Neuroprogression

- The Elephant in the room!
- Dr Michael Nelson DC
- March 2020
- Reno, NV

Disclaimers

- Dr Michael Nelson is the CEO of Sierra Nevada Bioscience LLC, Brain-Bean and Life-Enhancement products
- www.brain-bean.com
- www.life-enhancement.com

Overview:

WHAT IS NEUROPROGRESSION

NEW VIEW

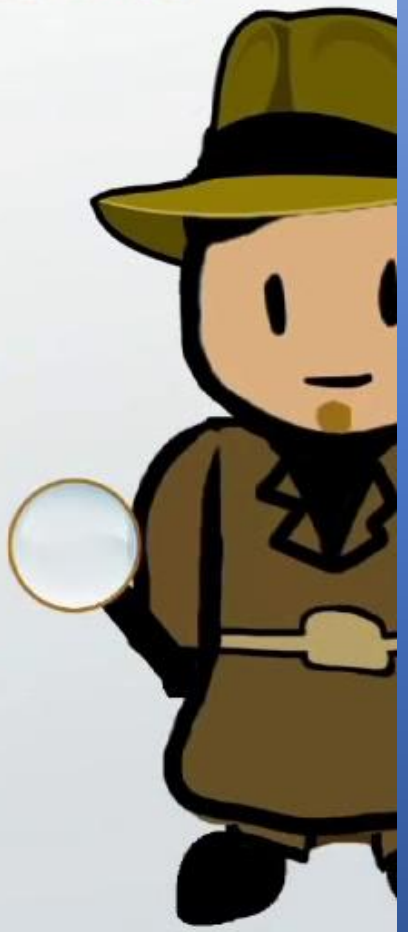
: PERFECT STORM!

HOW TO TO WEATHER THE STORM

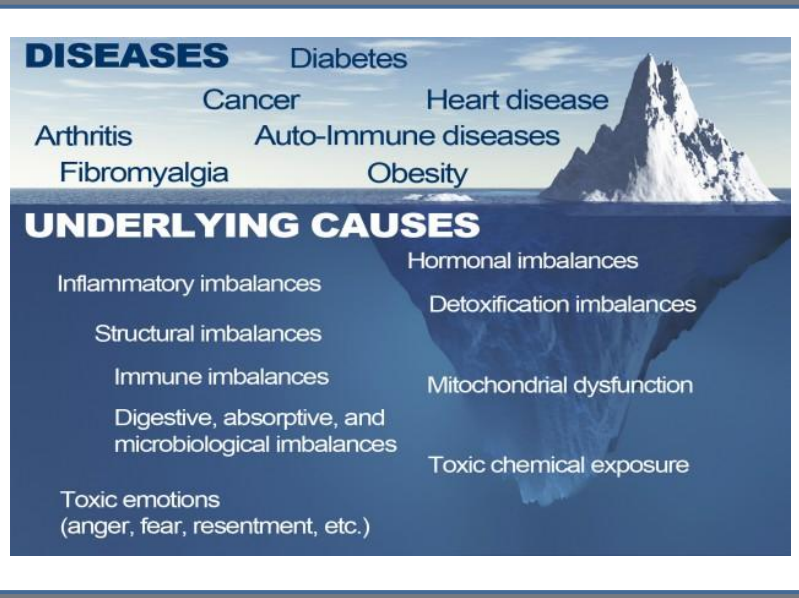
CIENTIFIC METHOD

e Scientific Method

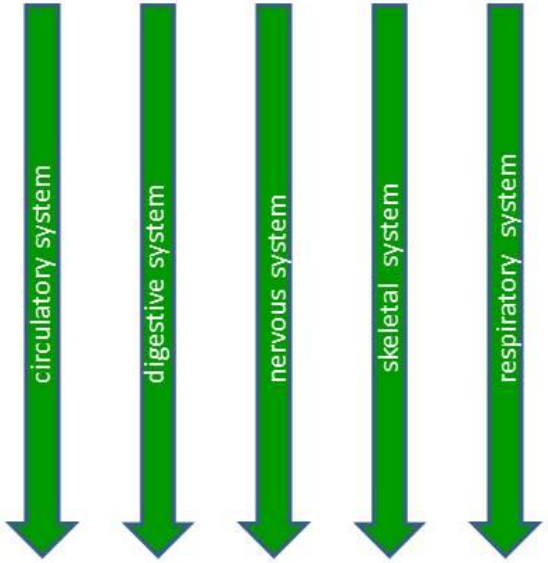
1. Question
2. Hypothesis
3. Experiment
4. Observation



Educ



Disconnected Systems




The good physician treats the disease; the great physician treats the patient who has the disease.
William Osler
quotefancy

The Functional-Medicine Matrix

Retelling the Patient's Story	Physiology and Function: Organizing the Patient's Clinical Imbalances
Antecedents *Type A personality, predisposition to gut issues*	
Triggering Events *Proton pump inhibitors*	
Mediators/ Perpetuators *Dysbiosis, leaky gut*	

Personalizing Lifestyle Factors

Sleep & Relaxation	Exercise & Movement	Nutrition & Hydration	Stress & Resilience	Relationships & Networks
Poor sleep	*Limited due to work hours*	*Limited diet, fast food*	*Marked stress*	*Good*

IFM

Name: Jared Date: _____ CC: _____

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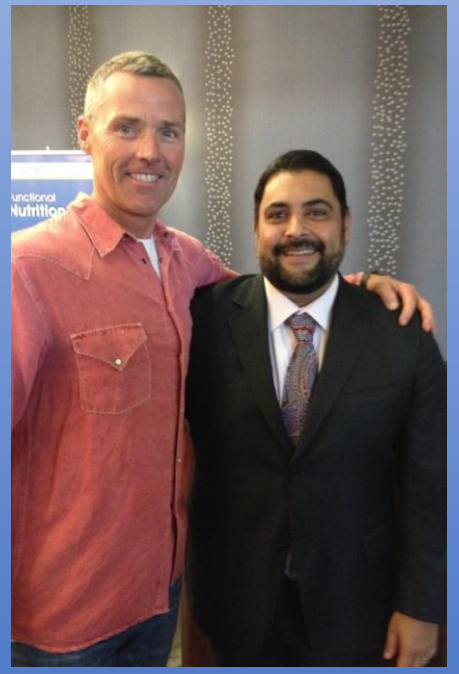



CYREX

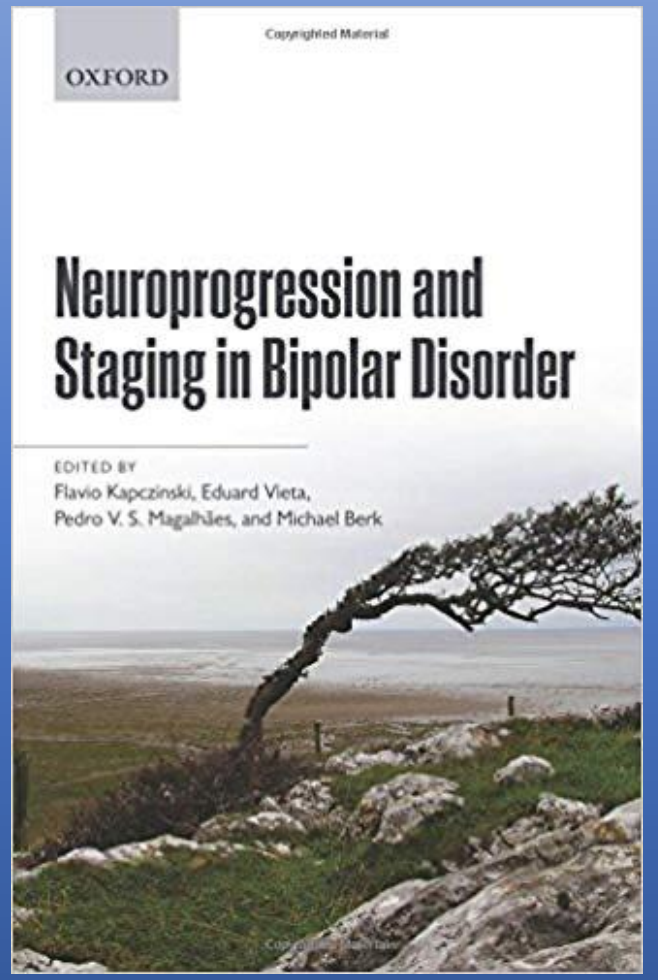
Neuro-Progression: A new perspective

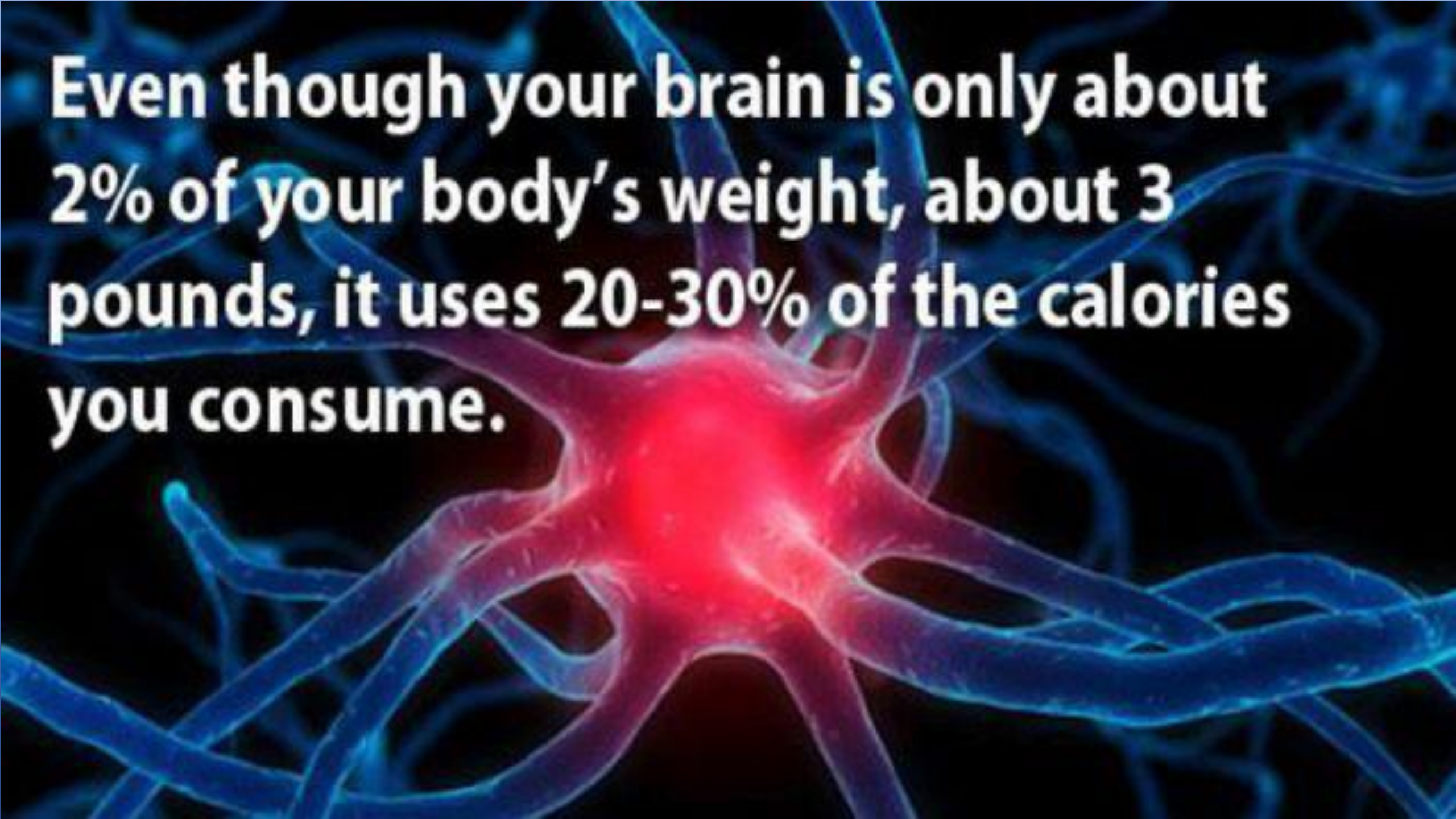
The pathological reorganization of the

central nervous system along the course of severe mental disorders. In BD, neural substrate reactivity is changed by repeated mood episodes, promoting a brain rewiring that leads to an increased vulnerability to

life stress.

Clinical stage	Definition	Potential interventions
0	Increased risk of severe mood disorder (e.g. family history, abuse, substance use), but currently asymptomatic	Mental health literacy, self help
1a	Mild or non-specific symptoms of mood disorder	Formal mental health literacy Psychoeducation Substance abuse reduction Cognitive behavioural therapy
1b	Prodromal features (ultra-high risk)	As for 1a plus therapy for episode: phase-specific or mood stabilizer
2	First episode of full-threshold mood disorder	As for 1b plus case management and vocational rehabilitation
3a	Recurrence of subthreshold mood symptoms	As for 2 plus emphasis on maintenance medications and psychosocial strategies for full remission
3b	First full-threshold relapse	As for 3a plus relapse prevention strategies
3c	Multiple relapses	As for 3b plus combination mood stabilizers
4	Persistent unremitting illness	As for 3c plus clozapine and other tertiary therapies Social participation despite disability

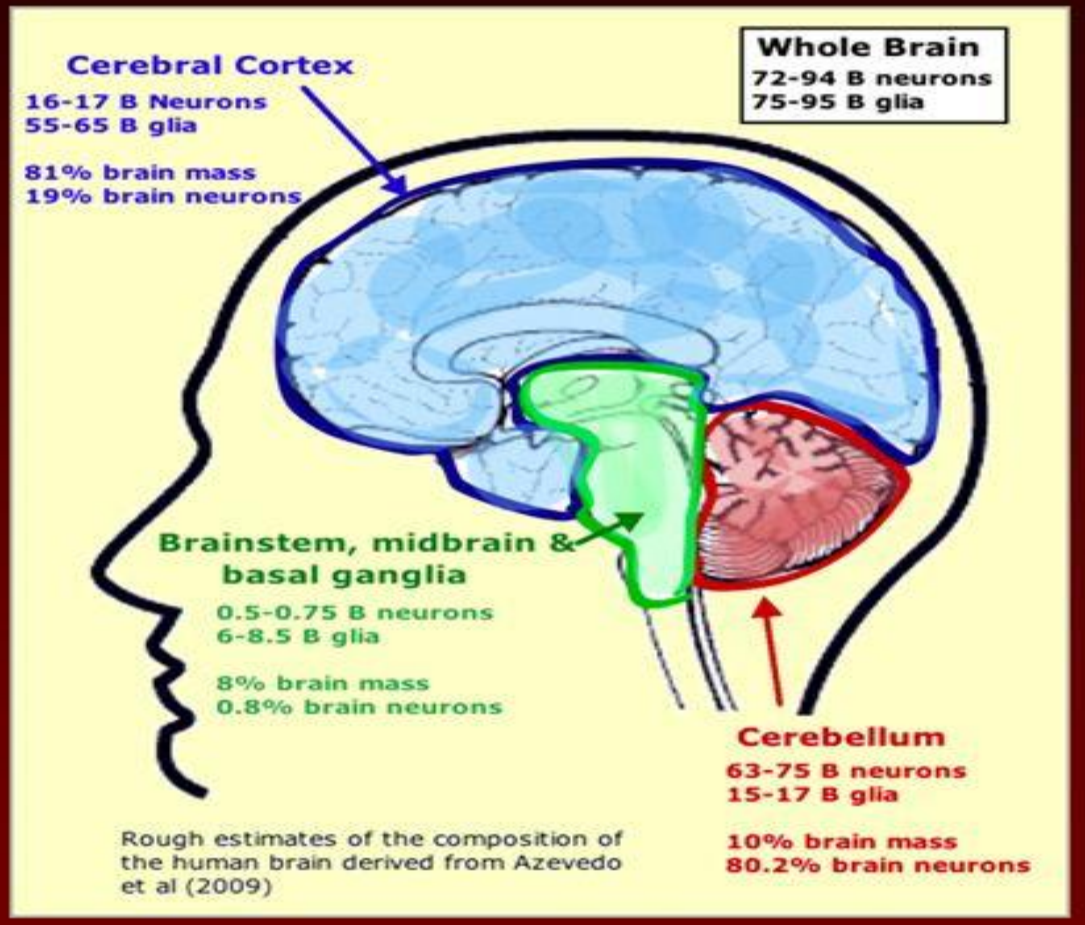



Even though your brain is only about 2% of your body's weight, about 3 pounds, it uses 20-30% of the calories you consume.

