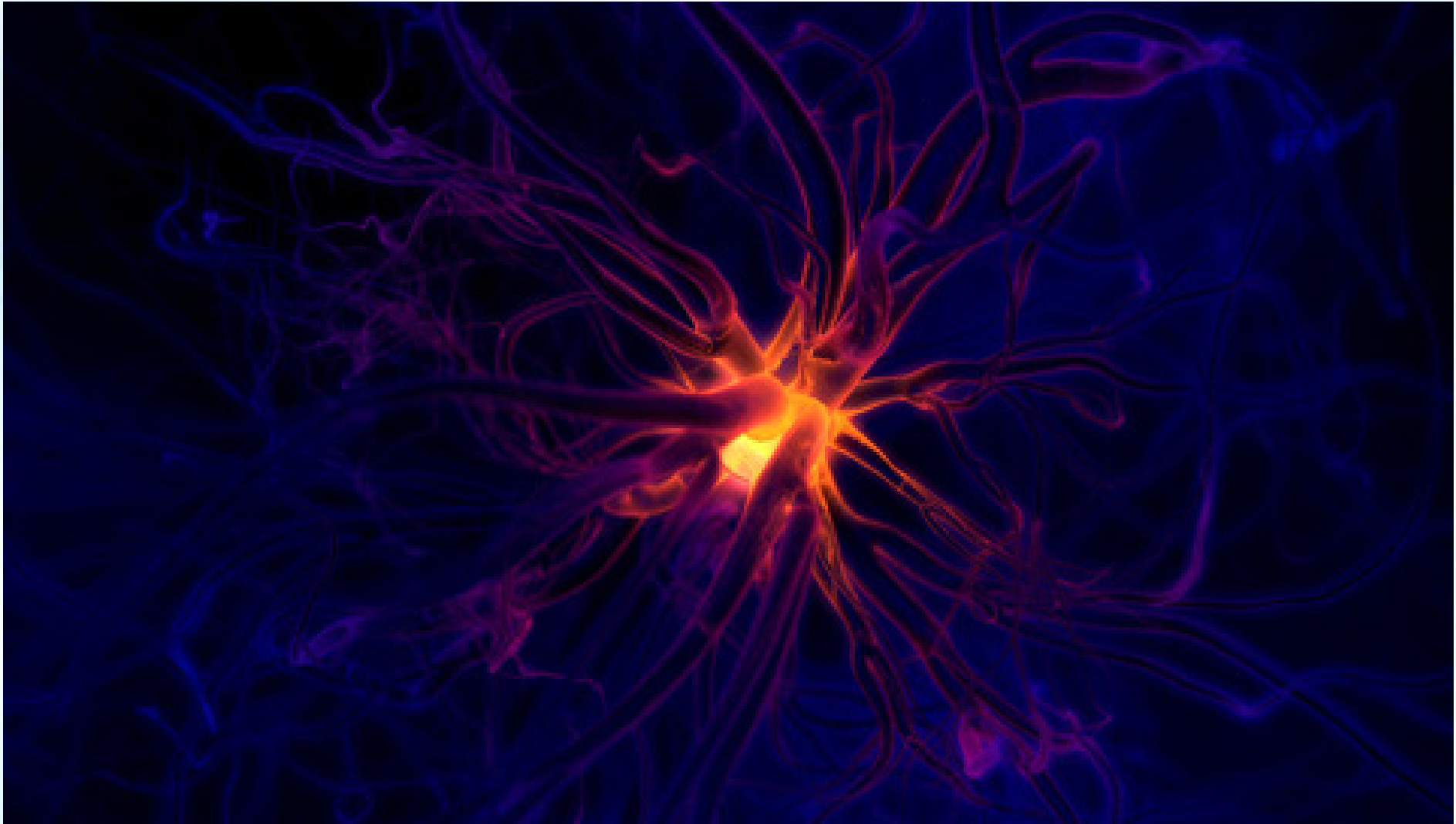


CHU SAINTE-JUSTINE 1 2 3 cm

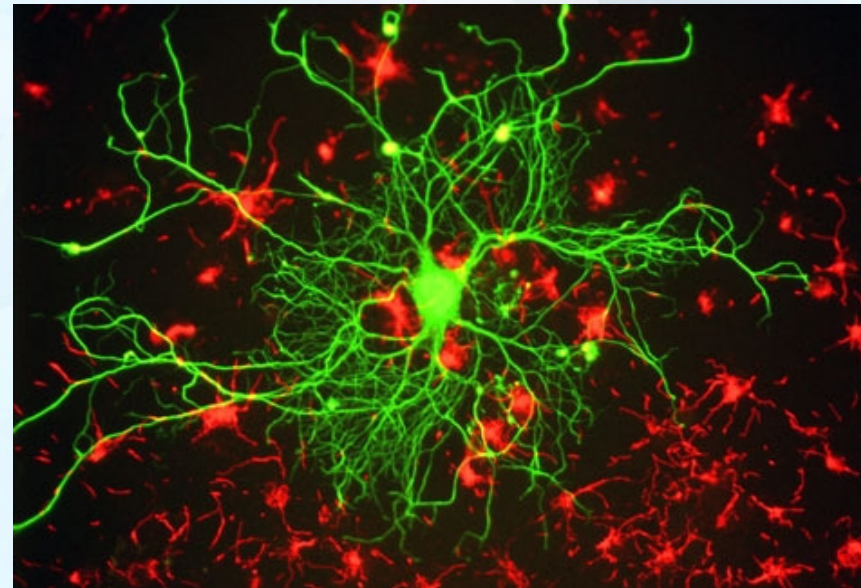
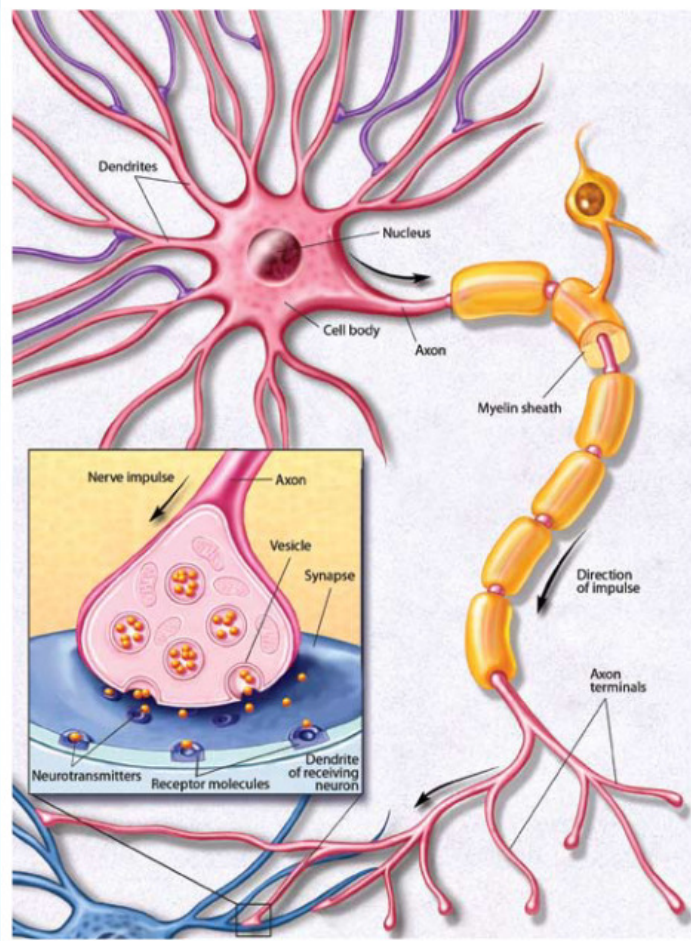
# MRI of the human brain



