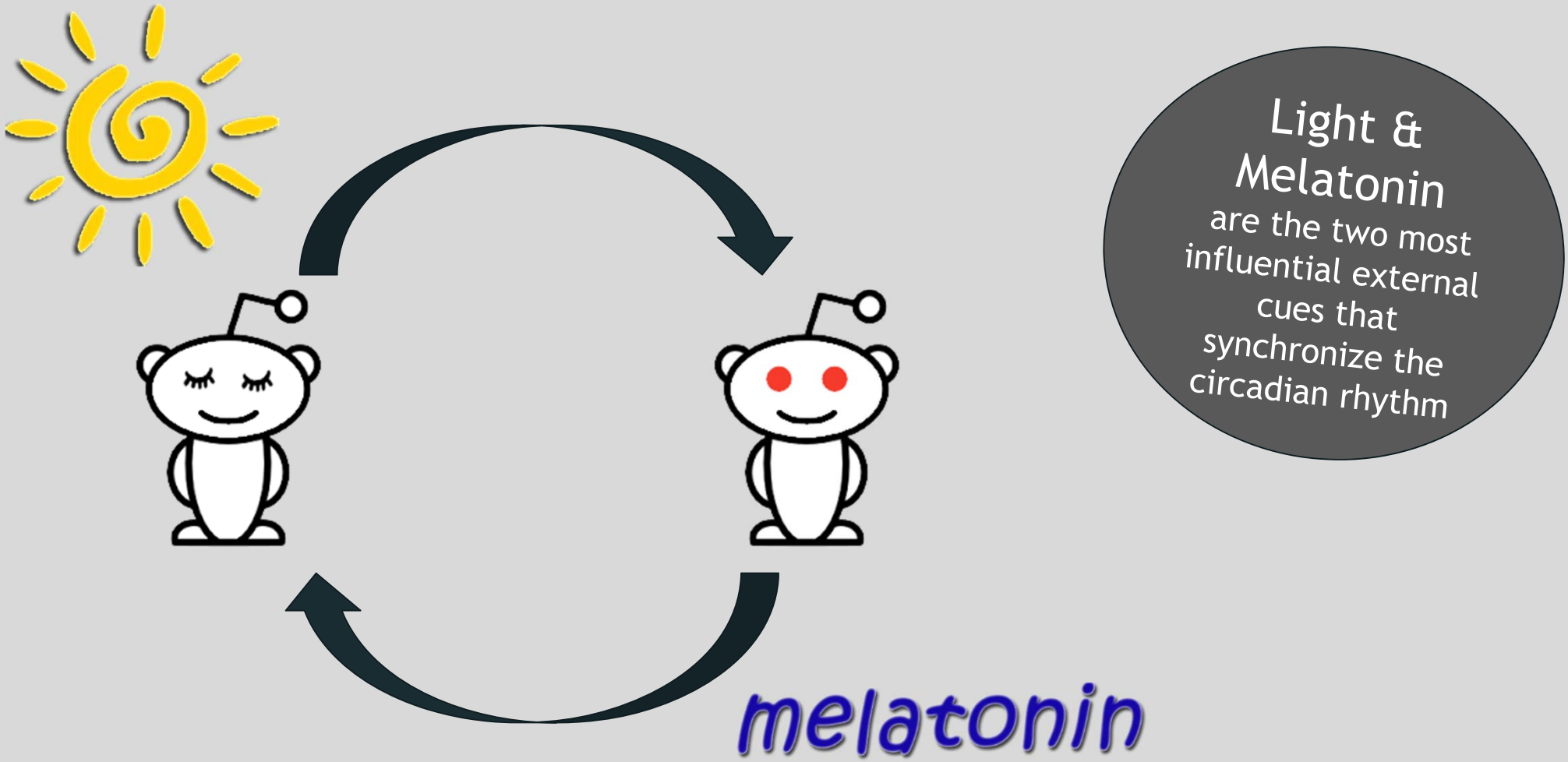
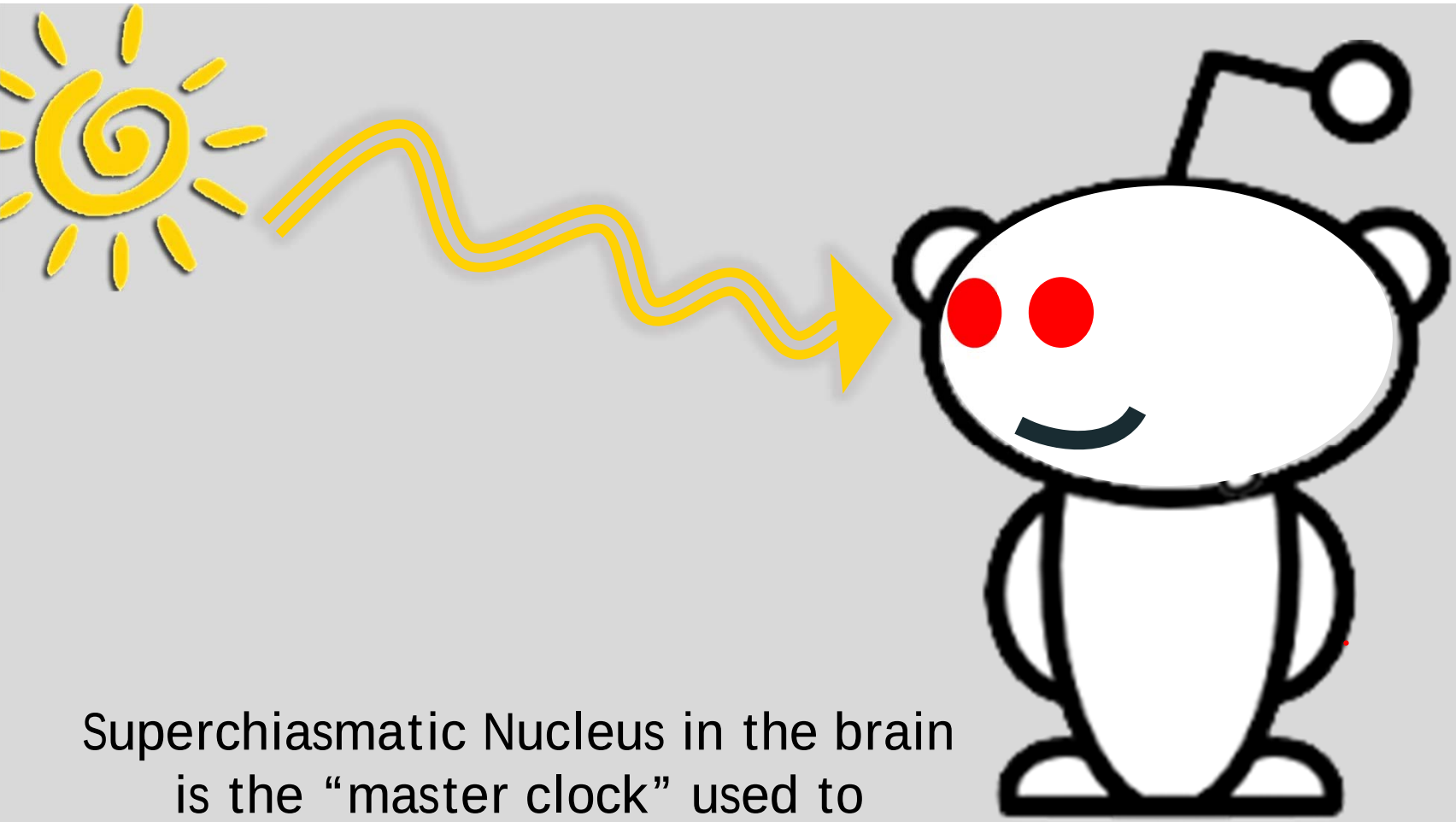
Sleep Cycle Shift and its effects on Cognitive Function

