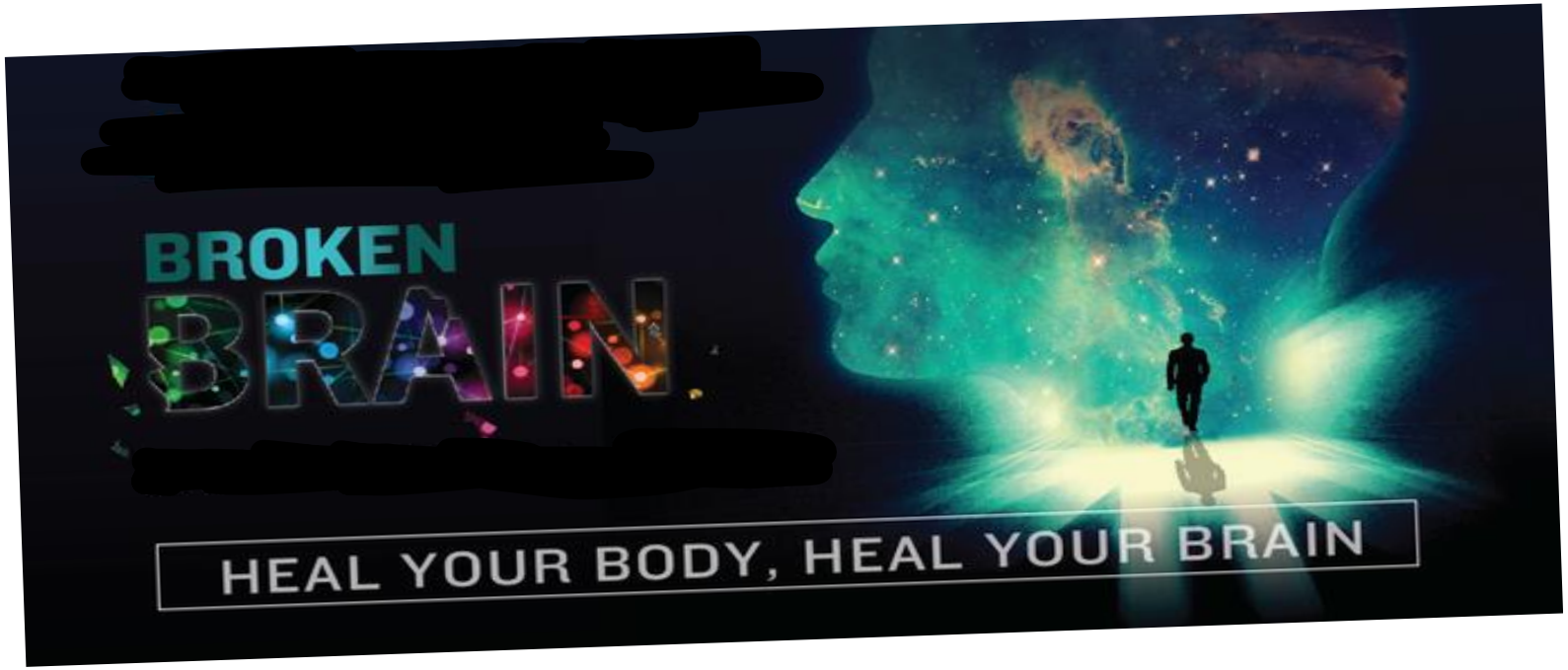

BROKEN
BRAIN
HEAL YOUR BODY, HEAL YOUR BRAIN

Part One

General Info

Everyone knows a cancer survivor no one know a Alzheimer's survivor

Treatments for Alzheimer's disease

Text S

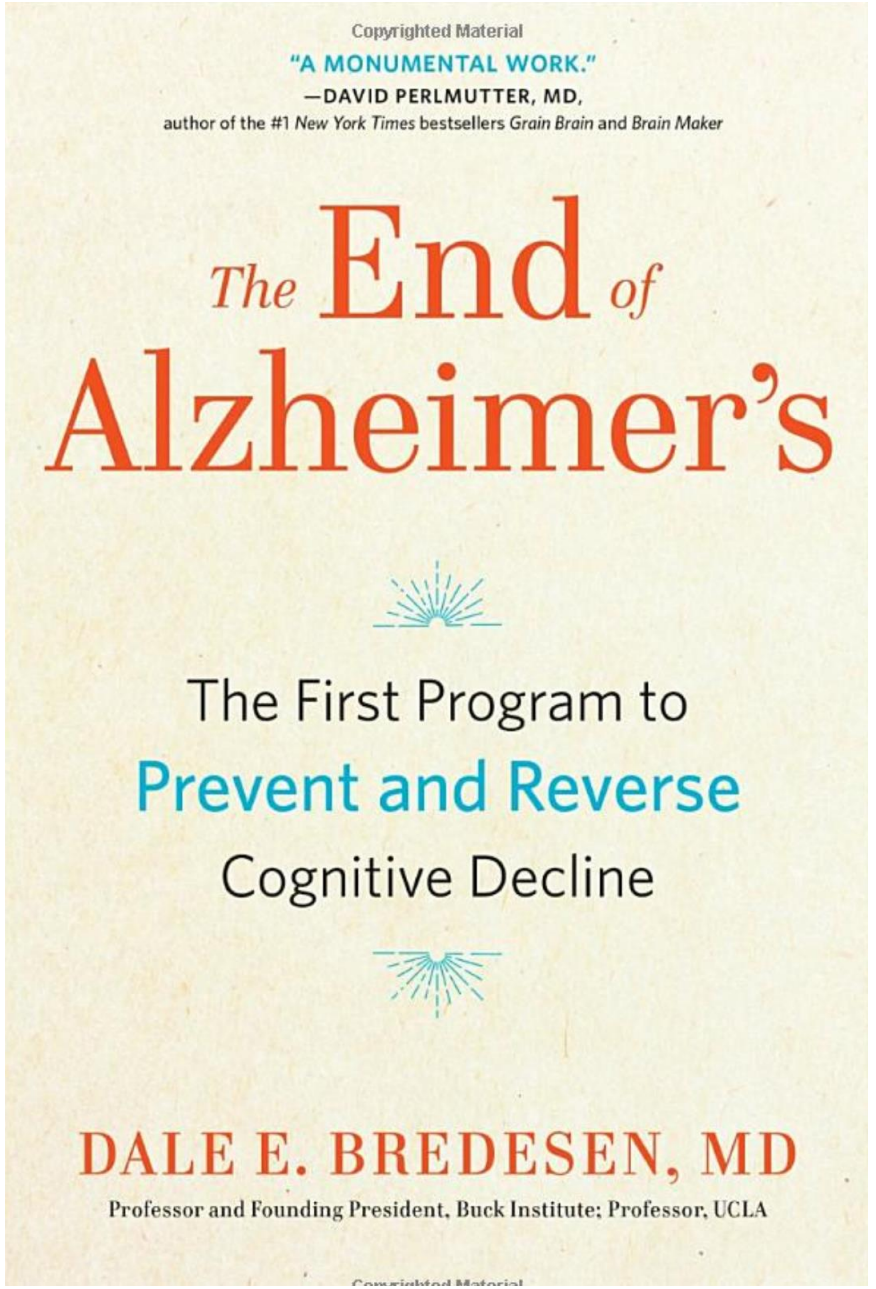
Currently, there is no cure for Alzheimer's. But drug and non-drug treatments may help with both cognitive and behavioral symptoms.

Researchers are looking for new treatments to alter the course of the disease and improve the quality of life for people with dementia.

“Let me say this as clearly as I can: Alzheimer’s disease can be prevented, and in many cases its associated cognitive decline can be reversed.”

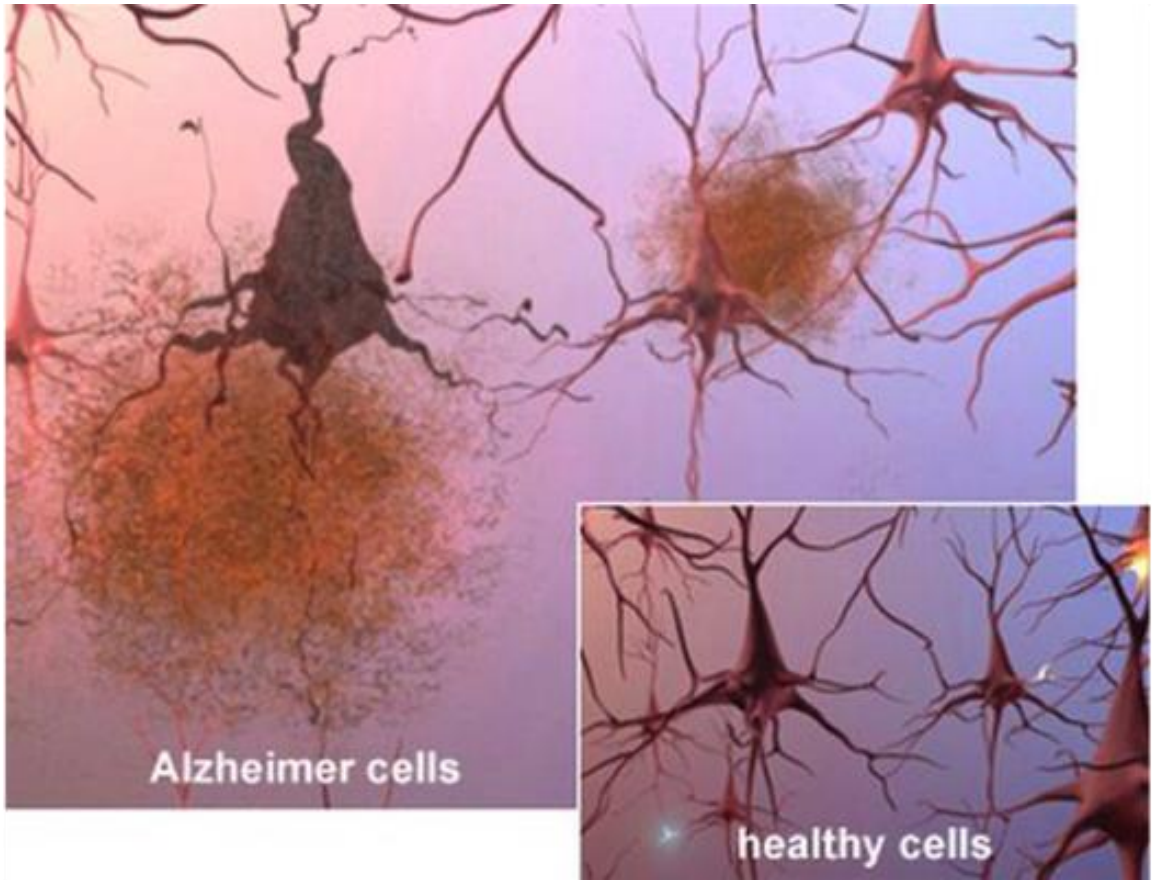
Dr. Dale Bredesen MD

The end of Alzheimer’s pg 9



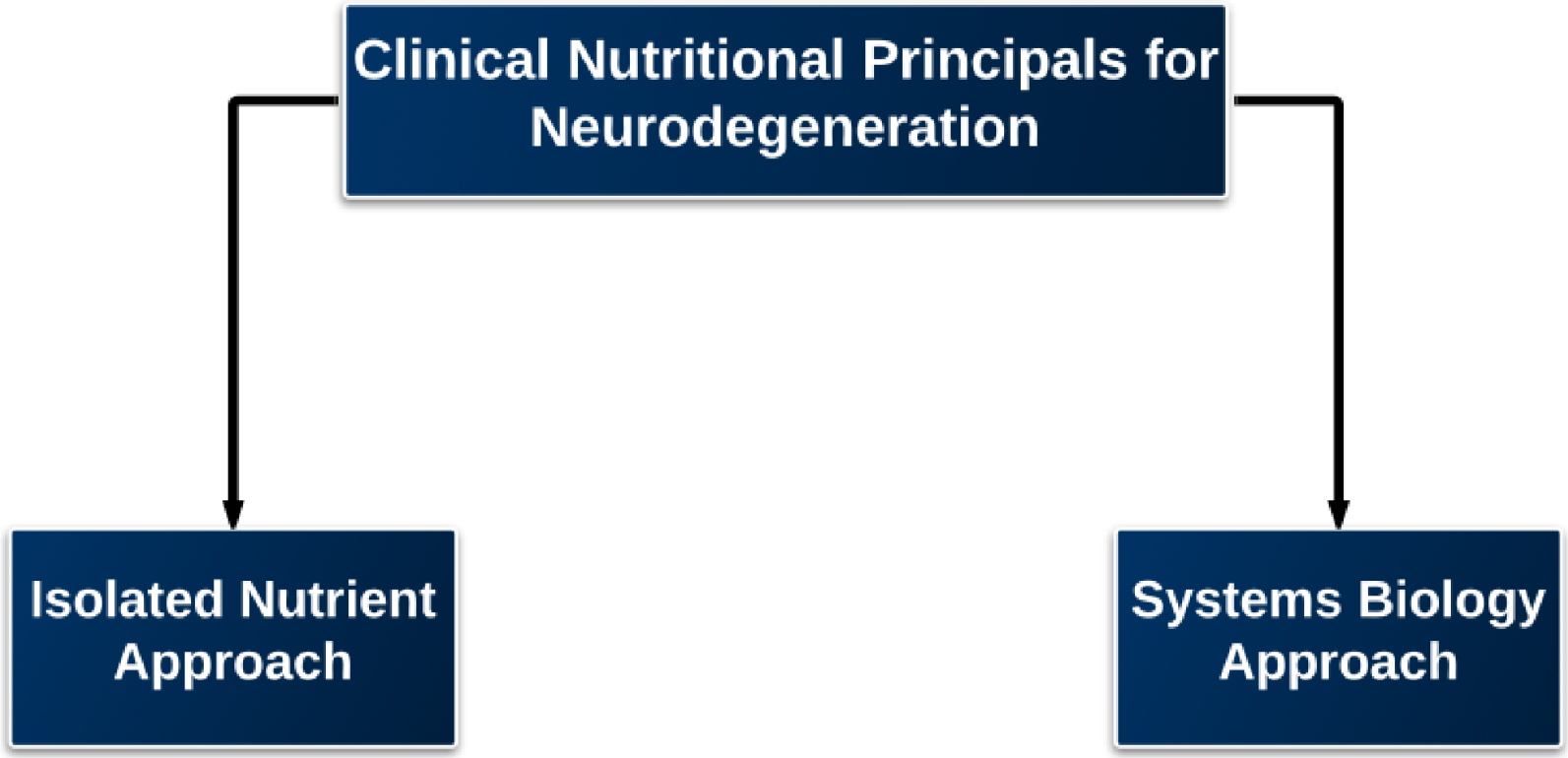
Goals for Workshop

- ✓ Stop neuron death
- ✓ Improve Neuron Branching



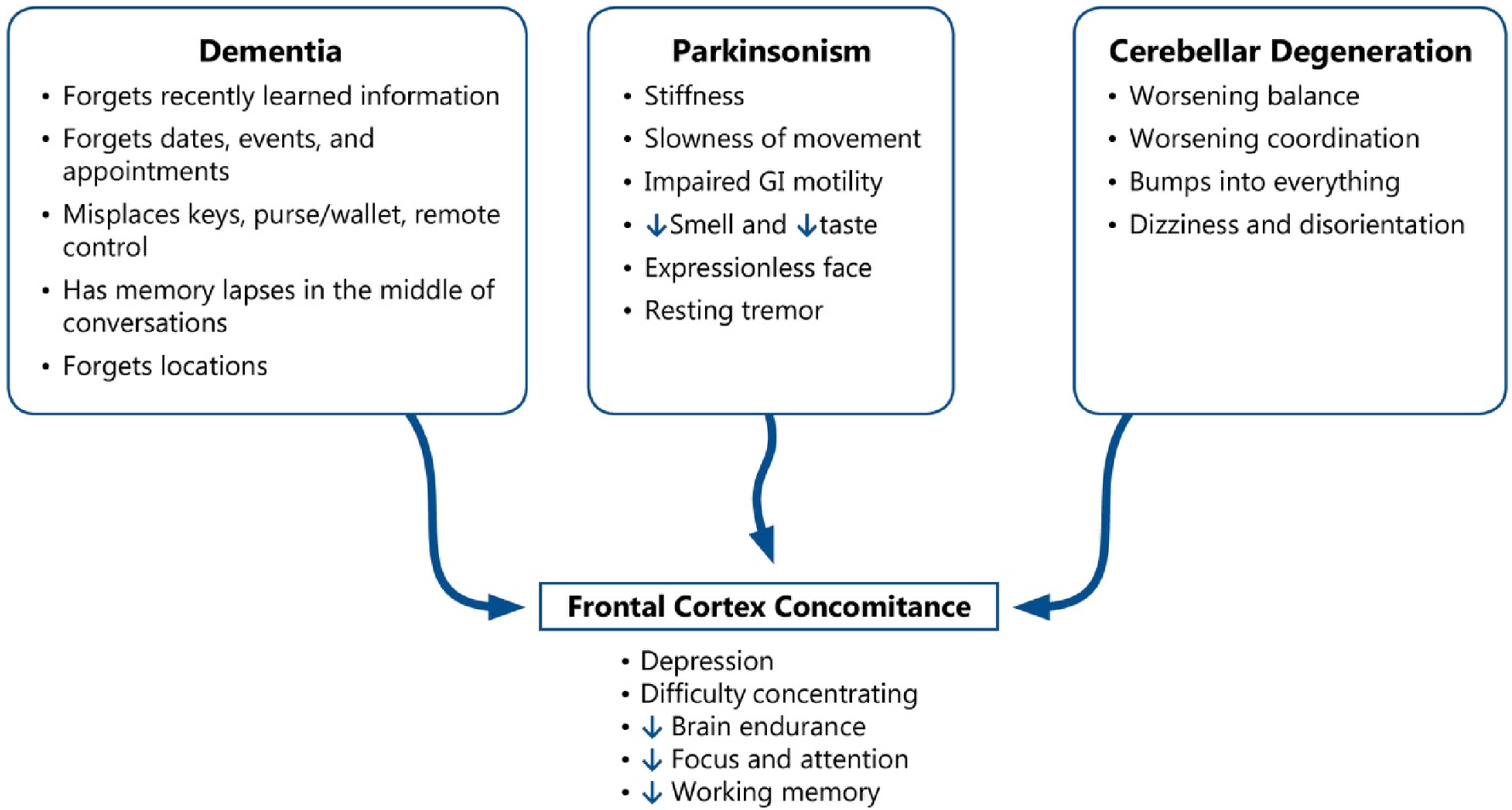
The perfect Alzheimer's drug would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization of Aβ, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvins, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFκB, increase telomere length, reduce glial scarring, enhance repair, etc.

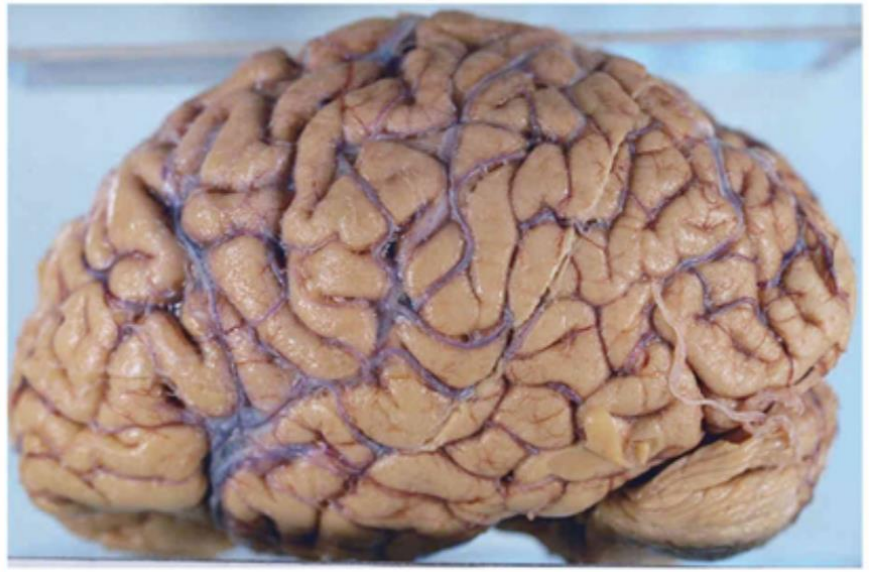


Systems biology is the computational and mathematical modeling of complex **biological systems**. It is a **biology**-based interdisciplinary field of study that focuses on complex interactions within **biological systems**, using a holistic **approach** (holism instead of the more traditional reductionism) to **biological** research.

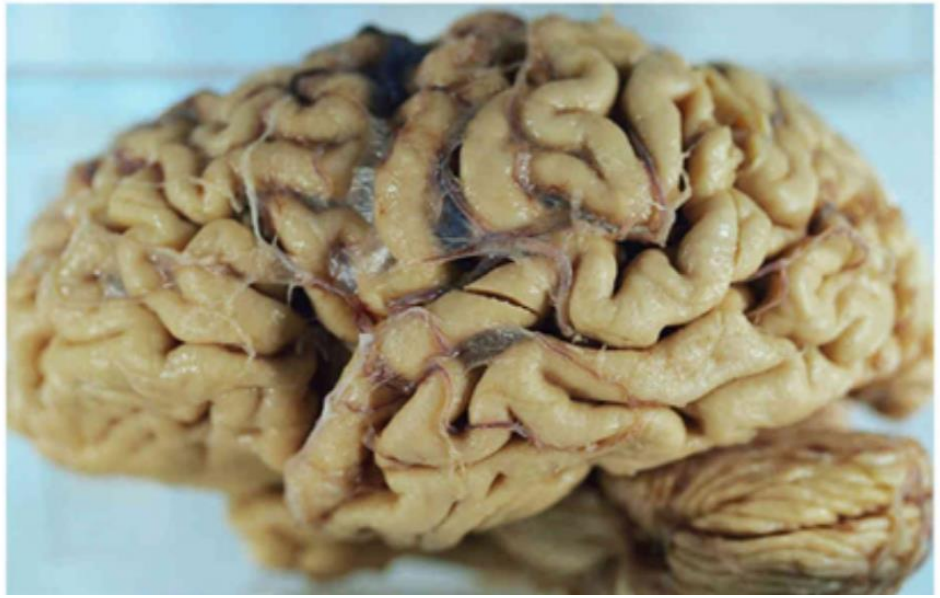
Three Common Neurodegenerative Diseases

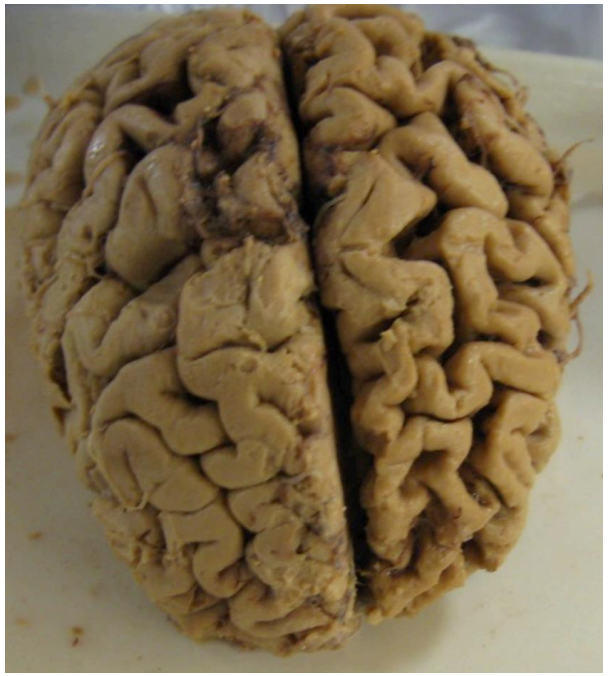


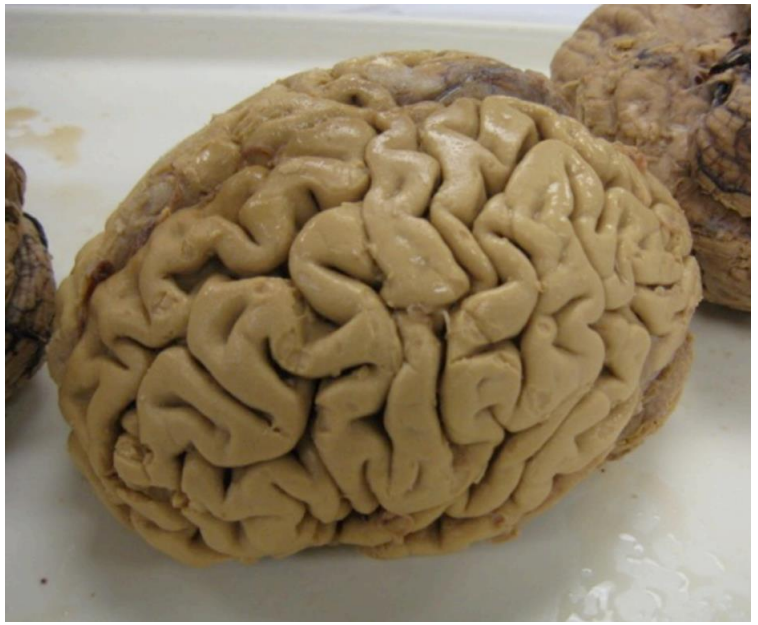
Healthy Brain

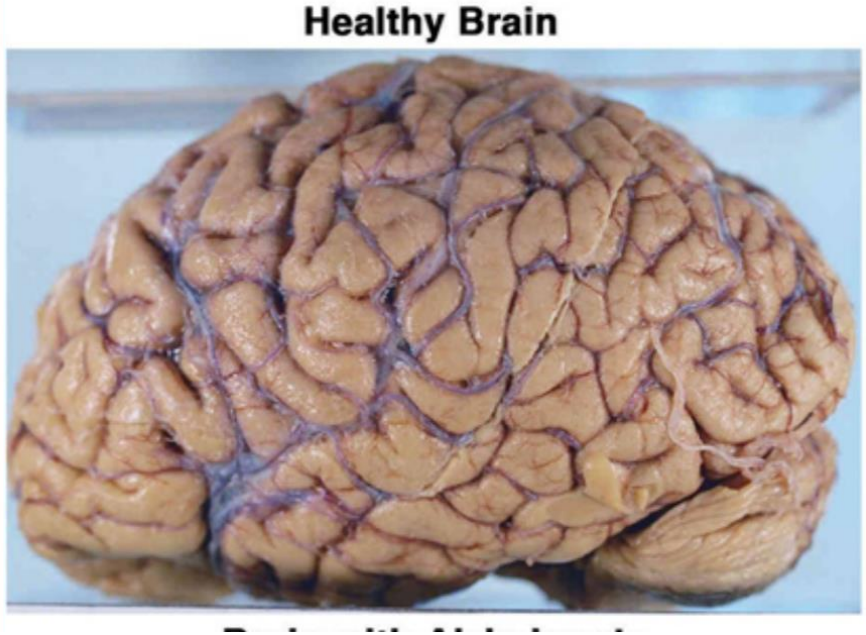


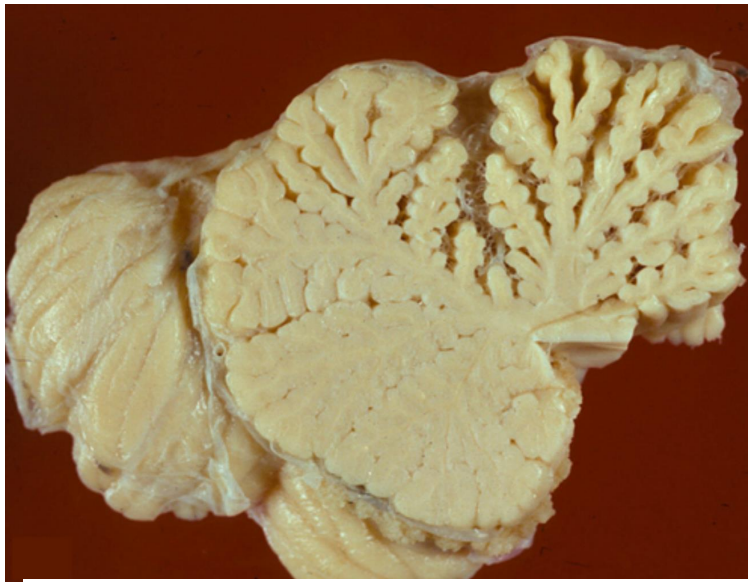
Brain with Alzheimer's

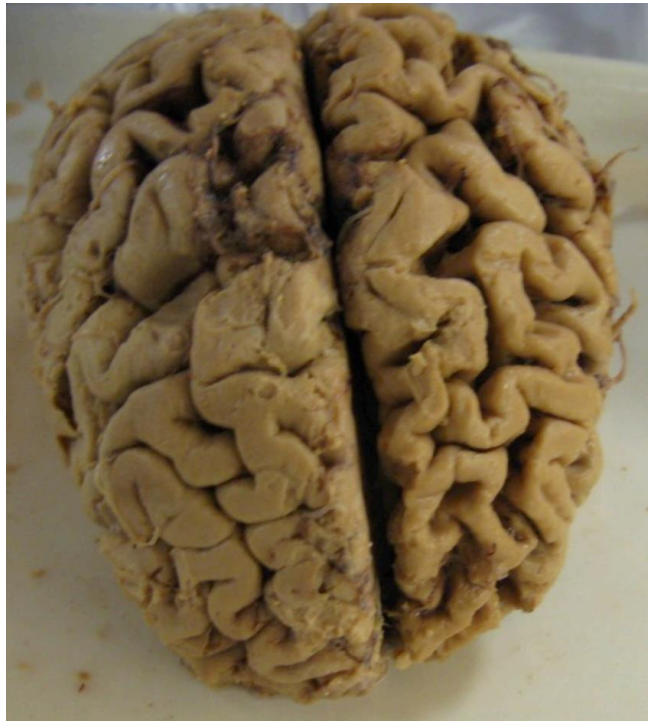












Cerebellum - Spinocerebellum		0	1	2	3	4
67.	Difficulty with balance, or balance that is worse on one side	○	○	○	○	○
68.	A need to hold the handrail or watch each step carefully when going down stairs	○	○	○	○	○
69.	Feeling unsteady and prone to falling in the dark	○	○	○	○	○
70.	Proness to sway to one side when walking or standing	○	○	○	○	○
Cerebellum - Cerebrocerebellum		**0**	**1**	**2**	**3**	**4**
71.	Recent clumsiness in hands	○	○	○	○	○
72.	Recent clumsiness in feet or frequent tripping	○	○	○	○	○
73.	A slight hand shake when reaching for something at the end of movement	○	○	○	○	○

Medial Temporal lobe and Hippocampus		0	1	2	3	4
49.	Memory less efficient	○	○	○	○	○
50.	Memory loss that impacts daily activities	○	○	○	○	○
51.	Confusion about dates, the passage of time, or place	○	○	○	○	○
52.	Difficulty remembering events	○	○	○	○	○
53.	Misplacement of things and difficulty retracing steps	○	○	○	○	○
54.	Difficulty with memory of locations (addresses) R	○	○	○	○	○
55.	Difficulty with visual memory R	○	○	○	○	○
56.	Always forgetting where you put items such as keys, wallet, phone, etc. R	○	○	○	○	○
57.	Difficulty remembering faces R	○	○	○	○	○
58.	Difficulty remembering names with faces L	○	○	○	○	○
59.	Difficulty with remembering words L	○	○	○	○	○
60.	Difficulty remembering numbers L	○	○	○	○	○
61.	Difficulty remembering to stay or be on time L	○	○	○	○	○

Frontal lobe Prefrontal, Dorsolateral and Orbitofrontal (Areas 9, 10, 11, and 12)		Level
1.	Difficulty with restraint and controlling impulses or desires	0 1 2 3 4
2.	Emotional instability (lability)	0 1 2 3 4
3.	Difficulty planning and organizing	0 1 2 3 4
4.	Difficulty making decisions	0 1 2 3 4
5.	Lack of motivation, enthusiasm, interest and drive (apathetic)	0 1 2 3 4
6.	Difficulty getting a sound or melody out of your thoughts (Perseveration)	0 1 2 3 4
7.	Constantly repeat events or thoughts with difficulty letting go	0 1 2 3 4
8.	Difficulty initiating and finishing tasks	0 1 2 3 4
9.	Episodes of depression	0 1 2 3 4
10.	Mental fatigue	0 1 2 3 4
11.	Decrease in attention span	0 1 2 3 4
12.	Difficulty staying focused and concentrating for extended periods of time	0 1 2 3 4
13.	Difficulty with creativity, imagination, and intuition R	0 1 2 3 4
14.	Difficulty in appreciating art and music R	0 1 2 3 4
15.	Difficulty with analytical thought L	0 1 2 3 4
16.	Difficulty with math, number skills and time consciousness L	0 1 2 3 4
17.	Difficulty taking ideas, actions, and words and putting them in a linear sequence L	0 1 2 3 4

Frontal Lobe Precentral and Supplementary Motor Areas (Area 4 and 6)		Level
18.	Initiating movements with your arm or leg has become more difficult	0 1 2 3 4
19.	Feeling of arm or leg heaviness, especially when tired	0 1 2 3 4
20.	Increased muscle tightness in your arm or leg	0 1 2 3 4
21.	Reduced muscle endurance in your arm or leg	0 1 2 3 4
22.	Noticeable difference in your muscle function or strength from one side to the other	0 1 2 3 4
23.	Noticeable difference in your muscle tightness from one side to the other	0 1 2 3 4

Frontal Lobe Broca's Motor Speech Area (Area 44 and 45)		Level
24.	Difficulty producing words verbally, especially when fatigued	0 1 2 3 4
25.	Find the actual act of speaking difficult at times	0 1 2 3 4
26.	Notice word pronunciation and speaking fluency change at times	0 1 2 3 4

Parietal Somatosensory Area and Parietal Superior Lobule (Areas 3,1,2 and 7)		Level
27.	Difficulty in perception of position of limbs	0 1 2 3 4
28.	Difficulty with spatial awareness when moving, laying back in a chair, or leaning against a wall	0 1 2 3 4
29.	Frequently bumping body or limbs into the wall or objects accidently	0 1 2 3 4
30.	Reoccurring injury in the same body part or side of the body	0 1 2 3 4
31.	Hypersensitivities to touch or pain perception	0 1 2 3 4

Parietal Inferior Lobule (Area 39 and 40)		Level
32.	Right/left confusion [L]	0 1 2 3 4
33.	Difficulty with math calculations [L]	0 1 2 3 4
34.	Difficulty finding words [L]	0 1 2 3 4
35.	Difficulty with writing [L]	0 1 2 3 4
36.	Difficulty recognizing symbols or shapes [R]	0 1 2 3 4
37.	Difficulty with simple drawings [R]	0 1 2 3 4
38.	Difficulty interpreting maps [R]	0 1 2 3 4
Temporal Lobe Auditory Cortex (Areas 41, 42)		**Level**
39.	Reduced function in overall hearing	0 1 2 3 4
40.	Difficulty interpreting speech with background or scatter noise	0 1 2 3 4
41.	Difficulty comprehending language without perfect pronunciation	0 1 2 3 4
42.	Need to look at someone's mouth when they are speaking to understand what they are saying	0 1 2 3 4
43.	Difficulty in localizing sound	0 1 2 3 4
44.	Dislike of left predictable rhythmic, repeated tempo and beat music [L]	0 1 2 3 4
45.	Dislike of non-predictable rhythmic with multiple instruments [R]	0 1 2 3 4
46.	Noticeable ear preference when using your phone	right, left, no preference
Temporal Lobe Auditory Association Cortex (Area 22)		**Level**
47.	Difficulty comprehending meaning of spoken words [L]	0 1 2 3 4
48.	Tend toward monotone speech without fluctuations or emotions [R]	0 1 2 3 4

Medial Temporal lobe and Hippocampus		Level
49.	Memory less efficient	0 1 2 3 4
50.	Memory loss that impacts daily activities	0 1 2 3 4
51.	Confusion about dates, the passage of time, or place	0 1 2 3 4
52.	Difficulty remembering events	0 1 2 3 4
53.	Misplacement of things and difficulty retracing steps	0 1 2 3 4
54.	Difficulty with memory of locations (addresses) [R]	0 1 2 3 4
55.	Difficulty with visual memory [R]	0 1 2 3 4
56.	Always forgetting where you put items such as keys, wallet, phone, etc. [R]	0 1 2 3 4
57.	Difficulty remembering faces [R]	0 1 2 3 4
58.	Difficulty remembering names with faces [L]	0 1 2 3 4
59.	Difficulty with remembering words [L]	0 1 2 3 4
60.	Difficulty remembering numbers [L]	0 1 2 3 4
61.	Difficulty remembering to stay or be on time (reduced left) [L]	0 1 2 3 4
Occipital Lobe (Area, 17, 18, and 19)		**Level**
62.	Difficulty in discriminating similar shades of color	0 1 2 3 4
63.	Dullness of colors in visual field	0 1 2 3 4
64.	Difficulty coordinating visual inputs and hand movements, resulting in an inability to efficiently reach out for objects	0 1 2 3 4
66.	Floater or halos in visual field	0 1 2 3 4

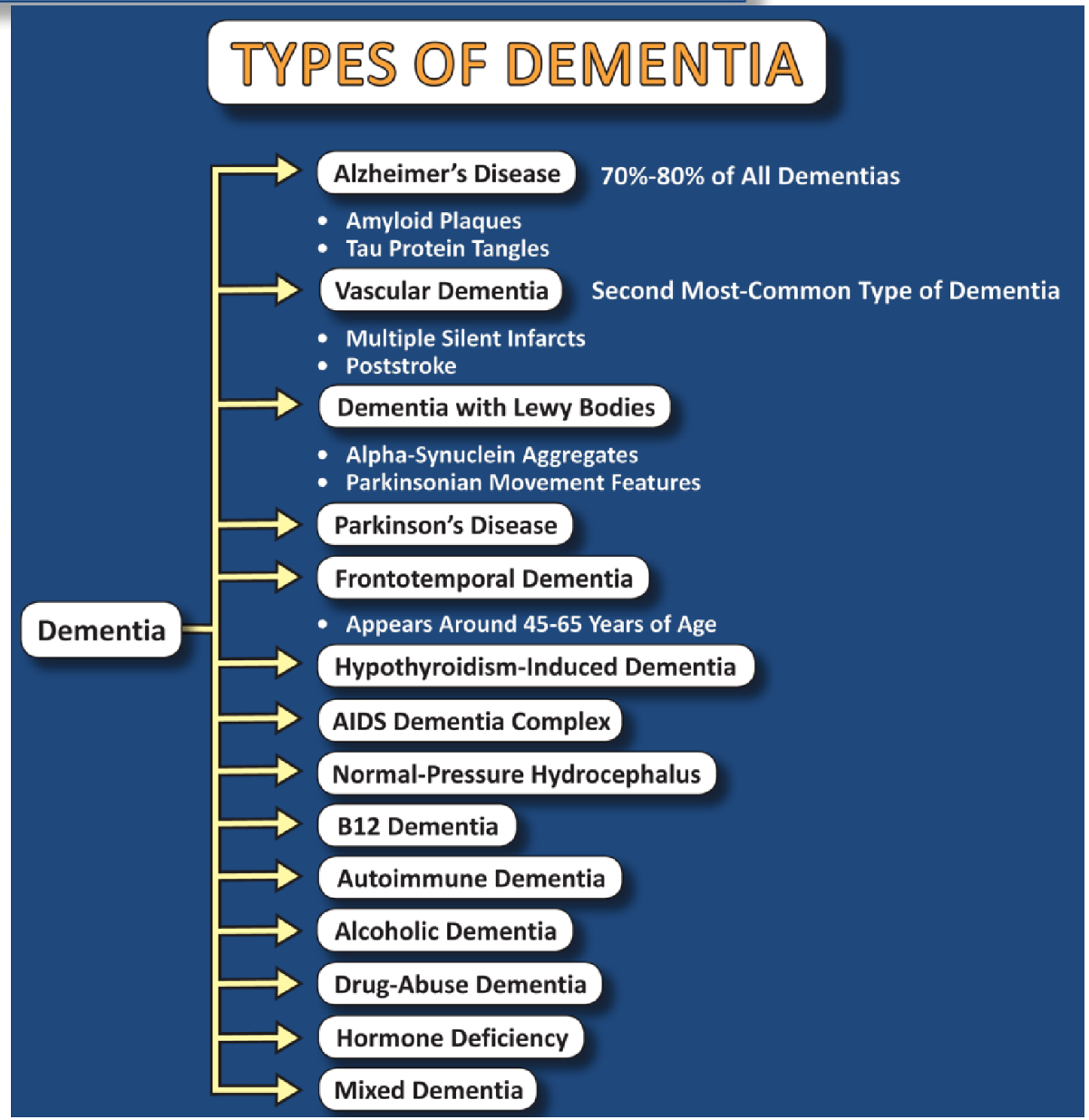
Part Two

3 Different cause of brain degeneration

Three Common Neurodegenerative Diseases

Dementia

- Forgets recently learned information
- Forgets dates, events, and appointments
- Misplaces keys, purse/wallet, remote control
- Has memory lapses in the middle of conversations
- Forgets locations



Three Common Neurodegenerative Diseases

Dementia

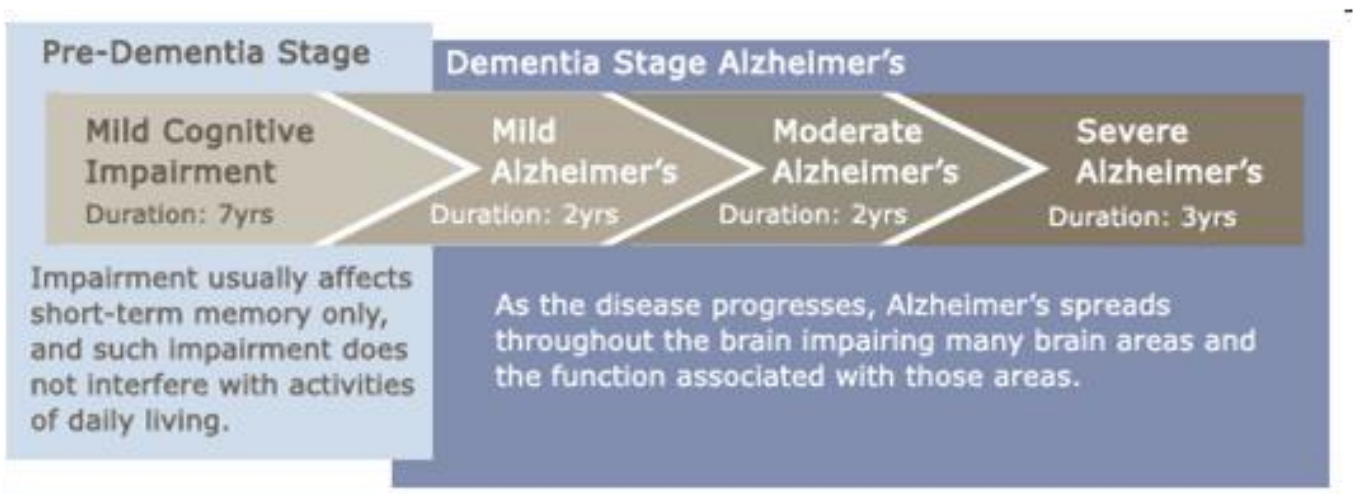
- Forgets recently learned information
- Forgets dates, events, and appointments
- Misplaces keys, purse/wallet, remote control
- Has memory lapses in the middle of conversations
- Forgets locations