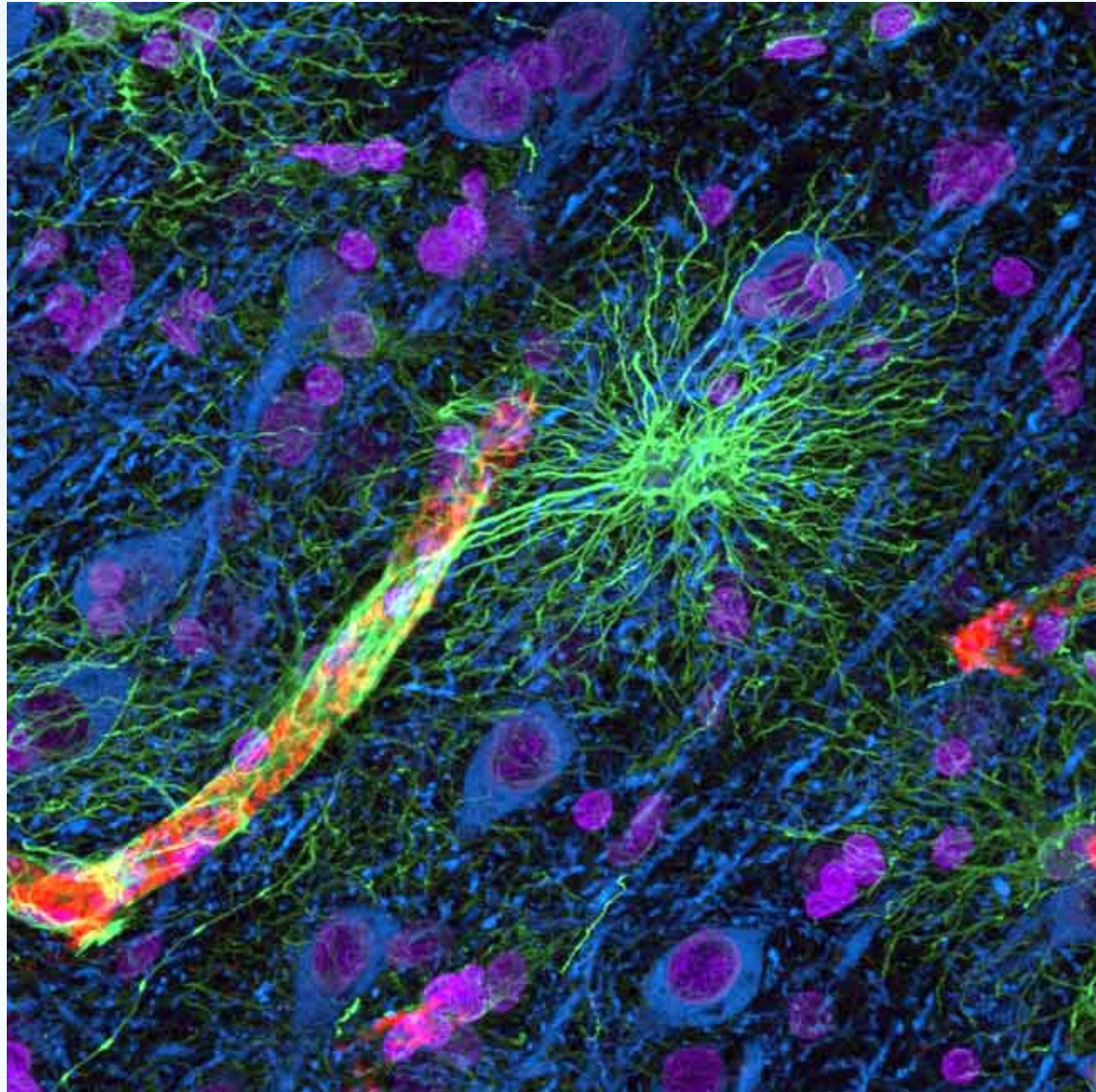
# The single neuron



# Neurons



# The tissue context



# Different types of neurons

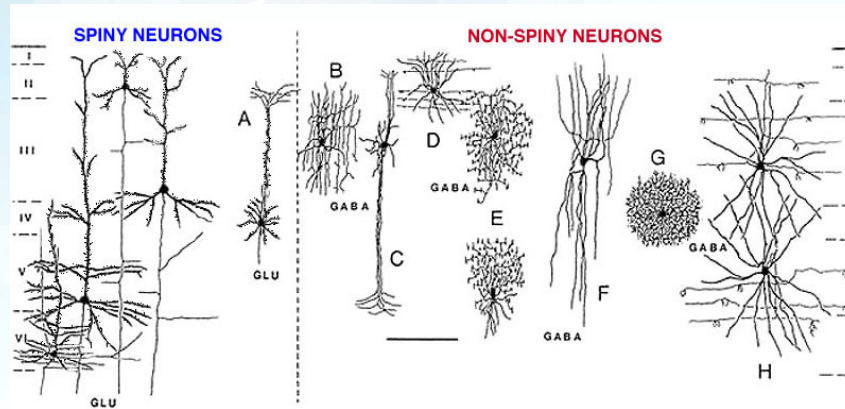
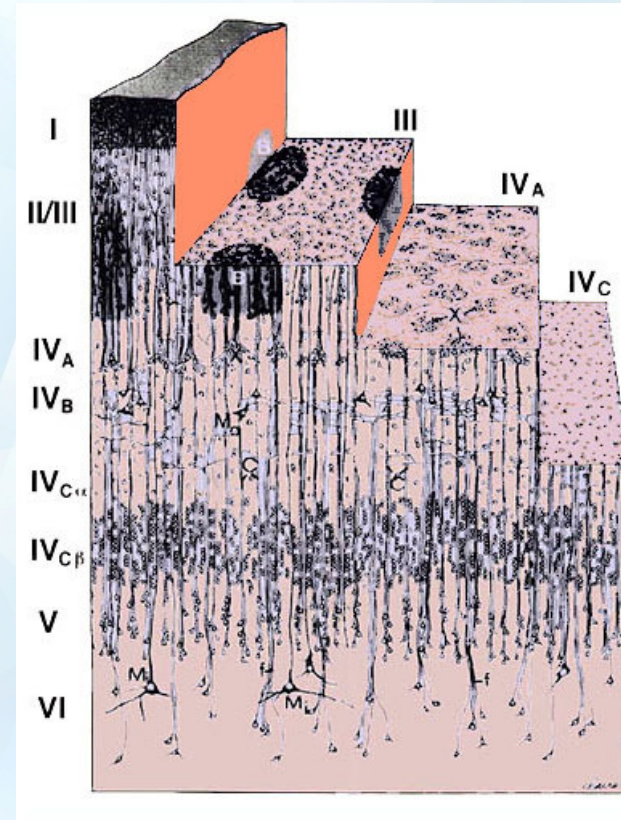


Figure 12. Basic cell types in the monkey cerebral cortex. Left: spiny neurons that include pyramidal cells and stellate cells (A). Spiny neurons utilize the neurotransmitter glutamate (Glu). Right: smooth cells that use the neurotransmitter GABA. B, cell with local axon arcades; C, double bouquet cell; D, H, basket cells; E, chandelier cells; F, bitufted, usually peptide-containing cell; G, neurogliaform cell.



# How neurons are organized

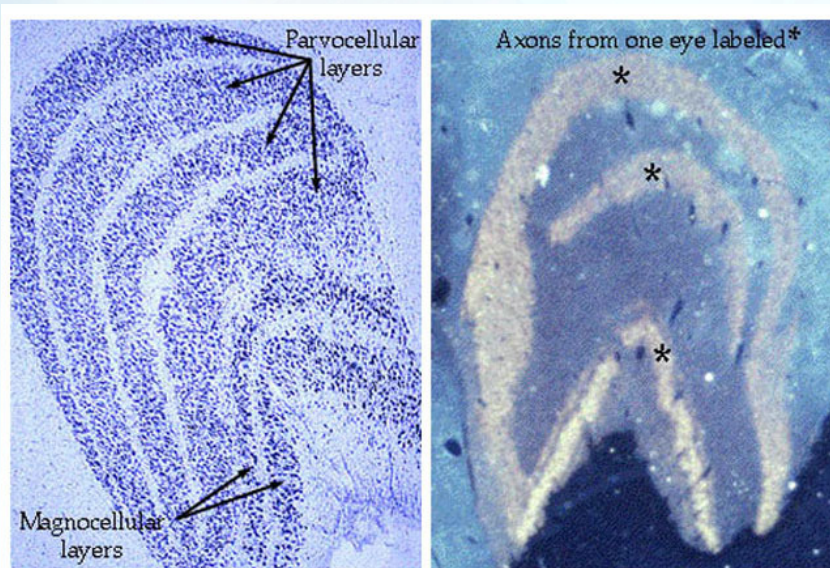
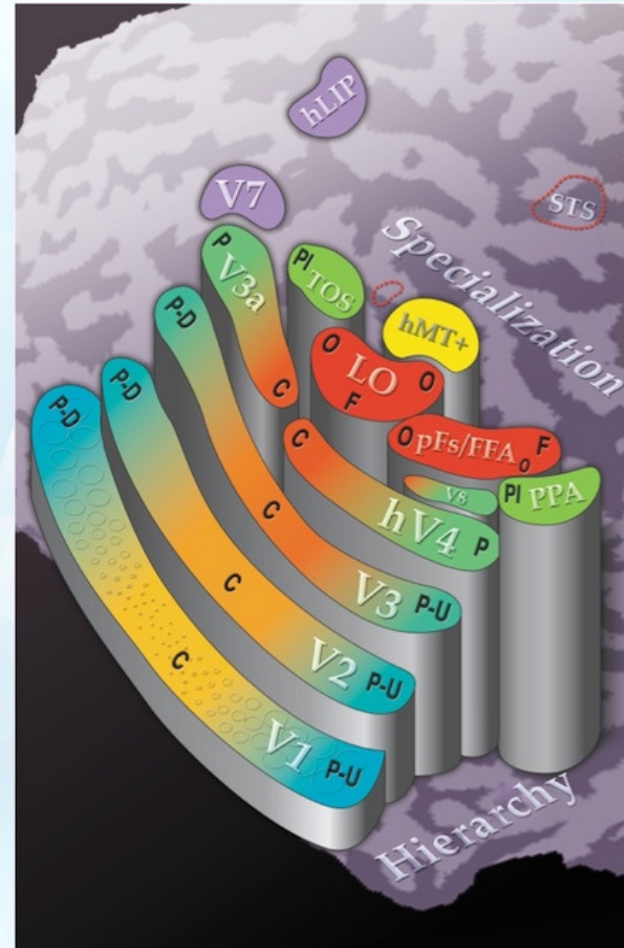
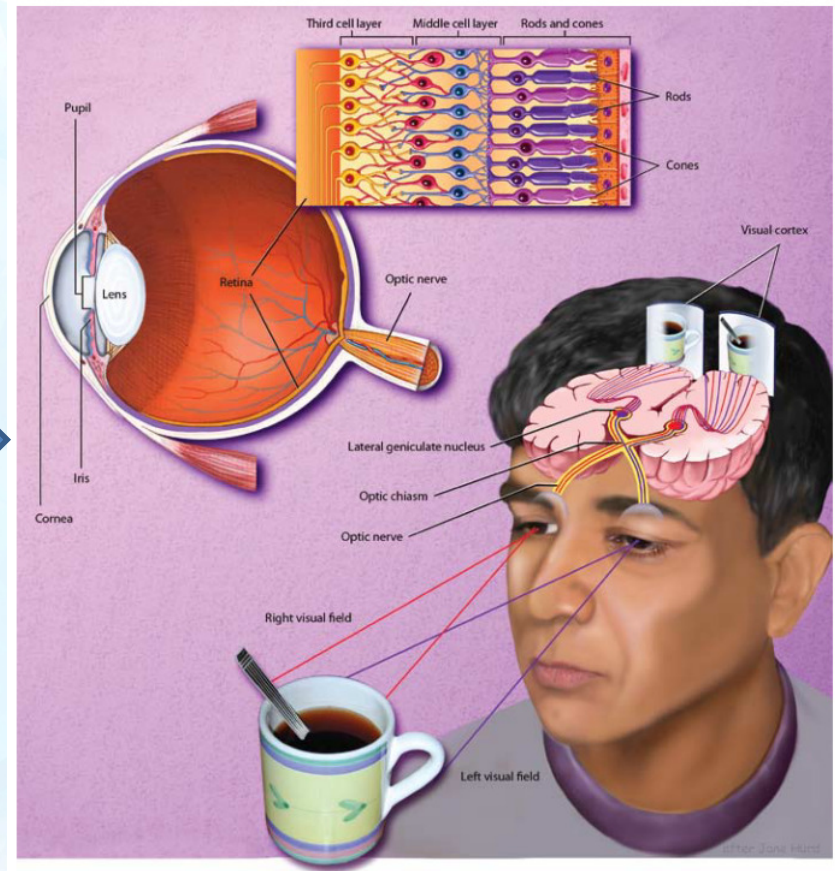
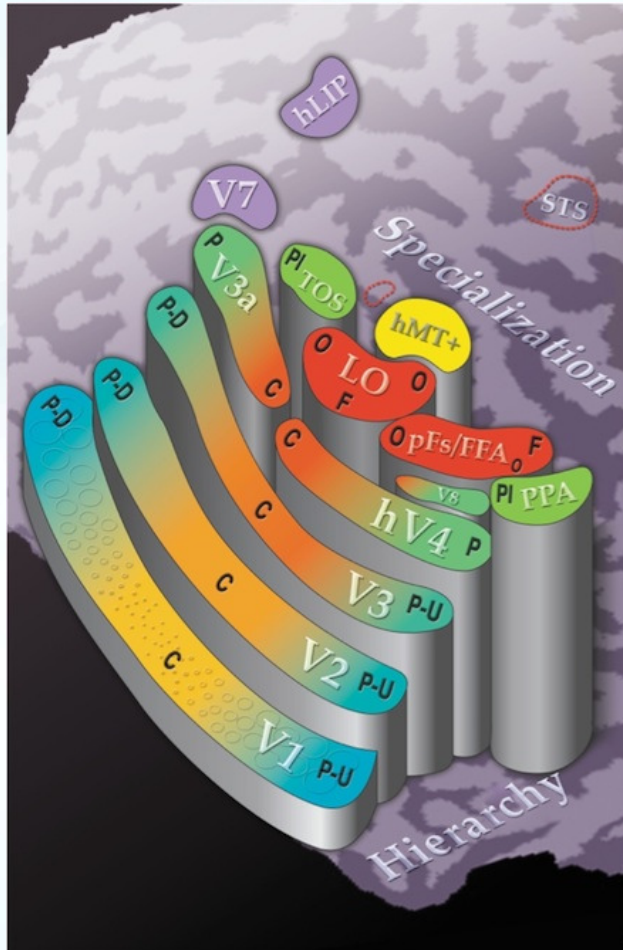


