Huntington's Disease Society of America

"How the HD Gene works"

Jeff Carroll PhD

Western Washington University

Ed Wild MD PhD

UCL

HDBuzz

We don't know.

How does HD science work?

Jeff Carroll PhD

Western Washington University

Ed Wild MD PhD

UCL

This, we know.

Presenter Disclosures

Dr Ed Wild and Dr Jeff Carroll

The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

No relationships to disclose
or list

Huntington's Disease Society of America

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HDBUZZ
HDBuzz
Huntington's disease research news.
In plain language.
Written by scientists.
For the global HD community.
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Unbiased and independent
Endorsed by all major HD associations
12 languages
PDFs to download, print & share

Ode to HD research

Ronald Roberts

On top of all the stress and strain,
The fears, the loss, the psychic drain,
Now comes the jargon of the lab
As science shares its chatty gab.

Now one more way our stomachs churn,
And one more language we must learn.

Ode to HD research

Ronald Roberts

Take ganglionic eminence
And other terms that make no sense.
There's not a one of them routine.
Explain striatal dopamine.
There's C-A-G and R-N-A
With dorsal caudate interplay,
And neurons that degenerate,
And aspartate and glutamate!
Excitotoxic neuron death-
There's hardly time to catch your breath.

Ode to HD research

Ronald Roberts

The other losses that depress
Are worse by far than this, I guess.
But still this abstract language mess
Is one more insult, I confess!

Before science, how'd we get here?

THE

MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

Original Department.

Communications.

ON CHOREA.

By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of

520

Reichsgesetzblatt

Teil I

1933	Ausgegeben zu Berlin, den 25. Juli 1933	Nr. 86

Inhalt: Gesetz zur Verhütung erbkranken Nachwuchses. Vom 14. Juli 1933 ..... S. 529
Erste Verordnung zur Durchführung des Gesetzes über die Gleichstellungsgesetzgebung. Vom 20. Juli 1933 ..... S. 531
Verordnung über die Errichtung einer medizinischen Prüfungskommission. Vom 22. Juli 1933 ..... S. 531
Verordnung über Zolländerungen und Notzollscheine. Vom 24. Juli 1933 ..... S. 533
Verordnung zur Durchführung des Gesetzes über die Verleihung des Ehrenkreuzes für die nationale Erhebung (Ehrenkreuz-Verordnung). Vom 25. Juli 1933 ..... S. 535

Gesetz zur Verhütung erbkranken Nachwuchses. Vom 14. Juli 1933.

Die Reichsregierung hat das folgende Gesetz beschlossen, das hiermit verkündet wird:

§ 1

(1) Wer erbkrank ist, kann durch chirurgischen Eingriff unfruchtbar gemacht (sterilisiert) werden, wenn nach den Erfahrungen der ärztlichen Wissenschaft mit großer Wahrscheinlichkeit zu erwarten ist, daß seine Nachkommen an schweren körperlichen oder geistigen Erbschäden leiden werden.

(2) Erbkrank im Sinne dieses Gesetzes ist, wer an einer der folgenden Krankheiten leidet:

1. angeborenem Schwachsinn,
2. Schizophrenie,
3. zirkulärem (manisch-depressivem) Irresein,
4. erblicher Fallsucht,
5. erblichem Veitstanz (Huntingtonsche Chorea),
6. erblicher Blindheit,
7. erblicher Taubheit,
8. schwerer erblicher körperlicher Mißbildung.

(3) Ferner kann unfruchtbar gemacht werden, wer an schwerem Alkoholismus leidet.

§ 2

(1) Den Antrag ist eine Bescheinigung eines für das Deutsche Reich approbierten Arztes beizufügen, daß der Unfruchtbarzumachende über das Wesen und die Folgen der Unfruchtbarmachung aufgeklärt worden ist.

(2) Der Antrag kann zurückgenommen werden.

§ 3

Die Unfruchtbarmachung können auch beantragen

1. der beamtete Arzt,
2. für die Insassen einer Kranken-, Heil- oder Pflegeanstalt oder einer Strafanstalt der Anstaltsleiter.

§ 4

Der Antrag ist schriftlich oder zur Niederschrift der Geschäftsstelle des Erbgesundheitsgerichts zu stellen. Die dem Antrag zu Grunde liegenden Tatsachen sind durch ein ärztliches Gutachten oder auf andere Weise glaubhaft zu machen. Die Geschäftsstelle hat dem beamteten Arzt von dem Antrag Kenntnis zu geben.

§ 5

Zuständig für die Entscheidung ist das Erbgesundheitsgericht, in dessen Bezirk der Unfruchtbarzumachende seinen allgemeinen Gerichtsstand hat.

§ 6

(1) Das Erbgesundheitsgericht ist einem Amts-

“Law for the Prevention of Genetically Diseased Offspring”

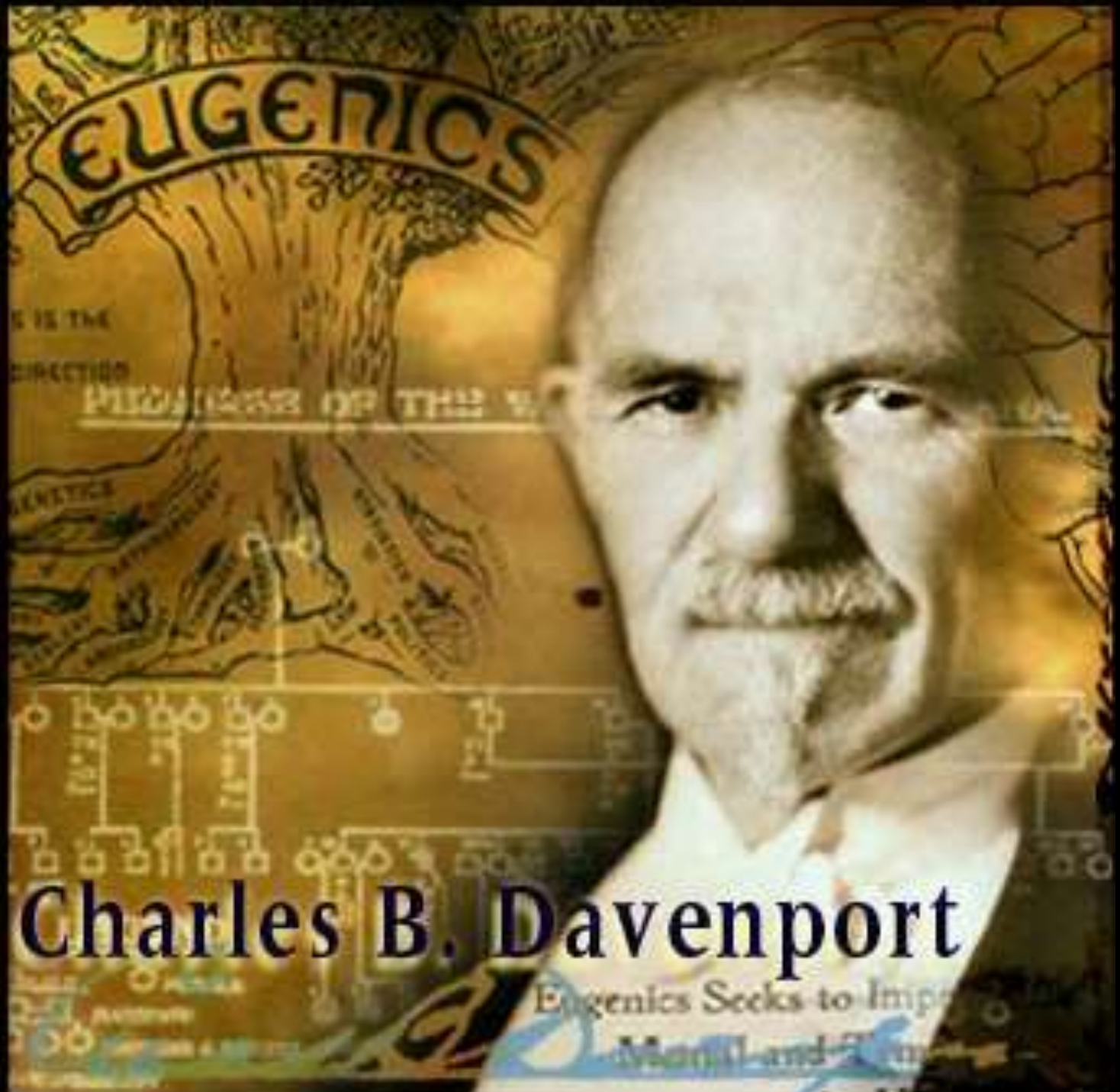
(1) Any person suffering from a hereditary disease ***may be rendered incapable of procreation by means of a surgical operation*** *(sterilization)*, if the experience of medical science shows that it is highly probable that his descendants would suffer from some serious physical or mental hereditary defect.

(2) For the purposes of this law, any person will be considered as hereditarily diseased who is suffering from any one of the following diseases: –

….

(5) Hereditary Chorea

…


EUGENICS
Charles B. Davenport

Huntington's Disease Society of America

M Y C H H H O O O R R E E A A Y E

WORDS & MUSIC: WOODY GUTHRIE

I DONT HAFTA PAY YOU BARMAN A DIME
MY OLD CHOREA MAKES ME DIZZY ALL TH' TIME
GOD MAKES ALL KINDSA SICKNESS AND MIZERY
AN' CHOREA FITS ME JUST FINE
NO I DONT HAFTA PAY YOU BARTENDERS ONE DIME
CHOREEAY MAKES ME DRUNKY AN' DRUNK ALLA TH' TIME
GOD MAKES ALL KINDSA SICKYNESS AN' MISERY
MY CHOREAEAEA FITS ME FINE

MY CHOREEY AINTA KETCHIN AND I FEEL NO PAINS
JUSTA DIZZERY BLUNDERY STAGGERYWALK BUT ITS NOT MY BRAIN
GOD MAKES ALL KINDSA SICKERNESS AND MISERIES
AN' MY CHOREA SUITS ME JUST FINE
I'VE GOTTA STAGGER MY SIXTY SIX DOLLERS WORTH
B'FORE I C'N GIT MY PENSIUN CHECK CASH'D
GOD MAKES ALL KINDSA SICKERNESS AND MISERY
MY CHOREA FITS ME FINE

State Insane Asylum, Morris Plains, N. J.

Woody Guthrie Chooooreaaaye

Cell, Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

The Huntington's Disease Collaborative Research Group*

Summary

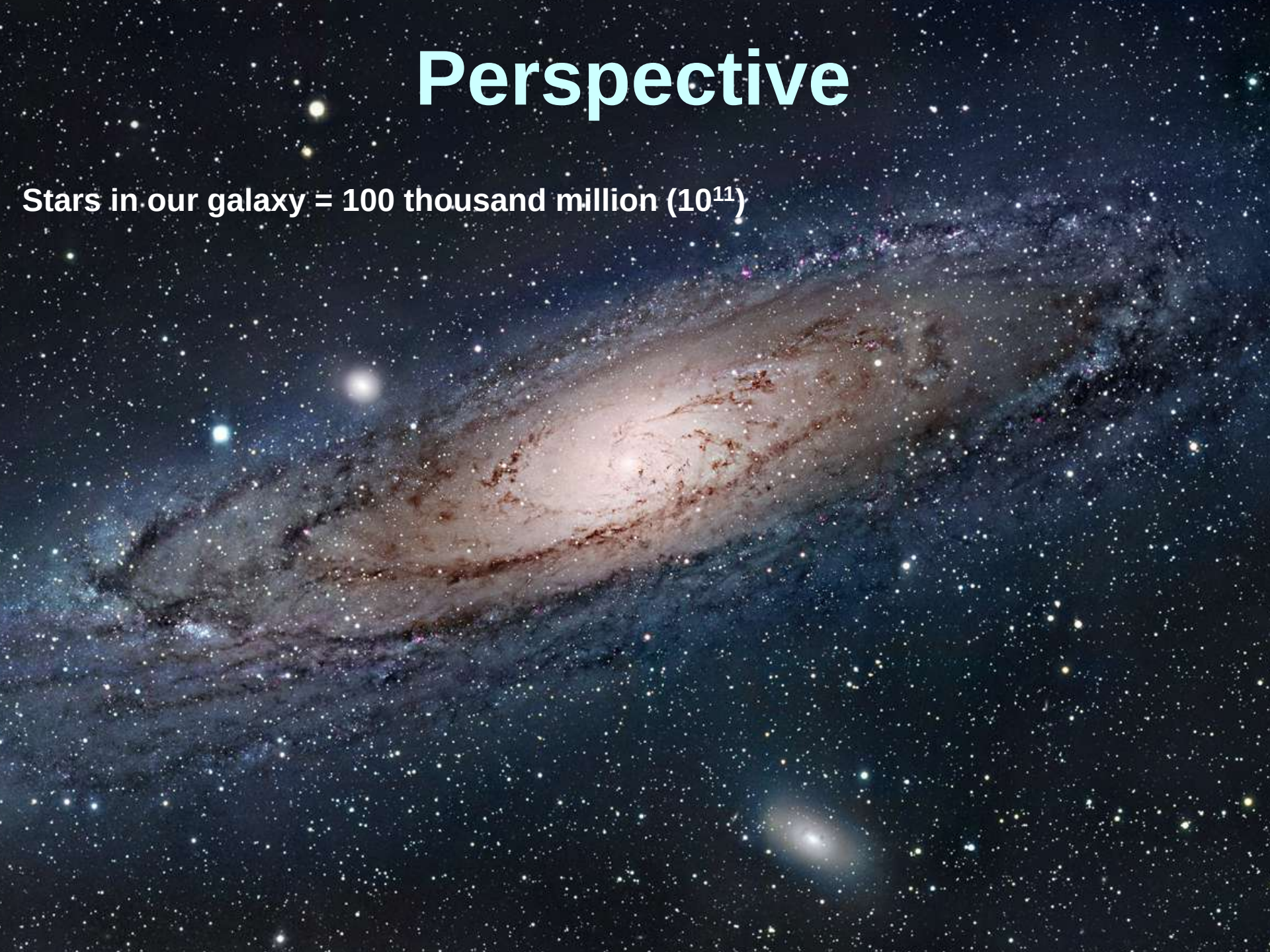
The Huntington's disease (HD) gene has been mapped in 4p16.3 but has eluded identification. We have used haplotype analysis of linkage disequilibrium to spotlight a small segment of 4p16.3 as the likely location of the defect. A new gene, IT15, isolated using cloned trapped exons from the target area contains a polymorphic trinucleotide repeat that is expanded and unstable on *HD* chromosomes. A $(CAG)_n$ repeat longer than the normal range was observed on *HD* chromosomes from all 75 disease families examined, comprising a variety of ethnic backgrounds and 4p16.3 haplotypes. The $(CAG)_n$ repeat appears to be located