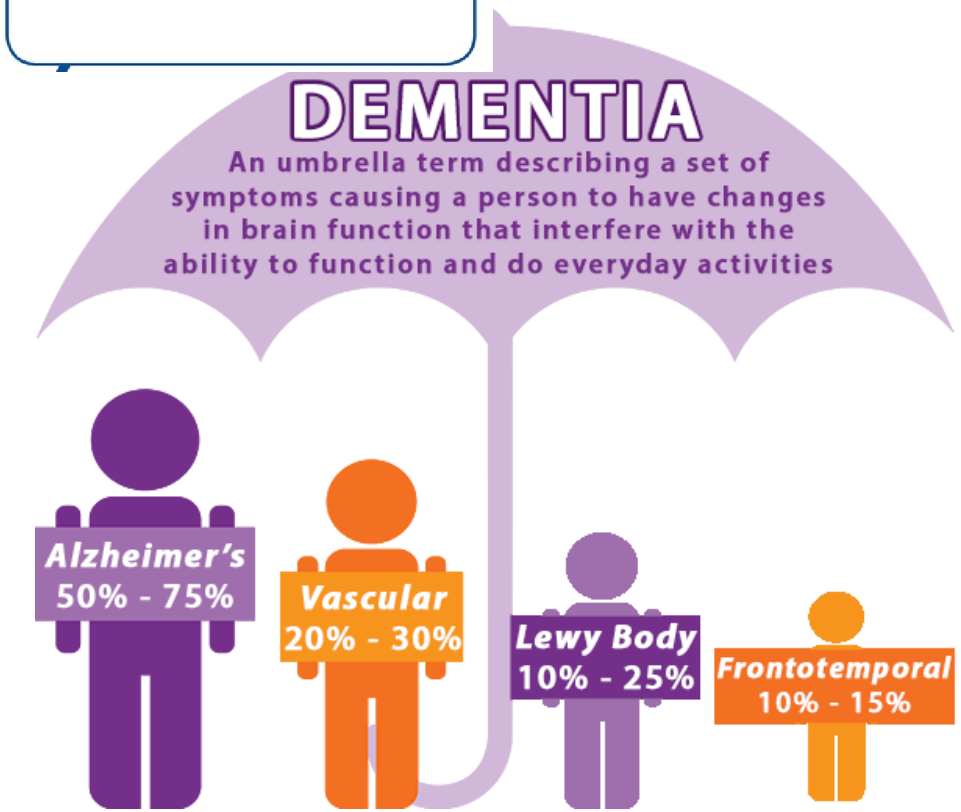
Parkinsonism

- Stiffness
- Slowness of movement
- Impaired GI motility
- ↓Smell and ↓taste
- Expressionless face
- Resting tremor

Cerebellar Degeneration

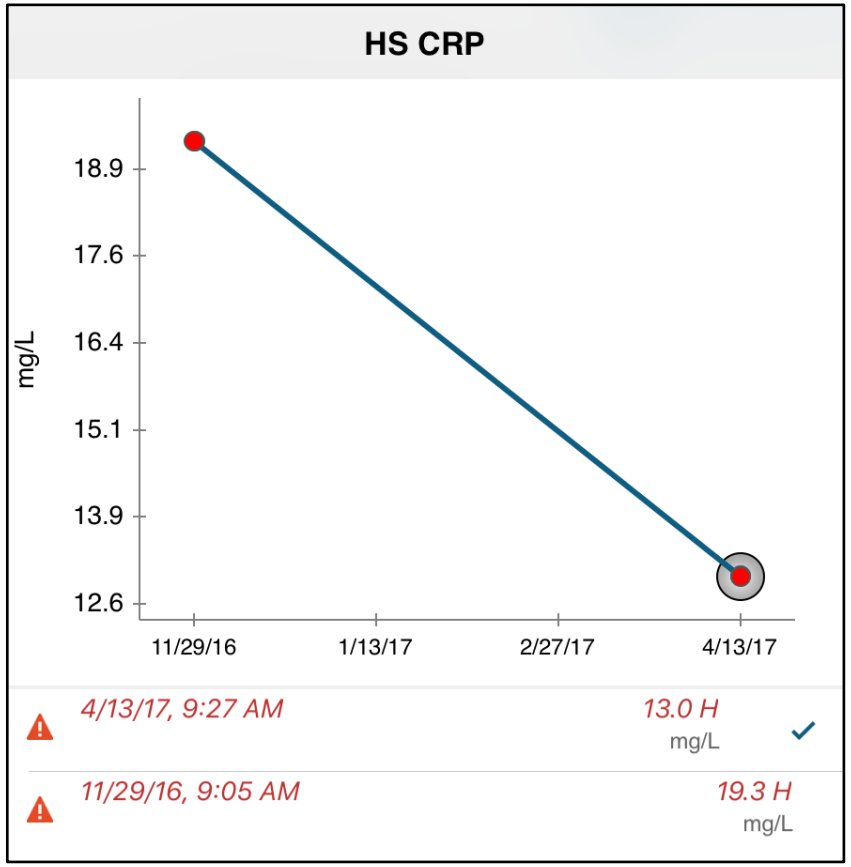
- Worsening balance
- Worsening coordination
- Bumps into everything
- Dizziness and disorientation

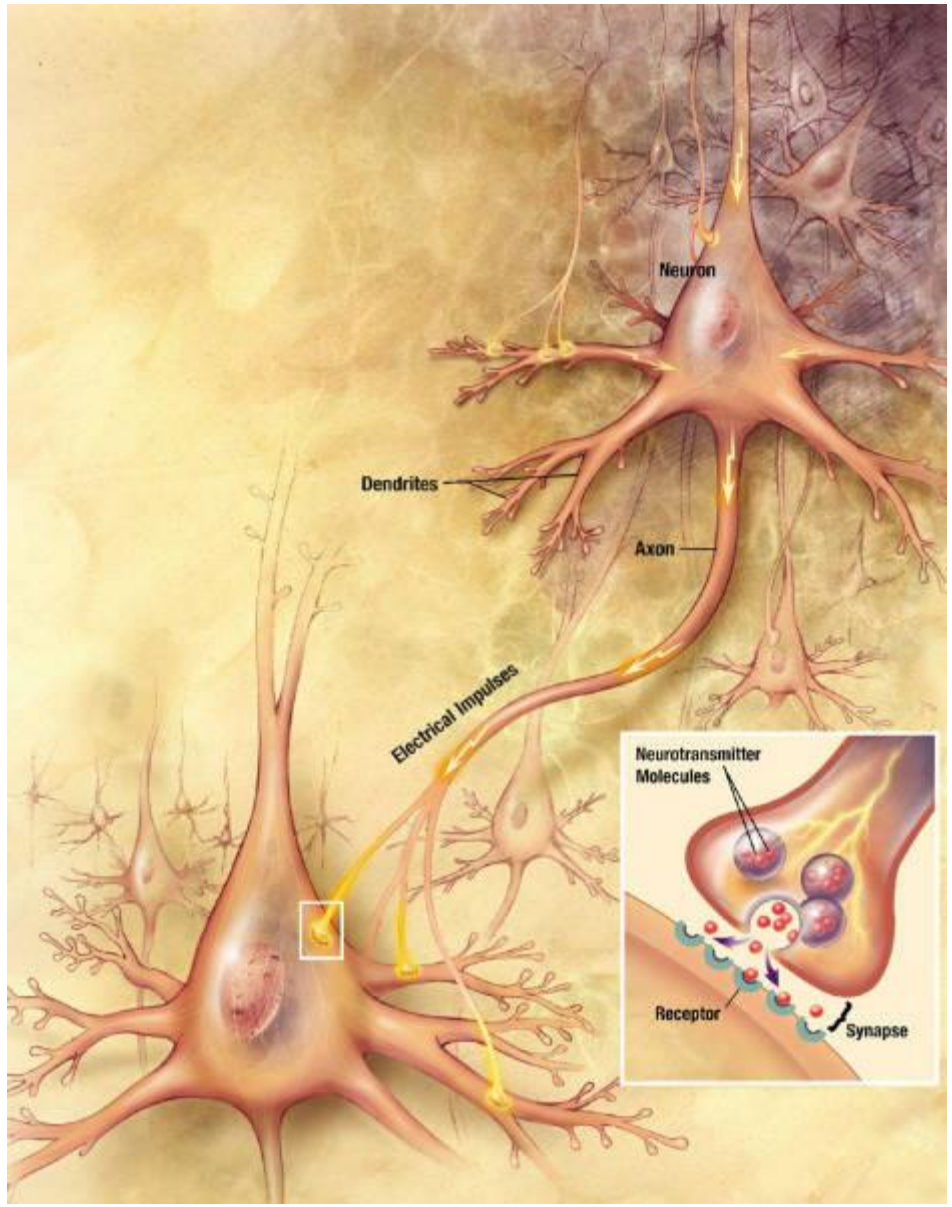




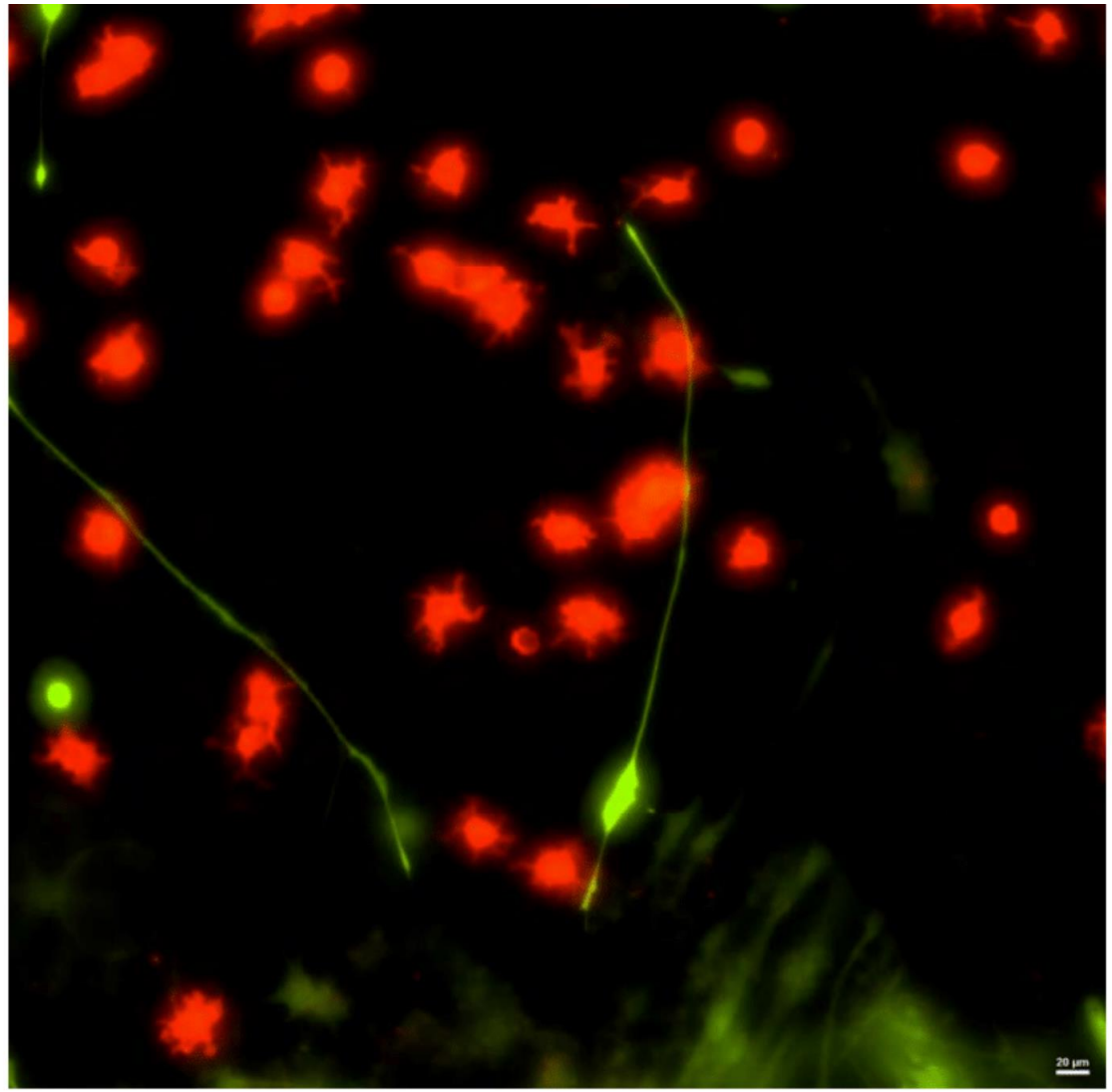
Specifically, Alzheimer's disease/Cognitive Decline is what happens when the brain tries to protect itself from three metabolic and toxic threats:

1)Inflammation (from infection, diet, or other causes)




Neuron
Dendrites
Axon
Electrical Impulses
Neurotransmitter Molecules
Receptor
Synapse

Plaques and tangles trigger brain neuro-inflammation. And…then microglia eat neurons!

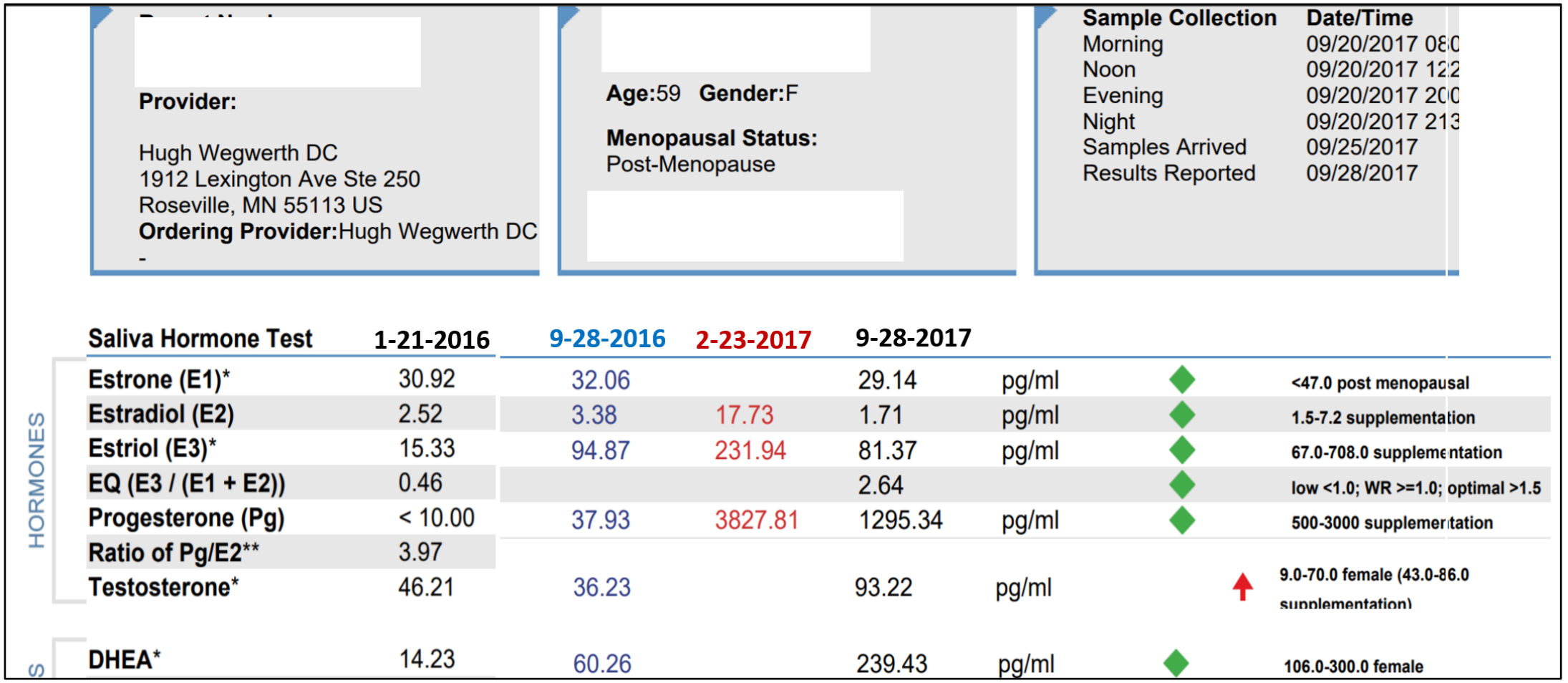


Preventing Alzheimer's requires curbing neuro-inflammation!

Video by Hansong Cho

Specifically, Alzheimer's disease/Cognitive Decline is what happens when the brain tries to protect itself from three metabolic and toxic threats:

2) Decline and shortage of supportive nutrients, hormones, and other brain-supporting molecules



Provider:

Hugh Wegwerth DC
1912 Lexington Ave Ste 250
Roseville, MN 55113 US
Ordering Provider: Hugh Wegwerth DC
-

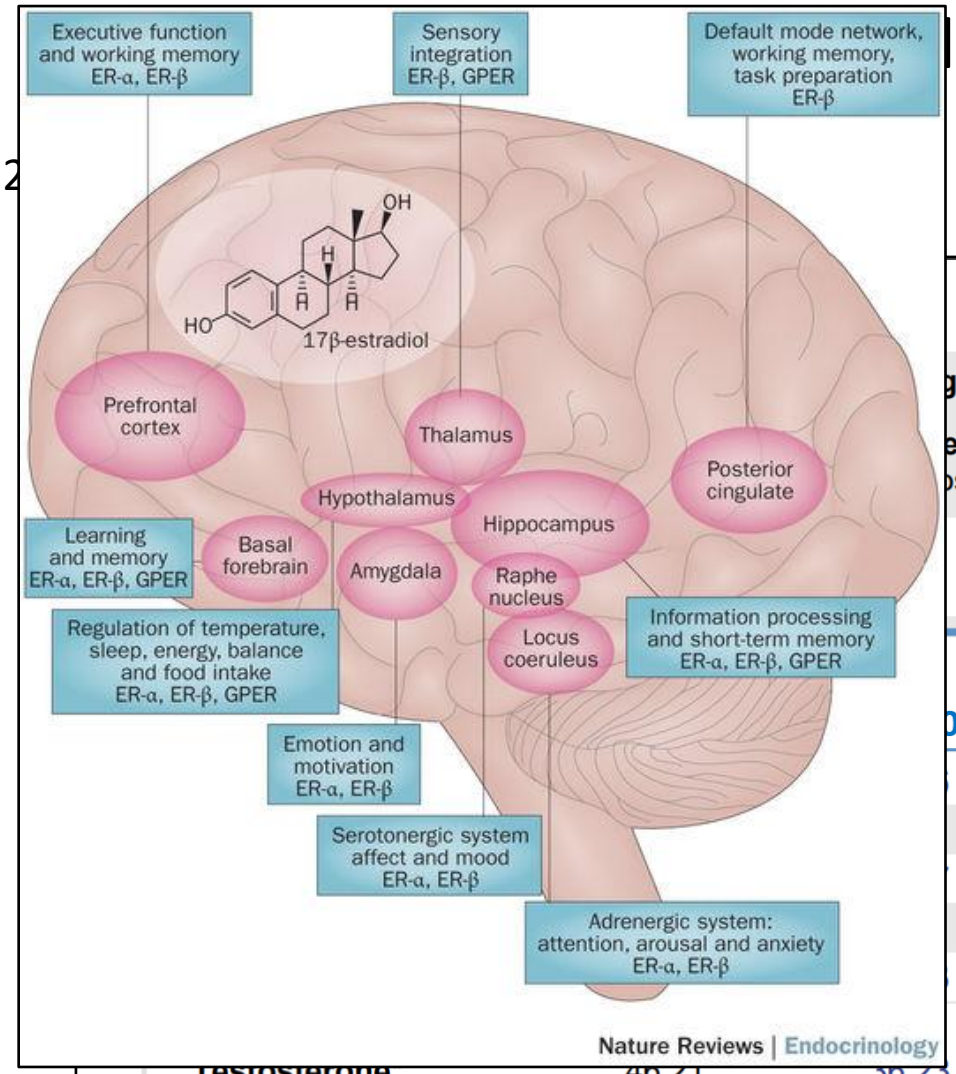
Age:59 **Gender:**F

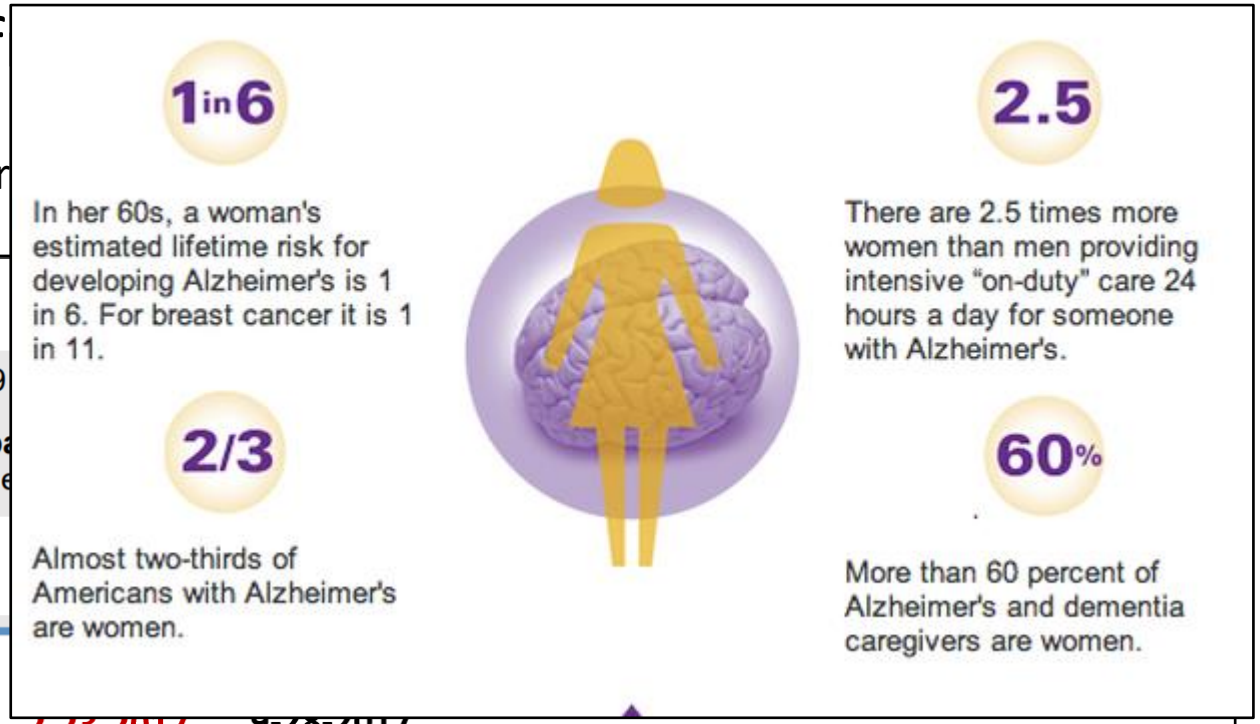
Menopausal Status:
Post-Menopause

Sample Collection	Date/Time
Morning	09/20/2017 08:0
Noon	09/20/2017 12:2
Evening	09/20/2017 20:0
Night	09/20/2017 21:3
Samples Arrived	09/25/2017
Results Reported	09/28/2017

	Saliva Hormone Test	1-21-2016	9-28-2016	2-23-2017	9-28-2017			
HORMONES	Estrone (E1)*	30.92	32.06		29.14	pg/ml	◆	<47.0 post menopausal
	Estradiol (E2)	2.52	3.38	17.73	1.71	pg/ml	◆	1.5-7.2 supplementation
	Estriol (E3)*	15.33	94.87	231.94	81.37	pg/ml	◆	67.0-708.0 supplementation
	EQ (E3 / (E1 + E2))	0.46			2.64		◆	low <1.0; WR >=1.0; optimal >1.5
	Progesterone (Pg)	< 10.00	37.93	3827.81	1295.34	pg/ml	◆	500-3000 supplementation
	Ratio of Pg/E2**	3.97						
	Testosterone*	46.21	36.23		93.22	pg/ml	▲	9.0-70.0 female (43.0-86.0 supplementation)
S	DHEA*	14.23	60.26		239.43	pg/ml	◆	106.0-300.0 female

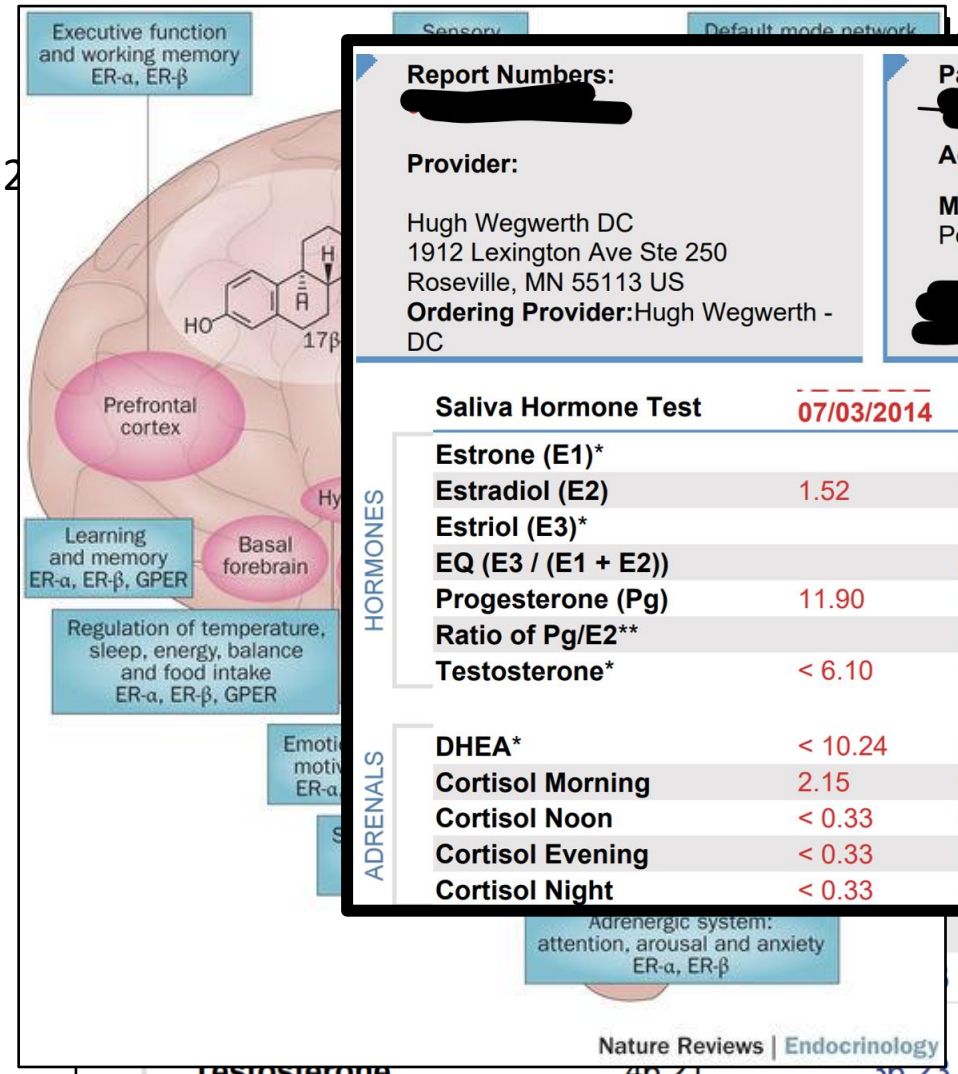
Specifically, Alzheimer's disease/Cognitive Decline is what happens when the





			29.14	pg/ml	◆	<47.0 post menopausal
	17.73		1.71	pg/ml	◆	1.5-7.2 supplementation
	231.94		81.37	pg/ml	◆	67.0-708.0 supplementation
			2.64		◆	low <1.0; WR >=1.0; optimal >1.5
	3827.81		1295.34	pg/ml	◆	500-3000 supplementation
Testosterone	46.21	36.23	93.22	pg/ml	▲	9.0-70.0 female (43.0-86.0 supplementation)
DHEA*	14.23	60.26	239.43	pg/ml	◆	106.0-300.0 female

Specifically, Alzheimer's disease/Cognitive Decline is what happens when the



Report Numbers: [redacted]

Provider:

Hugh Wegwerth DC
1912 Lexington Ave Ste 250
Roseville, MN 55113 US
Ordering Provider: Hugh Wegwerth - DC

Patient Info: [redacted]

Age:50 **Gender:**F

Menopausal Status:
Post-Menopause

[redacted]

Sample Collection	Date/Time
Morning	08/12/2016 0800
Noon	08/12/2016 1100
Evening	08/12/2016 1600
Night	08/12/2016 2300
Samples Arrived	08/19/2016
Results Reported	08/24/2016

	Saliva Hormone Test	07/03/2014	08/24/2016	Units	L	WR	H	Reference Range
HORMONES	Estrone (E1)*		37.48	pg/ml		◆		<47.0 post menopausal
	Estradiol (E2)	1.52	7.53	pg/ml		◆		1.5-10.8 supplementation
	Estriol (E3)*		290.88	pg/ml		◆		67.0-708.0 supplementation
	EQ (E3 / (E1 + E2))		6.46			◆		low <1.0; WR >=1.0; optimal >1.5
	Progesterone (Pg)	11.90	421.84	pg/ml	↓			500-3000 supplementation
	Ratio of Pg/E2**		56.04		↓			200-600 pre; post with supplementation
	Testosterone*	< 6.10	47.38	pg/ml		◆		6.1-49.0 female (30.0-60.0 supplementation)
ADRENALS	DHEA*	< 10.24	256.64	pg/ml		◆		106.0-300.0 female
	Cortisol Morning	2.15	9.99	nmol/L		◆		5.1-40.2; optimal range: 18-35†
	Cortisol Noon	< 0.33	0.73	nmol/L	↓			2.1-15.7; optimal range: 6-12†
	Cortisol Evening	< 0.33	4.66	nmol/L		◆		1.8-12; optimal range: 4-8†
	Cortisol Night	< 0.33	7.08	nmol/L		◆		0.9-9.2; optimal range: 2-6†

2.5

re 2.5 times more than men providing e "on-duty" care 24 day for someone zheimer's.

60%

an 60 percent of her's and dementia ers are women.

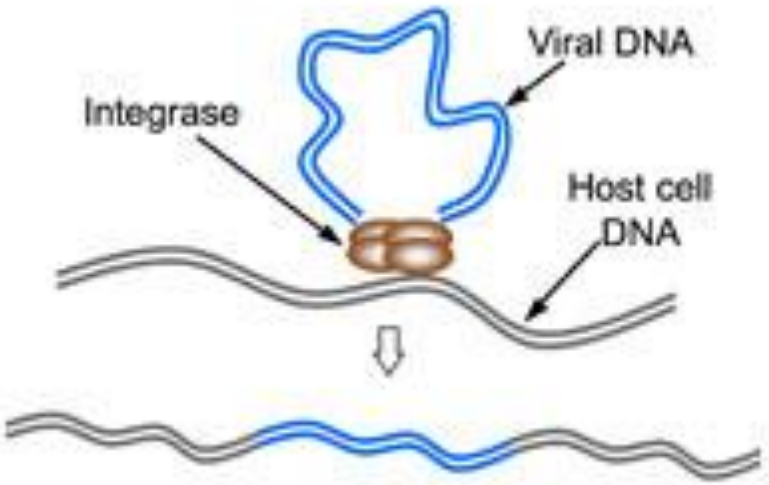
			2.64		◆		low <1.0; WR >=1.0; optimal >1.5
		3827.81	1295.34	pg/ml	◆		500-3000 supplementation
	Testosterone	46.21	93.22	pg/ml		↑	9.0-70.0 female (43.0-86.0 supplementation)
S	DHEA*	14.23	239.43	pg/ml	◆		106.0-300.0 female

Specifically, Alzheimer's disease/Cognitive Decline is what happens when the brain tries to protect itself from three metabolic and toxic threats:

1) Toxic substances such as metals or biotoxins (poisons produced by microbes such as molds)

CYTOMEGALOVIRUS ANTIBODY (IGG) **2.97 H**

Value	Interpretation
< or = 0.90	Negative
0.91-1.09	Equivocal
> or = 1.10	Positive



EBV VIRAL CAPSID AG (VCA) AB (IGG) **117.00 H** U/mL

U/mL	Interpretation
<18.00	Negative
18.00-21.99	Equivocal
>21.99	Positive

EBV NUCLEAR AG (EBNA) AB (IGG) **135.00 H** U/mL

U/mL	Interpretation
<18.00	Negative
18.00-21.99	Equivocal
>21.99	Positive

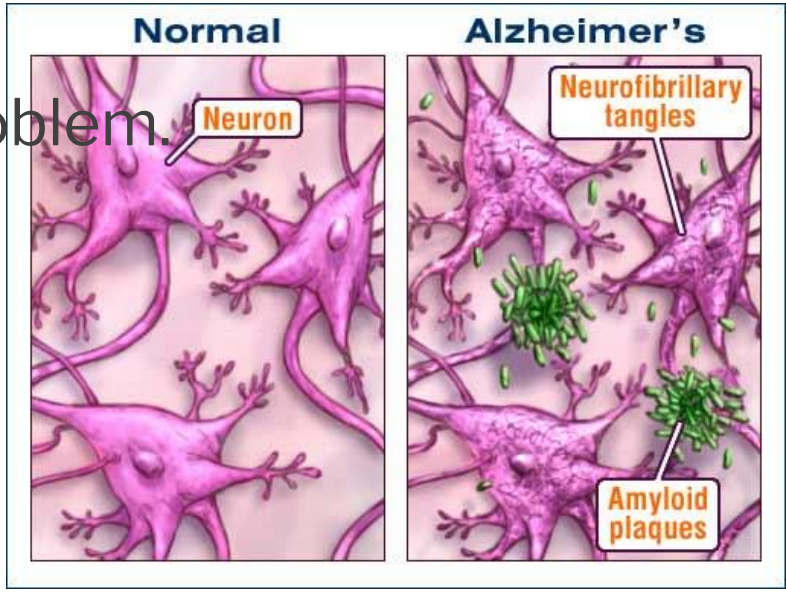
Part Three

Amyloid Plaques, Inflammation, Labs

Amyloid-Beta Plaque {Alzheimer's Disease (AD)}

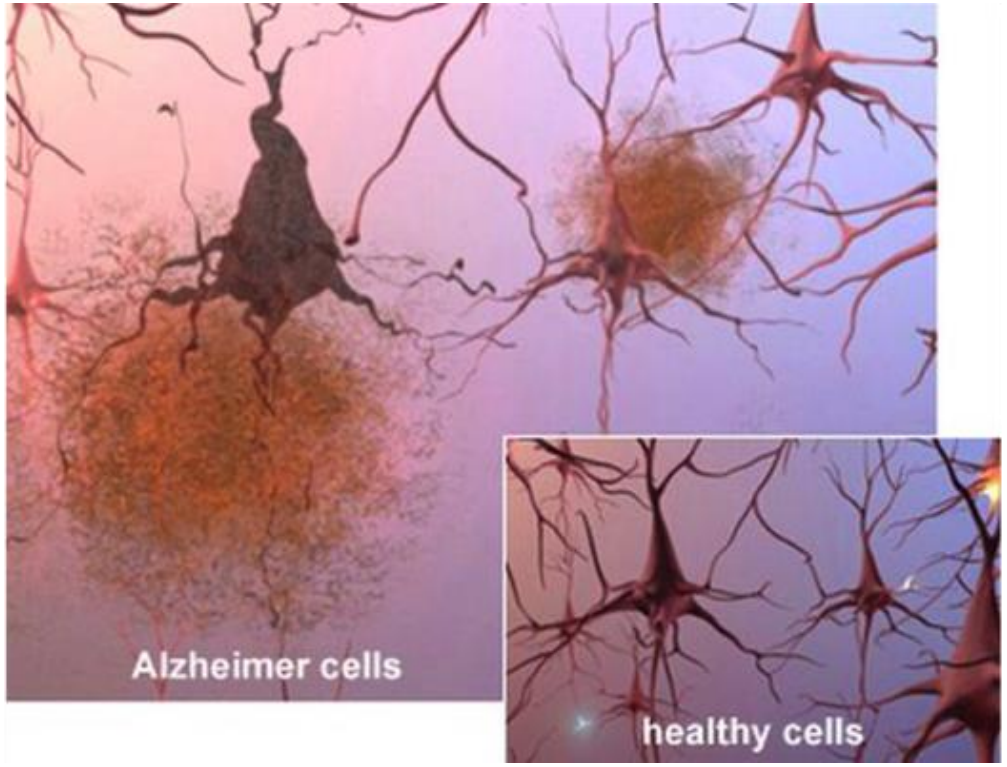
The dogma behind amyloid plaque (the sticky plaque that builds up in the brain of Alzheimer's patients) as the main evil in Alzheimer's Disease (AD) is actually incorrect.
In fact, it may be protective:
•Acts as an anti-microbial
•Binds to toxins (like heavy metals)
•Protects against inflammation

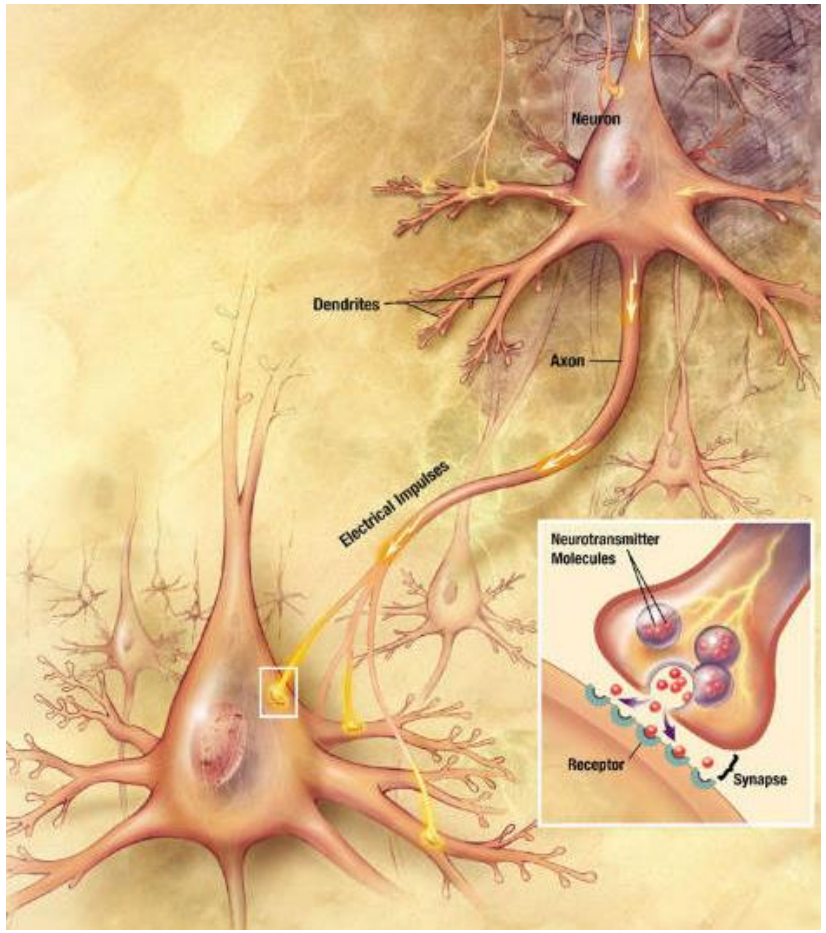
The Bredesen Protocol first targets the underlying problem.



“A genuinely new Alzheimer’s drug has not been approved since 2003, and the currently approved Alzheimer’s medications are ineffective in stopping or slowing the course of the disease,” said Carrillo. “The more than five million Americans living with Alzheimer’s, and the many millions more worldwide, demand new and innovative approaches. We are obligated to pursue all legitimate avenues for treatment, such as targeting neuroinflammation.”

Amyloid acts like a big SPONGE



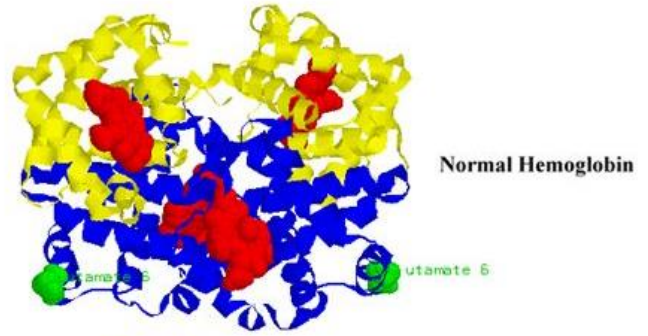


https://alz.org/documents_custom/ptc_grants_080216.pdf

Good protein structure good function
Chronic inflammation causes poor protein folding

Structure determines shape:

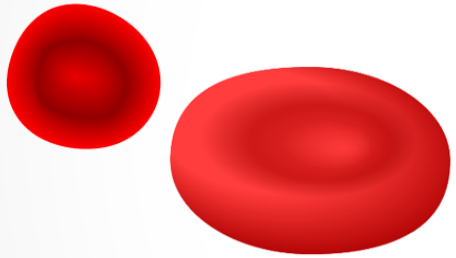
A mutation in the sickle cell gene (DNA) causes the amino acid valine to be substituted for glutamic acid in the final protein product. This changes the shape and function of the hemoglobin molecule.



Note: The Sickle hemoglobin image is drawn at 50% of the size of the Normal hemoglobin

What is Sickle Cell Anemia?

Sickle Cell Anaemia is the most common form of sickle cell disease (SCD). SCD is a serious disorder in which the body makes sickle-shaped red blood cells.



