



Cognitive Health: Mental Deterioration or Just Brain Fog: A Naturopathic and Genetics-Based Approach to Diagnosis and Management

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Cognitive Health: Mental Deterioration or Just Brain Fog

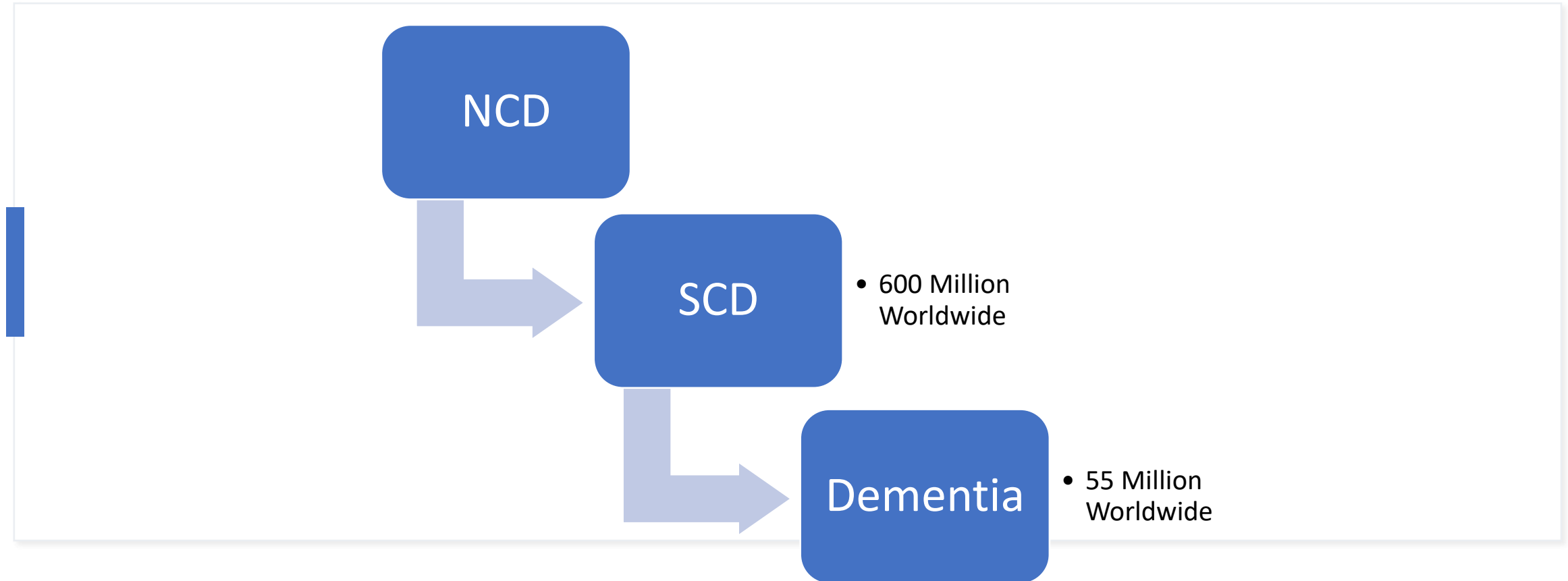
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- Feb 17th 2024
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Brain fog or Dementia





Progressive Stages



Subjective Cognitive Decline:

- Subjective Cognitive Decline (SCD) is a self reported experience of worsening of memory or more frequent confusion or memory loss.
- Over 600 million people worldwide suffer from cognitive dysfunction.
- SCD affects 1 in 9 adults over the age of 45.
- The prevalence is slightly higher in men vs women.
- 1/3 of adults with SCD report frequent mental distress (FMD) in the last 6 months prior to a significant decline.

Alzheimer's association

Alzheimer's/Dementia

- 1 in 3 seniors dies *with* dementia.
- 55 million people worldwide suffer from dementia.
- Deaths from Alzheimer's and dementia have increased 16% during the pandemic.
- Between 2000 and 2019, deaths from heart disease decreased 7.3% while deaths from Alzheimer's rose 145%.

Alzheimer's association



Symptomatology

Brain Fog

- Memory loss
- Lack of mental clarity
- Poor concentration
- Fatigue
- Sleep problems
- Confusion
- Feeling “out of it”
- Forgetting to complete a task
- Taking much longer to complete a task.
- Headaches

Dementia

- Memory loss
- Lack of mental clarity
- Poor concentration
- Fatigue
- Sleep problems
- Confusion
- Personality changes.
- Difficulties performing everyday tasks
- Communication problems



Etiology

Brain Fog

- Is not a medical condition, it is a symptom of another medical/lifestyle condition.