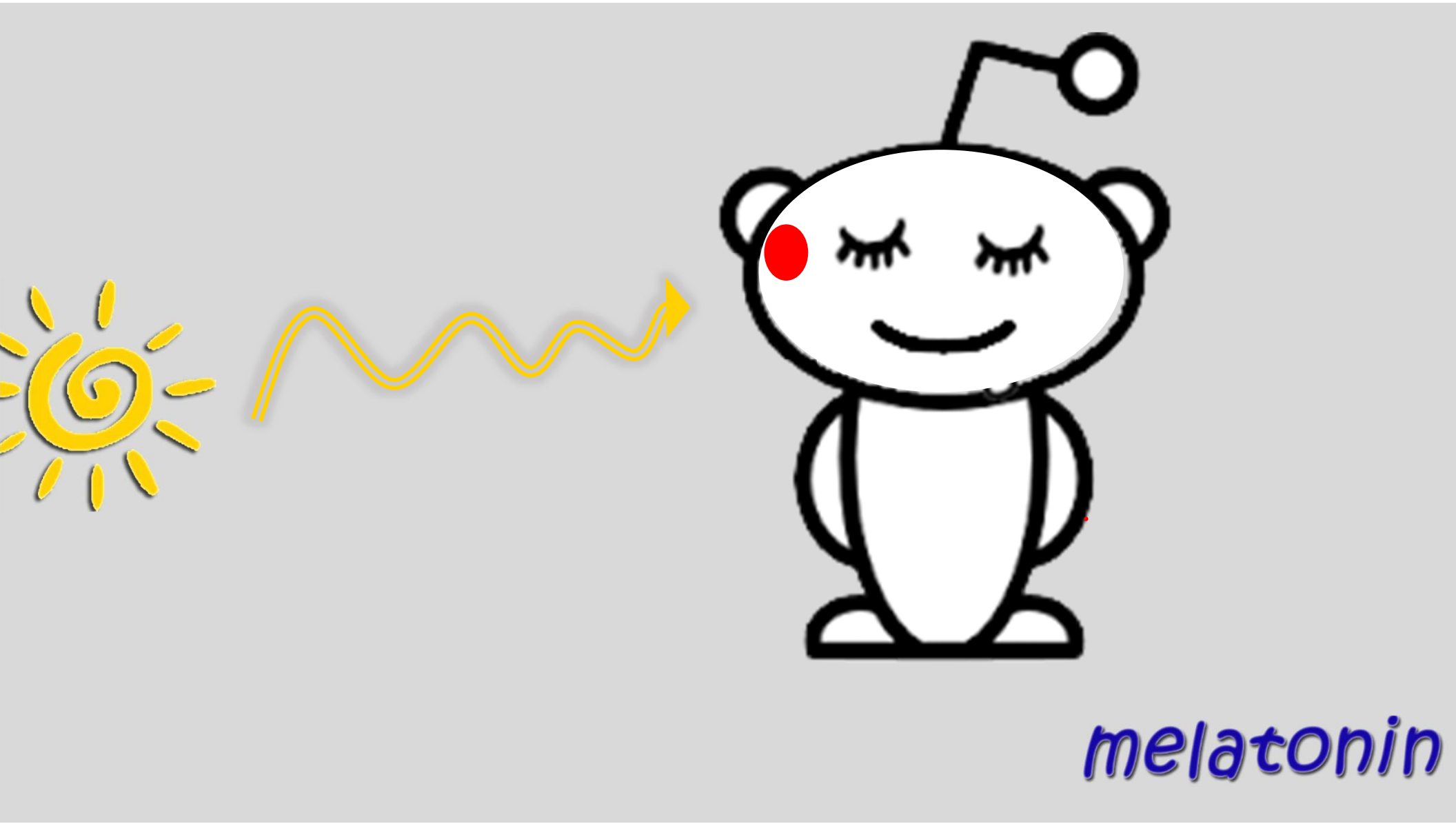
MARY ET BOYLE, PH. D. • DEPARTMENT OF COGNITIVE SCIENCE • UCSD

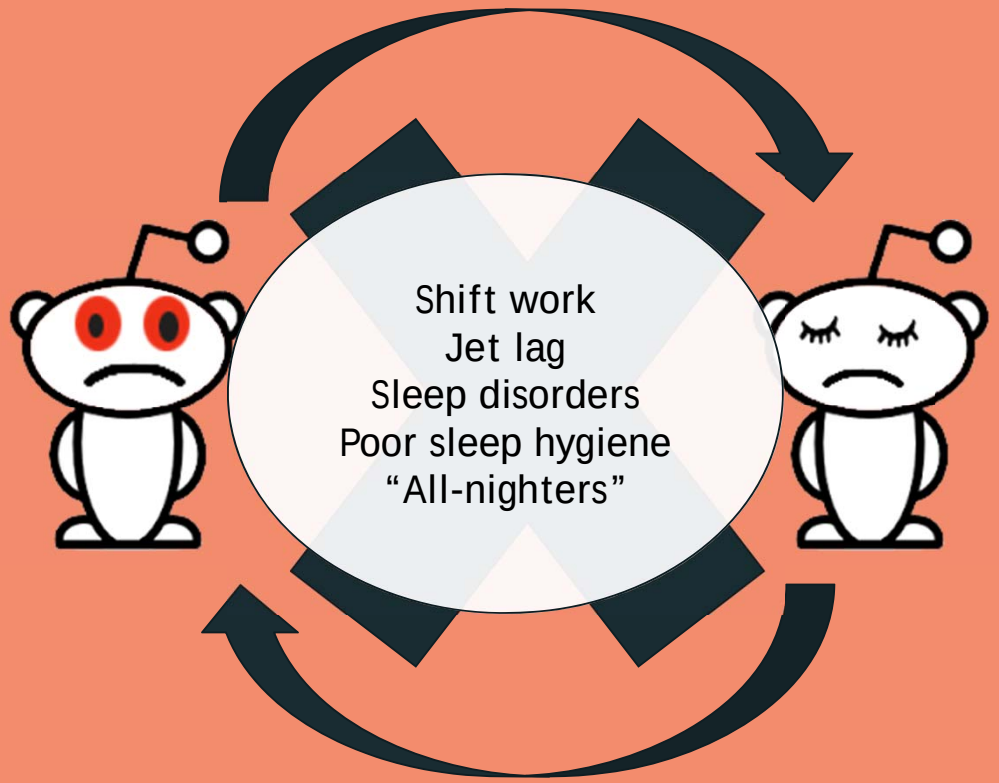


Sleep wake cycle is regulated by the circadian system.



Superchiasmatic Nucleus in the brain is the “master clock” used to coordinate and synchronize most of the body clocks in the periphery.