Figure 11. The projections of the small (P cells), and large (M cells) ganglion cells from the two eyes to parvocellular and magnocellular layers of the LGN respectively. Each eye projects to alternating layers as seen in the autoradiogram (right).

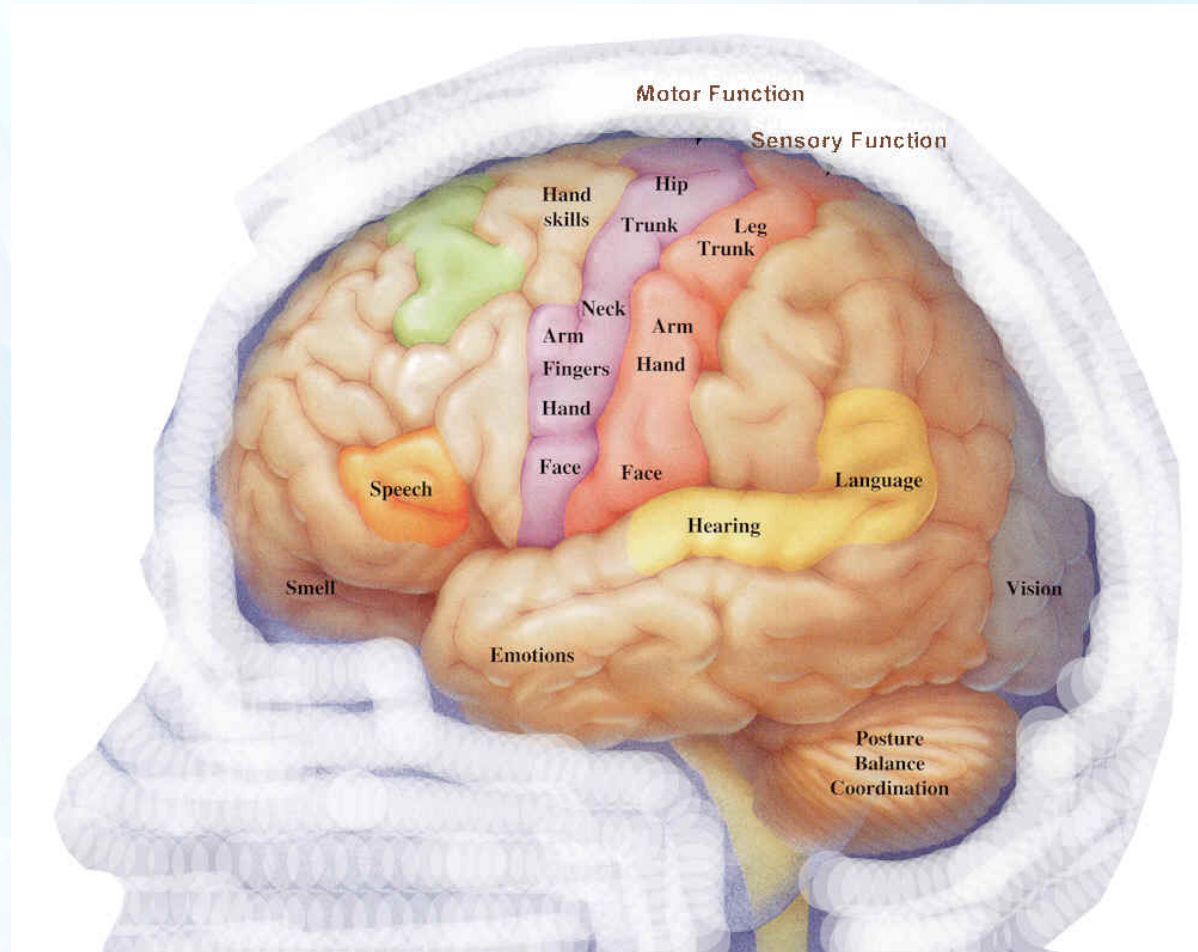
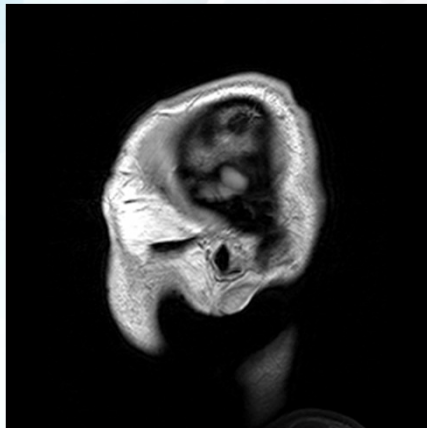