Introduction

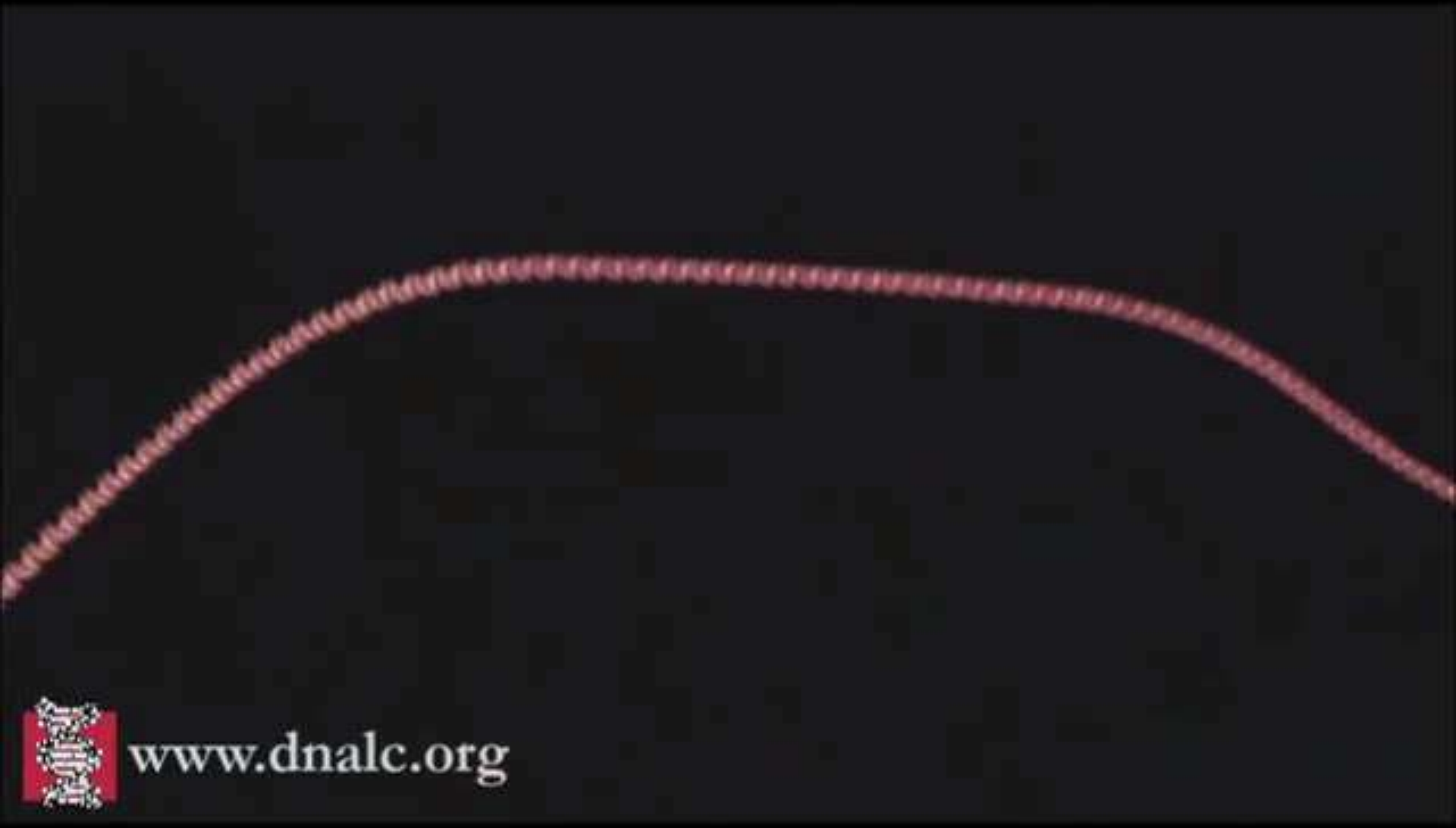
Huntington's disease (HD) is a progressive neurodegenerative disorder characterized by motor disturbance, cognitive loss, and psychiatric manifestations (Martin and Gusella, 1986). It is inherited in an autosomal dominant fashion and affects ~1 in 10,000 individuals in most populations of European origin (Harper et al., 1991). The hallmark of HD is a distinctive choreic movement disorder that typically has a subtle, insidious onset in the fourth to fifth decade of life and gradually worsens over a course of 10 to 20 years until death. Occasionally, HD is expressed in juveniles, typically manifesting with more severe symptoms including rigidity and a more rapid course. Juvenile onset of HD is associated with a preponderance of paternal transmission of the disease allele. The neuropathology of HD also displays a distinctive pattern, with selective loss of neurons that is most severe in the caudate

Lookout, here comes some science

Perspective



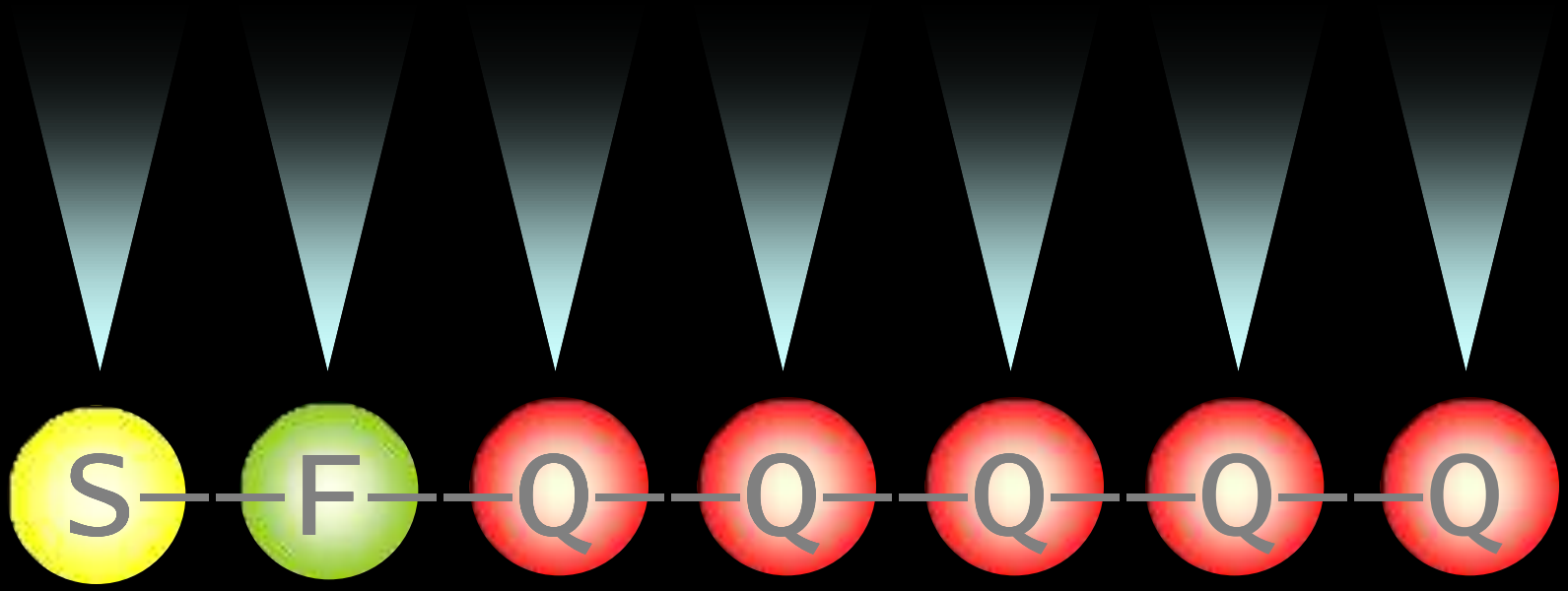
Stars in our galaxy = 100 thousand million (10^{11})


