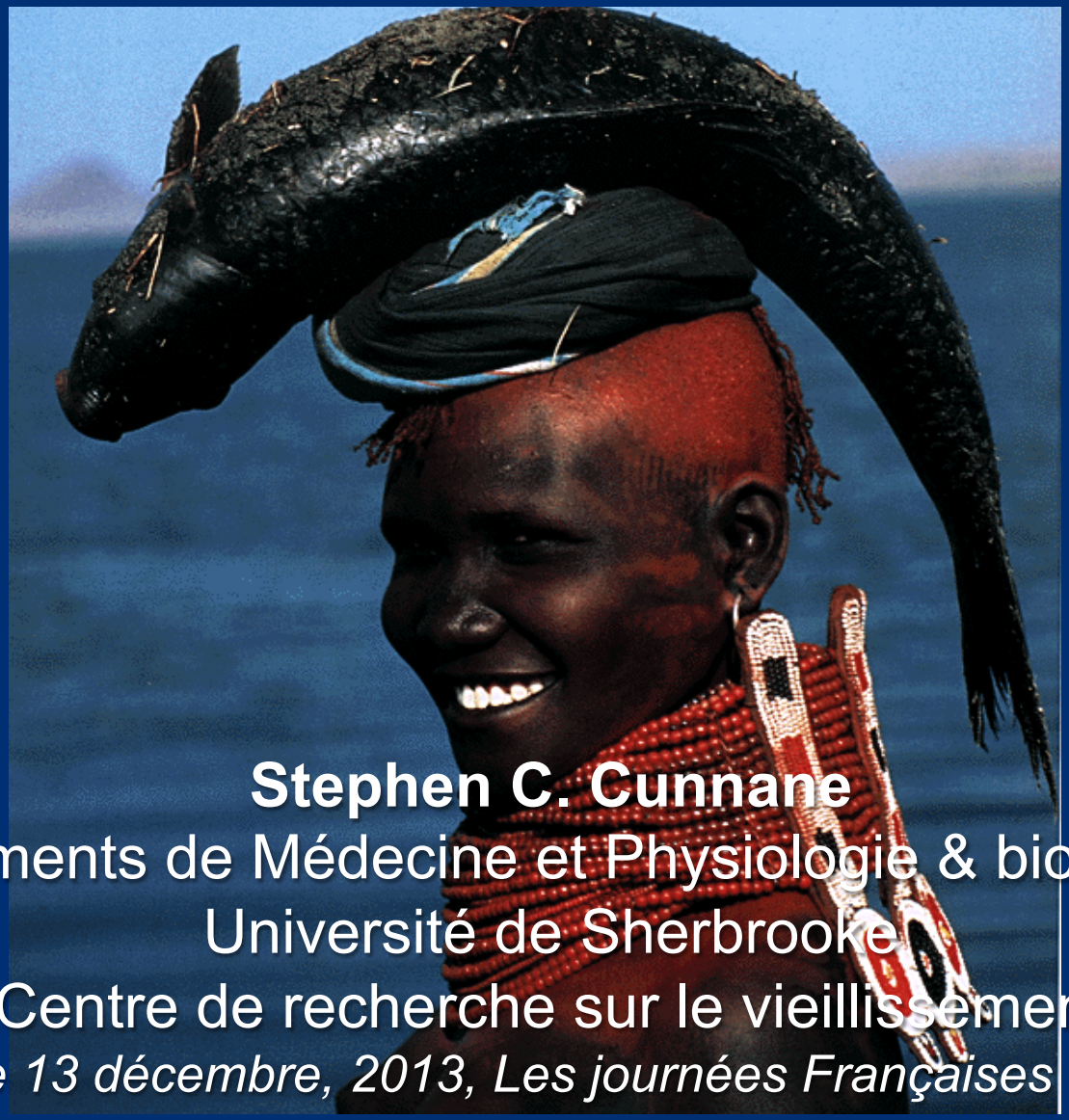
L'ÉVOLUTION DU CERVEAU HUMAIN:
des défis nutritionnels et énergétiques importants



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Centre de recherche sur le vieillissement

Bordeaux, le 13 décembre, 2013, Les journées Françaises de la Nutrition

(aucun conflit d'intérêt à déclarer)

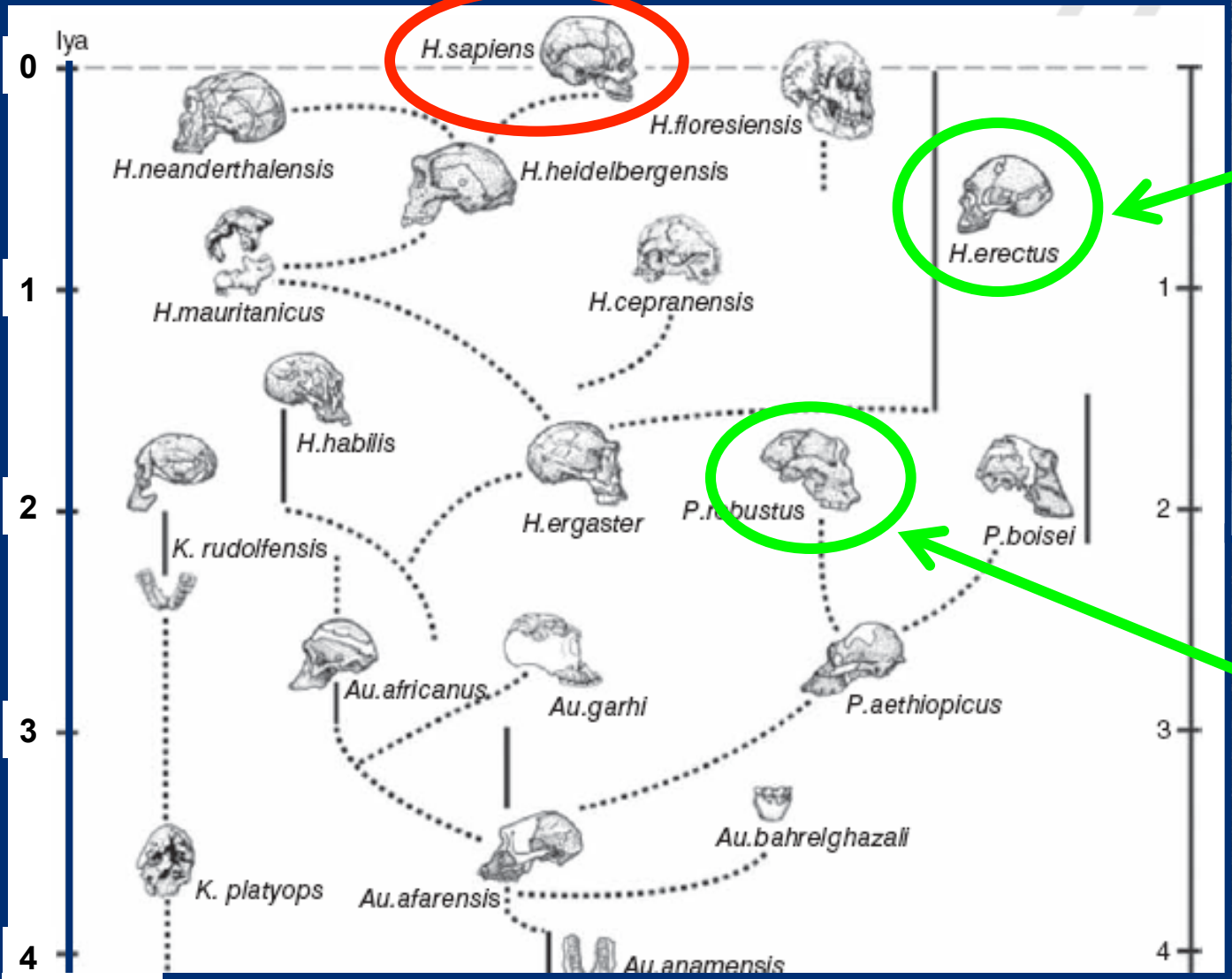
Humans: a burst of cognition, symbolic consciousness (art) and language