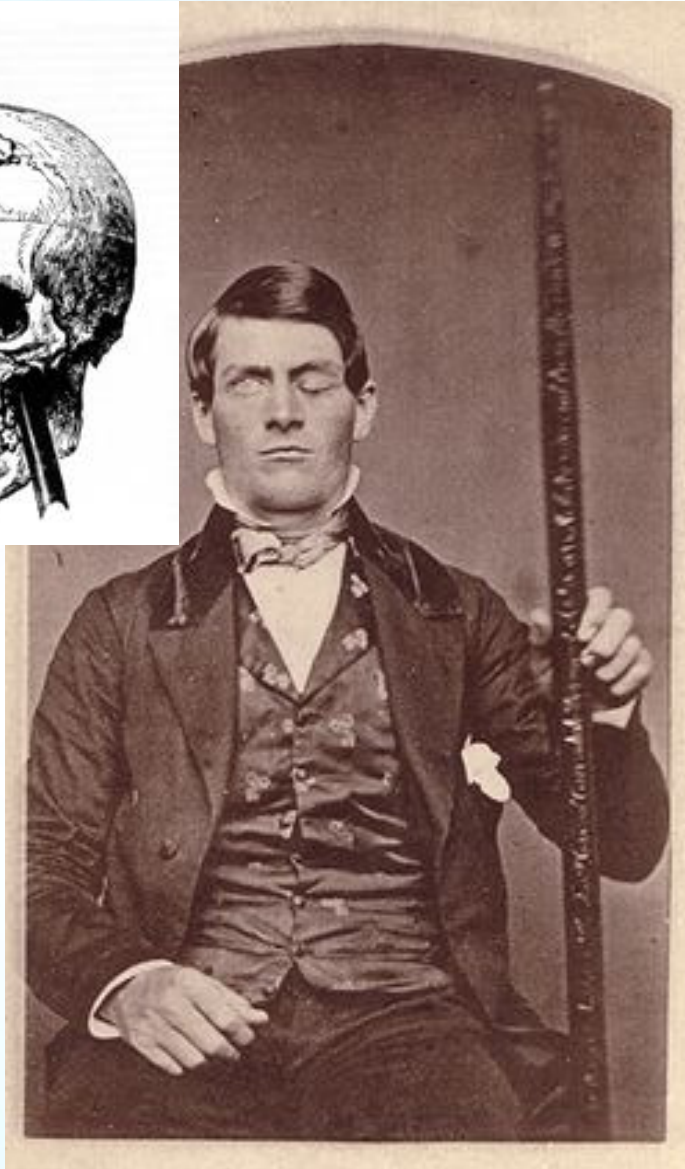
# Vision on the macroscopic scale



# Regional specialization



# September 13, 1848



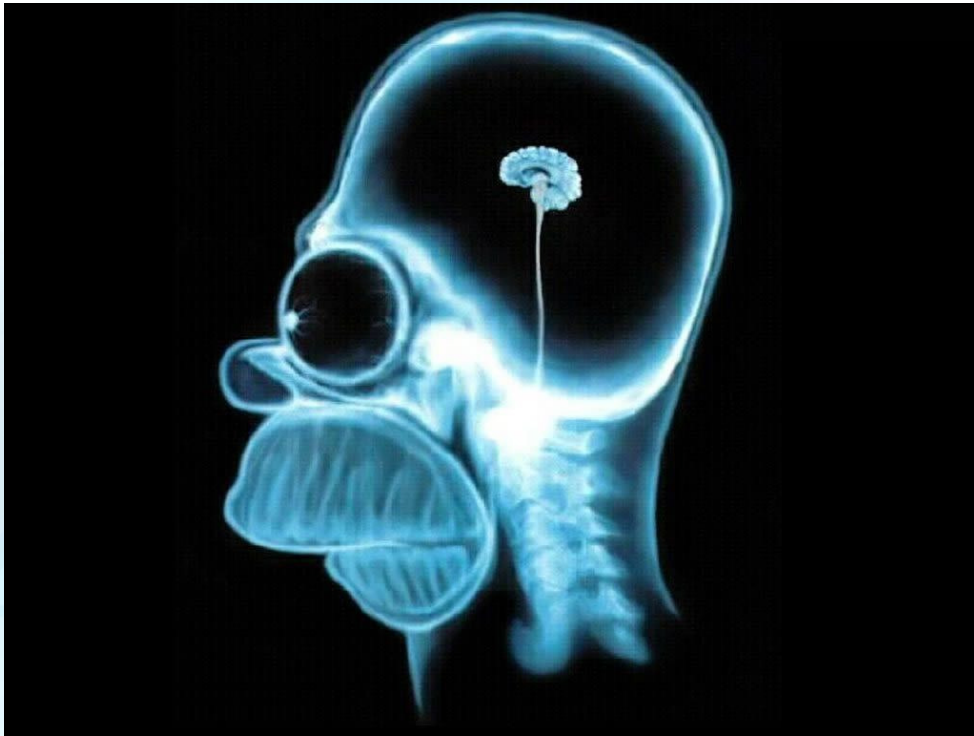
Mr Joseph Larkin Austin, eldest son of Mr Eleazer Austin, was found drowned near the south bridge in Salem; it is supposed he fell overboard between 2 and 3 o'clock in the morning, while fishing.

*Horrible Accident.*—As Phinoss P. Gage, a foreman on the railroad in Cavendish, was yesterday engaged in tankia for a blast, the powder exploded, carrying an iron instrument through his head an inch and a fourth in circumference, and three feet and eight inches in length, which he was using at the time. The iron entered on the side of his face, shattering the upper jaw, and passing back of the left eye, and out at the top of the head.

The most singular circumstance connected with this melancholy affair is, that he was alive at two o'clock this afternoon, and in full possession of his reason, and free from pain —*Ludlow, Vt., Union.*

The chief of the Philadelphia dogkillers, a black man named George Horsey, attempted to kill his wife. He broke into her room armed with a pistol and knife; she threw herself out of the second story window to escape, breaking her leg in the fall; he pursued her, and attacked and injured her severely. She was taken to the hospital. Horsey was fully committed for trial.

The *Boston Post*, September 21, 1848



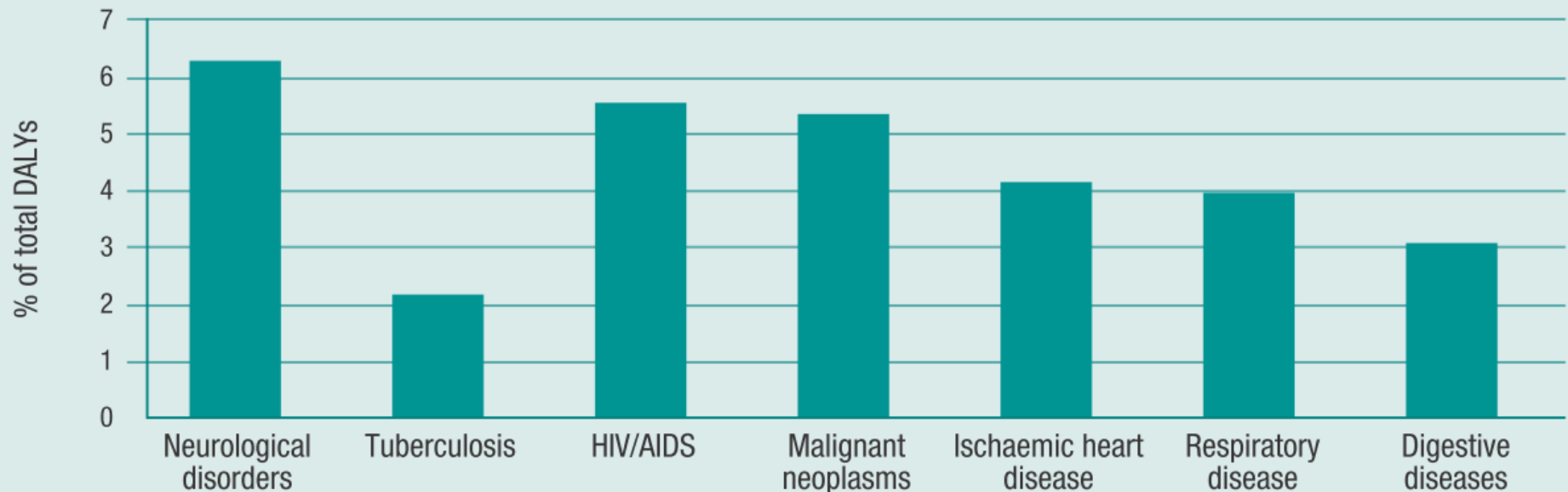
Presented clip



Clip reconstructed from brain activity



# Important disease group



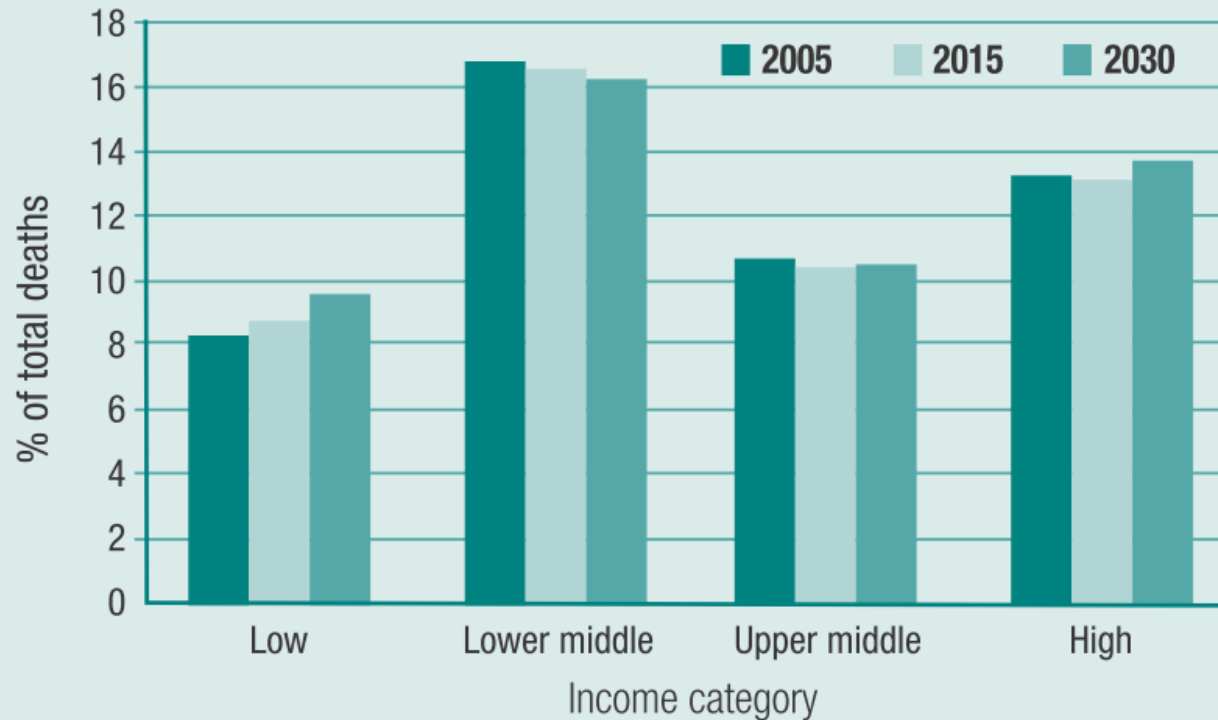
a GBD cause categories  
b Neuropsychiatric plus other categories