melatonin



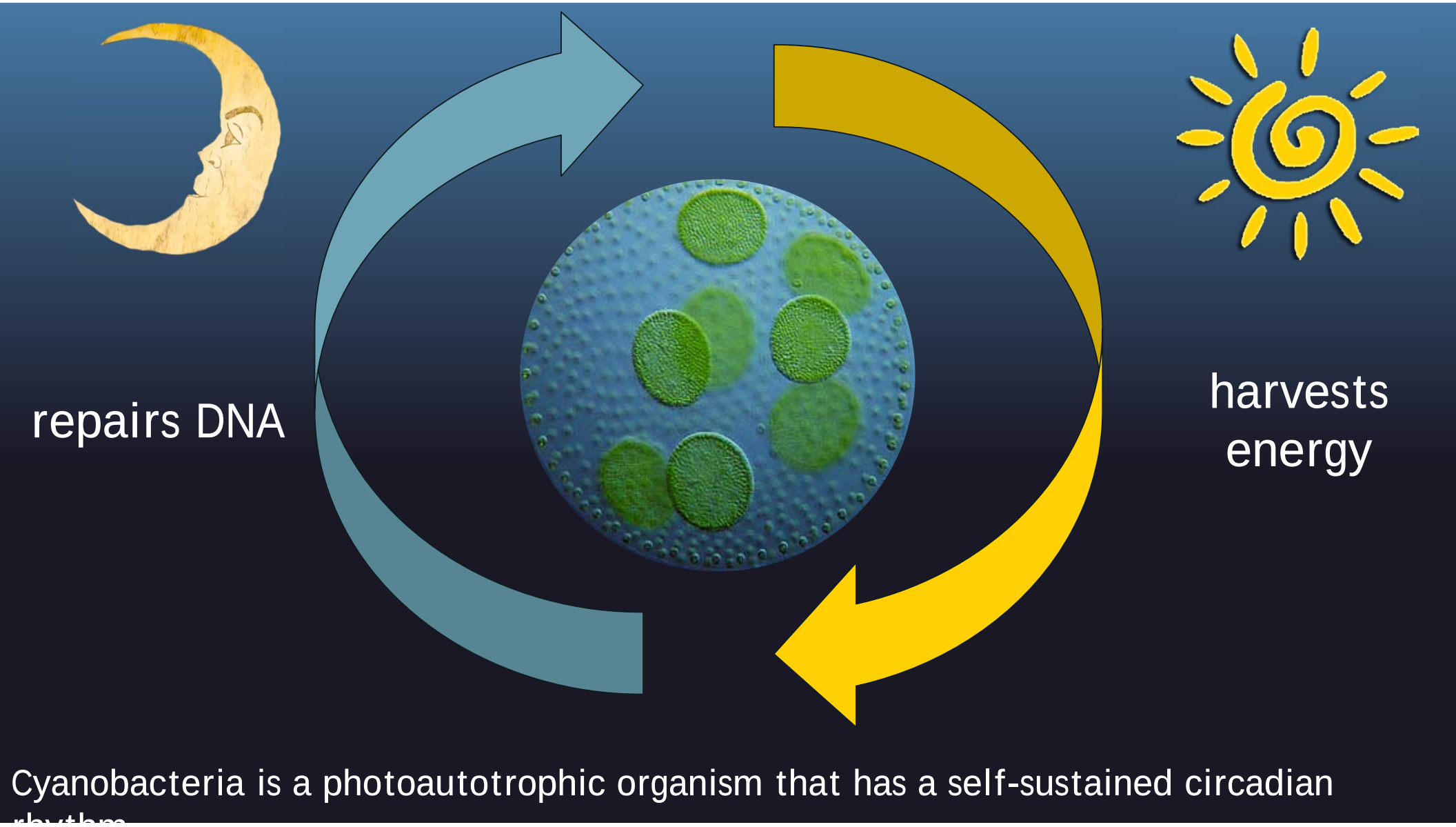
metabolic disruption

weight gain, obesity

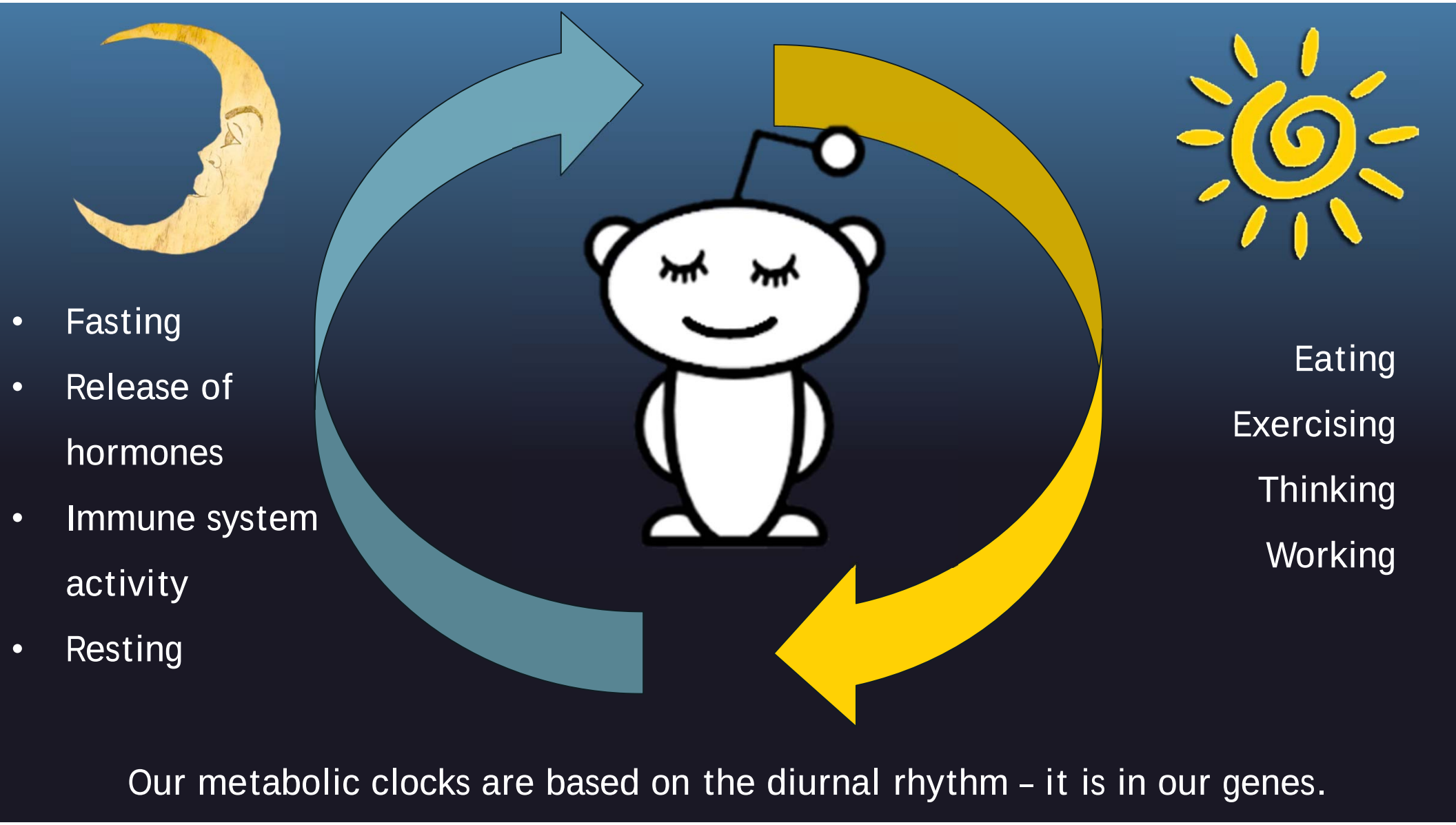
impaired immunity

cognitive malfunction

If the sleep wake cycle is disrupted it can cause metabolic dysregulation



Cyanobacteria is a photoautotrophic organism that has a self-sustained circadian rhythm


• Fasting
• Release of hormones
• Immune system activity
• Resting
Eating
Exercising
Thinking
Working
Our metabolic clocks are based on the diurnal rhythm – it is in our genes.

Shift workers are more prone to developing metabolic disorders

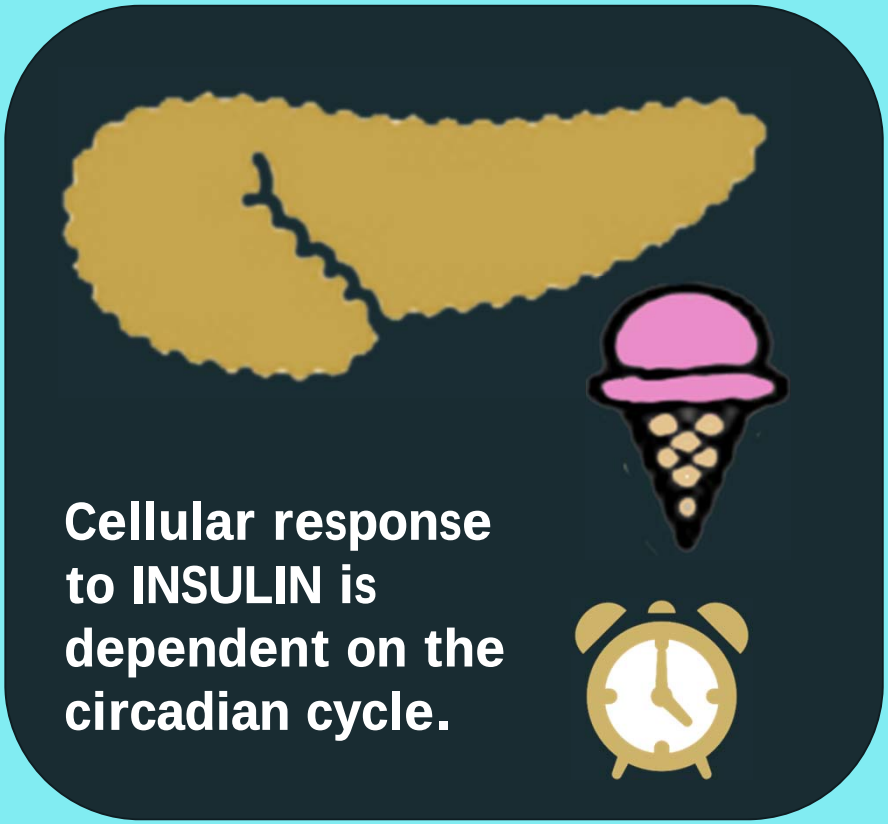
40% more likely to have: cardiovascular disease

Higher incidence of Diabetes Type II

Higher risk of cancer – melatonin disruption

Puttonen S, Härmä M, Hublin C.Scand J Work Environ Health. 2010 Mar; 36(2):96-108. Epub 2010 Jan 20.
The Health Survey for England (2013);
Davis S, Mirick DK.Cancer Causes Control. 2006 May; 17(4):539-45.