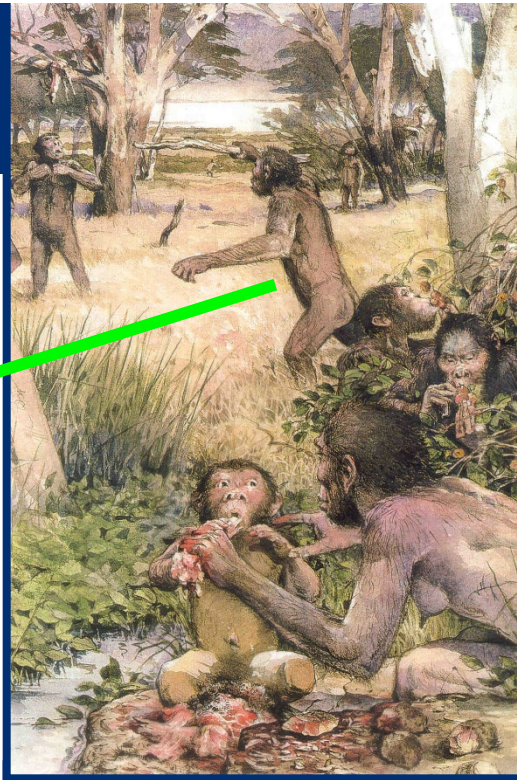
Lascaux

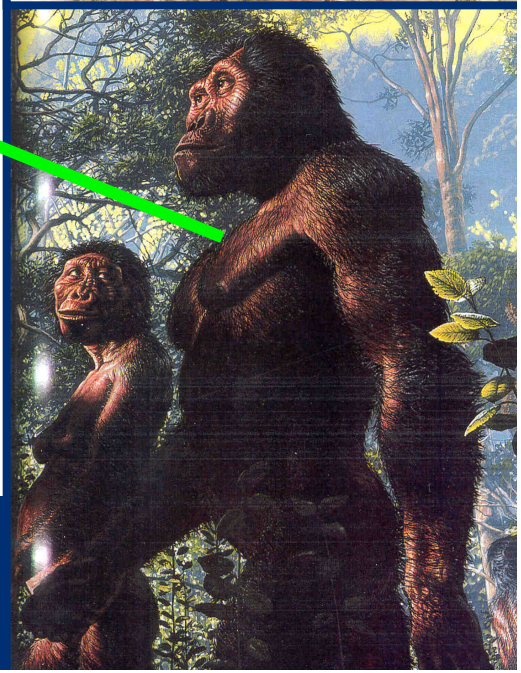
Rouffignac

L'abri du poisson

Hominin evolution – towards humans

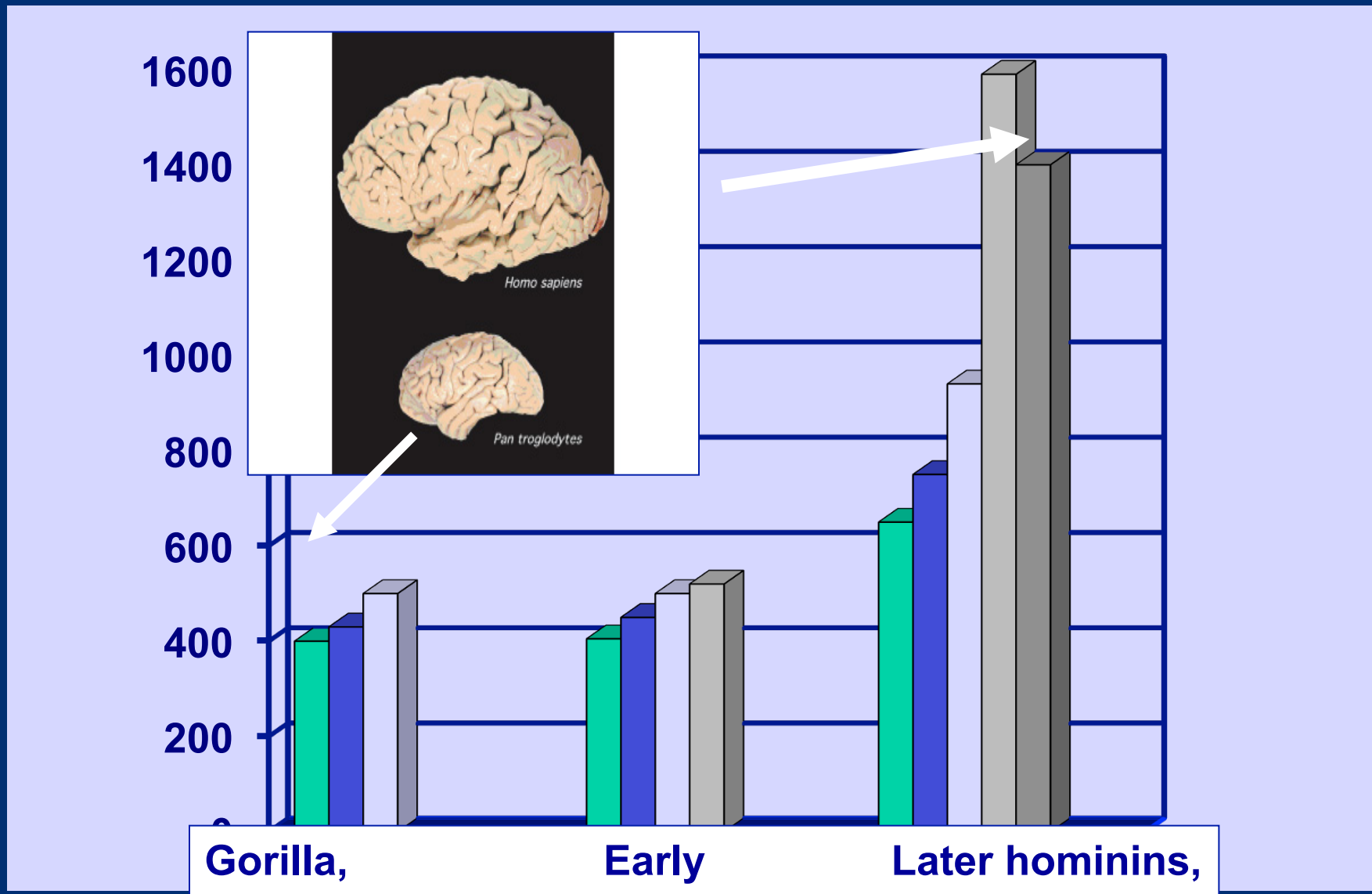






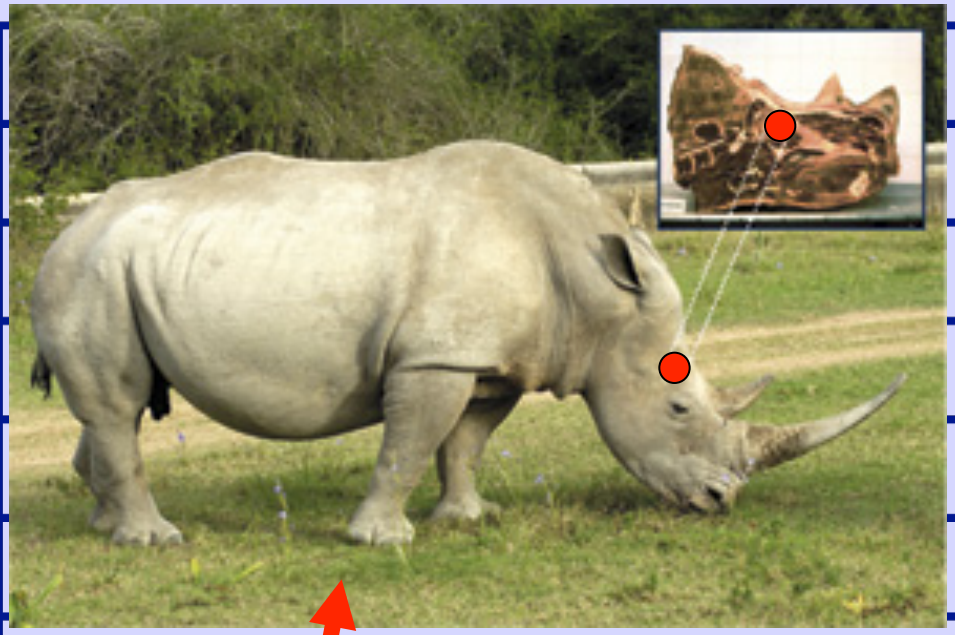
H - *Homo*, P = *Pananthropus*, Au – australopithecine
H. sapiens <150,000 ans

Brain weight (g) in adult primates



Brain to body weight ratios (%) in large mammals

(Michael Crawford)



2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0

Elephant
Rhino
Hippo
Ox
Primate
Dolphin
Human

Conventional explanation:

stone tools → hunting → meat-eating → big brain

PROBLEM –

Making sharp stone tools and using them to hunt are very sophisticated skills ….

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1. <u>require</u> a big brain, so how can tools be at the origin of the big brain?

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Making sharp stone tools and using them to hunt are very sophisticated skills ….

1. **<u>require</u> a big brain, so how can tools be at the origin of the big brain?**

2. **how does meat-eating explain the human brain's ongoing <u>developmental, functional vulnerability</u> ?**

Functional constraints: a new perspective

Key constraint:

Developmental brain vulnerability –

how was this vulnerability masked or overcome as the evolving hominin brain expanded ?

Normal human brain development depends on -

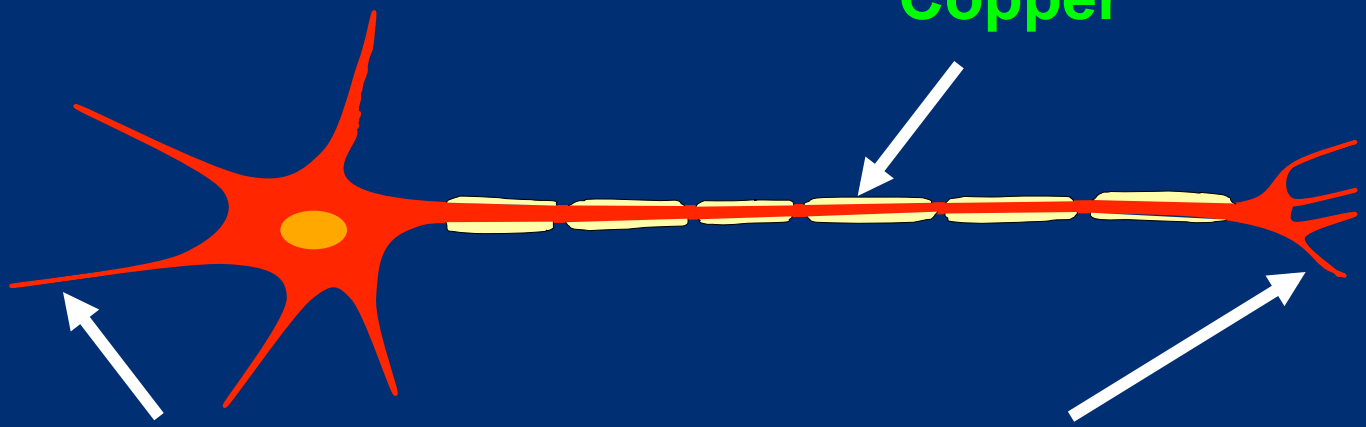
1. **a cluster of *brain selective nutrients***
2. **very high energy needs**

Solution:

multiple organ systems were implicated in assimilating the necessary *brain fuel insurance*

‘Brain selective nutrients’

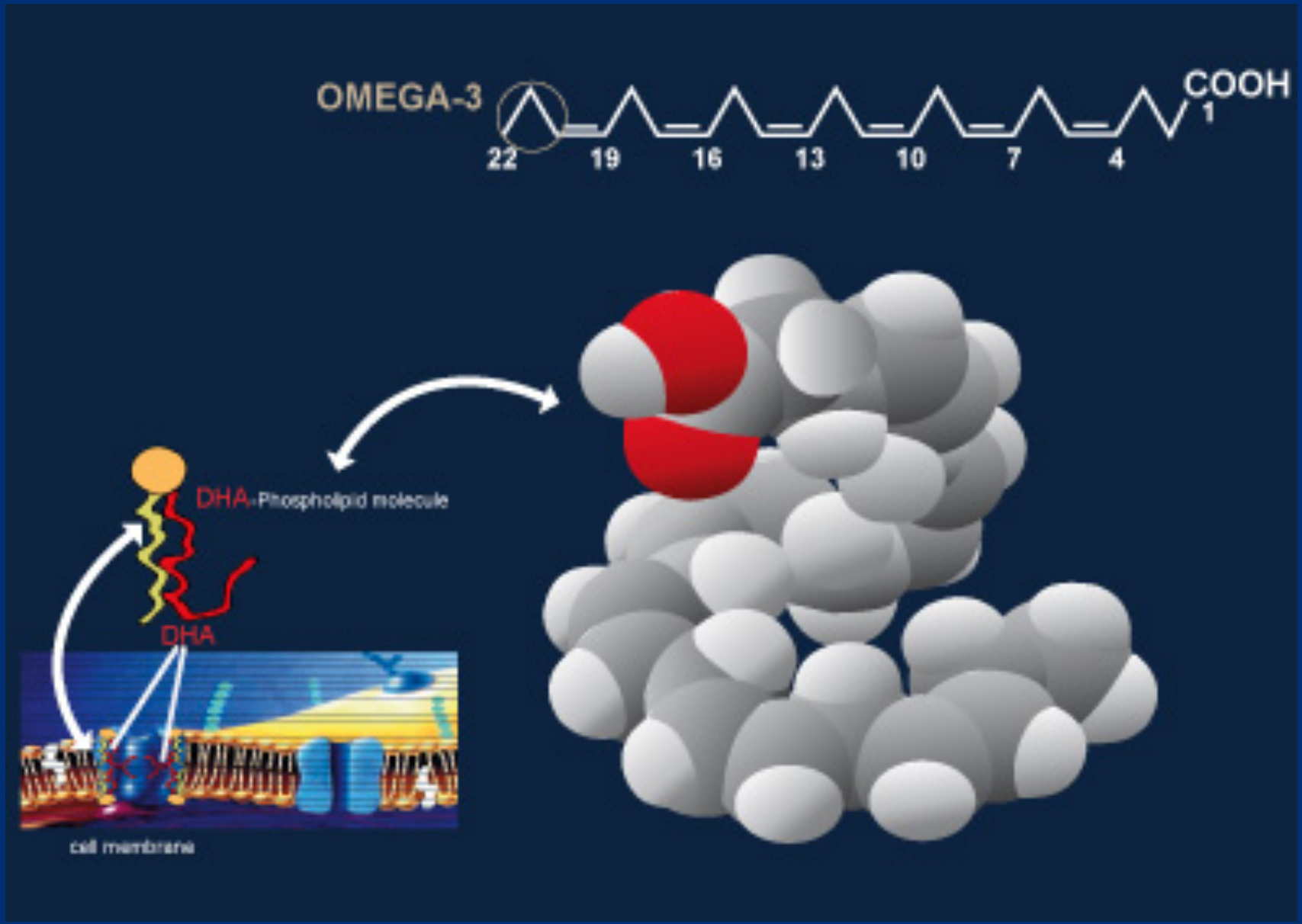
(Cunnane and Crawford, Nutr Health, 1993)



Brain’s, body’s energy management

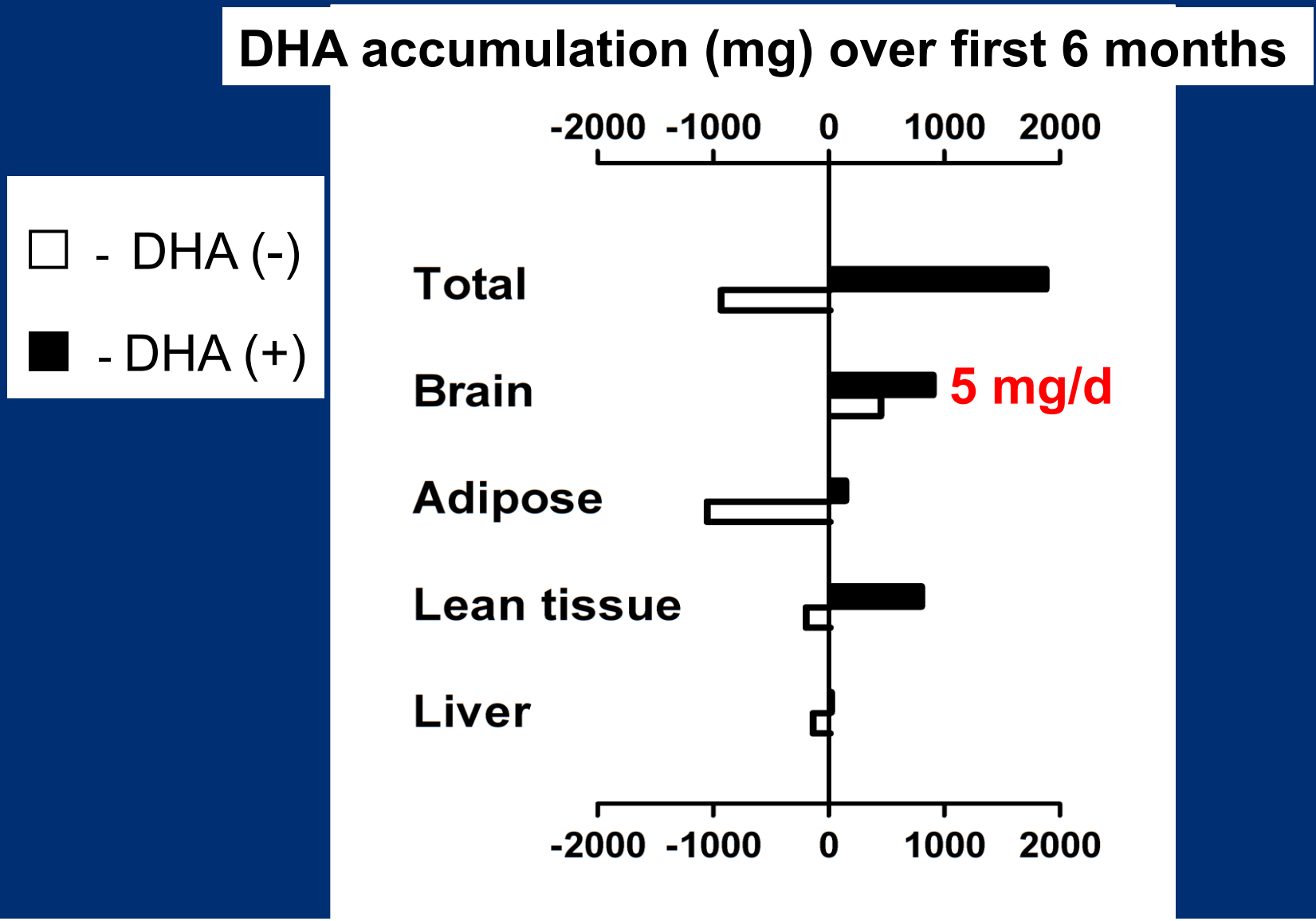
- **Iodine, Iron, Selenium**

Docosahexaenoic acid (DHA; 22:6ω3)