www.dnalc.org

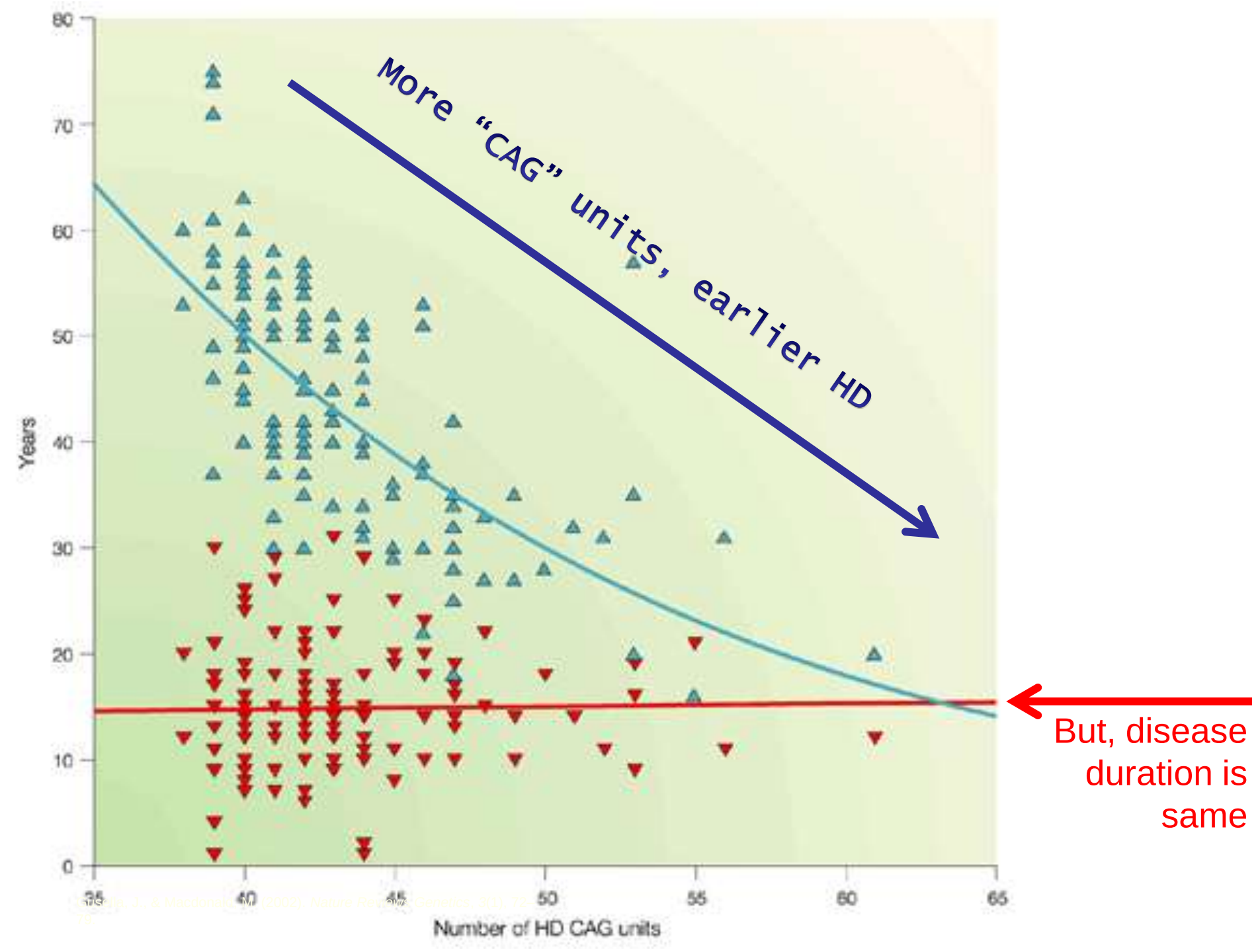

www.dnalc.org

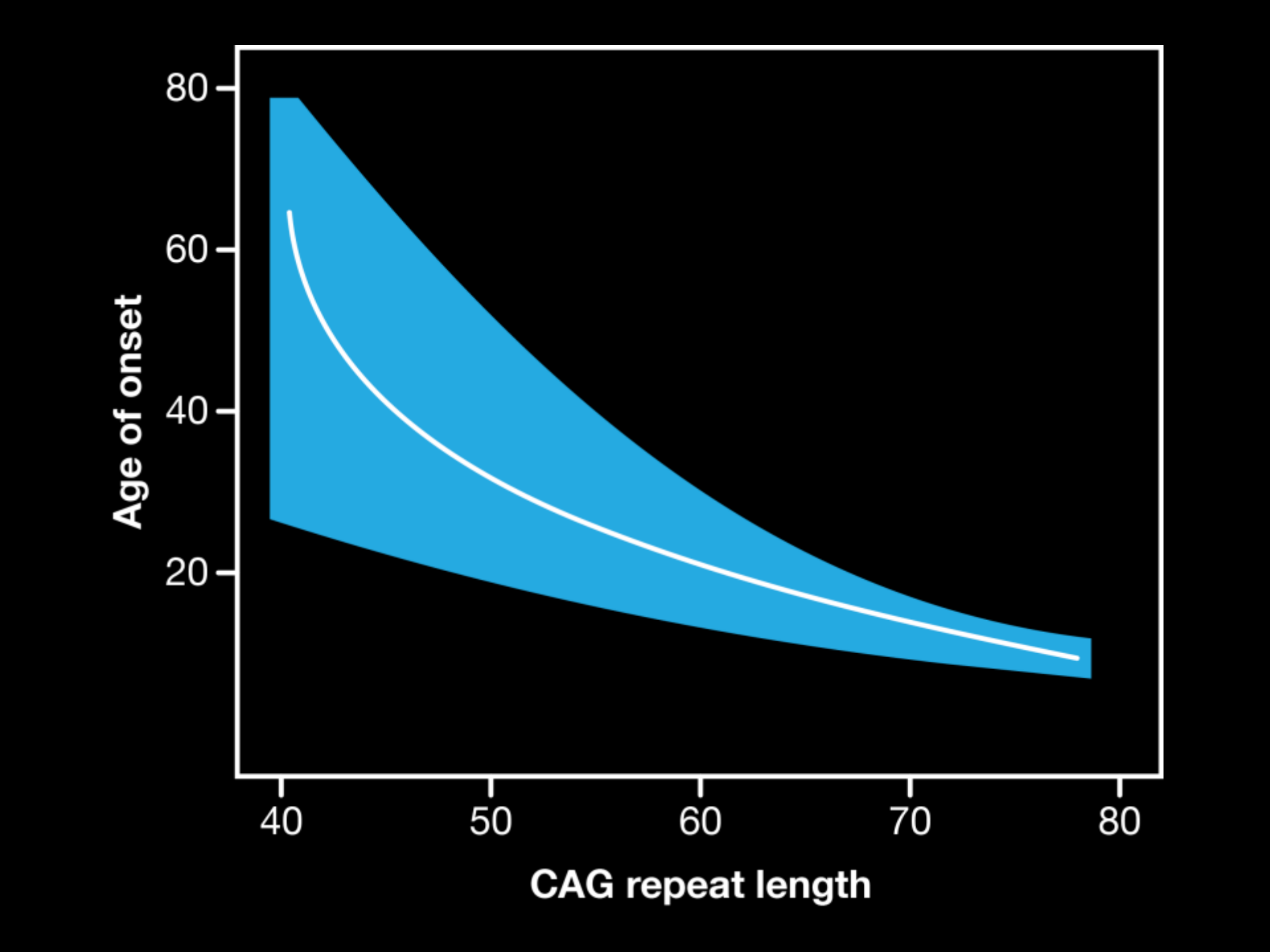
Gene

TCCTTCCAGCAGCAGCAGCAG



Protein


More "CAG" units, earlier HD
But, disease duration is same
Years
Number of HD CAG units
0
10
20
30
40
50
60
70
80
35
40
45
50
55
60
65


80
60
40
20
Age of onset
40
50
60
70
80
CAG repeat length

CAG “Expansion”

2

…CAGCAG…

7

…CAGCAGCAGCAGCAGCAG…

18

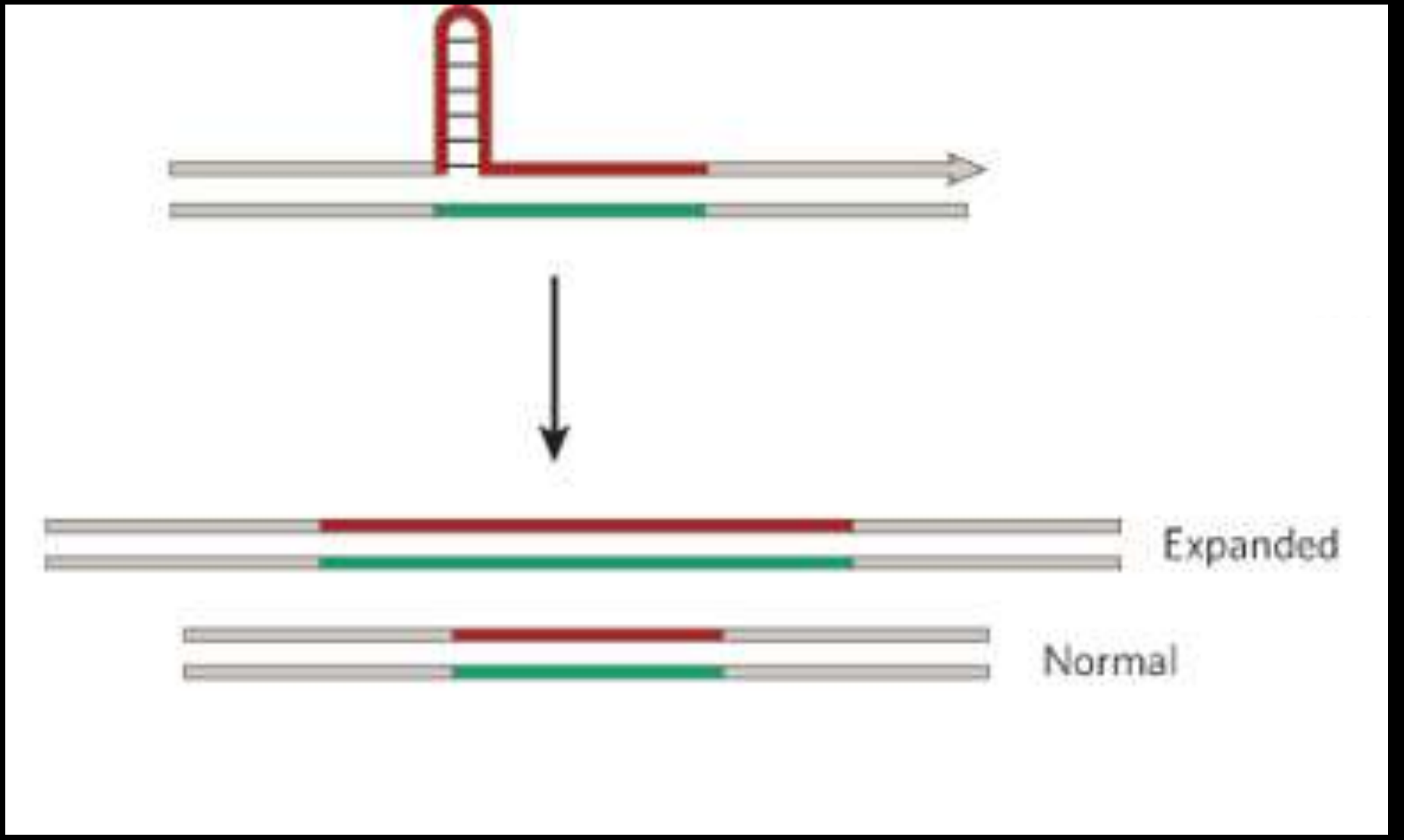
…CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG…

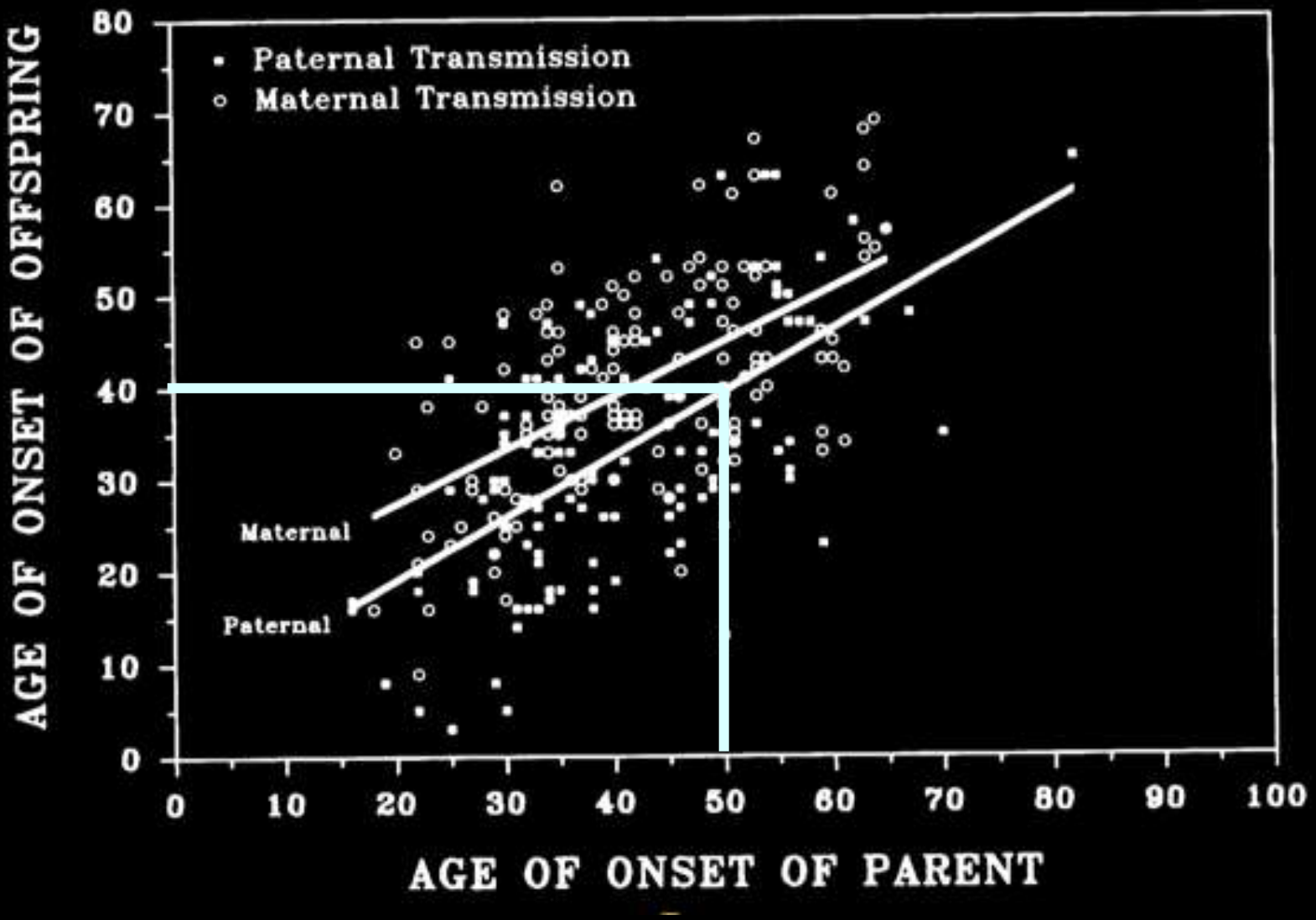
27

…CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG…

42

…CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG…


Expanded
Normal


Paternal Transmission
Maternal Transmission
Maternal
Paternal
AGE OF ONSET OF OFFSPRING
AGE OF ONSET OF PARENT
0
10
20
30
40
50
60
70
80
90
100

Ok, this all makes sense.

But how do all these extra CAG's kill brain cells?