SCN is not the only clock in the body



Time of eating has a huge effect on the liver and insulin efficacy

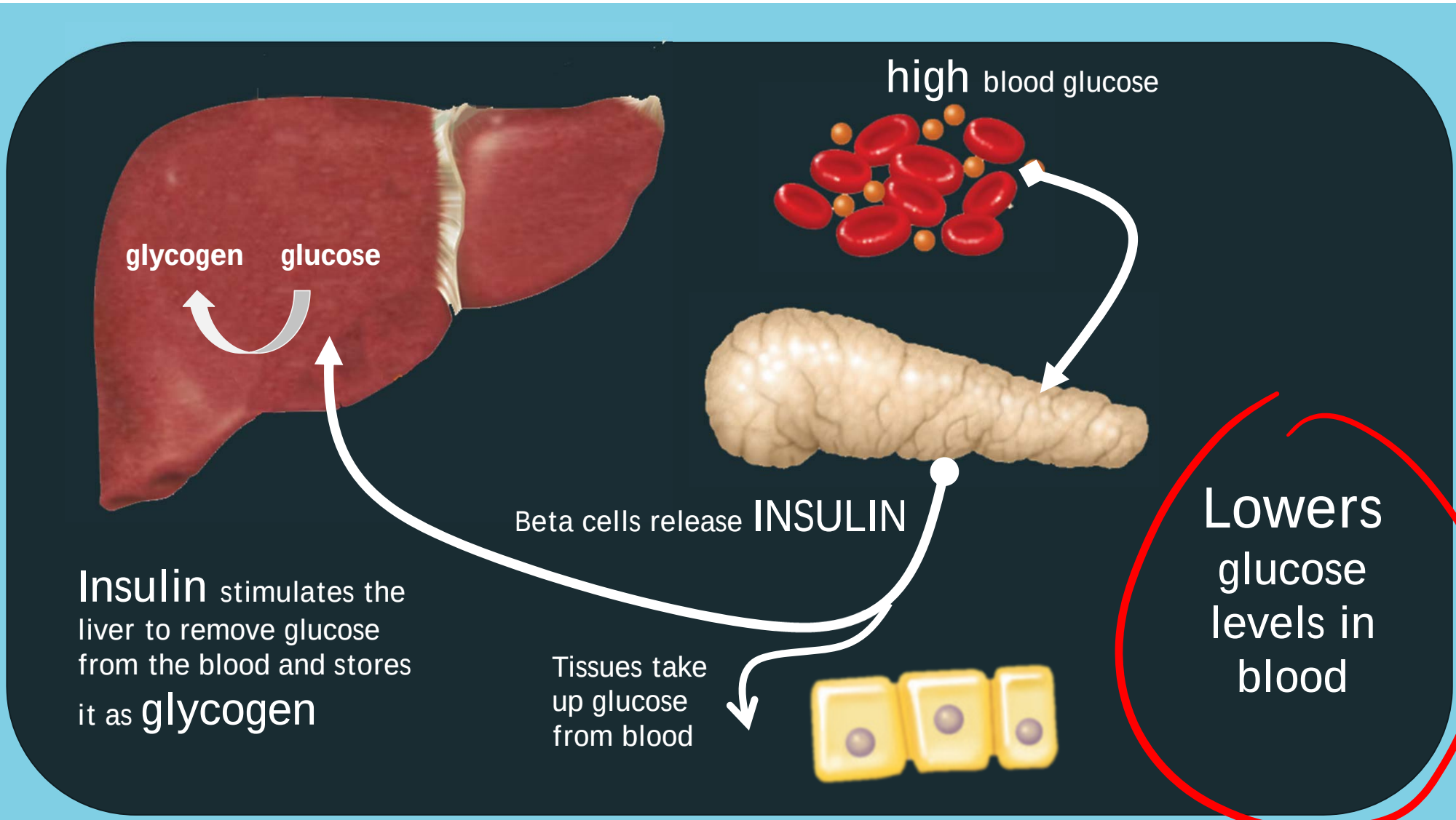


Figure adapted from Kaidanovich-Beilin, O. et al 201

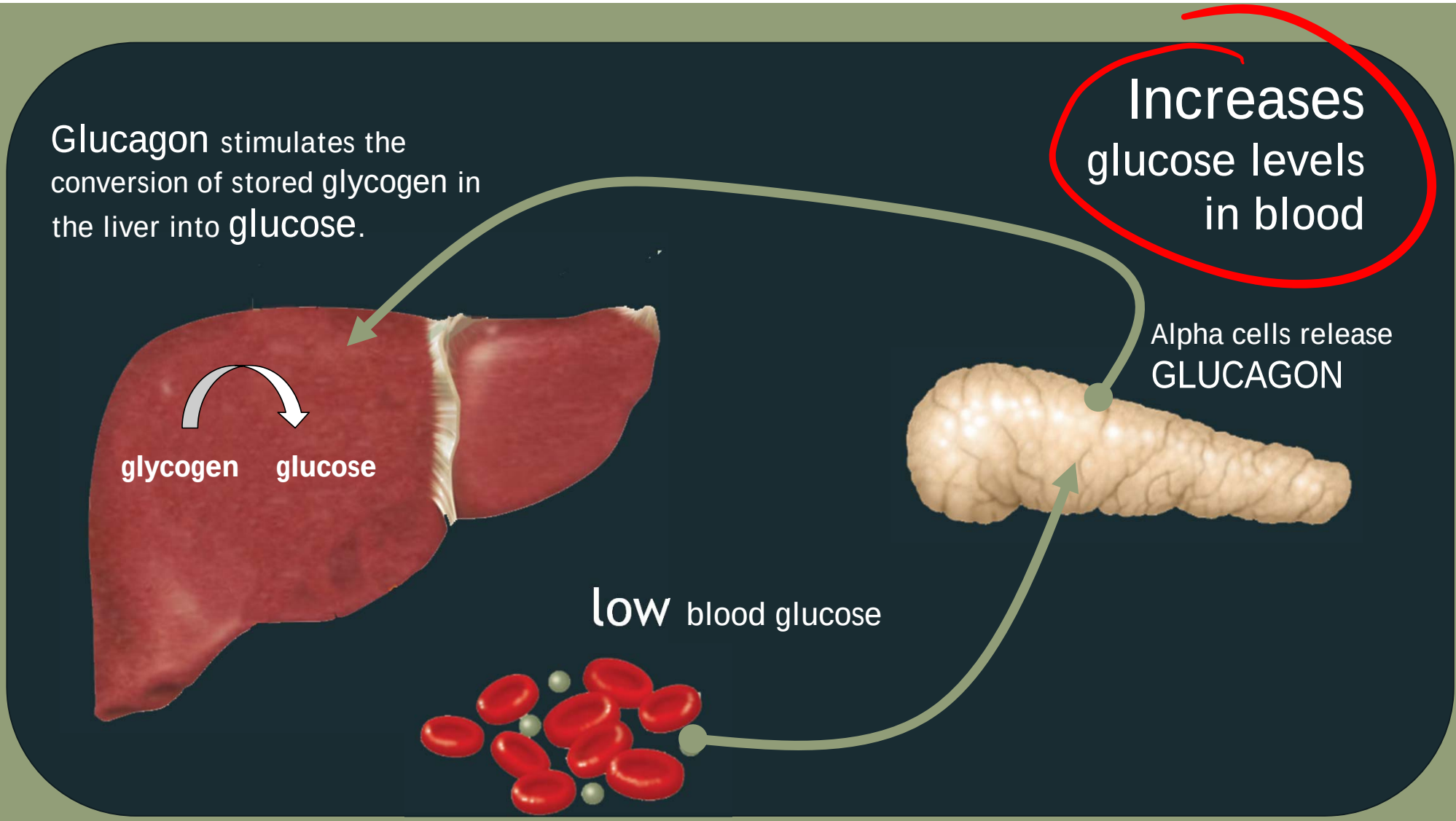
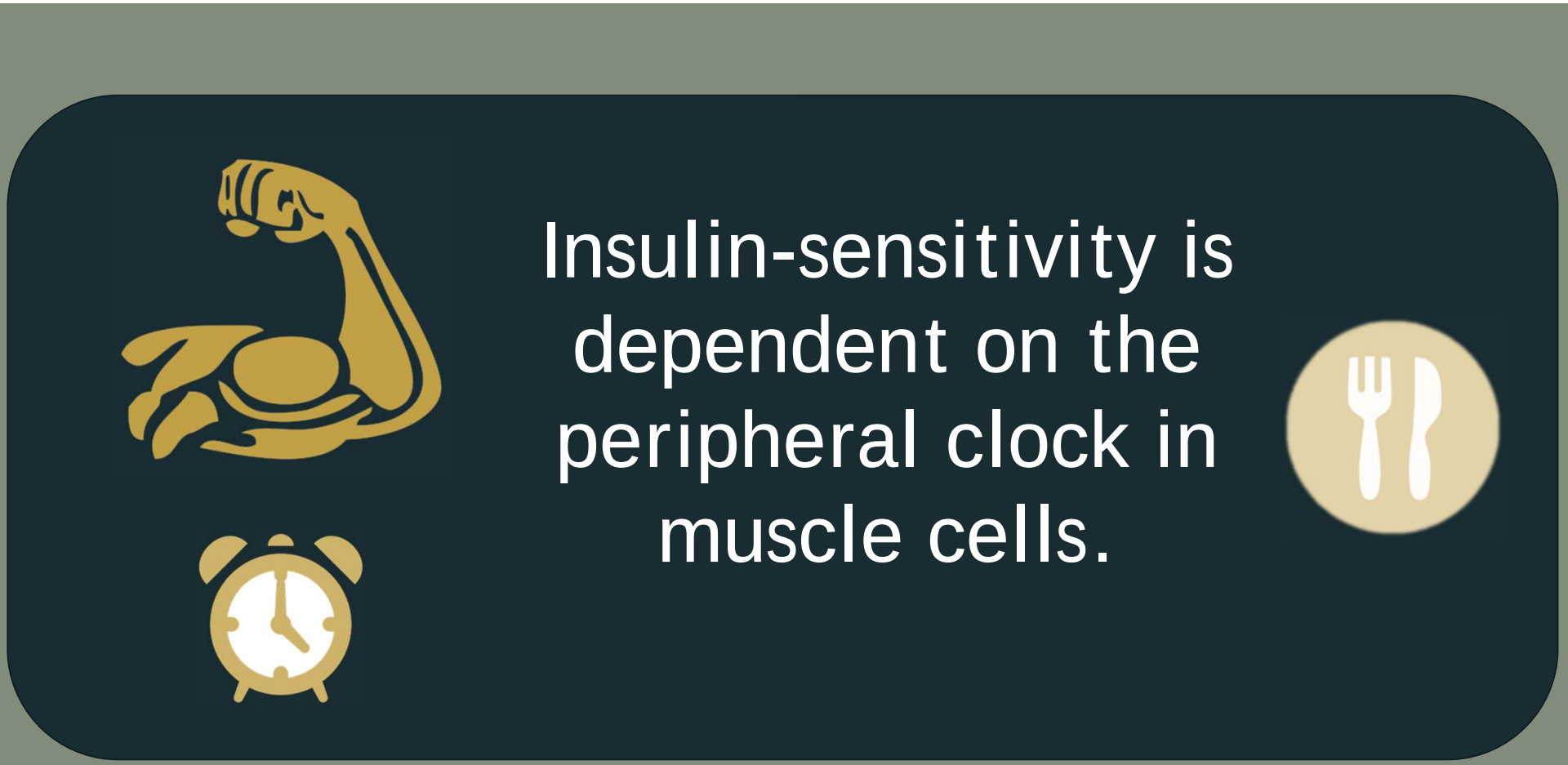
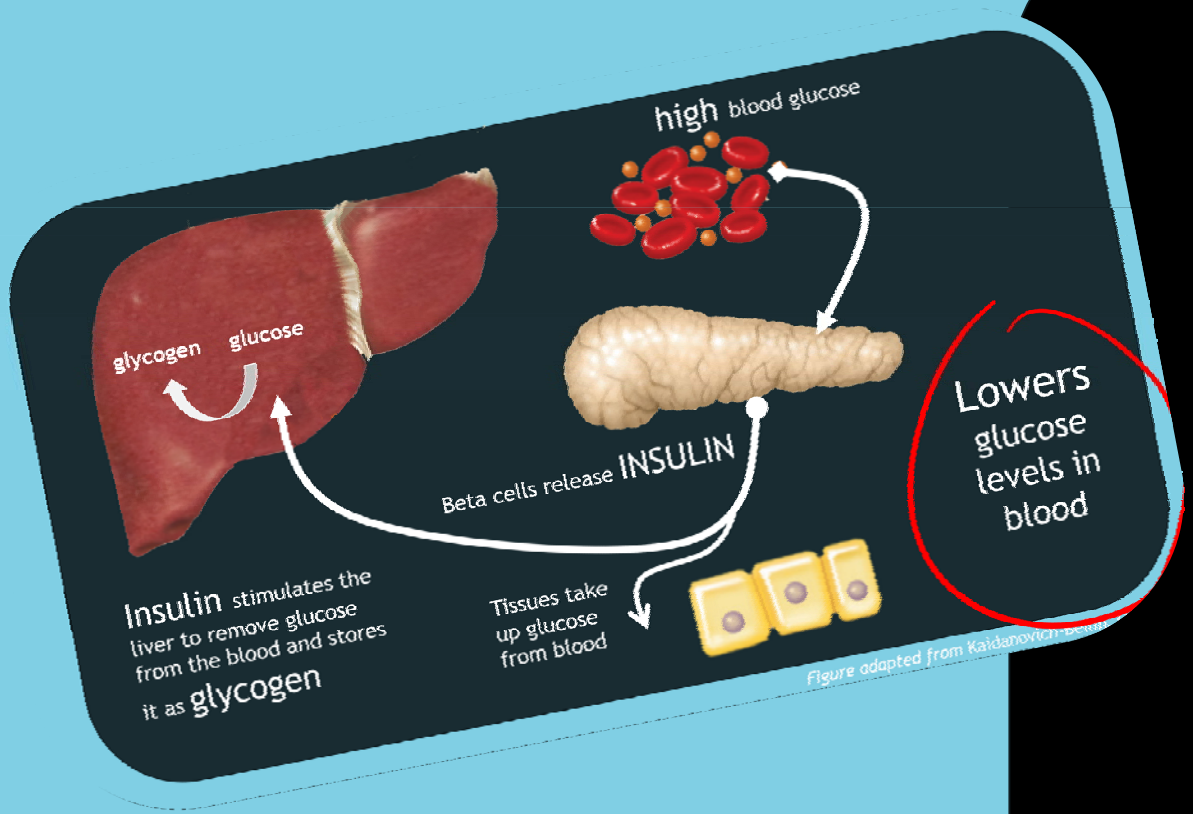