Brain DHA accumulation in infants depends on having DHA in the diet (milk)

(Farquharson et al 1995; Cunnane et al, Lipids, 2000)



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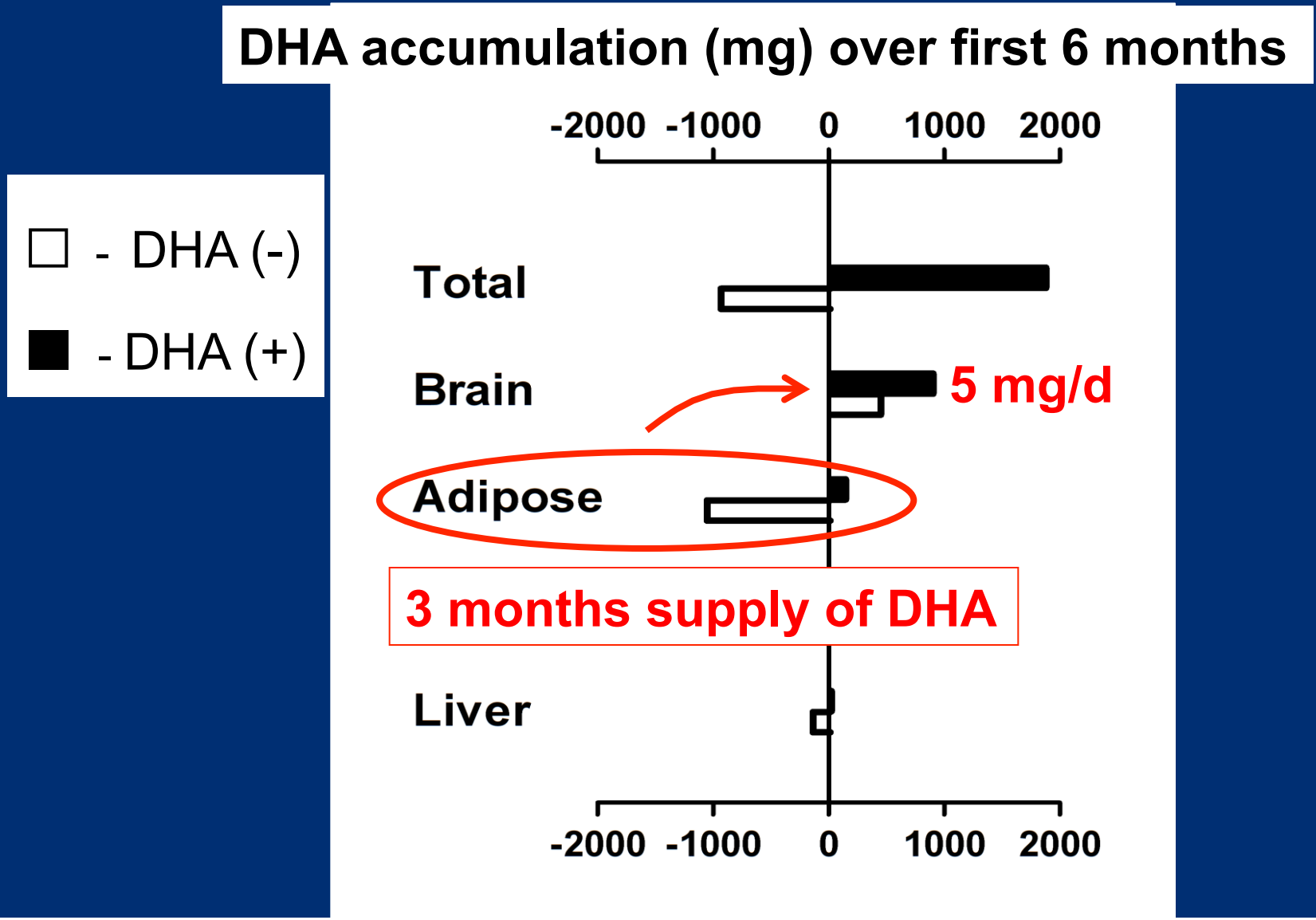
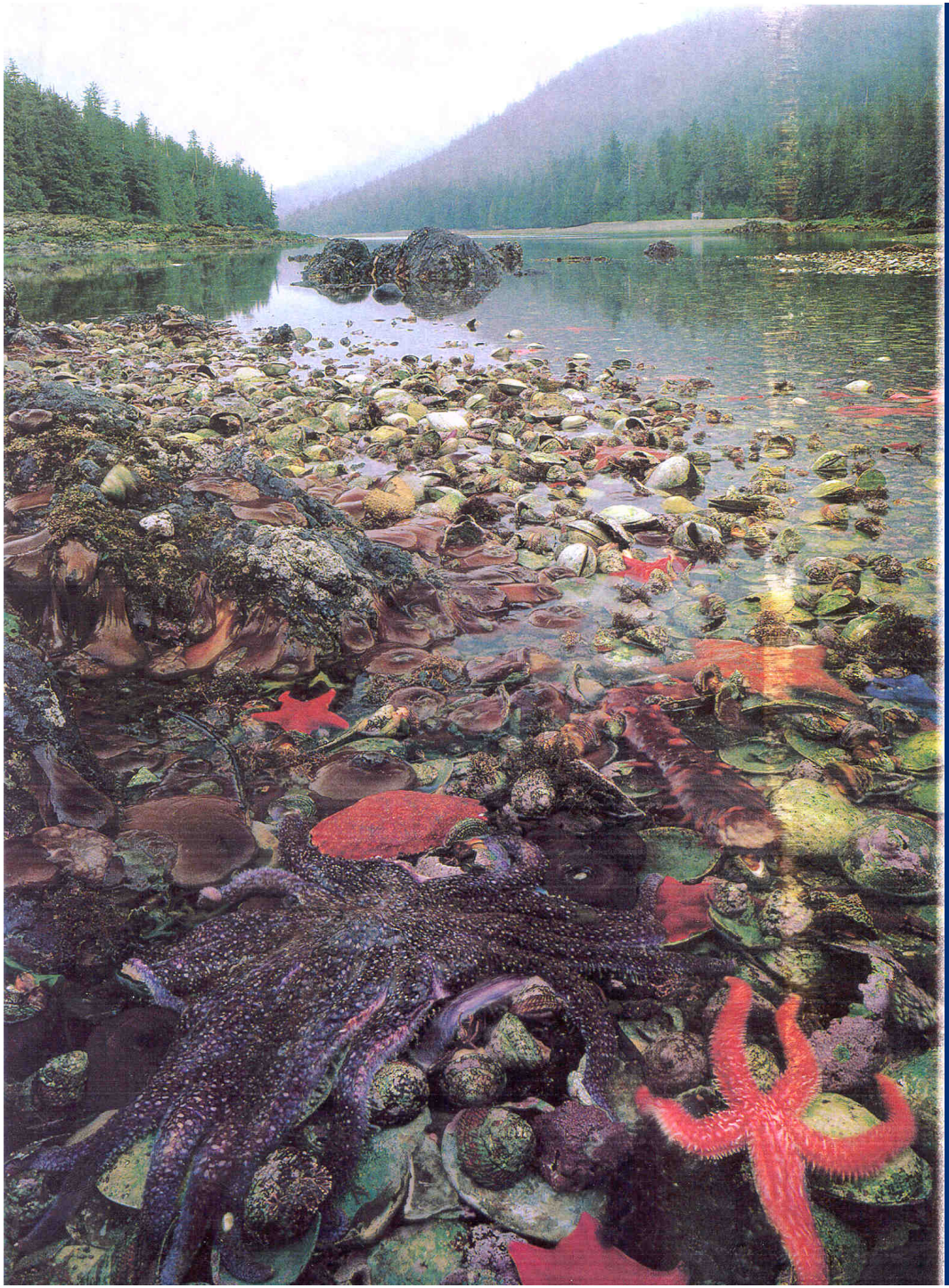


Iodine = body's 'energy management'

Iodine deficiency -

- **Commonest nutrient deficiency**
- **Causes goiter, suboptimal intelligence in >1 billion people worldwide**
- **Uncommon where fish and/or shellfish are eaten**

NOTE: Present day vulnerability to low iodine intake must have also been a challenge to brain evolution



Best dietary sources of 'brain selective minerals' (I, Fe, Se, Zn, Cu)

	Amount (kg) needed/day
Shellfish	0.9
Eggs	2.5
Fish	3.5
Meat	5.0
Nuts	5.5
Vegetables	8.7
Fruit	9.3

(Cunnane, 2005)

Cro-Magnon salmon

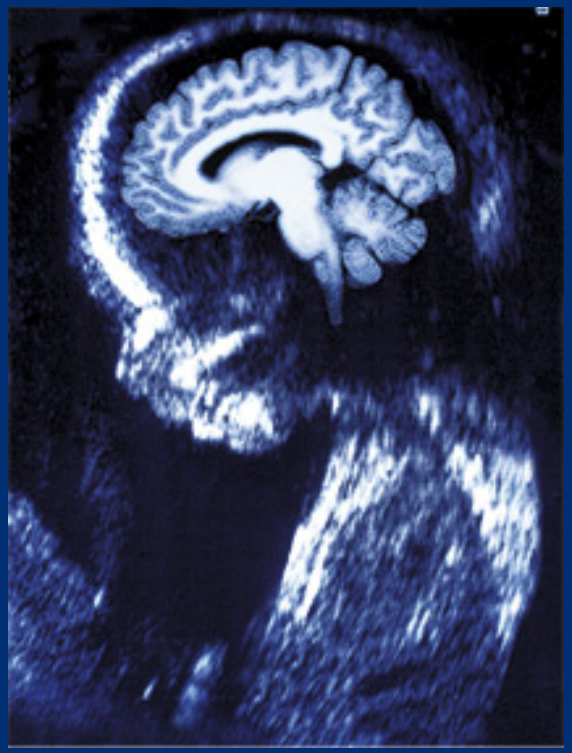
(Perigord region, France; 25,000 years ago)

ibut

Vulnerability of human brain development

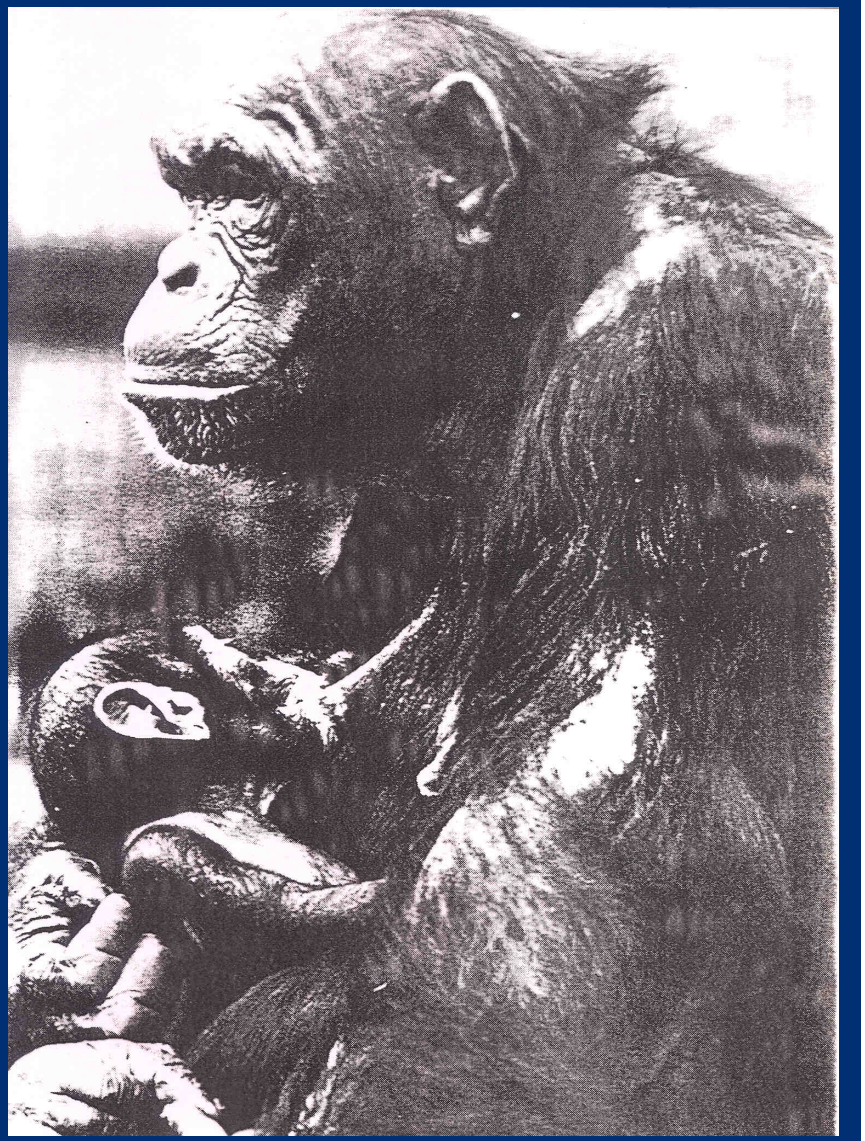
- Very high energy requirement
- Low/very low birth wt = low body fat =
  ↑ risk of neurodevelopmental delay
- Neurodevelopmental delay = lifelong deficit

BODY WEIGHT	BRAIN WEIGHT	% ENERGY TO BRAIN
Newborn (3.5 kg)	400 g	74
Adult (70 kg)	1400 g	23