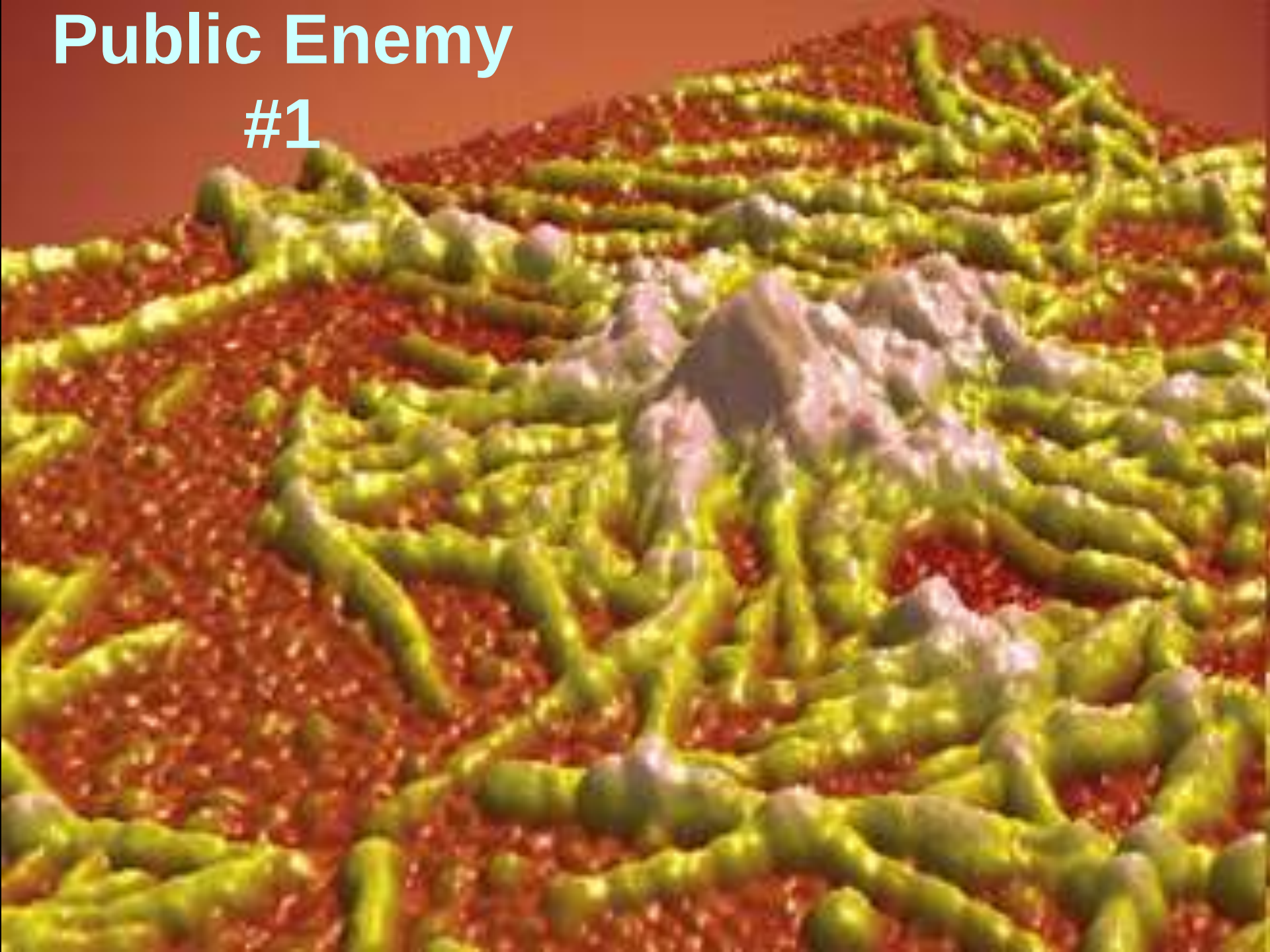
Normal huntingtin protein

Mutant huntingtin protein

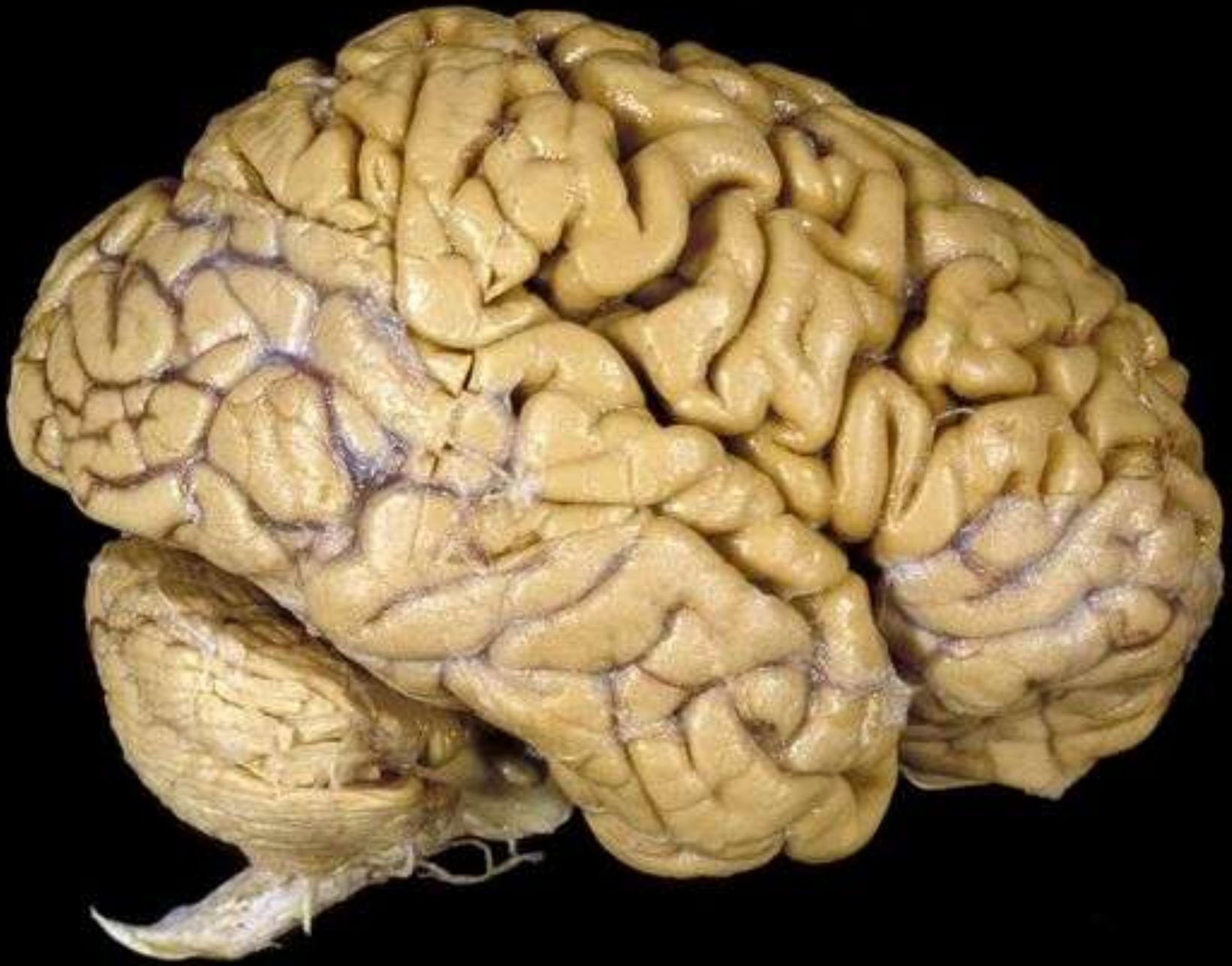
Change in shape

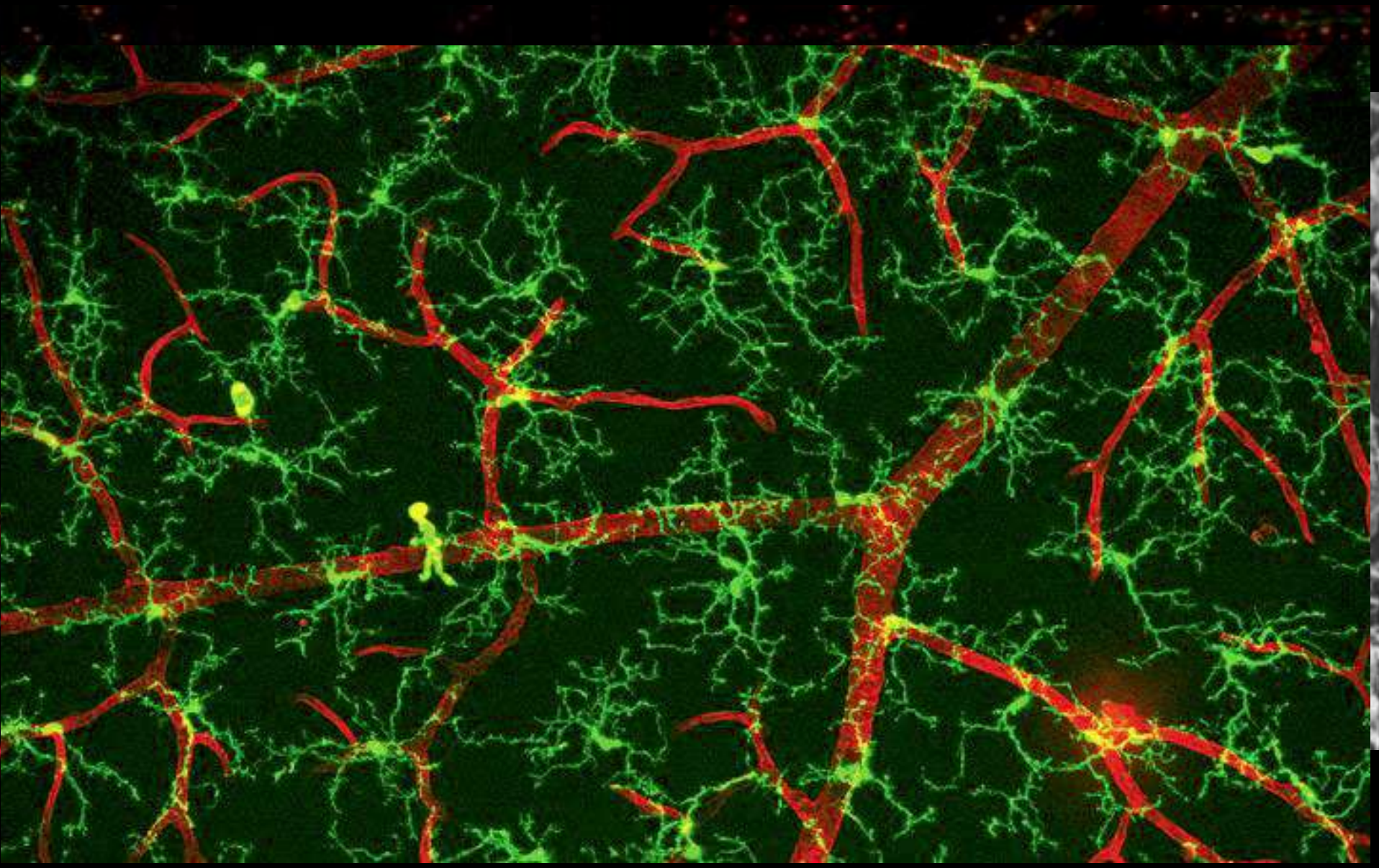
causes

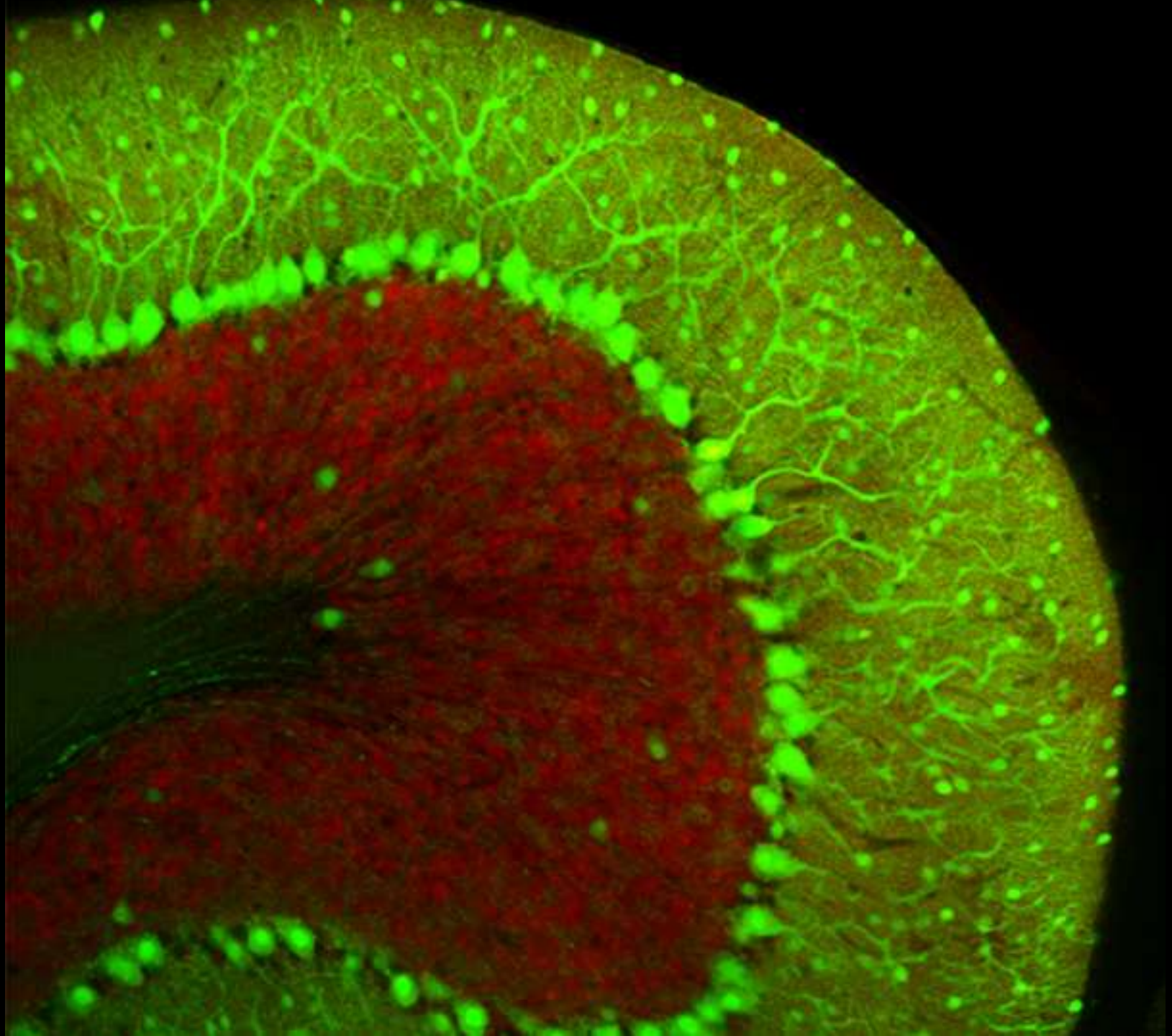
Change in function

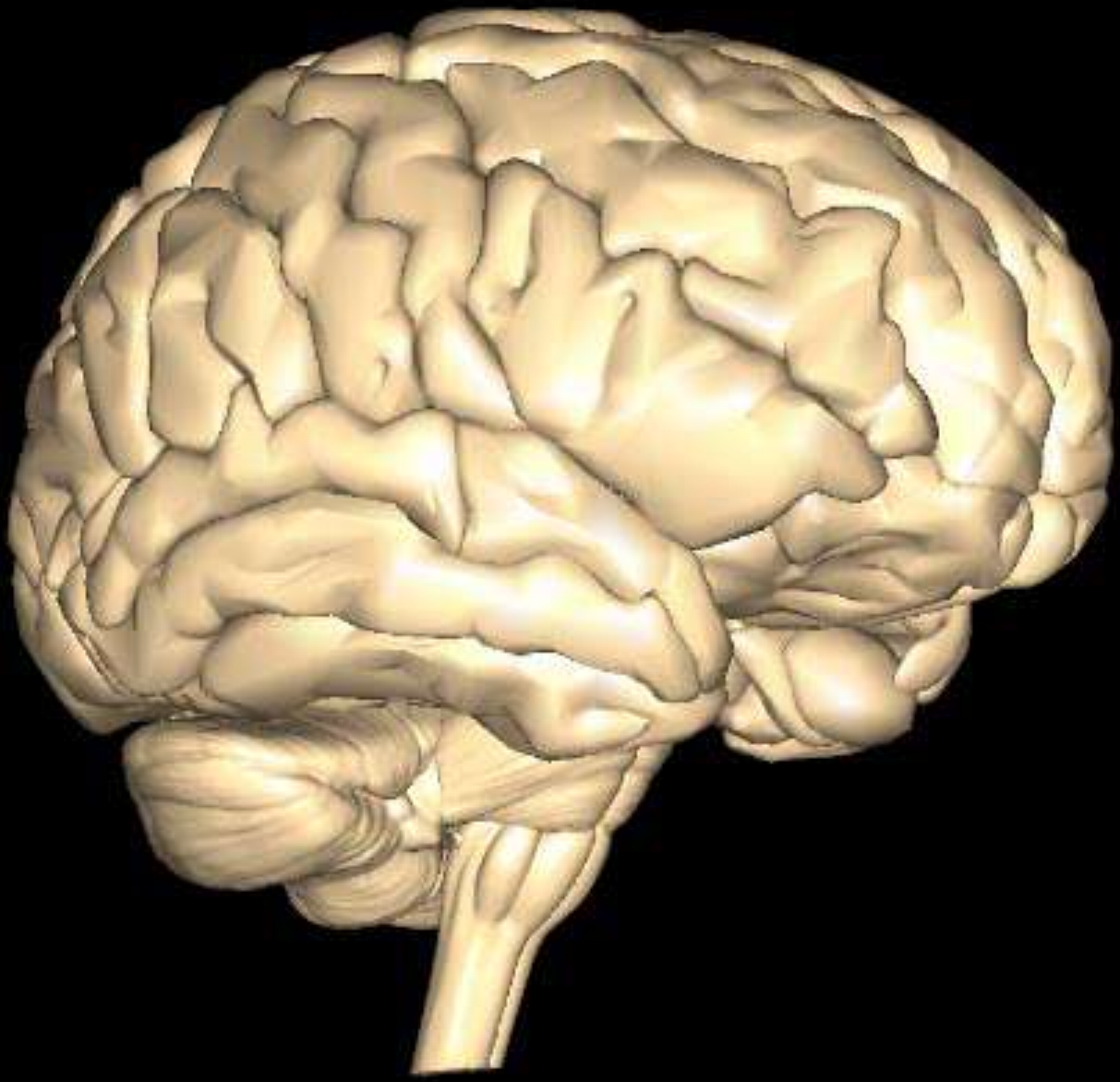

Public Enemy
#1