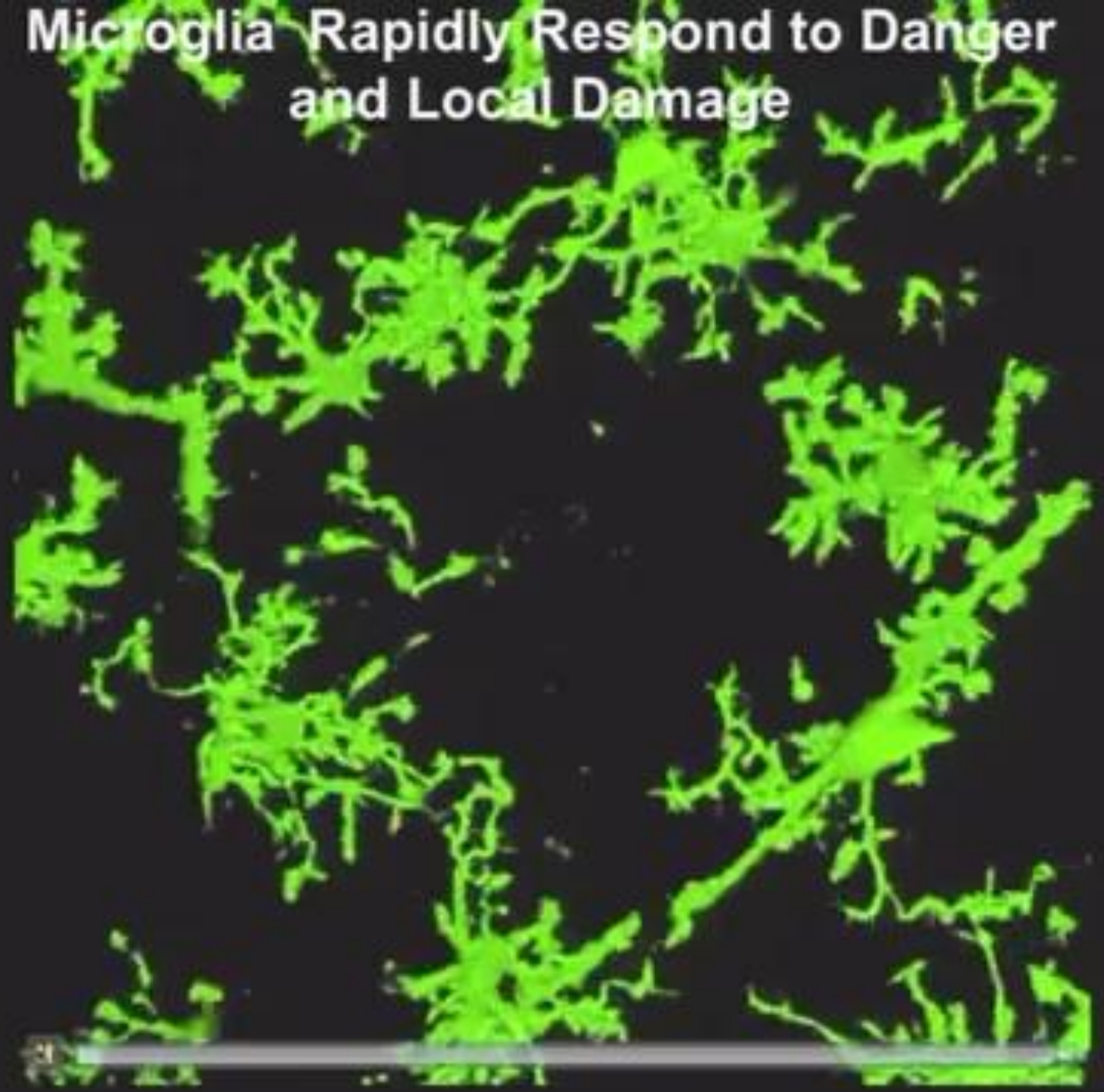
New Estimates of Glial Cell Numbers

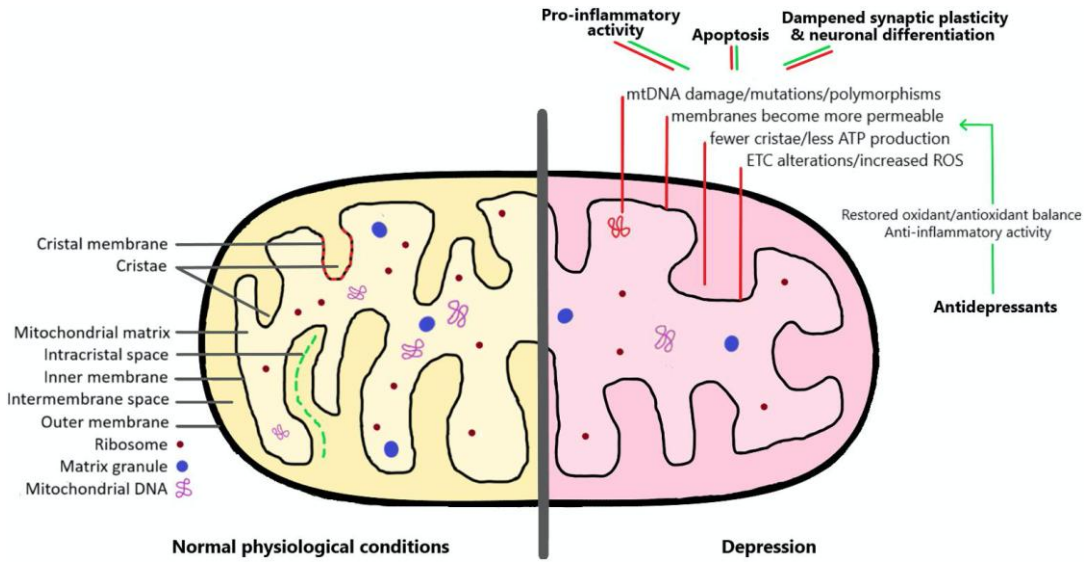
- Old belief: 10 glial cells for each neuron (glial cells only 10% of size of neuron)
- New data: ~ 1:1 ratio of glial cells to neurons, BUT
- Uneven ratios (G:N) across brain
  - Cortex: 3.7:1
  - Cerebellum: 0.23:1
  - Brain stem *et al*: 11.4:1

(Lent et al. 2012)



Microglia Rapidly Respond to Danger and Local Damage





frontiers in Neuroscience

REVIEW
published: 06 June 2018
doi: 10.3389/fnins.2018.00386

Mitochondria and Mood: Mitochondrial Dysfunction as a Key Player in the Manifestation of Depression

*Josh Allen[1], Raquel Romay-Tallon[1], Kyle J. Brymer[2], Hector J. Caruncho[1] and Lisa E. Kalynchuk[1]**

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Specialty section:
This article was submitted to Neurodegeneration, a section of the journal Frontiers in Neuroscience

Received: *27 February 2018*
Accepted: *22 May 2018*
Published: *06 June 2018*

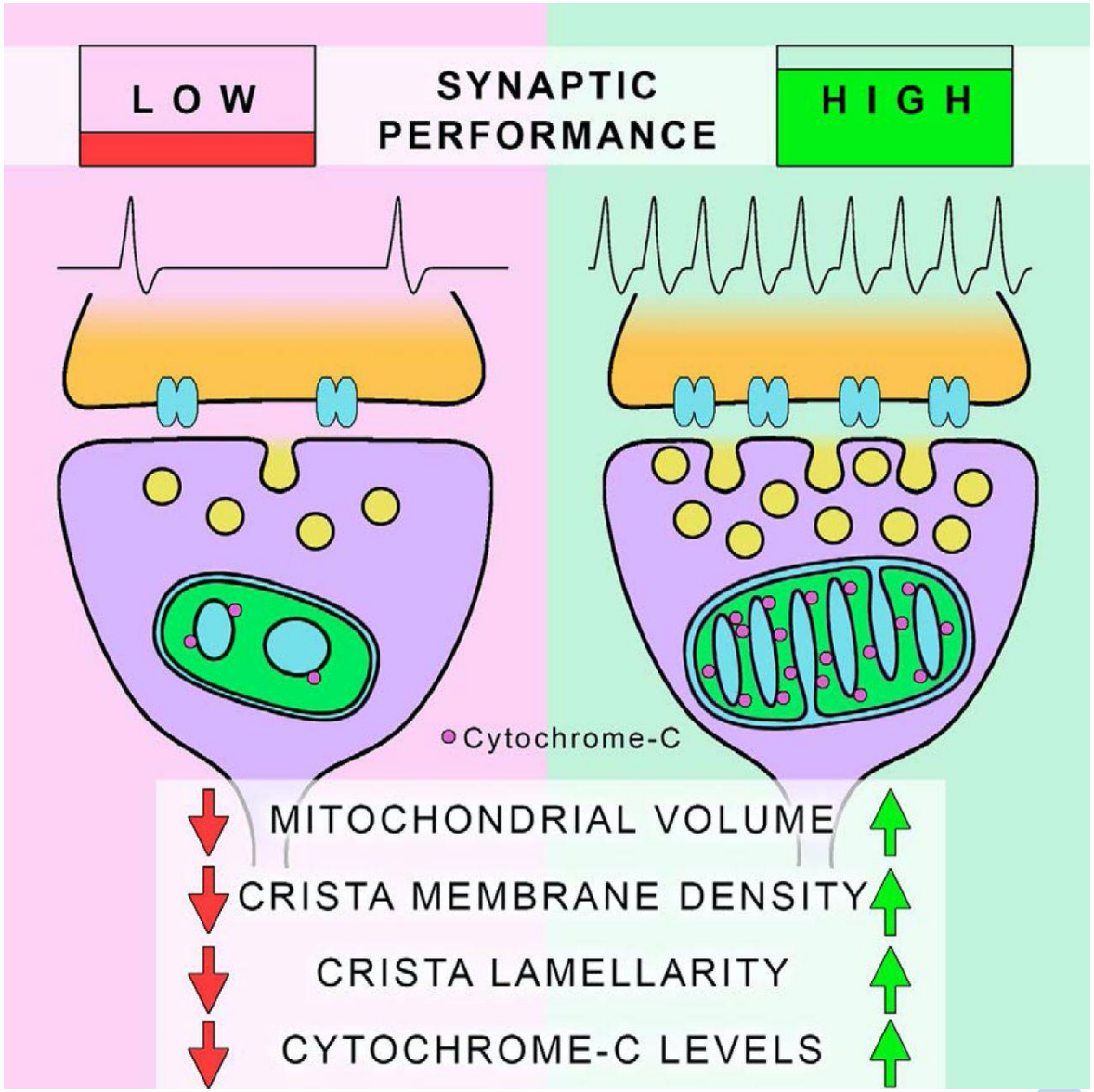
Citation:
Allen J, Romay-Tallon R, Brymer KJ, Caruncho HJ and Kalynchuk LE (2018) Mitochondria and Mood: Mitochondrial Dysfunction as a Key Player in the Manifestation of Depression. Front. Neurosci. 12:386. doi: 10.3389/fnins.2018.00386

Human and animal studies suggest an intriguing link between mitochondrial diseases and depression. Although depression has historically been linked to alterations in monoaminergic pharmacology and adult hippocampal neurogenesis, new data increasingly implicate broader forms of dampened plasticity, including plasticity within the cell. Mitochondria are the cellular powerhouse of eukaryotic cells, and they also regulate brain function through oxidative stress and apoptosis. In this paper, we make the case that mitochondrial dysfunction could play an important role in the pathophysiology of depression. Alterations in mitochondrial functions such as oxidative phosphorylation (OXPHOS) and membrane polarity, which increase oxidative stress and apoptosis, may precede the development of depressive symptoms. However, the data in relation to antidepressant drug effects are contradictory: some studies reveal they have no effect on mitochondrial function or even potentiate dysfunction, whereas other studies show more beneficial effects. Overall, the data suggest an intriguing link between mitochondrial function and depression that warrants further investigation. Mitochondria could be targeted in the development of novel antidepressant drugs, and specific forms of mitochondrial dysfunction could be identified as biomarkers to personalize treatment and aid in early diagnosis by differentiating between disorders with overlapping symptoms.

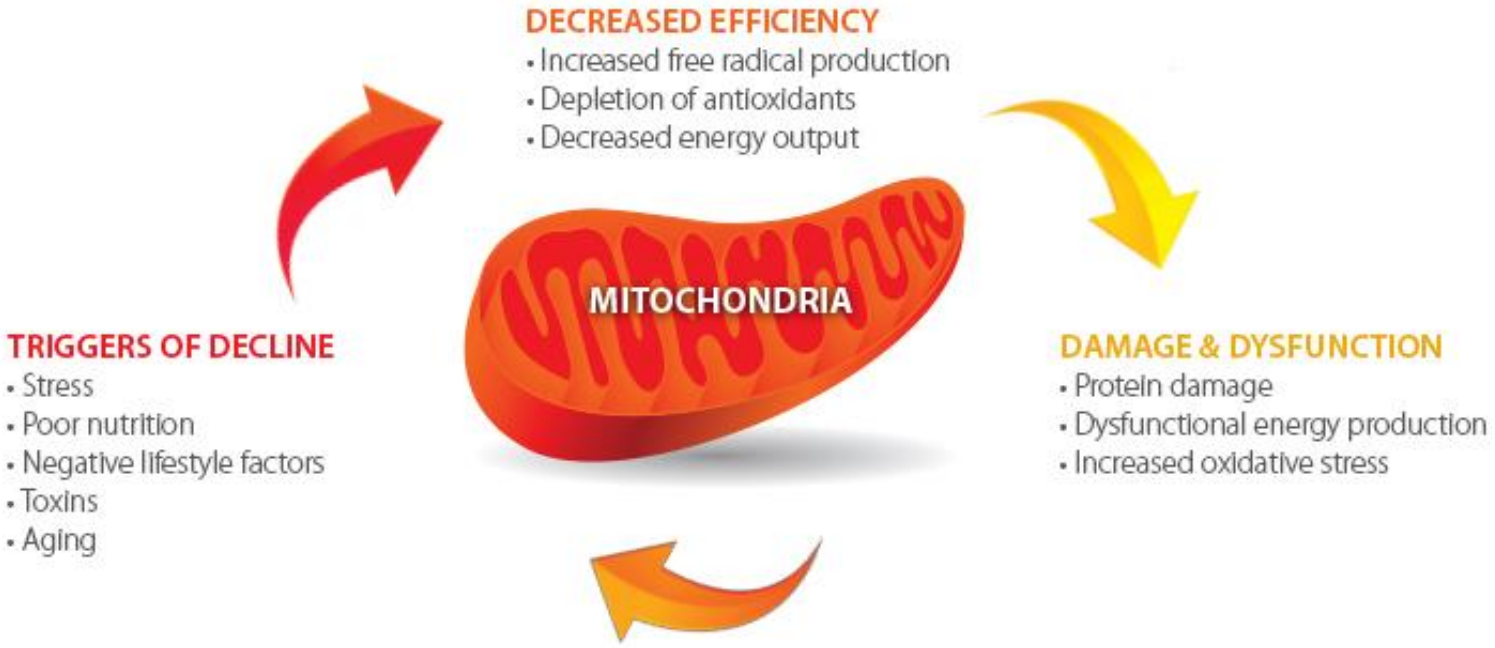
Keywords: depression, behavior, reelin, mitochondria, oxidative phosphorylation, antidepressants

MITOCHONDRIA

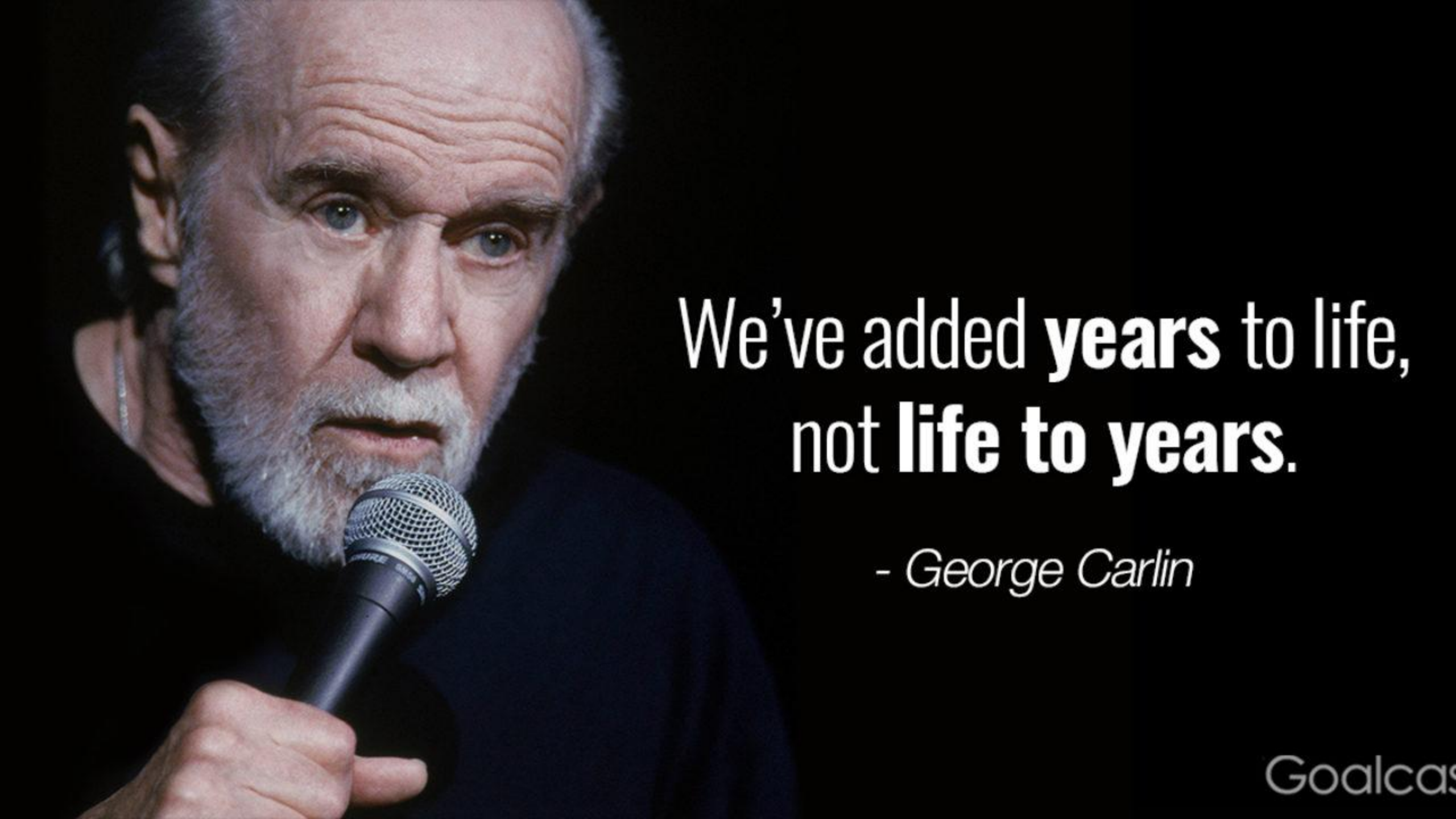
Mitochondria are the main energy factories of eukaryotic cells. The brain is particularly dependent on mitochondrial activity due to both its high levels of energy use and its inability to store large amounts of energy reserves in the form of glycogen. As a result of the their roles in energy production, mitochondria also generate reactive oxygen species (ROS) that may have a toxic effects in cells. In addition, mitochondria also play a prominent role in the regulation of apoptotic cell death (for examples, see Davidson and Hardison, 1984; Herrmann and Neupert, 2000; Calabrese et al., 2001; Chan, 2006; Chipuk et al., 2006; Fattal et al., 2006; McBride et al., 2006; Youle and van der Bliek, 2012; Tobe, 2013; Bansal and Kuhad, 2016).