Causes:

- Genetics
- Stress
- Lack of sleep
- Inflammation
- Hormonal changes
- Conditions such as diabetes, anxiety, depression, migraines, arthritis, dehydration, toxicity.

Dementia

- Medical Condition, damage or degeneration to the brain cells.

Causes:

- Genetics
- Stress
- Insomnia/lack of sleep
- Inflammation/toxicity
- Hormonal changes
- Dementia = damage can occur in several different areas of the brain.
- Alzheimer's = damage is in the hippocampus.

Genetics of Dementia and Alzheimer's???

- APOE4 gene – gene that controls the production of apolipoprotein E that transports cholesterol and other fats in the blood stream.
- 40-65% of people dx with Alzheimer's are APOE 4.
- Scientists estimate that **only 1%** of the Alzheimer's in these people is accounted for by this gene.
- Rather it is an amalgamation of genes that lead to damage of the effected area.

www.alz.org



Stress and Brain Function

- HPA stimulation hyperpolarizes nucleotide-gated ion channels causing an efflux of Na^+ and K^+ out of the cell, decreasing action potentials and inhibiting dopamine driven thoughts, behavior and memory consolidation.

Int J Dev Neurosci. 2011 29:215-223

- Excess NE in the PFC binds to low affinity alpha receptors rather than high affinity receptors, leading to lower working memory and silencing of the PFC network.

Biol Psychiatry 2014, 46:1266-1274

- GCs alter the firing of dopaminergic projections and decrease dendritic growth between synapses and reduces neural repair- tissue shrinkage!

2017.05.004 *Nat Neurosci.* 2017 10, 376-384

Stress, Dopamine and Brain Function

- Increased or decreased dopamine in the medial PFC and AS impair memory and executive functioning.
- Stress alters D1 vs D2 signaling in PFC suppressing noise related neurons and the appropriate signaling whereby information is “lost” and the PFC is unable to guide behavior.
- Stress pushes dopamine from the PFC to the AS decreasing focus and concentration and increasing emotion.

Nat Neuroscie. 2017 10, 376-384

Behavioural pharmacology 2018 Vol 29 (7):584-591



Inflammation and Brain Function

- IL6, TNFa and to a lesser degree IL1B cross the BBB.
- Cytokines alter synaptic plasticity by reducing neurotransmission and dendritic branching and directly stimulate HPA axis.

Brain Behav Immun 2011, 25:181-213

- Studies show that prolonged inflammation alters functional connectivity and cortical thickness in specific areas of the brain altering memory and focus.

Int J Obes 2020. 44:1487-96

- Cytokines reversibly mutate neurotransmitter receptors.

Front. Pediatr. 2020 doi.org/10.3389



Toxicity and Brain Function

- Neurotoxicity from lead, mercury and other exogenous toxins increase the risk of dementia disorders, especially Alzheimer's.
- Heavy metals increase oxidative stress, stimulate apoptosis in “normal” neurons and increase GC release.
- PCB's decrease neurotransmitter release, disrupt intracellular signaling especially in the hippocampus, cerebellum and cortex.
- Toxins directly raise IL6 and TNFa levels.