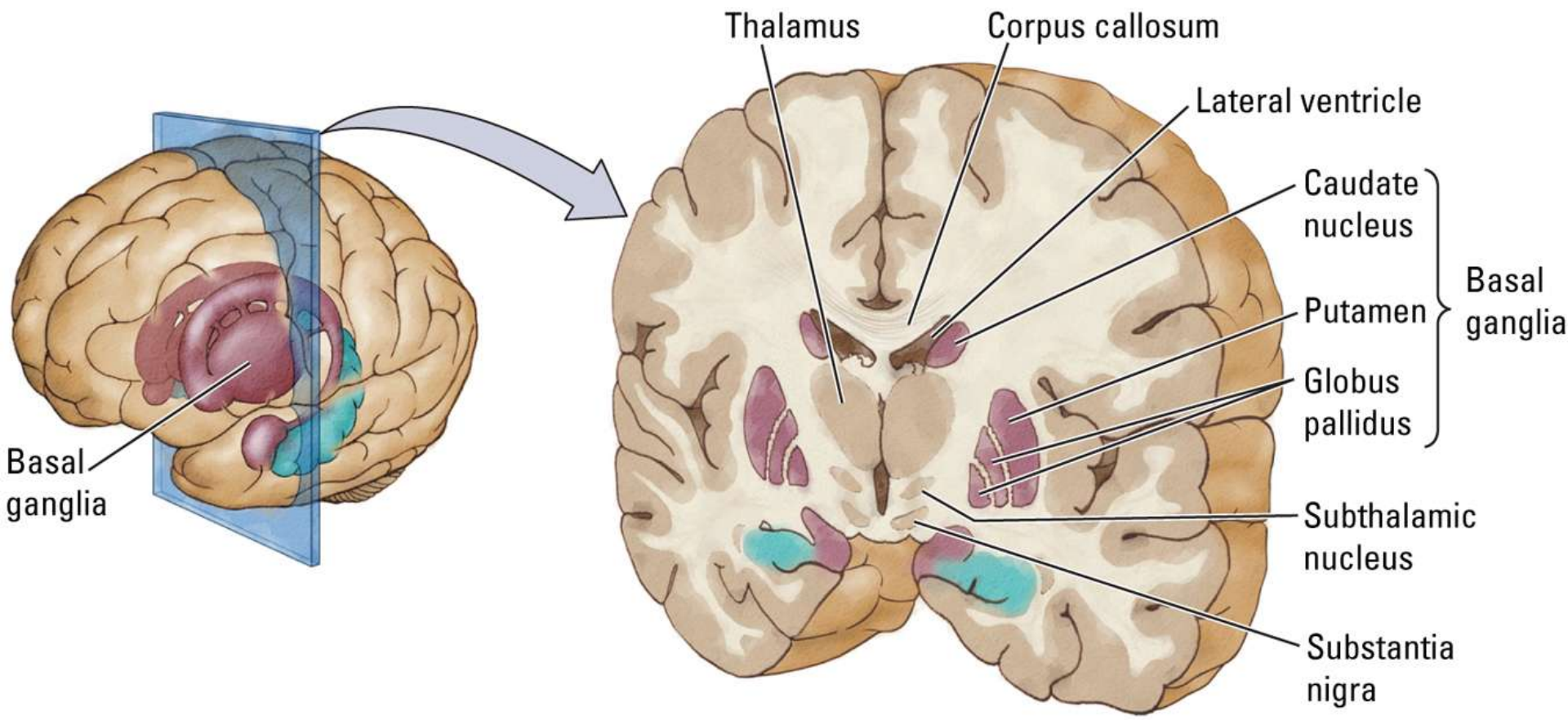
THE BRAIN

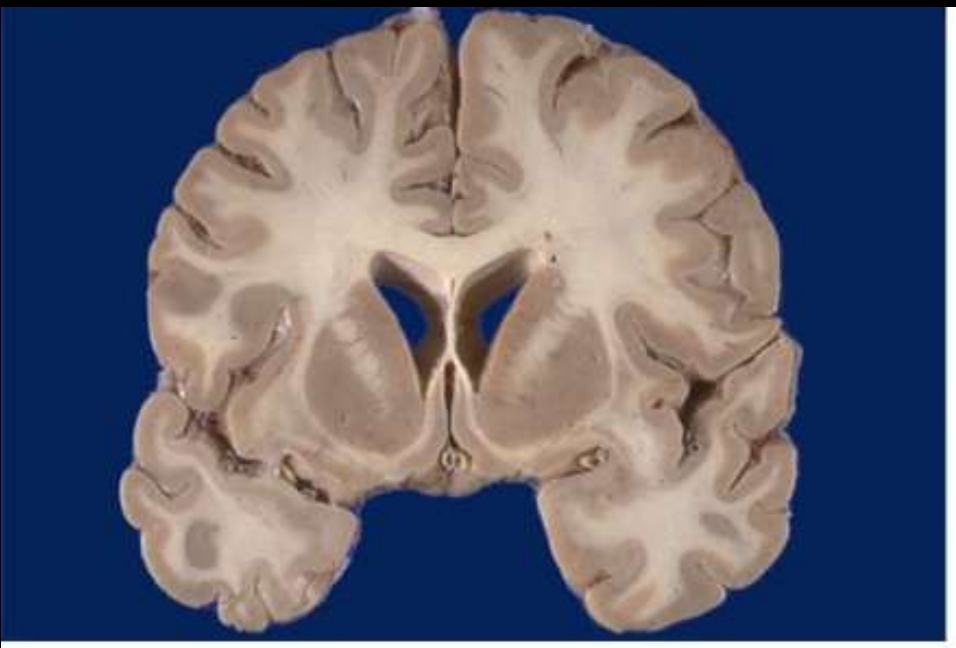


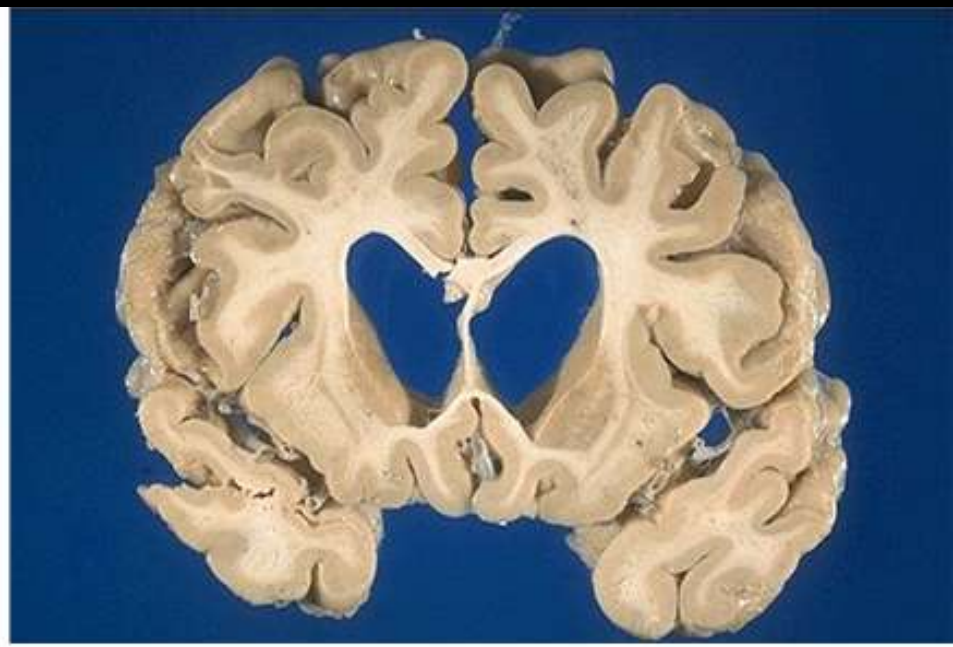






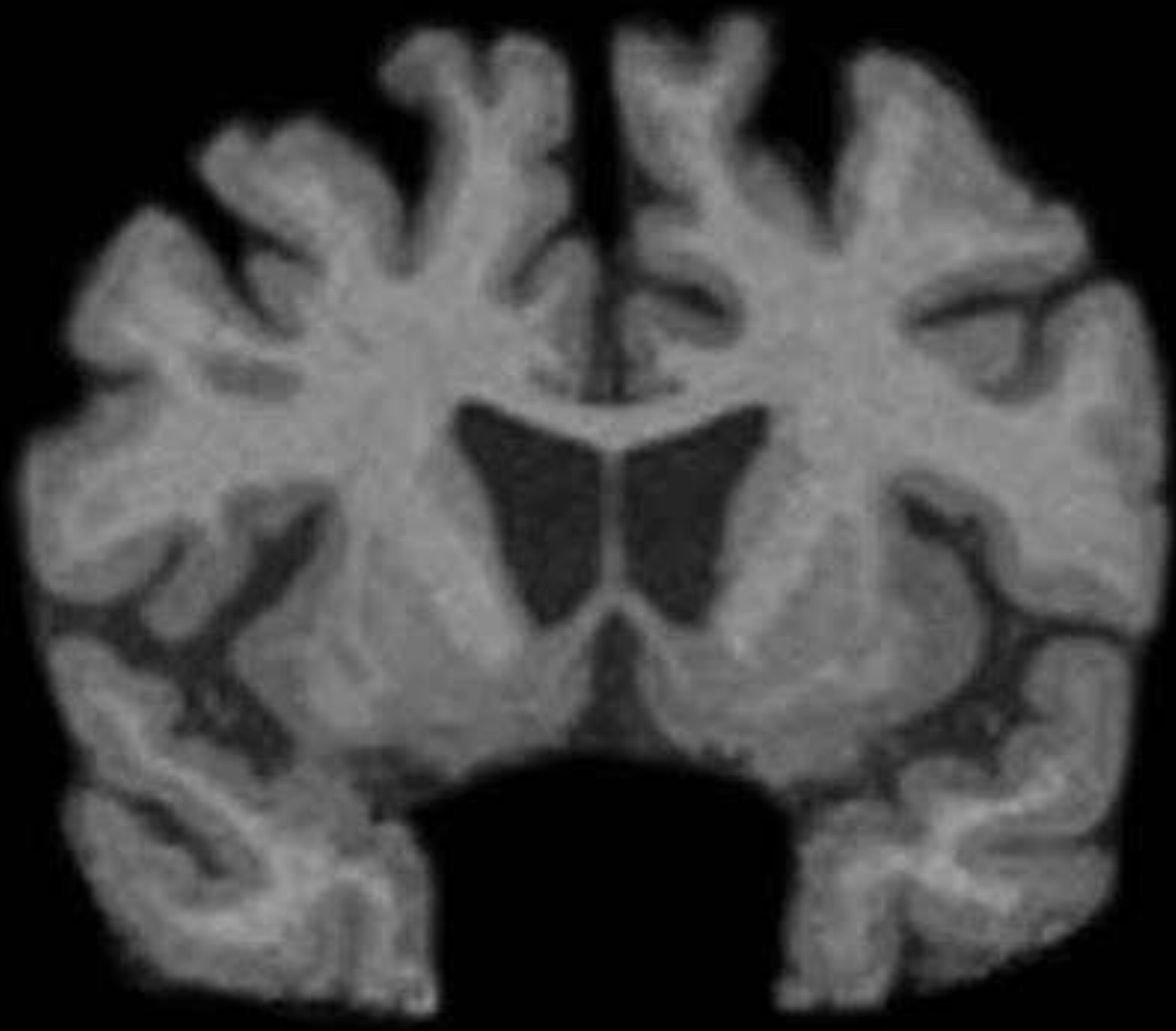

Thalamus
Corpus callosum
Lateral ventricle
Caudate nucleus
Putamen
Globus pallidus
Basal ganglia
Basal ganglia
Subthalamic nucleus
Substantia nigra