LOW
SYNAPTIC PERFORMANCE
HIGH
Cytochrome-C
MITOCHONDRIAL VOLUME
CRISTA MEMBRANE DENSITY
CRISTA LAMELLARITY
CYTOCHROME-C LEVELS

THE VICIOUS CYCLE OF MITOCHONDRIAL DECLINE



MITOCHONDRIAL DYSFUNCTION HAS BEEN ASSOCIATED WITH:


We've added **years** to life,
not **life to years**.
- George Carlin
Goalcas

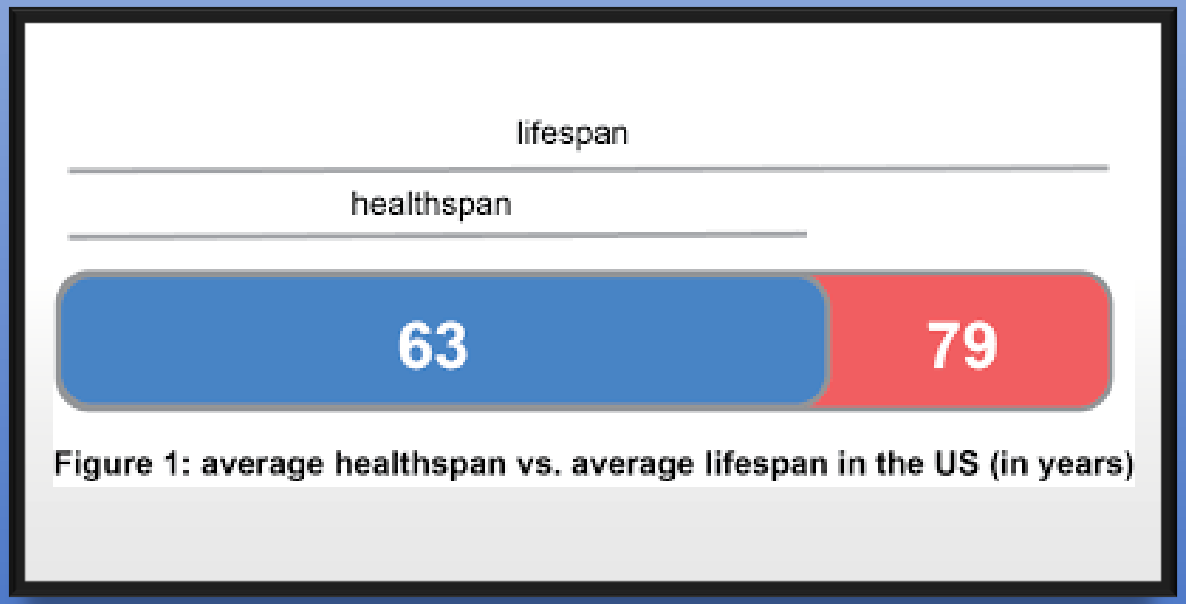
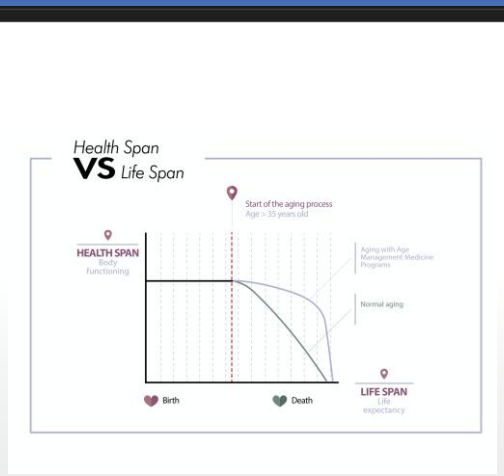
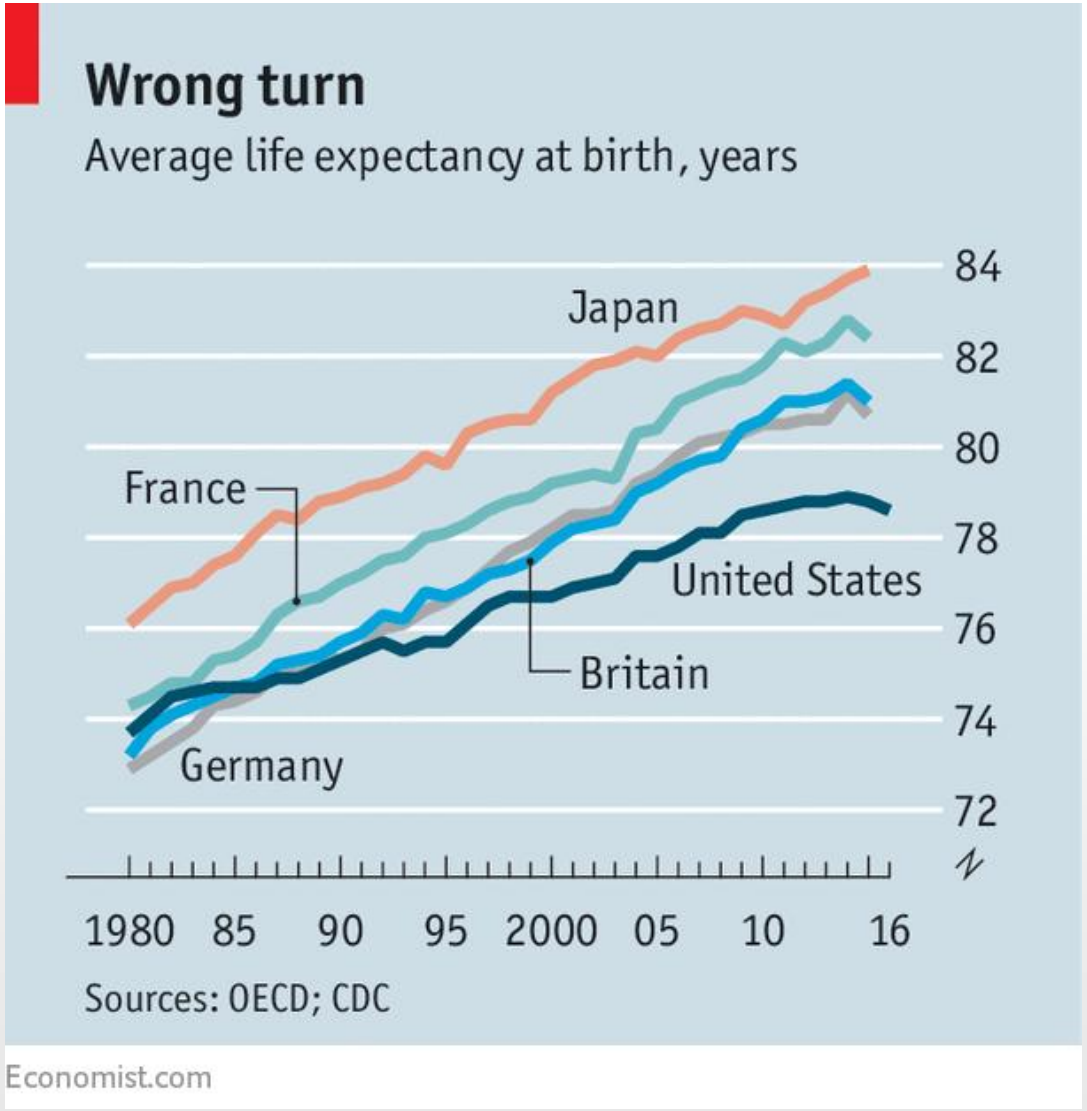


Figure 1: average healthspan vs. average lifespan in the US (in years)





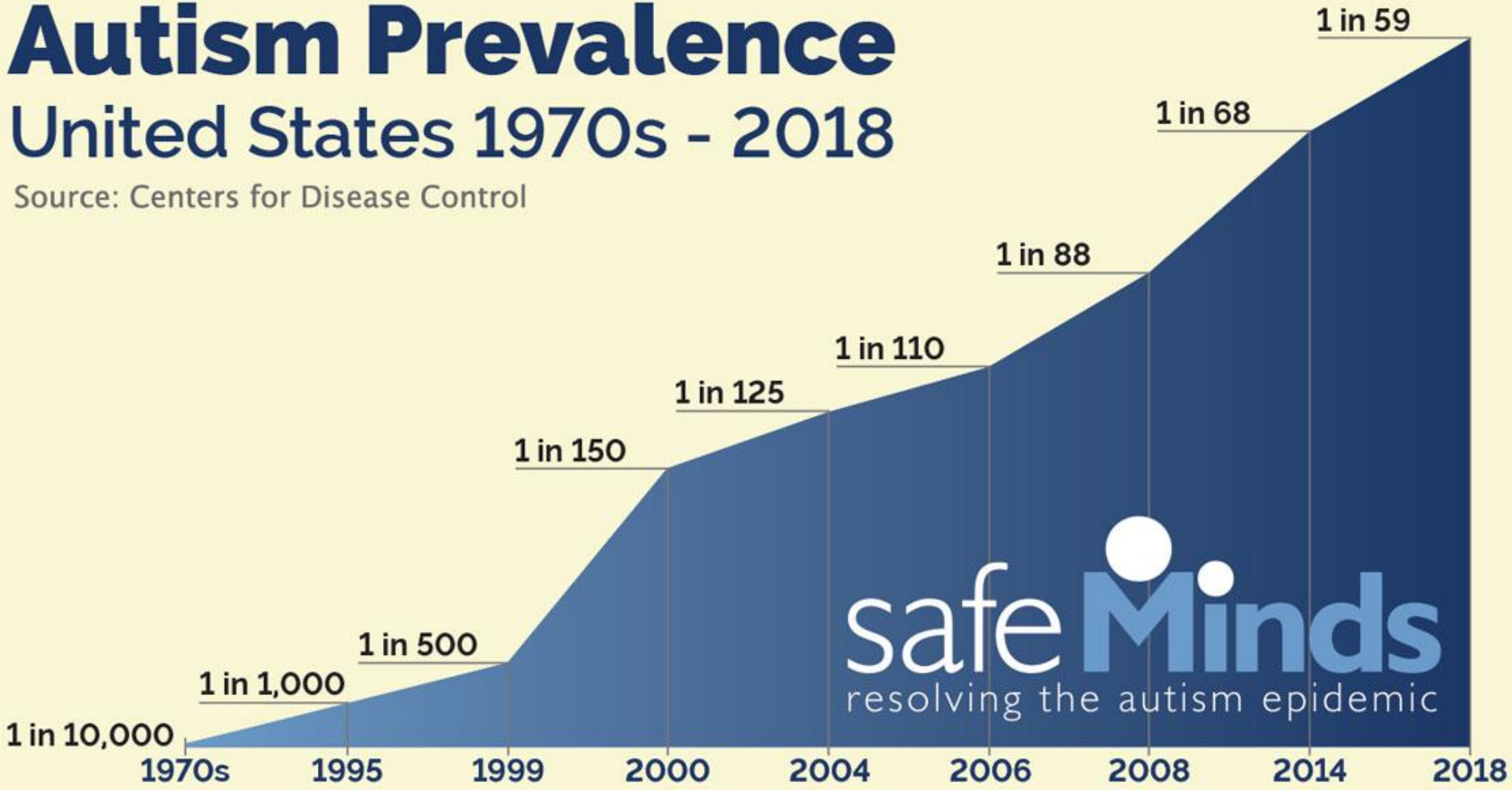
1 in 59

children living in ADDM sites are identified with ASD

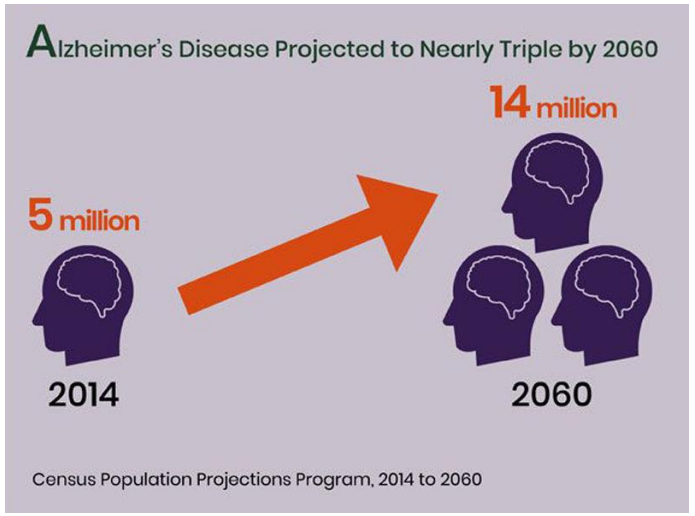
Autism Prevalence

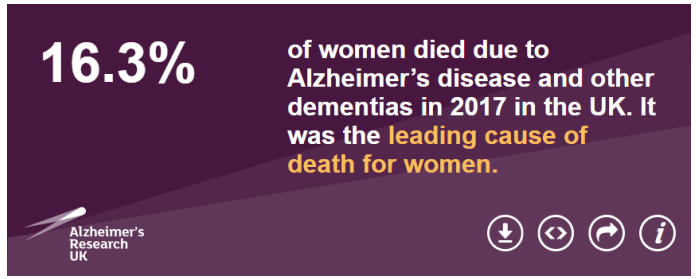
United States 1970s - 2018

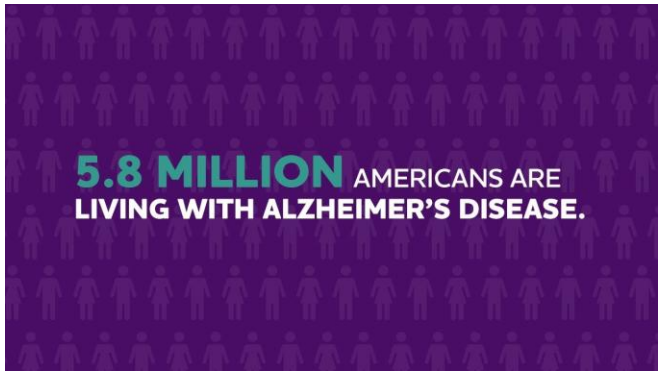
Source: Centers for Disease Control

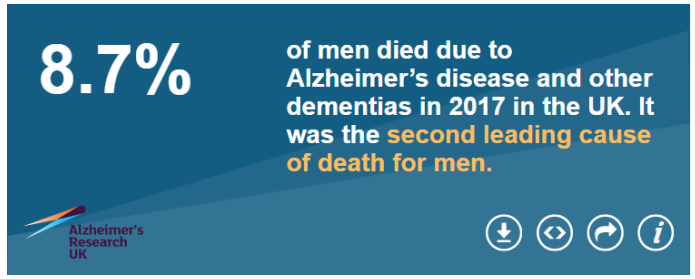



6TH
LEADING CAUSE OF DEATH
IN THE UNITED STATES

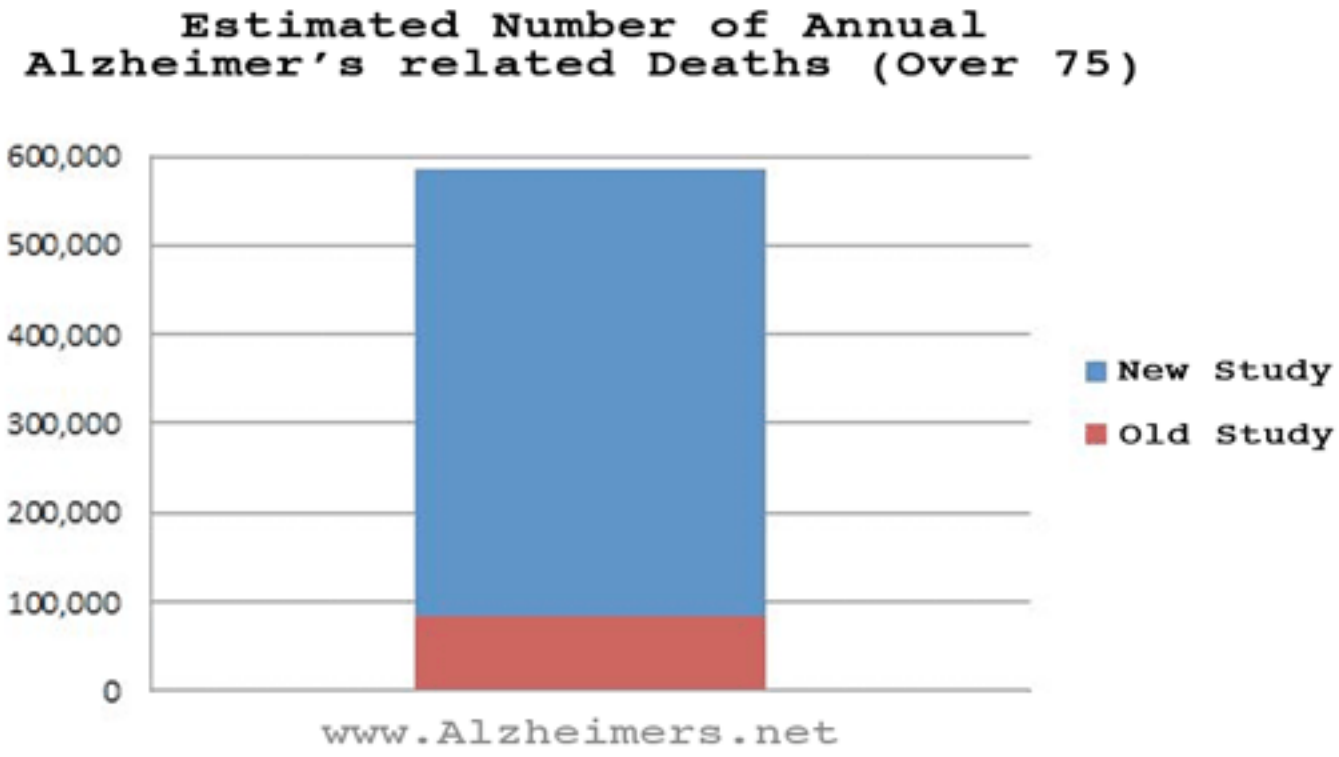

Alzheimer's Disease Projected to Nearly Triple by 2060
14 million
5 million
2014
2060
Census Population Projections Program, 2014 to 2060