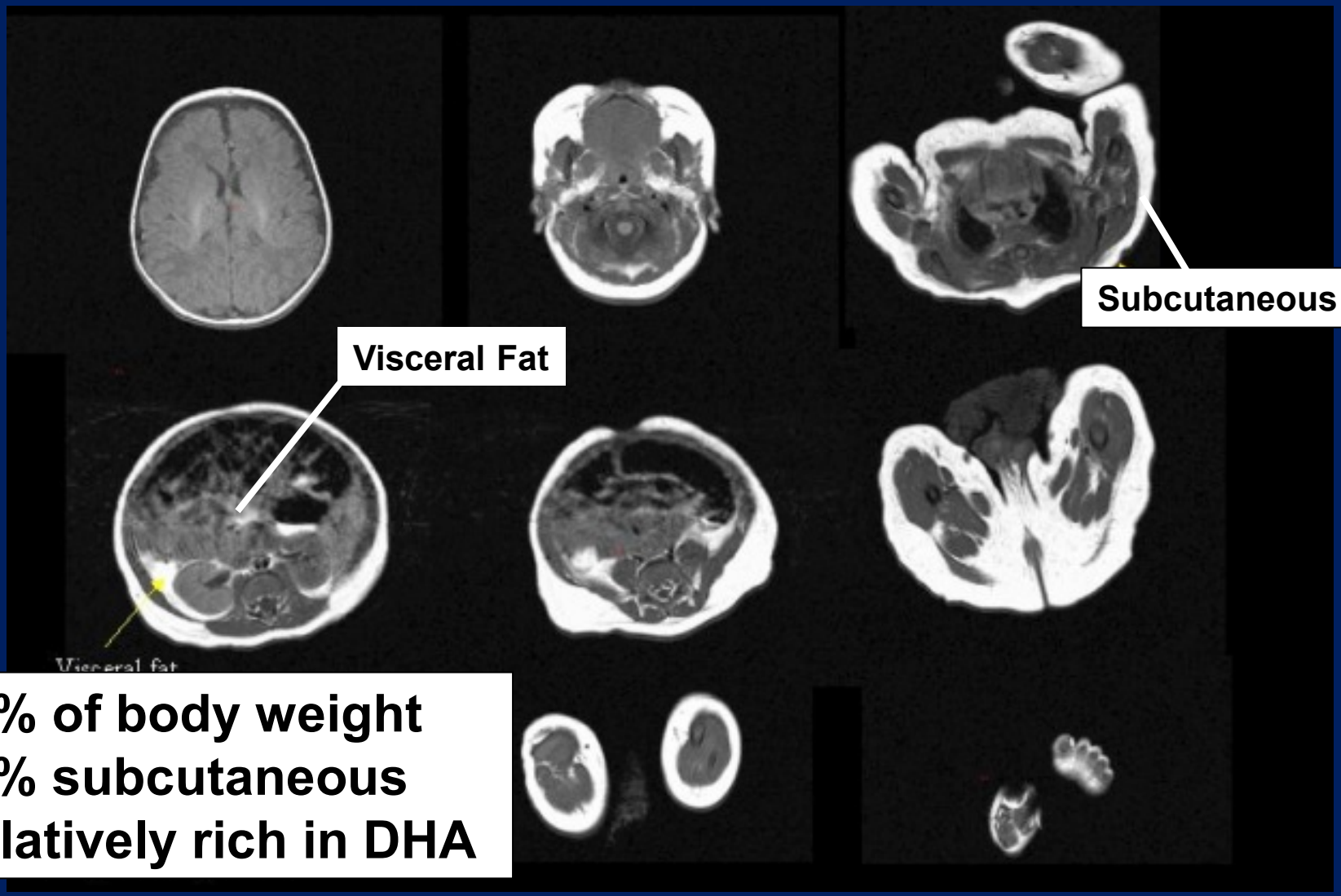
Chimpanzee infant

Similar brain size at birth to human infants (10-11%) but very low body fat (like premature human infants…)



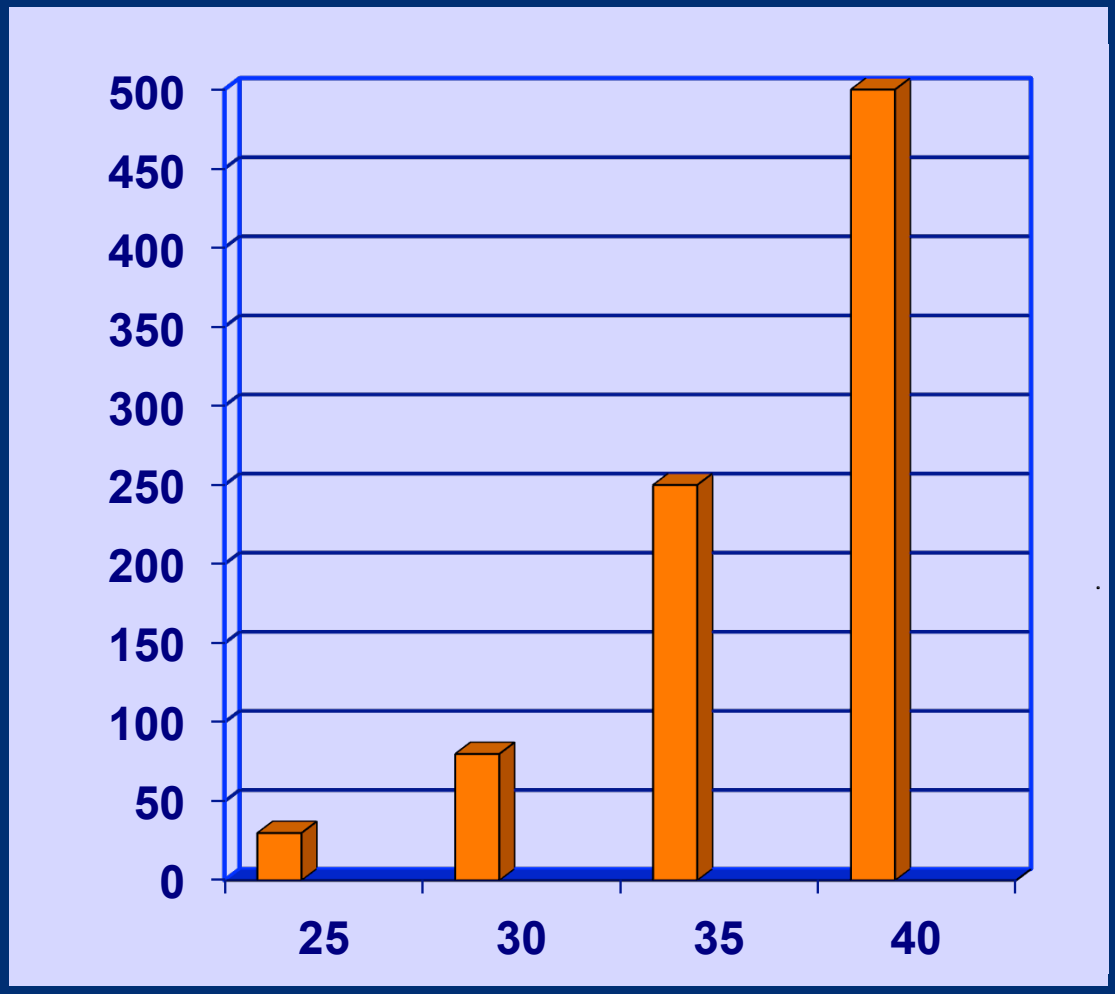
Amongst primates, humans are unique in having fat babies

(Harrington et al, Lipids, 2002)



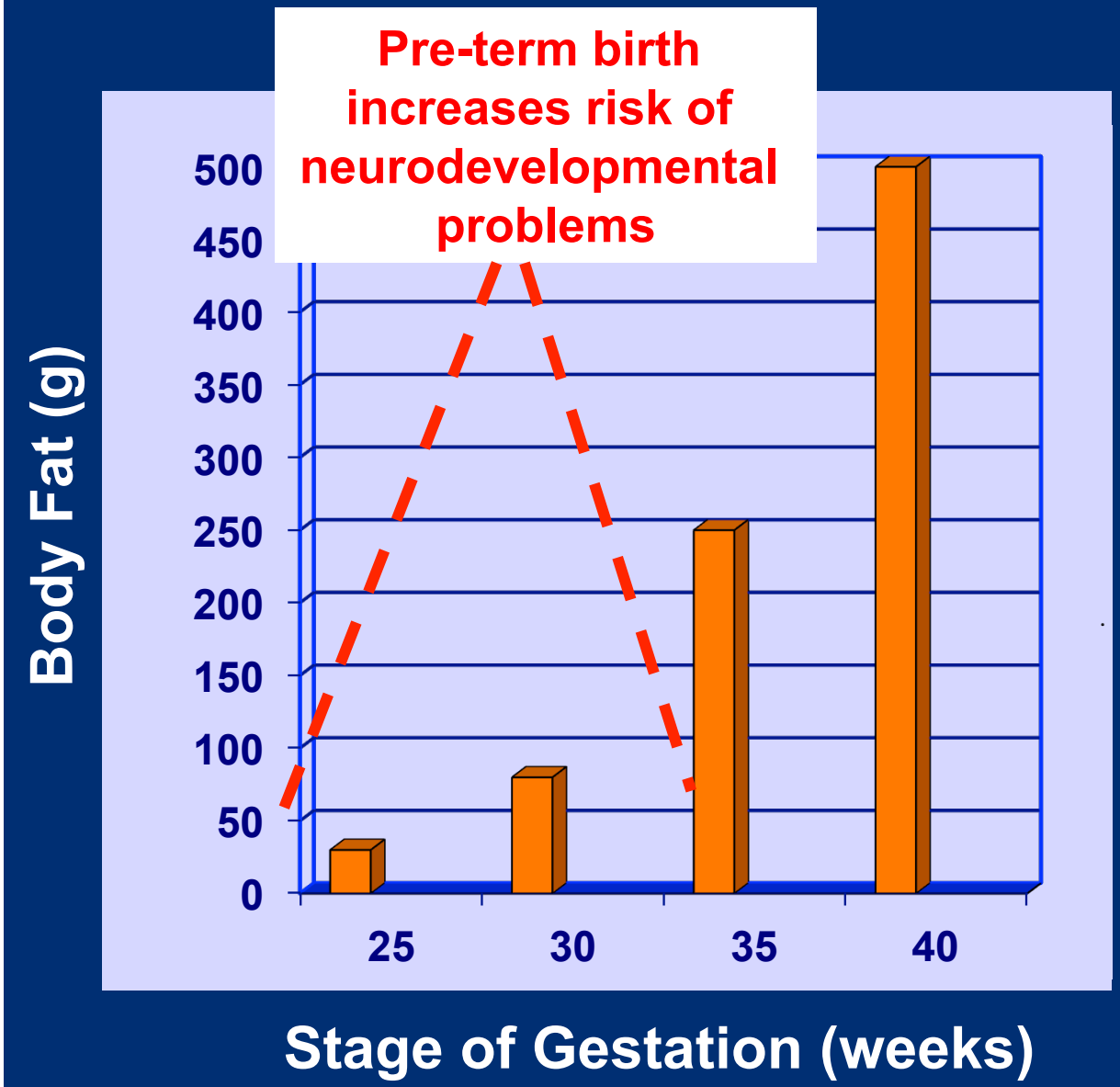
- 15% of body weight
- 89% subcutaneous
- Relatively rich in DHA

Fat deposition on the human fetus



1. 12-14% of birth weight is fat
2. 1 gram of pre-formed DHA (3 months supply for the brain)
3. 500 grams of fuel.

Fat deposition on the human fetus



1. 12-14% of birth weight is fat
2. 1 gram of pre-formed DHA (3 months supply for the brain)
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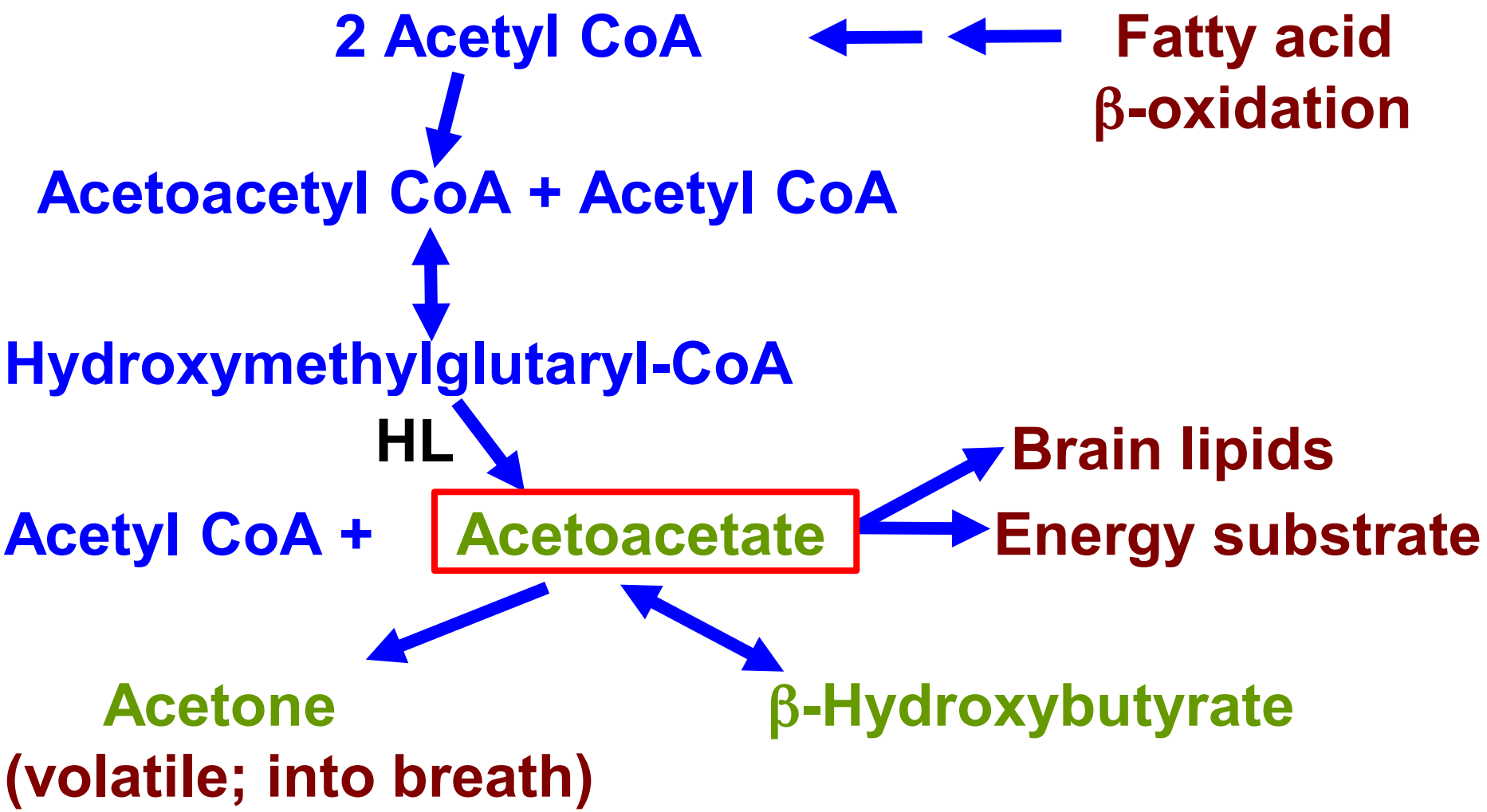
ibut