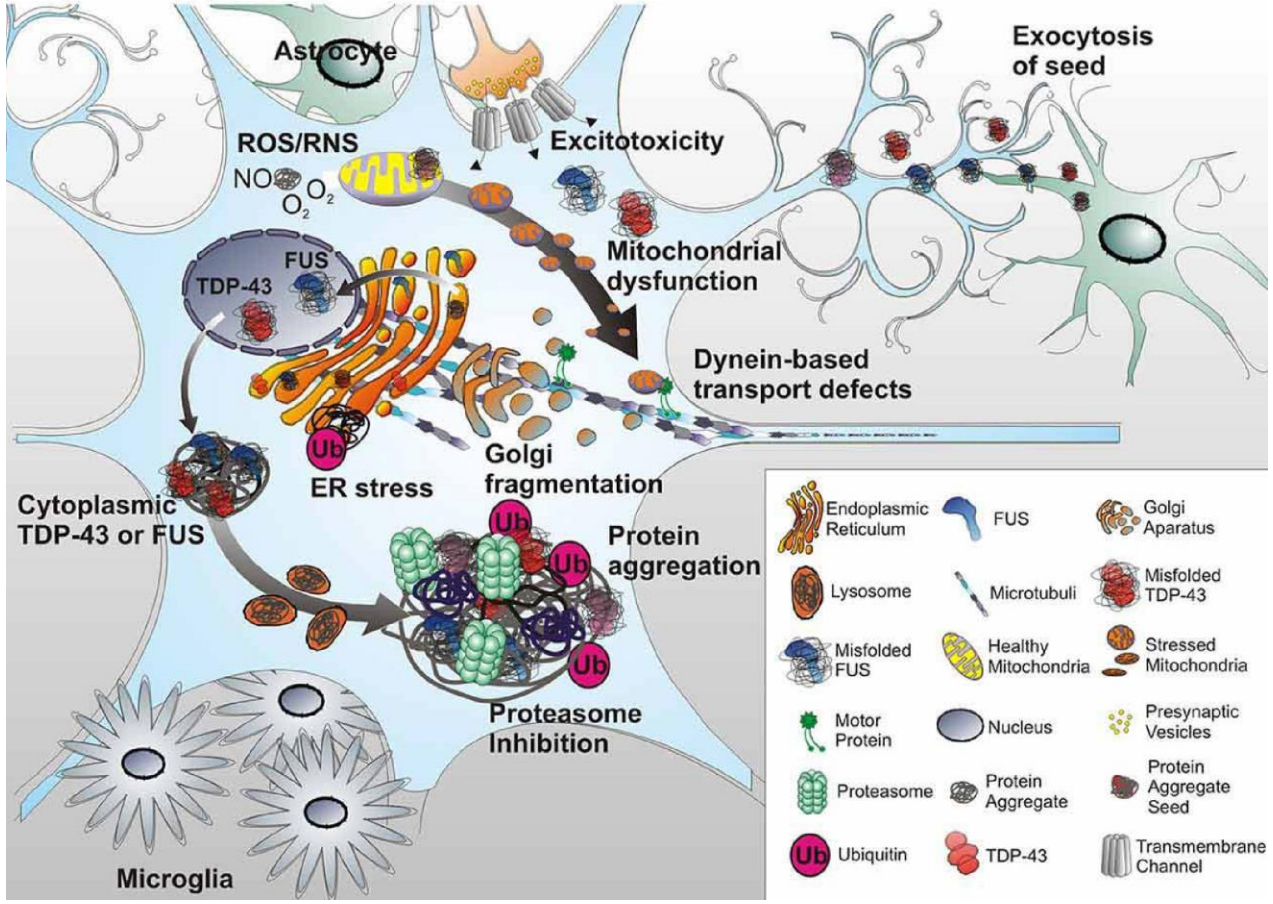
Normal Red Blood Cell

Sickle Red Blood Cell

DHARAMSHILA
Blood and Marrow Stem Cell Transplantation Centre

Dharamshila Blood and Marrow Stem Cell Transplant Centre

If you are inflamed



1) a protein mis folds. 2) Protein mis folds, breaks off and aggregate. 3)That protein aggregations and those tau proteins and alpha synuclein that's broken off start to cause neuro-inflammatory and neurodegenerative changes. 4)Those proteins then aggregate and cause a cluster of inflammatory reactions. 5) Those clusters of inflammatory reactions produce reactive oxygen species. 6) Those reactive oxygen species damage the mitochondria. 7) The mitochondria becomes inefficient, within the neuron 8) as the mitochondria becomes inefficient, the neuron can't make ATP. As the neuron loses its ability to make ATP, it can't block the 9) the calcium influx, you get inflammatory cascade, and neurons die. 10)When neurons die, they create their own inflammatory cascade, which then promotes a vicious cycle, and you get more protein misfolding that promotes that vicious cycle, and you get ongoing vicious cycles that then lead to a progressive neurodegenerative disease. You have to block it, right?

https://www.youtube.com/watch?v=NjgBnx1jVIU

Get Checked to see if you're inflamed

Element	Current Feb 09 2015	Previous Jan 05 2015	Impr	Optimal Range	Standard Range	Units
Glucose	99.00 ↑	101.00 ↑	👍	72.00 - 90.00	65.00 - 99.00	mg/dL
Insulin - Fasting	9.20 ↑	13.40 ↑	👍	0.00 - 5.00	0.00 - 23.00	µIU/ml
BUN	16.00	19.00 ↑	👍	10.00 - 16.00	7.00 - 25.00	mg/dL
Creatinine	0.98	0.92		0.80 - 1.10	0.40 - 1.35	mg/dL
BUN/Creatinine Ratio	16.00	20.65 ↑	👍	10.00 - 16.00	6.00 - 22.00	Ratio
eGFR Non-Afr. American	57.00 ↓	62.00	👎	60.00 - 128.00	60.00 - 128.00	/min/1.73r
eGFR African American	66.00	72.00		60.00 - 128.00	60.00 - 128.00	/min/1.73r
Sodium	142.00	139.00		135.00 - 142.00	135.00 - 146.00	mEq/L
Potassium	4.60 ↑	4.30	👎	4.00 - 4.50	3.50 - 5.30	mEq/L
Sodium/Potassium Ratio	30.86	32.32		30.00 - 35.00	30.00 - 35.00	ratio
Chloride	104.00	104.00		100.00 - 106.00	98.00 - 110.00	mEq/L
CO2	27.00	25.00		25.00 - 30.00	19.00 - 30.00	mEq/L
Anion gap	15.60 ↑	14.30 ↑	👎	7.00 - 12.00	6.00 - 16.00	mEq/L
Protein, total	7.10	6.80 ↓	👍	6.90 - 7.40	6.10 - 8.10	g/dL
Albumin	4.30	4.00		4.00 - 5.00	3.60 - 5.10	g/dL
Globulin, total	2.80	2.80		2.40 - 2.80	2.00 - 3.50	g/dL
Albumin/Globulin Ratio	1.50	1.40		1.40 - 2.10	1.00 - 2.50	ratio
Calcium	10.20 ↑	8.90 ↓	👎	9.40 - 10.10	8.60 - 10.40	mg/dL
Calcium/Albumin Ratio	2.37	2.22		0.00 - 2.60	0.00 - 2.70	ratio
Alk Phos	93.00	181.00 ⚠	👍	70.00 - 100.00	35.00 - 115.00	IU/L
AST (SGOT)	32.00 ↑	160.00 ⚠	👍	10.00 - 26.00	10.00 - 35.00	IU/L
ALT (SGPT)	23.00	300.00 ⚠	👍	10.00 - 26.00	6.00 - 29.00	IU/L
LDH	280.00 ↑	271.00 ↑	👎	140.00 - 200.00	120.00 - 250.00	IU/L
Bilirubin - Total	0.50	0.40		0.10 - 0.90	0.20 - 1.20	mg/dL
GGT	26.00	152.00 ⚠	👍	10.00 - 30.00	3.00 - 70.00	IU/L
Iron - Serum	66.00 ↓	34.00 ↓	👍	85.00 - 130.00	40.00 - 160.00	µg/dL

Ferritin	81.00	80.00		40.00 - 150.00
TIBC	321.00	294.00		250.00 - 350.00
% Transferrin saturation	21.00 ↓	12.00 ↓	👍	24.00 - 50.00
TSH	3.03	12.48 ↑	👍	1.00 - 3.50
Hs CRP, Female	5.70 ↑	27.90 ⚠	👍	0.00 - 0.99
Fibrinogen	453.00 ↑	509.00 ↑	👍	200.00 - 300.00

Part Four

Dementia and Alzheimers Disease

Dementia

Three Common Neurodegenerative Diseases

Dementia

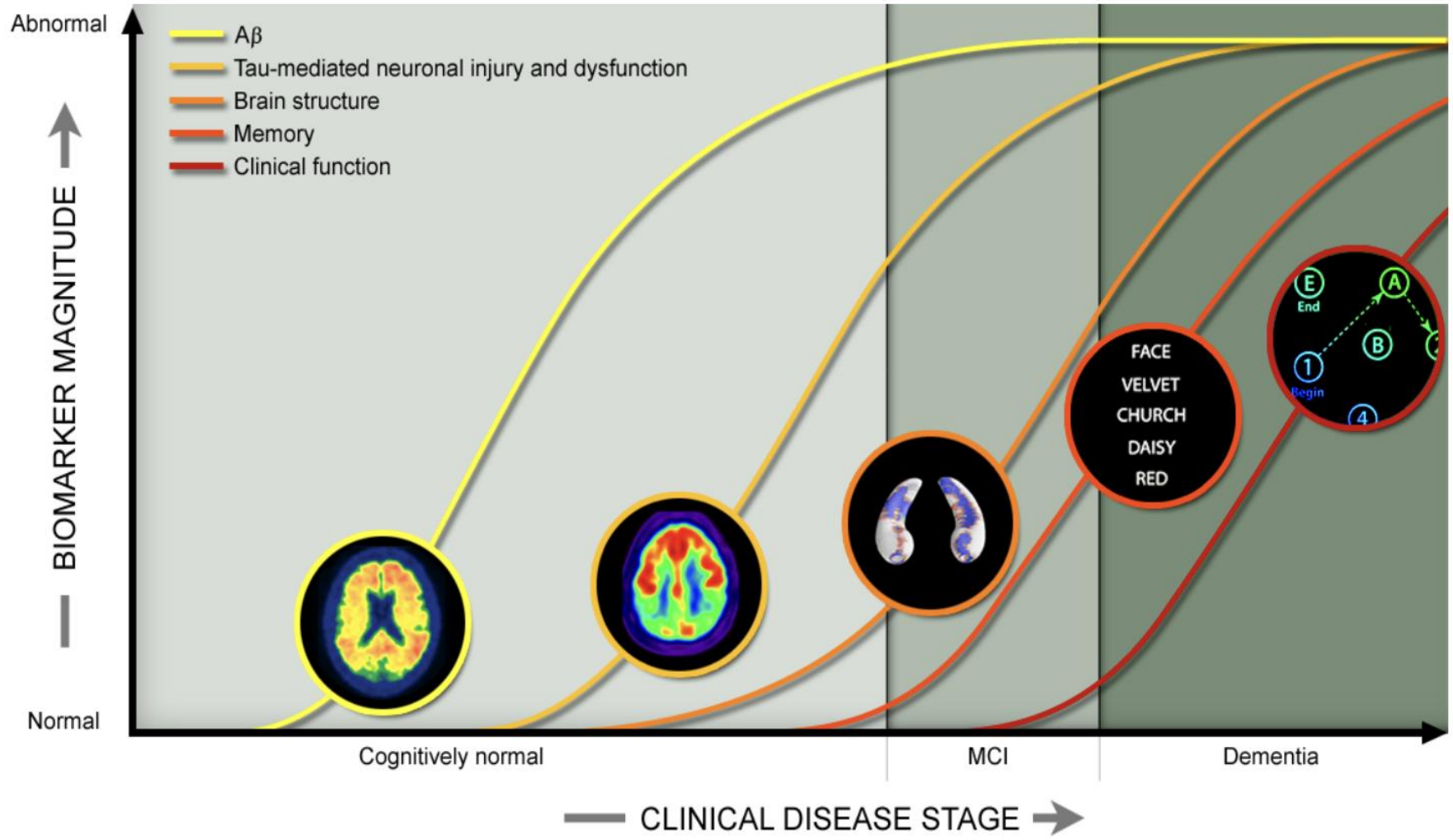
- Forgets recently learned information
- Forgets dates, events, and appointments
- Misplaces keys, purse/wallet, remote control
- Has memory lapses in the middle of conversations
- Forgets locations

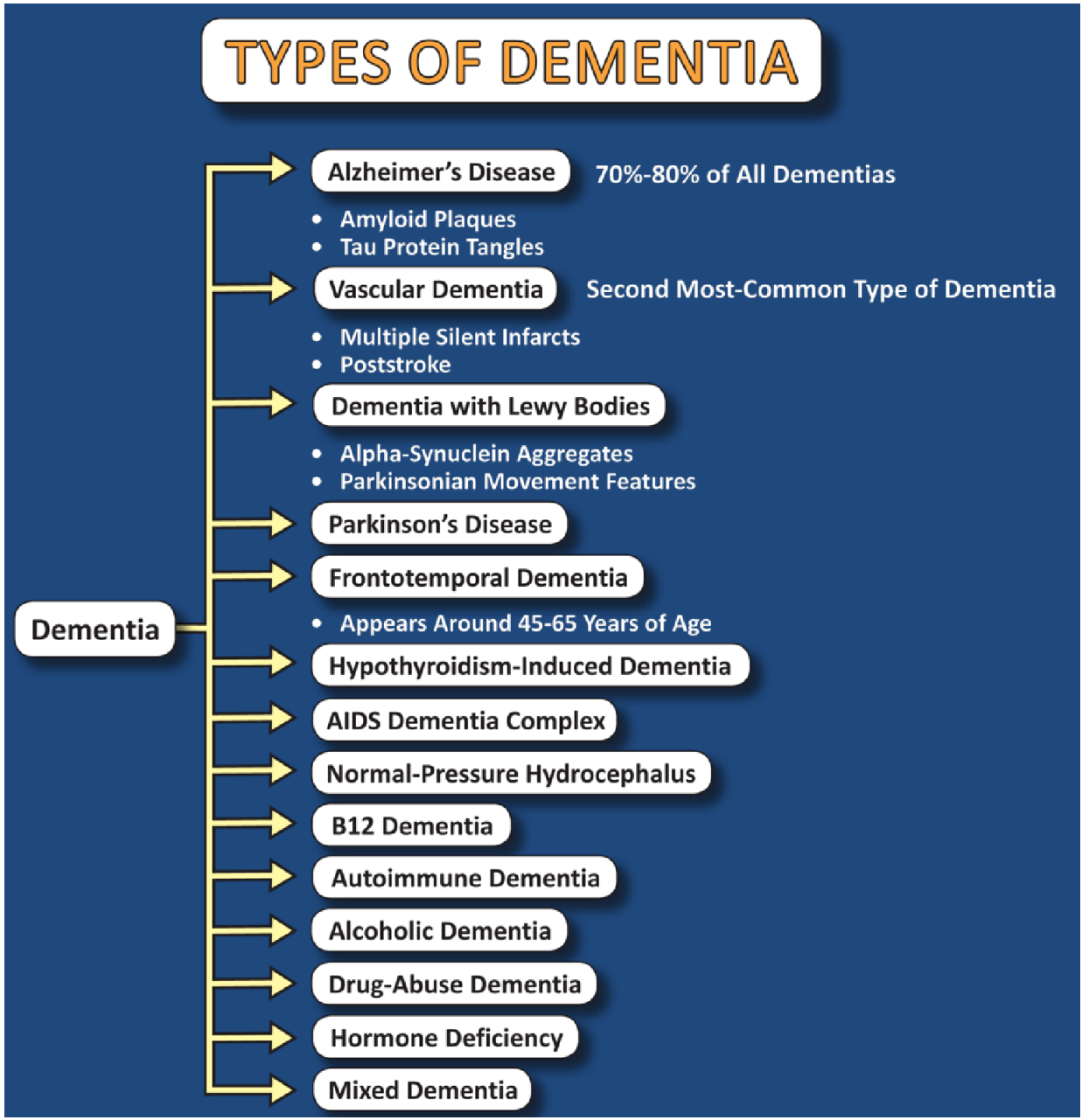
Parkinsonism

- Stiffness
- Slowness of movement
- Impaired GI motility
- ↓Smell and ↓taste
- Expressionless face
- Resting tremor

Cerebellar Degeneration

- Worsening balance
- Worsening coordination
- Bumps into everything
- Dizziness and disorientation


Abnormal
Normal
BIOMARKER MAGNITUDE
Aβ
Tau-mediated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
FACE
VELVET
CHURCH
DAISY
RED
E
End
A
B
1
Begin
4
Cognitively normal
MCI
Dementia
CLINICAL DISEASE STAGE


TYPES OF DEMENTIA
Dementia
Alzheimer's Disease
70%-80% of All Dementias
Amyloid Plaques
Tau Protein Tangles
Vascular Dementia
Second Most-Common Type of Dementia
Multiple Silent Infarcts
Poststroke
Dementia with Lewy Bodies
Alpha-Synuclein Aggregates
Parkinsonian Movement Features
Parkinson's Disease
Frontotemporal Dementia
Appears Around 45-65 Years of Age
Hypothyroidism-Induced Dementia
AIDS Dementia Complex
Normal-Pressure Hydrocephalus
B12 Dementia
Autoimmune Dementia
Alcoholic Dementia
Drug-Abuse Dementia
Hormone Deficiency
Mixed Dementia

10 EARLY WARNING SIGNS OF DEMENTIA/ALZHEIMER'S

Alzheimer's Association

1. Memory Loss That Disrupts Daily Life

- Forgets recently learned information
- Forgets dates and events

2. Challenges in Planning or Solving Problems

- Makes errors in balancing a checkbook
- Makes errors when following recipes

3. Difficulty Completing Familiar Tasks at Home, at Work, and at Leisure

- Needs help with setting electronics

4. Confusion With Time or Place

- Loses track of dates, seasons, and the passage of time

5. Trouble Understanding Visual Images and Spatial Relationships

- Has difficulty reading, judging distance, and determining color or contrast

6. New Problems With Words in Speaking or Writing

- Has difficulty finding the right word
- Stops in the middle of a conversation

7. Misplacing Things and Losing the Ability to Retrace Steps

- Misplaces keys, remote control, or purse

8. Decreased or Poor Judgment

- Shows poor grooming
- Gives money to telemarketers

9. Withdrawal From Work or Social Activities

10. Changes in Mood and Personality

SEVEN STAGES OF ALZHEIMER'S

Alzheimer's Association

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Stage 6	Stage 7
• No impairment • Normal function	• Very mild cognitive decline that may be normal, age related	• Mild cognitive decline • Early-stage Alzheimer's **MCI**	• Moderate cognitive decline • Early-stage Alzheimer's	• Moderately severe cognitive decline • Mid-stage Alzheimer's	• Severe cognitive decline • Mid-stage Alzheimer's	• Very severe cognitive decline • Late-stage Alzheimer's
• Normal medical interview • No memory problems	• Forgets familiar words • Forgets location of everyday objects	• Has trouble remembering names when introduced to new people • Forgets material that one has just read • Experiences increasing trouble with planning or organizing	• Forgets recent events • Has an impaired ability with mathematics (such as counting backwards from 100 by 7s) • Has difficulty planning, paying bills, or managing tasks • Forgets one's own personal history	• Unable to recall one's own address or telephone number • Becomes confused about what day it is • Needs help choosing appropriate clothing for the weather • Still does not require assistance with eating or using the toilet	• Has trouble remembering spouse's name • Needs help dressing normally • Has bowel and bladder incontinence • Has a major personality disorder • Tends to wander or become lost	• Loses the ability to respond to the environment • Must have a caregiver • Experiences impaired swallowing

Centers for Disease Control and Prevention.
National Diabetes Fact Sheet, 2011

- "About 60 to 70 percent of people with diabetes have mild to severe forms of nervous system damage."

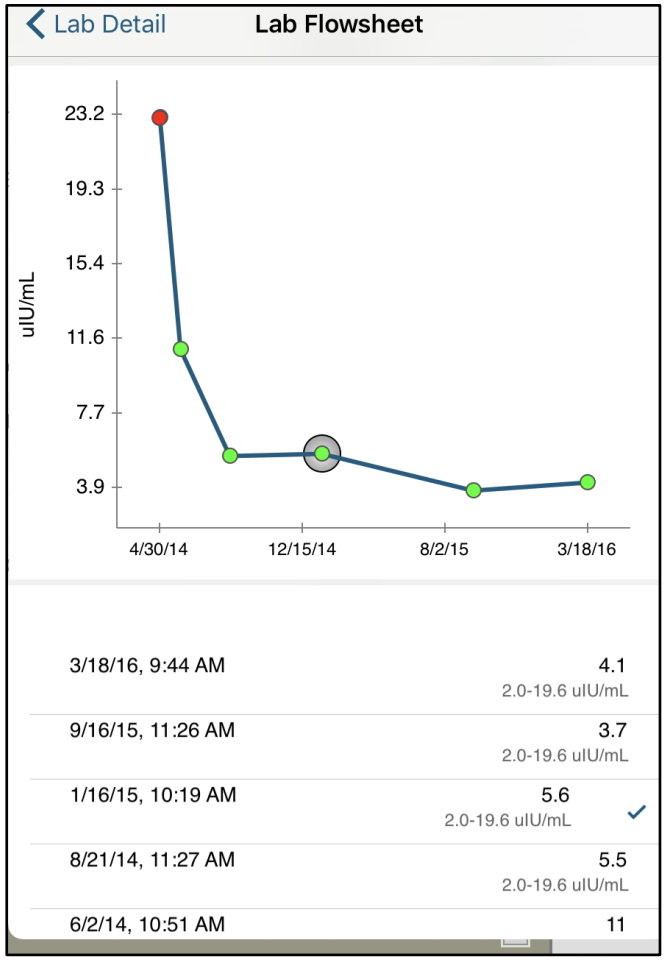
- "The risk for stroke is two to four times higher among people with diabetes."

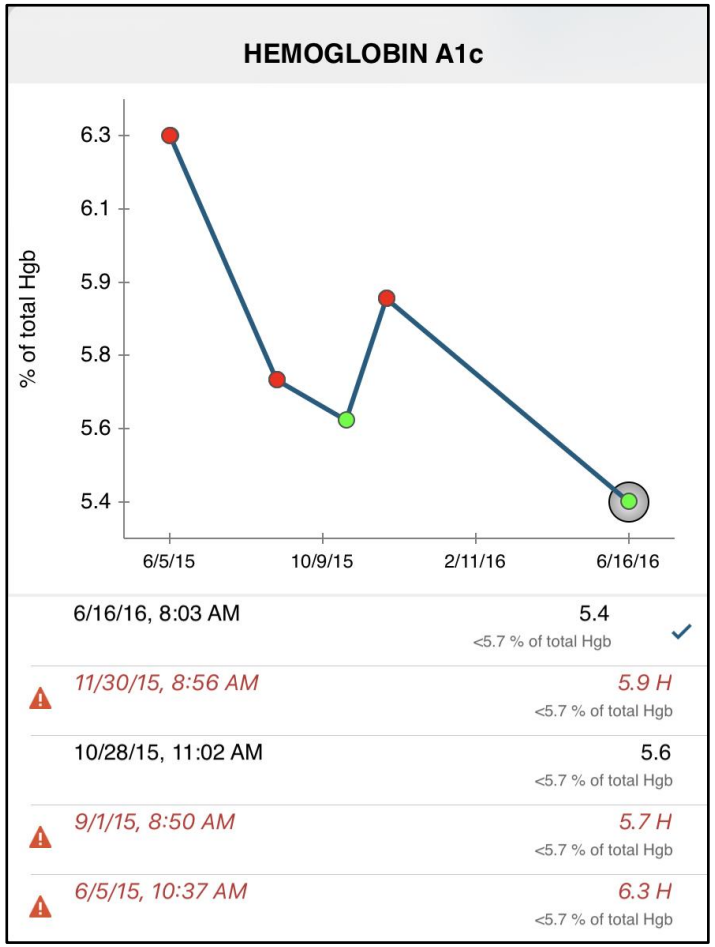
Altern Med Rev. 2009 Dec;14(4):373-379.

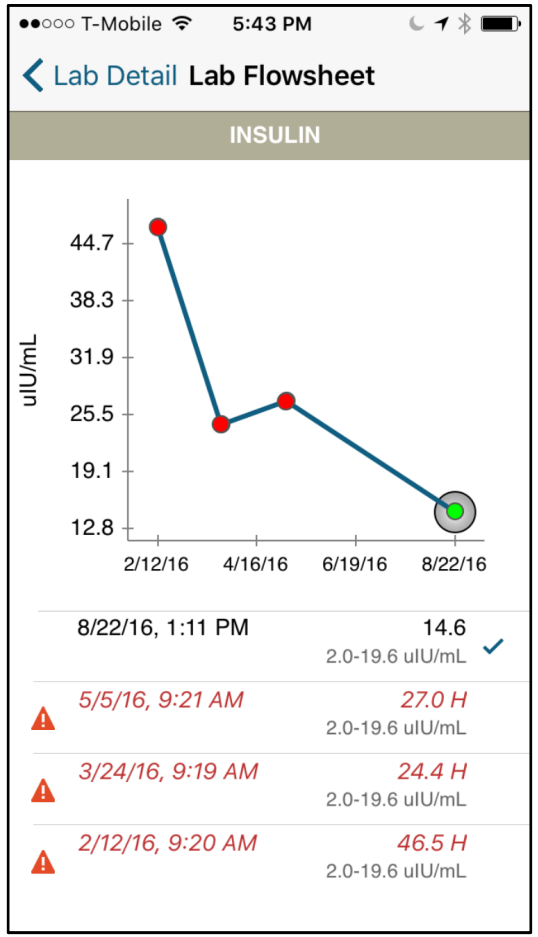
The relationship between Alzheimer's disease and diabetes: Type 3 diabetes?

- "In recent years, Alzheimer's disease (AD) has been considered to be, in part, a neuroendocrine disorder, even referred to by some as **type 3 diabetes**."
- "Insulin functions by controlling neurotransmitter release processes at the synapses and activating signaling pathways associated with learning and long-term memory."

Element	Current Feb 09 2015	Previous Jan 05 2015	Impr	Optimal Range	Standard Range	Units
Glucose	99.00 ↑	101.00 ↑		72.00 - 90.00	65.00 - 99.00	mg/dL
Insulin - Fasting	9.20 ↑	13.40 ↑		0.00 - 5.00	0.00 - 23.00	µIU/ml







MEDIAL TEMPORAL LOBE HIPPOCAMPUS

LOSS OF ACTIVITY AND EPILEPTIFORM ACTIVITY

Loss of activity leads to impaired declarative memory, impaired spatial memory and navigation, loss of visual memory and altered cortisol circadian rhythms. Bilateral injury leads to amnesia.

Epileptiform activity leads to episodes of deja vu

BRAIN REGION LOCALIZATION FORM SYMPTOMS

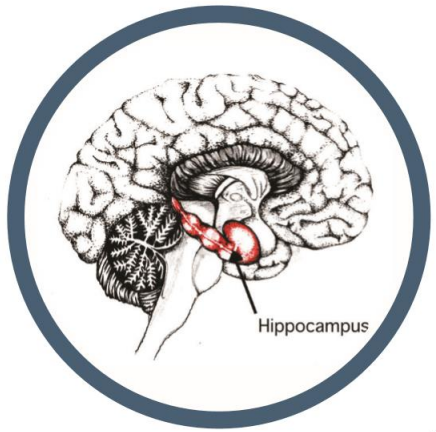
- Memory less efficient
- Memory loss that impacts daily activities
- Confusion about dates, the passage of time, or place
- Difficulty remembering events
- Misplacement of things and difficulty retracing steps
- Difficulty with memory of locations (addresses)
- Difficulty with visual memory
- Always forgetting where you put items such as keys, wallet, phone, etc.
- Difficulty remembering faces
- Difficulty remembering names with faces
- Difficulty with remembering words
- Difficulty remembering numbers
- Difficulty remembering to stay or be on time (reduced left)

EXAMINATION FINDINGS

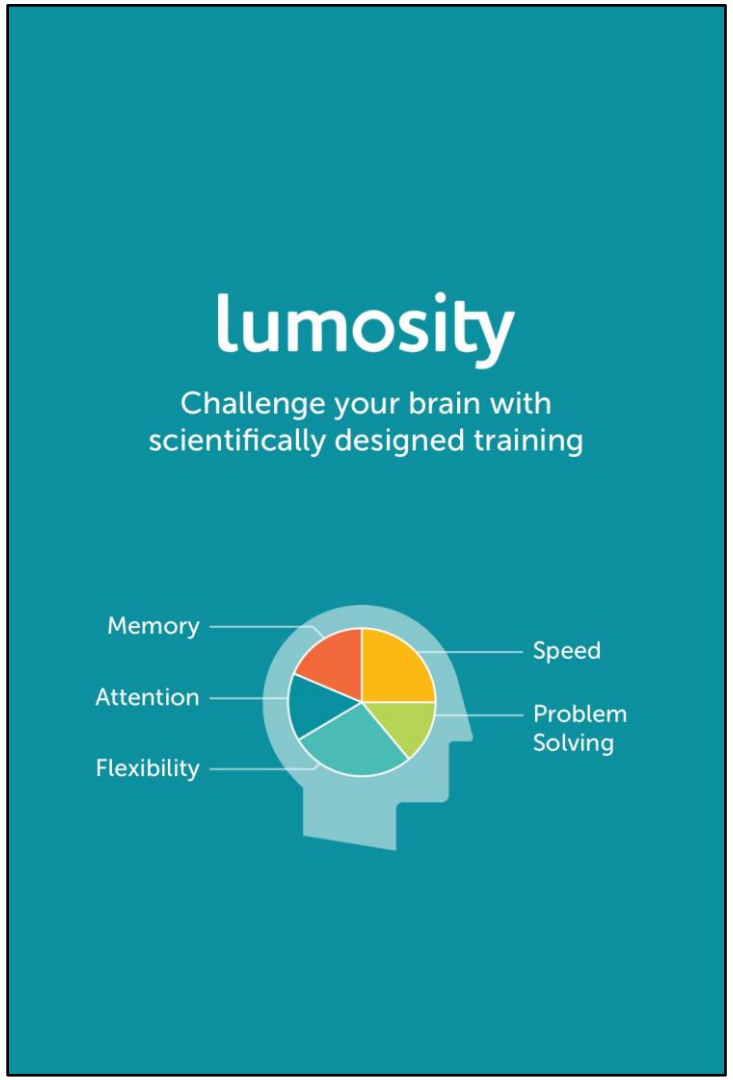
- Evaluate their recall in medical history
- Memory Recall (3 items after 3-5 minutes)
- Evaluate their recall in medical history
- Mini Mental Status Exam (MMSE)
- Self-Administered Gerocognitive Exam (SAGE)
- Clock Drawing Test
- Mini-Cog Test
- Cortisol Salivary Profile for circadian rhythm

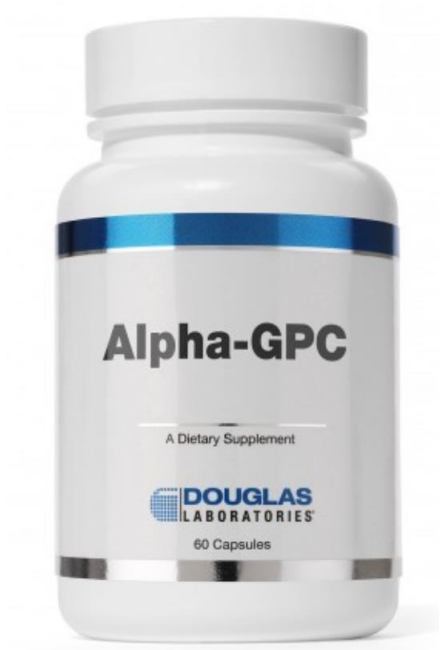
APPLICATIONS

- Lumosity and memory Apps
- Memorize phone numbers
- Think of 5 words that start and end with the same letter as another word
- Repeat a map in your head of a location you visited



Rev. 05|09|2016





Format: Abstract

Send to

Int J Neurosci. 2013 Jul;123(7):444-9. doi: 10.3109/00207454.2013.765870. Epub 2013 Feb 19.

Revisiting choline alphoscerate profile: a new, perspective, role in dementia?

Scapicchio PL[1].

Author information

Abstract

Choline alphoscerate (alpha-glyceryl-phosphorylcholine, alpha-GPC) is a semisynthetic derivative of phosphatidylcholine with central parasympathomimetic action. This action is, on the basis of its use in pathologies, characterized by cognitive deficits of neurodegenerative or vascular nature. In a number of clinical studies, alpha-GPC demonstrated benefit in patients with cognitive dysfunction. In light of the limited therapeutical results obtained in the past decades by the use of cholinesterase inhibitors in dementia, and of the relevance of their side effects in long-lasting therapies, it is desirable to reconsider alpha-GPC in larger carefully controlled studies not only as monotherapy but also in association with cholinesterase inhibitor drugs.

PMID: 23387341 DOI: 10.3109/00207454.2013.765870

[Indexed for MEDLINE]

Alpha-GPC

DESCRIPTION

Alpha-GPC, provided by Douglas Laboratories®, supplies 250 mg of glycerophosphocholine, a nutrient important for neurological health, in each vegetarian capsule.

FUNCTIONS

Glycerophosphocholine (also, known as alpha-GPC, and alpha-glycerophosphatidylcholine) is a water-soluble pro-phospholipid found in high quantities in adult tissue and breast milk. While not a true phospholipid, the body can convert it readily into phosphatidylcholine, the most abundant phospholipid found in the body. Glycerophosphocholine also plays important roles in the synthesis of acetylcholine and the attachment of phosphatidylcholine to DHA (docosahexaenoic acid, an essential fatty acid).

Human studies indicate that glycerophosphocholine may play important roles in maintaining neurological health.† In studies conducted on healthy, young adults, glycerophosphocholine offered significant protection against medication-induced memory loss and helped to enhance baseline mental performance. In middle-aged and elderly adults, glycerophosphocholine supports memory and proper cognitive function.† This compound has also shown superior benefit when compared to citicholine and oxiracetam. Glycerophosphocholine also has the ability to support growth hormone releasing hormone production, which in turn can promote proper growth hormone levels.

Nutrition. 2015 Feb;31(2):261-75. doi: 10.1016/j.nut.2014.06.016. Epub 2014 Jul 24.

Inadequate supply of vitamins and DHA in the elderly: implications for brain aging and Alzheimer-type dementia.

Mohajeri MH[1], Troesch B[2], Weber P[2].

Author information

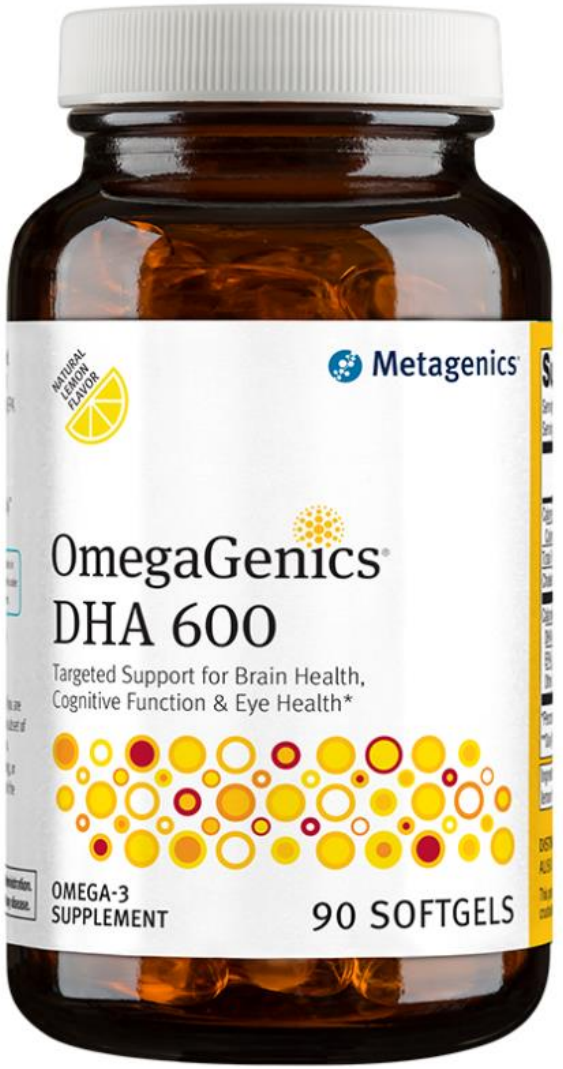
Abstract

Alzheimer's disease (AD) is the most prevalent, severe, and disabling cause of dementia worldwide. To date, AD therapy is primarily targeted toward palliative treatment of symptoms rather than prevention of disease progression. So far, no pharmacologic interventions have changed the onset or progression of AD and their use is accompanied by side effects. The major obstacle in managing AD and designing therapeutic strategies is the difficulty in retarding neuronal loss in the diseased brain once the pathologic events leading to neuronal death have started. Therefore, a promising alternative strategy is to maintain a healthy neuronal population in the aging brain for as long as possible. One factor evidently important for neuronal health and function is the optimal supply of nutrients necessary for maintaining normal functioning of the brain. Mechanistic studies, epidemiologic analyses, and randomized controlled intervention trials provide insight to the positive effects of docosahexaenoic acid (DHA) and micronutrients such as the vitamin B family, and vitamins E, C, and D, in helping neurons to cope with aging. These nutrients are inexpensive in use, have virtually no side effects when used at recommended doses, are essential for life, have established modes of action, and are broadly accepted by the general public. This review provides some evidence that the use of vitamins and DHA for the aging population in general, and for individuals at risk in particular, is a viable alternative approach to delaying brain aging and for protecting against the onset of AD pathology.

KEYWORDS: Aging; Alzheimer; Diet; Drug therapy; Vitamin intake

PMID: 25592004 DOI: 10.1016/j.nut.2014.06.016

[Indexed for MEDLINE] **Free full text**



ASN Neuro. 2015 Dec 18;7(6). pii: 1759091415618969. doi: 10.1177/1759091415618969. Print 2015 Nov-Dec.

Administration of DHA Reduces Endoplasmic Reticulum Stress-Associated Inflammation and Alters Microglial or Macrophage Activation in Traumatic Brain Injury.

Harvey LD[1], Yin Y[2], Attarwala IY[1], Begum G[1], Deng J[1], Yan HQ[3], Dixon CE[3], Sun D[4].

Author information

Abstract

We investigated the effects of the administration of docosahexaenoic acid (DHA) post-traumatic brain injury (TBI) on reducing neuroinflammation. TBI was induced by cortical contusion injury in Sprague Dawley rats. Either DHA (16 mg/kg in dimethyl sulfoxide) or vehicle dimethyl sulfoxide (1 ml/kg) was administered intraperitonially at 5 min after TBI, followed by a daily dose for 3 to 21 days. TBI triggered activation of microglia or macrophages, detected by an increase of Iba1 positively stained microglia or macrophages in peri-lesion cortical tissues at 3, 7, and 21 days post-TBI. The inflammatory response was further characterized by expression of the proinflammatory marker CD16/32 and the anti-inflammatory marker CD206 in Iba1(+) microglia or macrophages. DHA-treated brains showed significantly fewer CD16/32(+) microglia or macrophages, but an increased CD206(+) phagocytic microglial or macrophage population. Additionally, DHA treatment revealed a shift in microglial or macrophage morphology from the activated, amoeboid-like state into the more permissive, surveillant state. Furthermore, activated Iba1(+) microglial or macrophages were associated with neurons expressing the endoplasmic reticulum (ER) stress marker CHOP at 3 days post-TBI, and the administration of DHA post-TBI concurrently reduced ER stress and the associated activation of Iba1(+) microglial or macrophages. There was a decrease in nuclear translocation of activated nuclear factor kappa-light-chain-enhancer of activated B cells protein at 3 days in DHA-treated tissue and reduced neuronal degeneration in DHA-treated brains at 3, 7, and 21 days after TBI. In summary, our study demonstrated that TBI mediated inflammatory responses are associated with increased neuronal ER stress and subsequent activation of microglia or macrophages. DHA administration reduced neuronal ER stress and subsequent association with microglial or macrophage polarization after TBI, demonstrating its therapeutic potential to ameliorate TBI-induced cellular pathology.

KEYWORDS: cortical contusion injury; docosahexaenoic acid; microglial polarization; neuroinflammation; nuclear factor kappa-light-chain-enhancer of activated B cells; secondary injury

PMID: 26685193 PMCID: PMC4710127

[Indexed for MEDLINE] **Free PMC Article**

Eur J Neurol. 2004 Nov;11(11):734-41.

Long-term efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicenter trial.

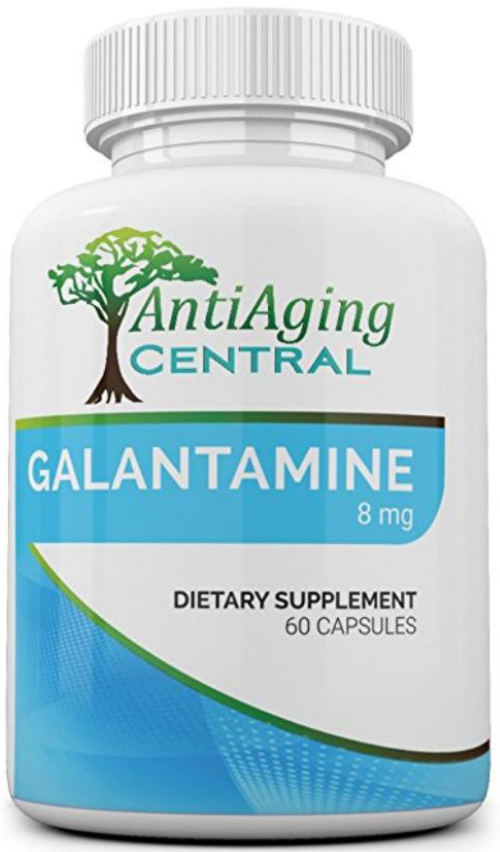
Pirttilä T[1], Wilcock G, Truyen L, Damaraju CV.

Author information

Abstract

In clinical trials, short-term galantamine treatment produces consistent positive effects on global ratings, cognitive tests, and assessments of activities of daily living and behavior in patients with mild-to-moderate Alzheimer's disease (AD), providing the rationale for longer-term, open-label treatment. In this continuation trial following enrollment in previous 12-month trials, patients received galantamine 24 mg/day for a total of 24 months (total exposure up to 36 months). Primary efficacy measures were the ADAS-cog/11 and DAD. Adverse events (AEs) were coded to WHO preferred terms, including AEs begun in previous trials. Initial improvement in cognitive function was followed by a gradual decline, as measured by increased ADAS-cog/11 scores. At 36 months, ADAS-cog/11 scores increased by a mean (SEM) of 12.4 (0.80) points ($P < 0.001$) versus a projected 22-point increase for untreated patients. Functional abilities, as measured by the DAD, had decreased significantly at each time point versus baseline ($P < 0.001$). The most common treatment-emergent AEs were agitation (16.1%), insomnia (12.4%), fall (11.2%), and urinary tract infection (10.2%). AEs were mainly mild to moderate, appropriate for an elderly population, with few judged treatment related. Galantamine 24 mg/day is safe and effective for long-term treatment of mild-to-moderate AD. Potential exists for prolonged benefit with galantamine therapy versus lack of treatment for the long-term.

PMID: 15525294 DOI: 10.1111/j.1468-1331.2004.00885.x



Neurology. 2000 Jun 27;54(12):2269-76.

A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group.

Tariot PN[1], Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C.

Author information

Abstract

OBJECTIVE: To investigate the efficacy and tolerability of galantamine, using a slow dose escalation schedule of up to 8 weeks, in 978 patients with mild to moderate AD.

METHODS: A 5-month multicenter, placebo-controlled, double-blind trial. Following a 4-week placebo run-in, patients were randomized to one of four treatment arms: placebo or galantamine escalated to final maintenance doses of 8, 16, or 24 mg/day. Outcome measures included the cognitive subscale of the AD Assessment Scale (ADAS-cog), the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus), the AD Cooperative Study Activities of Daily Living inventory, and the Neuropsychiatric Inventory. Standard safety evaluations and adverse event monitoring were carried out.

RESULTS: After 5 months, the galantamine-placebo differences on ADAS-cog were 3.3 points for the 16 mg/day group and 3.6 points for the 24 mg/day group ($p < 0.001$ versus placebo, both doses). Compared with placebo, the galantamine 16- and 24-mg/day groups also had a significantly better outcome on CIBIC-plus, activities of daily living, and behavioral symptoms. Treatment discontinuations due to adverse events were low in all galantamine groups (6 to 10%) and comparable with the discontinuation rate in the placebo group (7%). The incidence of adverse events in the galantamine groups, notably gastrointestinal symptoms, was low and most adverse events were mild.

CONCLUSIONS: Galantamine 16 and 24 mg/day significantly benefits the cognitive, functional, and behavioral symptoms of AD as compared with placebo. Slow dose escalation appears to enhance the tolerability of galantamine, minimizing the incidence and severity of adverse events.

PMID: 10881251

[Indexed for MEDLINE]

Part Five

Parkinsonism symptom,
Leaky Gut
And constipation

Parkinsonism

Three Common Neurodegenerative Diseases

Dementia

- Forgets recently learned information
- Forgets dates, events, and appointments
- Misplaces keys, purse/wallet, remote control
- Has memory lapses in the middle of conversations
- Forgets locations

Parkinsonism

- Stiffness
- Slowness of movement
- Impaired GI motility
- ↓Smell and ↓taste
- Expressionless face
- Resting tremor

Cerebellar Degeneration

- Worsening balance
- Worsening coordination
- Bumps into everything
- Dizziness and disorientation

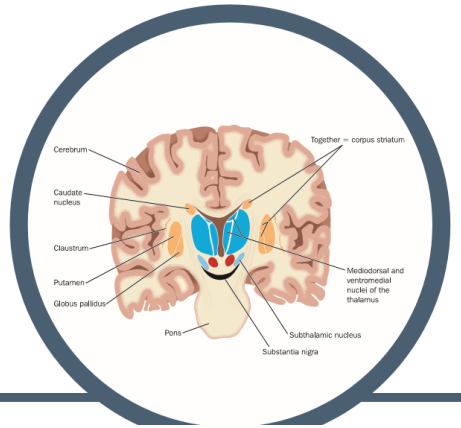
BASAL GANGLIA DIRECT PATHWAY

LOSS OF ACTIVITY AND EPILEPTIFORM ACTIVITY

Loss of activity leads to muscle stiffness and slowness of movements

BRAIN REGION LOCALIZATION FORM SYMPTOMS

- Slowness in movements
- Stiffness in muscles (not joints) that goes away during movement
- Cramping of hands when writing
- A stooped posture when walking
- Voice has become softer
- Facial expression changed leading people to frequently ask if you are upset or angry



EXAMINATION FINDINGS

- Mask face, reduced blinking, hypophonia, aprosody of speech, resting pill rolling tremor striatal postural deformities, camptocormia, drooling due to reduced swallowing, and slowness of thinking with initial survey
- Gait analysis demonstrates lack of arm swing, shuffling, slowness, freezing of gait, festination, hesitancy initiating first step, limitations in turning, and postural instability.
- Glabellar tap test demonstrating inability to attenuate blinking response after 3 taps
- Pull test – cannot stabilize after 3 steps
- Micrographia and/or tremor with handwriting
- Loss of smell
- Impaired bowel sound motility (constipation)
- Lead-pipe or cogwheel rigidity with passive stretch of the limbs
- Hypokinetic (bradykinesia) and decrementing movements of limbs with repeated motor tasks (finger-to-thumb, supination/ pronation, foot tapping).

APPLICATIONS

- Dietary, nutritional and lifestyle strategies to reduce protein aggregations.
- Brain rehabilitation strategies focused on frontal cortex activation to the striatum and or cerebellum activation of the ventral ascending dopaminergic system
- Non-linear movements. Alternating activity movements that are repetitive. Visualization and motor and limbic activation while moving.