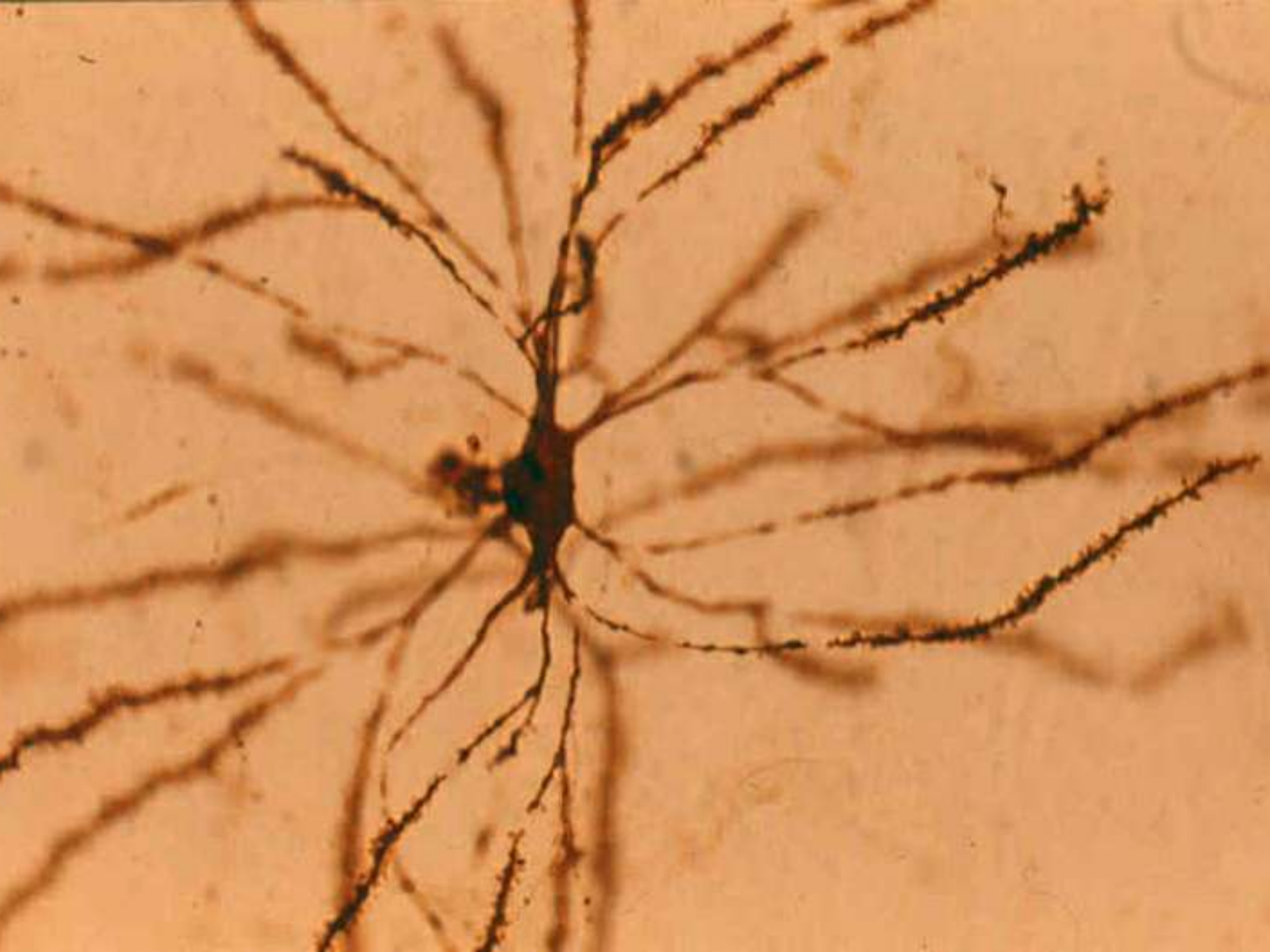


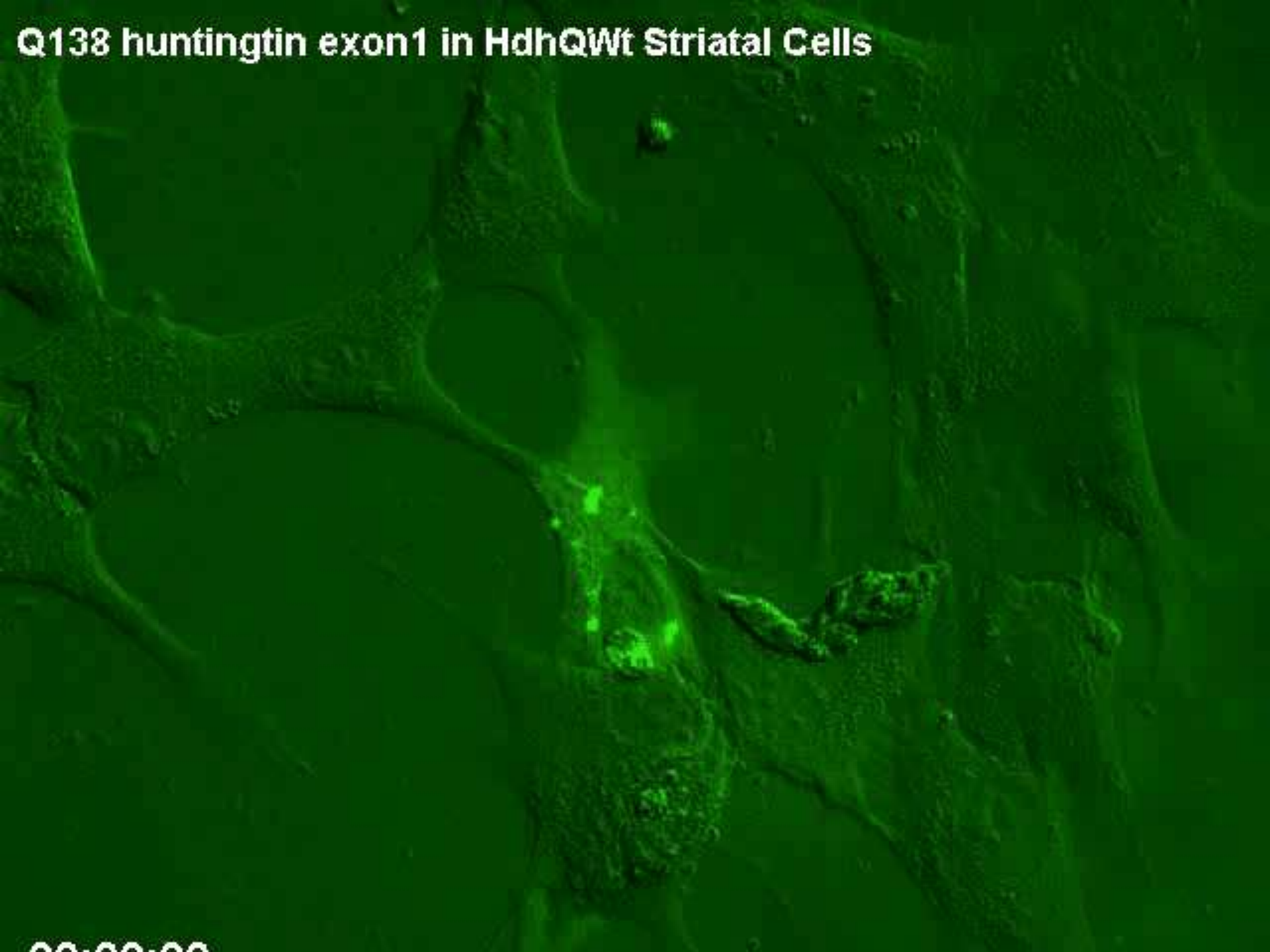


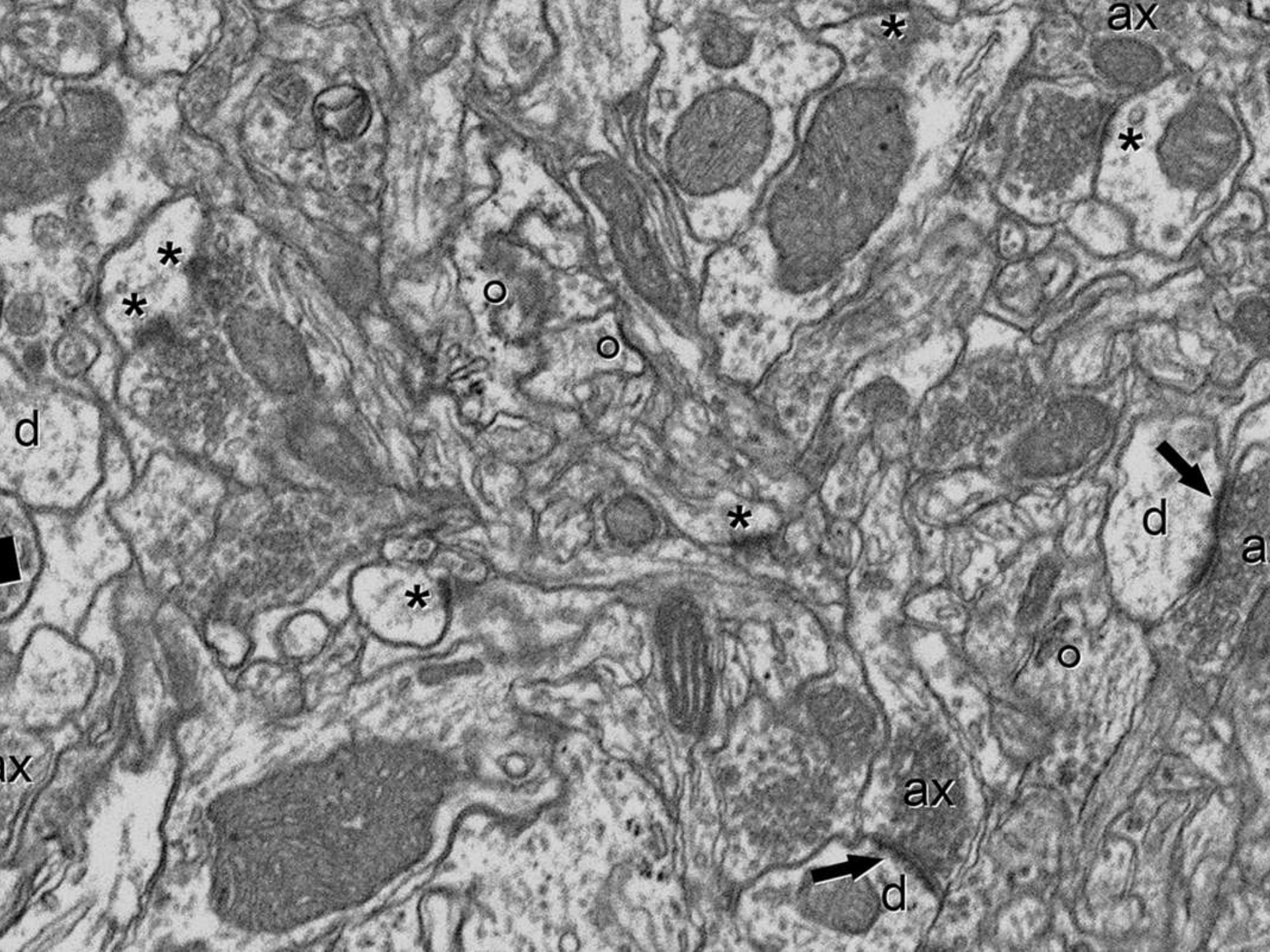
Control

Huntington’s Disease





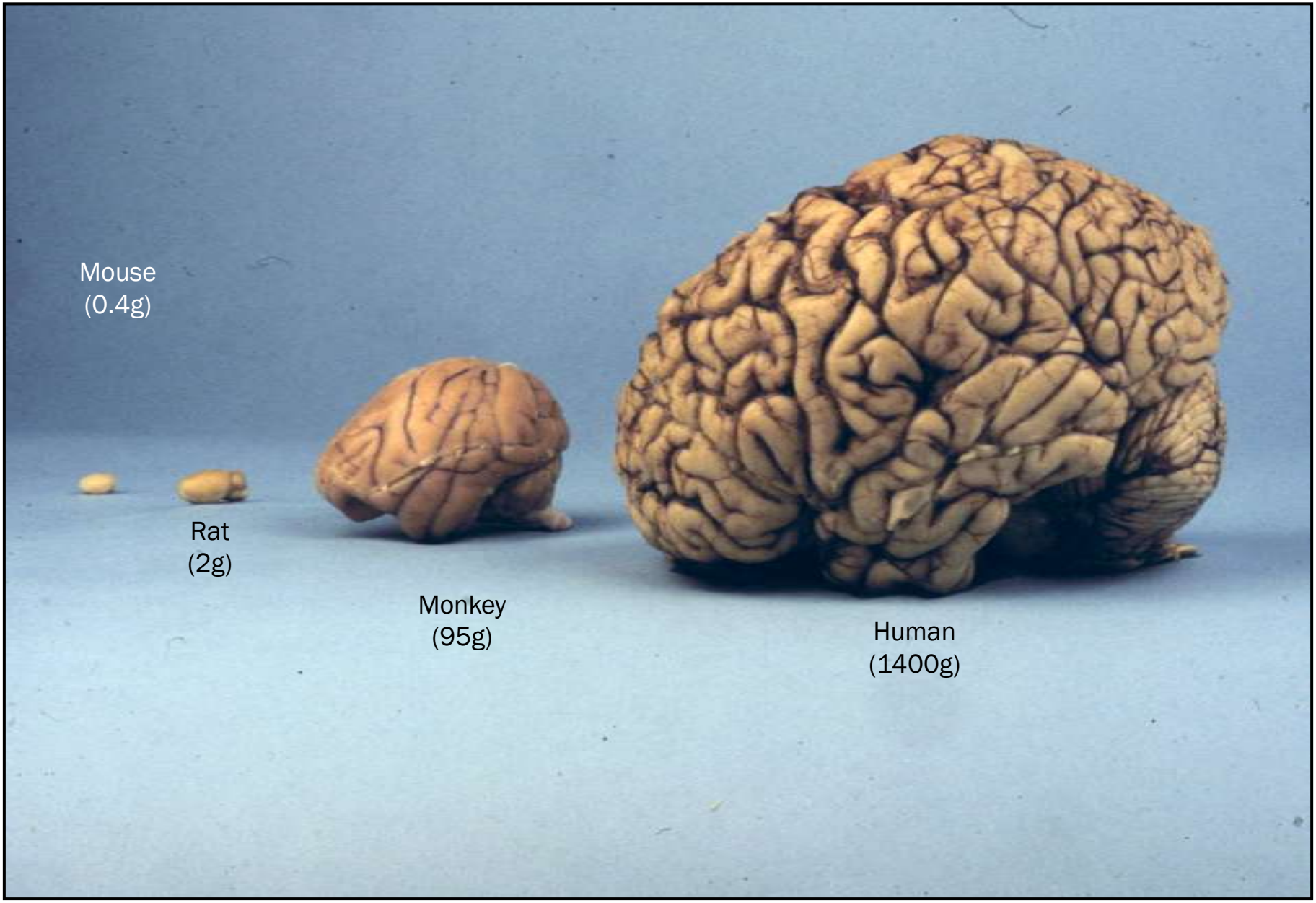

Q138 huntingtin exon1 in HdhQWt Striatal Cells


ax
d
d
ax
d

‘Animal models’ of HD

All these animals have an HD gene. None of them, as far as we know, ever gets HD because their CAG tracts don't grow like ours do.