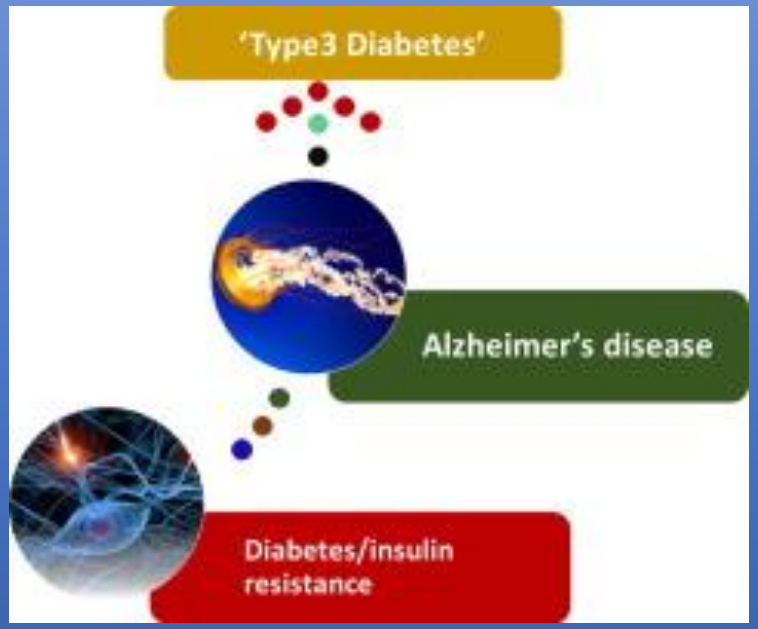

16.3%
of women died due to Alzheimer's disease and other dementias in 2017 in the UK. It was the leading cause of death for women.
Alzheimer's Research UK

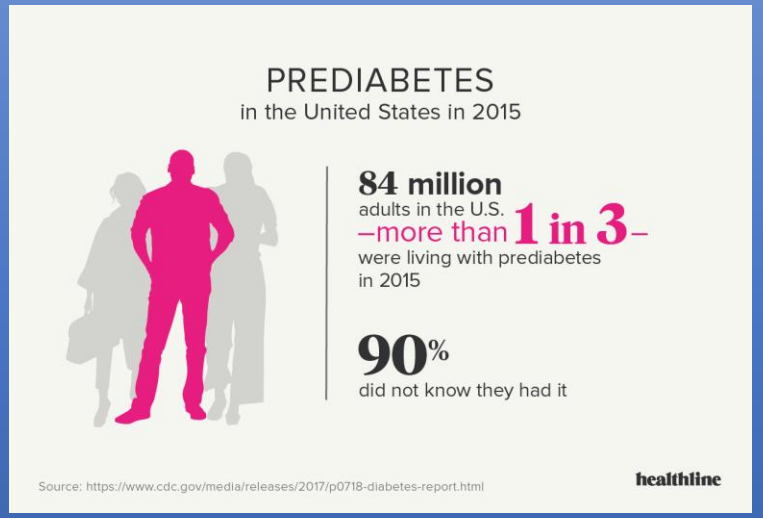

5.8 MILLION AMERICANS ARE
LIVING WITH ALZHEIMER'S DISEASE.

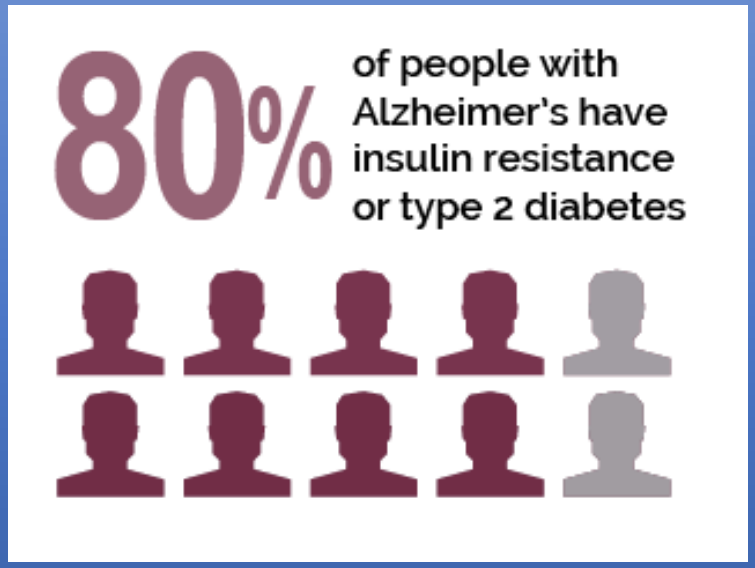

8.7%
of men died due to Alzheimer's disease and other dementias in 2017 in the UK. It was the second leading cause of death for men.
Alzheimer's Research UK

Deaths from Alzheimer's Could Be More Than Reported




'Type3 Diabetes'
Alzheimer's disease
Diabetes/insulin resistance


PREDIABETES
in the United States in 2015
84 million
adults in the U.S.
–more than 1 in 3–
were living with prediabetes
in 2015
90%
did not know they had it
Source: https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html
healthline

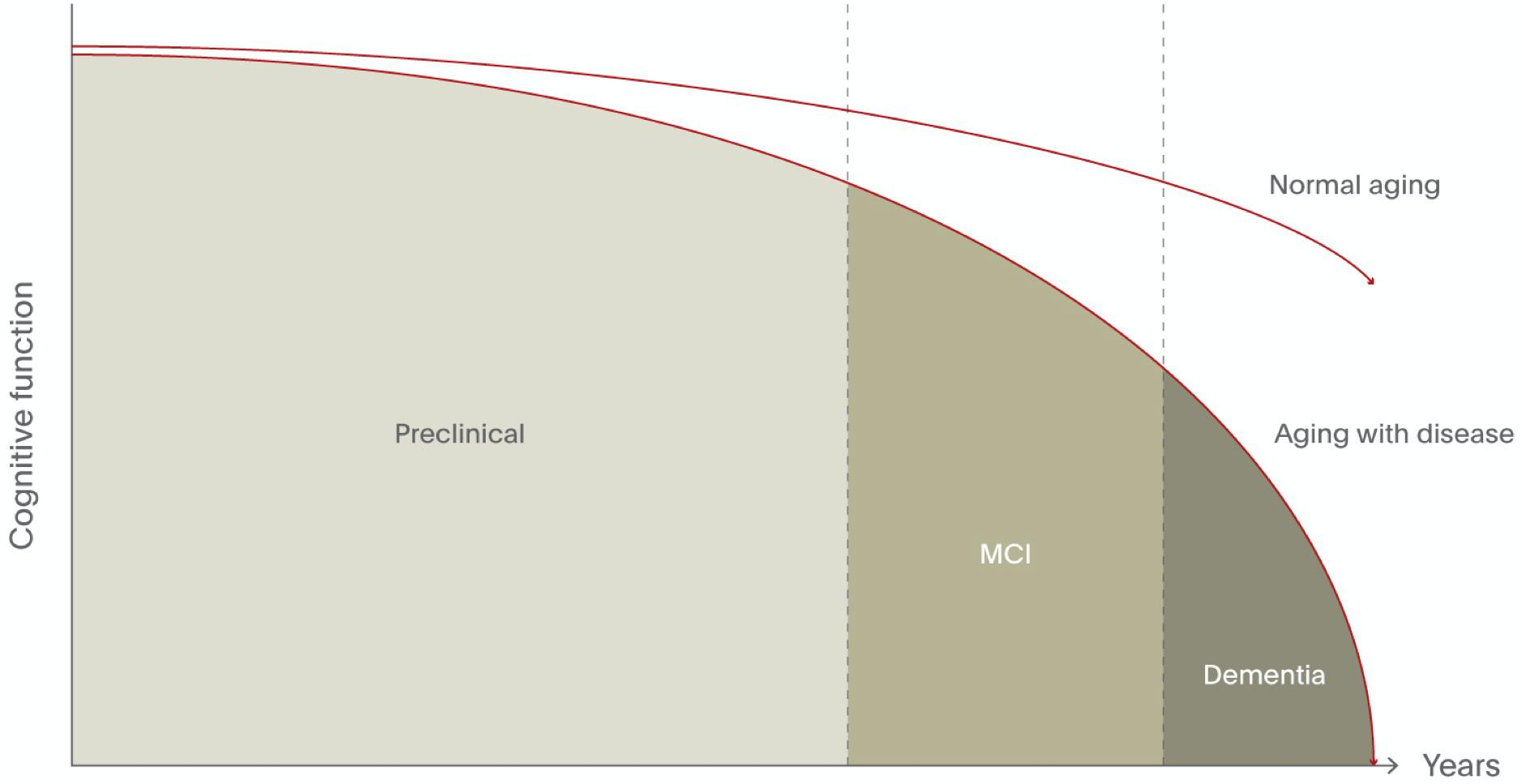

80%
of people with Alzheimer's have insulin resistance or type 2 diabetes

ALZHEIMER'S DRUG ATTRITION

A decade's worth of clinical trials identified only one approved drug.

©nature

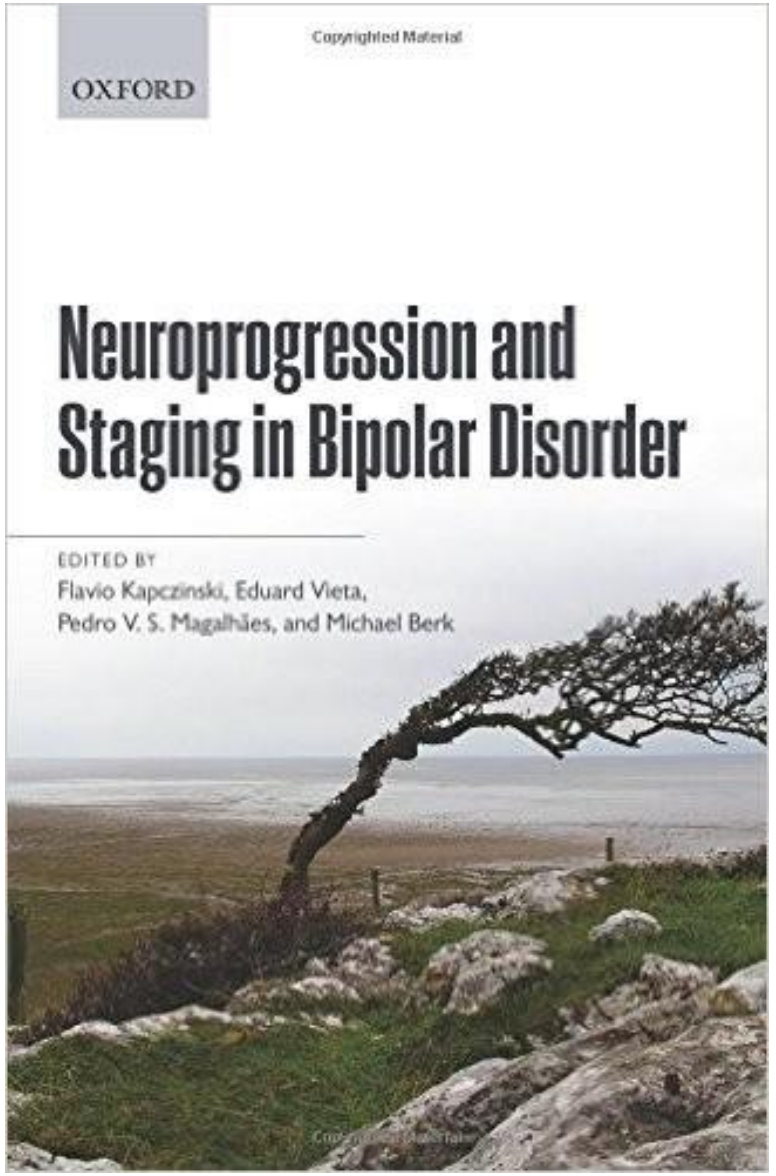
Hypothetical model for the pathological–clinical continuum of Alzheimer's disease



MCI=mild cognitive impairment

Sperling et al. Alzheimers Dement 2011;7(3):280–292


DEPRESSION
—
BY
THE
NUMBERS
32
Median age when depression is diagnosed
35%
Percentage of adults who do not receive treatment
17.7M
Annual number of Americans who experience depression
50%
The chance of having a second episode of depression
#1
Depression is the leading cause of disability in the U.S.
SOURCES: American Psychological Association; NIMH
Clinical Psychology Review
healthcentral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Neuroprogression and Staging in Bipolar Disorder
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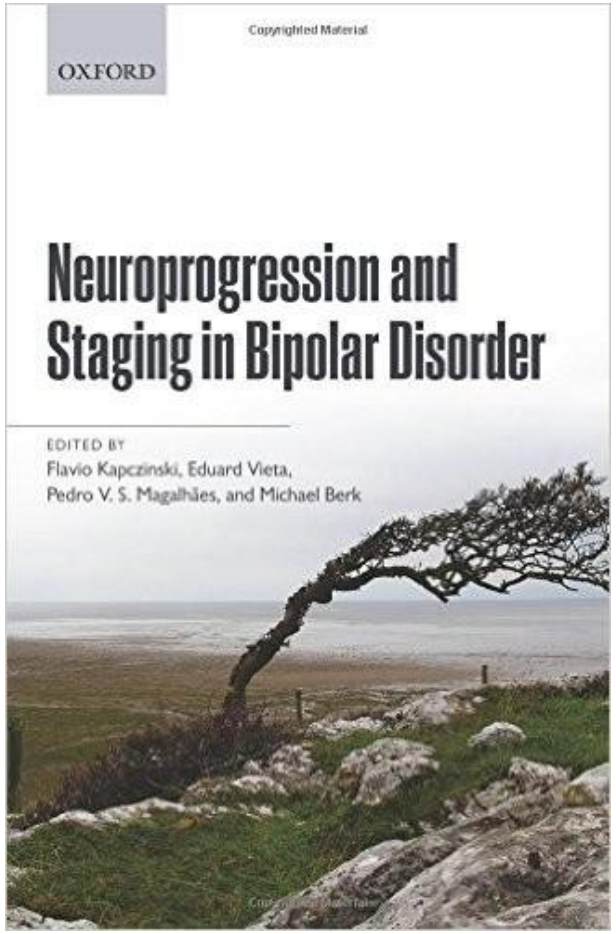
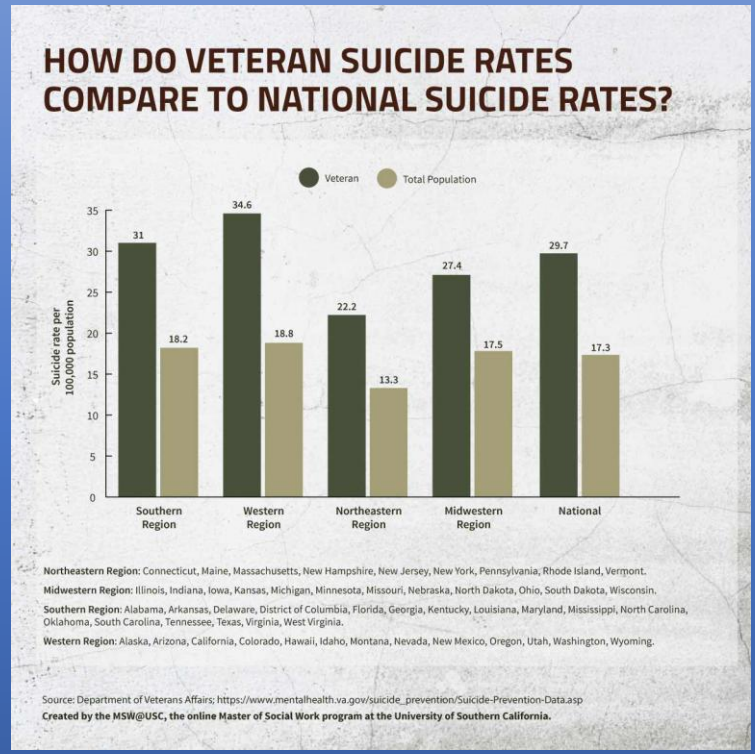


21% OF PEOPLE WHOSE DEPRESSIVE SYMPTOMS INCREASED OVER TIME

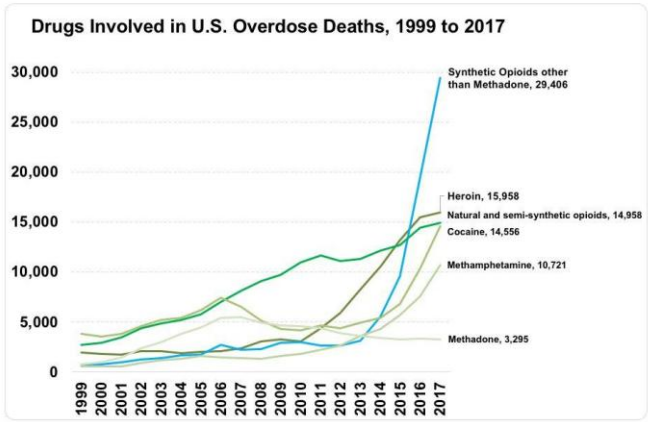
WERE EVENTUALLY DIAGNOSED WITH DEMENTIA

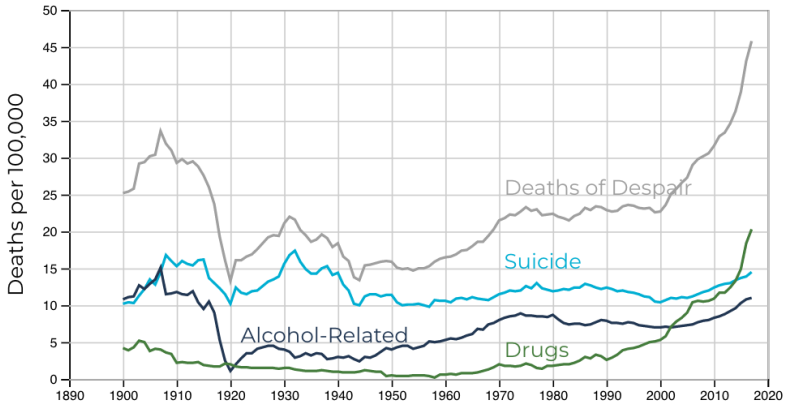
Antidepressant Black Box Warning

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. anyone considering the use of xxxxx or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need...