Rev. 05|11|2016

10 EARLY WARNING SIGNS OF PARKINSON'S DISEASE

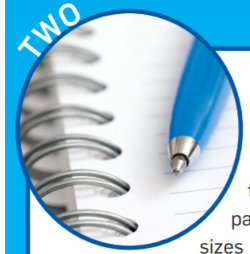
ONE

☐ **TREMOR OR SHAKING.**

Have you noticed a slight shaking or tremor in your finger, thumb, hand, chin or lip? Does your leg shake when you sit down or relax? Twitching or shaking of limbs is a common early sign of Parkinson's disease.

What is normal? Shaking can be normal after lots of exercise, if you have been injured, or could be caused by a medicine you take.

TWO



☐ **SMALL HANDWRITING.**

Has your handwriting suddenly gotten much smaller than in it was in the past? You may notice the way you write words on a page has changed, such as letter sizes are smaller and the words are crowded together. A sudden change in handwriting is often a sign of Parkinson's disease.

What is normal? Sometimes writing can change as you get older, if you have stiff hands or fingers or poor vision, but this happens over time and not suddenly.

THREE

☐ **LOSS OF SMELL.**

Have you noticed you no longer smell certain foods very well? If you seem to have more trouble smelling foods like bananas, dill pickles or licorice, you should ask your doctor about Parkinson's disease.

What is normal? Your sense of smell can be changed by a cold, flu or a stuffy nose, but it should come back after you are better.

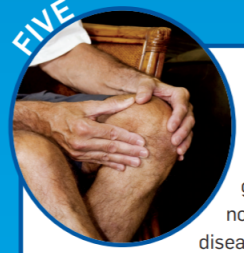
FOUR

☐ **TROUBLE SLEEPING.**

Do you thrash around in bed or kick and punch while you are deeply asleep? You might notice that you started falling out of bed while asleep. Sometimes, your spouse will notice, or will want to move to another bed. Sudden movements during sleep may be a sign of Parkinson's disease.

What is normal? It is normal for everyone to have a night when they 'toss and turn' instead of sleeping.

FIVE



☐ **TROUBLE MOVING OR WALKING.**

Do you feel stiff in your body, arms or legs? Sometimes stiffness goes away as you move. If it does not, it can be a sign of Parkinson's disease. You might notice that your arms don't swing when you walk, or maybe other people have said you look stiff. An early sign might be stiffness or pain in your shoulder or hips. People sometimes say their feet seem 'stuck to the floor.'

What is normal? If you have injured your arm or shoulder, you may not be able to use it as well until it is healed or another illness like arthritis might cause the same symptom.

SIX

☐ **CONSTIPATION.**

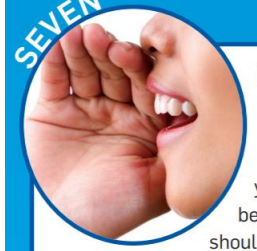
Do you have trouble moving your bowels without straining every day? Straining to move your bowels can be an early sign of Parkinson's disease and you should talk to your doctor.

What is normal? If you do not have enough water or fiber in your body, it can cause problems in the bathroom. Also some medicine will cause constipation too. If there is no other reason such as diet or medicine that would cause you to have trouble moving your bowels, you should speak with your doctor.

NATIONAL PARKINSON FOUNDATION

10 EARLY WARNING SIGNS OF PARKINSON'S DISEASE

SEVEN



☐ **A SOFT OR LOW VOICE.**

Have other people told you that your voice is very soft when you speak in a normal tone, or that you sound hoarse? If there has been a change in your voice you should see your doctor about whether it could be Parkinson's disease. Sometimes you might think other people are losing their hearing, when really you are speaking more softly.

What is normal? A chest cold or other virus can cause your voice to sound different but you should go back to sounding the same when you get over your cough or cold.

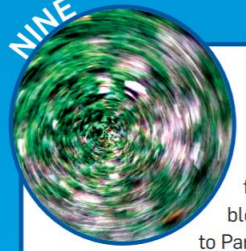
EIGHT

☐ **MASKED FACE.**

Have you been told that you have a serious, depressed or mad look on your face more often, even when you are not in a bad mood? This serious looking face is called masking. Also, if you or other people notice that you have a blank stare or do not blink your eyes very often, you should ask your doctor about Parkinson's disease.

What is normal? Some medicines can cause you to have the same type of serious or staring look, but you would go back to the way you were after you stopped the medication.

NINE



☐ **DIZZINESS OR FAINTING.**

Do you notice that you often feel dizzy when you stand up out of a chair? Feeling dizzy or fainting can be signs of low blood pressure and can be linked to Parkinson's disease.

What is normal? Everyone has had a time when they stood up and felt dizzy, but if it happens on a regular basis you should see your doctor.

TEN

☐ **STOOPING OR HUNCHING OVER.**

Are you not standing up as straight as you used to? If you or your family or friends notice that you seem to be stooping, leaning or slouching when you stand, it could be a sign of Parkinson's disease.

What is normal? If you have pain from an injury or if you are sick, it might cause you to stand crookedly. Also, a problem with your bones can make you hunch over.

NATIONAL PARKINSON FOUNDATION

EARLY SIGNS AND SYMPTOMS OF PARKINSON'S

- **Loss of Smell** – Leads to decreased taste and decreased appetite
- **Gastrointestinal Constipation** – Slowness of intestinal motility
- **Bradykinesia** – Slowness of movements
- **Depression or Anxiety**
- **Postural Instability** – Stumbles or has flexed-forward posture
- **Fatigue**
- **Sleep Disorder**

↓

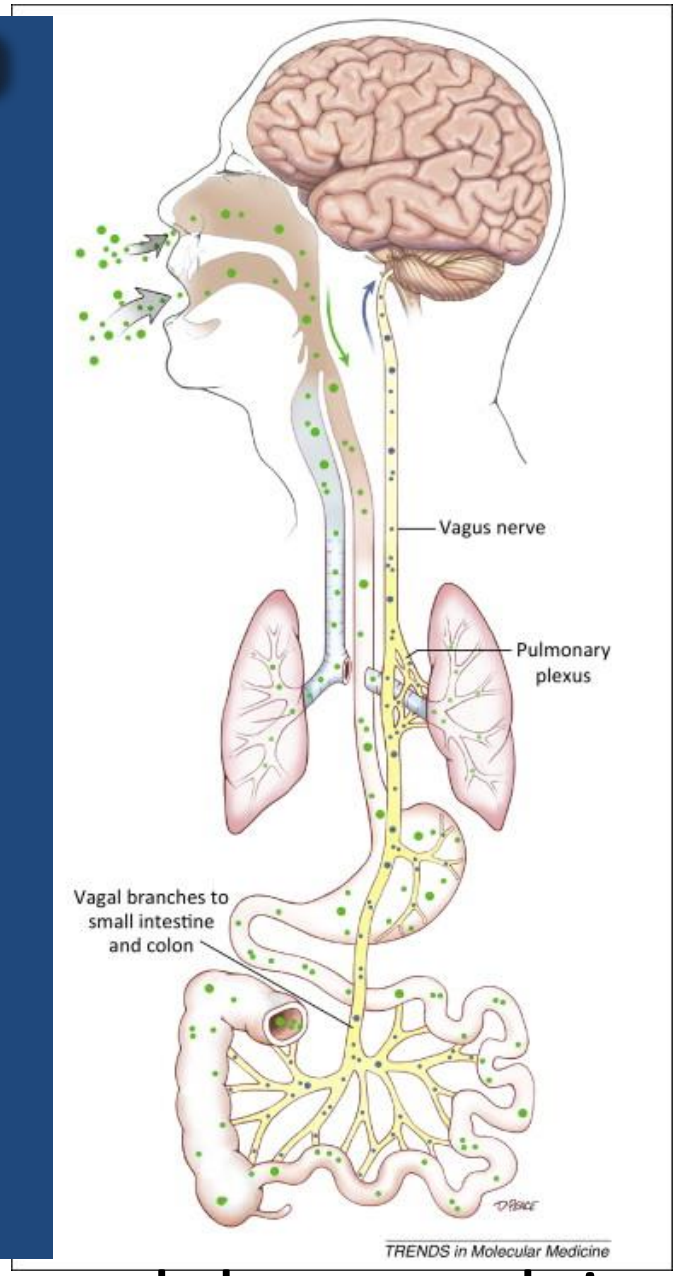
PROGRESSED SIGNS OF PARKINSON'S

- ⇩ **Dexterity**
- **Writing Cramps**
- **Softer Voice and Slurring Words**
- **Postural Instability**

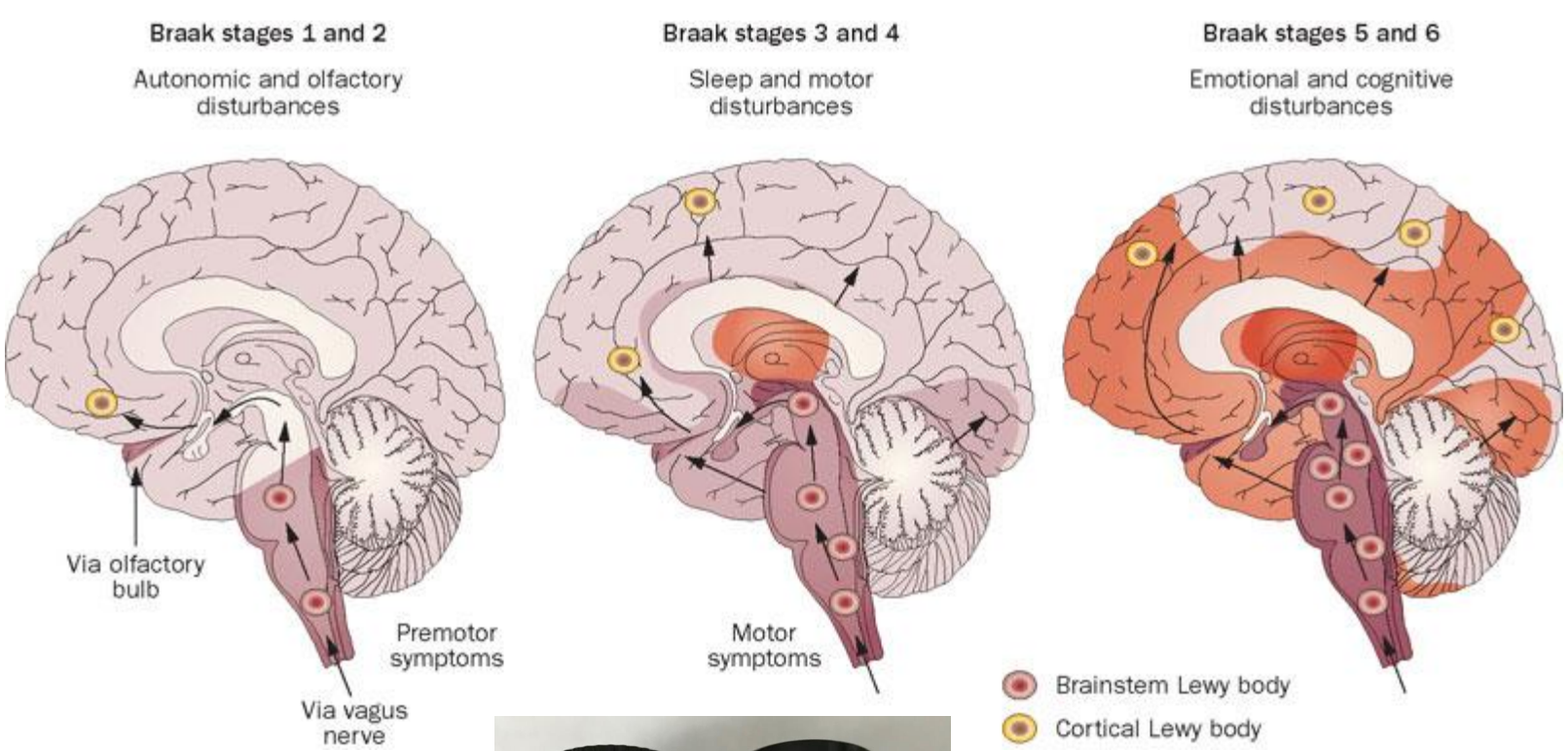
↓

PARKINSON'S DISEASE

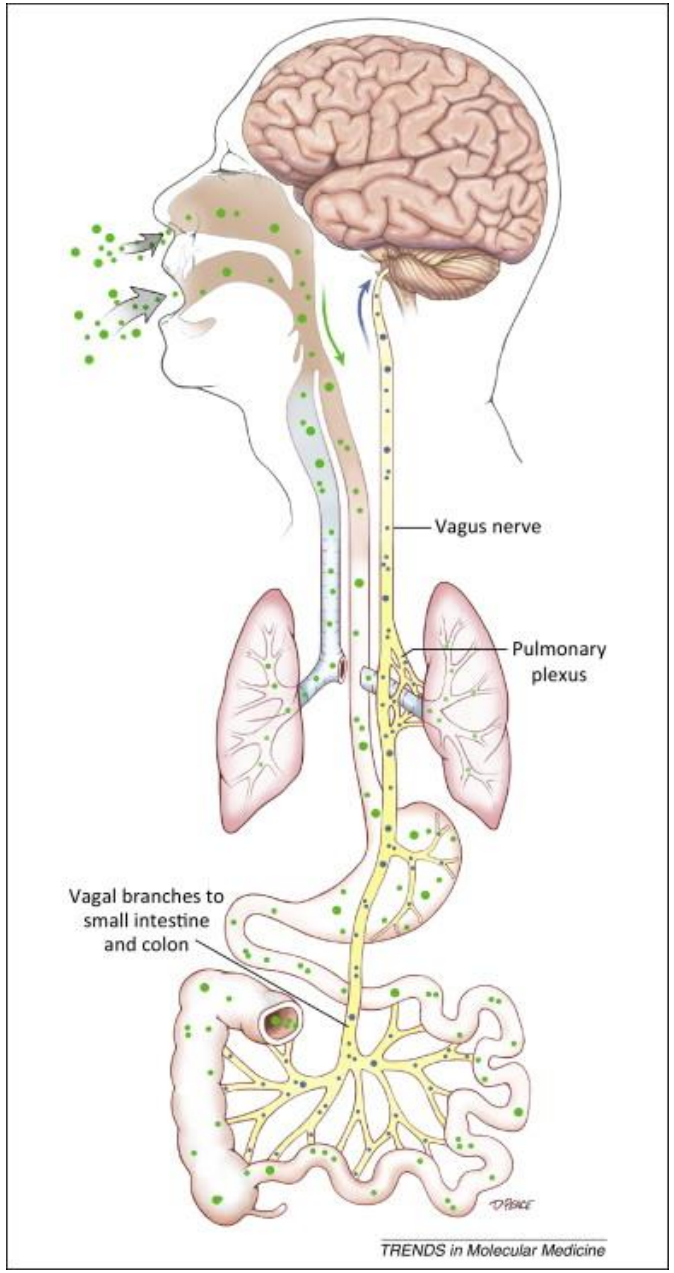
- **Resting Tremor**
- **Rigidity**
- **Dementia**
- **Expressionless Face**



alpha synuclein


Braak stages 1 and 2
Autonomic and olfactory disturbances
Braak stages 3 and 4
Sleep and motor disturbances
Braak stages 5 and 6
Emotional and cognitive disturbances
Via olfactory bulb
Premotor symptoms
Via vagus nerve
Motor symptoms
Brainstem Lewy body
Cortical Lewy body


NATURE'S
OIL
100% Pure
Therapeutic Grade
Aniseed
Essential Oil
India
Epigenetic Labs
PEPPERMINT
Mentha piperita
15mL .5oz


Vagus nerve
Pulmonary plexus
Vagal branches to small intestine and colon
TRENDS in Molecular Medicine

Diagnostic Value of the Impairment of Olfaction in Parkinson's Disease

Swaantje Casjens[1], Angelika Eckert[1], Dirk Woitalla[2], Gisa Ellrichmann[2], Michael Turewicz[3], Christian Stephan[3], Martin Eisenacher[3], Caroline May[3], Helmut E. Meyer[3], Thomas Brüning[1], Beate Pesch[1]*

1 Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germa
2 Neurological Clinic, St. Josef-Hospital, Ruhr-Universität Bochum, Bochum, Germany, **3** Medizinisches Proteom-Center, Ruhr-Universität Bochum, Bochum, Germany

Three odors that demonstrated the best sensitivity contrast between healthy controls and Parkinson's were coffee, peppermint and anise.

BRAIN
A JOURNAL OF NEUROLOGY

Severe olfactory dysfunction is a prodromal symptom of dementia associated with

(Signs and symptoms that indicate the onset of a disease)

Dementia is one of the most debilitating symptoms of Parkinson's disease. A recent longitudinal study suggests that up to 80% of patients with Parkinson's disease will eventually develop dementia. Despite its clinical importance, the development of dementia is still difficult to predict at early stages. We previously identified olfactory dysfunction as one of the most important indicators of cortical hypometabolism in Parkinson's disease. In this study, we investigated the possible associations between olfactory dysfunction and the risk of developing dementia within a 3-year observation period. Forty-four patients with Parkinson's disease without dementia underwent the odour stick identification test for Japanese, memory and visuoperceptual assessments, ^{18}F-fluorodeoxyglucose positron emission tomography scans and magnetic resonance imaging scans at baseline and 3 years later. A subgroup of patients with Parkinson's disease who exhibited severe hyposmia at baseline showed more pronounced cognitive decline at the follow-up survey. By the end of the study, 10 of 44 patients with Parkinson's disease had developed dementia, all of whom had severe hyposmia at baseline. The multivariate logistic analysis identified severe hyposmia and visuoperceptual impairment as independent risk factors for subsequent dementia within 3 years. The patients with severe hyposmia had an 18.7-fold increase in their risk of dementia for each 1 SD (2.8) decrease in the score of odour stick identification test for Japanese. We also found an association between severe hyposmia and a characteristic distribution of cerebral metabolic decline, which was identical to that of dementia associated with Parkinson's disease. Furthermore, volumetric magnetic resonance imaging analyses demonstrated close relationships between olfactory dysfunction and the atrophy of focal brain structures, including the amygdala and other limbic structures. Together, our findings suggest that brain regions related to olfactory function are closely associated with cognitive decline and that severe hyposmia is a prominent clinical feature that predicts the subsequent development of Parkinson's disease dementia.

Received July 28, 2011. Revised September 25, 2011. Accepted September 28, 2011

Published in final edited form as:
Neurobiol Dis. 2012 June ; 46(3): 527–552. doi:10.1016/j.nbd.2011.10.026.

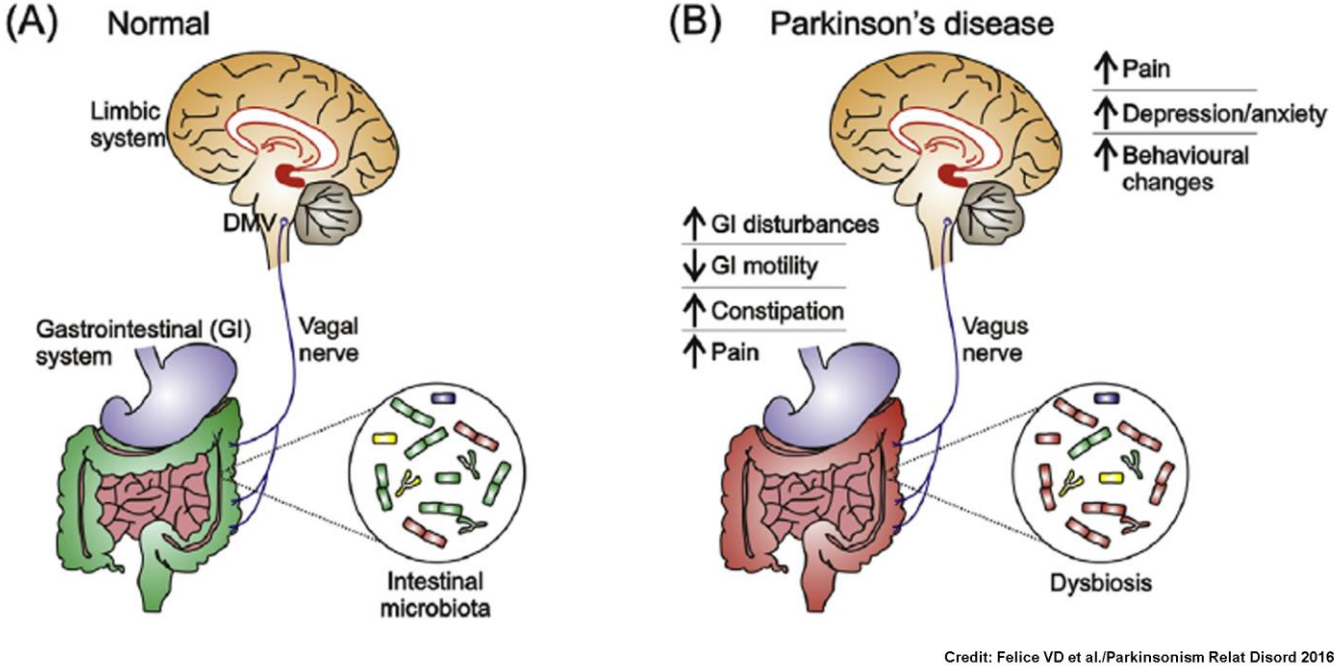
Olfaction in Parkinson's disease and related disorders

Richard L. Doty*
Smell & Taste Center, University of Pennsylvania School of Medicine, USA

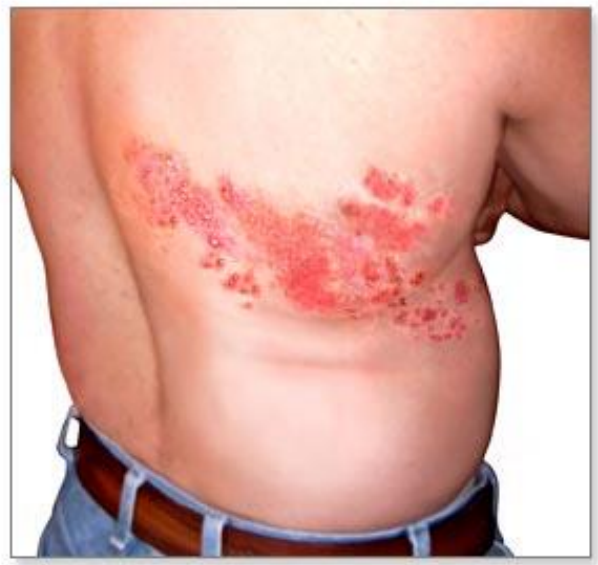
Abstract

"Olfactory dysfunction is an early 'pre-clinical sign of Parkinson's disease."

dysfunction is rarely observed in asymptomatic gene carriers, but is present in many of those that exhibit the motor phenotype. This suggests that such gene-related influences on olfaction, when present, take time to develop and depend upon additional factors, such as those from aging, other genes, formation of α-synuclein- and tau-related pathology,or lowered thresholds to oxidative stress from toxic insults. The limited data available suggest that the physiological determinants of the early changes in PD-related olfactory function are likely multifactorial and may include the same determinants as those responsible for a number of other non-motor symptoms of PD, such as dysautonomia and sleep disturbances.

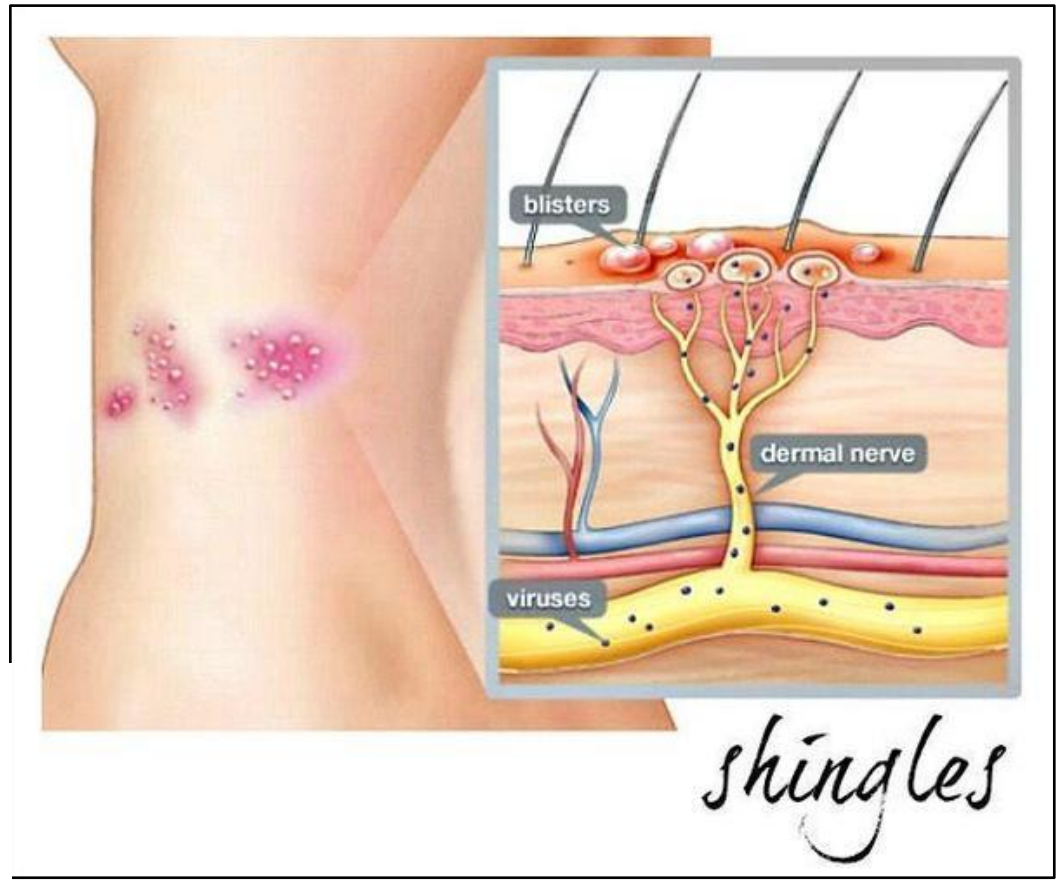


Credit: Felice VD et al./Parkinsonism Relat Disord 2016



Shingles

ADAM.



Vagotomy and Subsequent Risk of Parkinson's Disease

Elisabeth Svensson, PhD,[1] Erzsébet Horváth-Puhó, PhD,[1]
Reimar W. Thomsen, PhD,[1] Jens Christian Djurhuus, DMSc,[2] Lars Pedersen, PhD,[1]
Per Borghammer, DMSc,[2,3] and Henrik Toft Sørensen, DMSc[1]

Objective: Parkinson's disease (PD) may be caused by an enteric neurotropic pathogen entering the brain through the vagal nerve, a process that may take over 20 years. We investigated the risk of PD in patients who underwent

These findings, say the researchers, "suggest that having an intact vagus nerve increases the risk of developing PD. The finding is in accord with a primary pathological process being initiated in the gastrointestinal mucosa, which then uses the vagus as a major entry point into the brain."

are inconsistent for environmental factors associated with PD. A potential protective effect of smoking has been suggested,[3] but this association has recently been questioned.[4] There are also suggestions of a protective effect of coffee and nonsteroidal anti-inflammatory drugs and increased risk with pesticide exposure.[3,5]

The "dual hit" hypothesis for PD development posits that a neurotropic pathogen enters the brain by a nasal and/or gastric route by axonal transport through

is evidence from experimental animal models that alpha-synuclein (α-Syn) forms can be transmitted to the brain from the gut.[8–10] In one study, investigators instilled rotenone into the stomach of mice and observed progressive pathological α-Syn inclusions in the enteric nervous system, the vagal nerve, and, subsequently, the brainstem.[10] Additionally, vagotomy has been shown to eliminate transport of pathological proteins from the gut to the central nervous system (CNS).[11,12]

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.24448
Received Mar 16, 2015, and in revised form May 26, 2015. Accepted for publication May 26, 2015.

alpha synuclein

Nat Rev Neurol. 2015 Nov;11(11):625-36. doi: 10.1038/nrneurol.2015.197. Epub 2015 Oct 27.

Pathogenesis of Parkinson disease--the gut-brain axis and environmental factors.

Klingelhoefer L[1], Reichmann H[1].

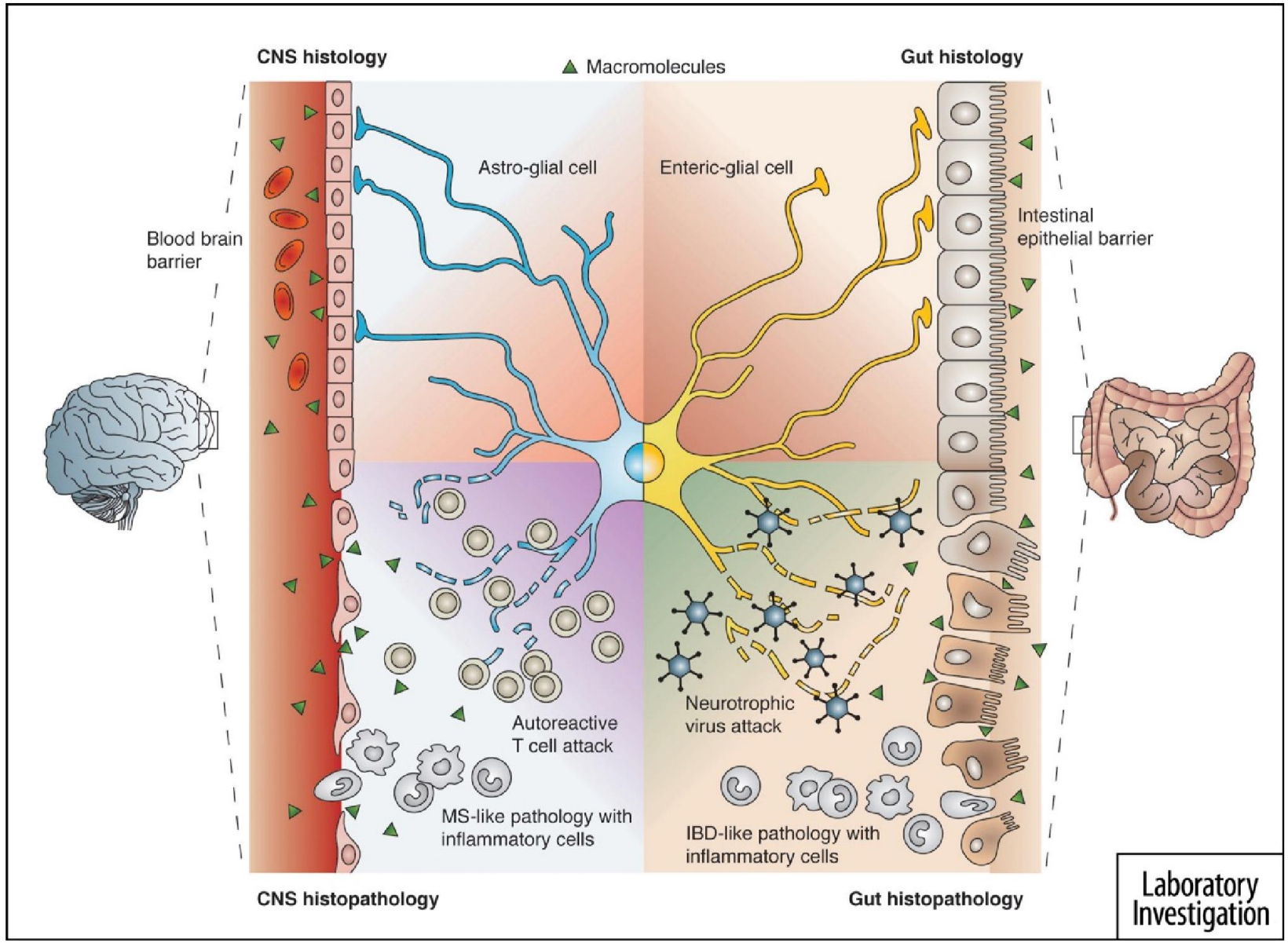
Author information

Abstract

Parkinson disease (PD) follows a defined clinical pattern, and a range of nonmotor symptoms precede the motor phase. The predominant early nonmotor manifestations are olfactory impairment and constipation. The pathology that accompanies these symptoms is consistent with the Braak staging system: α-synuclein in the dorsal motor nucleus of the vagus nerve, the olfactory bulb, the enteric nervous system (ENS) and the submandibular gland, each of which is a gateway to the environment. The neuropathological process that leads to PD seems to start in the ENS or the olfactory bulb and spreads via rostrocranial transmission to the substantia nigra and further into the CNS, raising the intriguing possibility that environmental substances can trigger pathogenesis. Evidence from epidemiological studies and animal models supports this hypothesis. For example, in mice, intragastric administration of the pesticide rotenone can almost completely reproduce the typical pathological and clinical features of PD. In this Review, we present clinical and pathological evidence to support the hypothesis that PD starts in the gut and spreads via trans-synaptic cell-to-cell transfer of pathology through the sympathetic and parasympathetic nervous systems to the substantia nigra and the CNS. We also consider how environmental factors might trigger pathogenesis, and the potential for therapeutically targeting the mechanisms of these initial stages.

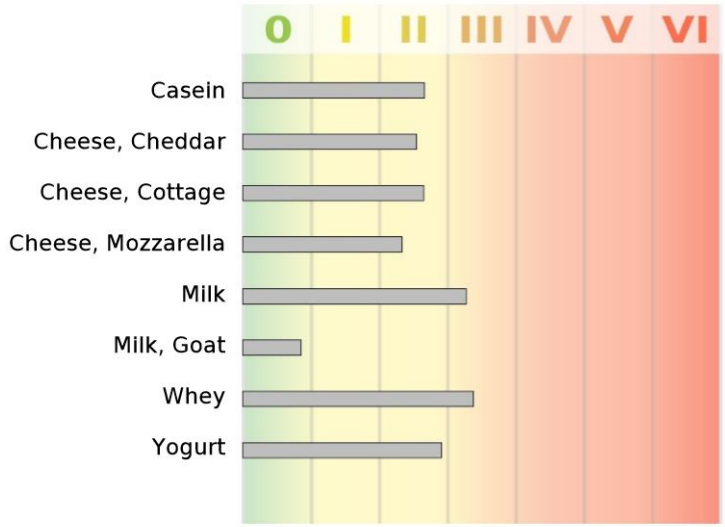
PMID: 26503923 DOI: 10.1038/nrneurol.2015.197

[Indexed for MEDLINE]

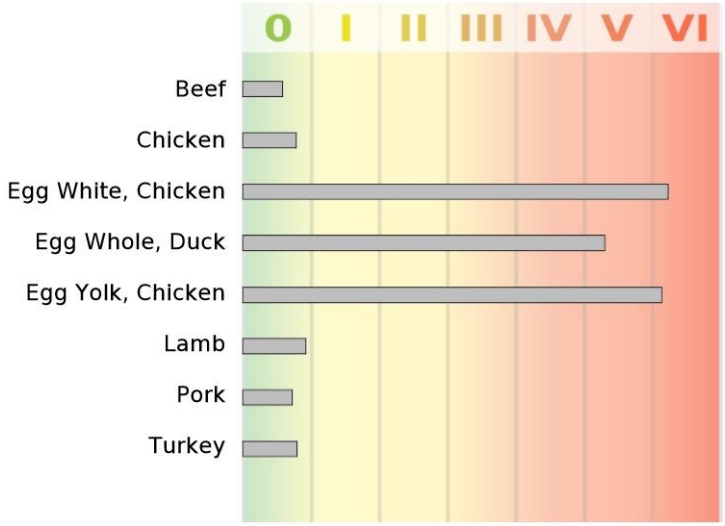

CNS histology
Macromolecules
Gut histology
Astro-glial cell
Enteric-glial cell
Blood brain barrier
Intestinal epithelial barrier
Autoreactive T cell attack
Neurotrophic virus attack
MS-like pathology with inflammatory cells
IBD-like pathology with inflammatory cells
CNS histopathology
Gut histopathology
Laboratory Investigation

Dairy

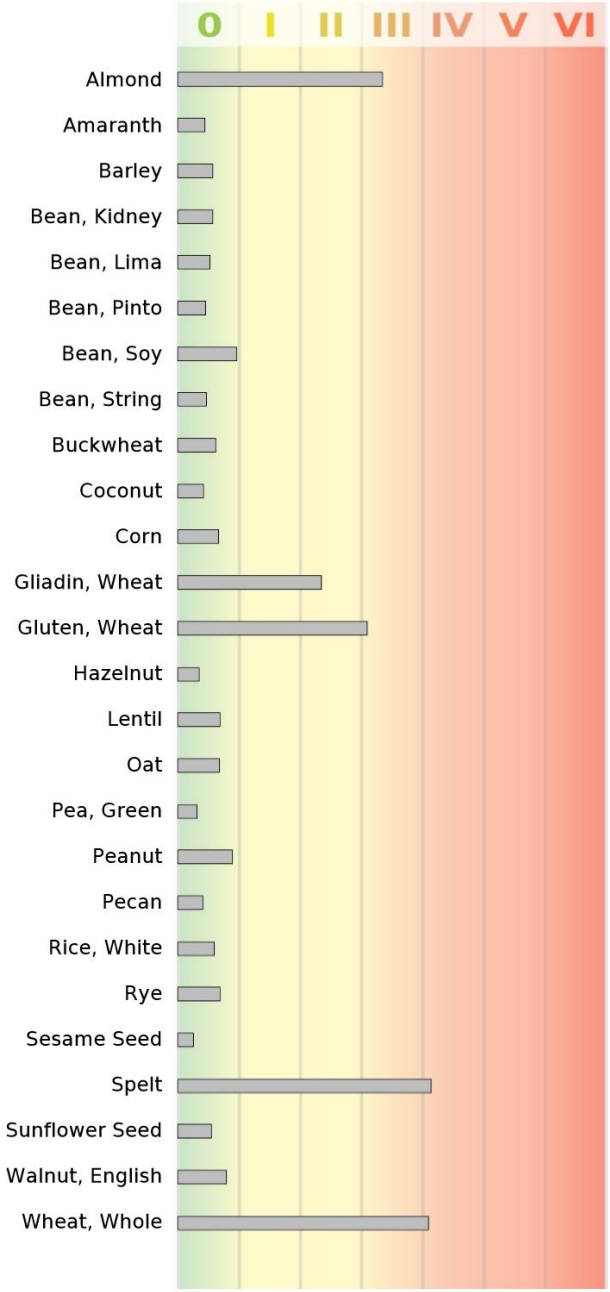
Bovine-derived unless specified



Meat/Fowl



Grains/Legumes/Nuts



MECHANISMS OF LEAKY GUT

Diet	Medications	Infections	Stress	Hormonal	Neurologic	Metabolic
• Alcohol • Gluten • Casein • Processed Foods • Excess Sugar • Fast Food	• Corticosteroids • Antibiotics • Antacids • Xenobiotics	• *H. pylori* • Bacterial Overgrowth • Yeast Overgrowth • Intestinal Virus • Parasitic Infection	⇧ Cortisol ⇧ CRH ⇧ Catecholamines	⇩ Thyroid ⇩ Progesterone ⇩ Estradiol ⇩ Testosterone	• Brain Trauma • Stroke • Neurodegeneration	• Glycosylated End Products • Intestinal Inflammation • Autoimmune Conditions

J Neurol. 2003 Oct;250 Suppl 3:III30-9.

Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study.

Abbott RD[1], Ross GW, White LR, Sanderson WT, Burchfiel CM, Kashon M, Sharp DS, Masaki KH, Curb JD, Petrovitch H.

Constipation is a common problem in Parkinson's disease (PD), occurring in about 50–60% of patients and may occur even before the motor symptoms appear.

Review Article

Parkinson's Disease and Sleep/Wake Disturbances

Todd J. Swick[1,2,3,4]

[1] *University of Texas School of Medicine, Houston, TX, USA*
[2] *Apnix Sleep Disorders Centers, Houston, TX, USA*

Sleep disturbances, which include sleep fragmentation, daytime somnolence, sleep-disordered breathing, restless legs syndrome (RLS), nightmares, and rapid eye movement (REM) sleep behavior disorder (RBD), are estimated to occur in 60% to 98% of patients with PD.

Lancet. 1995 Apr 8;345(8954):897-898.

Focal white-matter lesions in brain of patients with inflammatory bowel disease.

"Using magnetic-resonance imaging we found hyperintense focal white-matter lesions in the brain in 20 of 48 (42%) patients with Crohn's disease, in 11 of 24 (46%) patients with ulcerative colitis, but in only 8 of 50 (16%) healthy aged-matched controls…"

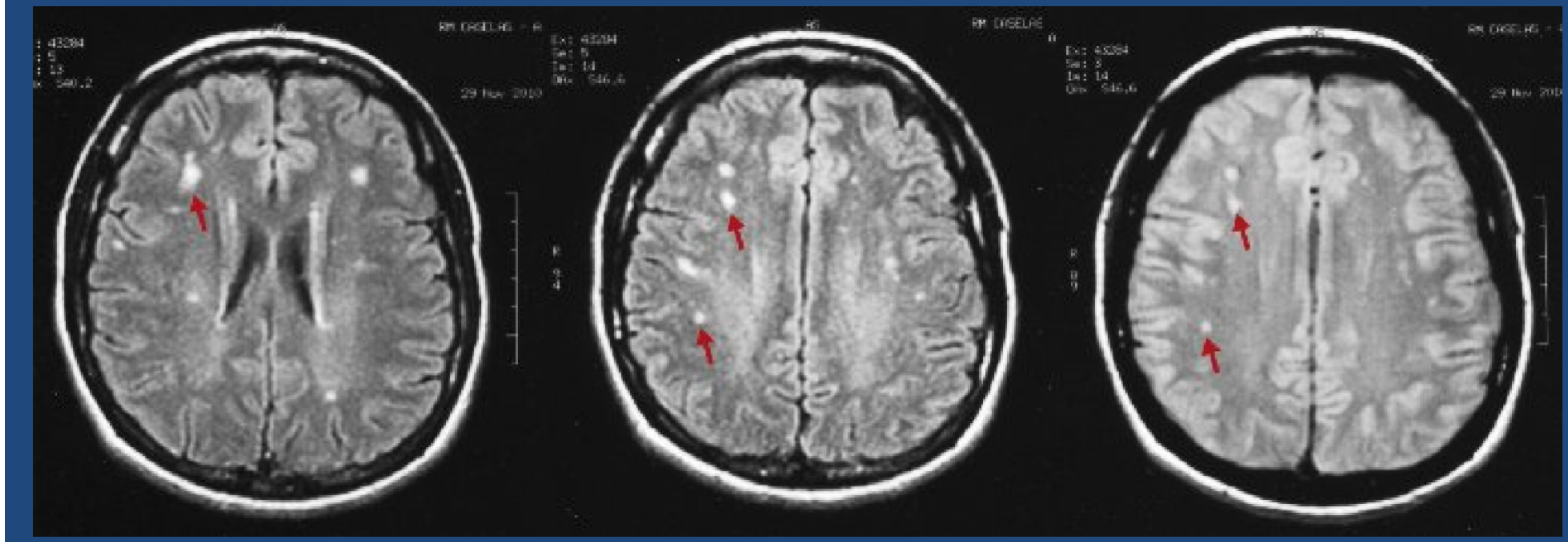
Eur J Neurol. 2007 May;14(5):483-493.

Neurologic manifestations of ulcerative colitis.