J Environ Health 2014, 76(6): 130-138

Estrogen and the Aging Brain

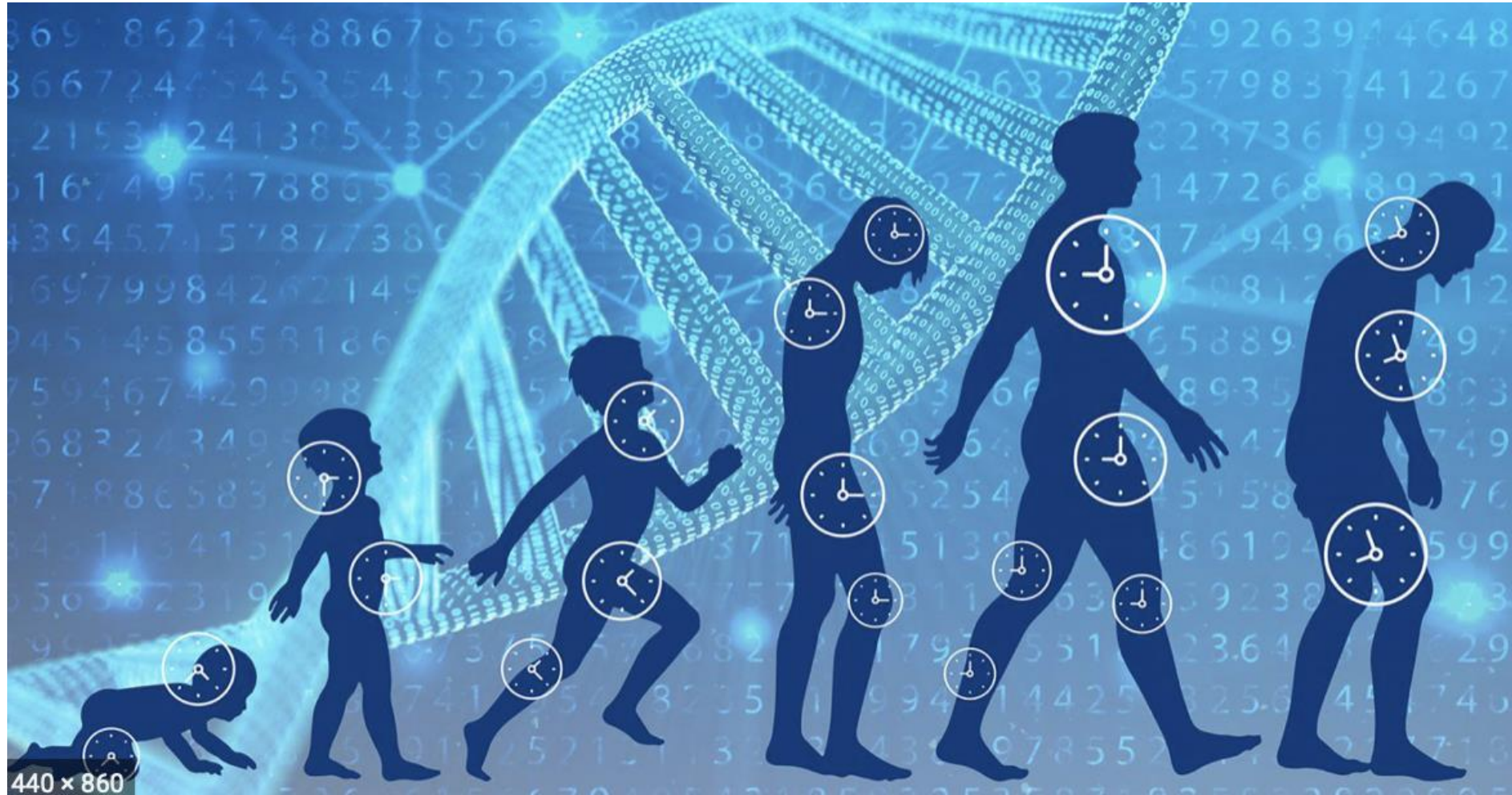
- E2 helps mediate hippocampal synaptic activity. *NeuroSci 2018*
- E2 increases dendritic spine density and cognitive performance.
Endocrinology 2011
- Loss of E2 at menopause and andropause has been shown to reduce synaptic density and connectivity as well as reduction the volume of grey matter.
Hormone Behav. 2011
- HRT was only shown to have minimal or partial recovery in synaptic density and self reported symptoms.
NeuroScie 2016.



Normal Forgetfulness - The Forgetting Curve

- Within 1 hour, people will have forgotten 50% of the information presented to them.
- Within 24hrs they will have forgotten 70%.
- Within 1 week they will have forgotten an approximate 90%.
- The hippocampus declines with time and by the age of 80, 20% of its nerve connections can be lost.





440 x 860



SIRT6 rs352493: Longevity gene

- Normal Allele is T Variant Allele is C
- Decreased DNA repair.
- Increased rate of telomere shortening.
- Increased ROS production.
- Decreased NRF2.
- Decreased autophagy.
- Increased CV dz., dyslipidemia and heart failure.
- Increased rate of aging.