Brain fuels – a unique situation

	BRAIN	OTHER ORGANS
Main fuel	glucose	glucose
Main alternative fuel	ketones *(essential in infant)*	fatty acids
Glucose uptake	mostly insulin-insensitive	insulin-sensitive

Ketone synthesis from fats



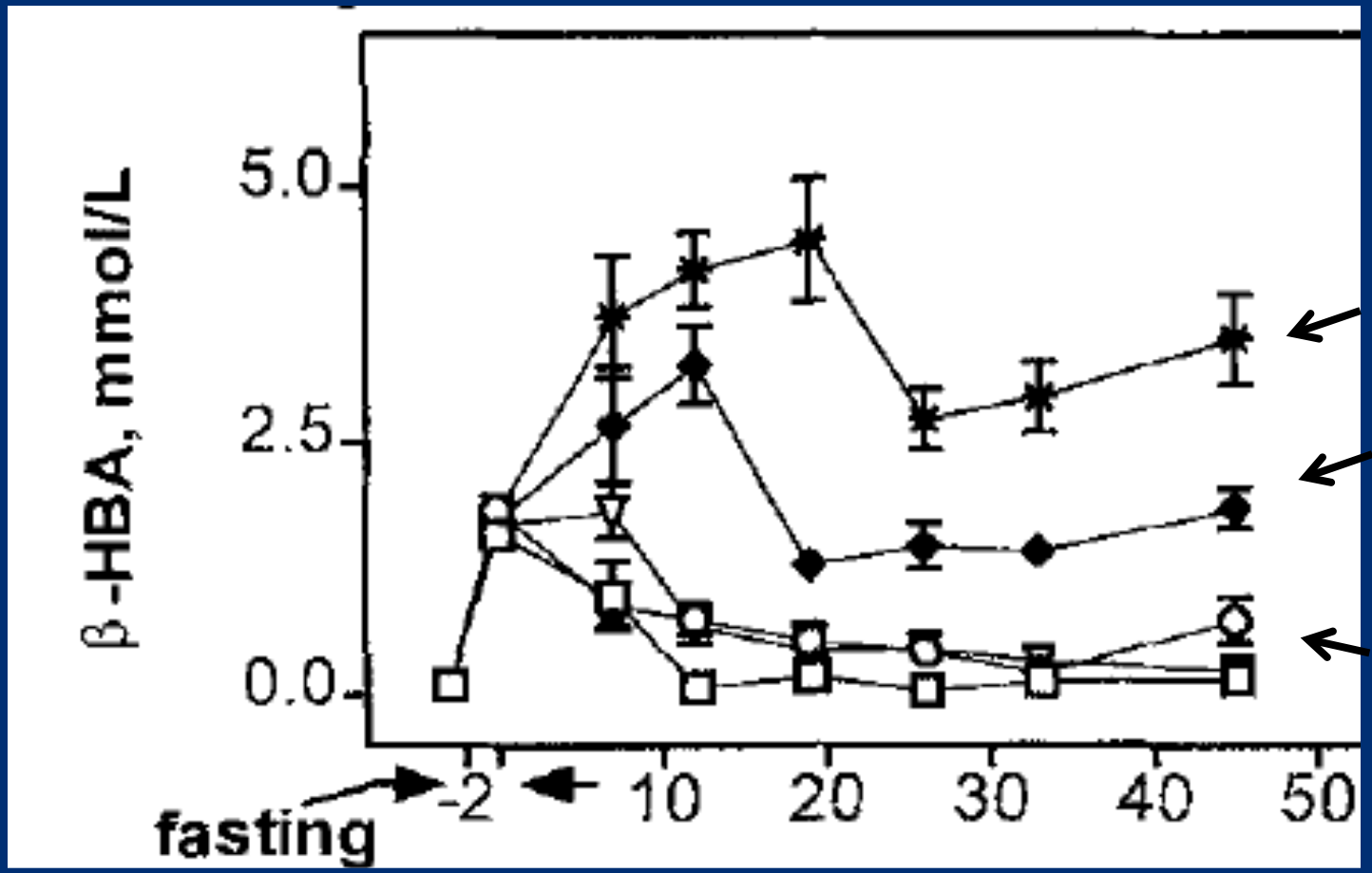
HL = HMG CoA Lyase

Ketones: essential for normal brain development in human infants

- Supply 30% of brain energy needs at birth; glucose alone is insufficient *(Adam et al 1975)*
- Ketonemia of 0.5-1.0 mM in infants is normal *(Hahn, 1978)*
- Brain ketone uptake in infants 4 fold that in adults *(Robinson & Williamson, 1980)*
- Supply 90% of carbon to make brain cholesterol, saturated fats *(Cunnane, 2003)*
- Much less important in other species *(Robinson & Williamson, 1980)*

Ketogenic efficacy of medium chain (MCT) vs. long chain triglycerides (LCT)

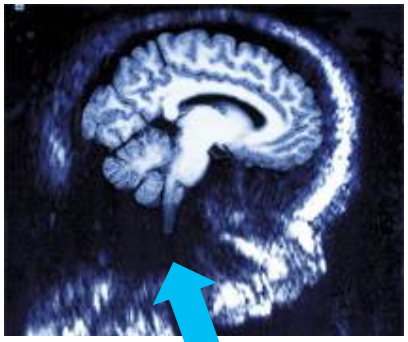
(Likhodii et al, 2000)

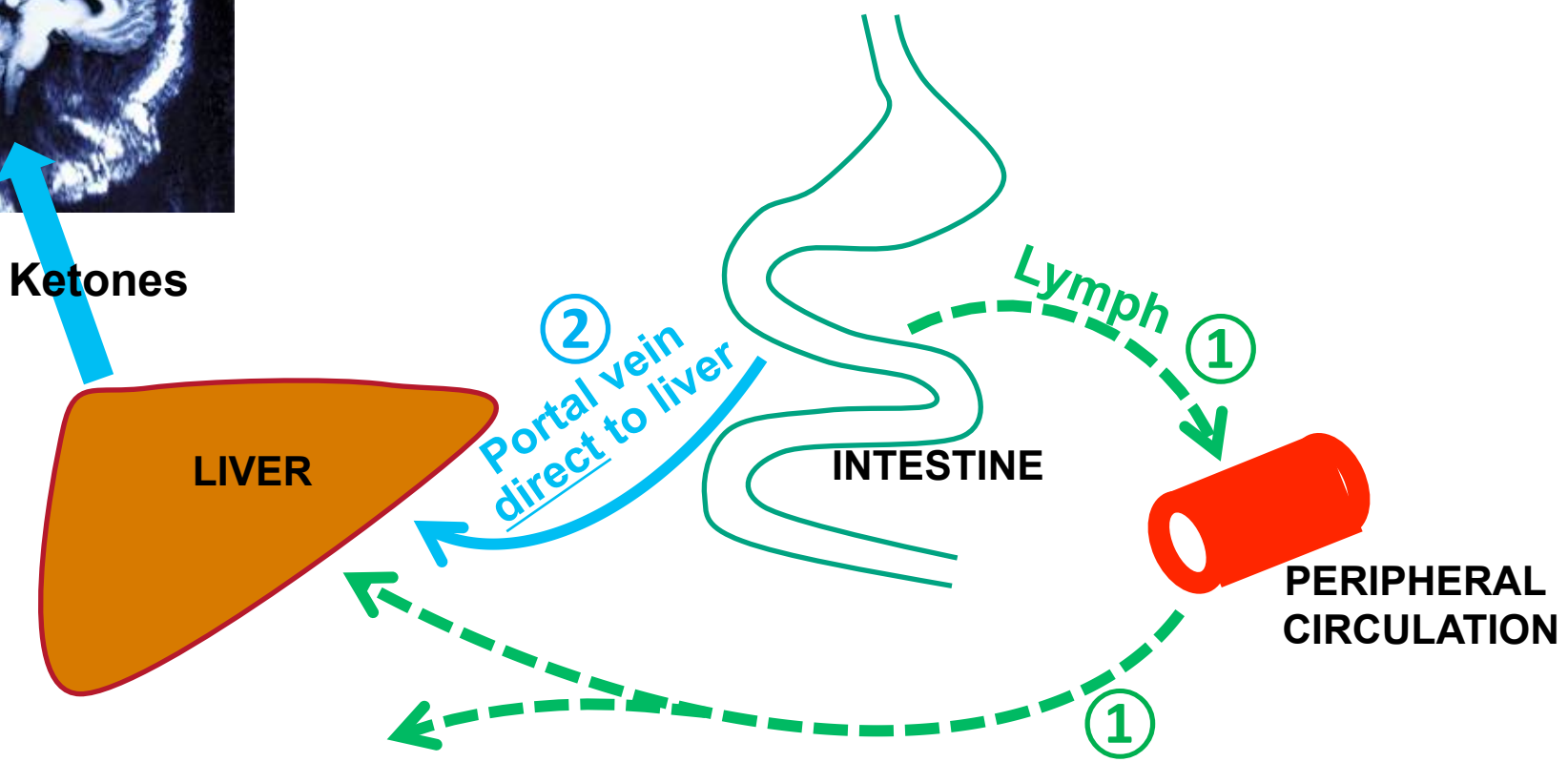


Medium chain 'ketogenic' fats – facilitated absorption and oxidation

② Route for ketogenic fats

① Route for dietary long chain fats



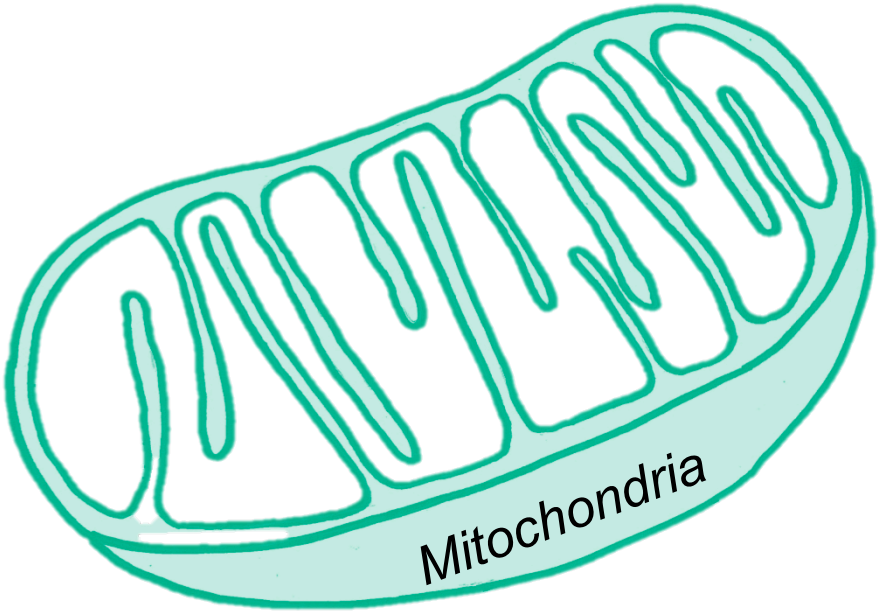


Distribution to many tissues besides the liver, i.e. muscle, fat, heart (not brain)

Natural sources of medium chain fatty acids

Mammalian milk	
Human	**7-10%**
Human adipose tissue	
Infants	**6-10%**
Adults	**<2%**
Coconut oil	**75-80%**

Medium chain 'ketogenic' fats – facilitated absorption and oxidation



Long chain dietary FA

Long chain FA-carnitine

SLOWER

(activation required)

Medium chain FA

RAPID

(no activation required)

β-oxidation → ketones and/or CO_2

Setting the metabolic stage for human brain evolution

- *more efficient brain use of ketones in human infants*
- *extended ketogenesis from MCFA in body fat*

LARGE BRAIN (humans)

FAT BABIES (humans)

LONGER GESTATION (primates)

FACILITATED ABSORPTION, OXIDATION OF KETOGENIC FATS (mammals)

Shore-based habitat = brain selective nutrients

SbS

Shore-based Scenario:

1. **Prediction:** **vulnerability** of brain to low intake of brain selective nutrients.