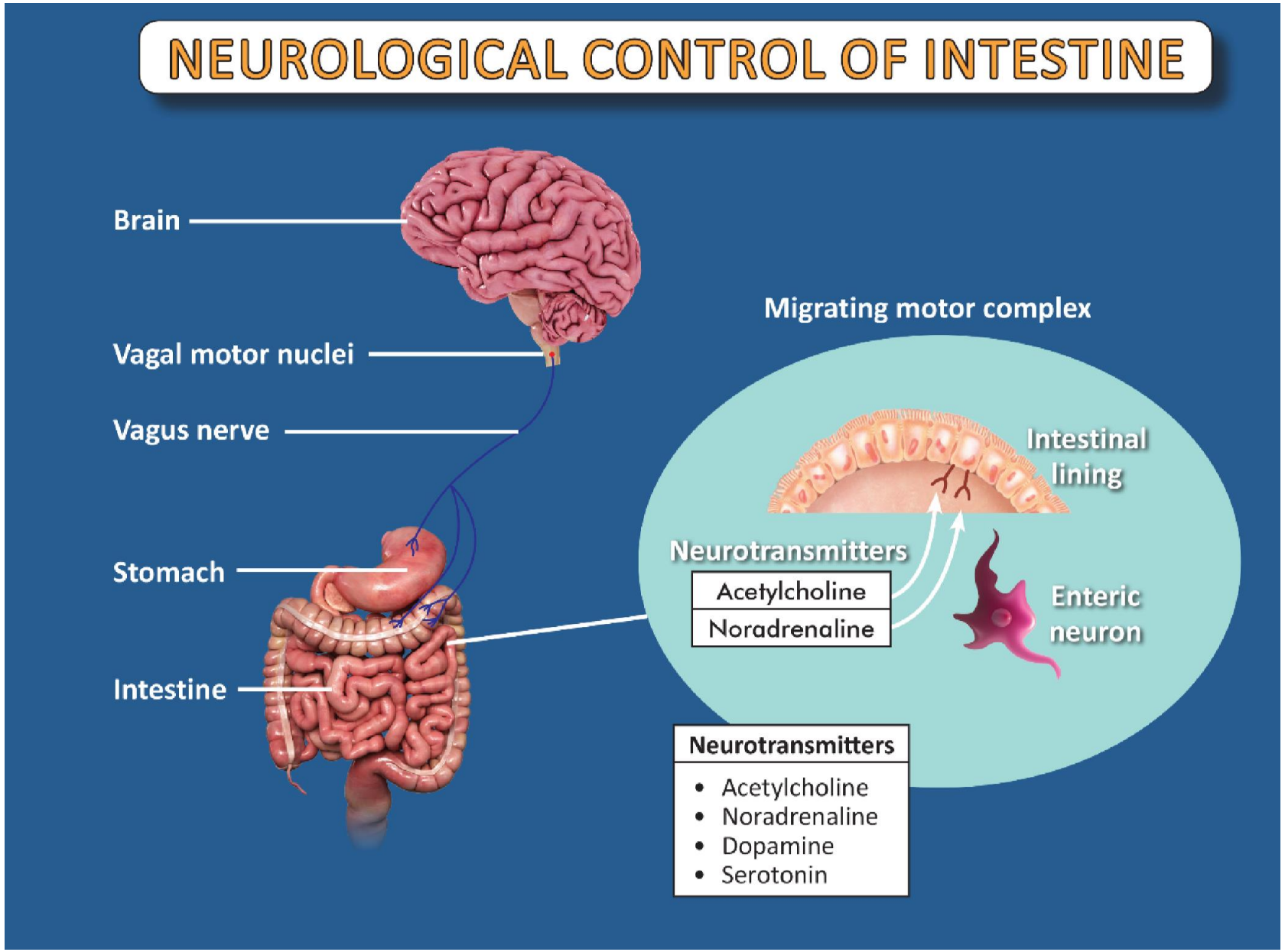
- "**Ulcerative colitis (UC)** has traditionally been considered to be an inflammatory disease limited to the colonic mucosa."
- "However, since it has been shown that UC is frequently accompanied by various extraintestinal disorders, there is increasing evidence that **UC may also manifest in the nervous system**."

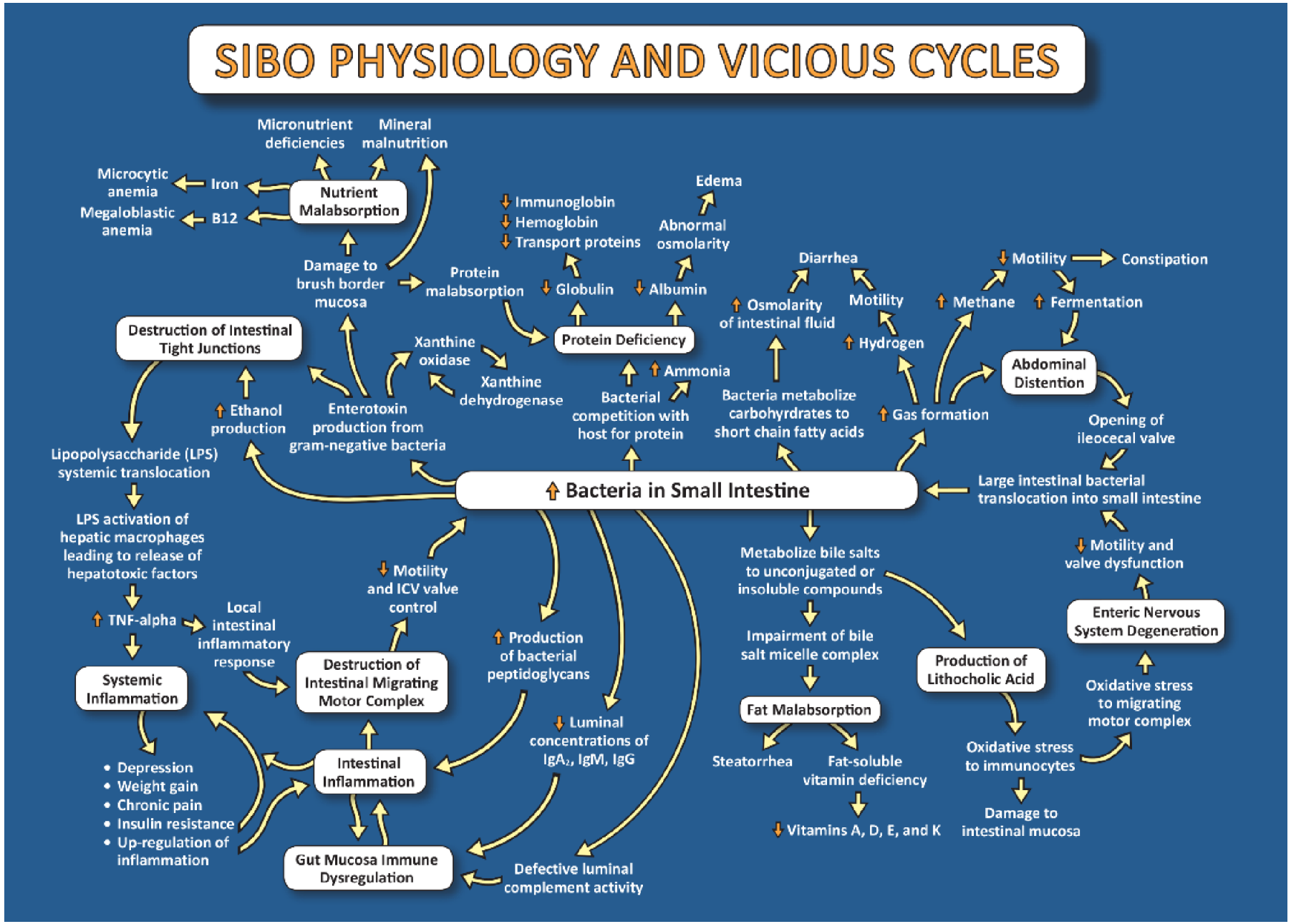
GE J Port Gastrenterol. 2013;20:79-82.

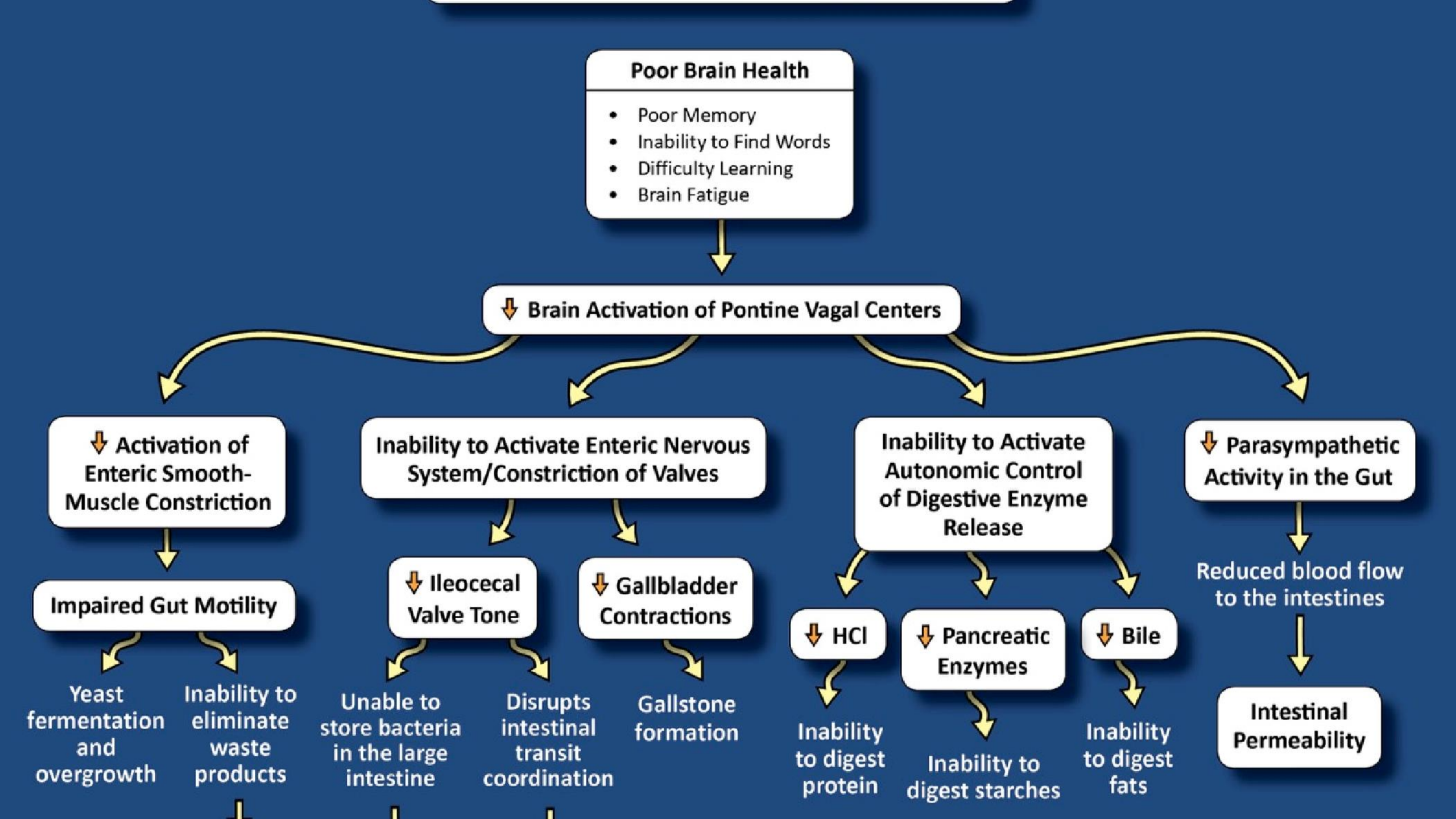
Demyelinating brain lesions in a Crohn's patient under adalimumab.



NEUROLOGICAL CONTROL OF INTESTINE




SIBO PHYSIOLOGY AND VICIOUS CYCLES
Micronutrient deficiencies
Mineral malnutrition
Microcytic anemia
Iron
Megaloblastic anemia
B12
Nutrient Malabsorption
Damage to brush border mucosa
Protein malabsorption
Immunoglobin
Hemoglobin
Transport proteins
Globulin
Albumin
Abnormal osmolarity
Edema
Diarrhea
Osmolarity of intestinal fluid
Motility
Hydrogen
Motility
Constipation
Methane
Fermentation
Abdominal Distention
Protein Deficiency
Destruction of Intestinal Tight Junctions
Xanthine oxidase
Xanthine dehydrogenase
Ammonia
Bacterial competition with host for protein
Bacteria metabolize carbohyrdrates to short chain fatty acids
Gas formation
Ethanol production
Enterotoxin production from gram-negative bacteria
Lipopolysaccharide (LPS) systemic translocation
Bacteria in Small Intestine
Large intestinal bacterial translocation into small intestine
Opening of ileocecal valve
LPS activation of hepatic macrophages leading to release of hepatotoxic factors
Motility and ICV valve control
Metabolize bile salts to unconjugated or insoluble compounds
Motility and valve dysfunction
TNF-alpha
Local intestinal inflammatory response
Production of bacterial peptidoglycans
Impairment of bile salt micelle complex
Enteric Nervous System Degeneration
Systemic Inflammation
Destruction of Intestinal Migrating Motor Complex
Production of Lithocholic Acid
Oxidative stress to migrating motor complex
Fat Malabsorption
Luminal concentrations of IgA2, IgM, IgG
Intestinal Inflammation
Steatorrhea
Fat-soluble vitamin deficiency
Oxidative stress to immunocytes
Depression
Weight gain
Chronic pain
Insulin resistance
Up-regulation of inflammation
Vitamins A, D, E, and K
Damage to intestinal mucosa
Gut Mucosa Immune Dysregulation
Defective luminal complement activity


Poor Brain Health
Poor Memory
Inability to Find Words
Difficulty Learning
Brain Fatigue
Brain Activation of Pontine Vagal Centers
Activation of Enteric Smooth-Muscle Constriction
Impaired Gut Motility
Yeast fermentation and overgrowth
Inability to eliminate waste products
Inability to Activate Enteric Nervous System/Constriction of Valves
Ileocecal Valve Tone
Unable to store bacteria in the large intestine
Disrupts intestinal transit coordination
Gallbladder Contractions
Gallstone formation
Inability to Activate Autonomic Control of Digestive Enzyme Release
HCl
Inability to digest protein
Pancreatic Enzymes
Inability to digest starches
Bile
Inability to digest fats
Parasympathetic Activity in the Gut
Reduced blood flow to the intestines
Intestinal Permeability

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E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(12):2776-2781
World Journal of Gastroenterology
 ISSN 1007-9327

• BASIC RESEARCH •

Alterations of intestinal mucosa structure and barrier function following traumatic brain injury in rats

Chun-Hua Hang, Ji-Xin Shi, Jie-Shou Li, Wei Wu, Hong-Xia Yin

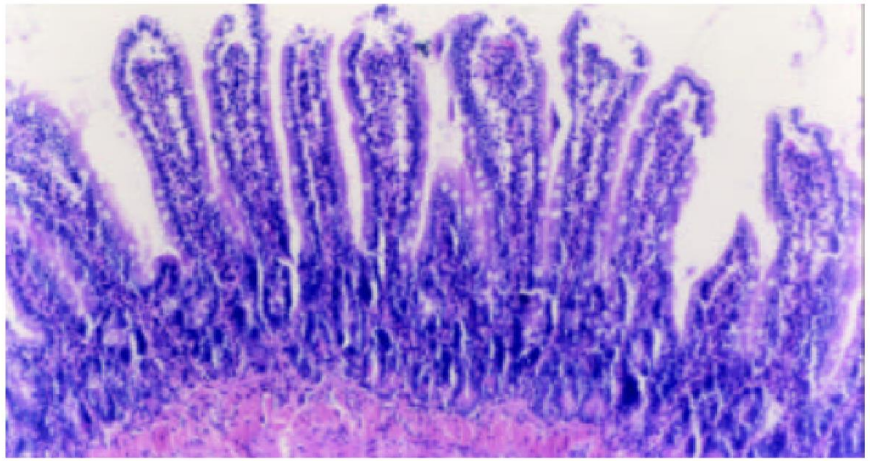


Figure 1 Epithelial cells shed from the top of villi with almost normal villous height and well defined arrangement of villi at 3 hours following TBI. H-E, magnification ×100.

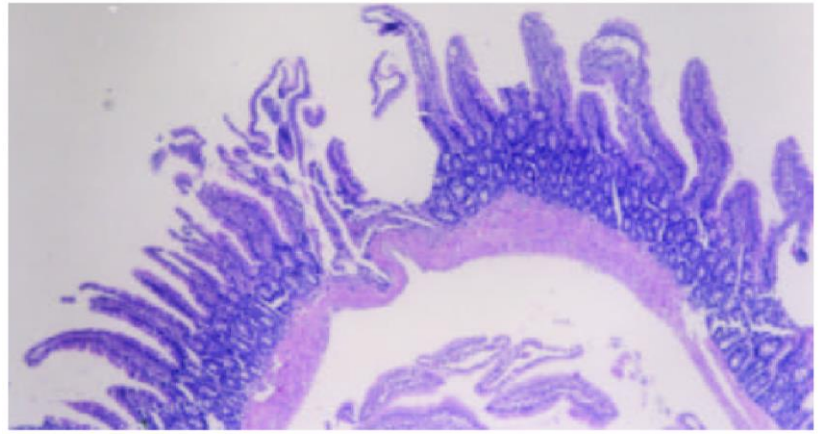


Figure 2 Markedly altered villous morphology and decreased height at 72 hours following TBI. Note the focal mucosa ulcer with exposure of submucosal interstitium and disarrangement of villi. H-E, magnification ×100.

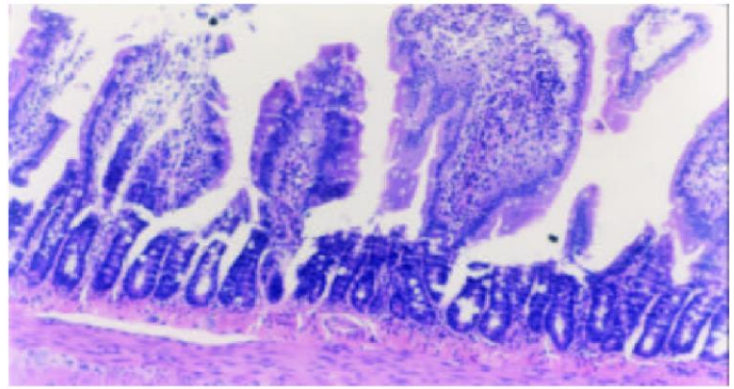


Figure 3 Marked alterations of villous morphology occurred 7 days following TBI, including mucosal atrophy, fusion of adjacent villi, inflammatory cell infiltration, and vascular dilation, congestion and edema in the villous interstitium and lamina propria. H-E, magnification ×100.

Part Six

Cerebellum

Balance, dizziness, worse cordination

Cerebellar Degeneration

Three Common Neurodegenerative Diseases

Dementia

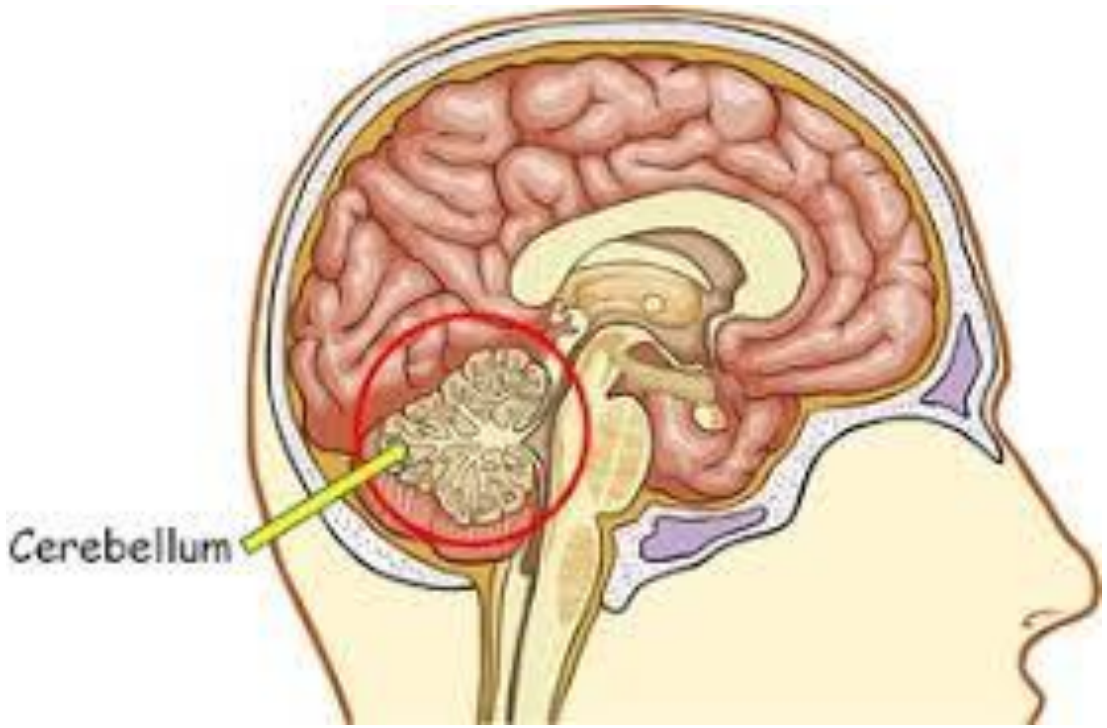
- Forgets recently learned information
- Forgets dates, events, and appointments
- Misplaces keys, purse/wallet, remote control
- Has memory lapses in the middle of conversations
- Forgets locations

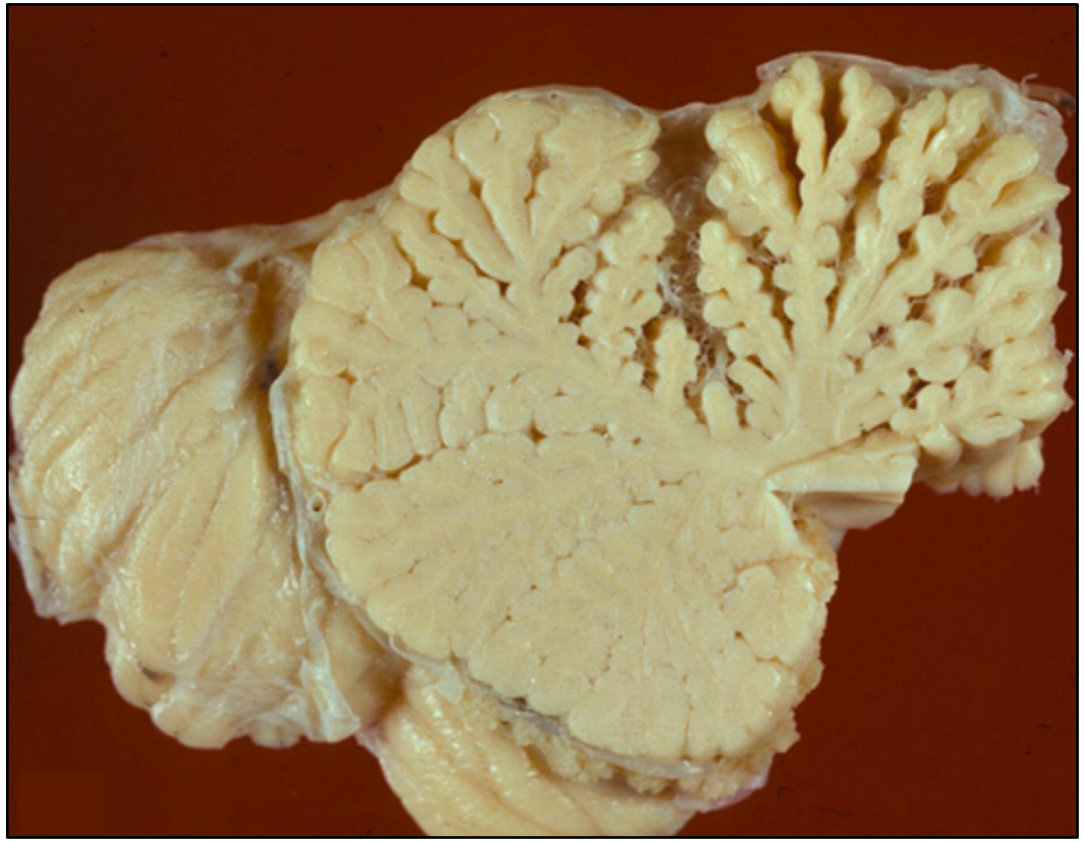
Parkinsonism

- Stiffness
- Slowness of movement
- Impaired GI motility
- ↓Smell and ↓taste
- Expressionless face
- Resting tremor

Cerebellar Degeneration

- Worsening balance
- Worsening coordination
- Bumps into everything
- Dizziness and disorientation


Cerebellum



Clinical Presentation of Cerebellar Degeneration

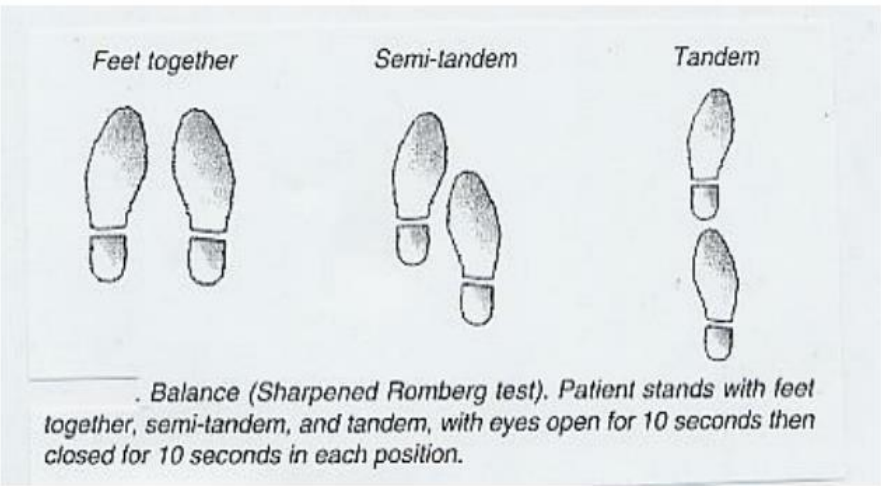
Symptoms

- Worsening balance
- Worsening car or seasickness
- Symptoms of nausea when looking at things in motion

Examination Findings

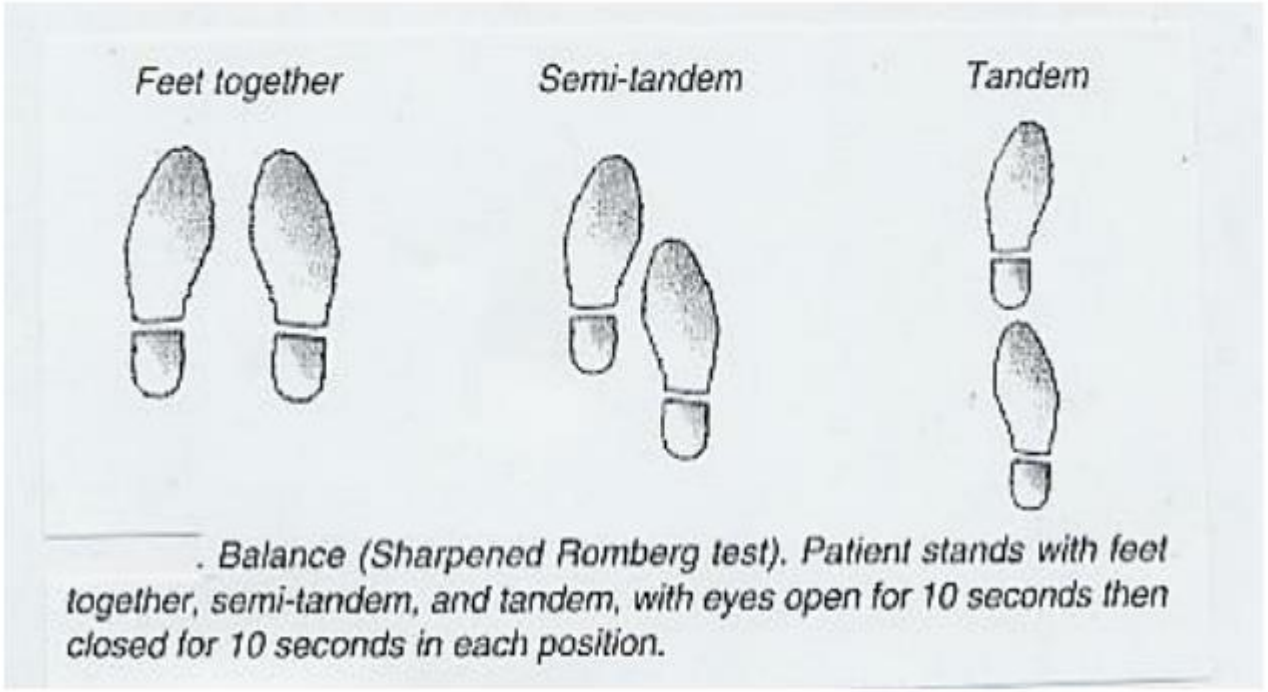
- Wide-stanced gait
- Positive Romberg's test
- Ataxia with tandem walking
- Termination tremor
- Dysdiadochokinesia
- Kinetic tremor (progressed stage)

Sharpened Romberg's



. Balance (Sharpened Romberg test). Patient stands with feet together, semi-tandem, and tandem, with eyes open for 10 seconds then closed for 10 seconds in each position.

Sharpened Romberg's

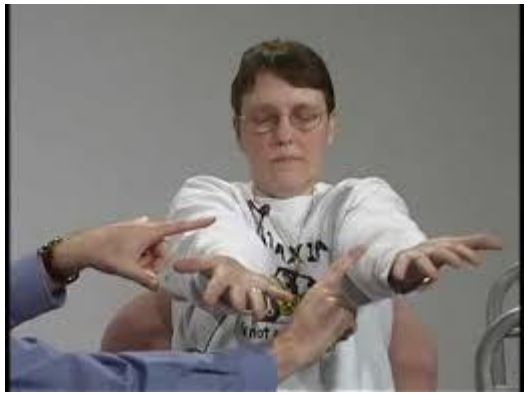


. Balance (Sharpened Romberg test). Patient stands with feet together, semi-tandem, and tandem, with eyes open for 10 seconds then closed for 10 seconds in each position.

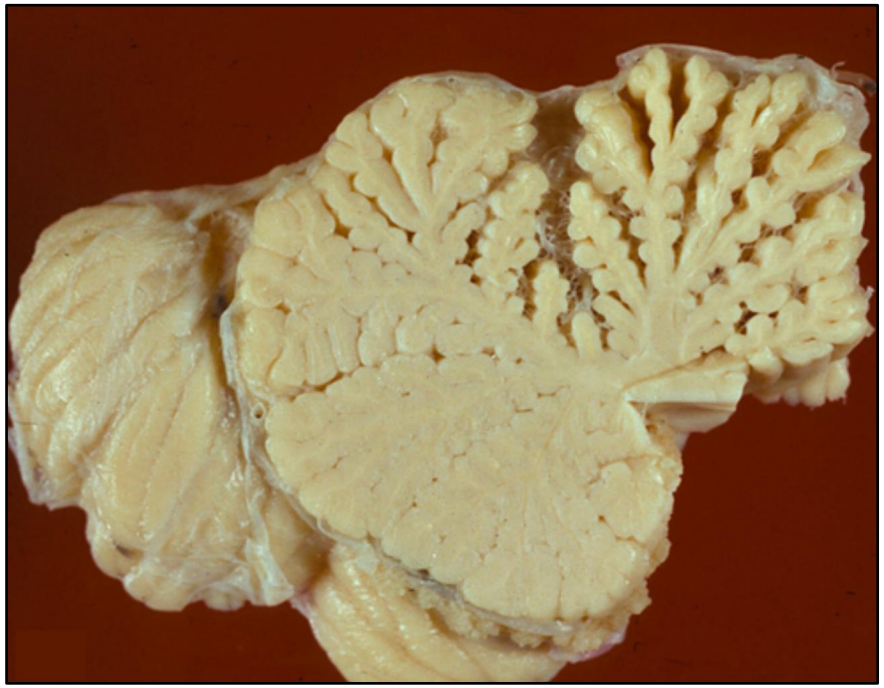
Finger-to-nose test

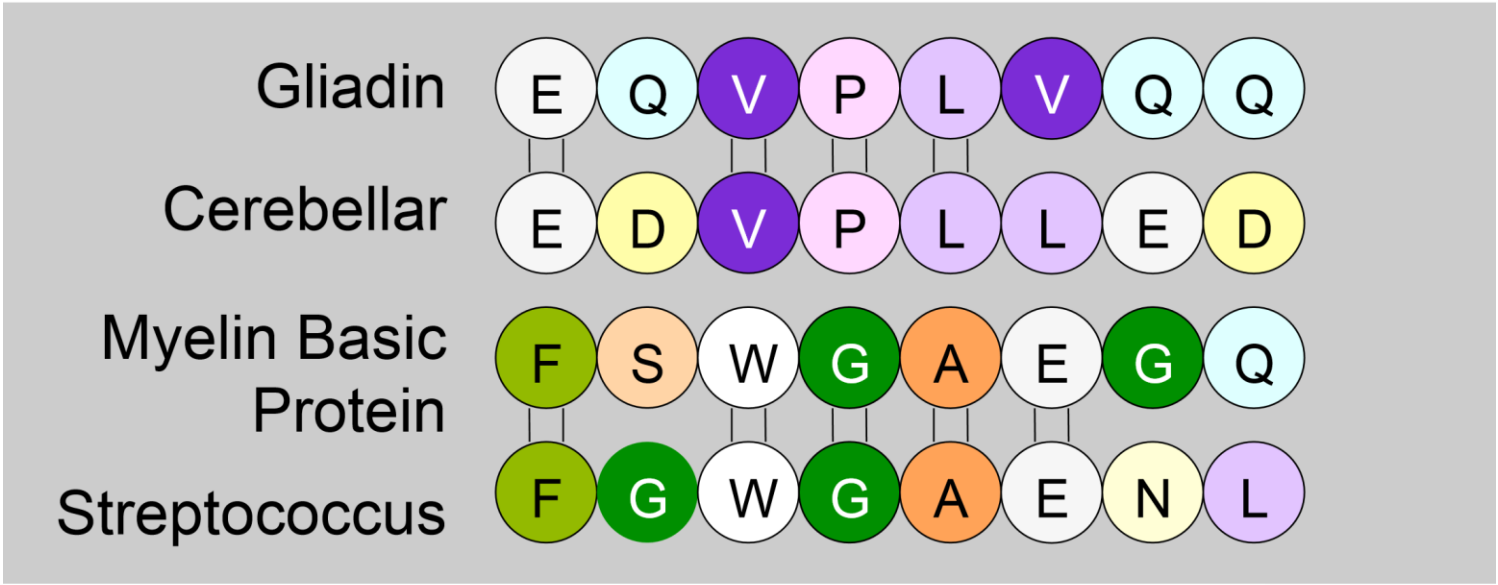
www.clinicalexams.co.uk

© Healthwise, Incorporated



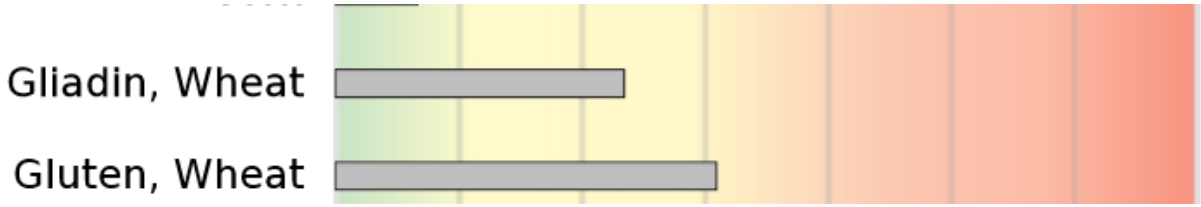
Cross-Reactive Amino Acid Sequences





"If amino acids were strung like the beads of a necklace, gliadin and cerebellar protein would look like the above representation, with commonalities, while myelin basic protein shares similarities with streptococcus. When sequence chains mimic each other (molecular mimicry), there is a chance for the production of cross-reactive antibodies, in the process of which the body's own immune system may attack itself (friendly fire)."

The Autism File. 2009;31:56-64.

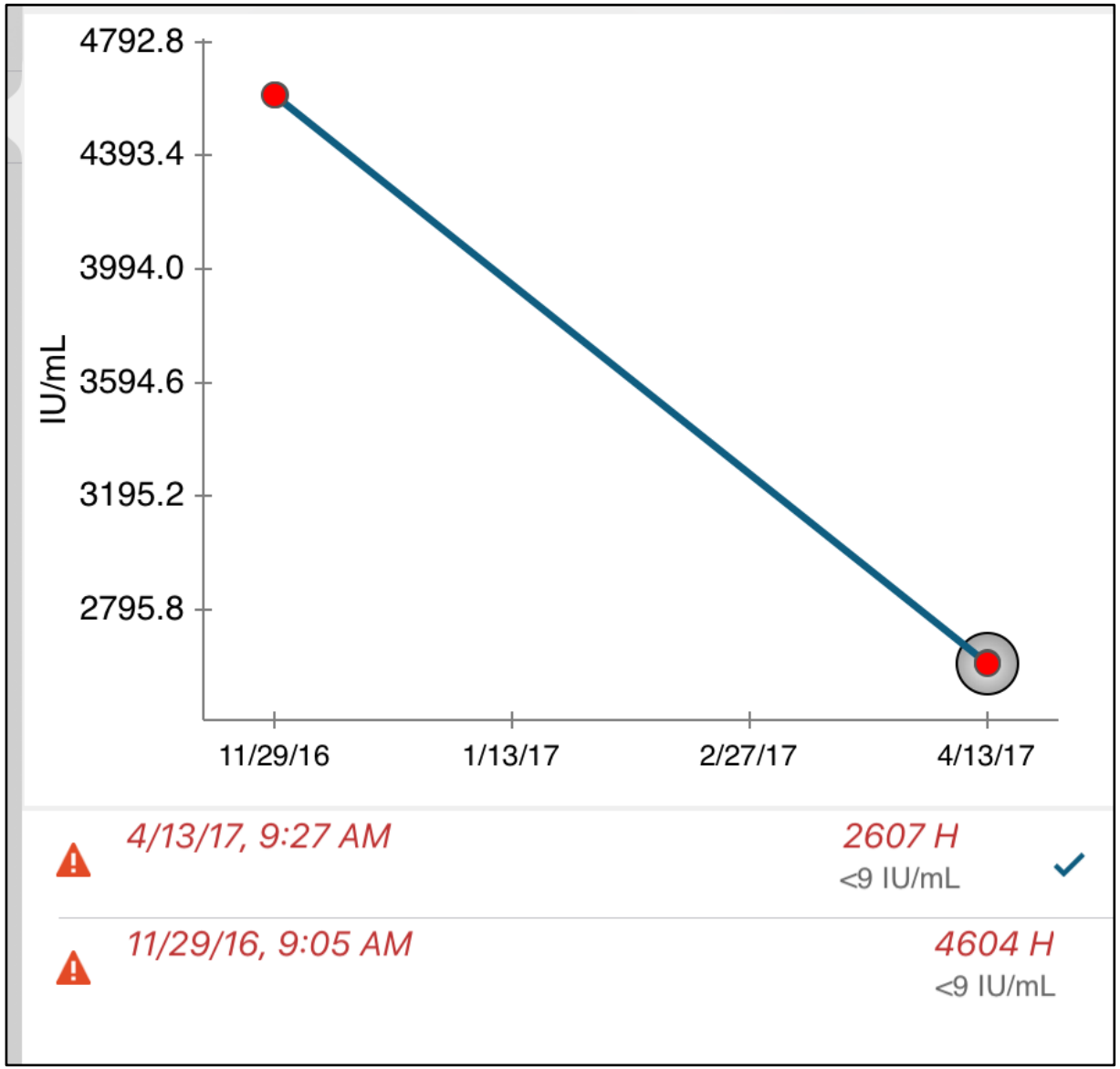


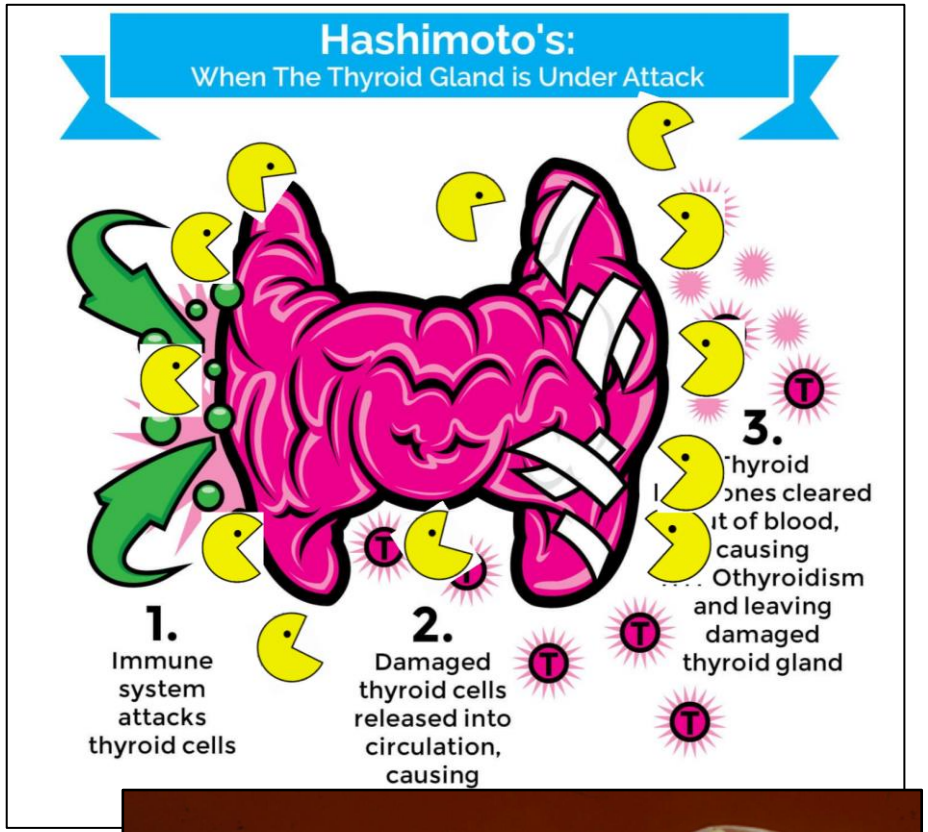
Anti-thyroperoxidase antibodies from patients with Hashimoto's encephalopathy bind to cerebellar astrocytes.

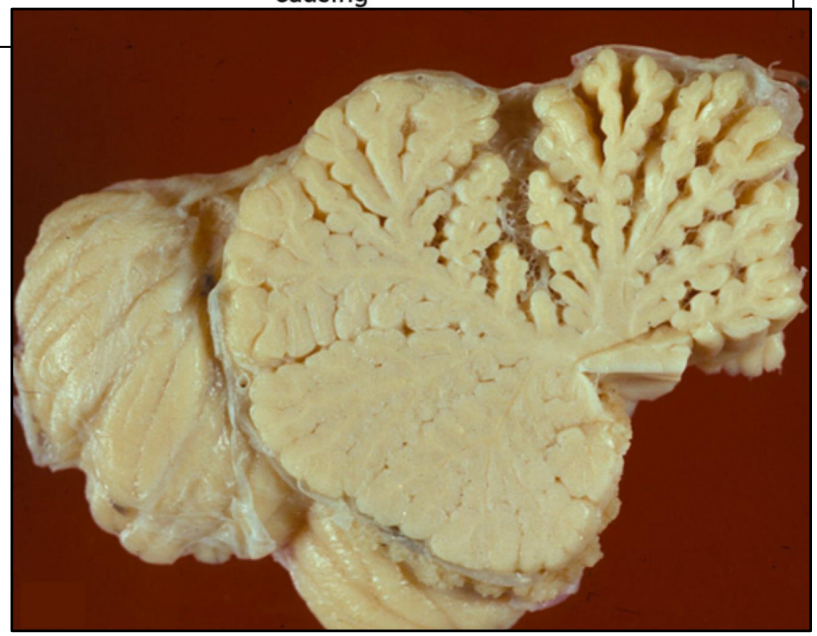
- “Normal human astrocytes from primary cultures also reacted with anti-TPO mAb.”

- “Specific astrocyte binding of anti-TPO aAb suggests a role of these aAb in the Hashimoto’s encephalopathy pathogenesis”

J Neuroimmunol. 2007 Dec;192(1-2):13-20.


4792.8
4393.4
3994.0
3594.6
3195.2
2795.8
IU/mL
11/29/16
1/13/17
2/27/17
4/13/17
4/13/17, 9:27 AM
2607 H
<9 IU/mL
11/29/16, 9:05 AM
4604 H
<9 IU/mL


Hashimoto's:
When The Thyroid Gland is Under Attack
1.
Immune system attacks thyroid cells
2.
Damaged thyroid cells released into circulation, causing
3.
hyroid
ones cleared
it of blood,
causing
Othyroidism
and leaving
damaged
thyroid gland



CEREBELLUM – CEREBROCEREBELLUM

LOSS OF ACTIVITY AND EPILEPTIFORM ACTIVITY

Loss of activity leads to termination and kinetic tremors, clumsiness, limb hypotonia, and impaired motor coordination

Epileptiform activity leads to vertigo, instability and post-synaptic projections induce dysautonomia such as increased heart rate, orthostatic hypotension, nausea, etc.