Front. Cell Dev. Biol March 2021

ScienceDaily April 2019

Support for SIRT6 rs352493 C Allele

- Flavonoids: especially **Resveratrol** (2-fold activation)
- Quercetin
- Catechins
- Anthocyanidins

Sci Reps 8, 4163(2018)



BDNF rs6265: Master Molecule of the Brain

- Normal Allele is C Variant Allele is T
- Decreased BDNF production.
- Decreased neuronal and synaptic repair.
- Decreased dendritic growth.
- Decreased memory and increased risk of dementia and Alzheimer's.
- Increased depression and anxiety.
- Increased rate of aging.
- Decreased autophagy.

Front Cell. Neurosci. Aug 2019

Am J of Med Genetics 2018;177B:143-167



Support for BDNF rs6265 T Allele

- Astaxanthin

Nutr Neurosci 2020;23(6):422-431

- Resveratrol

Neurochem Res. 2011 36(5):761-5

- Curcumin (if CYP1A2 is normal)

Prog Neuropsychopharmacol Biol Psychiatry 2010 1;34(1):147-53

- 5HTP (if serotonin genes are hetero or variant)-

Science Daily News, Feb 2010

- Theanine

Clin Neuropharmacol 2011;34(4):155-60

- Exercise (especially HIIT if genetics allow for it)- *Front Neurosci. 2018*



FKBP5 rs3800373 FK Binding Protein 5

Associated with altered HPA activity.

- Normal Allele is C Variant Allele is A

1. Increased FKBP5 production.
2. Increased loss of negative feedback in the HPA axis.
3. Prolonged stress response.
4. Increased insomnia or sleep disturbances.
5. Increased cytokine production.
6. Increased memory loss.

Wilker S, Translational Psychiatry. 2014;4:403
Binder E, Psychoneuroendocrinology. 2009 Dec; 34(1): 186-195



NR3C2 rs5522: Mineralocorticoid receptors

- Normal Allele is T Variant Allele is C
- Fewer mineralocorticoid receptors.
- Increased loss of negative feedback in the HPA axis.
- Increased ACTH.
- Increased cytokine production.
- Increased memory loss and brain aging.

Psychoneuroendocrinology 2015 Feb;52:92-110

J of clin Endocrinology and Metaboism, 2006 Dec;91(12): 5083-5089

CRHR1 rs242939 Corticotropin Releasing Hormone Receptor.

- Normal Allele is T Variant Allele is C
- Increased CRH Receptors.
- Increased loss of negative feedback in the HPA axis.
- Increased stimulation of HPA axis.
- Increased cytokine production.
- Increased memory loss.

Nat Neurosci. 2003 Oct;6 (10):1100-7

COMT rs4680: Catechol-O-methyltransferase

- Normal Allele is G Variant Allele is A
- Decreased COMT production.
- Decreased clearance of stress hormones and dopamine.
- Shift of dopamine to AS.
- Increased loss of feedback in HPA axis.
- Decreased focus and memory.

Hamidovic et al, 2010

Support for all Stress Genes

- Lactium – *LFASEB Journal June 2001*
- Theanine – *Nutrients 2019;11(10):2362*
- Hemi-Synch – www.hemi-synch.com
- Meditation
- Exercise
- Be careful with Rhodiola???

IL6 rs1800795

- Normal Allele is C Variant Allele is G
- Increased IL6.
- Increased inflammation and reduced glutathione.
- Crosses the BBB inflaming neural receptors.
- Increased blocking of neural receptors.
- Increased insomnia, sleep disturbances, anxiety and depression.
- Decreased memory.

Bashati M, et al, Cytokine 2017 Nov;99:132-138

TNFa rs1800629

- Normal Allele is G Variant Allele is A
- Increased TNFa production.
- Increased inflammation.
- Crosses the BBB inflaming neural tissues.
- Increased HPA activity and sleep disturbances.
- Decreased memory.

Greco L, et al, Am J Hum Gen 1998 62, 669-675

Saif K, et al, Sci Rep 2016;6:32

Support for IL6 and TNFa

- Liposomal Glutathione — *Antioxidants* 2020;9(7):62
- N-Acetyl Cysteine - *Curr Neurovasc Res* 2016;13(2):107-14
- Low sugar diet - *Evid based Complement Alternat Med* 2012:639469
- Sleep — *Neuropsychiatr Dis Treat* 2019;15:1695-1700
- Curcumin – dependent of CYP1A2

DRD2 rs6277 and DRD2/ANKK1 rs1800497

- Normal Allele is A (G) Variant Allele is G (A)
 - Reduced DRD2 receptors.
 - Reduced dopamine production.
 - Less pleasure derived from everyday events.
 - Frequent excitement seeking behavior.
 - Increased addictions.
 - Increased ADD and ADHD.
 - Increased memory loss and aging brain.