Brain disorders: challenge of the 21st century

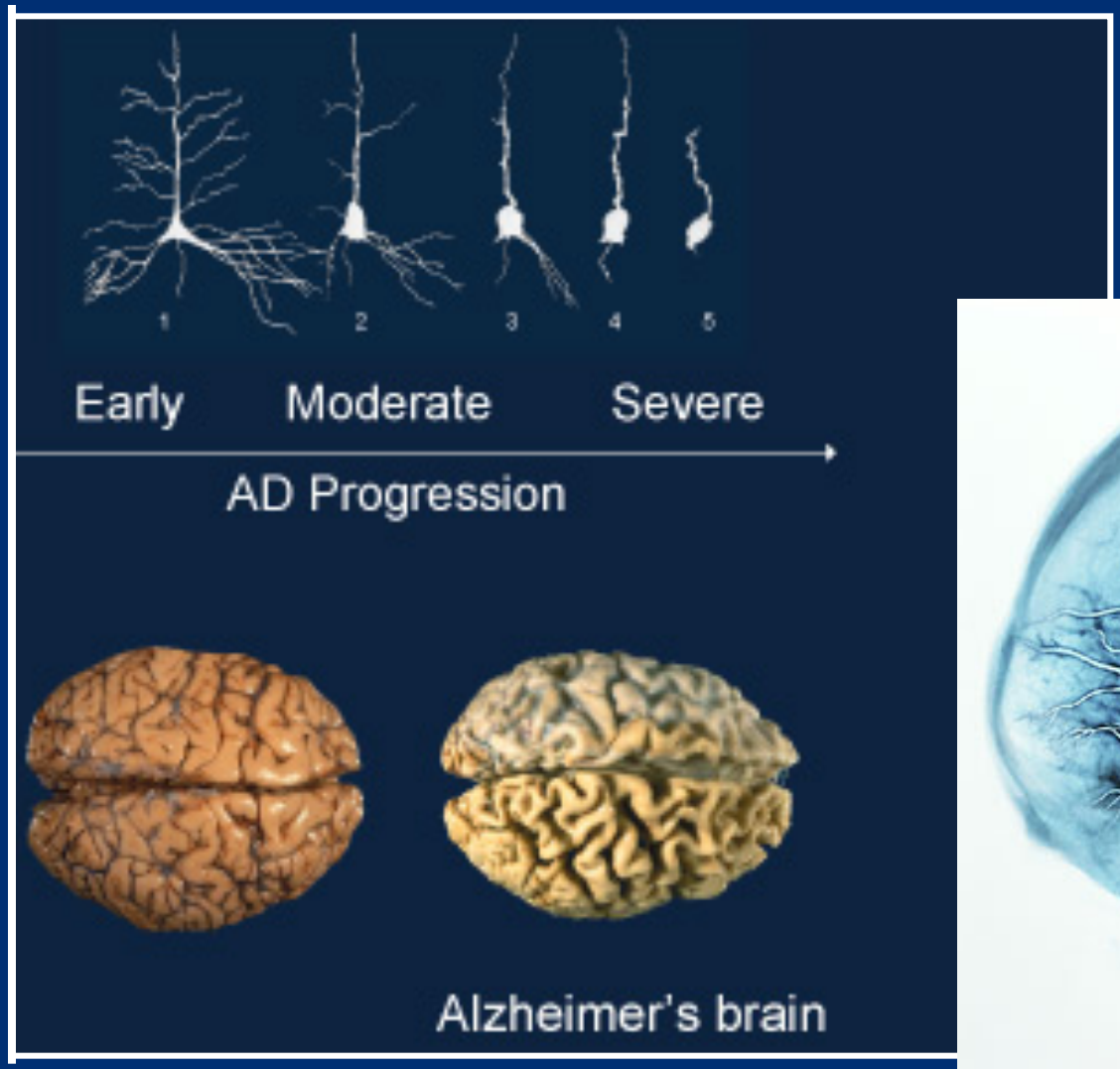
13% of total disease burden globally; 35% of disease burden in Europe *(Sobocki, Europ J Neurol 2005)*

Suboptimal brain development due to iodine, iron deficiencies in 20% of world population

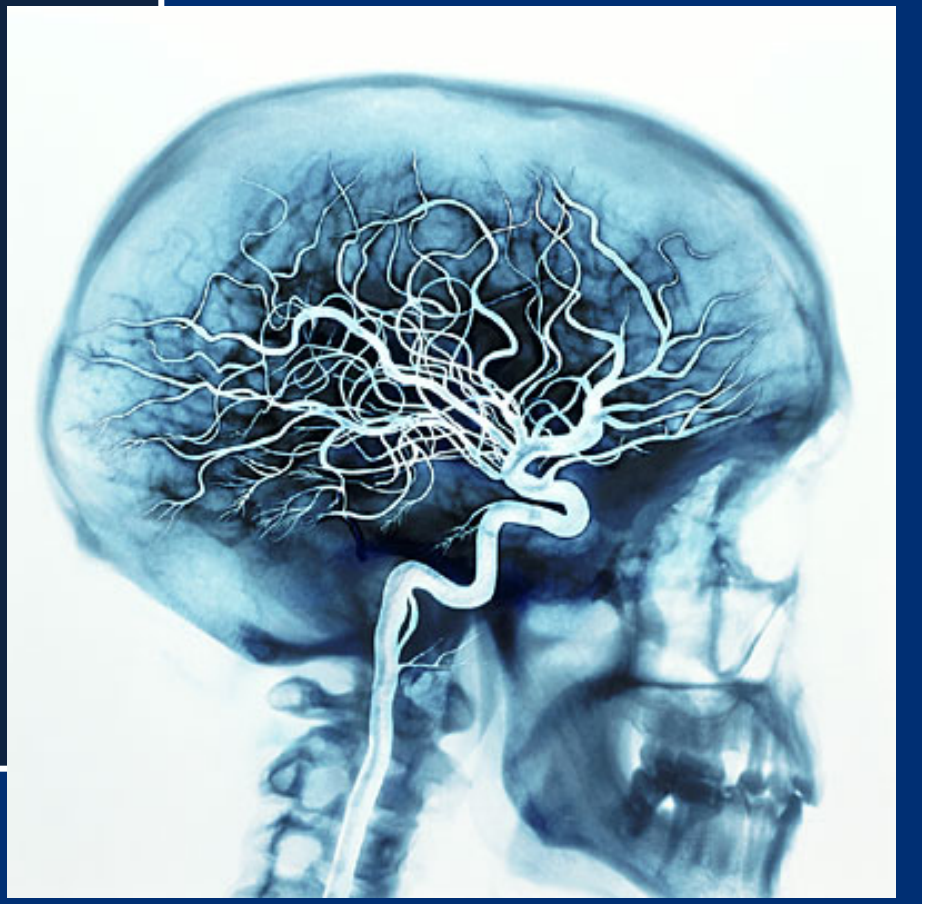
Nutrition and brain fuel supply affect risk/treatment of epilepsy, multiple sclerosis, stroke, dementia, anxiety, Parkinsonism, affective/psychotic disorders

Population - aging + unhealthy (obesity, diabetes)

Neurodegenerative diseases of aging – only in humans …



cardiovascular, brain health linked



Shore-based scenario:

1. **Prediction:** **vulnerability of brain to low intake of brain selective nutrients.**

2. **Parsimony: (simple explanations - better than more complex ones): still in shore-based phase.**

Coastal migration of *H. erectus* out of Africa; arrival in Australia 80,000 y ago (>60 km open water)

Shore-based scenario:

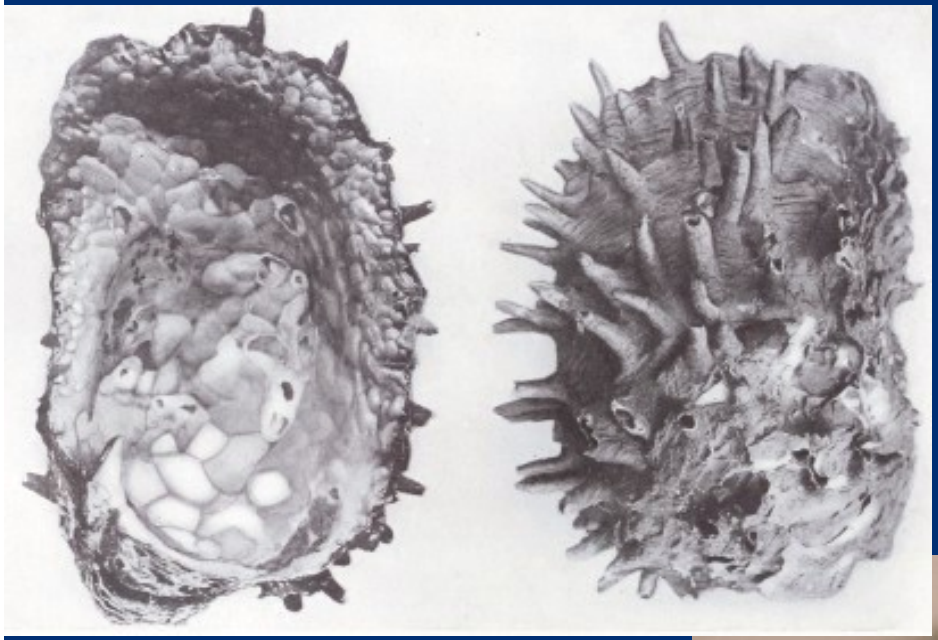
1. **Prediction:** **vulnerability of brain to low intake of brain selective nutrients.**

2. **Parsimony: (simple explanations - better than more complex ones): still in shore-based phase.**

3. **Plausibility: fish, shellfish remains present in the pre-human fossil record >2 million year ago (early in hominin brain evolution).**

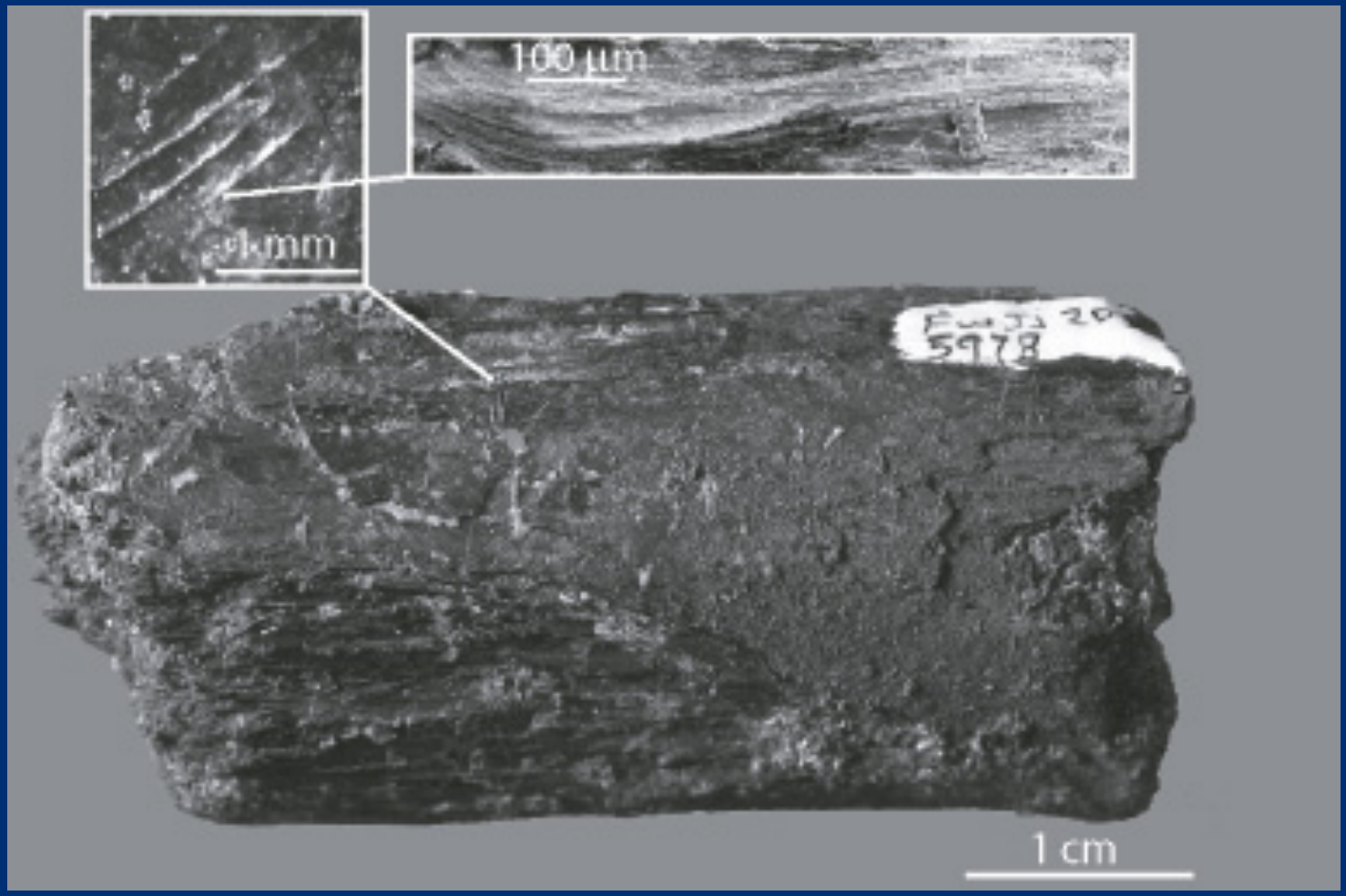
Freshwater oysters, other shellfish abundant in hominid fossil deposits