BRAIN REGION LOCALIZATION FORM SYMPTOMS

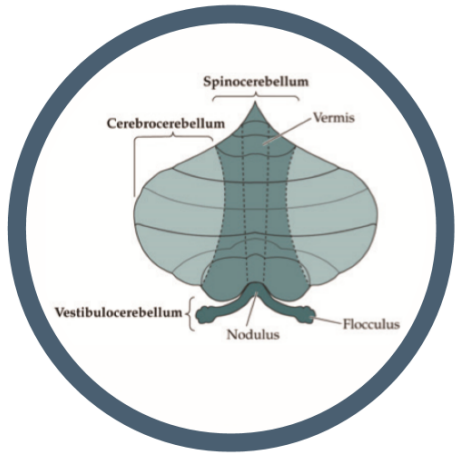
- Recent clumsiness in hands
- Recent clumsiness in feet or frequent tripping
- A slight hand shake when reaching for something at the end of movement

EXAMINATION FINDINGS

- Intention or Kinetic tremor
- Termination tremor with end-stage targeting (finger-to-nose
- Dysmetric (hypometric and hypermetric) targeting (finger-to-nose or heel)
- Dysdiadochokinesia with rapid alternation movements
- Ataxic dysarthria

APPLICATIONS

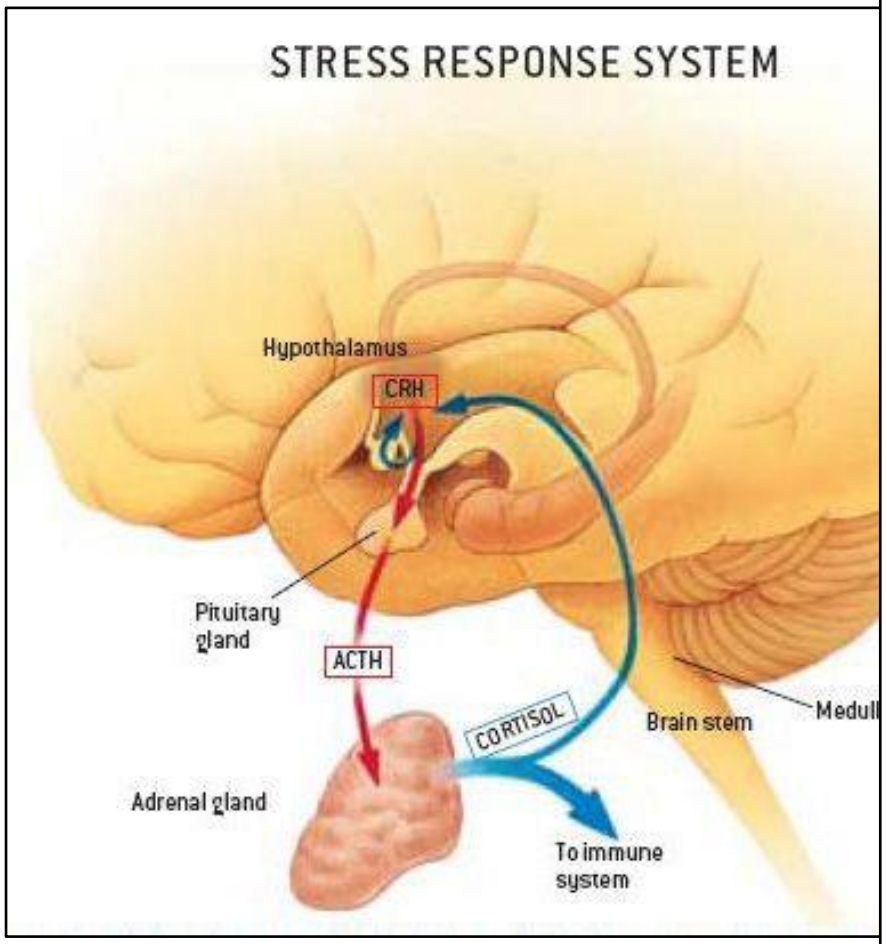
- Coordinated motor activities specific to limb and side of involvement
- Proximal for interpose region
- Spinal for midline cerebellar
- Hand specific for dentate



Rev. 05|09|2016

Part 7

Adrenal Glands



Provider:

Hugh Wegwerth DC
1912 Lexington Ave Ste 250
Roseville, MN 55113 US
Ordering Provider: Hugh Wegwerth - DC

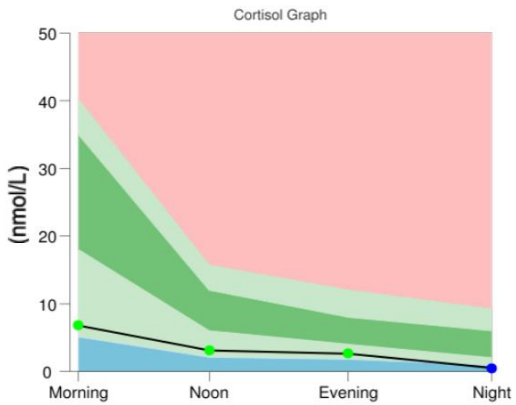
Age:56 **Gender:**F

Menopausal Status:
Post-Menopause

4322 Victor Path Unit
Hugo, MN 55038

Evening	10/16/2016 1630
Night	10/16/2016 2125
Samples Arrived	10/21/2016
Results Reported	10/26/2016

	Saliva Hormone Test	Result	Units	L	WR	H	Reference Range
HORMONES	**Estrone (E1)***	< 3.10	pg/ml		◆		**<47.0 post menopausal**
	Estradiol (E2)	1.82	pg/ml		◆		**1.0-3.2 post menopausal (1.5-10.8 supplementation)**
	Estriol (E3)*	< 5.00	pg/ml		◆		**<66.0 (67.0-708.0 supplementation)**
	EQ (E3 / (E1 + E2))	1.02			◆		**low <1.0; WR >=1.0; optimal >1.5**
	Progesterone (Pg)	< 10.00	pg/ml	↓			**18.0-126.0 post menopausal (500-3000 supplementation)**
	Ratio of Pg/E2**	5.49		↓			**200-600 pre; post with supplementation**
	Testosterone*	34.24	pg/ml		◆		**6.1-49.0 female (30.0-60.0 supplementation)**
ADRENALS	**DHEA***	184.23	pg/ml		◆		**106.0-300.0 female**
	Cortisol Morning	6.77	nmol/L		◆		**5.1-40.2; optimal range: 18-35†**
	Cortisol Noon	3.10	nmol/L		◆		**2.1-15.7; optimal range: 6-12†**
	Cortisol Evening	2.61	nmol/L		◆		**1.8-12; optimal range: 4-8†**
	Cortisol Night	0.50	nmol/L	↓			**0.9-9.2; optimal range: 2-6†**



Adrenal Phase: 3

Hormone Comments:

- Estrone, estradiol and estriol are within the reference ranges, however, the Estrogen Quotient (EQ) is suboptimal. Estriol is less potent than the other estrogens and when present in sufficient quantities (as indicated by an optimal EQ) it plays an antagonistic role, and may govern the proliferative effects of estrone and estradiol. Estriol supplementation is a consideration to optimize this quotient, reduce associated risks and address the reported vaginal dryness.
- Progesterone to estradiol (Pg/E2) ratio and reported symptoms are consistent with progesterone insufficiency (estrogen dominance). Supplementation with topical progesterone to correct this deficiency is a consideration.
- Diurnal cortisol pattern and reported symptoms are consistent with established (Phase 3) HPA axis (adrenal gland) dysfunction, although concomitant thyroid and/or iodine insufficiency cannot be ruled out.

Notes:

L=Low(below range) WR=Within Range (within range) H=High (above range)

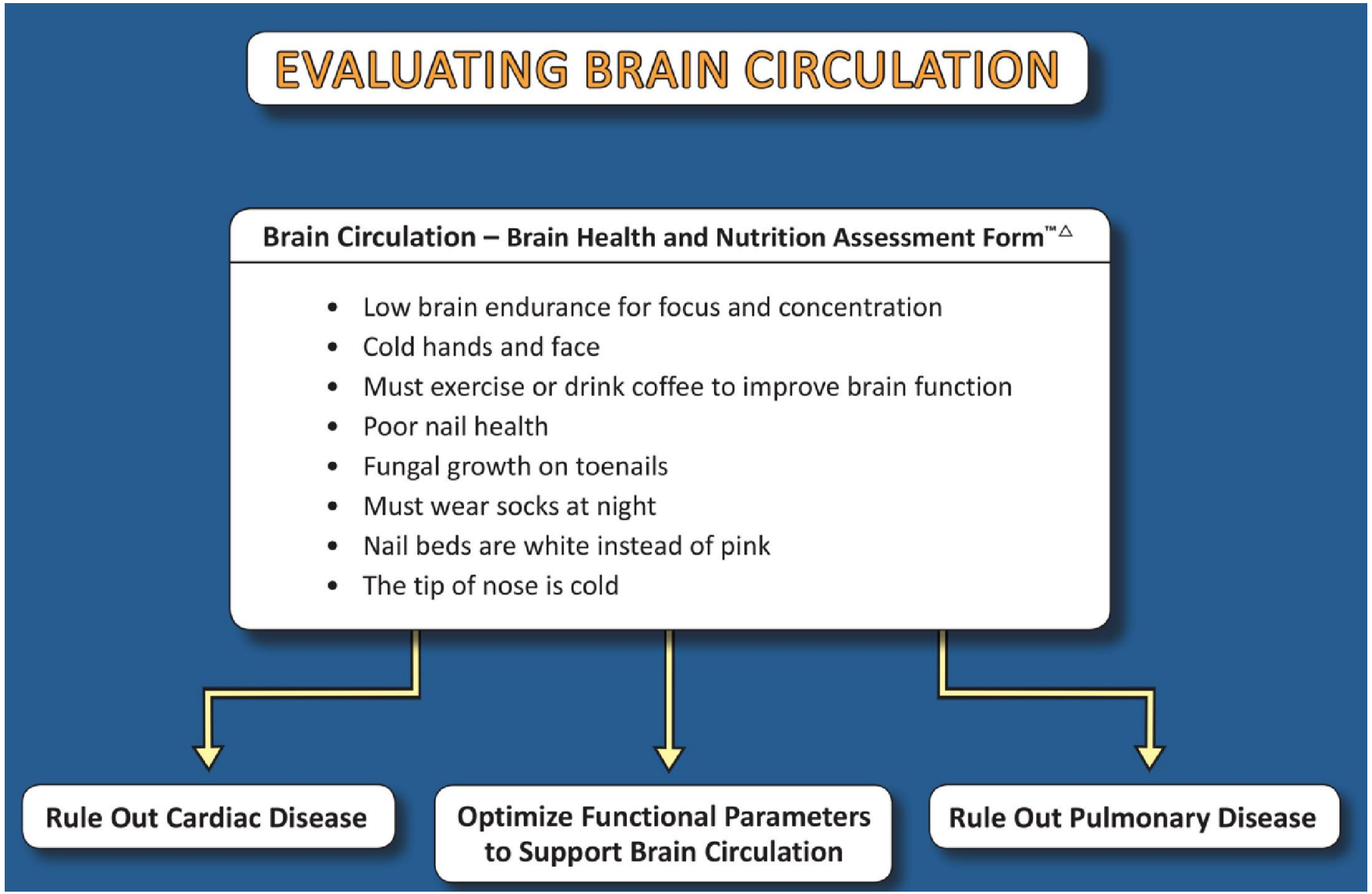
*This test was developed and its performance characteristics determined by Labrix Clinical Services, Inc. The US FDA has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

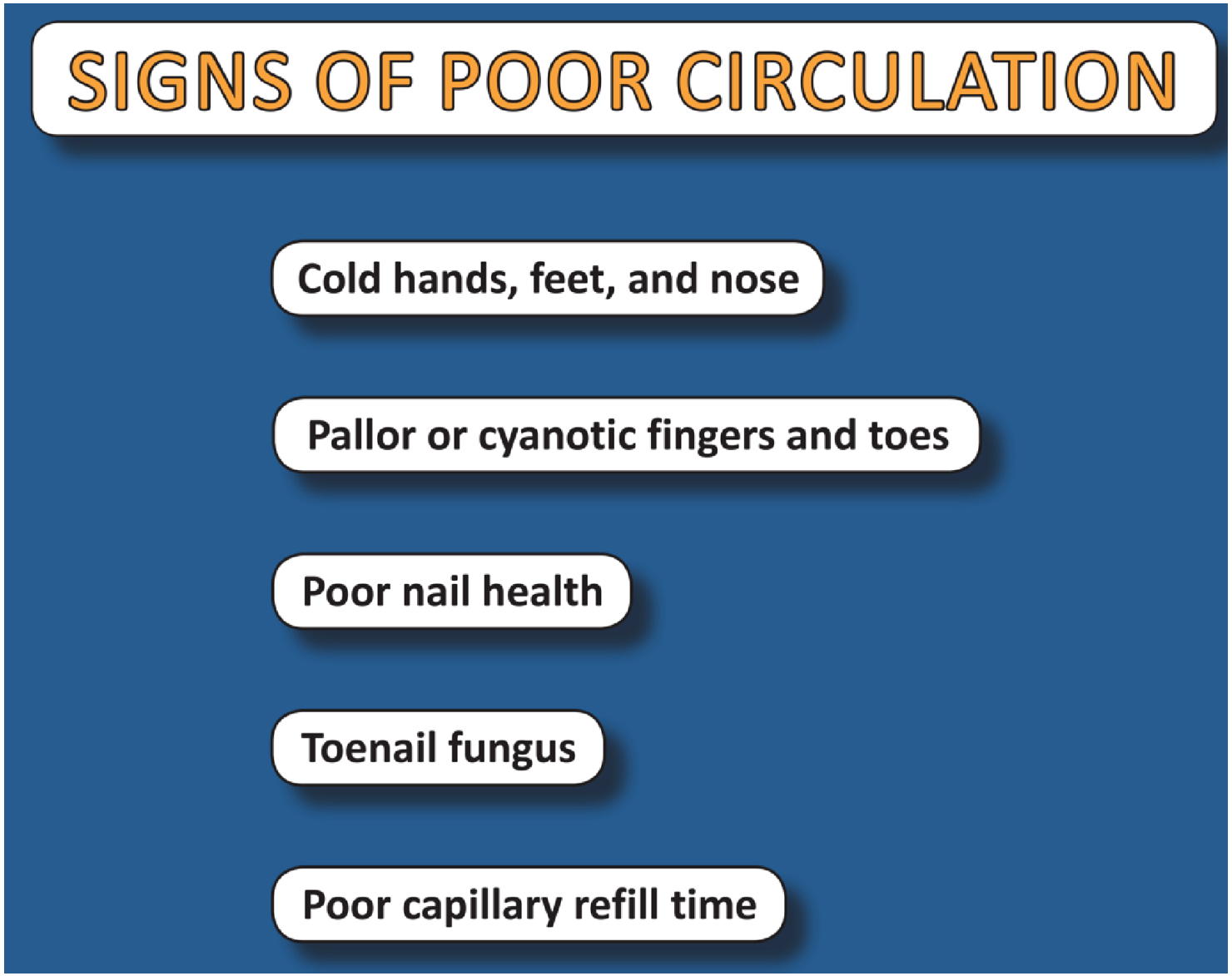
**The Pg/E2 ratio is an optimal range established based on clinical observation. Progesterone supplementation is generally required to achieve this level in men and postmenopausal women.

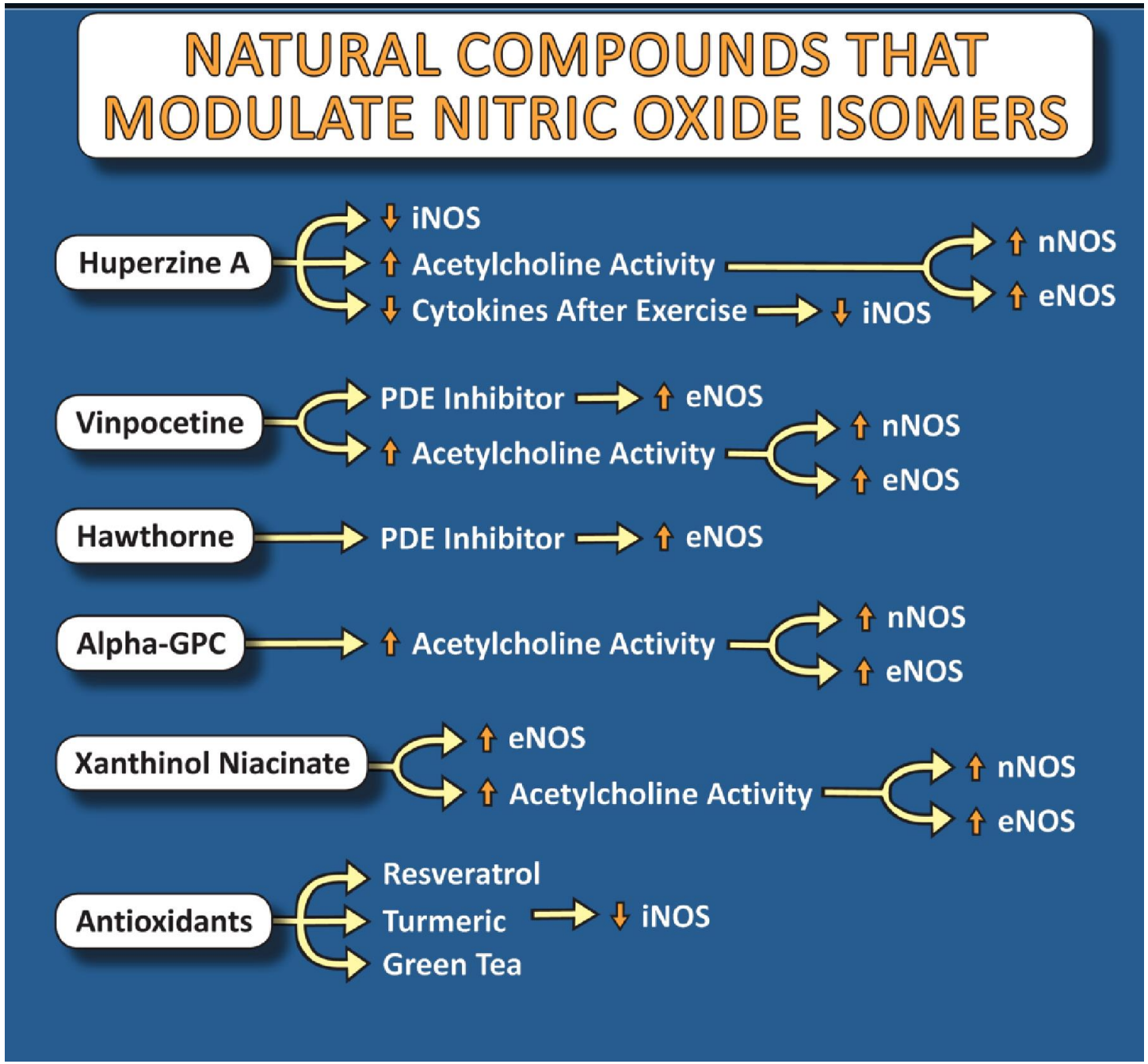
†Apply only when all four cortisols are measured. Clinical comments may override these generalized optimal ref. ranges.

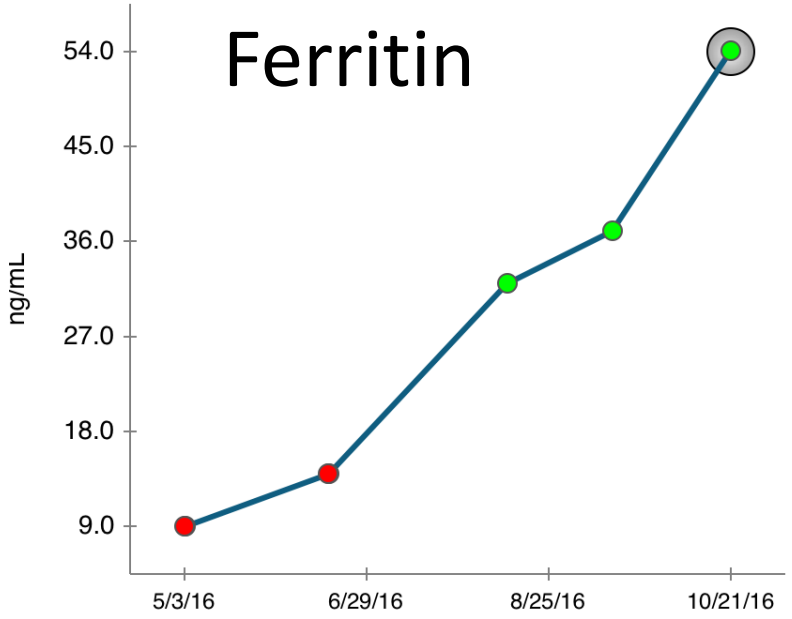
Part 8

Blood Flow and Iron Staus


EVALUATING BRAIN CIRCULATION
Brain Circulation – Brain Health and Nutrition Assessment Form™△
Low brain endurance for focus and concentration
Cold hands and face
Must exercise or drink coffee to improve brain function
Poor nail health
Fungal growth on toenails
Must wear socks at night
Nail beds are white instead of pink
The tip of nose is cold
Rule Out Cardiac Disease
Optimize Functional Parameters to Support Brain Circulation
Rule Out Pulmonary Disease


SIGNS OF POOR CIRCULATION
Cold hands, feet, and nose
Pallor or cyanotic fingers and toes
Poor nail health
Toenail fungus
Poor capillary refill time


NATURAL COMPOUNDS THAT MODULATE NITRIC OXIDE ISOMERS
Huperzine A
iNOS
Acetylcholine Activity
Cytokines After Exercise
iNOS
nNOS
eNOS
Vinpocetine
PDE Inhibitor
eNOS
Acetylcholine Activity
nNOS
eNOS
Hawthorne
PDE Inhibitor
eNOS
Alpha-GPC
Acetylcholine Activity
nNOS
eNOS
Xanthinol Niacinate
eNOS
Acetylcholine Activity
nNOS
eNOS
Antioxidants
Resveratrol
Turmeric
Green Tea
iNOS



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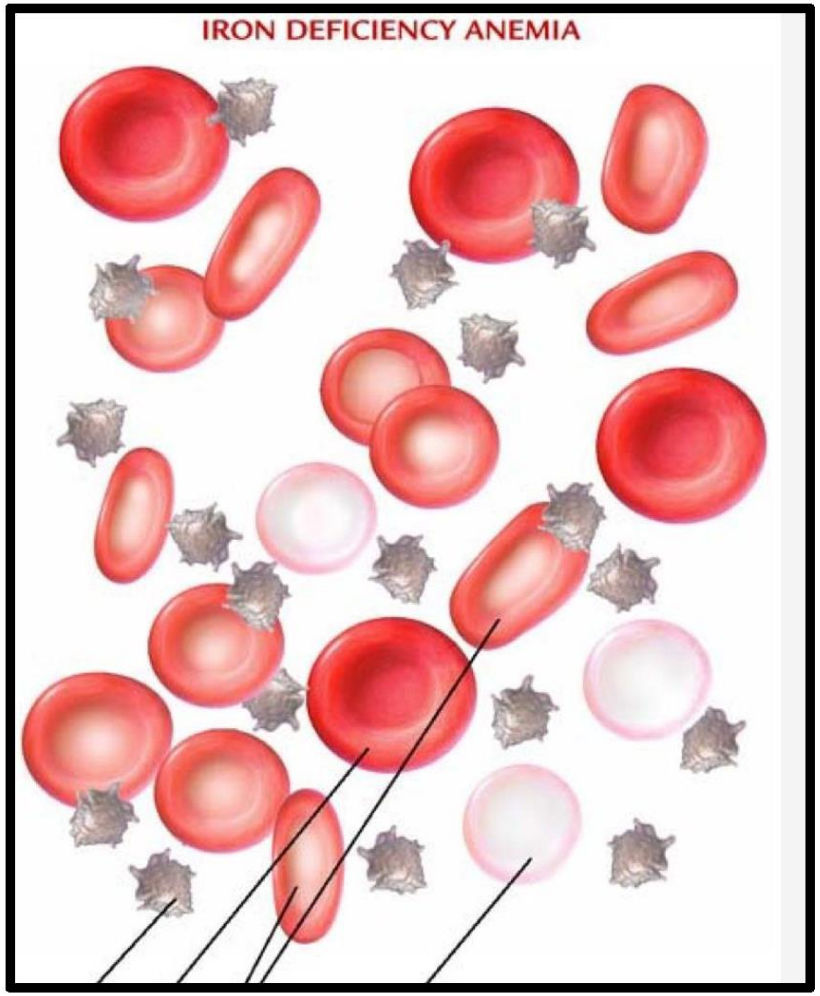
9/14/16, 8:52 AM	37 20-288 ng/mL	
8/12/16, 9:32 AM	32 20-288 ng/mL	
⚠ *6/17/16, 10:01 AM*	*14 L* 20-288 ng/mL	
⚠ *5/3/16, 10:06 AM*	*9 L* 20-288 ng/mL	



Neurology. 2013 Aug 6;81(6):528-33. doi: 10.1212/WNL.0b013e31829e701d. Epub 2013 Jul 31.

Anemia and risk of dementia in older adults: findings from the Health ABC study.

Hong CH[1], Falvey C, Harris TB, Simonsick EM, Satterfield S, Ferrucci L, Metti AL, Patel KV, Yaffe K.

Author information

Erratum in
Neurology. 2013 Sep 3;81(10):939.

Abstract

OBJECTIVE: To determine whether anemia is associated with incident dementia in older adults.

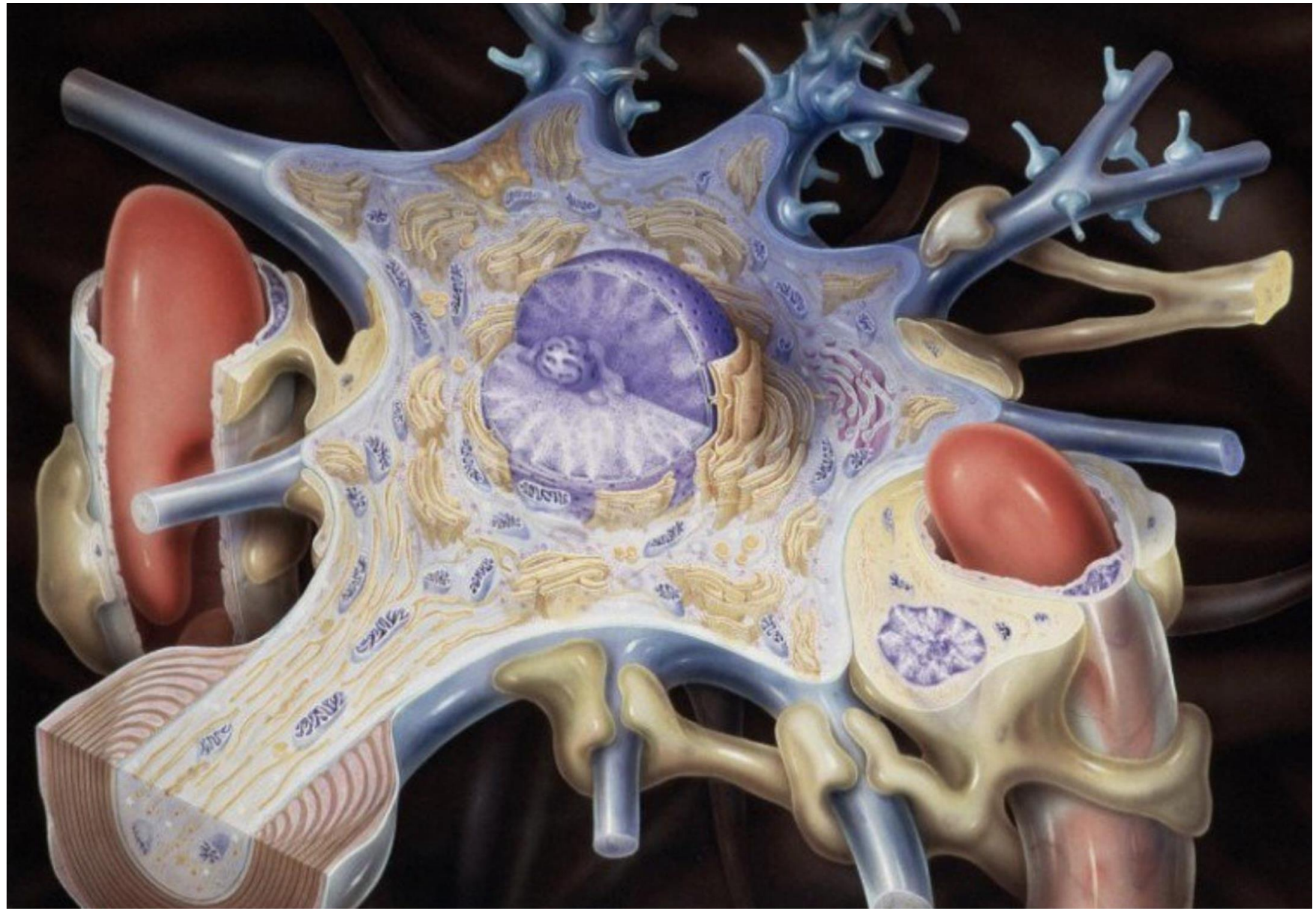
METHODS: We studied 2,552 older adults (mean age 76.1 years; 38.9% black; 51.8% female) participating in the Health, Aging, and Body Composition study and free of dementia at baseline. We defined anemia using WHO criteria (hemoglobin concentration <13 g/dL for men and <12 g/dL for women). Dementia diagnosis was determined by dementia medication use, hospital records, or a change in modified mini-mental state (3MS) score of more than 1.5 SD from mean. Discrete time Cox proportional hazard regression models were used to examine the hazard for developing dementia associated with anemia.

RESULTS: Of 2,552 participants, 393 (15.4%) older adults had anemia at baseline [corrected]. Over 11 years of follow-up, 455 (17.8%) participants developed dementia. In the unadjusted model, those with baseline anemia had an increased risk of dementia (23% vs. 17%, hazard ratio = 1.64; 95% confidence interval 1.30, 2.07) compared to those without anemia. The association remained significant after adjusting for demographics, APOE ε4, baseline 3MS score, comorbidities, and renal function. Additional adjustment for other anemia measures (mean corpuscular volume, red cell distribution width), erythropoietin, and C-reactive protein did not appreciably change the results. There was no interaction by sex and race on risk of developing dementia.

CONCLUSION: Among older adults, anemia is associated with an increased risk of developing dementia. Findings suggest that further study of anemia as a risk factor for dementia and a target for intervention for cognitive health is warranted.

PMID: 23902706 PMCID: PMC3775683 DOI: 10.1212/WNL.0b013e31829e701d

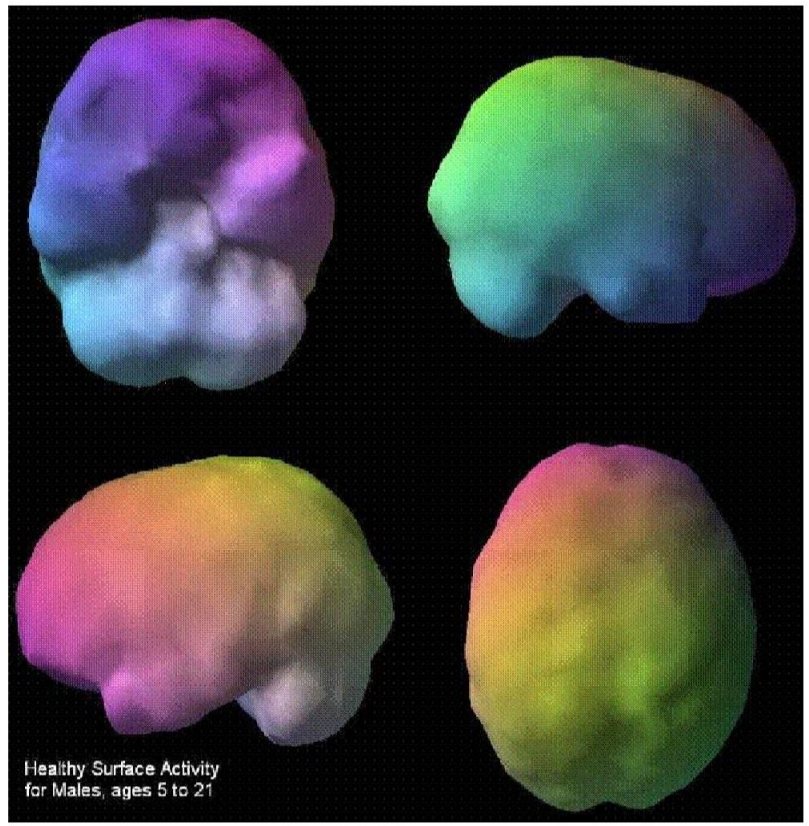
[Indexed for MEDLINE] **Free PMC Article**



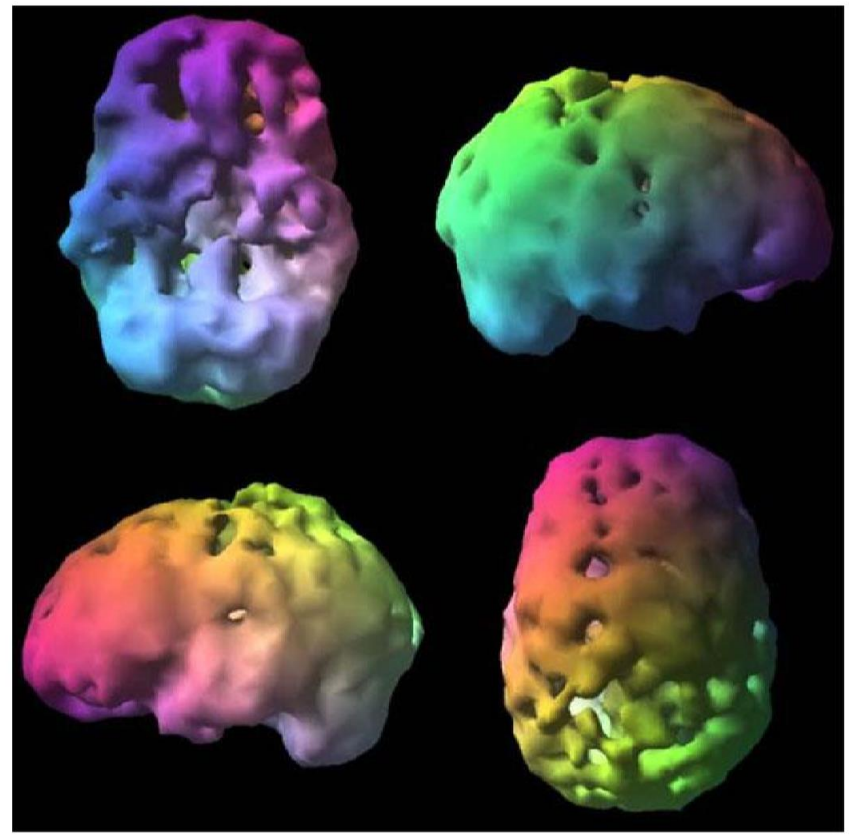
SPECT Scan

Measures *blood flow* to the brain

Healthy/Normal



Alzheimer's/Dementia



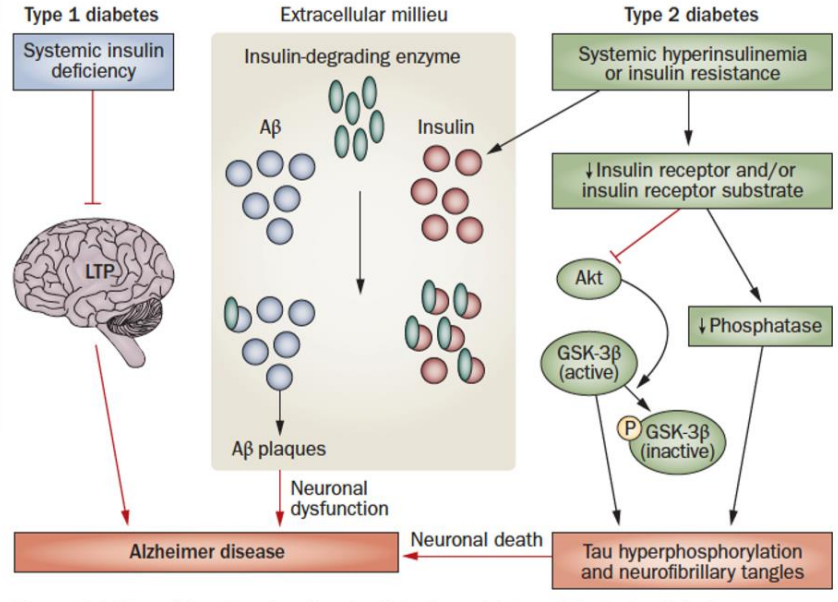
http://www.amenclinics.com/home/

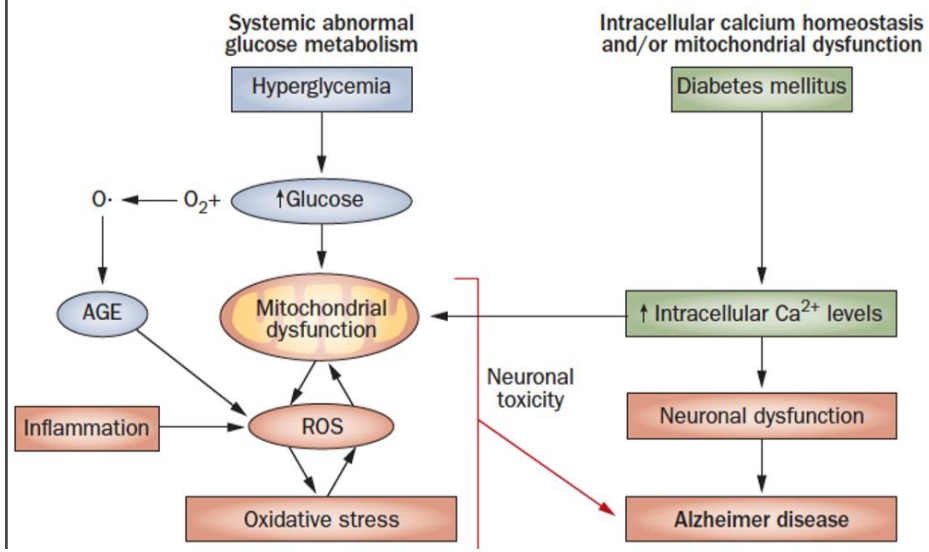
Part 9

Blood sugar and insulin

Key points

- Alzheimer disease (AD) and diabetes are both associated with enormous and increasing socioeconomic effects
- Diabetes affects the processing of amyloid-β and tau, and might increase the rate of formation of senile plaques and neurofibrillary tangles, the main neuropathological hallmarks of AD
- Hyperinsulinemia is associated with amyloid-β accumulation and regulates tau phosphorylation
- Oxidative stress activates inflammatory pathways and, hence, might exacerbate AD neuropathology
- Mitochondrial dysfunction is associated with both diabetes and AD, and leads to intracellular calcium dysregulation and abnormal processing of the amyloid precursor protein
- Induction of diabetes exacerbates AD neuropathology in mouse models of this neurodegenerative disease





REVIEWS

How does diabetes accelerate Alzheimer disease pathology?

Catrina Sims-Robinson, Bhumsoo Kim, Andrew Rosko and Eva L. Feldman

Centers for Disease Control and Prevention.
National Diabetes Fact Sheet, 2011

- "About 60 to 70 percent of people with diabetes have mild to severe forms of nervous system damage."

- "The risk for stroke is two to four times higher among people with diabetes."

Altern Med Rev. 2009 Dec;14(4):373-379.

The relationship between Alzheimer's disease and diabetes: Type 3 diabetes?

- "In recent years, Alzheimer's disease (AD) has been considered to be, in part, a neuroendocrine disorder, even referred to by some as **type 3 diabetes**."
- "Insulin functions by controlling neurotransmitter release processes at the synapses and activating signaling pathways associated with learning and long-term memory."