Support for Dopamine

- L-Tyrosine *eNeuro 2018 PMC6084775*
- DL-Phenylalanine. *NIH PubChem*
- Velvet-bean seed (*Mucuna pruriens*) *Biol Sci Space 2001;18(3):165-6*
- *Rhodiola rosea* (watch COMT) *Med Hyp 2007;69(5):1054-60*
- Exercise - look to exercise genes
- Walnuts, aged cheese and wine!!!



Phase 1 detoxification CYP1A2 rs762551

A allele – Normal

1. **Fast Metabolizer.** Increased production of phase 1 substrates.
2. Increased TNF α , IL6 and inflammation.
3. Increased risk of colon cancer and polyps with BBQ'd meats.
4. Decreased production of 2-OH estrogen>increased breast cancer.

Zhou SF et al. Drug Metabolism Reviews. 2010; 42:268-354/. UniProt. P05177 (CYP1A2_HUMAN)

C allele – Variant

1. **Slow Metabolizer.** Decreased production of phase 1 substrates.
2. Increased activation of carcinogenic PAH's and aromatic heterocyclic amines > increased breast and bladder cancer.
3. Increased production of 2-OH estrogen>decreased breast cancer.

Molecular Cancer Research AACR publication Feb 2005



Support for Phase 1 Detoxification

A allele – Normal =fast

- 2-3 cups of caffeine per day (reduce your risk of a myocardial infarction).
- Curcumin
- COOK your cruciferous vegetables.
- Avoid Milk Thistle, mint and Echinacea.

Genes Nutr., 2007; 2(1):155-15

C allele – Variant = slow

- Avoid caffeine
- Avoid acetaminophen (Tylenol).
- Avoid curcumin
- Increase RAW cruciferous vegetables.
- DIM
- Milk Thistle

Molecular Cancer Research AACR publication Feb 2005



Phase 2 Detoxification

- GSTP1 – rs1695 (AG)
- SOD2 – rs4880 (AG, CT)
- NQO1 – rs1800566 (GA, CT)
- Variants have up to 75% less GSH production.
- Lower GSH increases IL6 and TNFa.
- IL6 and TNFa decrease intracellular GSH.
- Free Radic Biol Med 2014; 77(8) Pharmacogenet Genomics 2005; 15(5) Cell 2004;116 (2)

Support for Phase 2 genes.

- HIIT exercise if exercise genes allow for it.
- Liposomal Glutathione
- NAC
- DIM
- Astaxanthin for SOD2

Am J Clin Nutr 2010 Jun;95(6).

Nutrients 2018, 10(4).

Research Gate June 2015J.

Clin Endocrinol Metab 2011 96(5)

Case Studies 1 & 2

2 men, similar age,
experienced accelerated memory loss,
fatigue and general “slowing”.





Case Study 1 - John

- John is a 63-year-old male who despite a good diet and regular exercise has always felt “sub-par”, tired and slow. He said, “I feel 10 years older than I should”.
- His short-term memory and mental clarity had been declining to which he attributed to stress.
- No personal health hx of significance.
- Family hx of dementia and lung cancer - smokers.

John's Genotyping

- SIRT6-CC: Decreased DNA repair, autophagy, increased telomere shortening, inflammation and rate of aging.
- BDNF- TT: Decreased neuronal/synaptic repair and dendritic growth.
- FOXO3- TG: Increased inflammation, decreased DNA repair.
- GSTP1- AA: Normal toxic clearance.
- SOD2- AG: Increased ROS especially with exercise.
- FKBP5 – CC, NR3C2, TT, COMT- GA: fairly normal stress response.
- IL6- GG and TNFa – GA: Increased inflammation.



John's Interpretation

- John has a significant decreased ability to repair damaged or inflamed neural tissue.
- He also has a direct increased inflammatory response in his neural tissue through his longevity genes which is greatly augmented via his inflammatory genes.
- This stimulation of inflammation and decreased ability to repair any consequential damage is what led to his cognitive decline.
- His stress and detox genes were close to normal and were not greatly contributing.