But, what if we could manipulate them to artificially give them a long "C-A-G" repeat in their HD gene, would that make them sick?



Courtesy of Dr. Russ Lonser

Motor signs of Huntington’s Disease

Is this testing HD?

Research in HD patients

Quantitative motor

Fear

Anger

Disgust

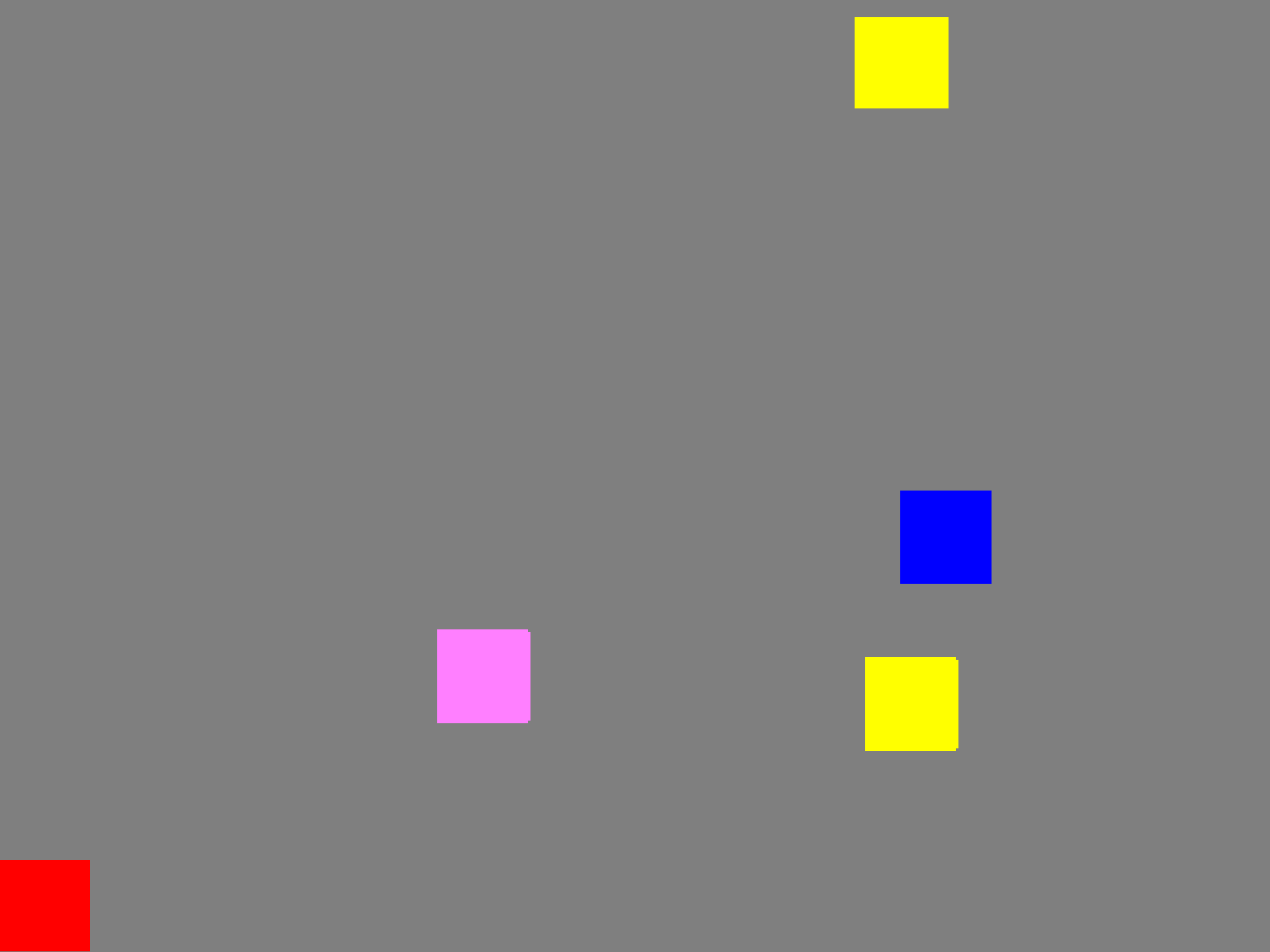
Sadness

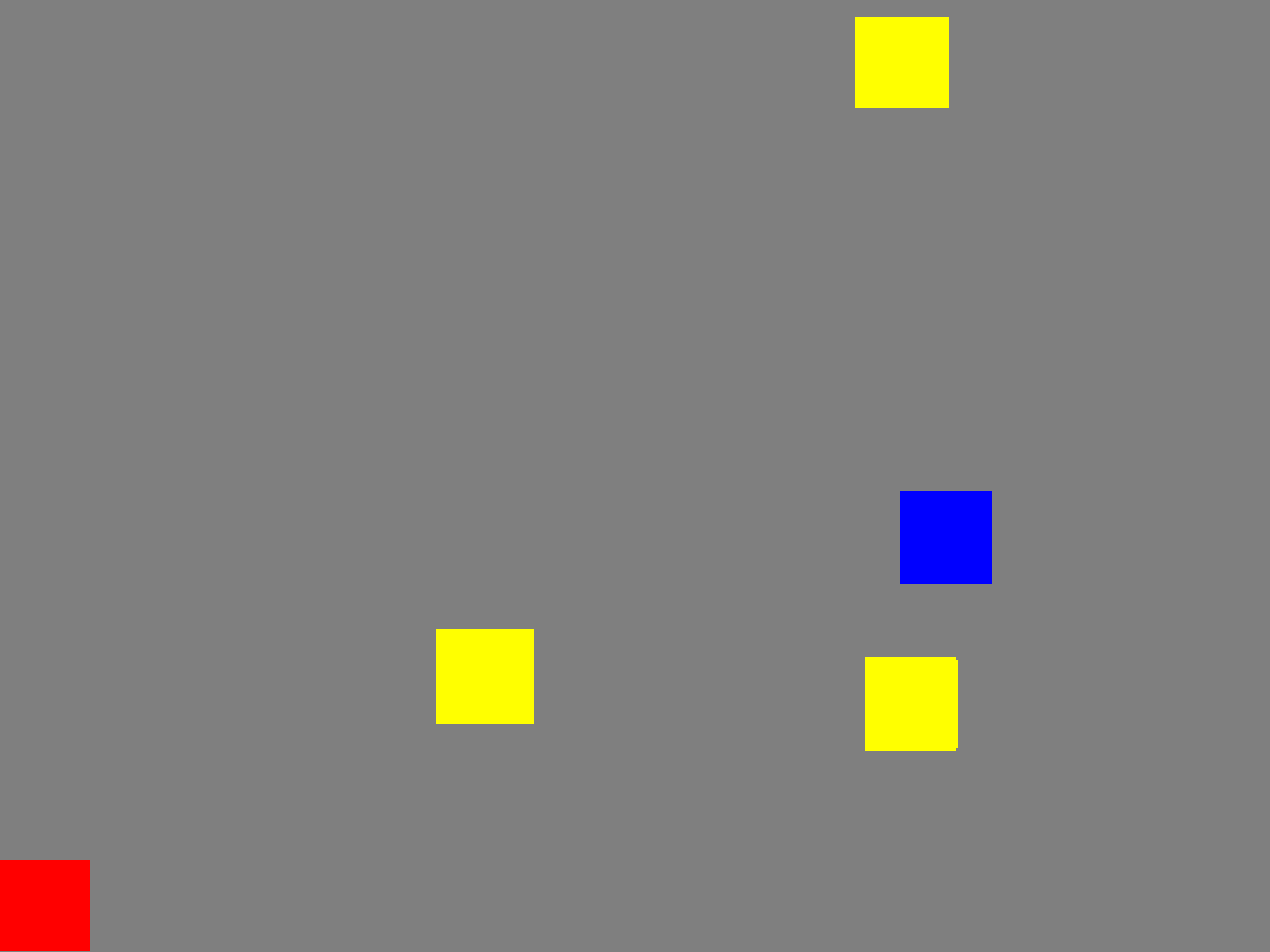
Happiness

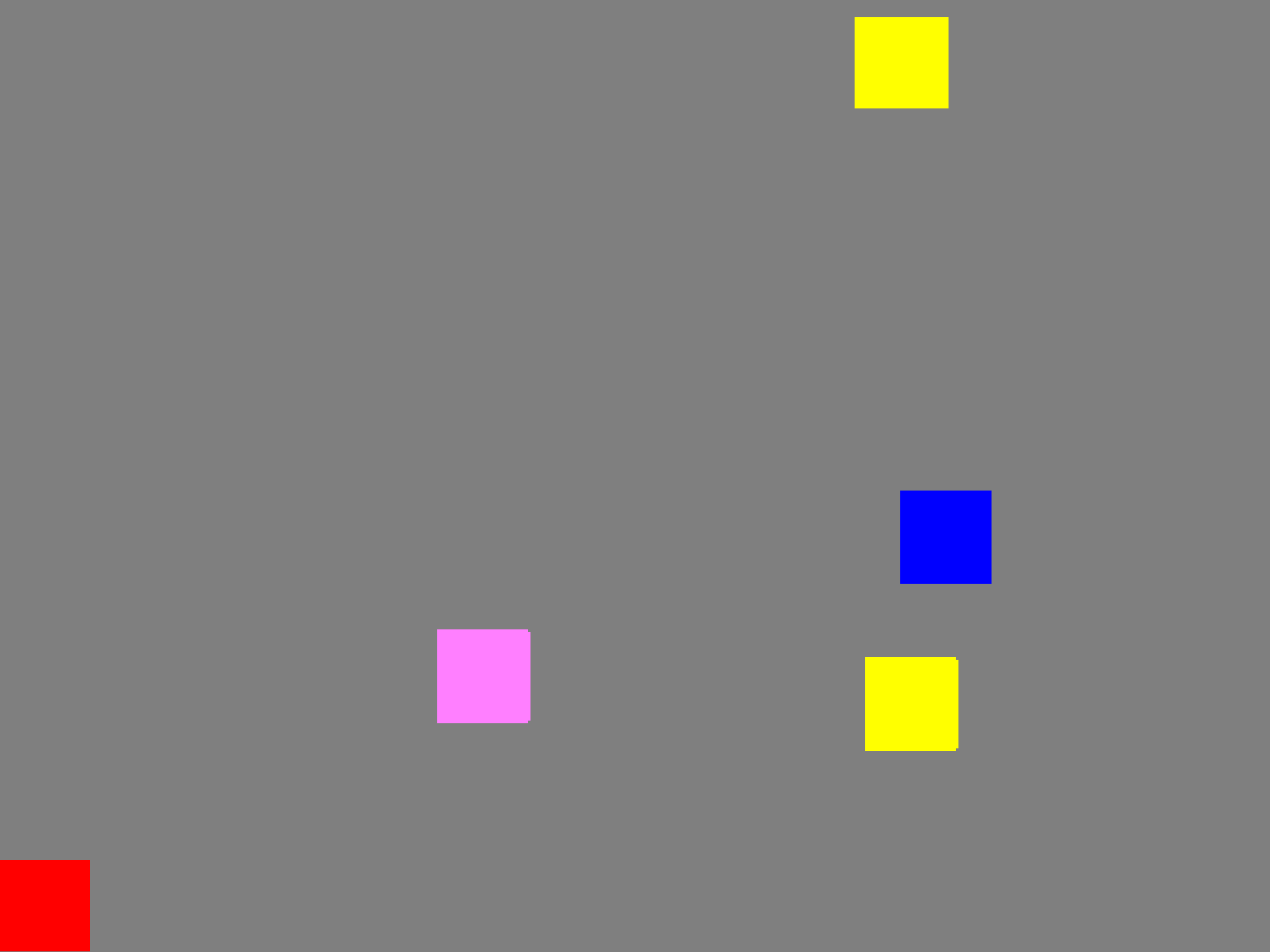
Surprise

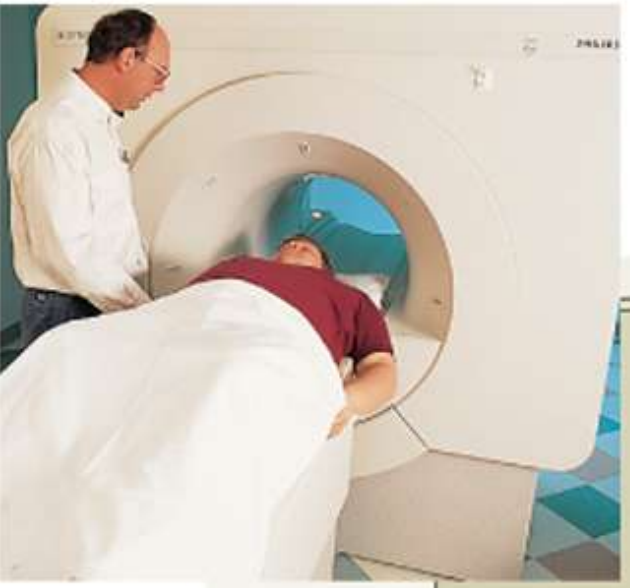
Neutral

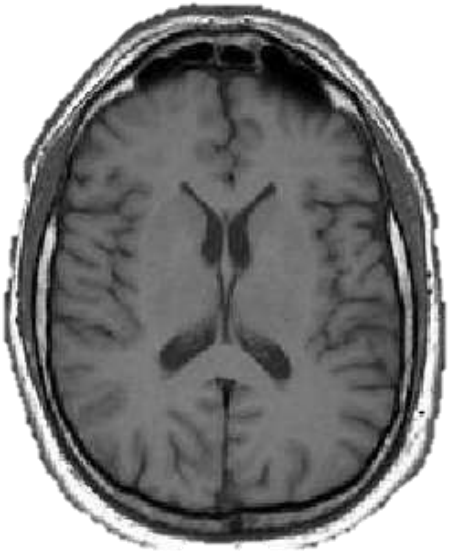
Home

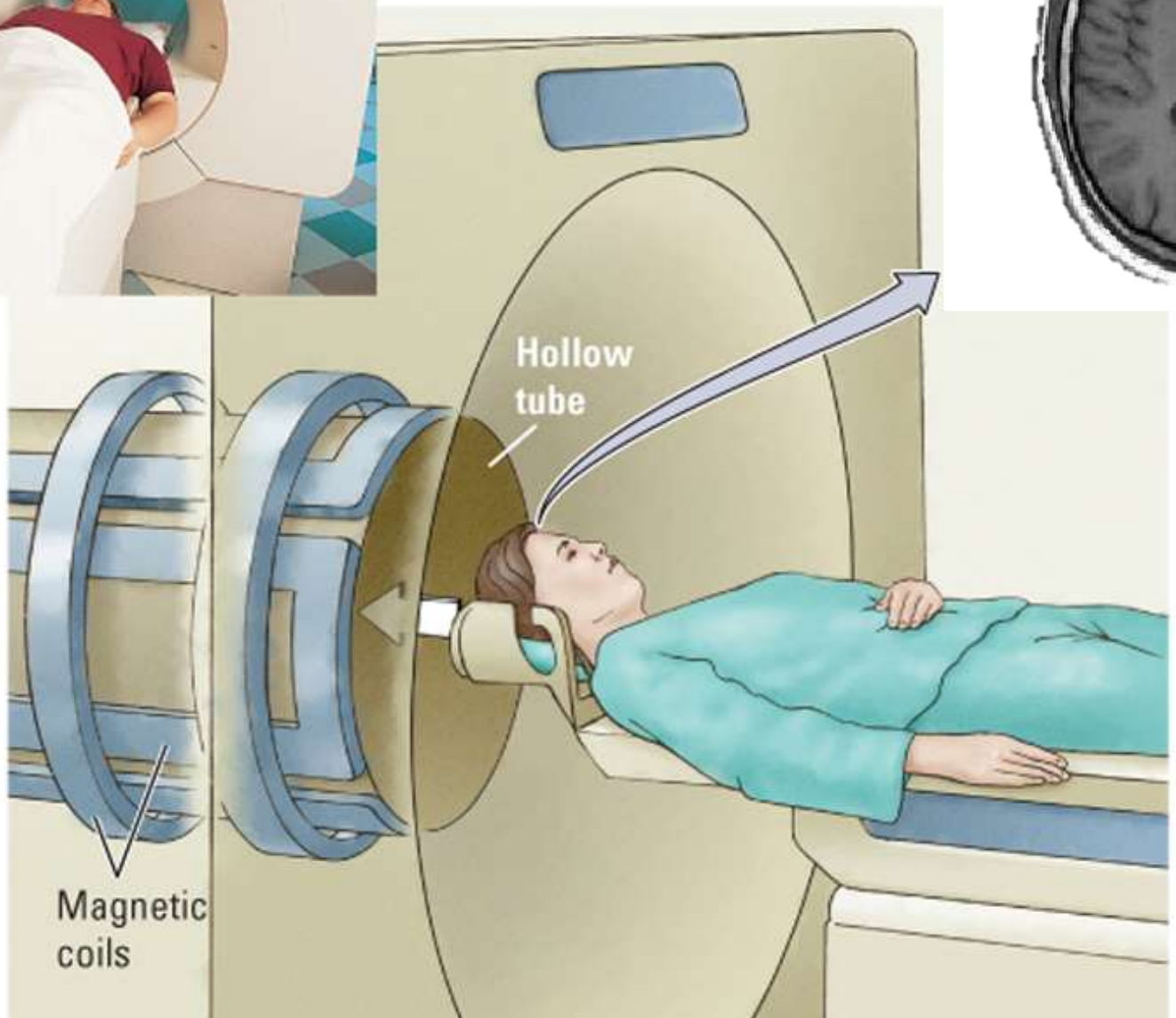