DIETARY AND LIFESTYLE MECHANISMS PROMOTING INSULIN RESISTANCE

Insulin Resistance Diet and Lifestyle

- Lack of physical activity
- Overeating
- High-sugar and high-starch snacks and meals
- Social and pleasure eating
- Lack of fiber in diet

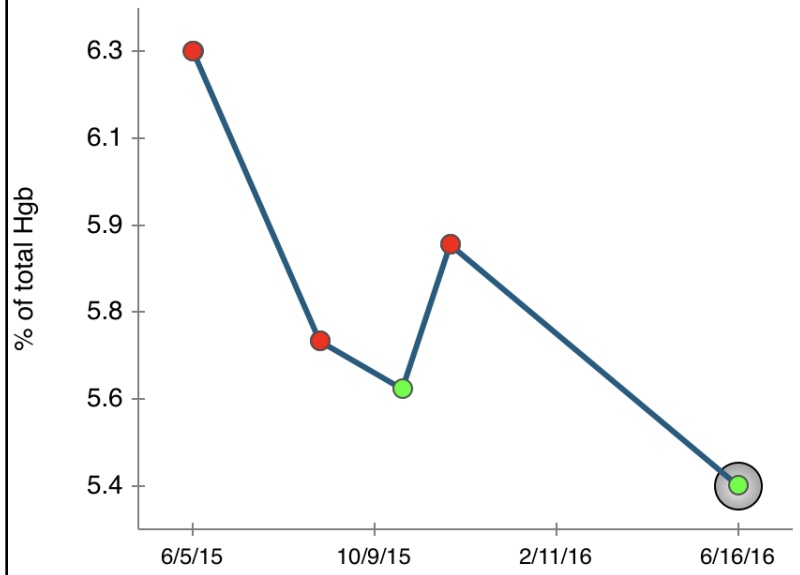
Insulin Resistance Symptoms

- Fatigue after meals
- Crave sweets during the day
- Eating sweets does not resolve cravings
- Difficulty losing weight
- Must have sweets after meals

Chief Clinical Complaints

- Fatigue
- Inability to lose weight
- Joint pain
- Depression and mood disorder
- Infertility
- Thinning hair
- Hormone imbalances

HEMOGLOBIN A1c



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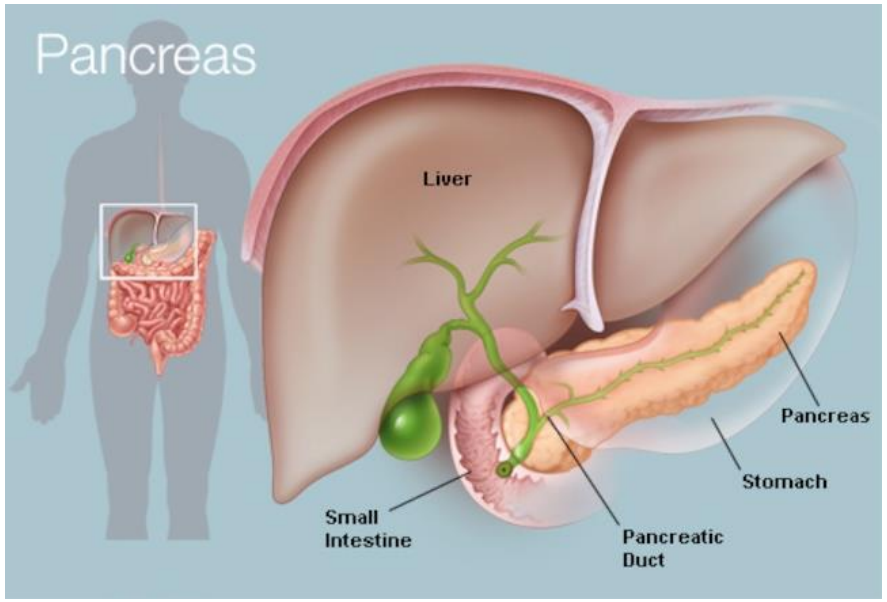
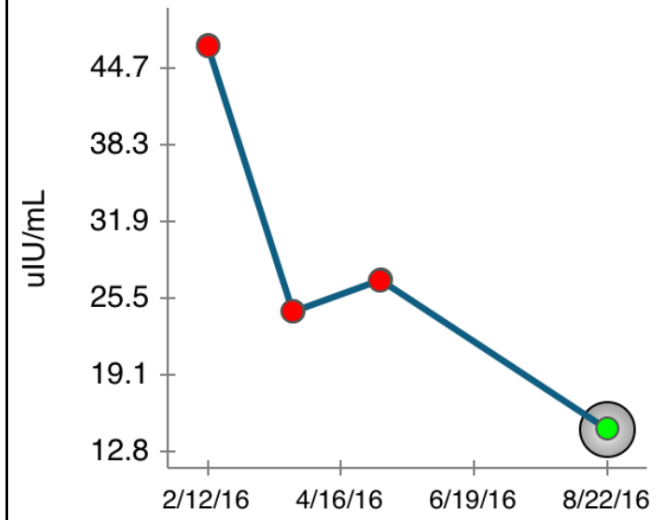
⚠ *11/30/15, 8:56 AM*	*5.9 H* <5.7 % of total Hgb	
10/28/15, 11:02 AM	5.6 <5.7 % of total Hgb	
⚠ *9/1/15, 8:50 AM*	*5.7 H* <5.7 % of total Hgb	
⚠ *6/5/15, 10:37 AM*	*6.3 H* <5.7 % of total Hgb	



T-Mobile 5:43 PM

Lab Detail **Lab Flowsheet**

INSULIN



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⚠ *5/5/16, 9:21 AM*	*27.0 H* 2.0-19.6 uIU/mL	
⚠ *3/24/16, 9:19 AM*	*24.4 H* 2.0-19.6 uIU/mL	
⚠ *2/12/16, 9:20 AM*	*46.5 H* 2.0-19.6 uIU/mL	

Part 10

Suplements

Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 359 (2007) 697–702
BBRC
www.elsevier.com/locate/ybbrc

Estrogen has anti-amyloidogenic effects on Alzheimer's β-amyloid fibrils in vitro

Akiyoshi Morinaga, Mie Hirohata, Kenjiro Ono, Masahito Yamada *

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Received 8 May 2007
Available online 4 June 2007

Testosterone reduces neuronal secretion of Alzheimer's β-amyloid peptides

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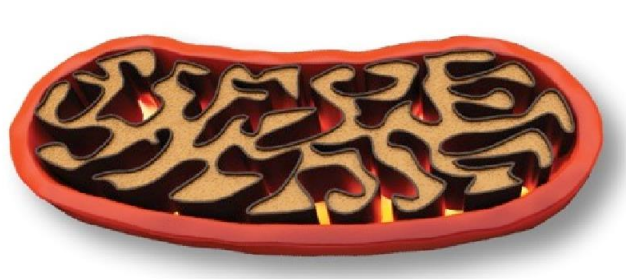
*Laboratory of Molecular and Cellular Neuroscience and Fisher Center for Research on Alzheimer's Disease, and §Laboratory of Mass Spectrometry, The Rockefeller University, 1230 York Avenue, New York, NY 10021; and †Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY 10021

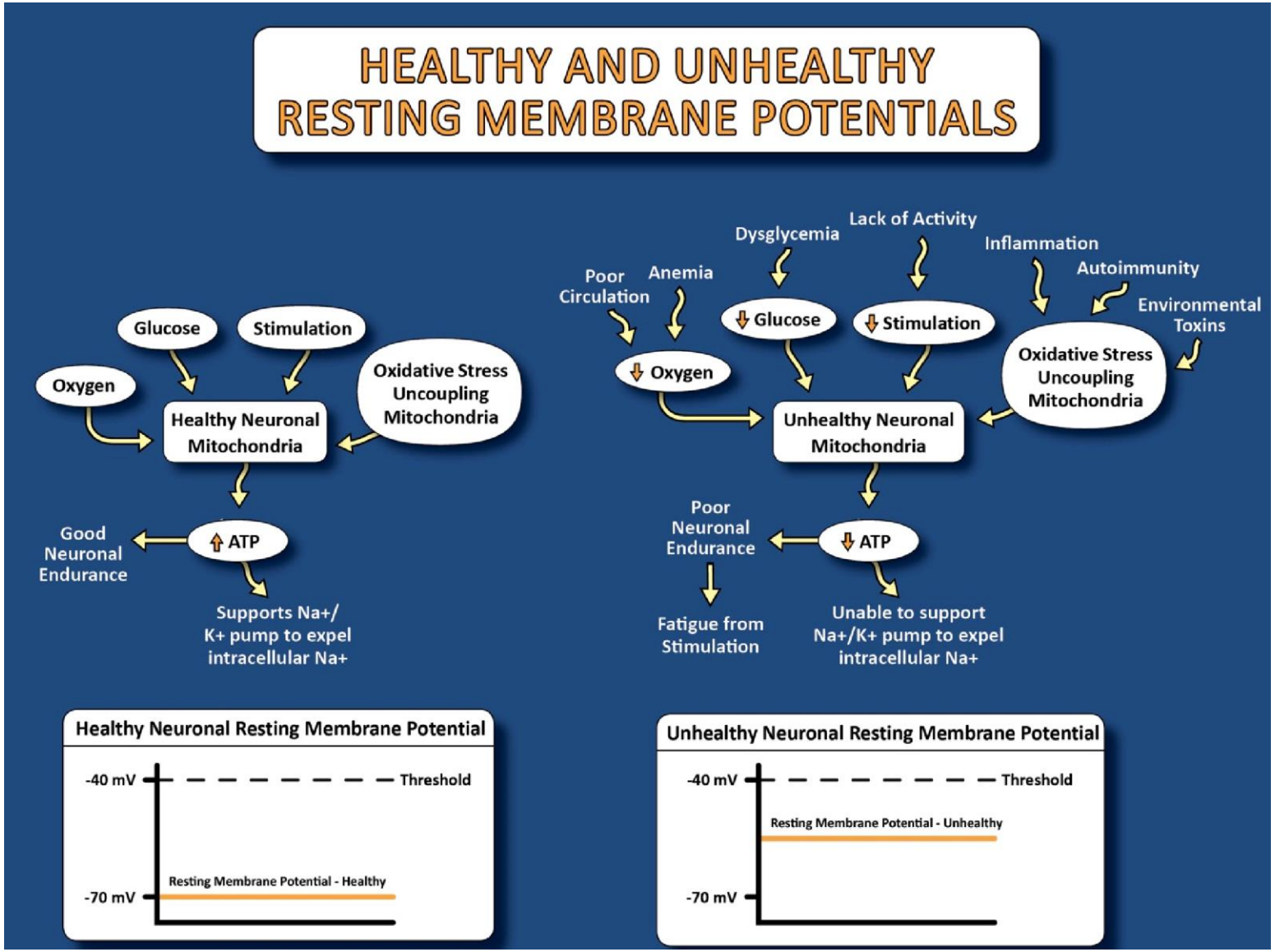
Contributed by Paul Greengard, December 2, 1999

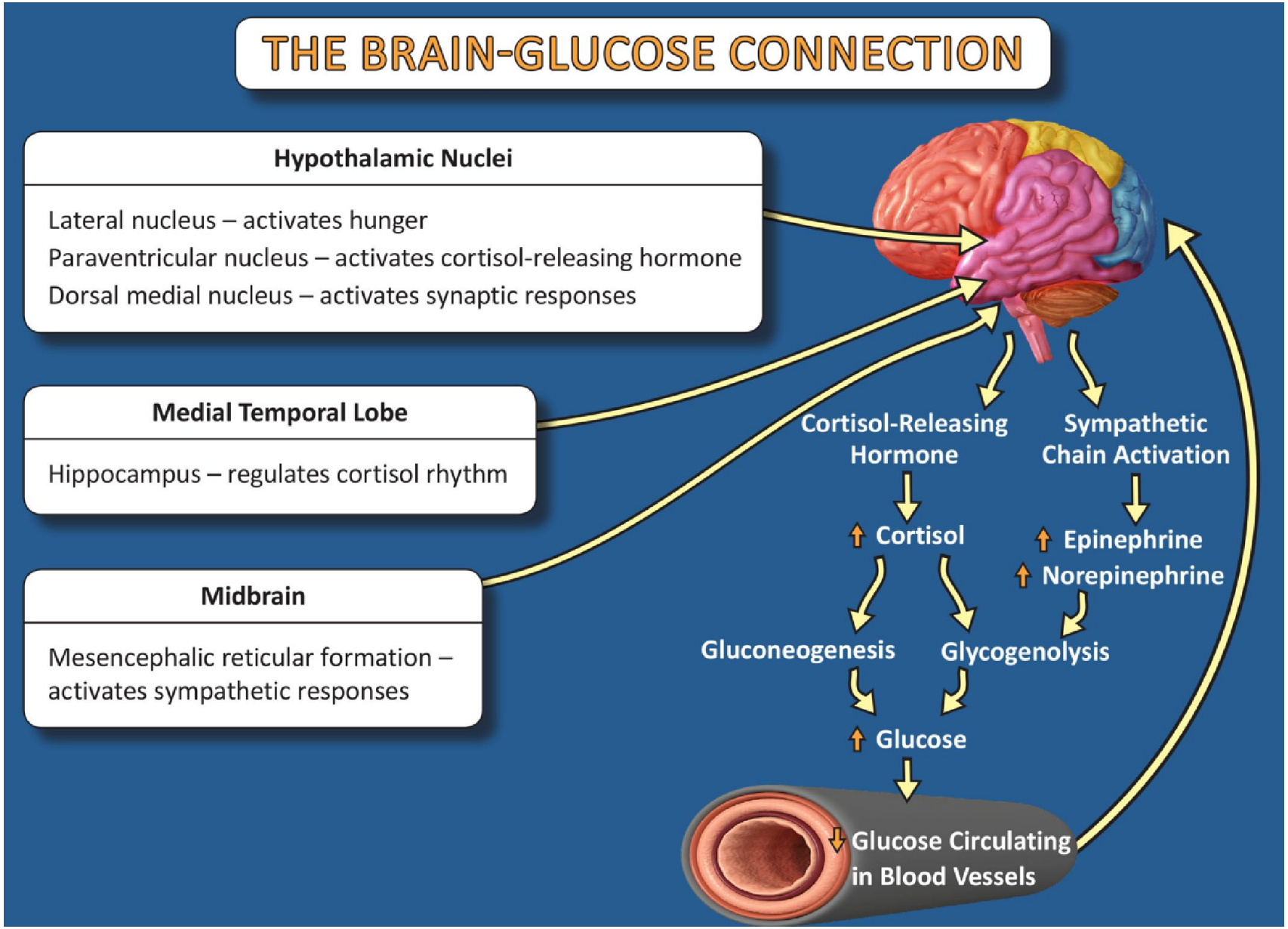
Memory

- ## Working memory (Frontal – Parietal Lobes)
  - The ability to actively hold information in the mind needed to do complex tasks such as reasoning, comprehension and learning. Working memory tasks are those that require the goal-oriented active monitoring or manipulation of information or behaviors in the face of interfering processes and distractions.
- ## Declarative memory (Medial temporal Lobe)
  - It refers to memories which can be consciously recalled such as facts and events. Its counterpart is known as non-declarative, or procedural memory, which refers to unconscious memories such as skills (e.g. learning to ride a bicycle). Declarative memory can be divided into two categories: *episodic memory,* which stores specific personal experiences, and *semantic memory,* which stores factual information.
- ## Procedural memory (Cerebellum)
  - When needed, procedural memories are automatically retrieved and utilized for the execution of the integrated procedures involved in both cognitive and motor skills; from tying shoes to flying an airplane to reading.
- ## Short term memory (Hippocampus)
  - is the capacity for holding a small amount of information in mind in an active, readily available state for a short period of time.



340 page stopped




THE BRAIN-GLUCOSE CONNECTION
Hypothalamic Nuclei
Lateral nucleus – activates hunger
Paraventricular nucleus – activates cortisol-releasing hormone
Dorsal medial nucleus – activates synaptic responses
Medial Temporal Lobe
Hippocampus – regulates cortisol rhythm
Midbrain
Mesencephalic reticular formation – activates sympathetic responses
Cortisol-Releasing Hormone
Sympathetic Chain Activation
Cortisol
Epinephrine
Norepinephrine
Gluconeogenesis
Glycogenolysis
Glucose
Glucose Circulating in Blood Vessels

2. Metabolic/Trophins Loss

This type of AD is usually caused by imbalances in the **endocrine system** (hormones) and **nutrient depletion**, as well as **neurotrophic loss** (brain breaking down faster than it can regrow).

This includes:

- ApoE4 R
- Hormone Imbalances (Vitamin D, Sex and Neuro Steroids, Thyroid)
- Insulin Resistance
- Methylation Problems
- Mitochondrial Damage
- Neurotrophic Loss (atrophy in brain)
- Nutrient Depletio

3. Toxins

The **toxin/infectious** type of AD is more **environmental** and can be caused by:

- ApoE3 (more common)
- Heavy Metals (including amalgams)
- Hormonal Imbalances
- HPA-Axis Imbalances
- Infections (such as mold, Lyme, HSV, active EBV, oral/nasal/gut dysbiosis) R
- Low Zinc/high copper ratio R
- Psychiatric disorders (correlation)
- Toxins (including pesticides, NSAIDS, PPIs, statins, and other drugs) R

This usually occurs after 80 y/o.

Implications Of Normal Or Higher ApoE Activity

Benefits of high ApoE levels (e.g. ApoE2/ApoE3):

1. **Antibacterial Effects** - ApoE can act as an antibacterial - can kill Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*) bacteria R R
2. **Antiparasitic Effects** - ApoE can modulate parasites (e.g. *Plasmodium* spp) R
3. **Antiviral Effects** - ApoE can modulate **Herpes Simplex Virus-1** (HSV-1), **Hepatitis C virus** (HCV), and **HIV** R R
4. **Bigger Brain** - ApoE2 is associated with greater cortical thickness R
5. **Clearance of Amyloid-beta** - as seen in ApoE3 individuals R
6. **Cholesterol Efflux** R
7. **Decreased Risk Of Depression** R
8. **Higher ATP levels in brain** R
9. **Neuroprotection Against Cognitive Decline** - ApoE2 has lower associations to Alzheimer's Disease R R
10. **Longevity** - ApoE2 is associated with increased longevity R
11. **Protection Against Tau Tangles** R
12. **Stimulation of Neurite Growth** (such as **BDNF**) R

https://mybiohack.com/blog/apoe-increase-alzheimers-genetics

3. Toxins

The **toxin/infectious** type of AD is more **environmental** and can be caused by:

- ApoE3 (more common)
- Heavy Metals (including amalgams)
- Hormonal Imbalances
- HPA-Axis Imbalances
- Infections (such as mold, Lyme, HSV, active EBV, oral/nasal/gut dysbiosis) R
- Low Zinc/high copper ratio R
- Psychiatric disorders (correlation)
- Toxins (including pesticides, NSAIDS, PPIs, statins, and other drugs) R

This usually occurs after 80 y/o.

Supplements on the ReCODE program that help with cognition and inflammation:

- ALCAR
- Citicoline
- Coffee fruit extract
- DHA/EPA (fish oil or krill oil) R
- Nicotinamide riboside (combines well with resveratrol)
- Pantothenic acid (use B6/B12/folate if homocysteine ≥ 6)
- PQQ
- Resveratrol
- Ubiquinol
- Vitamin B1
- Vitamin C
- Vitamin D
- Vitamin E
- Vitamin K2

Herbs on the ReCODE program that help with cognition and inflammation: R
- Ashwagandha
- Bacopa
- Gotu Kola
- Guduchi
- Guggul (or activated charcoal)
- Lion's Mane
- Rhodiola
- Skullcap
- Triphala (**Amalaki** + **Haritaki** + **Bibhitaki**)

Also, pro-resolving mediators (like SPM Active), such as **resolvins**, **protectins**, and **maresins** will also help against inflammation. R

Treatment

Treatment is different for everyone, but simply goes like this:

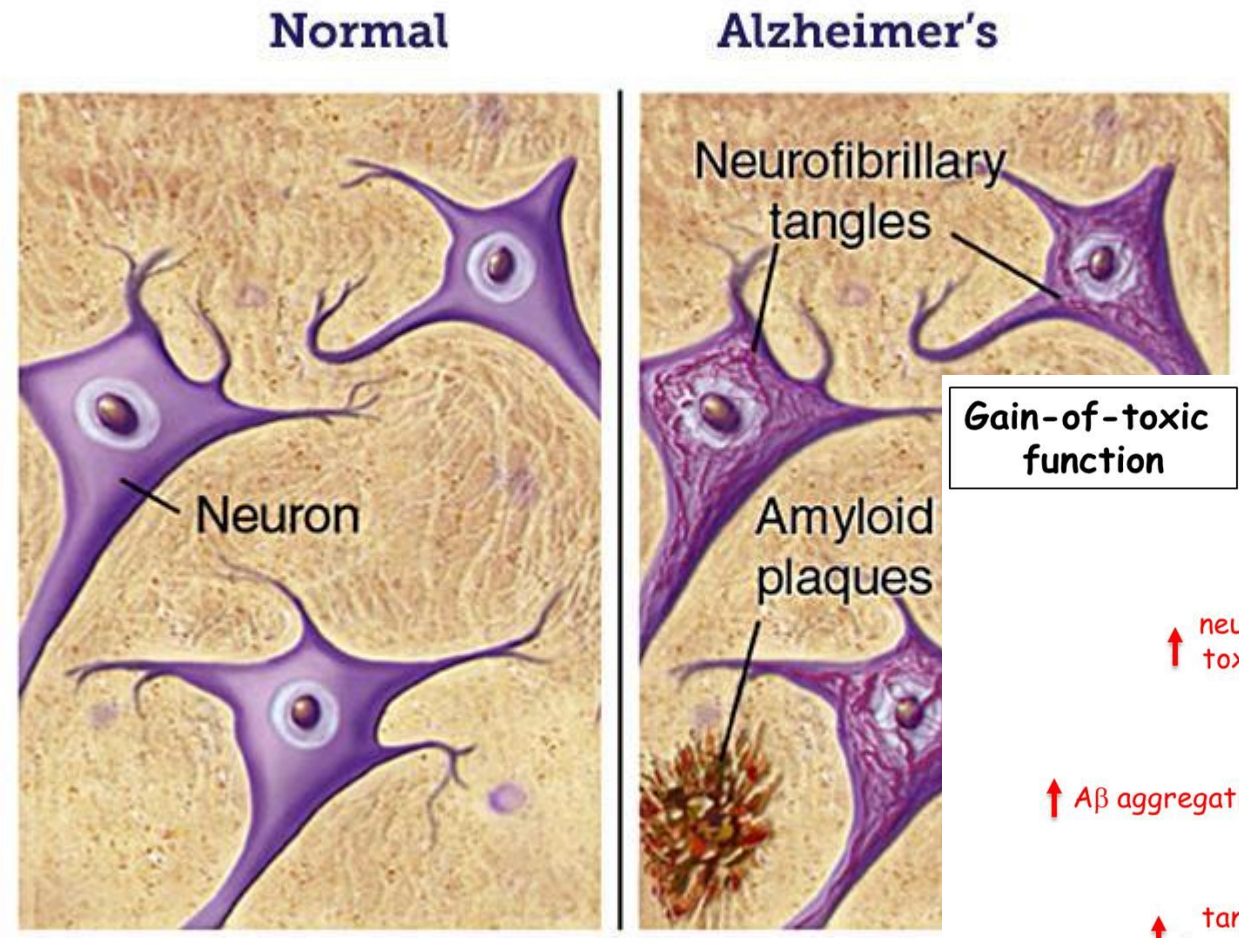
1.Fixing the **underlying cause** (infections, toxin exposure, chronic inflammation)
2.Changing lifestyle to **increase neurotrophic factors** and proper autophagy
3.Using diet and treatments to **restore biomes** and **insulin sensitivity** in the brain/body
4.Optimizing hormones and other **biomarkers** using bioidentical hormones, supplements, and herbs

Here are all the functions that the ReCODE protocol aims to accomplish:

- Increase **α-cleavage**
- Increase **ADNP**
- Increase **autophagy**
- Improve axoplasmic transport
- Increase **BDNF**
- Increase **cAMP**
- Increase **GABA**
- Increase **glutathione**
- Increase **IDE**
- Increase **insulin** sensitivity
- Improve **LTP**
- Increase **NGF**
- Increase microglial clearance of **Aβ**
- Increase **netrin-1**
- Increase **neprilysin**
- Increase **PPAR-γ**
- Increase phagocytosis index
- Increase **PP2A**
- Increase resolvins
- Increase **SirT1**
- Increase synaptoblastic signaling
- Increase **telomere** length
- Improve vascularization
- Increase **VIP**

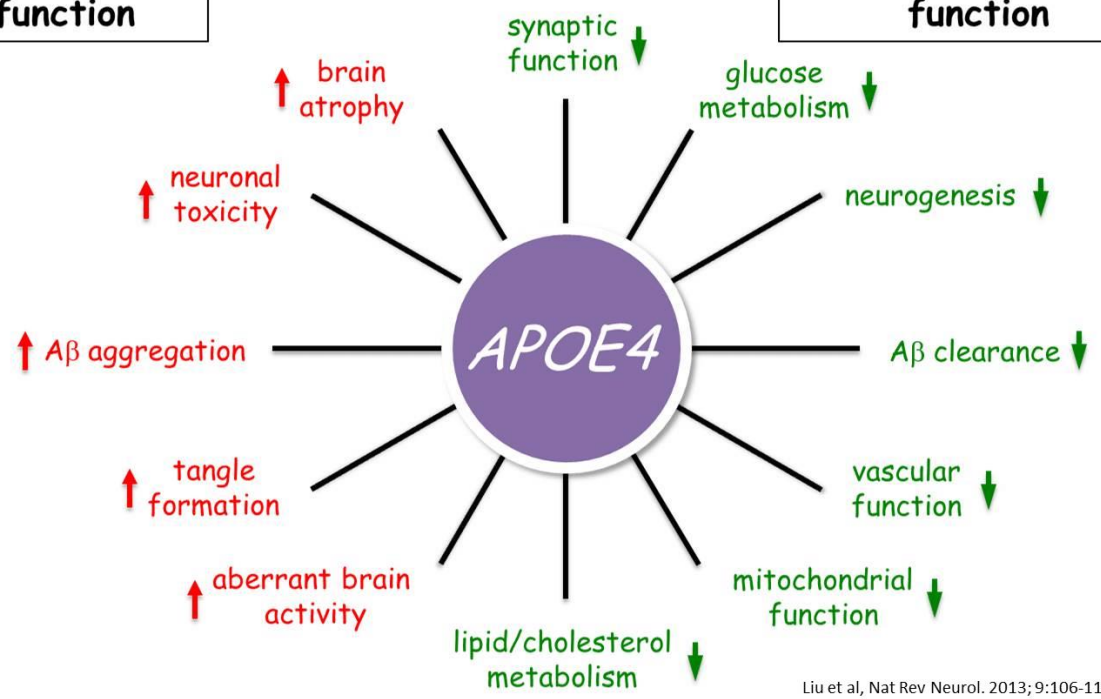
- Increase **vitamin D** signaling
- Optimize all **metals**
- Optimize cholinergic neurotransmission
- Optimize **cortisol**
- Optimize detoxification
- Optimize **DHEA**
- Optimize E2:P (estradiol to progesterone) ratio
- Optimize **estradiol**
- Optimize **free T3**
- Optimize **free T4**
- Optimize insulin secretion and signaling
- Optimize **leptin**
- Optimize **mitochondrial** function and biogenesis
- Optimize **pregnenolone**
- Optimize **progesterone**
- Optimize stem-cell-mediated brain repair
- Optimize synaptic components
- Optimize **testosterone**
- Optimize **TSH**
- Reduce amyloid-beta oligomerization
- Reduce **APPβ**-cleavage
- Reduce **caspase-6** cleavage
- Reduce **caspase-3** cleavage
- Reduce **γ-cleavage**
- Reduce glial scarring
- Reduce **homocysteine**
- Reduce inflammation
- Reduce **mTOR** activation R
- Reduce **NF-κB**
- Reduce phospho-tau
- Reduce oxidative damage and optimize **ROS**
- Reduce synaptoclastic signaling

Normal vs. Alzheimer's Diseased Brain

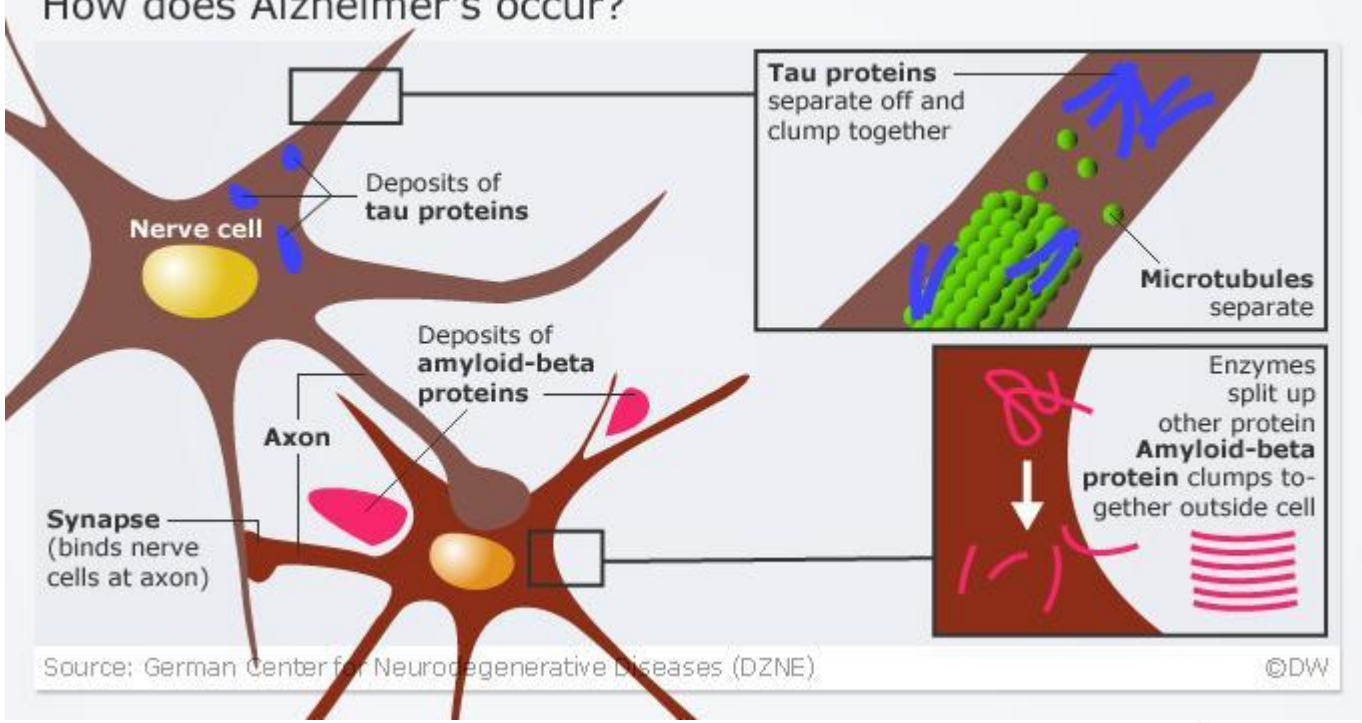


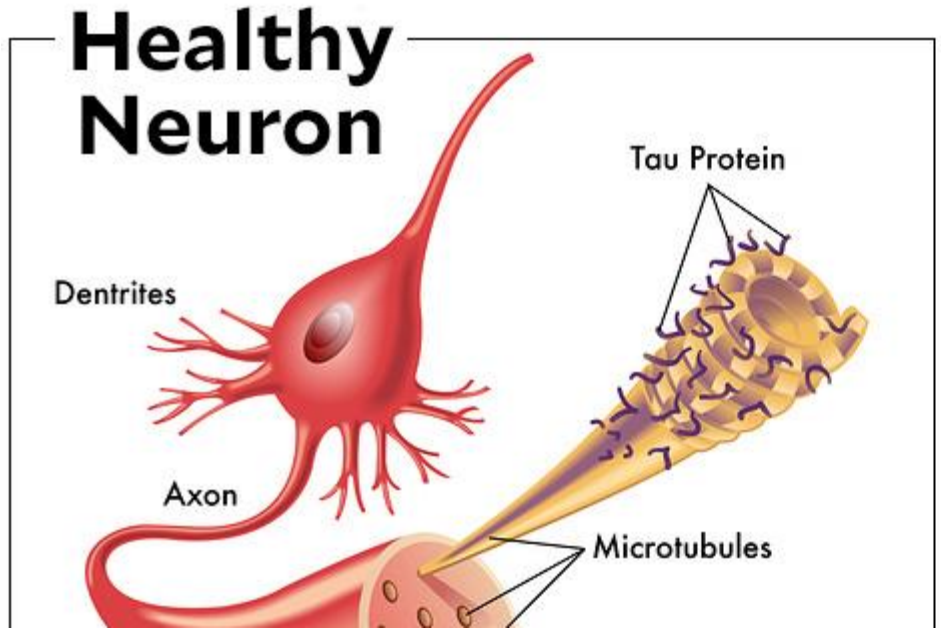
Gain-of-toxic function

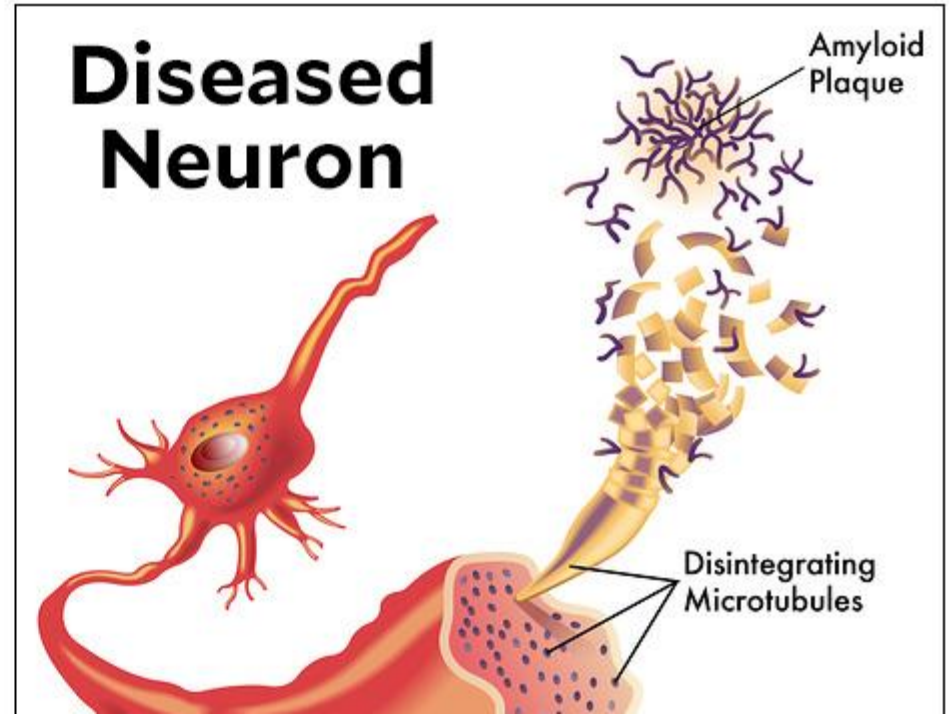
Loss-of-physiological function

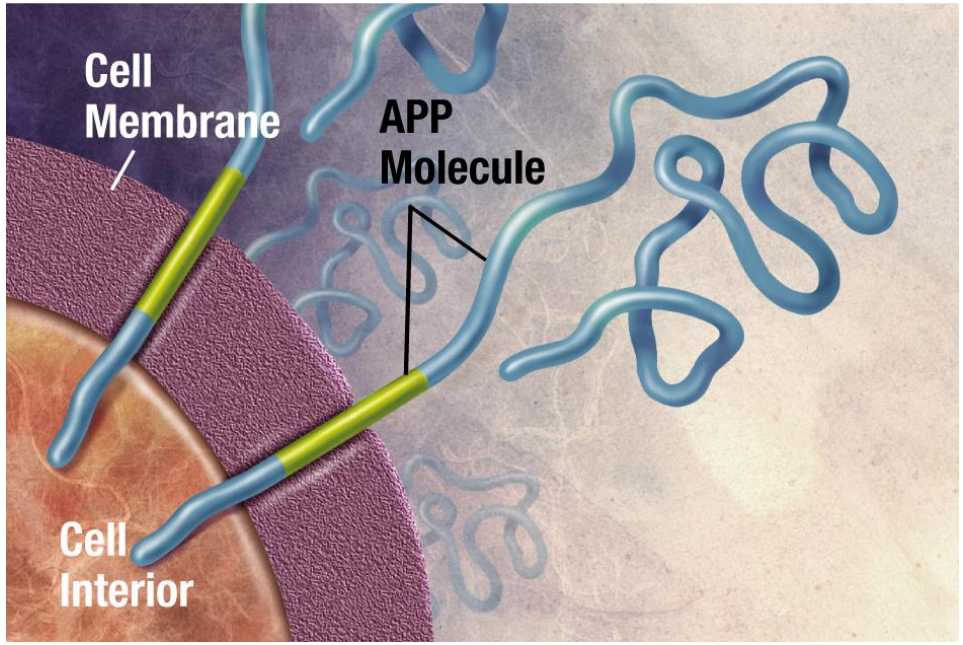


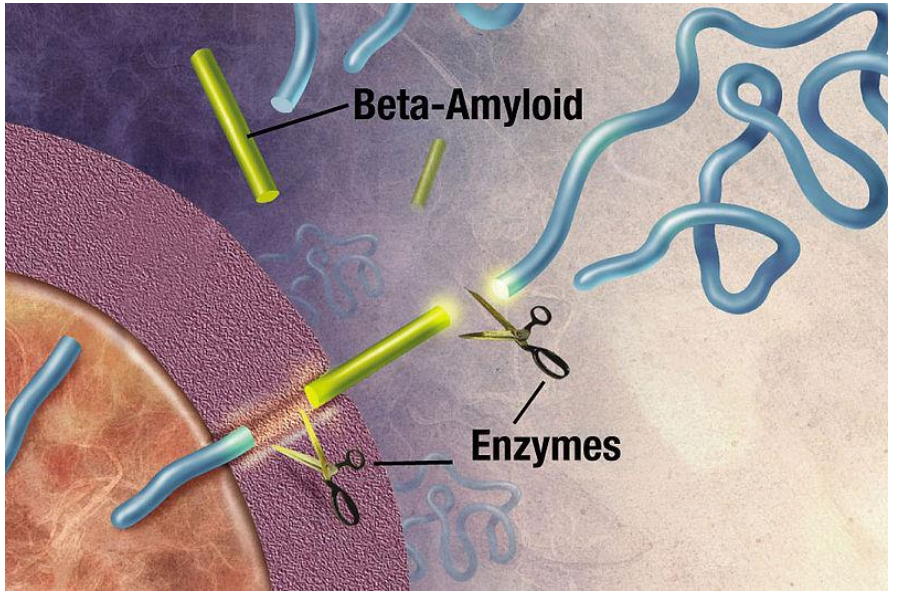
Liu et al, Nat Rev Neurol. 2013; 9:106-118.


How does Alzheimer's occur?
Tau proteins separate off and clump together
Deposits of tau proteins
Nerve cell
Microtubules separate
Deposits of amyloid-beta proteins
Axon
Enzymes split up other protein Amyloid-beta protein clumps together outside cell
Synapse (binds nerve cells at axon)
Source: German Center for Neurodegenerative Diseases (DZNE)
©DW


Healthy Neuron
Tau Protein
Dentrites
Axon
Microtubules


Diseased Neuron
Amyloid Plaque
Disintegrating Microtubules


Cell
Membrane
APP
Molecule
Cell
Interior


Beta-Amyloid
Enzymes

[redacted]

Provider:

Hugh Wegwerth DC

[redacted]

Ordering Provider: Hugh Wegwerth

[redacted]

Age: 74 **Gender:** F

Menopausal Status:
Post-Menopause

,

Sample Collection [redacted]
Morning
Noon
Evening
Night
Samples Arrived
Results Reported

	Saliva Hormone Test	04/14/2017	01/25/2018	Units	L	WR	H	Reference Range
HORMONES	Estrone (E1)*	7.22	24.40	pg/ml		◆		<47.0 post menopausal
	Estradiol (E2)	1.40	1.60	pg/ml		◆		1.5-7.2 supplementation
	Estriol (E3)*	18.38	30.30	pg/ml	↓			67.0-708.0 supplementation
	EQ (E3 / (E1 + E2))		1.17			◆		low <1.0; WR >=1.0; optimal >1.5
	Progesterone (Pg)	135.73	1220.00	pg/ml		◆		500-3000 supplementation
	Ratio of Pg/E2**		762.50				↑	200-600 pre; post with supplementation
	Testosterone*	28.40	47.80	pg/ml		◆		30.0-60.0 female, supplementation
S	DHEA*	81.18	192.00	pg/ml		◆		106.0-300.0 female

iPad 5:22 PM 32%

wegwerth, hugh
11/09/1973 43y M

Allergies

Labs Problems

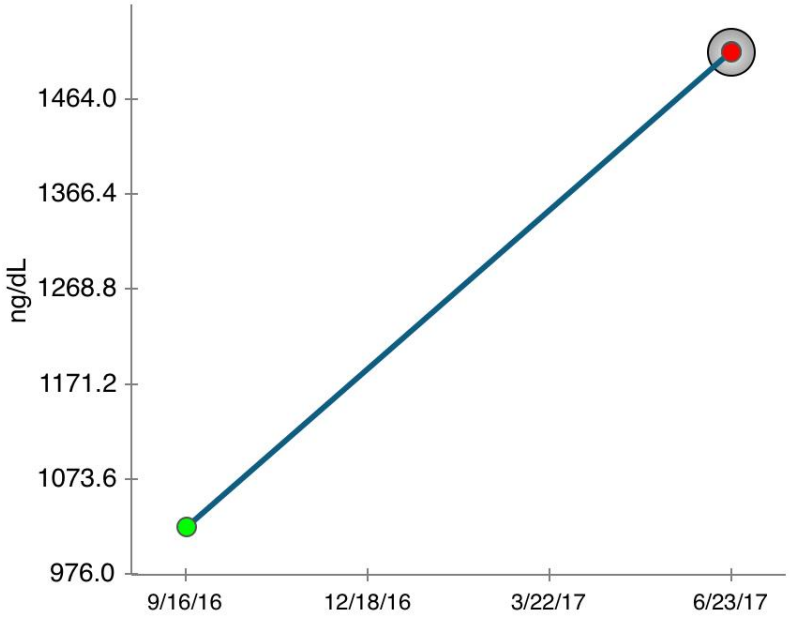
Collected: 6/23/17,
CBC (INCLUDES
HS CRP
DHEA SULFATE
INSULIN
PROGESTERON
ESTRADIOL
SEX HORMONE
T3, FREE
VITAMIN D,25-O
HEMOGLOBIN A
VITAMIN A (RET
TESTOSTERO

Collected: 9/16/16,
LIPID PANEL
URIC ACID
COMPREHENSI

Clinical Notes

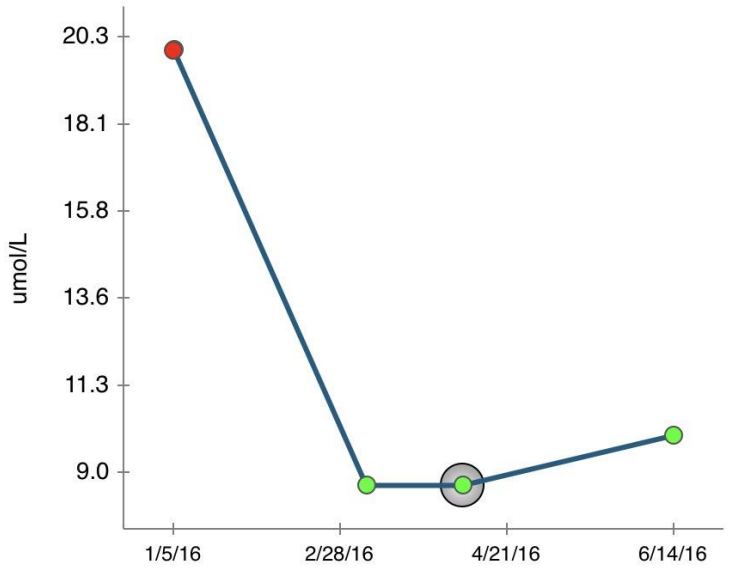
Lab Detail

Lab Flowsheet



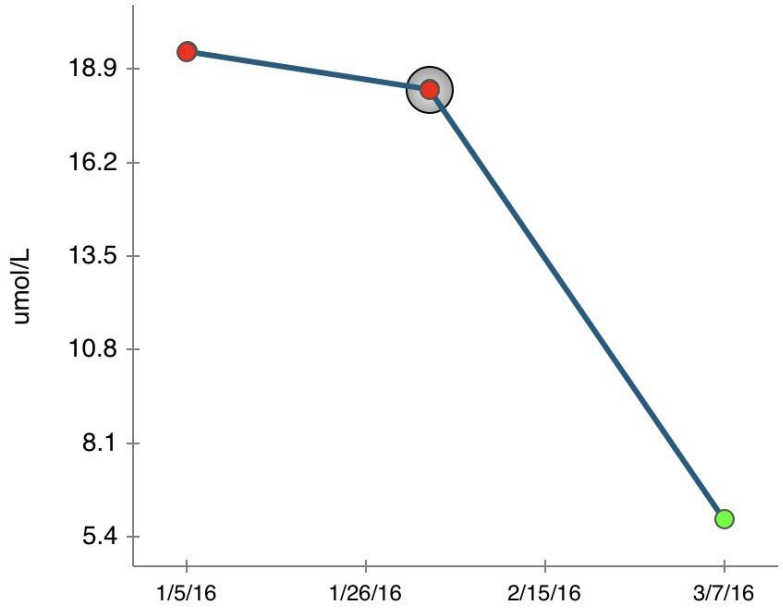
6/23/17, 9:39 AM	*1512 H*	
	250-1100 ng/dL	
9/16/16, 10:57 AM	1024	
	250-1100 ng/dL	

Lab Detail **Lab Flowsheet**

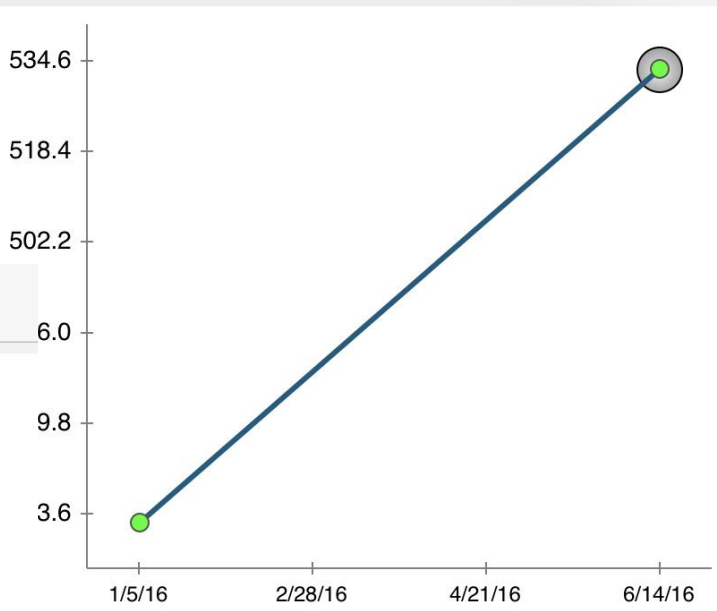


6/14/16, 8:03 AM	10.0 <11.4 umol/L	
4/7/16, 9:10 AM	8.7 <11.4 umol/L	✓
3/7/16, 9:06 AM	8.7 <11.4 umol/L	
⚠ *1/5/16, 8:33 AM*	*20.0 H* <11.4 umol/L	