John – Program

- Resveratrol 100 mg – 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Astaxanthin 4 mg– 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Liposomal Glutathione 150 mg– 1 cap BID with food for 8 weeks and then reduce to 1 per day.
- NAC 900 mg- 1 BID empty stomach for 8 weeks and then reduce to 1 per day.



John Outcome

- After 2 weeks his body felt “lighter” and by week 4 his energy had improved by ~ 60%.
- At 6 weeks his mental clarity and recall was notably better and by the 8th week his wife was commenting that he “was like his old self again” (energy and memory).
- At 9 months John stopped the supplements and 5 weeks later symptoms began to appear again.
- He restarted the supplements again, and 2 years later he continues to feel stronger and younger than he did 3 years ago.



Case Study 2

- David is a 65-year-old male whose memory and recall greatly declined over the past 3 years.
- He also experienced lower moods, and poor recovery from his workouts.
- He attributed much of this to increased stress (IPO with his company) and a move to downtown TO from the countryside.
- No family hx of dementia or Alzheimer's.



David's Genotyping

- SIRT6-TT: Normal DNA repair, autophagy, telomere shortening, inflammation and rate of aging.
- BDNF- CC: Normal neuronal/synaptic repair and dendritic growth.
- FOXO3- TG: Increased inflammation, decreased DNA repair.
- GSTP1- GG: Decreased toxic clearance.
- SOD2- GG: Increased ROS especially with exercise.
- FKBP5 – AA, NR3C2, TC, COMT- GA: Augmented stress response.
- Serotonin genes – all hetero.
- IL6- CG and TNFa – GA: Increased inflammation.



David's Interpretation

- David has a close to the normal rate of aging response, with good neural and body tissue repair.
- He has poor detoxification genes which were triggered by moving to Toronto and by his stress genes during the IPO, which then increased his inflammatory response.
- This in turn triggered his serotonin genes decreasing N-acetylserotonin turning off his BDNF and SIRT6 genes.



David's Program

- Liposomal Glutathione 150 mg– 1 cap BID with food for 10 weeks and then reduce to once per day.
- NAC 900 mg- 1 BID empty stomach for 10 weeks and then reduce to 1 per day.
- 5-HTP 100 mg – 1 BID (1 dose at 8:30 pm) for 8 weeks, then reduce to nighttime dose only.
- Lactium 150 mg, L-theanine 100 mg– 2 BID empty stomach for 8 weeks and then reduce to 1 BID.



David Outcome

- 3 weeks into the program David's mood significantly improved and he no longer felt exhausted after a workout. Overall energy during the day was still low.
- 6 weeks into the program his mental clarity and recall was better than it had been in years, and his daytime energy and recovery from workouts was "normal".
- 1.5 years later he felt strong, energetic and no decline in memory.



Comparison

John

- True genetic increased rate of aging.
- Healthy brain aging is about improving neural repair and lowering inflammation.

David

- Normal genetic rate of aging.
- Healthy brain aging is about reducing inflammation, resetting HPA axis and improving detoxification.



Case Study 3 - Tracy

- Tracy is a 51-year-old female who “feels like she aged a decade overnight”. She was frequently tired on waking.
- Without any change in diet or exercise, she gained 11 lbs., LDL cholesterol rose to 4.8 mmol/L (185.6 mg/dl), CRP increased from 1.2 to 4.5 mg/L, and she started experiencing anxiety for the first time.
- Her greatest concern was her forgetful memory and increased joint pain/injury.



Tracy's Genotyping

- SIRT6-CC: Decreased DNA repair, increased lipid production, heart failure and rate of aging. and decreased metabolism.
- BDNF- TT: Decreased neuronal/synaptic repair and dendritic growth.
- FOXO3- TT: Normal inflammation, normal DNA repair.
- MMP3 – CC: Increased metalloproteases breaking down collagen.
- CRY1 – GG: Poor transition between stages of sleep.
- FKBP5 – CA, NR3C2, TC, COMT- AA: Augmented stress response.
- IL6- CC and TNFa – GG: Normal inflammation.



Tracy's Interpretation

- Tracy entered menopause 1.5 yrs. ago. This triggered many of her genes.
- Directly triggered her SIRT6 and BDNF decreasing recall/memory and increasing cholesterol and weight.
- Menopause also triggered her CRY1 gene, decreasing her stage 4 sleep and body repair, as well as her MMP3 gene contributing to her joint pain/injury and stimulating IL6 and TNFa (even though they are normal) creating a cyclic inflammatory response between neural tissues, metabolism, and joints.