Social isolation has the same mortality and risk factors as smoking a pack of cigarettes a day.
Starkey


Drugs Involved in U.S. Overdose Deaths, 1999 to 2017
30,000
25,000
20,000
15,000
10,000
5,000
0
Synthetic Opioids other than Methadone, 29,406
Heroin, 15,958
Natural and semi-synthetic opioids, 14,958
Cocaine, 14,556
Methamphetamine, 10,721
Methadone, 3,295
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017


Deaths per 100,000
50
45
40
35
30
25
20
15
10
5
0
Deaths of Despair
Suicide
Alcohol-Related
Drugs
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
2020

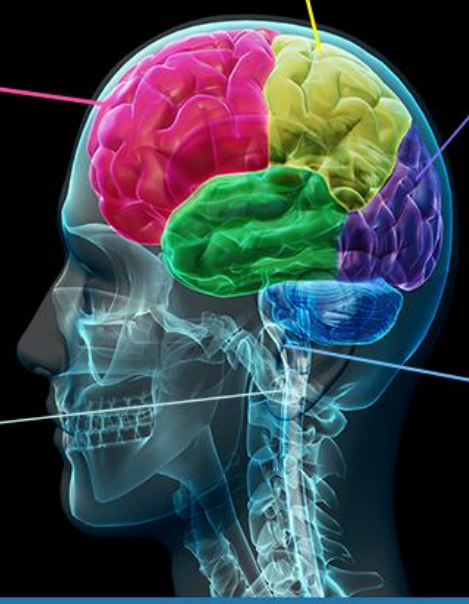
DIGITAL DEMENTIA

A sensory mismatch in the brain from over utilization of technology and excessive slouched sitting postures, leading to signs and symptoms of dementia.

UNDER-STIMULATION OF THE PARIETAL LOBE:
For proprioception and spatial awareness

UNDER-STIMULATION OF THE FRONTAL LOBE:
For reading, motivation, problem solving, memory, and movement

OVER-STIMULATION OF THE OCCIPITAL LOBE:
Due to bombardment of visual signals from technologic devices



UNDER-STIMULATION OF THE PMRF:
For proper posture and pain reduction

UNDER-STIMULATION OF THE CEREBELLUM:
For accuracy, balance, and coordination of movem

AMERIC
POSTURE INST

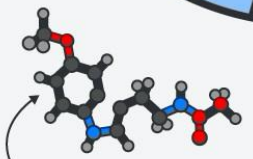
How exposure to **blue light** affects your brain and body

BY DISRUPTING MELATONIN **SMARTPHONE LIGHT** RUINS SCHEDULES. THIS LEADS TO KINDS OF **HEALTH PROBLEM**

The disruption to your sleep schedule might leave you distracted and impair your **MEMORY** the next day.

A poor night's sleep caused by smartphone light can make it **HARDER TO LEARN.**

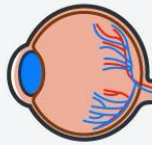
Over the long term, not getting enough sleep can lead to **NEUROTOXIN** buildup that makes it even harder for you to get good sleep.



People whose melatonin levels are suppressed and whose body clocks are thrown off by light exposure are more prone to **DEPRESSION.**

By disrupting melatonin and sleep, smartphone light can also mess with the hormones that control hunger, potentially increasing **OBESITY RISK.**

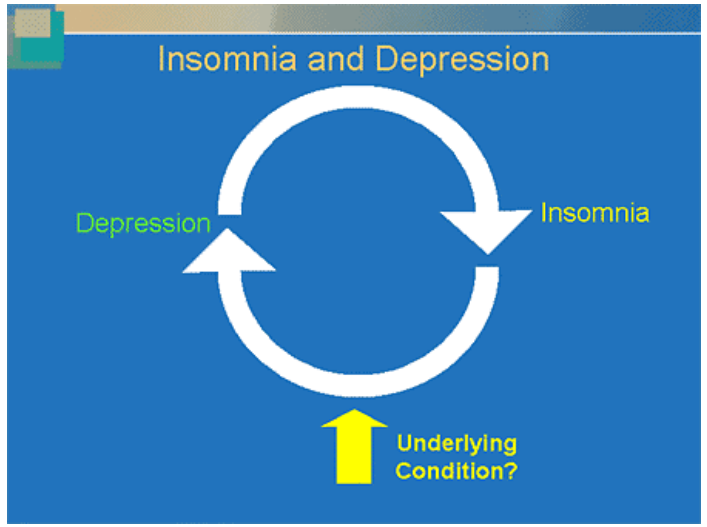
There's some evidence th light could damage our v harming the **RETINA** ove though more research is

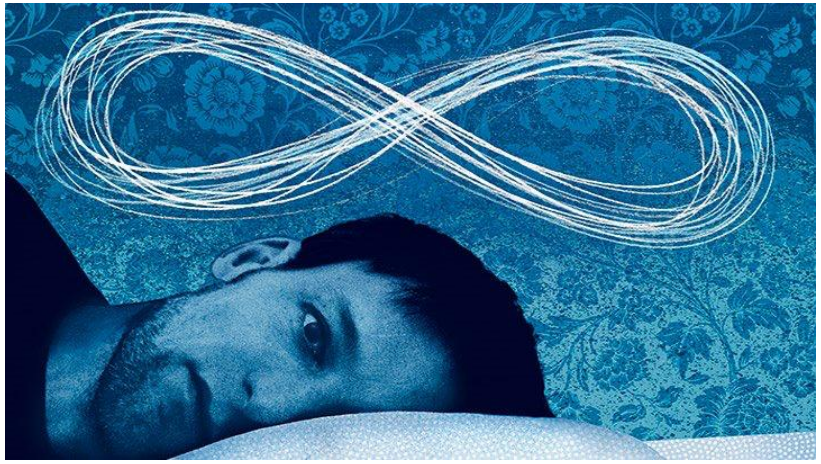


Researchers are inves whether or not blue li lead to **CATARACTS.**

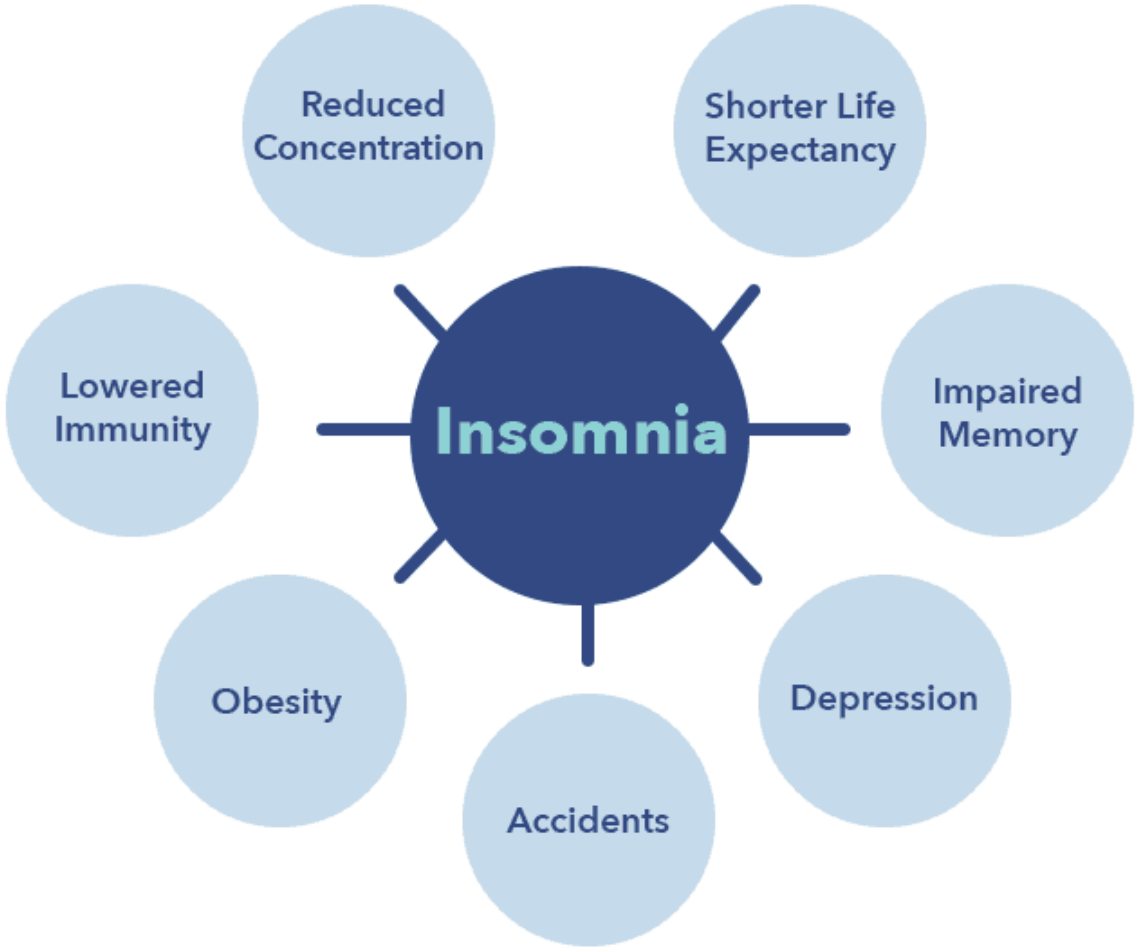
There's a connection bet exposure at night and the sleep that come with it a increased risk of breast a prostate **CANCERS.**

SOURCES: Nature Neuroscience; Harvard Health Publications; ACS, Sleep Med Rev, American Macular Degeneration Foundation; European Society of Cataract and Refractive Surgeons; JAMA Neurology





Risks of Insomnia

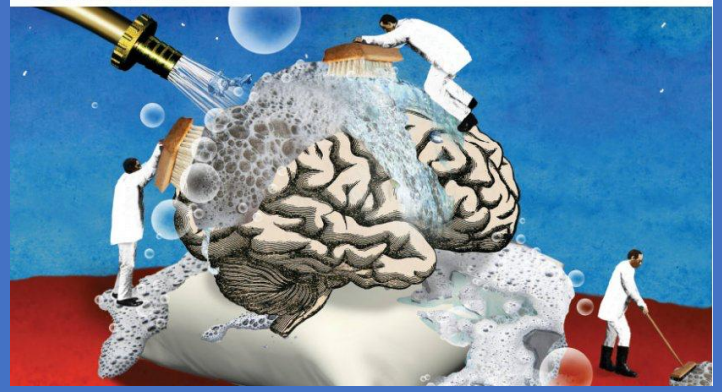


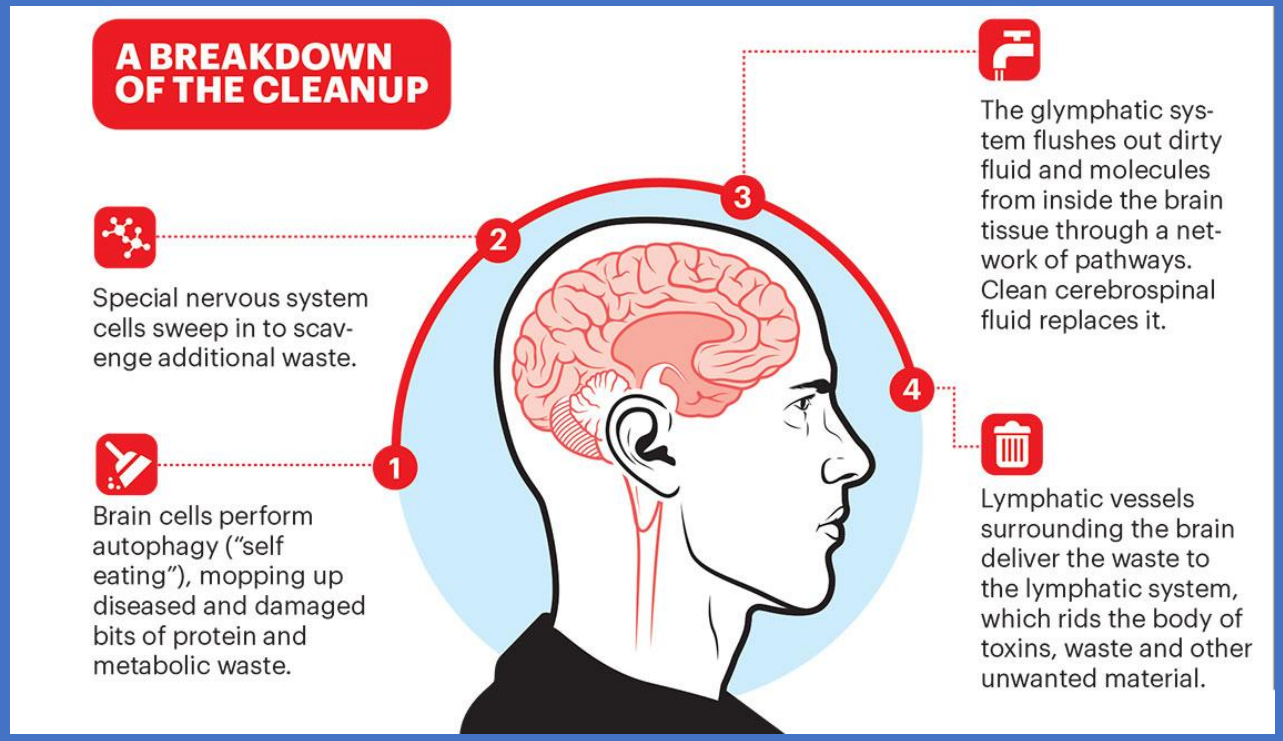
FEATURE BIOMEDICINE, NEUROSCIENCE, MENTAL HEALTH

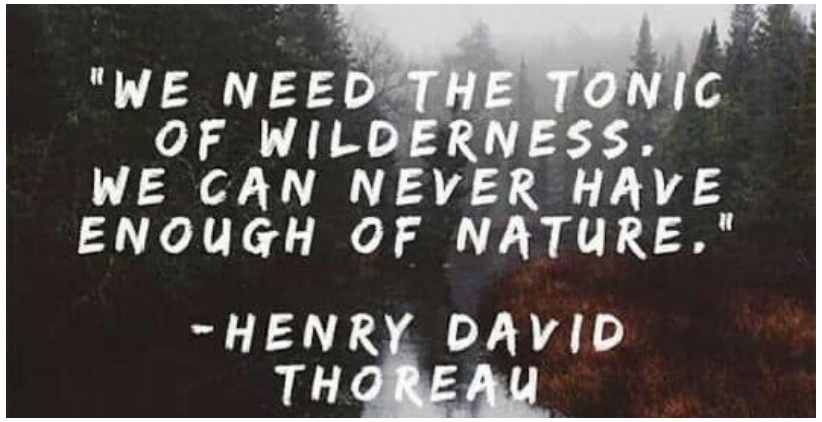
The brain may clean out Alzheimer's plaques during sleep

If sleep deprivation puts garbage removal on the fritz, the memory-robbing disease may develop

BY LAURA BEIL 6:00AM, JULY 15, 2018







NATURE-DEFICIT DISORDER

WHAT IS IT?

The combined psychological, physical and cognitive costs we suffer due to our alienation from nature, especially affecting children in vulnerable developing years.

CAUSES

- Parental fears
- Restricted access to natural areas
- Increasing consumption of electronic media

COSTS

- Attention and mood disorders
- Lower grades
- Obesity
- Limited respect for the environment

WHAT CAN WE DO?