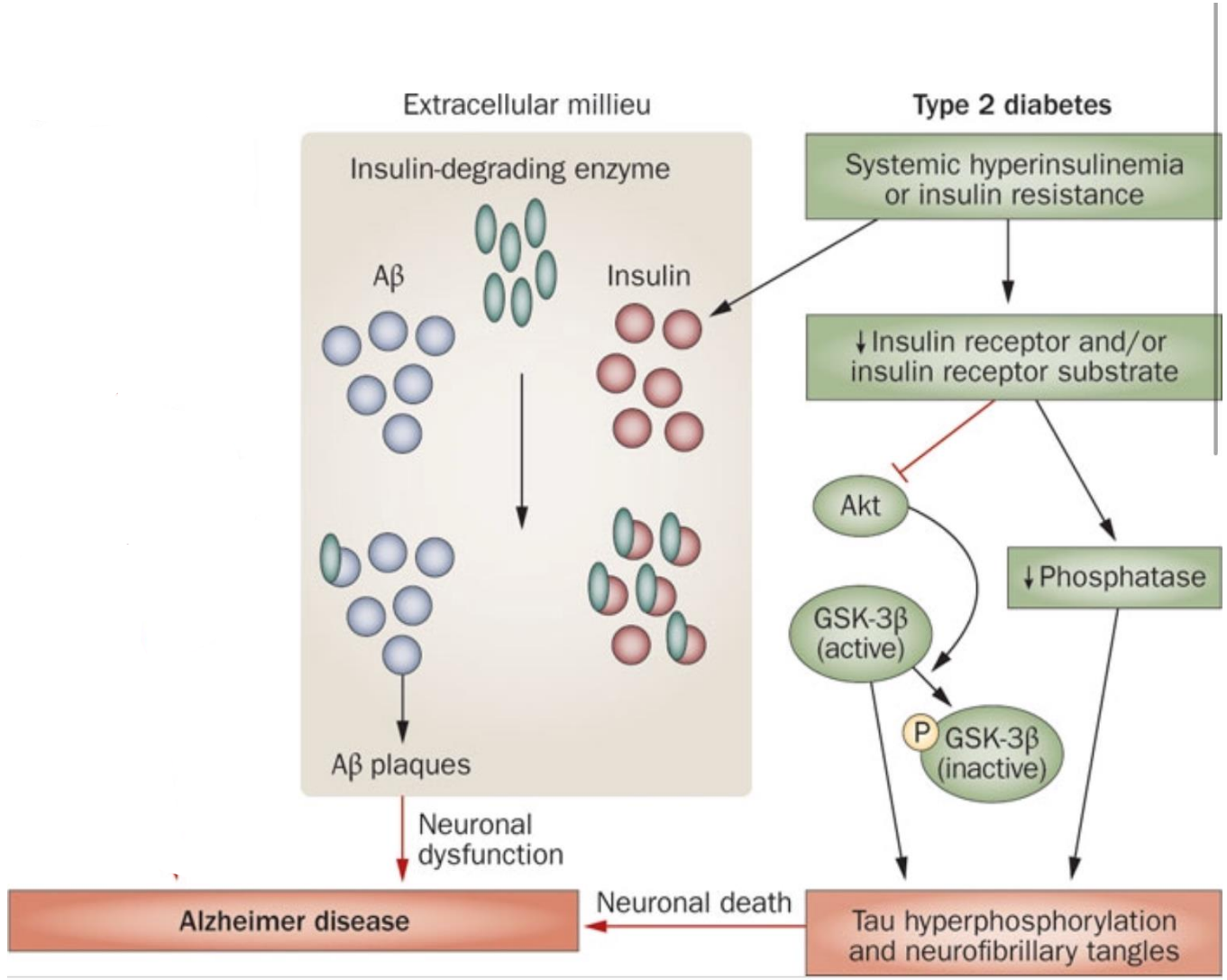
Lab Detail **Lab Flowsheet**



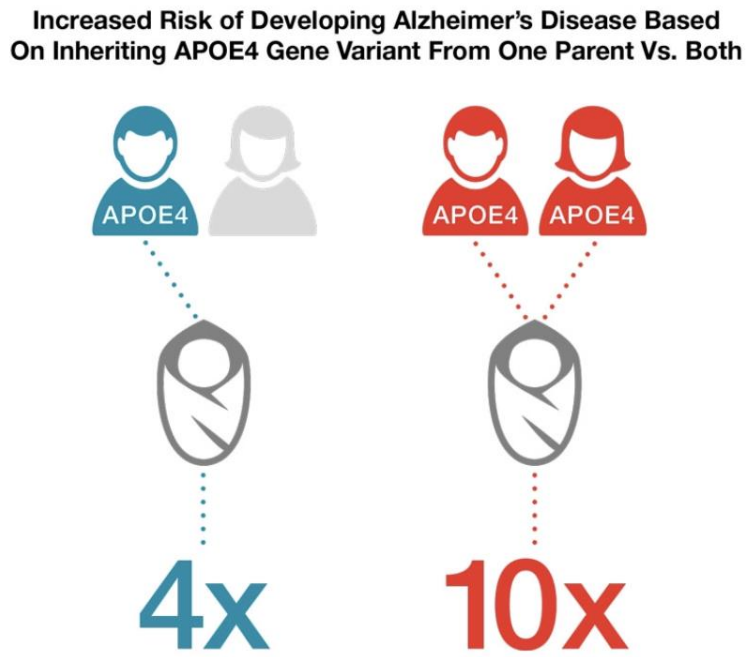
3/7/16, 9:00 AM	5.9 <10.4 umol/L	
⚠ *2/2/16, 8:14 AM*	*18.3 H* <10.4 umol/L	✓
⚠ *1/5/16, 8:23 AM*	*19.4 H* <10.4 umol/L	



/14/16, 8:03 AM	533 250-1100 ng/dL	✓
/5/16, 8:33 AM	452 250-1100 ng/dL	


Extracellular millieu
Type 2 diabetes
Insulin-degrading enzyme
Systemic hyperinsulinemia or insulin resistance
Aβ
Insulin
↓Insulin receptor and/or insulin receptor substrate
Akt
↓Phosphatase
GSK-3β (active)
P GSK-3β (inactive)
Aβ plaques
Neuronal dysfunction
Alzheimer disease
Neuronal death
Tau hyperphosphorylation and neurofibrillary tangles

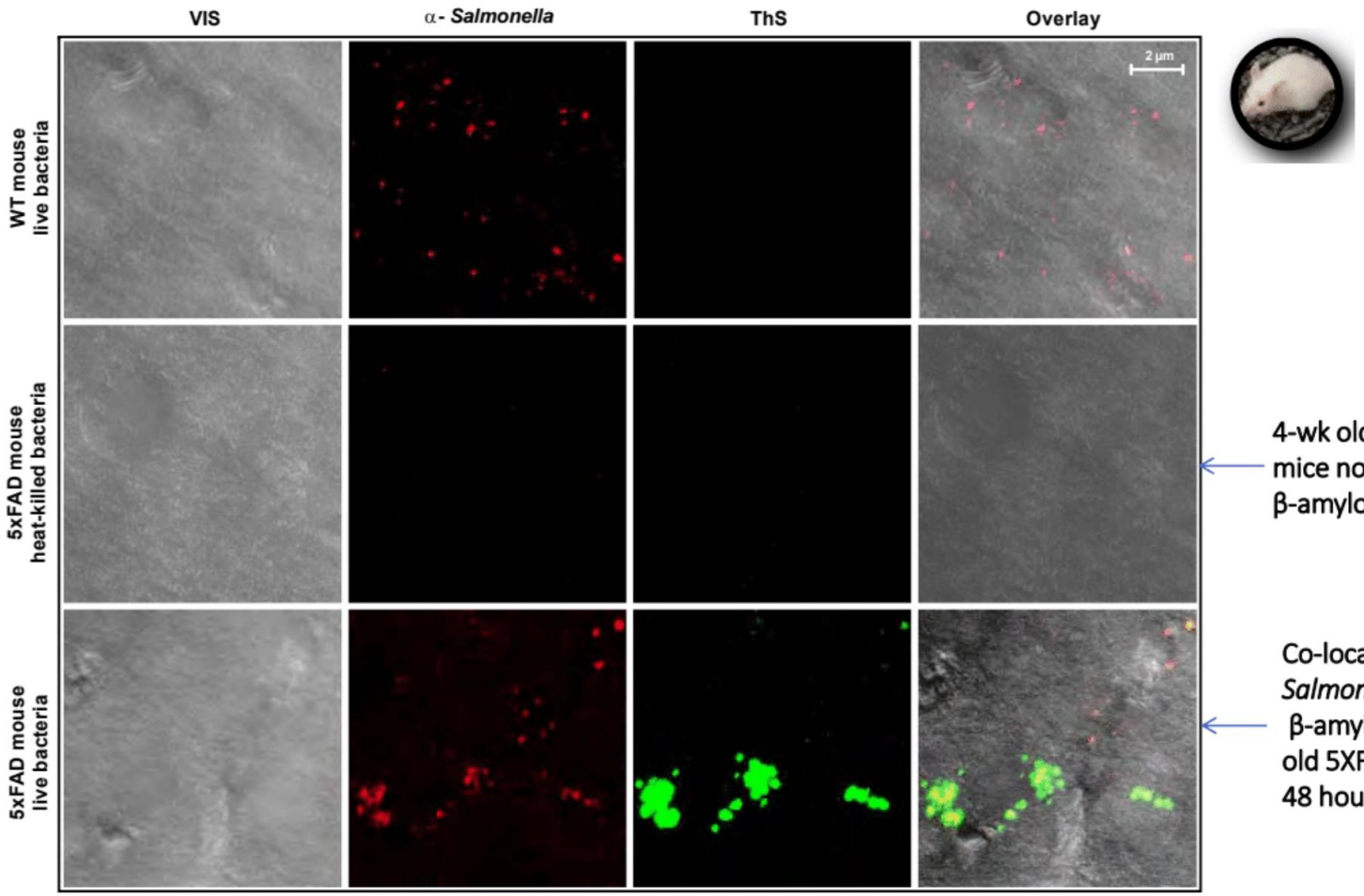
Genetic factors



Several genes are now known to confer risk – or in some cases, protect against – Alzheimer's disease. This means that Alzheimer's can run in families. For example, inheriting one copy of the APOE4 gene variant, which is found in about a quarter of the population, will cause up to four times the normal risk of developing Alzheimer's. Inheriting two copies (one from each parent) will raise risk up to ten times normal levels.

Known genetic factors account for a small percentage of all Alzheimer's cases, but current research supported by CAF and others indicates far more genetic influence than was previously known. Many candidate genes are currently being discovered and studied for their role in the disease. The genes we know about account for a larger percentage of early-onset cases. The rare Presenilin 1 and 2 genes, for instance, virtually guarantee development of early-onset Alzheimer's.

Bacterial brain infection rapidly triggers plaques in young mice
Plaques trap bacteria to protect the brain



4-wk old 5XFAD mice normally lack β-amyloid deposits

Co-localization of *Salmonella* and β-amyloid in 4-wk old 5XFAD mice 48 hours after infection

, Moir and Tanzi

J Geriatr Psychiatry Neurol. 2010 Mar;23(1):49-53. doi: 10.1177/0891988709351832. Epub 2009 Nov 20.

Decreased C-reactive protein levels in Alzheimer disease.

O'Bryant SE[1], Waring SC, Hobson V, Hall JR, Moore CB, Bottiglieri T, Massman P, Diaz-Arrastia R.

Author information

Abstract

C-reactive protein (CRP) is an acute-phase reactant that has been found to be associated with Alzheimer disease (AD) in histopathological and longitudinal studies; however, little data exist regarding serum CRP levels in patients with established AD. The current study evaluated CRP levels in 192 patients diagnosed with probable AD (mean age = 75.8 +/- 8.2 years; 50% female) as compared to 174 nondemented controls (mean age = 70.6 +/- 8.2 years; 63% female). Mean CRP levels were found to be significantly decreased in AD (2.9 microg/mL) versus controls (4.9 microg/mL; P = .003). In adjusted models, elevated CRP significantly predicted poorer (elevated) Clinical Dementia Rating Scale sum of boxes (CDR SB) scores in patients with AD. In controls, CRP was negatively associated with Mini-Mental State Examination (MMSE) scores and positively associated with CDR SB scores. These findings, together with previously published results, are consistent with the hypothesis that midlife elevations in CRP are associated with increased risk of AD development though elevated CRP levels are not useful for prediction in the immediate prodrome years before AD becomes clinically manifest. However, for a subgroup of patients with AD, elevated CRP continues to predict increased dementia severity suggestive of a possible proinflammatory endophenotype in AD.

PMID: 19933496 PMCID: PMC3204581 DOI: 10.1177/0891988709351832

[Indexed for MEDLINE] Free PMC Article

Alzheimers Dement. 2009 Jul;5(4):318-23. doi: 10.1016/j.jalz.2009.04.1230.

Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old.

Kravitz BA[1], Corrada MM, Kawas CH.

Author information

Abstract

BACKGROUND: C-reactive protein (CRP) is a nonspecific marker of inflammation that is increased in the brain and serum of patients with Alzheimer's disease (AD), and has been associated with increased risk of developing dementia. Inflammation increases with age, and the number of people reaching age 90 years and older is growing, making the association between inflammation and dementia increasingly relevant. Using a cross-sectional design, we examined whether high levels of serum CRP are associated with increased odds of prevalent dementia in the oldest-old.

METHODS: Serum CRP levels of 305 participants (mean age +/- standard deviation, 94.3 +/- 2.9 years) from the 90+ Study, a longitudinal cohort study of people aged 90 years and older, were evaluated with respect to all-cause dementia. Levels of CRP were divided into three categories: undetectable (<0.5 mg/dL), detectable (0.5-0.7 mg/dL), and elevated (> or =0.8 mg/dL). Odds ratios (ORs) were calculated using logistic regression, and were adjusted for covariates.

RESULTS: Relative to participants with undetectable CRP levels, participants with detectable or elevated CRP levels had increased odds of all-cause dementia (detectable: OR, 3.0; 95% confidence interval, 1.2-7.3; elevated: OR, 5.0; 95% confidence interval, 1.9-12.9). When participants were subdivided by gender, significantly increased ORs were seen only in women.

CONCLUSIONS: In the oldest-old, high CRP levels are associated with increased odds of all-cause dementia, particularly in women. Prospective studies are necessary to confirm whether increased CRP levels are associated with an increased risk of developing dementia in this age group.

PMID: 19560102 PMCID: PMC2740472 DOI: 10.1016/j.jalz.2009.04.1230

Front Aging Neurosci. 2015 Oct 29;7:209. doi: 10.3389/fnagi.2015.00209. eCollection 2015.

C-Reactive Protein, Advanced Glycation End Products, and Their Receptor in Type 2 Diabetic, Elderly Patients with Mild Cognitive Impairment.

Gorska-Ciebiada M[1], Saryusz-Wolska M[1], Borkowska A[1], Ciebiada M[2], Loba J[1].

Author information

Abstract

OBJECTIVE: The aim of the study was to evaluate serum levels of advanced glycation end products (AGEs), receptor for advanced glycation end products (RAGE), and C-reactive protein (CRP) in elderly patients with type 2 diabetes mellitus with and without mild cognitive impairment (MCI) and to determine the predictors (including AGEs, RAGE, and CRP levels) of having MCI in elderly patients with type 2 diabetes.

METHODS: Two hundred seventy-six diabetics elders were screened for MCI (using the Montreal Cognitive Assessment: MoCA score). Data of biochemical parameters and biomarkers were collected.

RESULTS: Serum AGEs, RAGE, and CRP levels were significantly increased in MCI patients compared to controls. In group of patients with MCI, serum RAGE level was positively correlated with AGEs level and with CRP level. RAGE, AGEs, and CRP concentrations were positively correlated with HbA1c levels and negatively correlated with MoCA score. The univariate logistic regression models revealed that variables, which increased the likelihood of diagnosis of MCI in elderly patients with type 2 diabetes were higher levels of HbA1c, RAGE, AGEs, CRP, TG, lower level of HDL cholesterol, previous CVD, HA, or use of HA drugs, hyperlipidemia, retinopathy, nephropathy, increased number of co-morbidities, older age, and less years of formal education. HA or use of HA drugs, previous CVD, higher level of RAGE and CRP, older age and less years of formal education are the factors increasing the likelihood of having MCI in elderly patients with type 2 diabetes in multivariable model.

CONCLUSION: In summary, serum AGEs, RAGE, and CRP are increased in the circulation of MCI elderly diabetic patients compared to controls. A larger population-based prospective study needs to be performed to further confirm the relationship between AGEs, RAGE, and the cognitive decline or progress to dementia.

KEYWORDS: AGEs; RAGE; cognitive impairment; diabetes; elderly

PMID: 26578953 PMCID: PMC4625092 DOI: 10.3389/fnagi.2015.00209

Free PMC Article

Stroke. 2005 Dec;36(12):2637-41. Epub 2005 Nov 3.

Fibrinogen is associated with an increased risk of Alzheimer disease and vascular dementia.

van Oijen M[1], Witteman JC, Hofman A, Koudstaal PJ, Breteler MM.

Author information

Abstract

BACKGROUND AND PURPOSE: Vascular and inflammatory factors may play an important role in the pathogenesis of dementia. Studies reported an association between plasma levels of inflammation markers and the risk of dementia. Both fibrinogen and C-reactive protein are considered inflammatory markers. Fibrinogen also has important hemostatic properties. We investigated the association of fibrinogen and C-reactive protein with dementia.

METHODS: The study was based on the prospective population-based Rotterdam Study. Fibrinogen was measured in a random sample of 2835 persons. High-sensitivity C-reactive protein was measured in the total cohort of 6713 persons. We identified 395 incident dementia cases during follow-up (mean, 5.7 years). We estimated the associations of fibrinogen and C-reactive protein with dementia using Cox proportional hazard models.

RESULTS: Persons with higher levels of fibrinogen had an increased risk of dementia. The hazard ratio for dementia per SD increase of fibrinogen was 1.26 (95% CI, 1.11 to 1.44), adjusted for age and gender, and 1.30 (95% CI, 1.13 to 1.50) after additional adjustment for cardiovascular factors and stroke. For Alzheimer disease, the adjusted hazard ratio was 1.25 (95% CI, 1.04 to 1.49), and for vascular dementia it was 1.76 (95% CI, 1.34 to 2.30). High levels of C-reactive protein were not associated with an increased risk of dementia.

CONCLUSIONS: High fibrinogen levels were associated with an increased risk of both Alzheimer disease and vascular dementia, but levels of C-reactive protein were not. This suggests that the increased risk of dementia associated with fibrinogen is because of the hemostatic rather than the inflammatory properties of fibrinogen.

PMID: 16269641 DOI: 10.1161/01.STR.0000189721.31432.26

Arch Neurol. 2004 May;61(5):668-72.

Inflammatory proteins in plasma and the risk of dementia: the rotterdam study.

Engelhart MJ[1], Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, Stijnen T, Hofman A, Witteman JC, Breteler MM.

Author information

Abstract

BACKGROUND: Increased levels of inflammatory proteins have been found in the brains and plasma samples of patients with dementia. Whether the levels of inflammatory proteins in plasma samples are elevated before clinical onset of dementia is unclear.

OBJECTIVE: To determine whether high levels of inflammatory proteins in plasma samples are associated with an increased risk of dementia.

DESIGN AND SETTING: A case-cohort study within the Rotterdam Study, a population-based prospective cohort study in the Netherlands.

PARTICIPANTS: The source population comprises 6713 subjects who, at baseline (1990-1993), were free of dementia and underwent venipuncture. From these, we selected both a random subcohort of 727 subjects and 188 cases who had developed dementia at follow-up.

MAIN OUTCOME MEASURES: The associations between plasma levels of alpha1-antichymotrypsin, C-reactive protein, interleukin 6, the soluble forms of intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 and the risk of dementia were examined using the Cox proportional hazards regression models.

RESULTS: High levels of alpha1-antichymotrypsin, interleukin 6, and, to a lesser extent, C-reactive protein were associated with an increased risk of dementia; rate ratios per standard deviation increase were 1.49 (95% confidence interval, 1.23-1.81), 1.28 (95% confidence interval, 1.06-1.55), and 1.12 (95% confidence interval, 0.99-1.25), respectively. Similar associations were observed for Alzheimer disease, whereas rate ratios of vascular dementia were higher for alpha1-antichymotrypsin and C-reactive protein. Soluble forms of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 were not associated with dementia.

CONCLUSION: Plasma levels of inflammatory proteins are increased before clinical onset of dementia, Alzheimer disease, and vascular dementia.

Neurology. 2004 Oct 12;63(7):1187-92.

Hyperinsulinemia and risk of Alzheimer disease.

Luchsinger JA[1], Tang MX, Shea S, Mayeux R.

Author information

Abstract

OBJECTIVE: To explore the association between fasting insulin levels and dementia.

METHODS: Fasting insulin levels were measured from frozen sera using solid-phase chemiluminescent enzyme immunoassay in a sample of elderly subjects chosen at random from a cohort of persons aged 65 years and older from northern Manhattan. Dementia was diagnosed using standard methods. Neuropsychiatric testing was available on all subjects at each follow-up interval.

RESULTS: A total of 683 subjects without prevalent dementia were followed for 3,691 person-years and 149 persons developed dementia (137 Alzheimer disease [AD], 6 dementia associated with stroke, 6 other). The risk of AD doubled in the 39% of the sample with hyperinsulinemia (HR = 2.1; 95% CI: 1.5, 2.9) and was highest in people without diabetes. The HR relating presence of hyperinsulinemia or diabetes in 50% of our sample to AD was 2.2 (95% CI: 1.5, 3.1). The risk of AD attributable to the presence of hyperinsulinemia or diabetes was 39%. The HR of AD for the highest quartile of insulin compared to the lowest was 1.7 (95% CI: 1.0, 2.7; p for trend = 0.009). Hyperinsulinemia was also related to a significant decline in memory-related cognitive scores, but not to decline in other cognitive domains.

CONCLUSIONS: Hyperinsulinemia is associated with a higher risk of AD and decline in memory.

PMID: 15477536

[Indexed for MEDLINE]

Clin Interv Aging. 2015 Mar 10;10:549-60. doi: 10.2147/CIA.S74042. eCollection 2015.

Link between type 2 diabetes and Alzheimer's disease: from epidemiology to mechanism and treatment.

Li X[1], Song D[2], Leng SX[3].

Author information

Abstract

The aim of this paper is to provide a comprehensive review of the epidemiological evidence linking type 2 diabetes mellitus and its related conditions, including obesity, hyperinsulinemia, and metabolic syndrome, to Alzheimer's disease (AD). Several mechanisms could help to explain this proposed link; however, our focus is on insulin resistance and deficiency. Studies have shown that insulin resistance and deficiency can interact with amyloid-β protein and tau protein phosphorylation, each leading to the onset and development of AD. Based on those epidemiological data and basic research, it was recently proposed that AD can be considered as "type 3 diabetes". Special attention has been paid to determining whether antidiabetic agents might be effective in treating AD. There has been much research both experimental and clinical on this topic. We mainly discuss the clinical trials on insulin, metformin, thiazolidinediones, glucagon-like peptide-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors in the treatment of AD. Although the results of these trials seem to be contradictory, this approach is also full of promise. It is worth mentioning that the therapeutic effects of these drugs are influenced by the apolipoprotein E (APOE)-ε4 genotype. Patients without the APOE-ε4 allele showed better treatment effects than those with this allele.

KEYWORDS: Alzheimer's disease; insulin; type 2 diabetes mellitus

Comment in

Importance of hypoglycemia on the risk of Alzheimer's disease in elderly subjects with diabetes mellitus. [Clin Interv Aging. 2015]

Diabetes Care. 2013 Sep;36(9):2600-6. doi: 10.2337/dc12-2158. Epub 2013 Mar 20.

Type 2 diabetes and 10-year risk of dementia and cognitive impairment among older Mexican Americans.

Mayeda ER[1], Haan MN, Kanaya AM, Yaffe K, Neuhaus J.

Author information

Abstract

OBJECTIVE: Type 2 diabetes has been linked with increased risk of dementia and cognitive impairment among older adults and with premature mortality in young and middle-aged adults. No studies have evaluated the association between diabetes and dementia among Mexican Americans, a population with a high burden of diabetes. We evaluated the association of diabetes with incidence of dementia and cognitive impairment without dementia (CIND) among older Mexican Americans while accounting for competing risk from death.

RESEARCH DESIGN AND METHODS: This study included 1,617 participants 60-98 years of age from the Sacramento Area Latino Study on Aging followed up to 10 years from 1998. We evaluated the association between diabetes and dementia/CIND with competing risk regression models.

RESULTS: Participants free of dementia/CIND at baseline (n = 1,617) were followed annually up to 10 years. There were 677 (41.9%) participants with diabetes, 159 (9.8%) incident dementia/CIND cases, and 361 (22.3%) deaths. Treated and untreated diabetes (hazard ratio 2.12 [95% CI 1.65-2.73] and 2.15 [1.58-2.95]) and dementia/CIND (2.48 [1.75-3.51]) were associated with an increased risk of death. In models adjusted for competing risk of death, those with treated and untreated diabetes had an increased risk of dementia/CIND (2.05 [1.41-2.97] and 1.55 [0.93-2.58]) compared with those without diabetes.

CONCLUSIONS: These findings provide evidence that the association between type 2 diabetes and dementia/CIND among Mexican Americans remains strong after accounting for competing risk of mortality. Treatments that modify risk of death among those with diabetes may change future dementia risk.

PMID: 23514732 PMCID: PMC3747945 DOI: 10.2337/dc12-2158

[Indexed for MEDLINE] **Free PMC Article**

CNS Neurol Disord Drug Targets. 2014 Mar;13(2):271-82.

Fighting Alzheimer's disease and type 2 diabetes: pathological links and treatment strategies.

Dai Y, Kamal MA[1].

Author information

Abstract

The incidence of Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) with associated serious complications continues to grow rapidly especially in developed countries. Emerging evidence indicates that AD and T2DM share some common risk factors with comparable pathological features including insulin resistance, amyloidogenesis, glucocorticoid imbalance, inflammation, mitochondrial function and oxidative stress. T2DM has been identified as a risk factor for AD. It has even been hypothesized that AD might be "type 3 diabetes". In addition to amyloid precursor protein processing and tau phosphorylation, commonalities between T2DM and AD in molecular mechanisms provide clues to the identification of novel therapeutic targets such as glucagon-like peptide 1, butyrylcholinesterase, and receptor for advanced glycosylation end products. Although several classes of anti-diabetic drugs are available, achieving long-term glycaemic control without side effects is often challenging. This review summarizes recent evidence for the pathological links, common therapeutic targets, currently the U.S. Food and Drug Administration approved and potential future therapies, giving special attention to ongoing clinical trials of antidiabetic drugs in AD patients and common therapeutic strategies in the management of both AD and T2DM.

PMID: 24059324

[Indexed for MEDLINE]

Nat Rev Neurol. 2015 Mar;11(3):127-8. doi: 10.1038/nrneurol.2015.17. Epub 2015 Feb 17.

Dementia: type 2 diabetes has a slow and insidious effect on cognition.

Umegaki H[1].

Author information

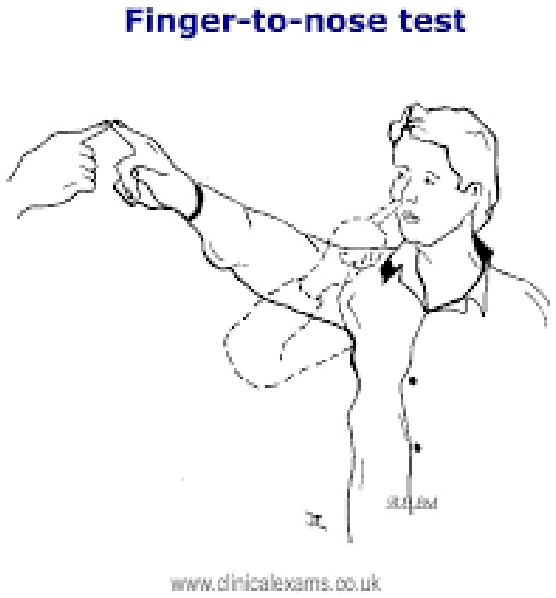
Comment on

Diabetes mellitus is independently associated with more severe cognitive impairment in Parkinson disease. [Parkinsonism Relat Disord. 2014]

Diabetes in midlife and cognitive change over 20 years: a cohort study. [Ann Intern Med. 2014]

PMID: 25686756 DOI: 10.1038/nrneurol.2015.17

[Indexed for MEDLINE]



http://www.neuroexam.com/neuroexam/content36.html

Great neuro exams

[redacted]

Provider:

Hugh Wegworth DC

[redacted]

DC

[redacted]

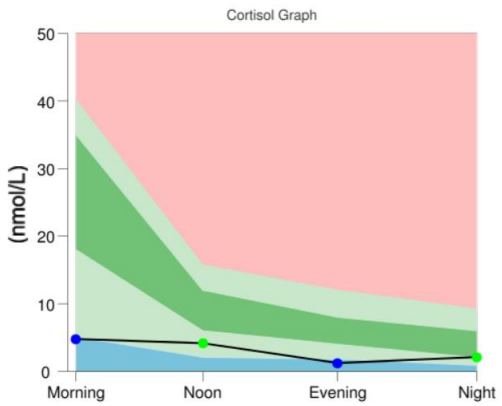
Age:30 **Gender:**F

Menopausal Status:
Pre-Menopause

[redacted]

M[redacted]
Noon
Evening
Night
Samples Arrived
Results Reported

	Saliva Hormone Test	Result	Units	L	WR	H	Reference Range
HORMONES	**Estrone (E1)***		pg/ml				
	Estradiol (E2)	< 1.00	pg/ml	↓			1.0-10.8 pre menopausal (1.5-10.8 supplementation)
	Estriol (E3)*		pg/ml				
	EQ (E3 / (E1 + E2))						
	Progesterone (Pg)	17.49	pg/ml	↓			127.0-446.0 pre menopausal (luteal) (500-3000 supplementation)
	Ratio of Pg/E2**	17.49		↓			200-600 pre menopausal
	Testosterone*	19.41	pg/ml		◆		6.1-49.0 female (30.0-60.0 supplementation)
ADRENALS	**DHEA***	752.47	pg/ml			↑	106.0-300.0 female
	Cortisol Morning	4.79	nmol/L	↓			5.1-40.2; optimal range: 18-35†
	Cortisol Noon	4.16	nmol/L		◆		2.1-15.7; optimal range: 6-12†
	Cortisol Evening	1.23	nmol/L	↓			1.8-12; optimal range: 4-8†
	Cortisol Night	2.12	nmol/L		◆		0.9-9.2; optimal range: 2-6†

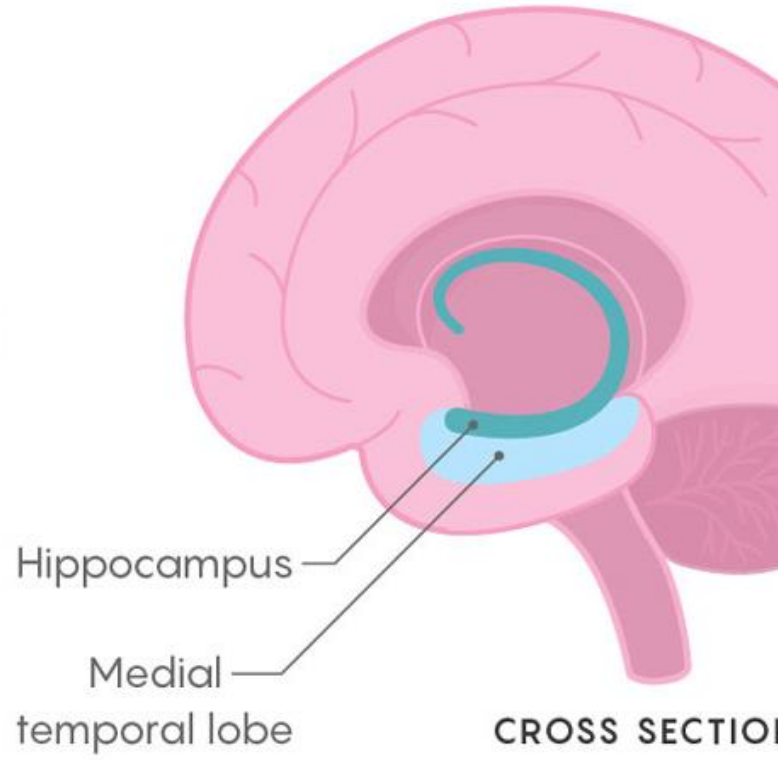


Hormone Comments:

- The estradiol and progesterone levels are strongly suggestive of an anovulatory cycle, luteal phase failure or collection outside of luteal phase. Query BCP usage. Progesterone to estradiol (Pg/E2) ratio and reported symptoms are consistent with estrogen dominance. Supplementation with topical progesterone to correct this relative deficiency is a consideration.
- Suboptimal testosterone may relate to increased risk of osteoporosis, low libido, vaginal dryness and heart disease.
- DHEA level is consistent with stress response or supplementation (not reported), although metabolic syndrome cannot be ruled out. Serum vitamin D, fasting glucose and insulin testing may be warranted.
- Diurnal cortisol pattern and reported symptoms are consistent with established (Phase 3) adrenal gland fatigue (hypoadrenia).

Notes:

L=Low(below range) WR=Within Range (within range) H=High (above range)



Report Number:
013PLQ

Provider:

Hugh Wegwerth DC
1912 Lexington Ave Ste 250
Roseville, MN 55113 US
Ordering Provider: Hugh Wegwerth - DC

Patient Info:
[redacted]on

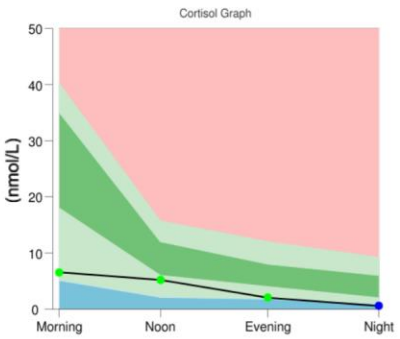
Age:37 **Gender:**F

Menopausal Status:
Pre-Menopause

5842 212th St N
Forestlake, MN 55025

Sample Collection	**Date/Time**
Morning	[redacted]
Noon	
Evening	
Night	
Samples Arrived	
Results Reported	

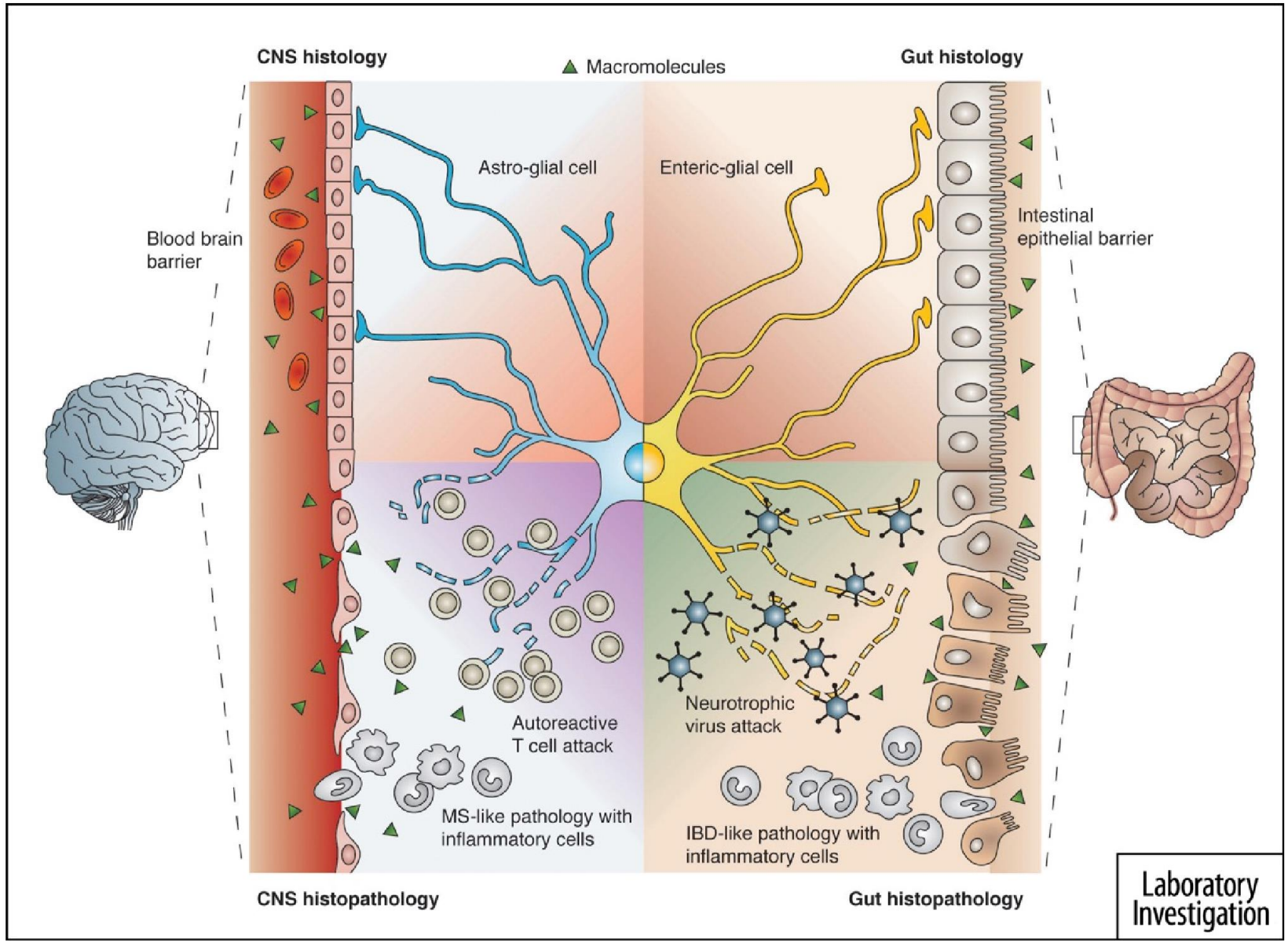
	Saliva Hormone Test	Result	Units	L	WR	H	Reference Range
HORMONES	Estrone (E1)*		pg/ml				
	Estradiol (E2)	2.68	pg/ml		◆		1.0-10.8 pre menopausal (1.5-10.8 supplementation)
	Estriol (E3)*		pg/ml				
	EQ (E3 / (E1 + E2))						
	Progesterone (Pg)	25.77	pg/ml	↓			127.0-446.0 pre menopausal (luteal) (500-3000 supplementation)
	Ratio of Pg/E2**	9.61		↓			200-600 pre menopausal
	Testosterone*	44.49	pg/ml		◆		6.1-49.0 female (30.0-60.0 supplementation)
ADRENALS	DHEA*	75.17	pg/ml	↓			106.0-300.0 female
	Cortisol Morning	6.56	nmol/L		◆		5.1-40.2; optimal range: 18-35†
	Cortisol Noon	5.19	nmol/L		◆		2.1-15.7; optimal range: 6-12†
	Cortisol Evening	2.02	nmol/L		◆		1.8-12; optimal range: 4-8†
	Cortisol Night	0.56	nmol/L	↓			0.9-9.2; optimal range: 2-6†

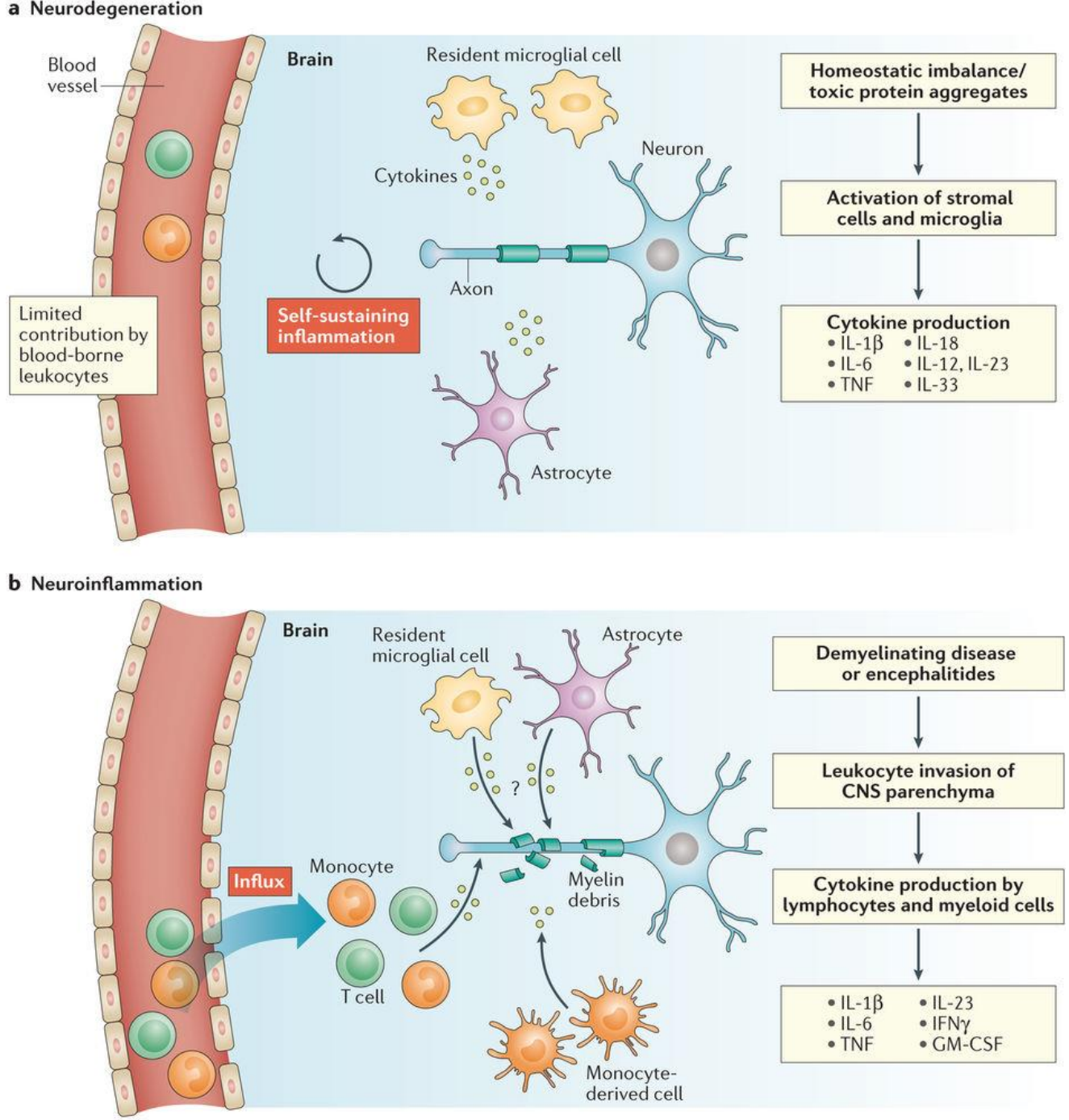


Hormone Comments:

- Progesterone to estradiol (Pg/E2) ratio and reported symptoms are consistent with estrogen dominance. Supplementation with topical progesterone to correct this relative deficiency is a consideration. Note: The progesterone level is suggestive of an anovulatory cycle, luteal phase failure or collection outside of luteal phase.
- The upper range testosterone level and reported symptoms are suggestive of PCOS or metabolic syndrome (insulin resistance). Serum vitamin D, fasting glucose and insulin testing may be warranted.
- DHEA level is consistent with the expected decline with age (adrenopause). Note: Supplementation with DHEA may increase testosterone and/or estradiol levels.
- Diurnal cortisol pattern and reported symptoms are consistent with established (Phase 3) adrenal gland fatigue (hypoadrenia).

Notes:


CNS histology
Macromolecules
Gut histology
Astro-glial cell
Enteric-glial cell
Blood brain barrier
Intestinal epithelial barrier
Autoreactive T cell attack
Neurotrophic virus attack
MS-like pathology with inflammatory cells
IBD-like pathology with inflammatory cells
CNS histopathology
Gut histopathology
Laboratory Investigation


a Neurodegeneration
Blood vessel
Brain
Resident microglial cell
Neuron
Cytokines
Axon
Self-sustaining inflammation
Limited contribution by blood-borne leukocytes
Astrocyte
Homeostatic imbalance/ toxic protein aggregates
Activation of stromal cells and microglia
Cytokine production
• IL-1β • IL-18
• IL-6 • IL-12, IL-23
• TNF • IL-33
b Neuroinflammation
Brain
Resident microglial cell
Astrocyte
?
Influx
Monocyte
Myelin debris
T cell
Monocyte-derived cell
Demyelinating disease or encephalitides
Leukocyte invasion of CNS parenchyma
Cytokine production by lymphocytes and myeloid cells
• IL-1β • IL-23
• IL-6 • IFNγ
• TNF • GM-CSF