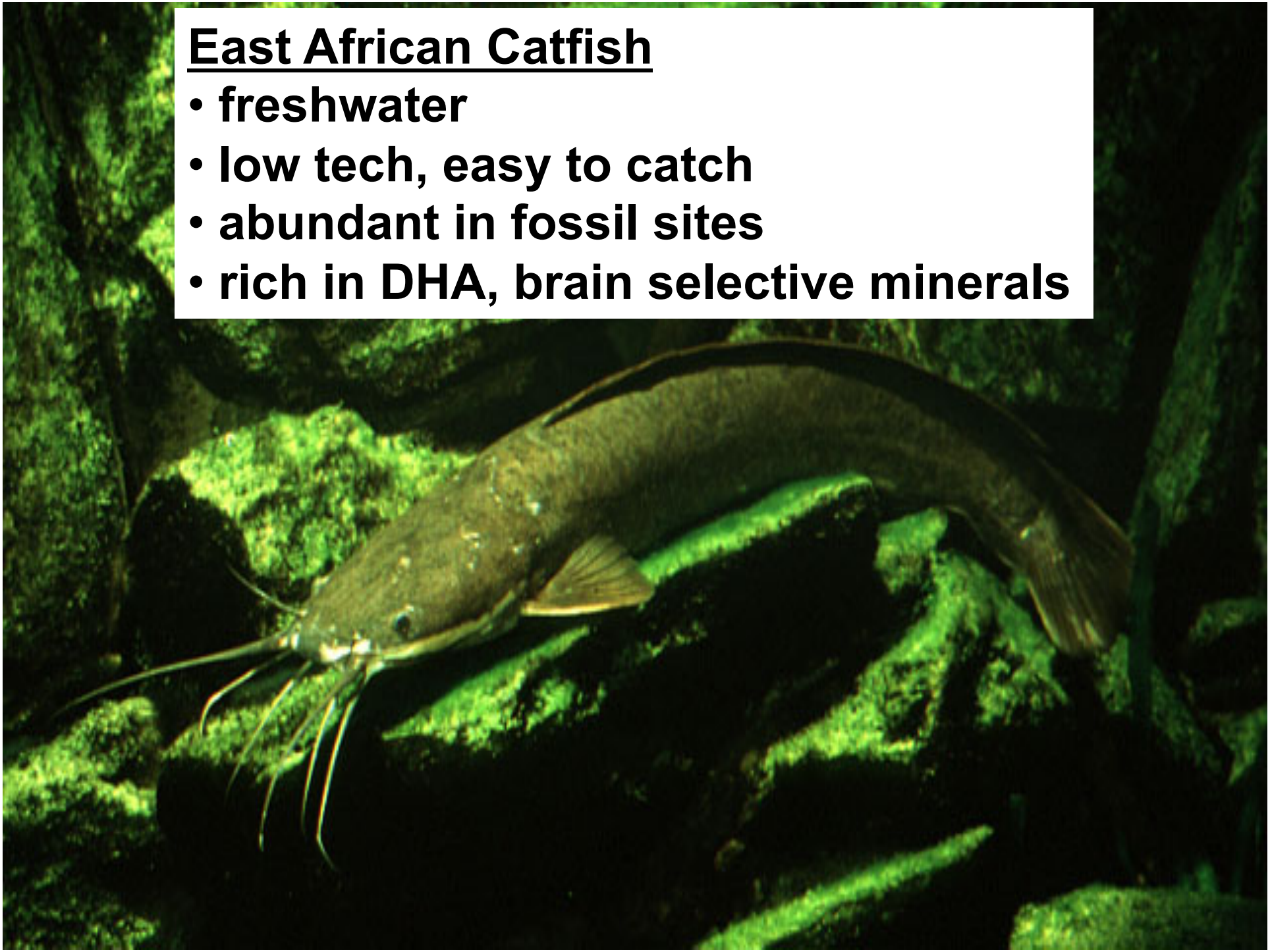
(2+ million years old)



Cutmarks on fish bones = intentional use

(Stewart, J Human Evolution, 1994)



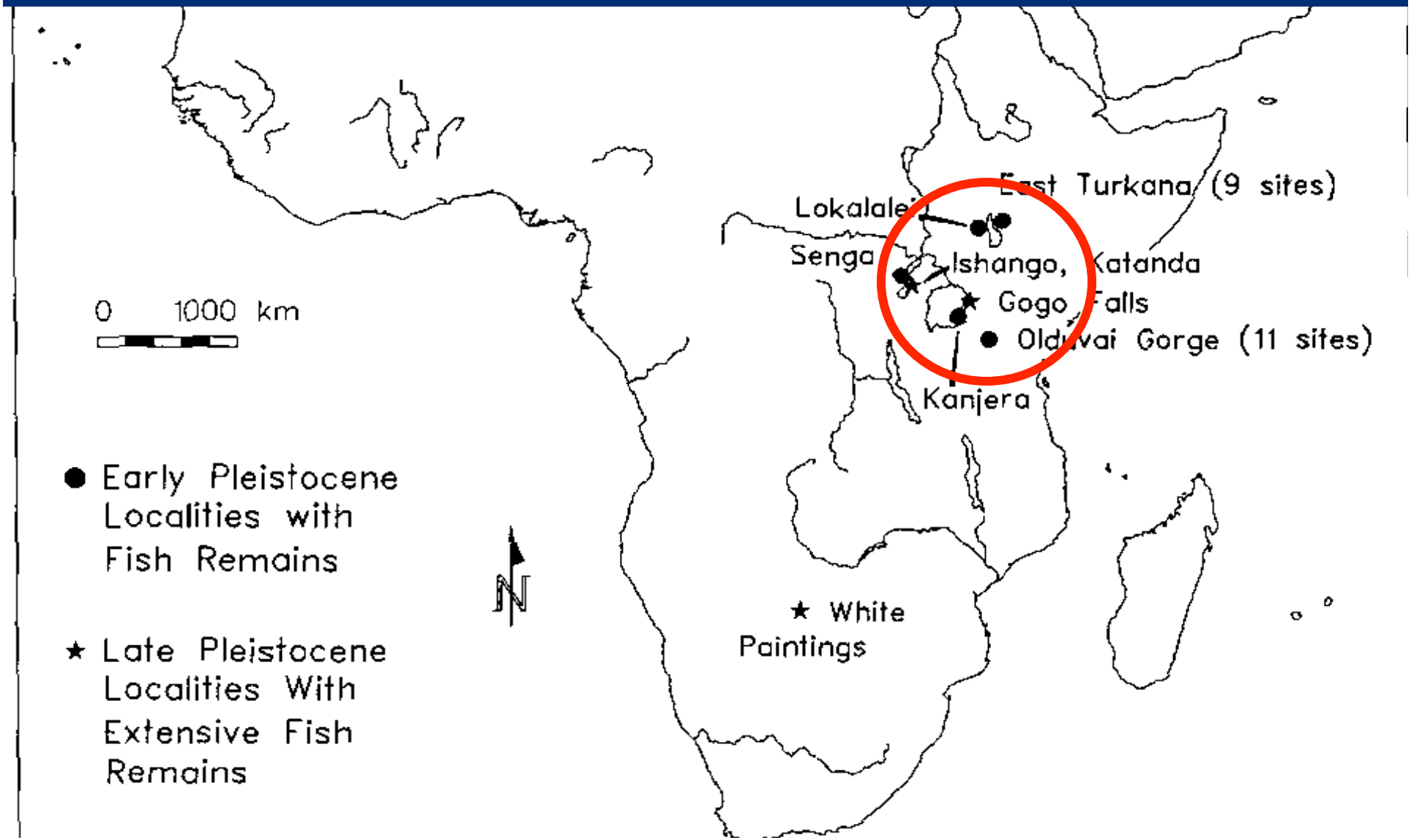


East African Catfish

- freshwater
- low tech, easy to catch
- abundant in fossil sites
- rich in DHA, brain selective minerals

African hominid fossil sites contain abundant fish, shellfish remains

(Stewart, J Human Evolution, 1994)



In summary

A SHORE-BASED (fresh or salt water) HABITAT WAS ESSENTIAL FOR EVOLUTION OF THE MODERN HUMAN BRAIN.

WHY?

1. **High brain energy demands in infants**
2. **Accessibility, abundance of nutrient-rich foods = time to accumulate fat and to develop skills**
3. **Richest source of 'brain selective' nutrients, especially iodine and DHA (also Fe, Zn, Cu, Se)**
4. **Fish remains in hominin fossil beds**
5. **Ongoing brain vulnerability, predominantly in humans not living near the shores**

Collaborators –

David Horrobin (Oxford, McGill, Efamol, Amarin)
Michael Crawford (Imperial College London)
Tom Brenna (Cornell University)
Philippe Guesnet (INRA, Jouy-en-Josas)
Jean-Marie Bourre (INSERM U54, Paris)
Kathy Stewart (Museum of Nature, Ottawa)
Ian Tattersall (Am Museum of Natural History, NY)
Elaine Morgan (Wales)

NSERC Support

Major publications –

Survival of the Fattest (World Scientific, 2005)
Human Brain Evolution (Wiley, 2010)
Thematic issue, J Human Evolution (2014)

World Alzheimer Report

2009

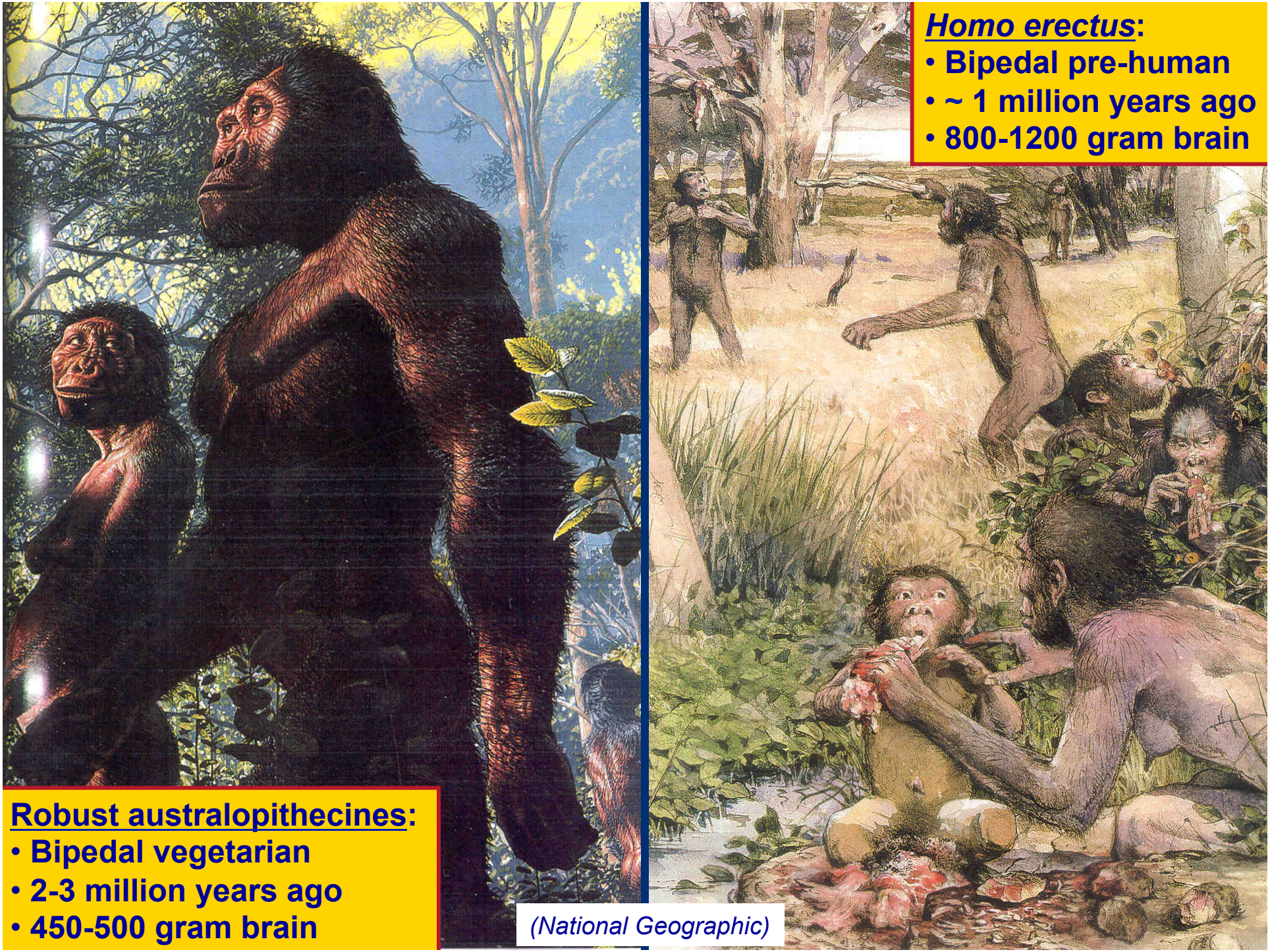
Executive Summary

Generic primate brain → human brain:

1. More dietary energy intake, fat reserves:
   - higher energy demands of larger brain
   - *unique and simultaneous* accumulation of fat stores in the fetus and baby

2. More 'brain-selective' nutrients:
   - polyunsaturated fatty acids (DHA)
   - iodine, iron, zinc, copper, selenium
   - Others (?)