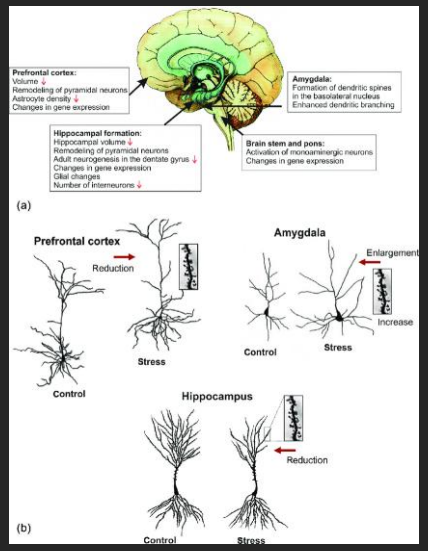
GO WILD!

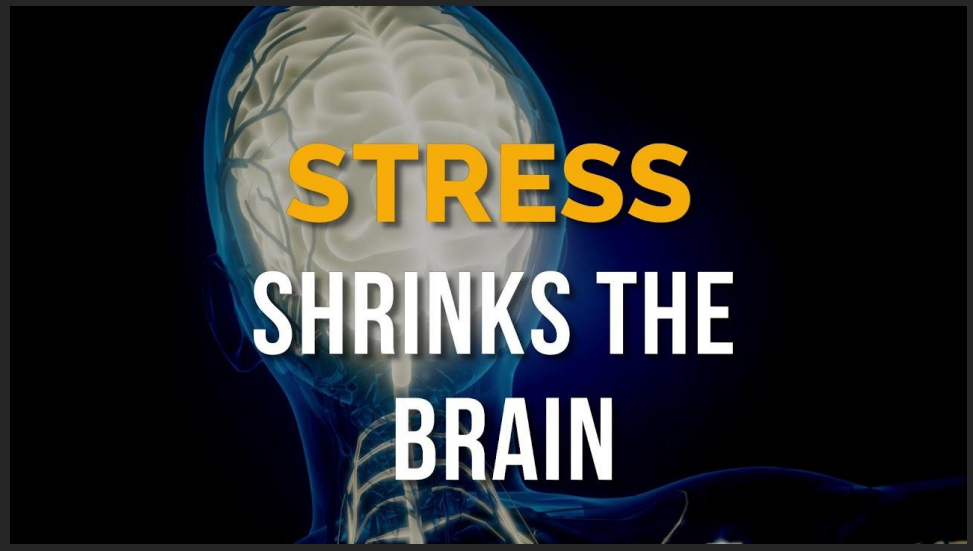
IGNITE CHILDREN'S INTEREST IN THE OUTDOORS

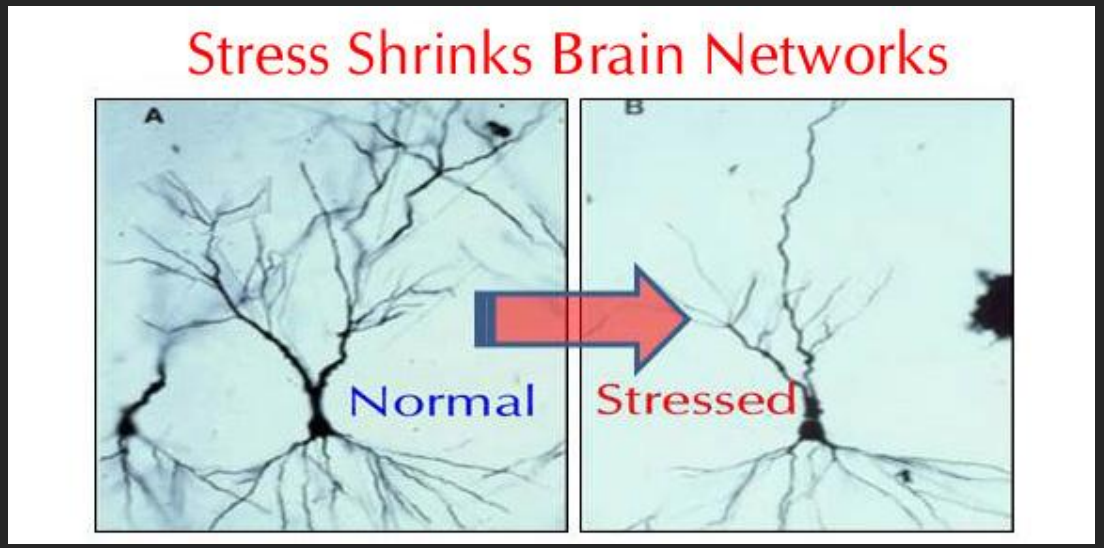
ENCOURAGE NATURE EXPLORATION

THE WILDERNESS SOCIETY

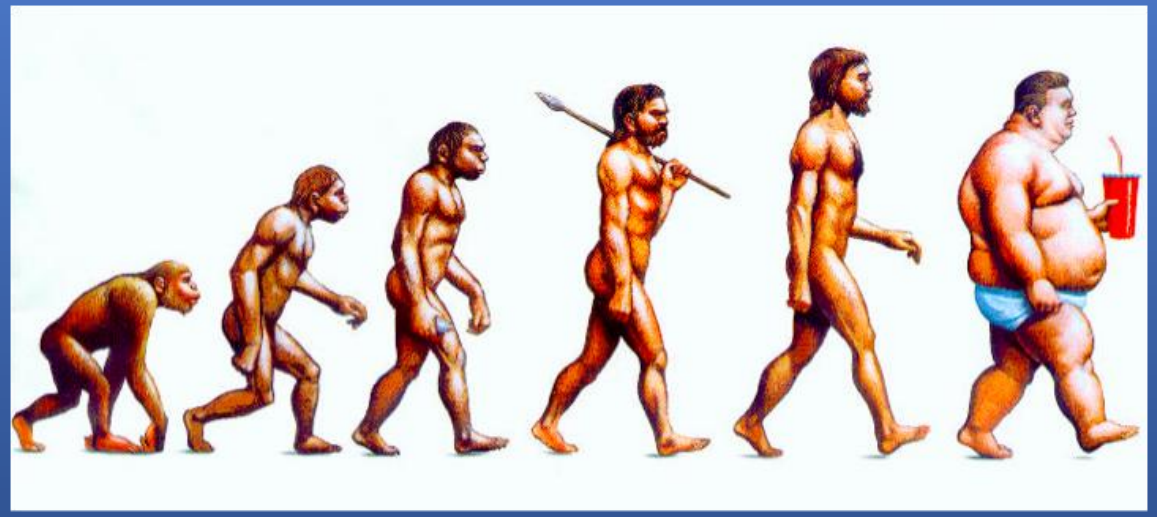
WILDERNESS.ORG


Prefrontal cortex:
Volume ↓
Remodeling of pyramidal neurons
Astrocyte density ↓
Changes in gene expression
Amygdala:
Formation of dendritic spines in the basolateral nucleus
Enhanced dendritic branching
Hippocampal formation:
Hippocampal volume ↓
Remodeling of pyramidal neurons
Adult neurogenesis in the dentate gyrus ↓
Changes in gene expression
Glial changes
Number of interneurons ↓
Brain stem and pons:
Activation of monoaminergic neurons
Changes in gene expression
(a)
Prefrontal cortex
Reduction
Stress
Control
Amygdala
Enlargement
Increase
Control
Stress
Hippocampus
Reduction
(b)
Control
Stress

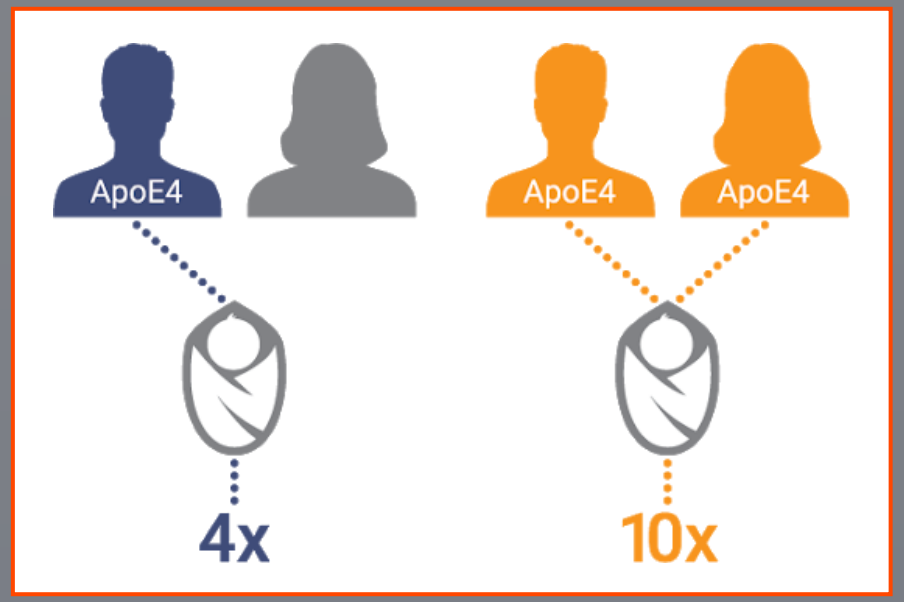

STRESS
SHRINKS THE
BRAIN

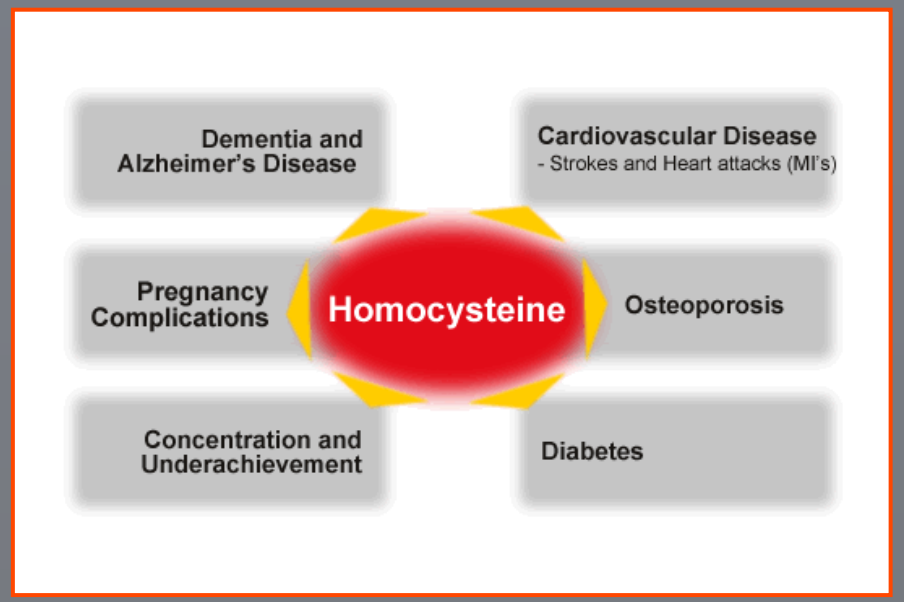

Stress Shrinks Brain Networks
A
B
Normal
Stressed


MISMATCH
PODIUM




CLICK -
CLICK..





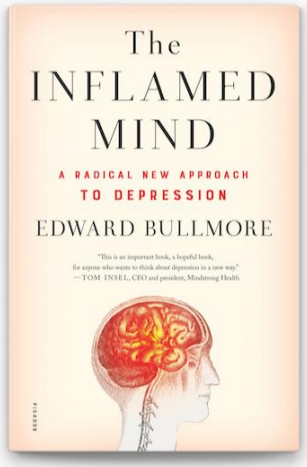
What is comorbidity?

- Defined as the co-occurrence of two or more disorders in the same person (Matson & Nebel-Schwaim, 2007).
- A comorbid condition is a second order diagnosis which offers core symptoms that differ from the first disorder (Mannion & Leader, 2013).

- **The Semmelweis** reflex (or effect) is a metaphor for the reflex-like tendency to reject new evidence or new knowledge because it contradicts established norms, beliefs or paradigms.

Table 1 – Clinical predictors of treatment resistance related to inflammation

Predictor of antidepressant nonresponse	Relationship to inflammation
Obesity	Dose-response relationship between BMI and inflammatory markers
Early life stress	Increased inflammation and inflammatory response to stress in exposed individuals
Medical illness	Increased inflammatory markers in diabetes, cardiovascular disease, and cancer
Personality disorders/anxiety	Increased inflammatory markers in patients with anxiety disorders, borderline personality disorder, and neuroticism

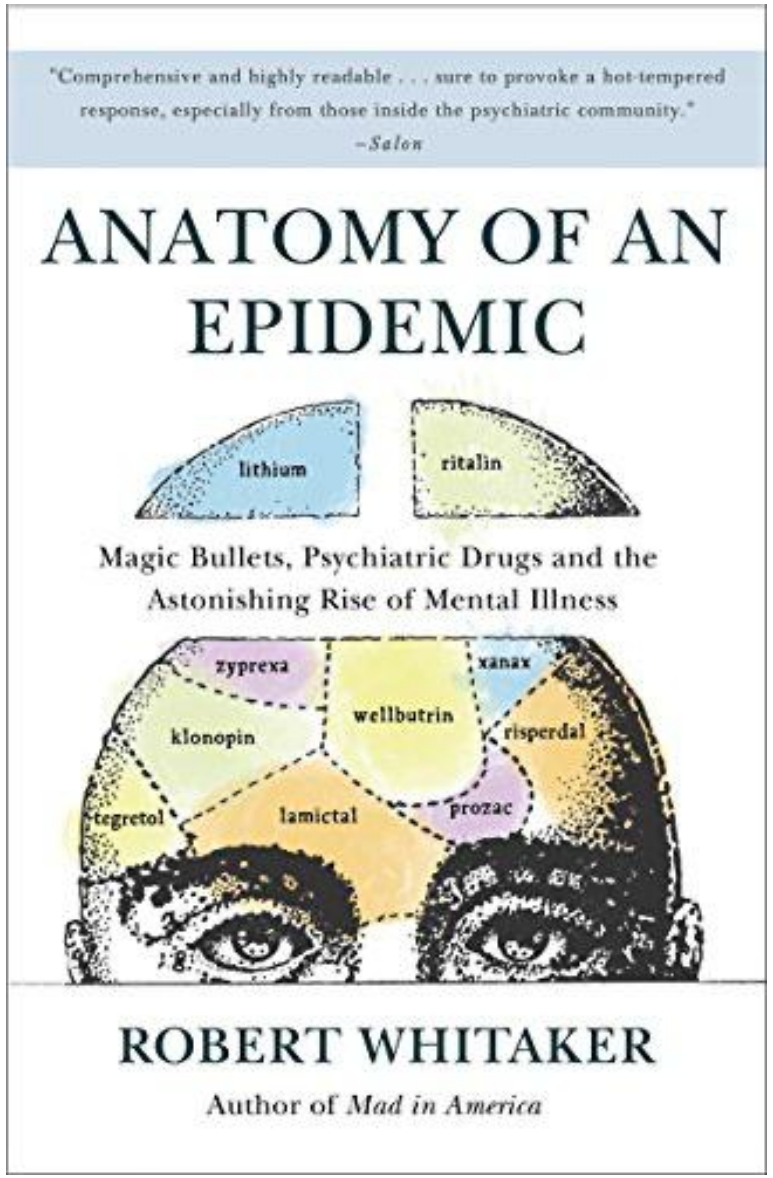


ON THE JOB Dr. Kline at his desk in the Rockland Research Institute, circa 1954.

HISTORY OF ANTIDEPRESSANTS

Iproniazid, the first modern antidepressant, was originally developed as an antitubercular drug in the early 1950's. In addition to its ability to treat tuberculosis, Iproniazid was observed to elevate mood and stimulate activity in many patients.

These effects led researchers to investigate the ability of iproniazid to treat the symptoms of depression. After promising preliminary findings reported in 1957, iproniazid was prescribed widely to patients with major depression. Within the first year it was available as an antidepressant, four hundred thousand depressed people were treated with iproniazid.



Original Paper

Minocycline as an adjunct for treatment-resistant depressive symptoms: A pilot randomised placebo-controlled trial

Psychopharm

Journal of Psychopharmacology
1–10
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DOI: 10.1177/0269881117724352
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Muhammad I Husain[1], Imran B Chaudhry[2], Nusrat Husain[3], Ameer B Khoso[2], Raza R Rahman[4], Munir M Hamirani[5], John Hodsoll[6], Inti Qurashi[7], John FW Deakin[8] and Allan H Young[6]

Abstract

Background: Evidence suggests that anti-inflammatory medication may be effective in the treatment of depressive symptoms. In this study, we aimed to investigate whether minocycline added to treatment as usual (TAU) for 3 months in patients with treatment-resistant depression will lead to an improvement in depressive symptoms.

Methods: Multi-site, 12-week, double-blind, placebo-controlled, pilot trial of minocycline added to TAU for patients suffering from DSM-5 major depressive disorder, whose current episode has failed to respond to at least two antidepressants. The primary outcome measure was mean change in Hamilton Depression Rating Scale (HAMD-17) scores from baseline to week 12. Secondary measures were the Clinical Global Impression scale (CGI), Patient Health Questionnaire-9 (PHQ-9), the Generalised Anxiety Disorder scale (GAD-7) and EuroQol (EQ-5D) quality-of-life questionnaire. Side-effect checklists were also used. Minocycline was started at 100 mg once daily (OD) and increased to 200 mg after 2 weeks.

Results: A total of 41 participants were randomised, with 21 in the minocycline group and 20 in the placebo group. A large decrease in HAMD scores was observed in the minocycline group compared to the placebo group (standardised effect size (ES) -1.21, $p < 0.001$). CGI scores in the minocycline group also showed a large improvement compared with placebo (odds ratio (OR): 17.6, $p < 0.001$). PHQ-9, GAD-7 and EQ-5D total showed more moderate improvements (ES ~ 0.4–0.5).