Figure adapted from Kaidanovich-Beilin, O. et al 2012



Glucose uptake in muscle is dependent on the circadian rhythm.



Insulin activates insulin receptors in the brain → affects feeding behaviors, reward, body metabolism, normal emotion & cognitive behaviors.

insulin receptors are found throughout the brain – cortex, midbrain and hypothalamus.

The risk of developing Alzheimer's disease is increased by 50 percent in people with diabetes.

Craft, S. Nat. Rev. Neurol. 8, 360–362 (2012);

Diabetes is a risk factor for dementia

J Neural Transm (1989) 75: 227–232

Journal of Neural Transmission

Cerebral excess release of neurotransmitter amino acids subsequent to reduced cerebral glucose metabolism in early-onset dementia of Alzheimer type

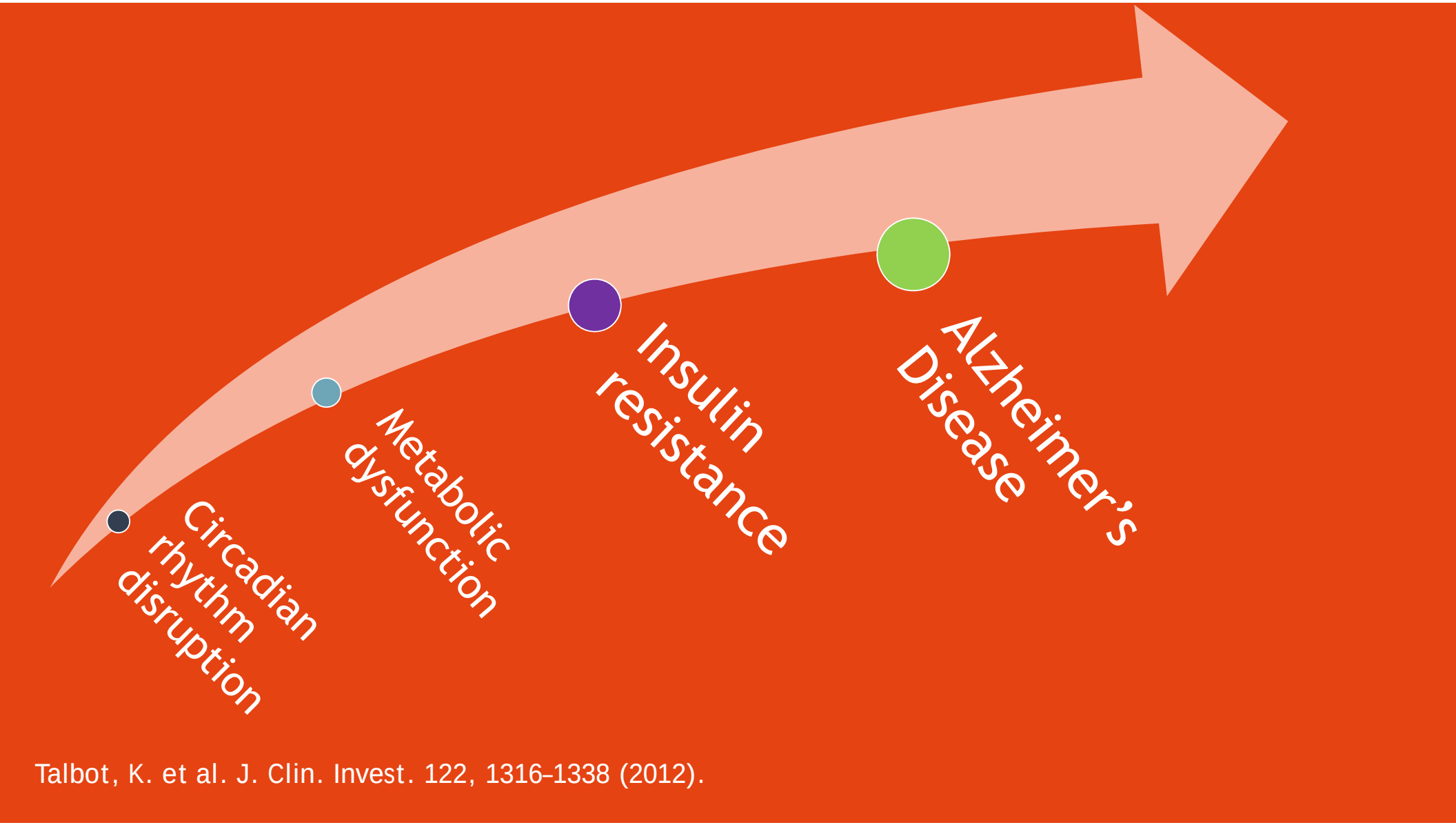
Short Note

S. Hoyer and **R. Nitsch**

Department of Pathochemistry and General Neurochemistry, University of Heidelberg, Heidelberg, Federal Republic of Germany

Accepted November 2, 1988

Summary. A massive cerebral release of amino acids and ammonia was found in early-onset dementia of Alzheimer type. Aspartate and glycine were liberated whereas glutamate remained rather unchanged. This [illegible] in cerebral glucose