- Stone tools and hunting were a consequence not a cause of brain evolution
- Brain vulnerability remains a problem ……



Robust australopithecines:
- Bipedal vegetarian
- 2-3 million years ago
- 450-500 gram brain

***Homo erectus*:**
- Bipedal pre-human
- ~ 1 million years ago
- 800-1200 gram brain

(National Geographic)

Shore-based Scenario:

1. **Prediction:** **vulnerability of brain to low intake of brain selective nutrients.**

2. **Parsimony (simple explanations - better than more complex ones): still in shore-based phase.**

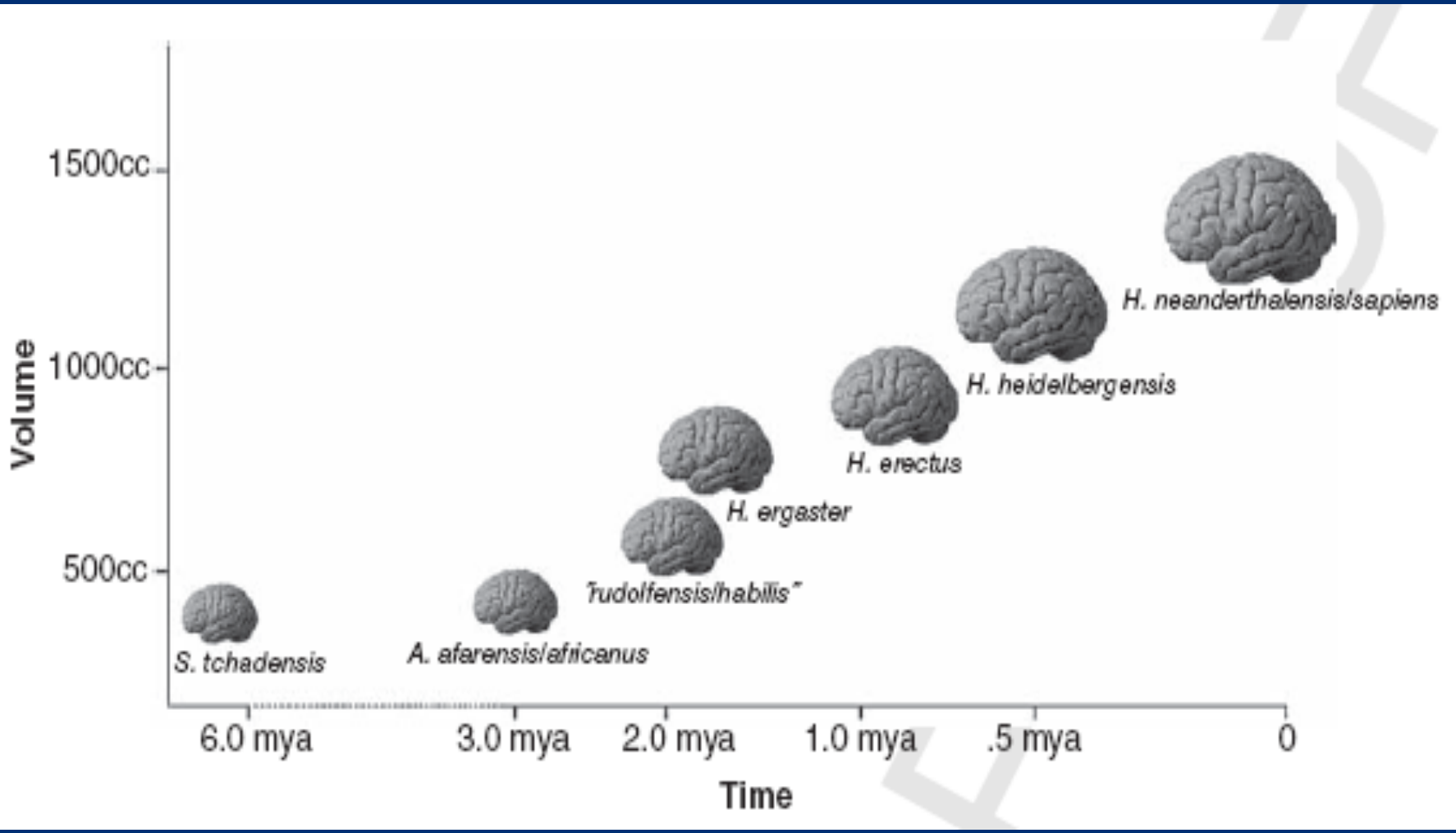
Prediction

Parsimony

Plausibility

Docosahexaenoic acid (DHA; 22:6ω3, fish oils)

- Membrane polyunsaturate, *par excellence*
- Vision (photoreceptors; rhodopsin; G proteins)
- Brain (synapses):
    - Learning during brain development.
    - Low in Zellweger's syndrome (severe mental, physical retardation).
    - Modulates glucose uptake by brain
    - Seizure control ?
    - Cognitive function during aging ?
    - Depression, psychiatric illness ?


1500cc
1000cc
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Volume
S. tchadensis
A. afarensis/africanus
"rudolfensis/habilis"
H. ergaster
H. erectus
H. heidelbergensis
H. neanderthalensis/sapiens
6.0 mya
3.0 mya
2.0 mya
1.0 mya
.5 mya
0
Time

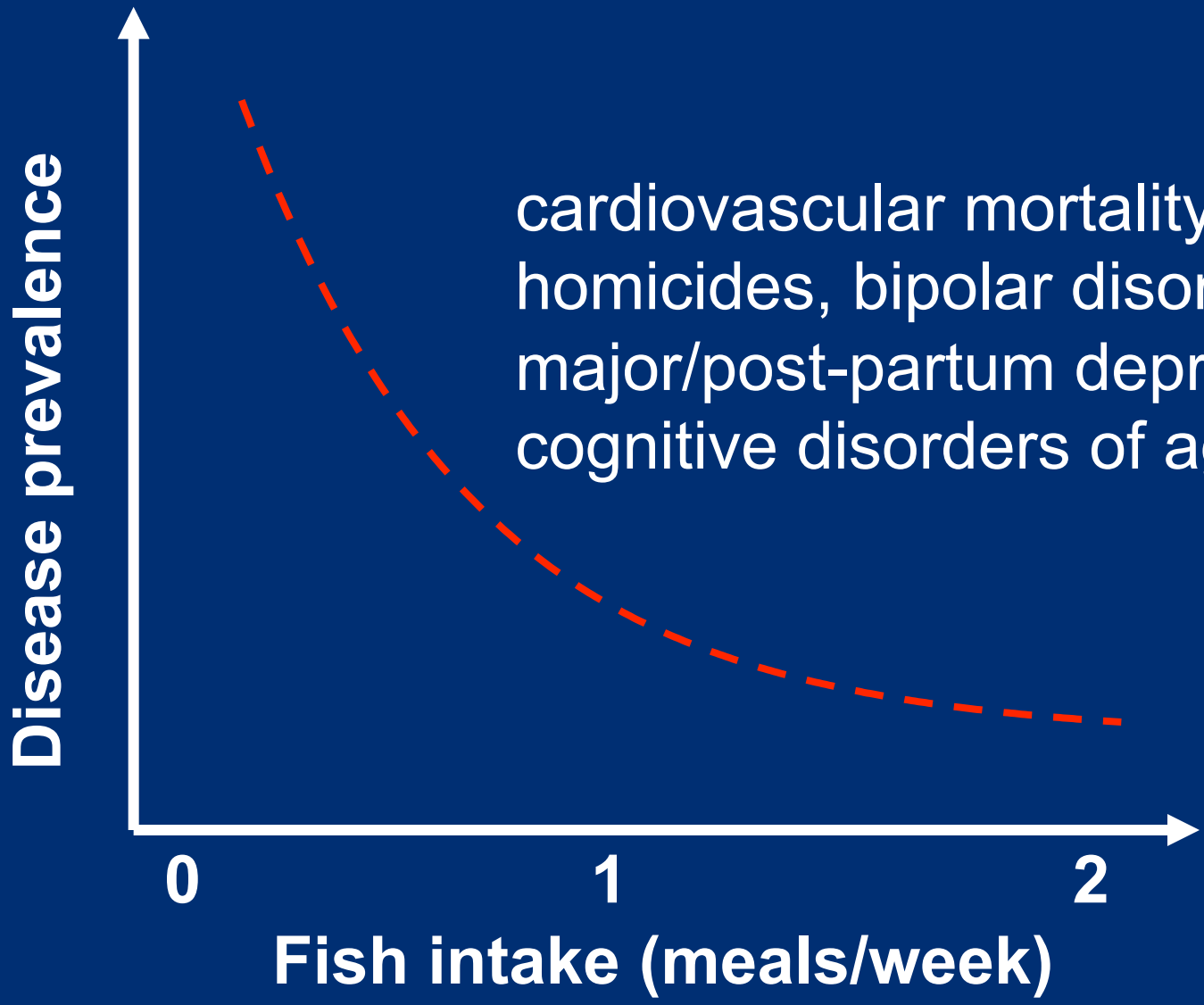
QUESTIONS –

1. How did we become human ?
2. What is the origin of the ‘big, uniquely sophisticated human brain’ ?

CONTEXT –

1. Genetic background of humans and chimpanzees ~99% equivalent.
2. Conditions of existence … *(Darwin, 1859)*

Fish protects the brain and heart



(Hibbeln, Barberger-Gateau, Cunnane, others)

Clinical evidence for beneficial effects of a ketogenic supplement on cognition in the elderly

- moderate Alzheimer's (Reger et al, 2004)
- moderate Alzheimer's (Henderson et al, 2009)
- mild cognitive impairment (Krikorian et al 2011)

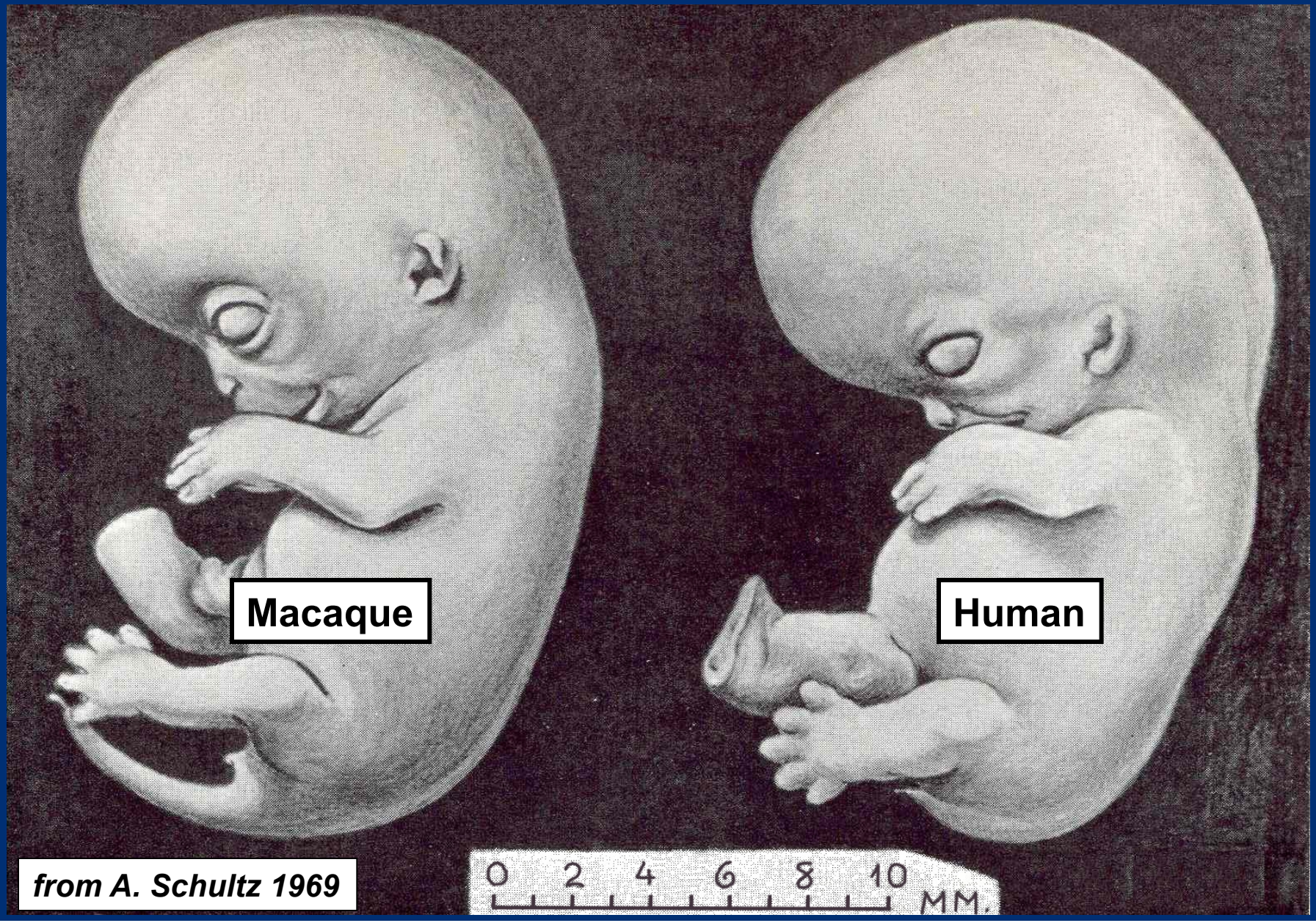
KEY POINT:

- Partial improvement in cognition, i.e. exhaustion not neuronal death. Fuel supply? Other effect?

IDDM post-insulin injection (Page et al 2010)

45-50 day old embryos

(40% of body volume is brain in both species)



from A. Schultz 1969