*WHO Global Burden of Disease 2005*

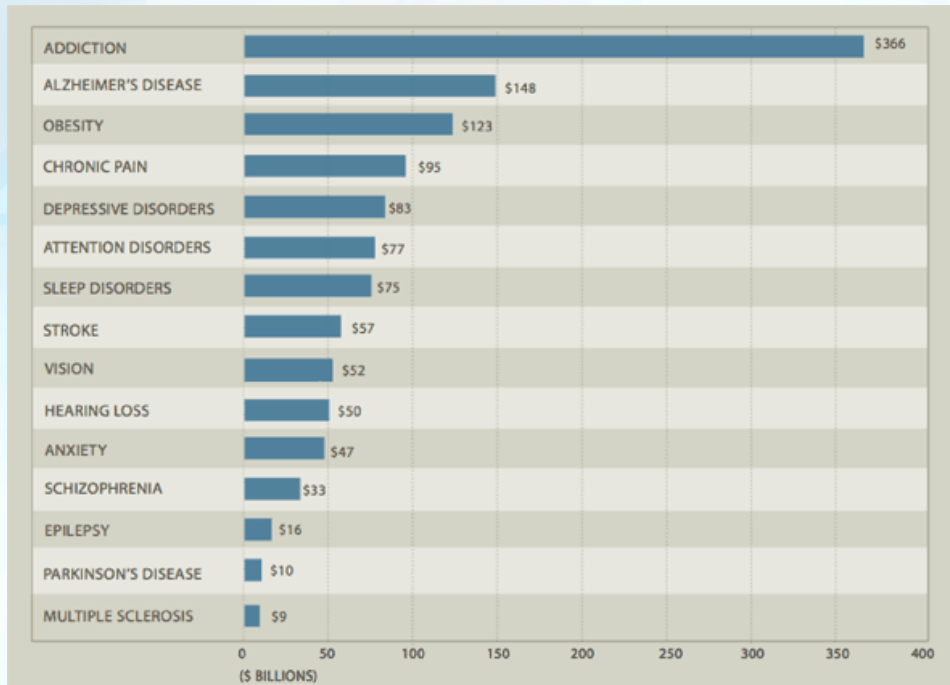
DALY = Disease-Adjusted Life Years, a total measure of the impact of a disease  
= [ Number of deaths ] x [ Years of life lost ] + [ Number of non-fatal cases ]  
x [ Disability weight ] x [ Duration of disease ]

# First-world problem

Figure 2.6 Neurological disorders as percentage of total deaths for 2005, 2015 and 2030 across World Bank income category



# Cost of brain disorders



# Neurologic diseases

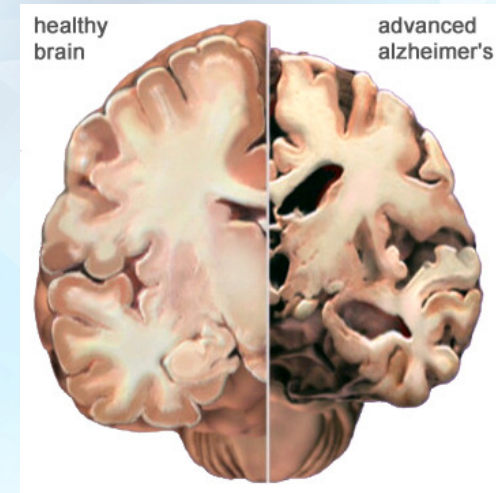
## Paroxysmal diseases

- Epilepsy
- Migraine
- Sleep disorders
- Cerebrovascular disorders
- Ataxias



## Neurodegenerative diseases

- Alzheimer's
- ALS
- Huntington's
- Parkinson



Neuropsychiatric  
(e.g. schizophrenia)

Neurodevelopmental  
(e.g. autism)



# Symptoms overlap

## Paroxysmal

Episodic ataxia



## Neurodegenerative

Spinocerebellar ataxia

Hemiplegic migraine



Stroke

# Genetics of neurological diseases in the Pre-GWAS era

- SOD-1 in ALS
  - Identified in 1991
  - Explain around 20%
- APOEe4 in Alzheimer's
  - Identified in 1993
  - Two alleles -> risk increase 10x – 30x