Tracy's program

- Resveratrol 100 mg – 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Astaxanthin 4 mg– 1 BID empty stomach for 8 weeks and then reduce to 1 per day.
- Hydrolyzed Collagen 10 gms – 1 scoop BID for 1 tub then once per day.
- Lactium 150 mg, L-theanine 100 mg– 2 BID empty stomach for 8 weeks then reduce to 1 BID.
- Melatonin (time released) 3mg – 2 caps at 8:30 pm.



Tracy's Outcome

- Within 10 days her joint pain began to reduce significantly.
- At 4 weeks she had lost 6 lbs. and by 8 weeks she had lost 12 lbs. and blood work was back to normal despite no change in diet or exercise.
- At 4 weeks her memory improved by “50%” and by 8 weeks she reported her mental agility and recall was as it was 10 yrs. ago.
- 3 yrs. later Tracy feels just as strong, and all blood is normal.



Case Study 4 - Marnie

- Marnie is a 54-year-old female who went into menopause 4 years ago.
- Since then, she has noticed a rapid decline in memory, energy and adipose tissue around the upper thighs and abdomen. (all blood work remained normal.
- She also started experiencing more nighttime hot flashes in the last year vs 4 years ago and waking at 3:30 am almost nightly.
- This made her focus and mental clarity worse and increased more abdominal weight.
- She put herself on L-Tyrosine, but it made her focus worse and increased anxiety.



Marnie's Genotyping

- SIRT6-TT: Normal DNA repair, normal lipid production, heart failure and rate of aging. and decreased metabolism.
- BDNF- CT: Slightly decreased neuronal/synaptic repair and dendritic growth.
- FOXO3- TT: Normal inflammation, normal DNA repair.
- CYP17A1-AG, CYP1A1-AC, CYP1B1-GG: Increased overall estrogen and 4-OH estrogen.
- CRY1 – AA: Normal transition between stages of sleep.
- FKBP5 – AA, NR3C2, TC, COMT- AA: Very augmented stress response, (metabolism, neural inflammation and reduced dopamine binding in PFC).
- IL6- GG and TNFa – GA: Increased inflammation (in adipose) and neural inflammation.
- DRD2 and DRD2/ANKK1 – Normal dopamine production and binding.



Marnie's Interpretation

- Marnie has essentially normal aging genes, but menopause naturally triggered her stress genes increasing cortisol which increased as the years went by.
- Higher cortisol reduces the metabolism rate from 92% to 35%, increases puffy weight gain around the abdomen, nighttime sweats and reduced PFC dopamine binding as well as triggering her inflammatory genes (adipose and neural inflammation).
- She also had higher estrogen and pushed a great deal to the 4-OH side, increased puffy upper thigh weight gain.
- Increasing dopamine to one who makes normal DA, pushes DA to the anterior striatum.



Marnie's Program

- Lactium 150mg, L-theanine 100 mg– 2 caps BID empty stomach for 10 weeks and reduce to 1 BID thereafter. 1 cap if waking in the night.
- DIM 100 mg– 1 cap BID for 4 weeks and then 1/day.
- Liposomal Glutathione 150 mg – 1 cap BID with food for 10 weeks and then reduce to once per day.
- NAC- 900 mg- 1 BID empty stomach for 10 weeks and then reduce to 1 per day.



Marnie's Outcome

- Sleep and nighttime flashes began to reduce in 3 days and were almost normal by the 2-week mark.
- Her abdominal and thigh weight gain reduced consistently 1 lb. a week until it was gone – no change in diet or exercise.
- Her memory and mental clarity improved by 40% at week 4 and 80% by week 8.
- 2.5 years later, she is sleeping through the night, normal weight, feeling energetic and mentally clear.



Comparison

Tracy

- True genetic increased rate of aging.
- Healthy aging is about increasing neural repair and stage 4 sleep, as well as reducing MMP3's.

Marnie

- Normal genetic rate of aging.
- Healthy aging is about regulating HPA axis, reducing inflammation and 4-OH estrogen.



Questions?

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Saturday 2:00pm – 3:00pm

**Cognitive Health: Mental Deterioration
or Just Brain Fog: A Naturopathic and
Genetics-Based Approach to Diagnosis
and Management**

Please scan this QR code on you mobile
or tablet device to access the session feedback survey



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