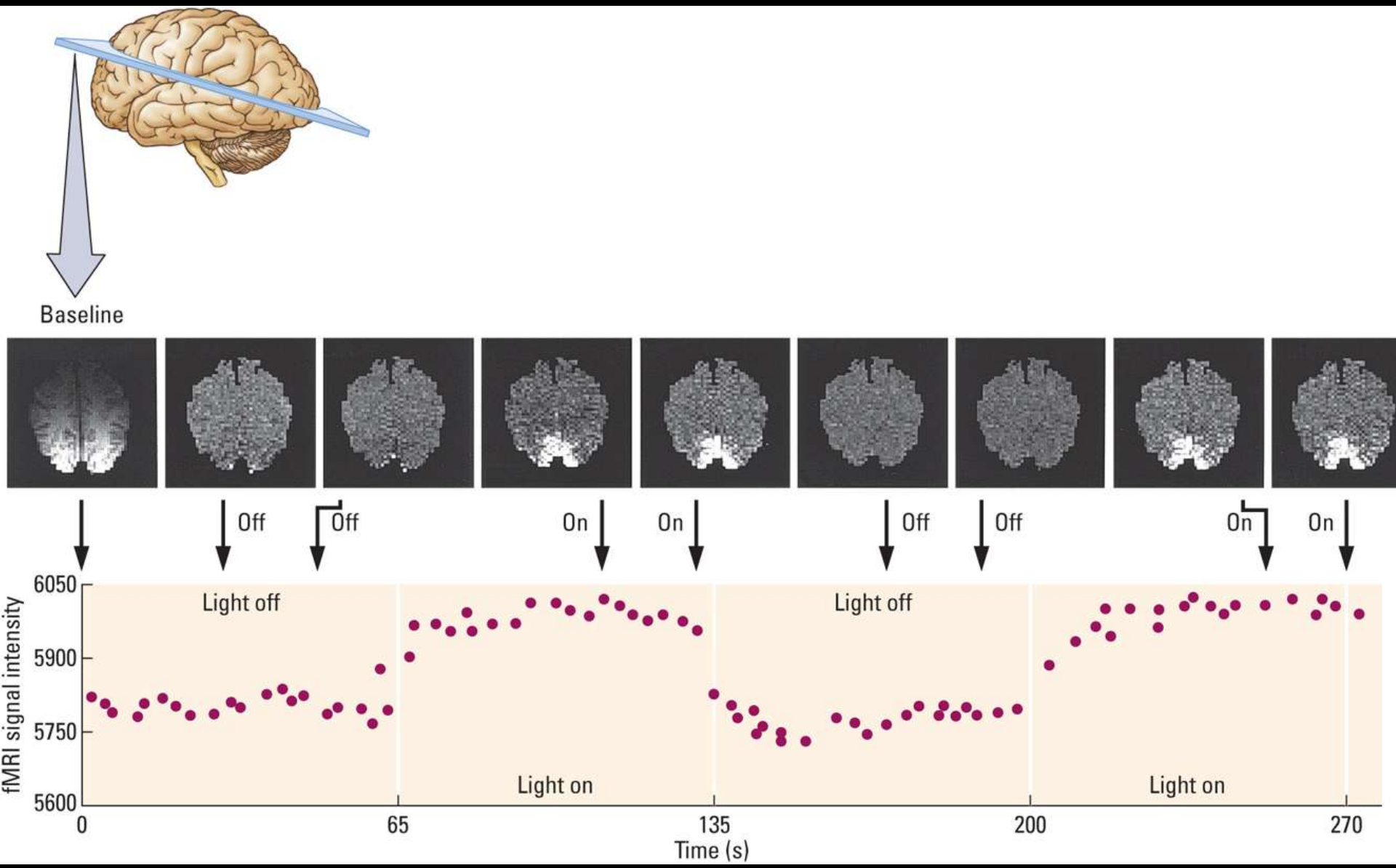


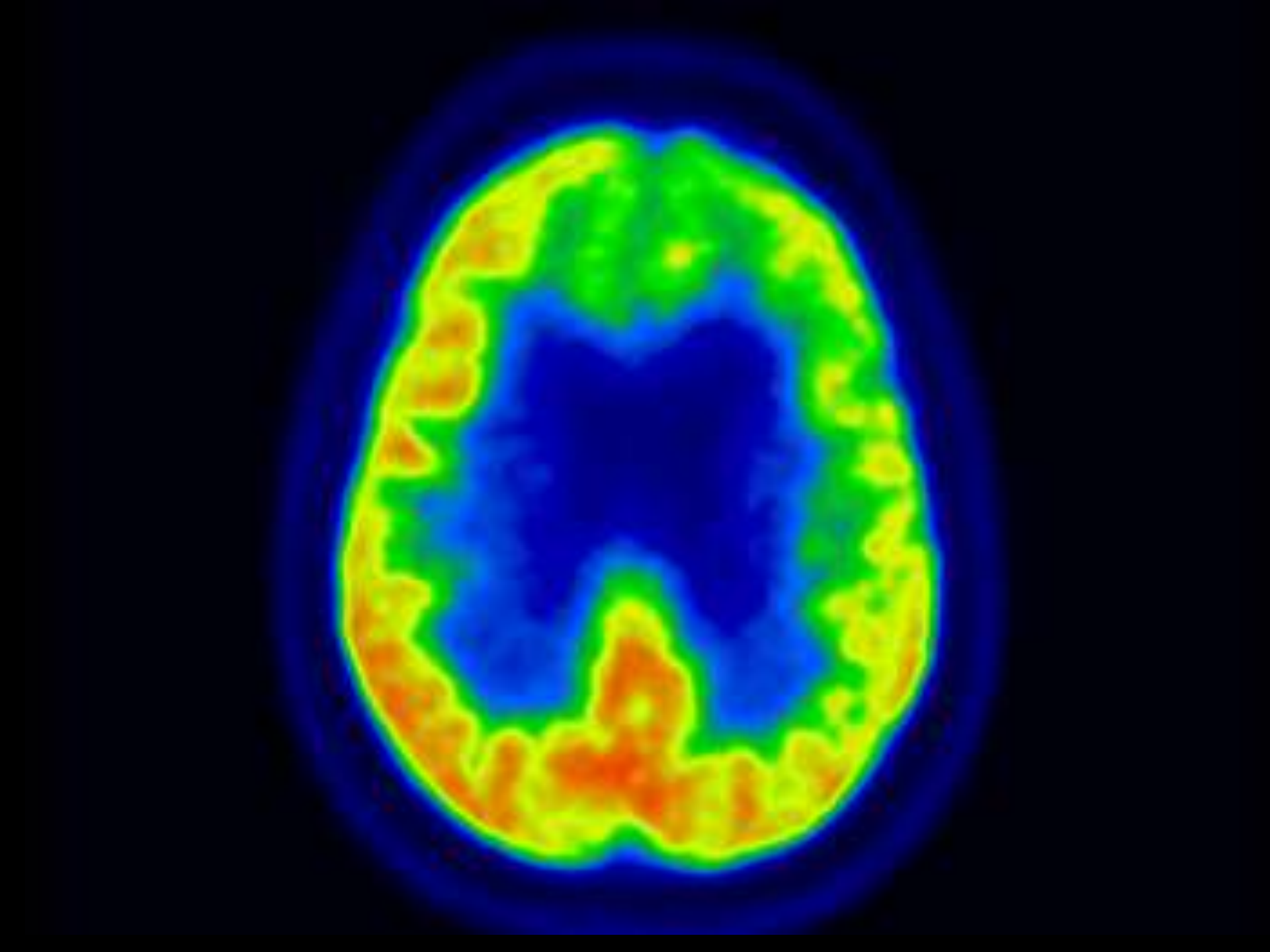







Hollow tube
Magnetic coils

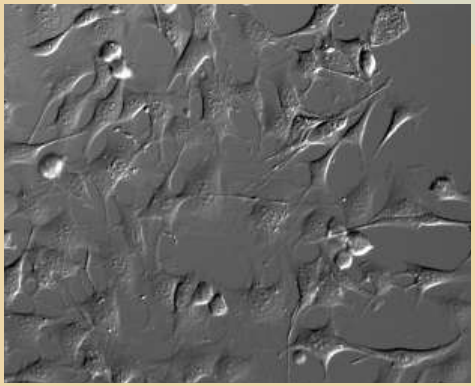

Baseline
Off
Off
On
On
Off
Off
On
On
6050
5900
5750
5600
fMRI signal intensity
Light off
Light on
Light off
Light on
0
65
135
200
270
Time (s)



RECAP

Patients

Cells



Animal Models

Tomorrow...

Drug discovery
Identifying targets, finding or making molecules

Preclinical phase
Testing in cells and animals

Clinical trials
In humans

Approval

Phase 1

Healthy volunteers

Phase 2

Small numbers of patients

Phase 3

Large numbers of patients