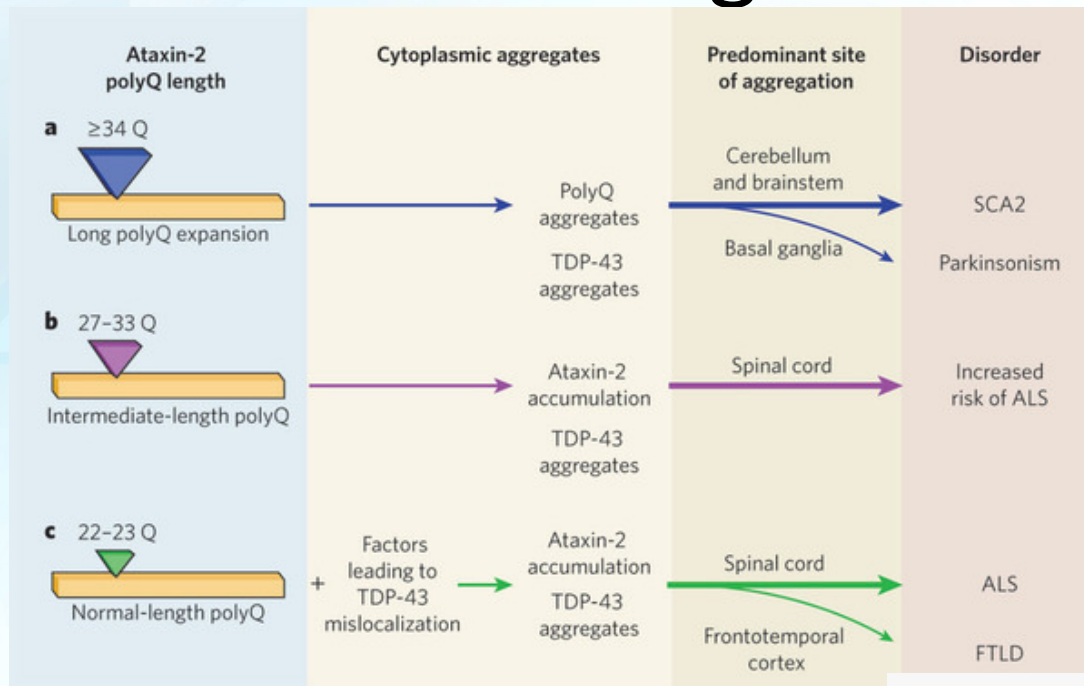


Stephen Hawking

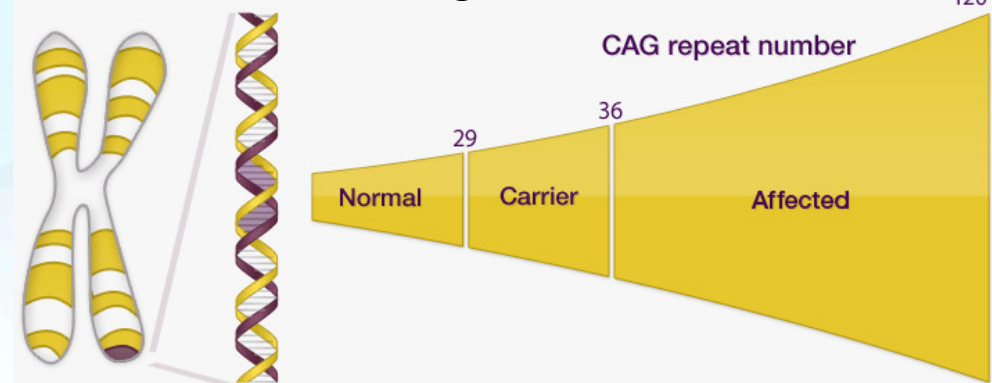


Terry Pratchett

# Extended repeats in neurodegenerative diseases



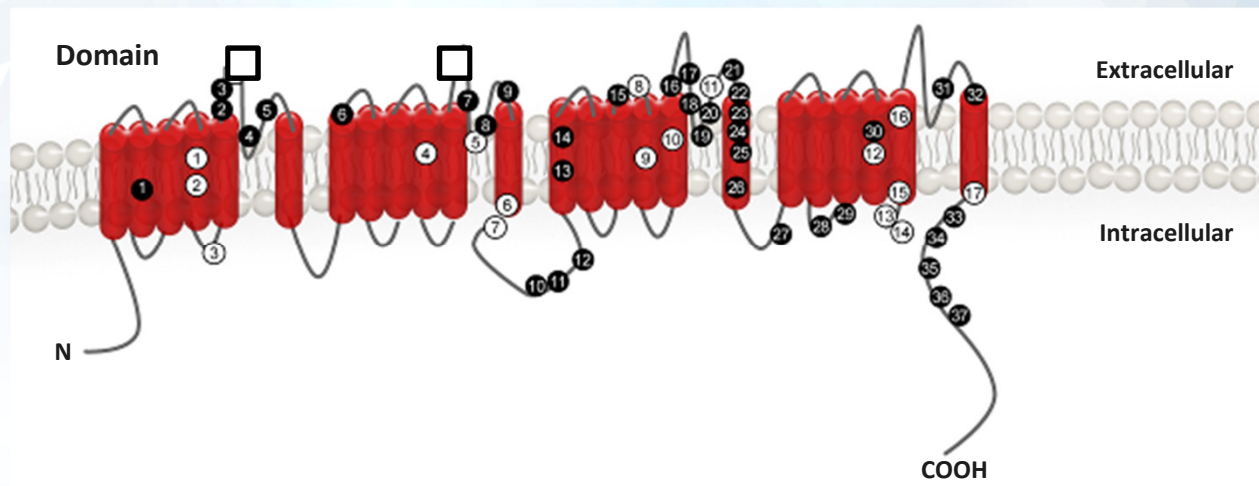
## Huntington's disease



# Genetic overlap

## CACNA1A

P/Q voltage-gated  $\text{Ca}^{2+}$  channel



Familial hemiplegic  
migraine mutations ○

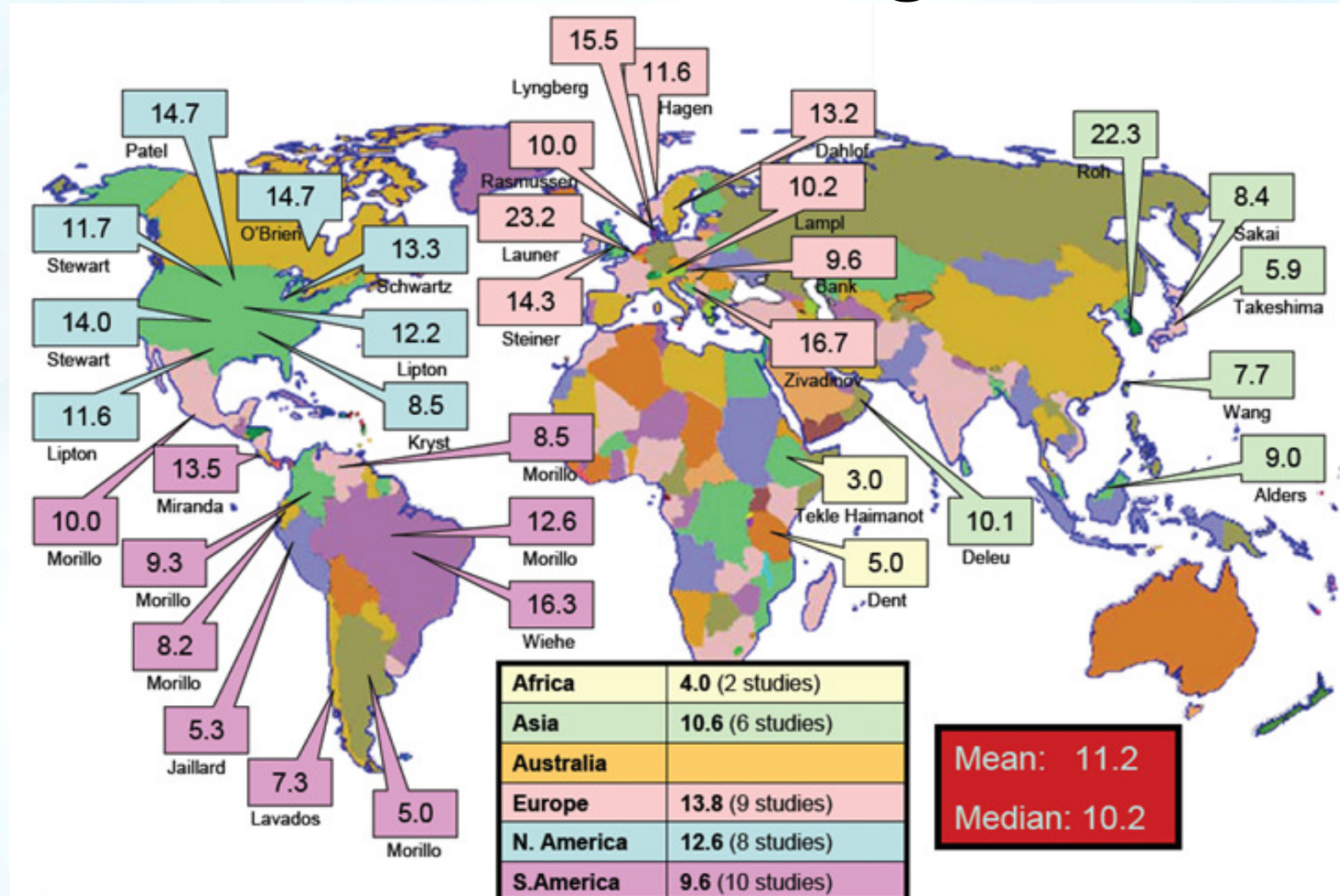
Episode ataxia  
mutations ●

Spinocerebellar  
ataxia □

# Headache



# Prevalence of Migraine

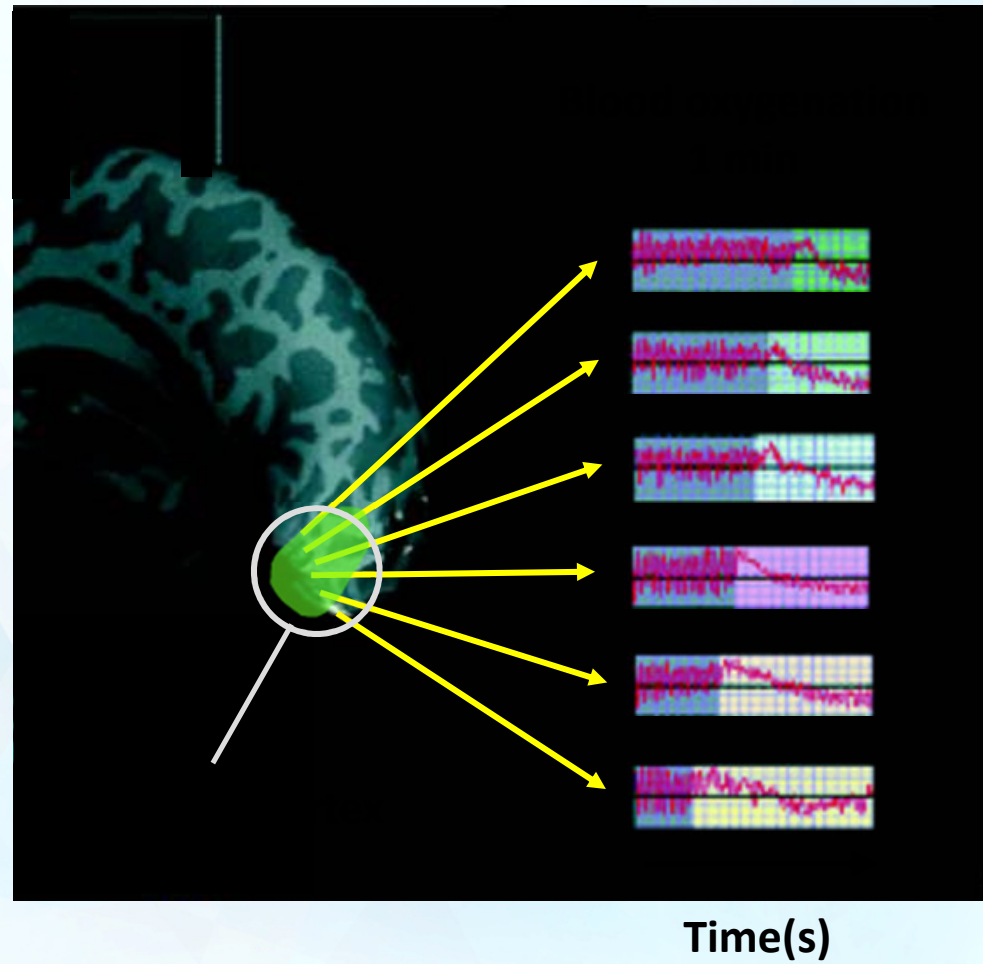
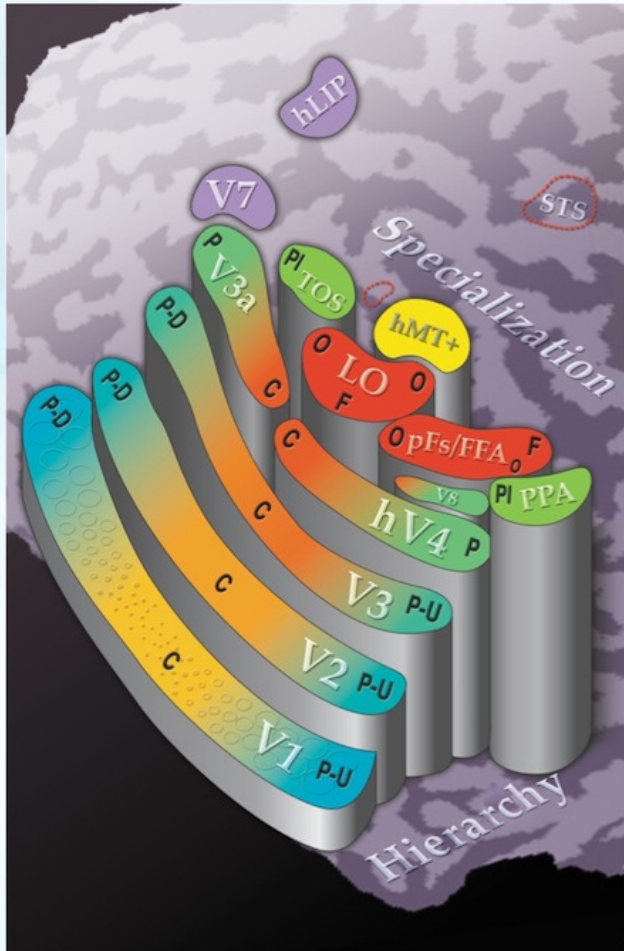


# Familial Hemiplegic Migraine (FHM)

	<b>Gene</b>	<b>Protein</b>	<b>Consequence</b>
FHM-1	<i>CACNA1A</i>	P/Q Ca <sup>2+</sup> channels	↑ presynaptic Ca <sup>2+</sup>
FHM-2	<i>ATP1A2</i>	Na <sup>+</sup> /K <sup>+</sup> -ATPase	↓ K <sup>+</sup> and glutamate clearance
FHM-3	<i>SCN1A</i>	Na <sup>+</sup> channel	Persistent Na <sup>+</sup> influx

ATPase = adenosine triphosphatase.