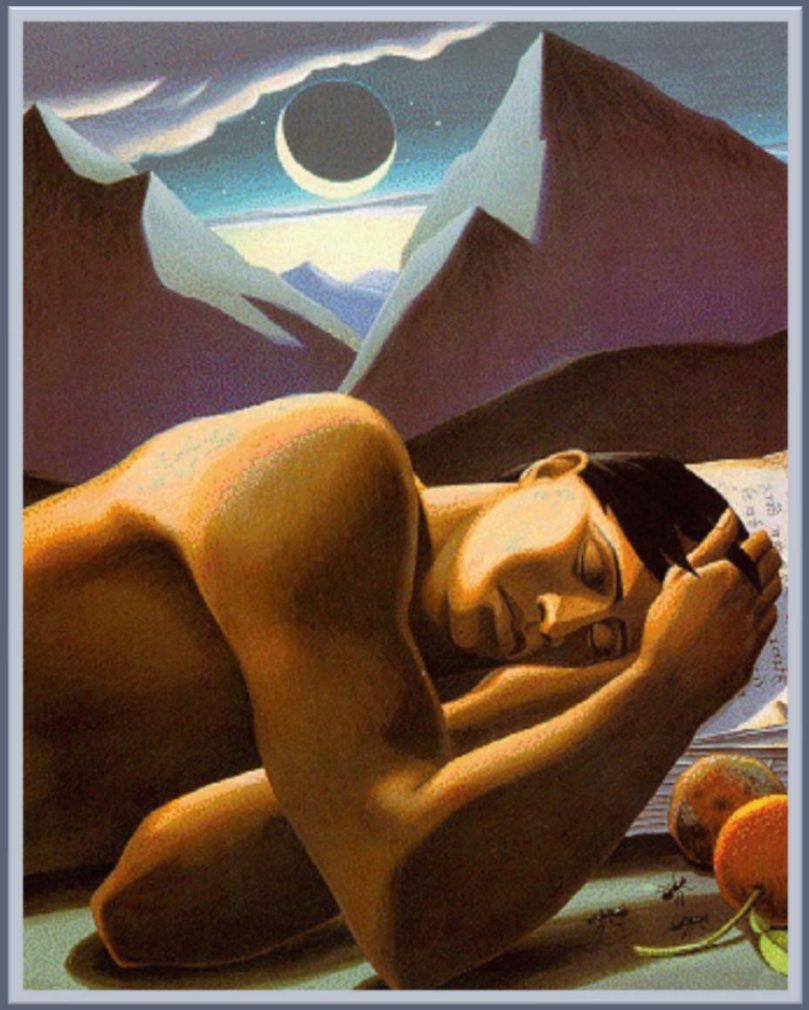
Talbot, K. et al. J. Clin. Invest. 122, 1316–1338 (2012).

Alzheimer's Disease

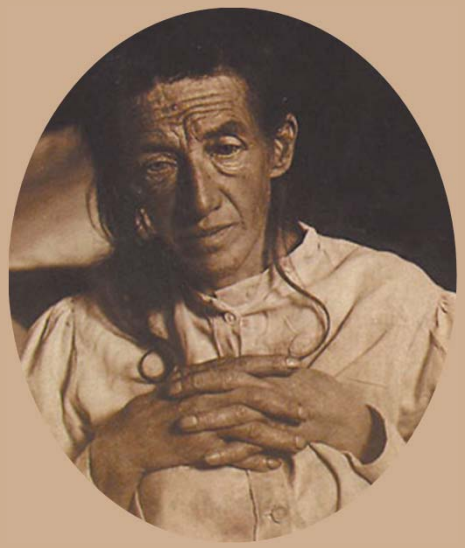
A mind in darkness awaiting the drink of a gentle color.

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD

Gabriel García Márquez



One Hundred Years of Solitude



- Case of Auguste D., 50 year old woman in Germany - 1906
- Her disruptive behavior prompted her husband to see Dr. Alois Alzheimer.

dementia appeared before she was 50 years old

Auguste showed signs of dementia such as:
Loss of memory
Delusions
Temporary vegetative states

insight: dementia is physical

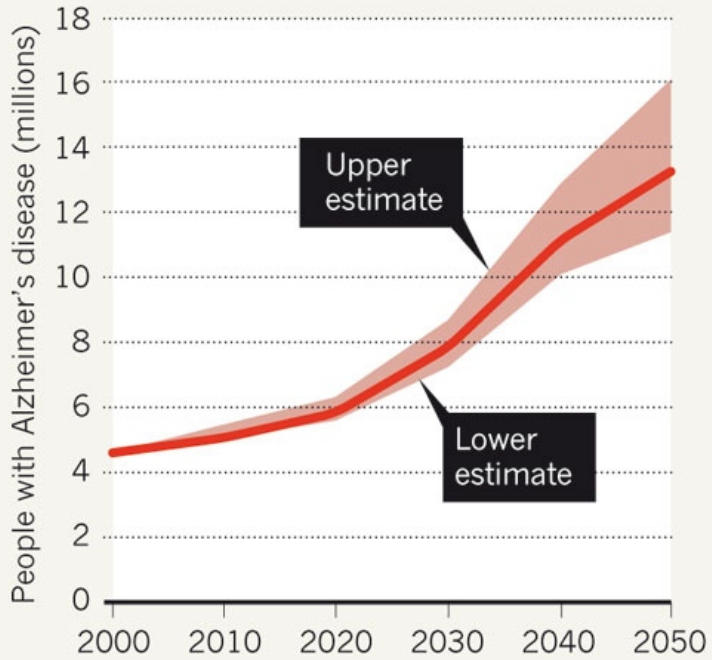
- Alzheimer examined Auguste D.'s brain.
- Discovered plaques and tangles.
- At the time it was thought that dementia was normal aging.

Sleep disturbances:
Trouble sleeping
"drag sheets across the house and scream for hours in the middle of the night."

http://en.wikipedia.org/wiki/Auguste_Deter

DEGENERATION GENERATION

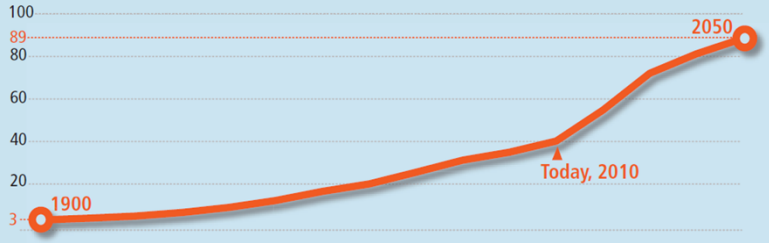
The prevalence of Alzheimer's disease is expected to rise sharply in the United States as its population ages.



L. E. Hebert et aL. Arch. Neurol. 69, 670–671 (2012)

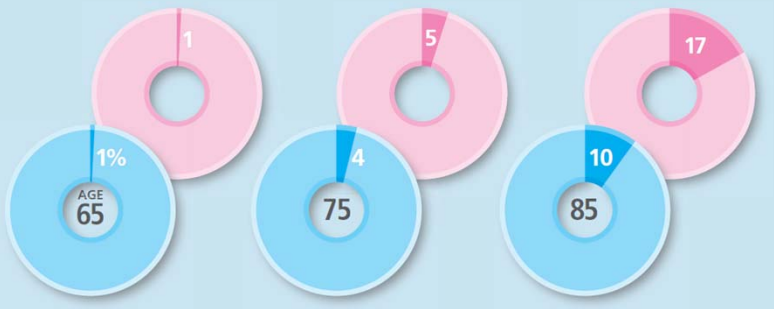
THE POPULATION IS AGING ...

Millions of people aged 65 and older, living in the U.S.



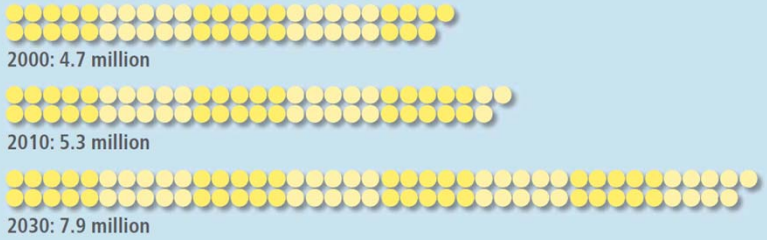
... AND AGE IS THE BIGGEST RISK FACTOR FOR ALZHEIMER'S ...

Risk of developing Alzheimer's at a given age over the next 10 years, for males and females.



... SO THE NUMBER OF CASES IS GROWING

Numbers of people diagnosed with Alzheimer's will increase by nearly 50 percent during the next 20 years.
1 dot represents 100,000 people diagnosed with Alzheimer's.



Scientific American (June 2010) *Alzheimer's:* **Forestalling the Darkness**

EARLY ONSET:

Memories begin failing in one's 40s, occasionally as early as 32.

By 47, on average, full-blown Alzheimer's develops.

New York Times, The Vanishing Mind 2010

THE VANISHING MIND

Alzheimer's Stalks a Colombian Family

The New York Times

YARUMAL, Colombia — Tucked away on a steep street in this rough-hewn mountain town, an old woman found herself diapering her middle-age children.

At frighteningly young ages, in their 40s, four of Laura Cuartas's children began forgetting and falling apart, assaulted by what people here have long called La Bobera, the foolishness. It is a condition attributed, in hushed rumors, to everything from touching a mysterious tree to the revenge of a wronged priest.

It is Alzheimer's disease, and at 82, Mrs. Cuartas, her gray raisin of a face grave, takes care of three of her afflicted children.

One son, Darío, 55, babbles incoherently, shreds his socks and diapers, and squirms so vigorously he is sometimes tied to a chair with baggy blue shorts.

A daughter, María Elsy, 61, a nurse who at 48 started forgetting patients' medications, and whose rages made her attack a sister who bathed her, is a human shell, mute, fed by nose tube.

Another son, Oderis, 50, denies that his memory is dying, that he remembers to buy only one thing at a time: milk, not milk and plantains. If he gets Alzheimer's, he says, he will poison himself.

"To see your children like this ... ," Mrs. Cuartas said. "It's horrible, horrible. I wouldn't wish this on a rabid dog. It is the most terrifying illness on the face of the earth."