Conclusion: The findings indicate that adjunctive minocycline leads to improvement in symptoms of treatment-resistant depression. However, our findings require replication in a larger sample.

Trial Registration: ClinicalTrials.gov identifier: NCT02263872, registered October 2014.

Keywords
Inflammation, depression, minocycline

Introduction

Depression is the leading cause of disability worldwide (World Health Organisation, 2017). Although depressive symptoms are amenable to antidepressant treatments, a high proportion of patients neither responds adequately nor achieves remission (Rush et al., 2006). For example, in the Sequenced Treatment Alternatives for the Relief of Depression (STAR*D) study, the response and remission rates with stage 1 treatment (citalopram) were 49% and 37%, respectively. The additional response rates decreased to 16% and 13%, respectively, over the subsequent next three treatment steps (Rush et al., 2006). A recent meta-analysis of current pharmacological treatments for depressive disorder in primary care showed only a relatively small effect size for antidepressant treatments when compared with placebo (Linde et al., 2015). Thus, there remains a clear need for more efficacious and novel treatment approaches.

Recently, there have been promising preclinical and clinical data implicating inflammatory processes in a range of psychiatric disorders including depression. The findings include: a meta-analysis showing that pro-inflammatory cytokines are increased in the blood of patients with major depressive disorder (O'Donovan et al., 2013); and that peripheral administration of a pro-inflammatory cytokine (IFN-α) induces a depressive syndrome in many patients receiving it as a treatment for hepatitis (Van Gool et al., 2003). Treatment with cytokine IFN-α corresponded with the development of depressive symptoms in up to 45% of patients with no previous history of depression (Capuron and Miller, 2011). Longitudinal studies have demonstrated that high plasma pro-inflammatory protein levels precede, and thus potentially cause depressive symptoms (Gimeno et al., 2009; Khandaker et al., 2014). The most convincing evidence for a close relationship between inflammation and depression is the

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[6]Institute of Psychiatry, King's College London, London, UK
[7]Mersey Care NHS Foundation Trust, Liverpool, UK
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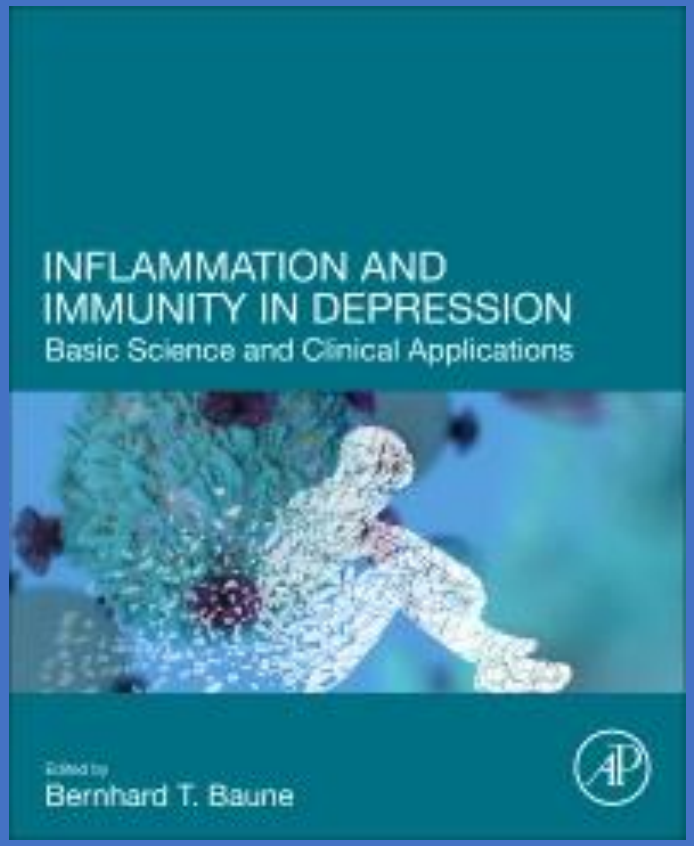

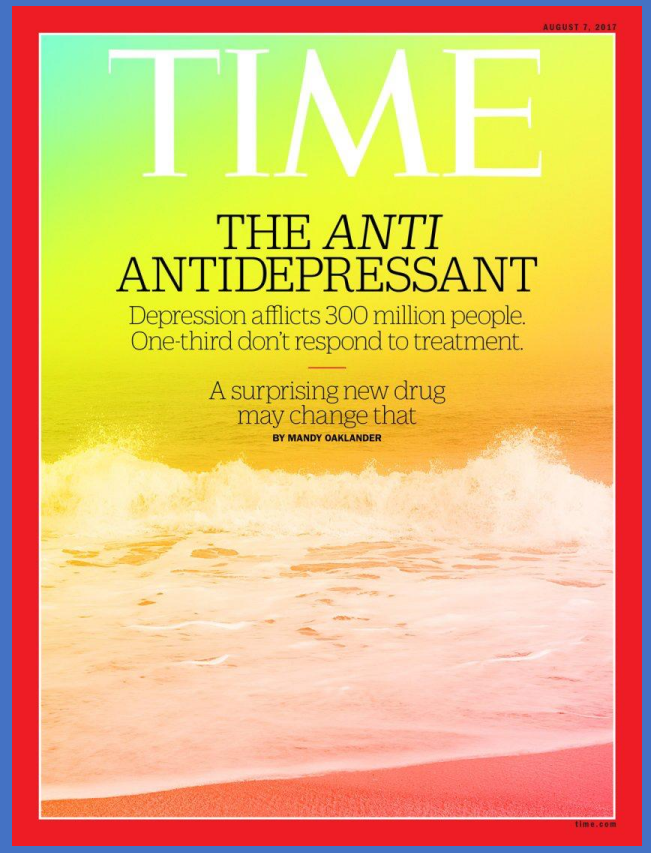

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Neurobiology of Stress xxx (2016) 1–7

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: http://www.journals.elsevier.com/neurobiology-of-stress/

Association between serum C-reactive protein and DSM-IV generalized anxiety disorder in adolescence: Findings from the ALSPAC cohort

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ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form
2 February 2016
Accepted 9 February 2016
Available online xxx

Keywords:
Biological markers
C-reactive protein
Systemic inflammation
Generalized anxiety disorder
Birth cohort study

ABSTRACT

Background: Animal studies suggest a role of inflammation in the pathophysiology of anxiety, but human studies of inflammatory markers and anxiety disorders are scarce. We report a study of serum C-reactive protein (CRP) and generalised anxiety disorder (GAD) from the general population-based ALSPAC birth cohort.

Methods: DSM-IV diagnosis of GAD was obtained from 5365 cohort members during face-to-face clinical assessment at age 16 years, of which 3392 also provided data on serum high sensitivity CRP levels. Logistic regression calculated odds ratio (OR) for GAD among individuals in top and middle thirds of CRP distribution compared with the bottom third. Effect of comorbid depression was assessed. Age, sex, body mass, ethnicity, social class, maternal education, maternal age at delivery, and family history of inflammatory conditions were included as potential confounders.

Results: Forty participants met DSM-IV criteria for GAD (0.74%). CRP levels were higher in GAD cases compared with the rest of the cohort ($P = 0.005$). After adjusting for potential confounders, participants in the top third of CRP values compared with the bottom third were more likely to have GAD; adjusted OR 5.06 (95% CI, 1.31–19.59). The association between CRP and GAD was consistent with a linear dose-response relationship. The pattern of association between CRP and GAD remained unchanged after excluding cases with co-morbid depression.

Conclusions: The findings are consistent with a role of inflammation in anxiety disorders. Longitudinal studies of inflammatory markers, subsequent anxiety taking into account current and past psychological stress are required to understand this association further.

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1. Introduction

Emerging evidence indicates an important role of inflammation in the pathophysiology of mood and anxiety disorders where inflammatory cytokines are thought to play a key role (Khandaker et al., 2014; Dantzer et al., 2008; Hodes et al., 2014). In healthy volunteers, simulated bacterial infection with the injection of an immune activating agent, lipopolysaccharide (LPS, a bacterial cell wall endotoxin), has been reported to produce anxiety and low mood as well as increased serum levels of interleukin 6 (IL-6, an inflammatory cytokine) (Reichenberg et al., 2001). Similarly, in mice immune activation is associated with anxiety-like behaviour as well as increased proinflammatory cytokines both in peripheral circulation and the brain (Gibney et al., 2013; Rossi et al., 2012). Moreover, anxiety inducing effects of social stress could be blocked by intra-cerebroventricular (ICV) administration of IL-1β (a

Abbreviations: CRP, C-reactive protein; GAD, generalized anxiety disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; ICV, intra-cerebroventricular; CNS, central nervous system; DAWBA, Development and Well-being Assessment; BMI, body mass index; IQR, interquartile range; OR, odds ratio; CI, confidence interval.

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E-mail address: gmk24@medschl.cam.ac.uk (G.M. Khandaker).

http://dx.doi.org/10.1016/j.ynstr.2016.02.003
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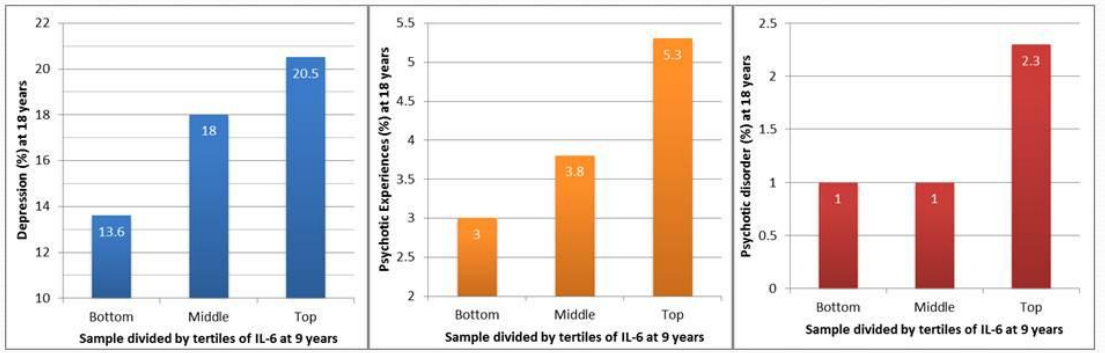
Please cite this article in press as: Khandaker, G.M., et al., Association between serum C-reactive protein and DSM-IV generalized anxiety disorder in adolescence: Findings from the ALSPAC cohort, Neurobiology of Stress (2016), http://dx.doi.org/10.1016/j.ynstr.2016.02.003

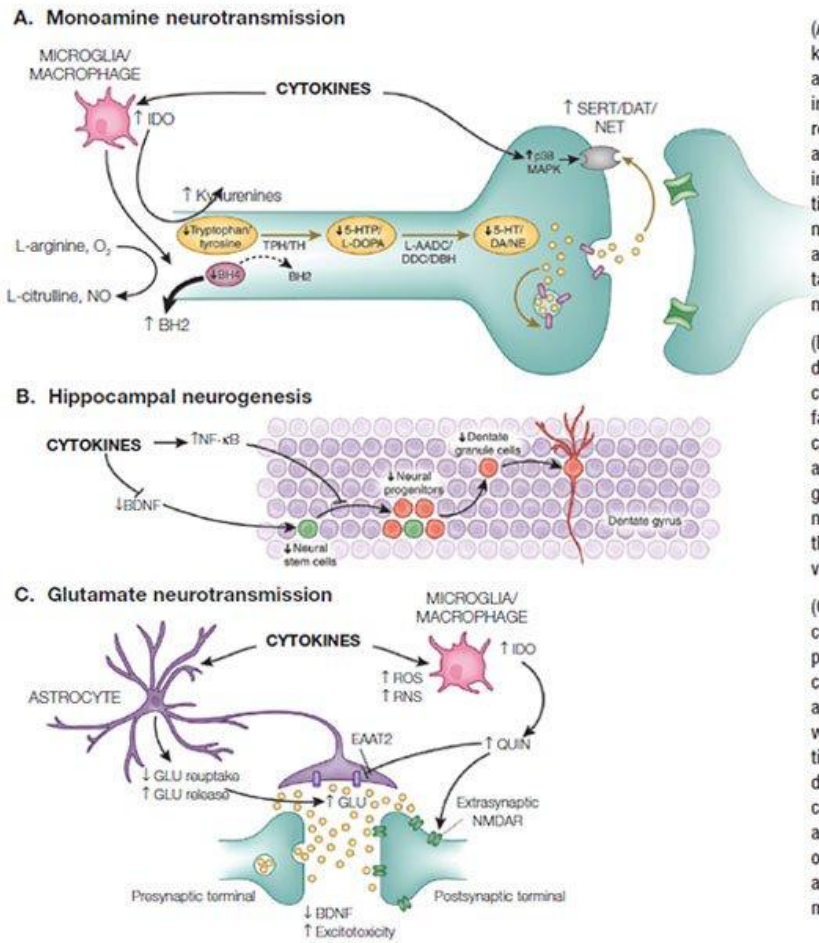
Psychiatric outcomes at 18 years by tertiles of IL-6 at 9 years in the ALSPAC birth cohort



Depression **Psychotic Experiences** **Psychotic Disorder**

Khandaker *et al.* JAMA Psychiatry (2014)

Figure 2. Cytokines sabotage and circumvent mechanisms of action of conventional antidepressants



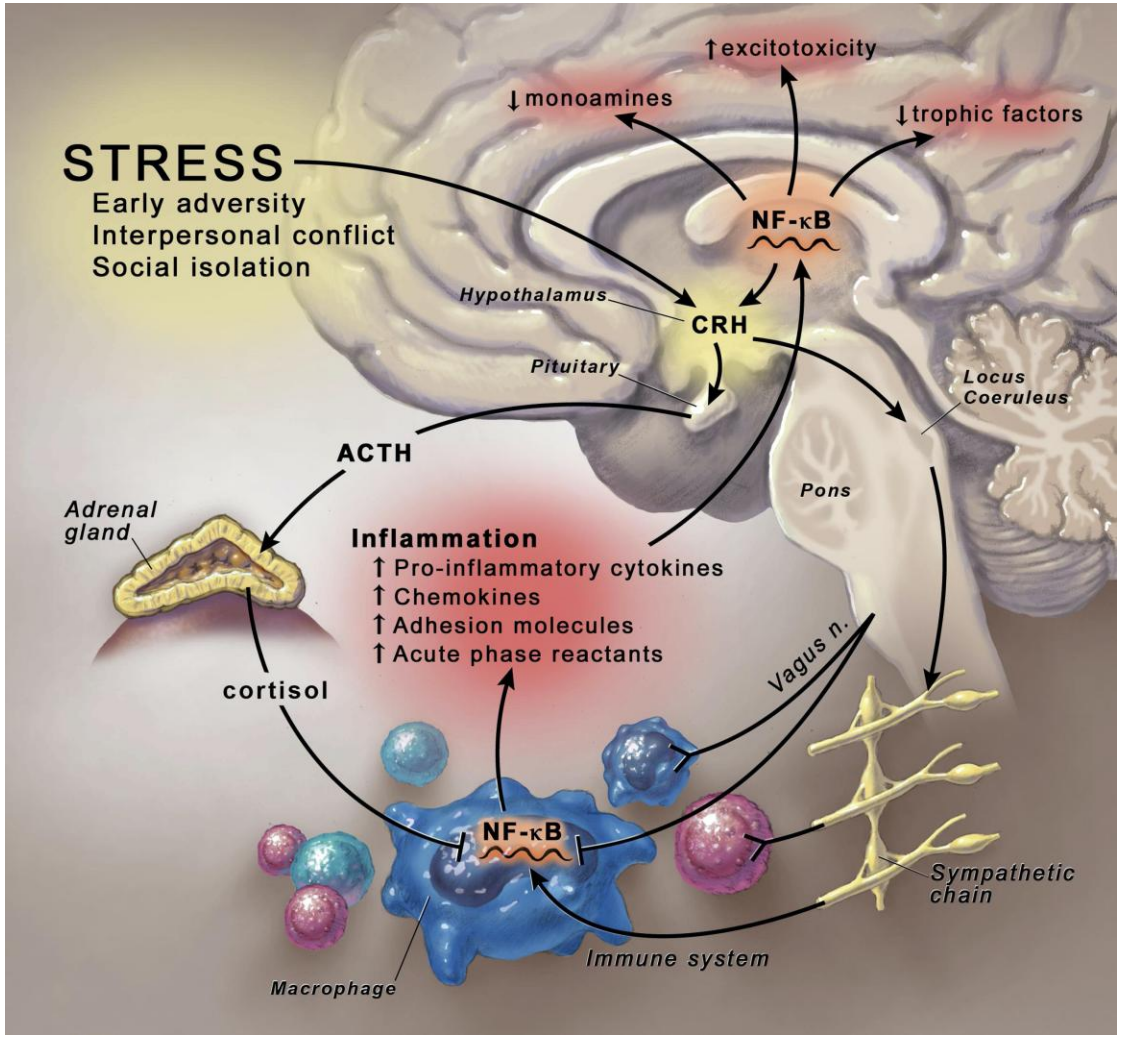
(A) Through activation of the MAPK signaling cascade, cytokines can increase the expression and activity of monoamine transporters, such as the SERT, NET, and DAT, resulting in decreased synaptic availability of monoamine neurotransmitters. Through effects on enzyme pathways such as IDO and enzyme cofactors such as BH4, cytokines can influence the activity of synthetic enzymes and the production of intermediate metabolites as well as end product neurotransmitters. This double hit on neurotransmitter availability via effects on synthesis and reuptake can sabotage the ability of antidepressants to increase monoamine neurotransmission.