# Cortical Spreading Depression





# What the patient sees



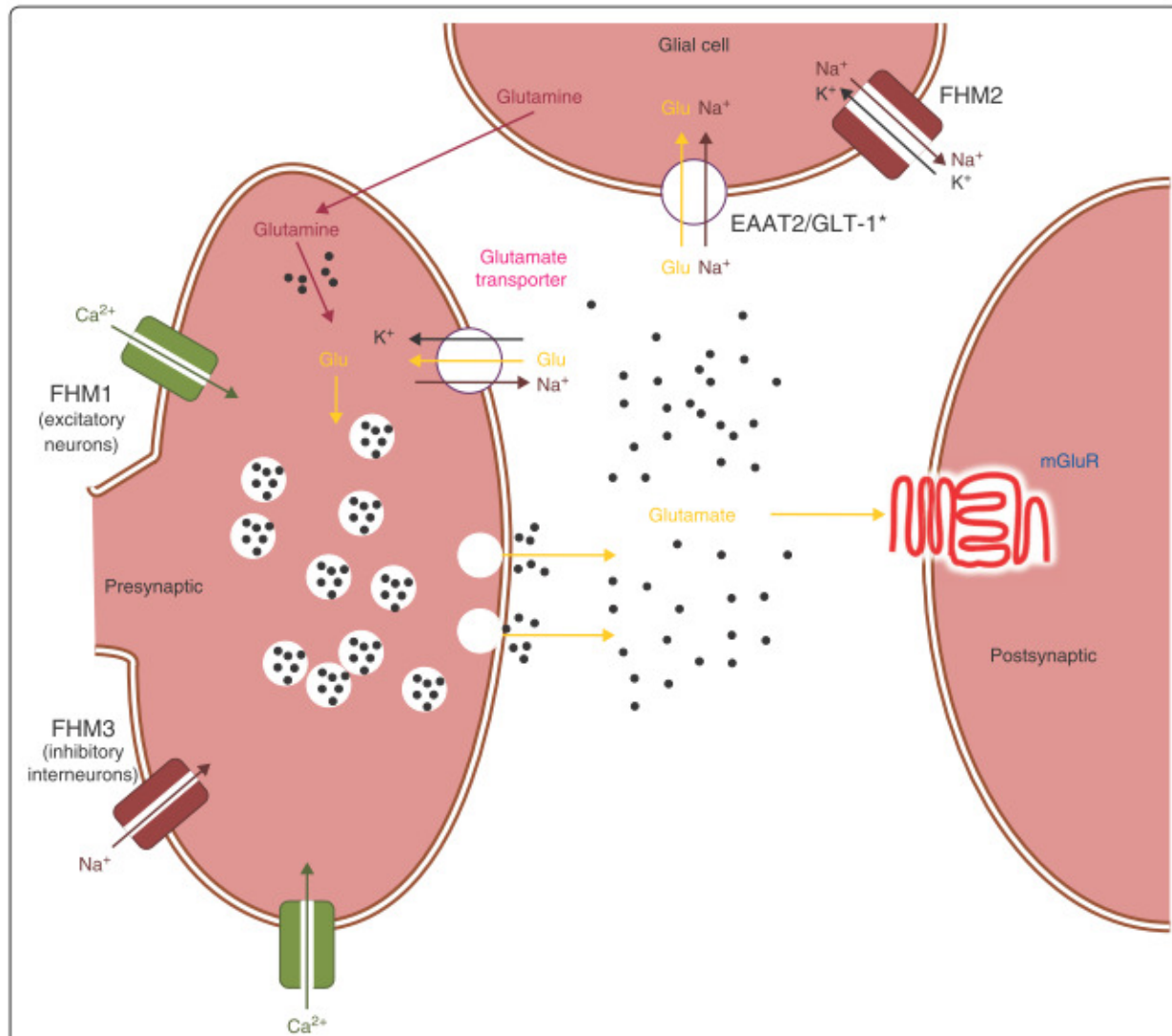
# First GWAS of migraine

LETTERS

nature  
genetics

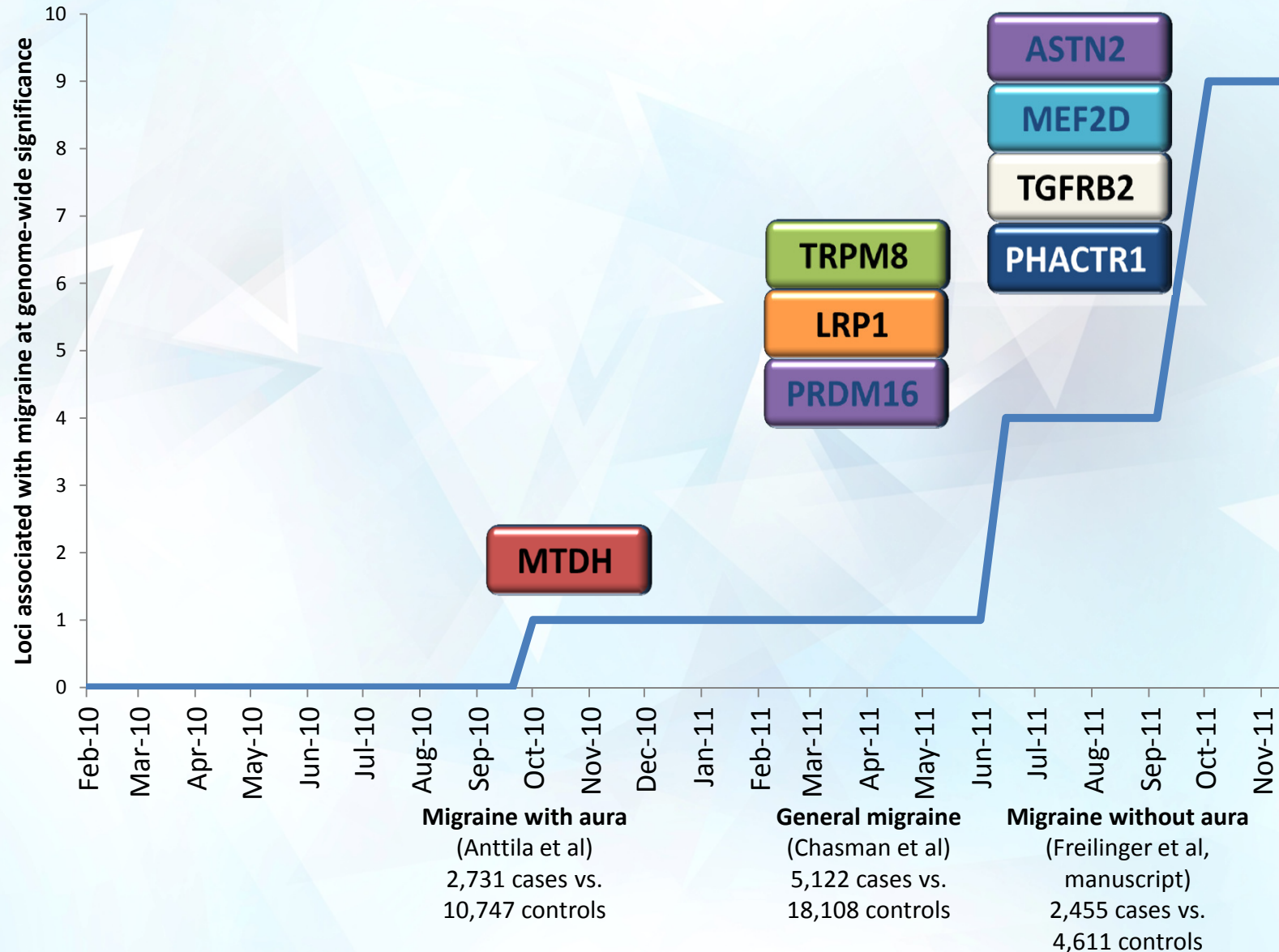
## Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1

Verner Anttila<sup>1,2,\*</sup>, Hreinn Stefansson<sup>3</sup>, Mikko Kallela<sup>4</sup>, Unda Todt<sup>5,6</sup>, Gisela M Terwindt<sup>7</sup>, M Stella Calafato<sup>1,8</sup>, Dale R Nyholt<sup>9</sup>, Antigone S Dimas<sup>1,10,11</sup>, Tobias Freilinger<sup>12,13</sup>, Bertram Müller-Myhsok<sup>14</sup>, Ville Artto<sup>4</sup>, Michael Inouye<sup>1,15</sup>, Kirsi Alakurtti<sup>1,2</sup>, Mari A Kaunisto<sup>2,16</sup>, Eija Hämäläinen<sup>1,2</sup>, Boukje de Vries<sup>15</sup>, Anine H Stam<sup>7</sup>, Claudia M Weller<sup>15</sup>, Axel Heinze<sup>17</sup>, Katja Heinze-Kuhn<sup>17</sup>, Ingrid Goebel<sup>5,6</sup>, Guntram Borck<sup>5,6</sup>, Hartmut Göbel<sup>17</sup>, Stacy Steinberg<sup>3</sup>, Christiane Wolf<sup>14</sup>, Asgeir Björnsson<sup>3</sup>, Gretar Gudmundsson<sup>18</sup>, Malene Kirchmann<sup>19</sup>, Anne Hauge<sup>19</sup>, Thomas Werge<sup>20</sup>, Jean Schoenen<sup>21</sup>, Johan G Eriksson<sup>16,22-24</sup>, Knut Hagen<sup>25</sup>, Lars Stovner<sup>25</sup>, H-Erich Wichmann<sup>26-28</sup>, Thomas Meitinger<sup>29,30</sup>, Michael Alexander<sup>31,32</sup>, Susanne Moebus<sup>33</sup>, Stefan Schreiber<sup>34,35</sup>, Yurii S Aulchenko<sup>36</sup>, Monique M B Breteler<sup>36</sup>, Andre G Uitterlinden<sup>37</sup>, Albert Hofman<sup>36</sup>, Cornelia M van Duijn<sup>36</sup>, Päivi Tikka-Kleemola<sup>38</sup>, Salli Vepsäläinen<sup>4</sup>, Susanne Lucae<sup>14</sup>, Federica Tozzi<sup>39</sup>, Pierandrea Muglia<sup>39,40</sup>, Jeffrey Barrett<sup>1</sup>, Jaakko Kaprio<sup>2,24,41</sup>, Markus Färkkilä<sup>4</sup>, Leena Peltonen<sup>1,2,42,48</sup>, Kari Stefansson<sup>3</sup>, John-Anker Zwart<sup>25,43</sup>, Michel D Ferrari<sup>7</sup>, Jes Olesen<sup>19</sup>, Mark Daly<sup>42</sup>, Maija Wessman<sup>2,16</sup>, Arn M J M van den Maagdenberg<sup>7,15</sup>, Martin Dichgans<sup>12,13</sup>, Christian Kubisch<sup>5,6,44,45</sup>, Emmanouil T Dermitzakis<sup>11</sup>, Rune R Frants<sup>15</sup> & Aarno Palotie<sup>1,2,42,46,47</sup> for the International Headache Genetics Consortium