For generations, the illness has tormented these and thousands of others among a sprawling group of relatives: the world's largest family to experience Alzheimer's disease. Now, the Colombian clan is center stage in a potentially groundbreaking assault on Alzheimer's, a plan to see if giving treatment before dementia starts can lead to preventing Alzheimer's altogether.

Most family members come from one Andes region, Antioquia. Geography, and Basque ancestry, have isolated people here, who call themselves paisas, countrymen. Over three centuries, many in this clan of 5,000 people have inherited a single genetic mutation guaranteeing that they will develop Alzheimer's.

Large families, and intermarriage, have accelerated the spread. Mrs. Cuartas's fourth debilitated child, in Medellín, Carlos Alberto Villegas, a former livestock trader and guitar serenade her now often fed by baby bottle, married a distant cousin. His mother-in-law is an addled ghost; three of his wife's 11 siblings, so far, are developing dementia.

With Alzheimer's in both parents' families, Mr. Villegas's three children could face extraordinary risk. One, Natalia, 22, asks: "How long have I got, till I'm 35? There's no way out."

Memories begin failing in one's 40s, occasionally as early as 32. By 47, on average, full-blown Alzheimer's develops.

Their form of Alzheimer's, early-onset, was once considered too different to provide clues about far more common late-onset Alzheimer's, which has unknown causes and primarily affects people over 65.

But it turns out that both forms produce nearly identical brain changes and symptoms. Now, scientists will test as-yet-unproven treatments on Colombians genetically destined for Alzheimer's but not yet showing symptoms. They will give a to-be-determined drug or vaccine and see if it prevents memory loss or brain atrophy. If their disease can be halted, that could generate treatments to protect millions worldwide from common Alzheimer's.

Devising an Early Attack

Alzheimer's has repeatedly resisted attempts to treat it. Current drugs, for people who are already impaired, show little benefit. Now scientists want to attack earlier. New findings show "the brain is badly damaged by the time they have dementia," said Dr. John C. Morris, an Alzheimer's researcher at Washington University in St. Louis. "Perhaps the reason our therapies have been ineffective or mostly ineffective is that we're administering them too late."

With Alzheimer's afflicting 5.3 million Americans and 30 million people worldwide, numbers that some predict will double or triple by 2050, "we can't wait to try to do prevention until we are absolutely certain what causes" the disease, said Neil Buckholtz, chief of dementias of aging at the National Institute on Aging. "This public health emergency," he said, is "just going to get out of control if we don't do something."

But preventive research is difficult. Participants should be people guaranteed, or highly likely, to develop dementia, and with common Alzheimer's identifying such people is challenging because the disease's cause is

Over three centuries, many in this lineage of 5,000 people have inherited a single genetic mutation guaranteeing that they will develop Alzheimer's.

New York Times, The Vanishing Mind 2010

A Clouded Inheritance

A group of 25 families in Colombia has inherited a genetic mutation from common ancestors, making members prone to early-onset Alzheimer's.

At right, Alzheimer's cases among the founding members of the clan and some of their early descendants, who number in the thousands today.

KEY

- *No Alzheimer's*
- *Suspected cases*
- *Known cases*

Javier San Pedro Gómez
Lived into his 70s

María Luisa Chavarriaga Mejía
Suspected carrier of the Paisa mutation

Born circa 1745

Mauricio
Common ancestor of Carlos Alberto and Blanca Nelly

1770

1790

1810

1850

1890

1910

PAISA MUTATION
The inherited disease is caused by a mutation of the presenilin 1 gene on chromosome 14.

Note: the chart has been simplified and does not show all children or descendants.

TODAY Carlos Alberto Villegas, his wife and their siblings descend from a common ancestor, circled above, who had the Paisa mutation.

Carlos Alberto, 53. *Onset of memory problems at 41.*

María Elsy, 61 **(his sister)** *48 at onset.*

Darío, 55 **(his brother)** *47 at onset.*

Oderis, 50 (his brother) *46 at onset.*

Blanca Nelly, 41 **(his wife)** *Currently no symptoms.*

William, 48 (her brother) *45 at onset.*

Gladys, 36 **(her sister)** *Too afraid to have childen.*

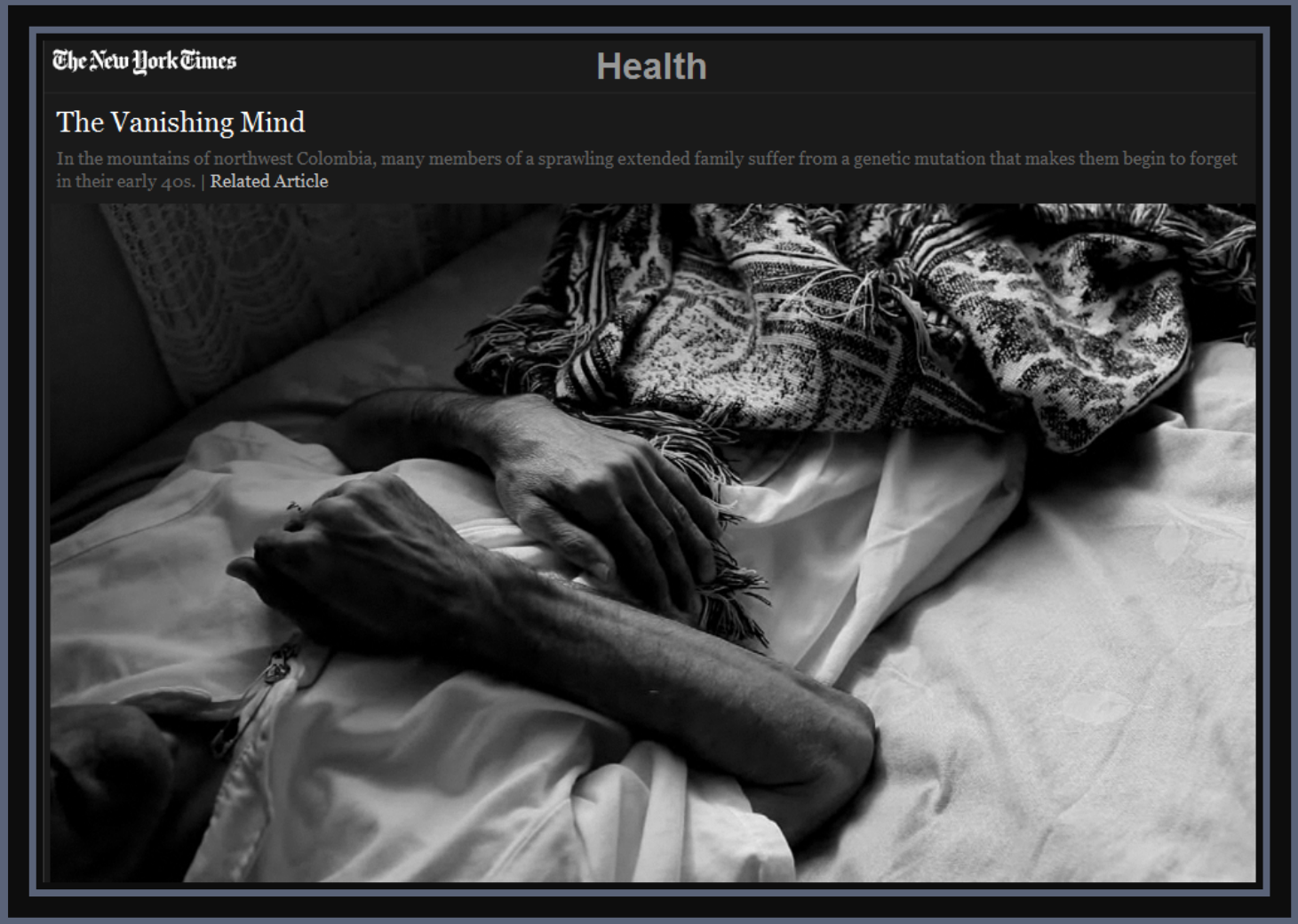
Liliana, 29 **(her sister)** *Terrified of any memory lapse.*

Two sisters show early symptoms but deny it.