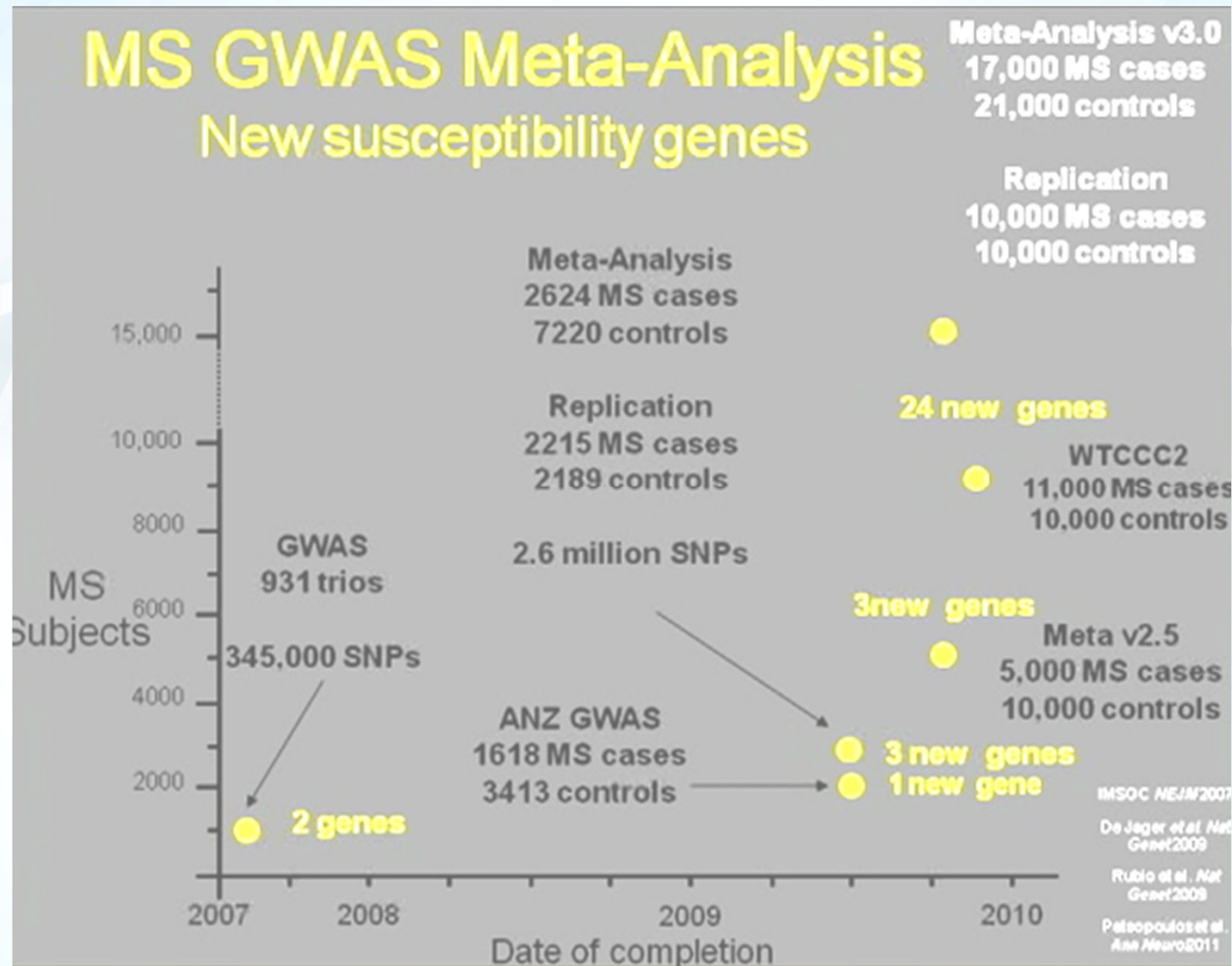


**Figure 1. Localization and effect of a variant identified in the recent genome-wide association study of migraine in synaptic transmission, together with the previously known mutations in familial hemiplegic migraine (FHM: genes are FHM1, *CACNA1A*; FHM2, *ATP1A2*; FHM3, *SCN1A*). The asterisk indicates the excitatory amino acid transporter 2 (EAAT2/GLT-1) recently linked to migraine. Glu, glutamate; FHM1-3, products of genes reported for familial hemiplegic migraine; mGluR, metabolic glutamate receptor. Black dots indicate the accumulation of the neurotransmitter glutamate in the synaptic cleft.**

# First eight reported migraine loci

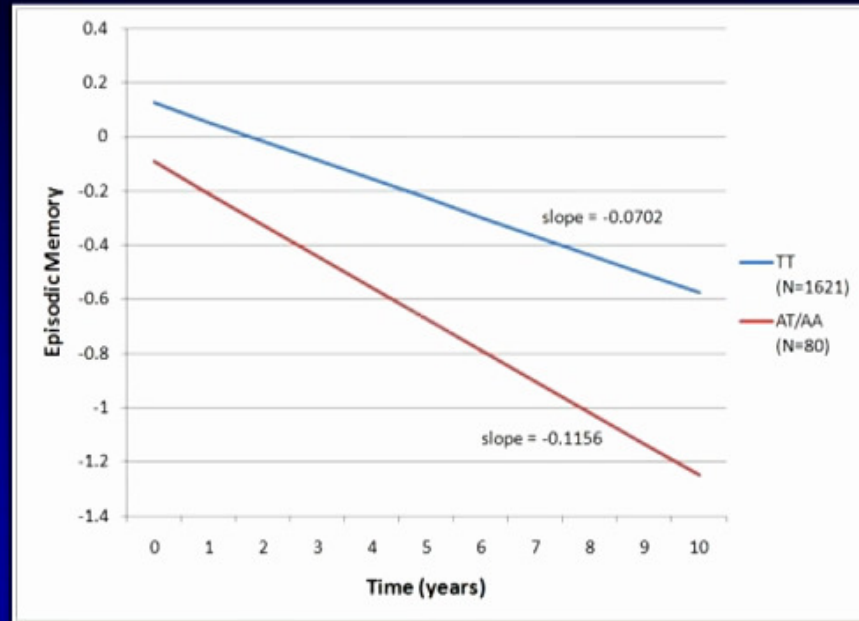


# Multiple sclerosis in the GWAS era



# GWAS findings refine old hits

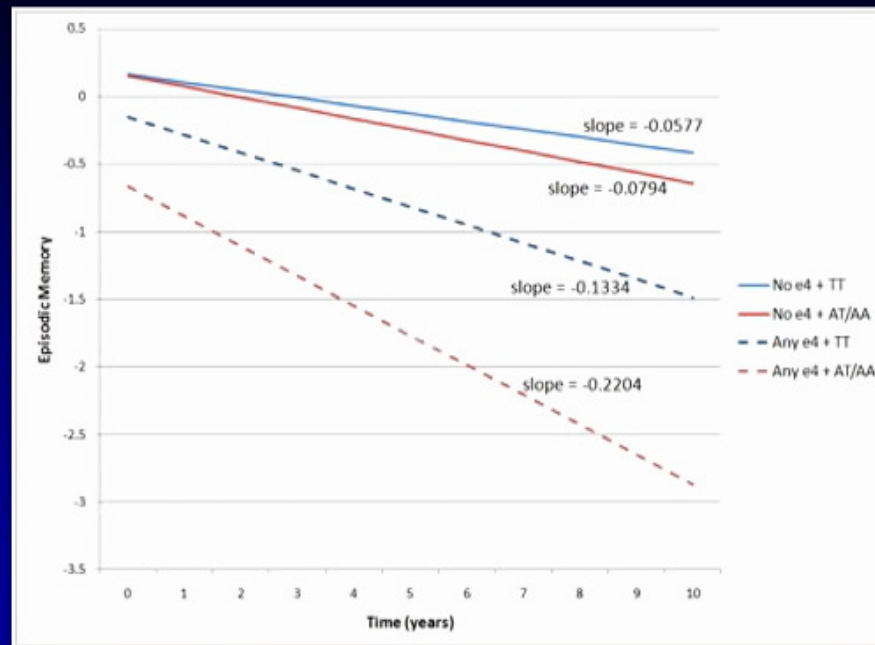
## CR1 : Mean cognitive trajectories



rs4844609<sup>A</sup> is the allele associated with increased risk of AD

# GWAS findings refine old hits

## CR1 : Mean cognitive trajectories



rs4844609<sup>A</sup> and APOE e4 are the alleles associated with increased risk of AD

# Summary

- Genetics of common brain disorders are still poorly understood
- Lifestyle factors modulate risk
- Genetics provides a useful shortcut to identifying those at risk