Source: University of Antioquia

New York Times, The Vanishing Mind 2010

THE NEW YORK TIMES



New York Times, The Vanishing Mind 2010

eFAD

- Early onset familial Alzheimer disease – symptoms can start in 30's, 40's or 50's

family

- Dominant genetic trait
- One parent had eFAD
- Siblings: 50%

same, (mostly)

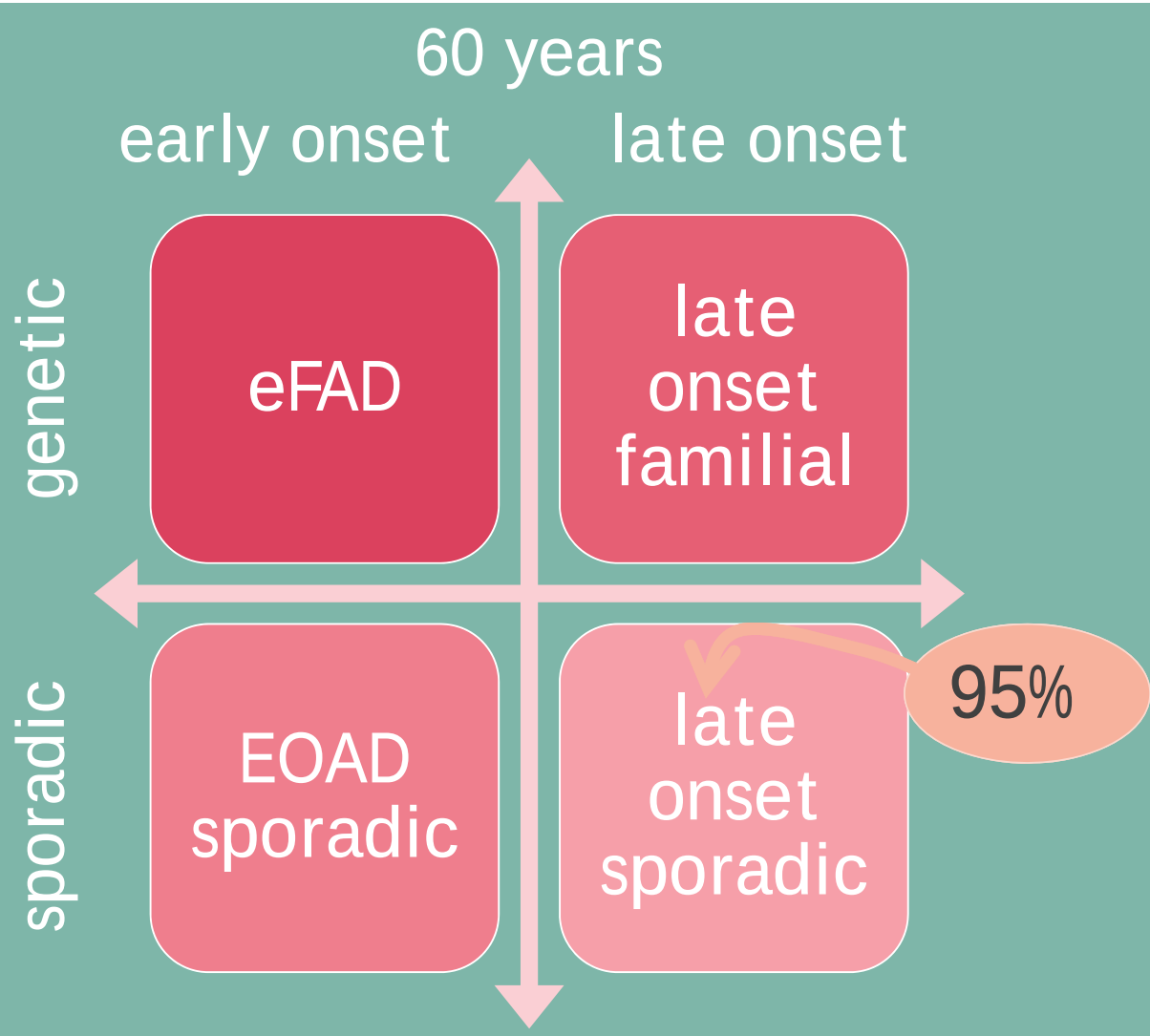
- eFAD and late-onset AD is essentially has the same clinical phenotype – however, they may have different etiologies.

"accounts for less than 1 percent of the 27 million Alzheimer's cases worldwide documented in 2006"

200,000 is the number of people with AD who are younger than 65.

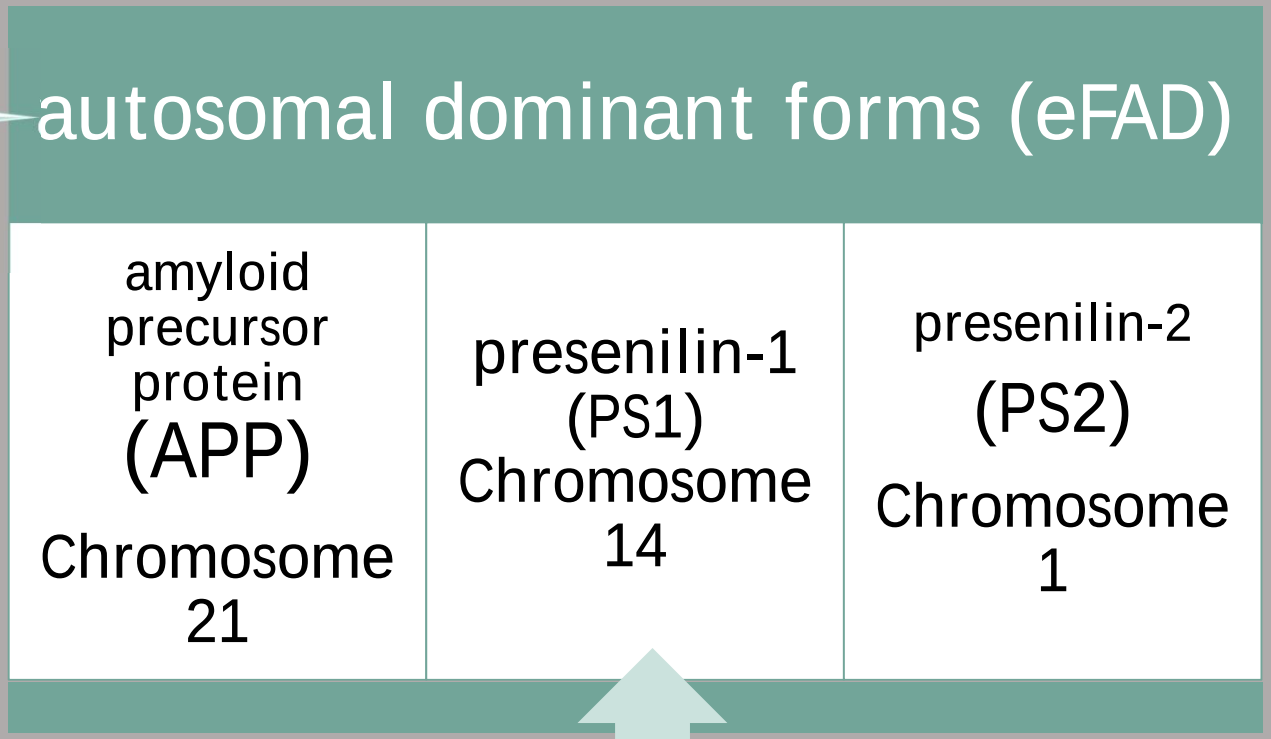
http://www.alz.org/national/documents/topicsheet_alzdisease.pdf

- eFAD is the consequence of mutated genes.
- Late-onset disease is more likely due to a gradual accumulation of age-related malfunctions.



Brickell, K. L. et al *Arch Neurol.* 2006;63(9):1307-1311

these are deterministic mutations



Accounts for most eFAD

Brickell, K. L. et al *Arch Neurol.* 2006;63(9):1307-1311

these are genetic risk factors

12 to 15 fold increase risk for AD with two copies of ApoE4

Not autosomal dominant (ApoE)

ApoE4

ApoE4 is thought to lower the age of onset by a decade

Note:
Amyloid-B is cleared from the brain by attaching to ApoE. If it is not attached it can become toxic to the brain

Brickell, K. L. et al *Arch Neurol.* 2006;63(9):1307-1311

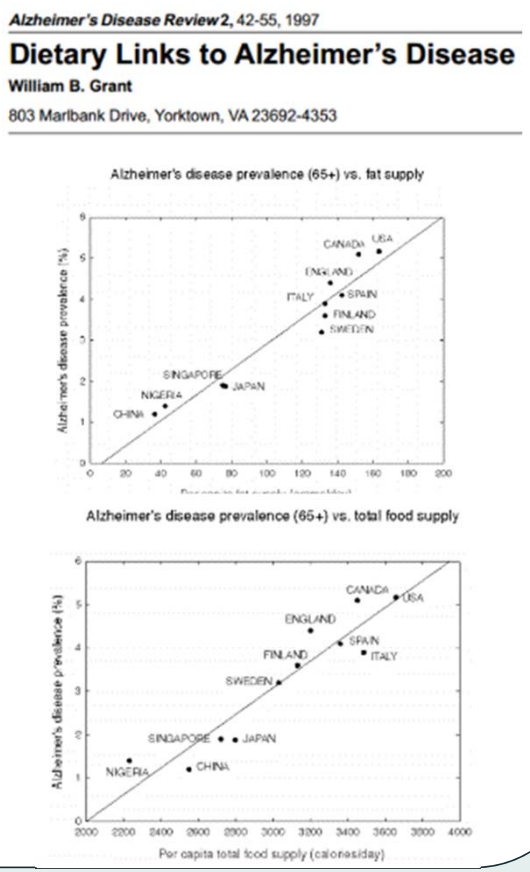
what increases the risk of 95% of the LOAD?

amyloid cascade hypothesis

- peptides generated from APP (amyloid precursor protein) cause AD
- so, reducing the generation or accumulation will treat the disease

diet hypothesis

- 1997 William Grant- correlated food consumption with AD worldwide
- found positive correlation between total calories and total fat in the incidence of AD.



Alzheimer's Disease Review 2, 42-55, 1997

Dietary Links to Alzheimer's Disease

William B. Grant

803 Marlbank Drive, Yorktown, VA 23692-4353

Alzheimer's disease prevalence (65+) vs. fat supply

Alzheimer's disease prevalence (65+) vs. total food supply

Grant, W. (1995) Alzheimer's Disease Review 2, 42-55