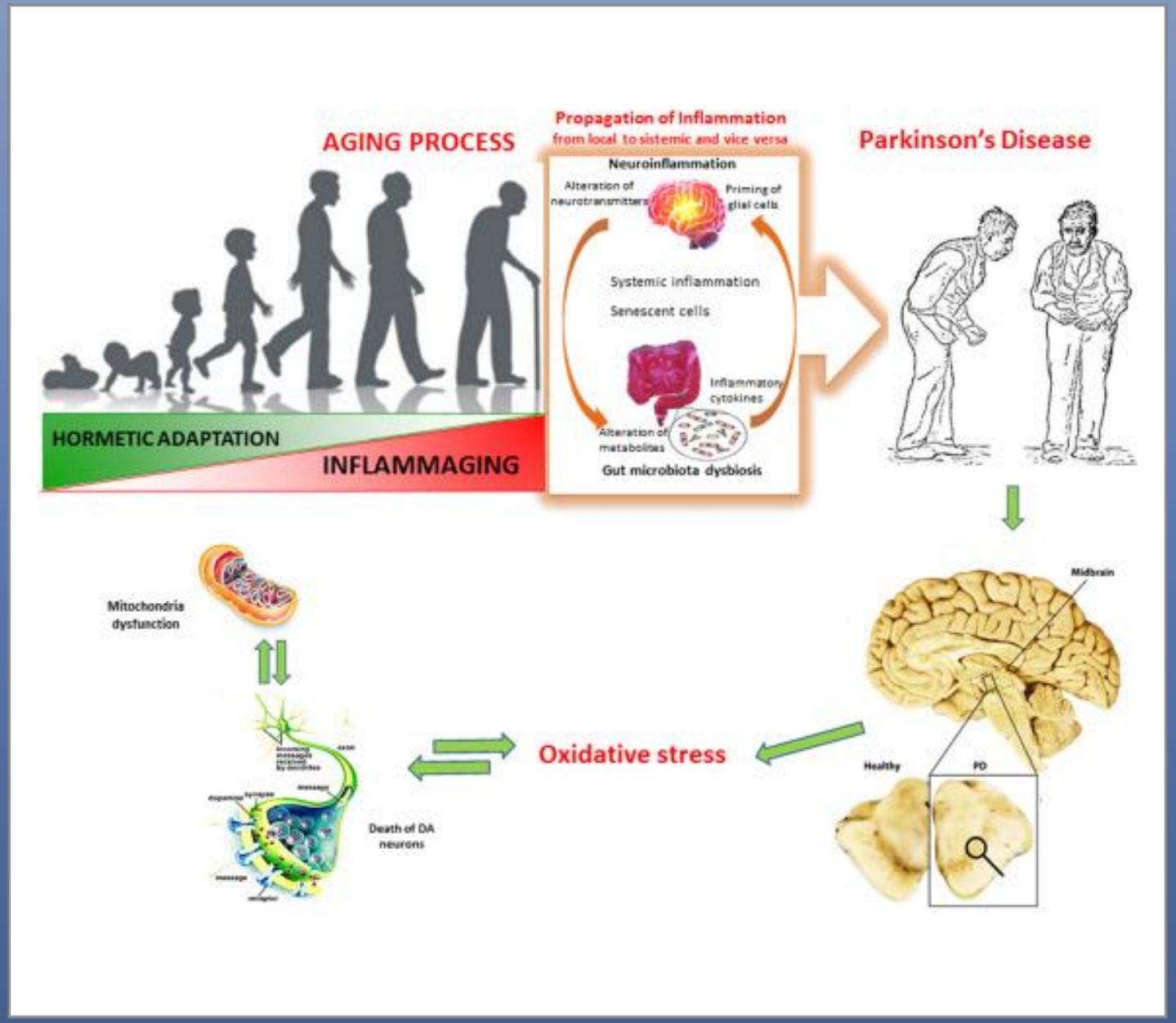
(B) Neurogenesis is a salient requisite for multiple antidepressant effects on behavior; inflammatory cytokines can decrease neurogenesis through blockade of growth factors (eg, BDNF that supports the growth of neural stem cells and activates inflammatory signaling pathways such as NF-κB), which inhibit the development of neural progenitor cells. Cytokines thus can inhibit the development of new neurons in the brain, including dentate granule cells in the hippocampus, thereby undermining the effects of conventional antidepressants.

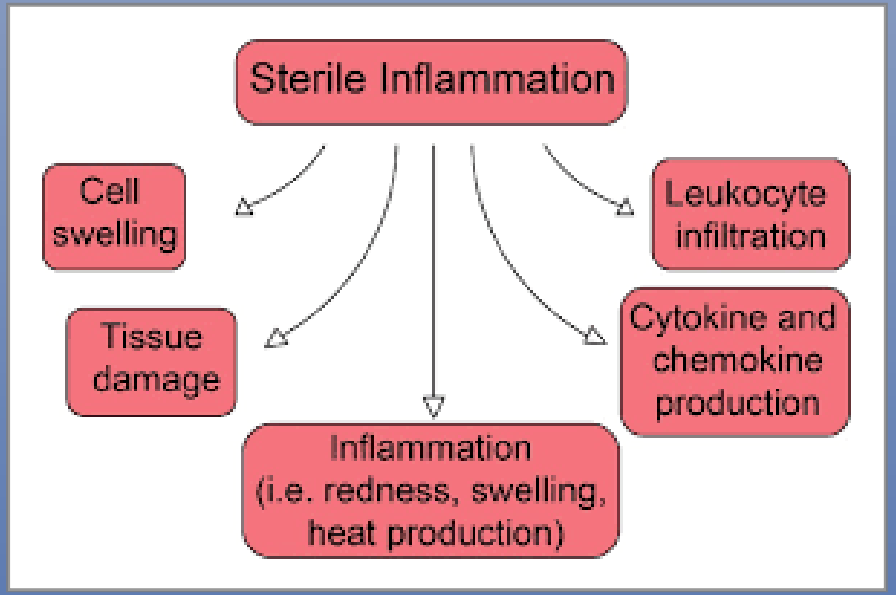
(C) Direct effects of inflammatory cytokines on astrocytes can lead to increased GLU release as well as reduced expression of GLU transporters, including the EAAT-2, thereby contributing to decreased GLU reuptake. Stimulation of IDO and kynurenine pathways can lead to the release of QUIN, which, in turn, can inhibit further GLU transporters and activate extrasynaptic NMDAR, which are associated with decreased production of BDNF as well as increased excitotoxicity. Release of ROS and RNS can also endanger astrocytic integrity and further compromise the regulation of synaptic and extrasynaptic GLU concentrations, which are not a direct target of conventional antidepressant medications.

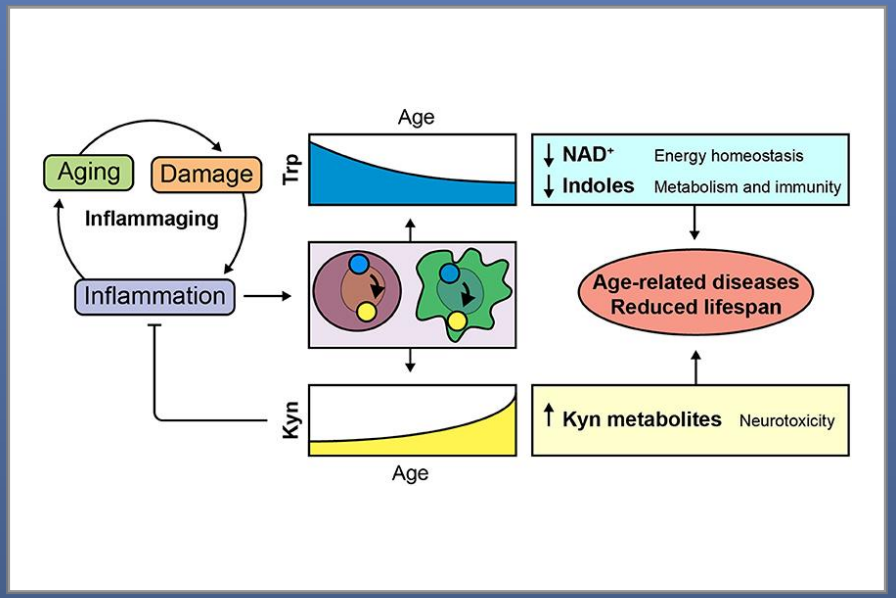
MAPK, mitogen-activated protein kinase; SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; IDO, indoleamine 2,3 dioxygenase; BH4, tetrahydrobiopterin; BDNF, brain-derived neurotrophic factor; NF-κB, nuclear factor-κB; GLU, glutamate; EAAT-2, excitatory amino acid transporter-2; QUIN, quinolinic acid; NMDAR, *N*-methyl-D-aspartate receptor; ROS, reactive oxygen species; RNS, reactive nitrogen species; 5-HTP, 5-hydroxytryptophan; 5-HT, serotonin; BH2, dihydrobiopterin; DA, dopamine; DBH, dopamine β-hydroxylase; DDC, dopamine decarboxylase; L-AADC, L-amino acid decarboxylase; NE, norepinephrine; NO, nitric oxide; NOS, nitric oxide synthase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase.

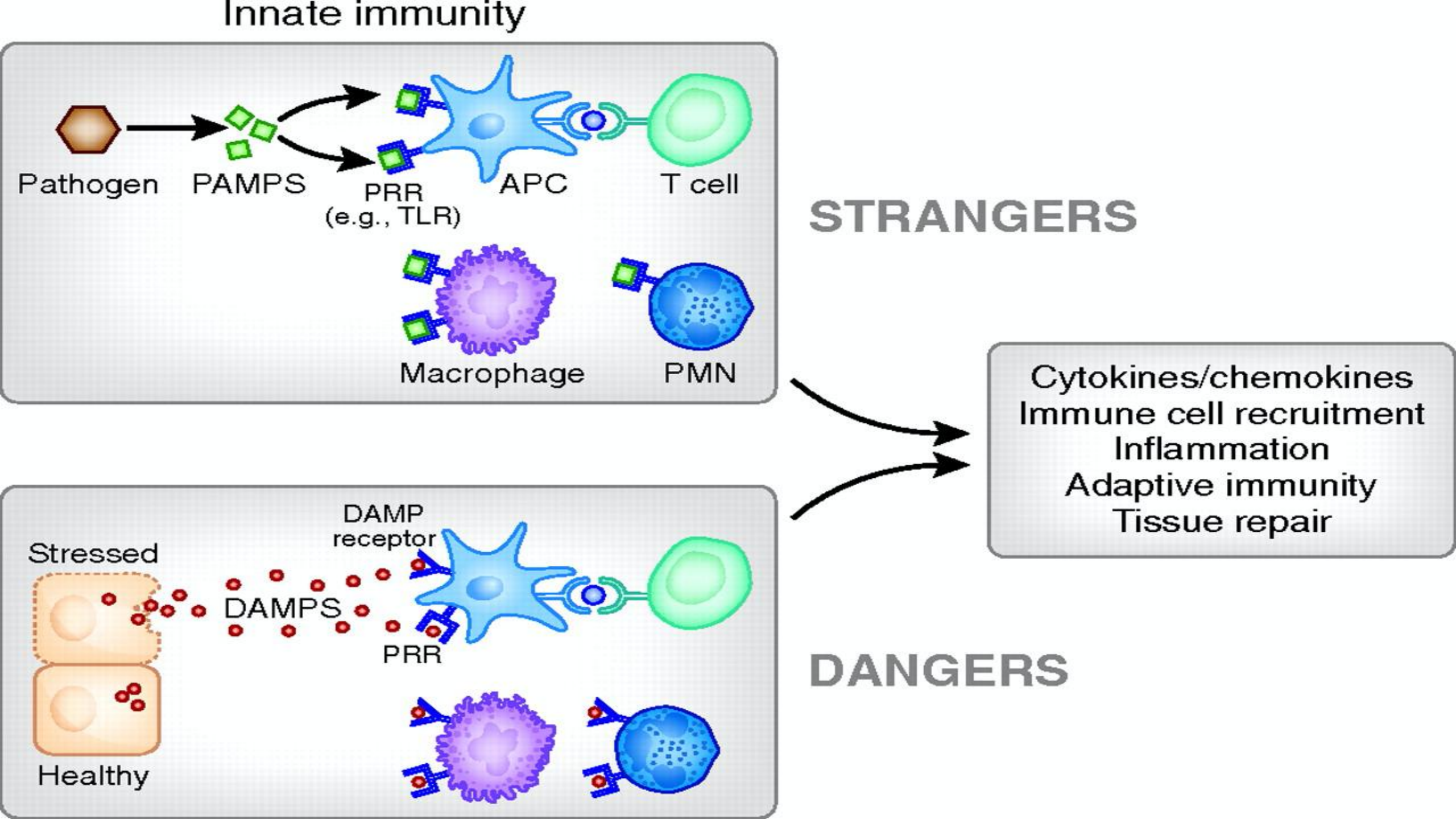
- Peripheral inflammation activates brain cytokine signaling which results in sickness behavior
- Intense and/or prolonged activation of the innate immune system induces **depression** in vulnerable individuals. Depression includes both neurovegetative symptoms and psychological symptoms. **Fatigue** is an important neurovegetative component of inflammation-associated depression.
- Because aging is associated with inflammation, aged subjects have a higher risk of developing symptoms of depression and fatigue.



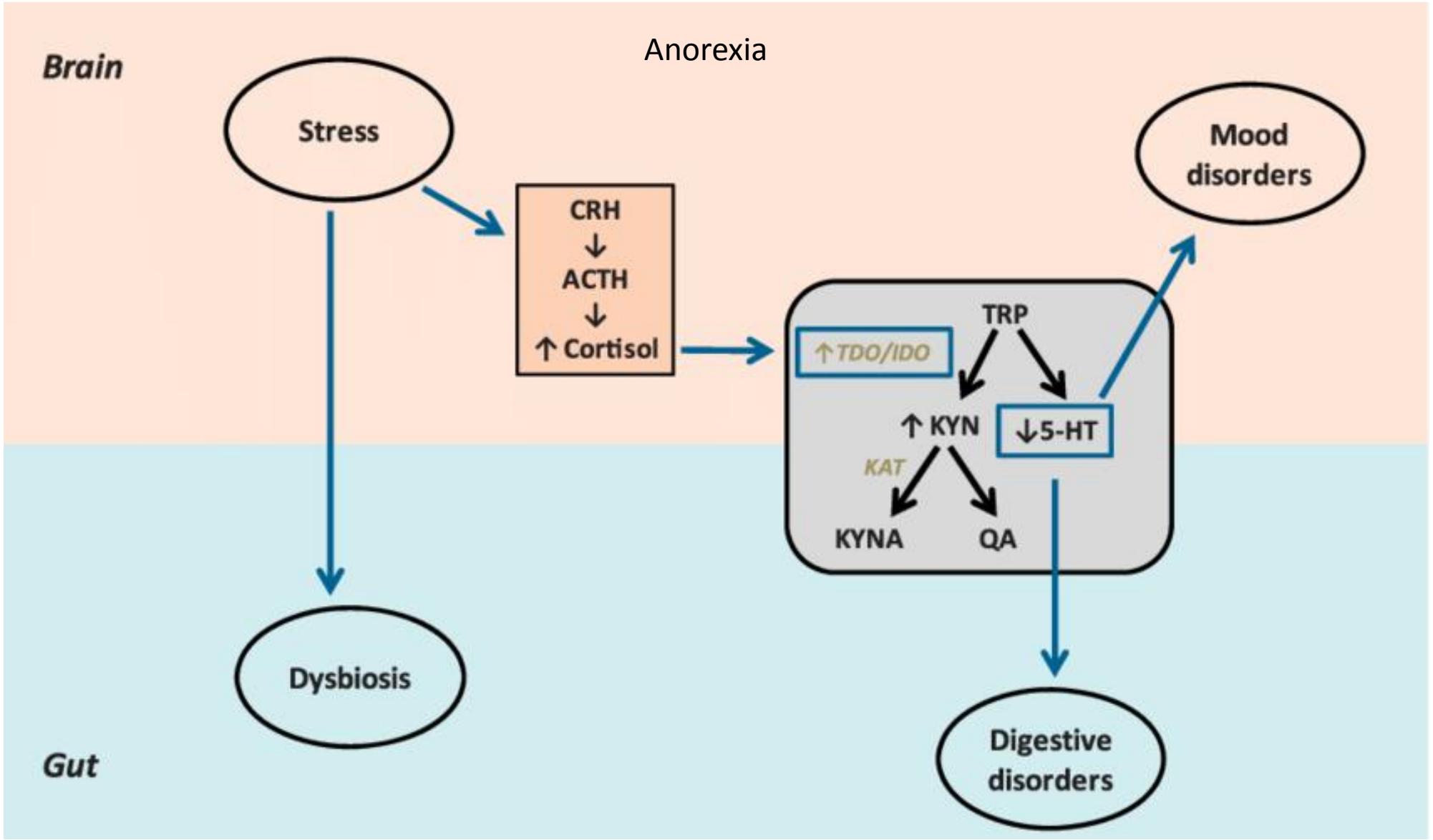

AGING PROCESS
HORMETIC ADAPTATION
INFLAMMAGING
Propagation of Inflammation
from local to sistemic and vice versa
Neuroinflammation
Alteration of neurotransmitters
Priming of glial cells
Systemic inflammation
Senescent cells
Inflammatory cytokines
Alteration of metabolites
Gut microbiota dysbiosis
Parkinson's Disease
Midbrain
Healthy
PD
Mitochondria dysfunction
Death of DA neurons
Oxidative stress

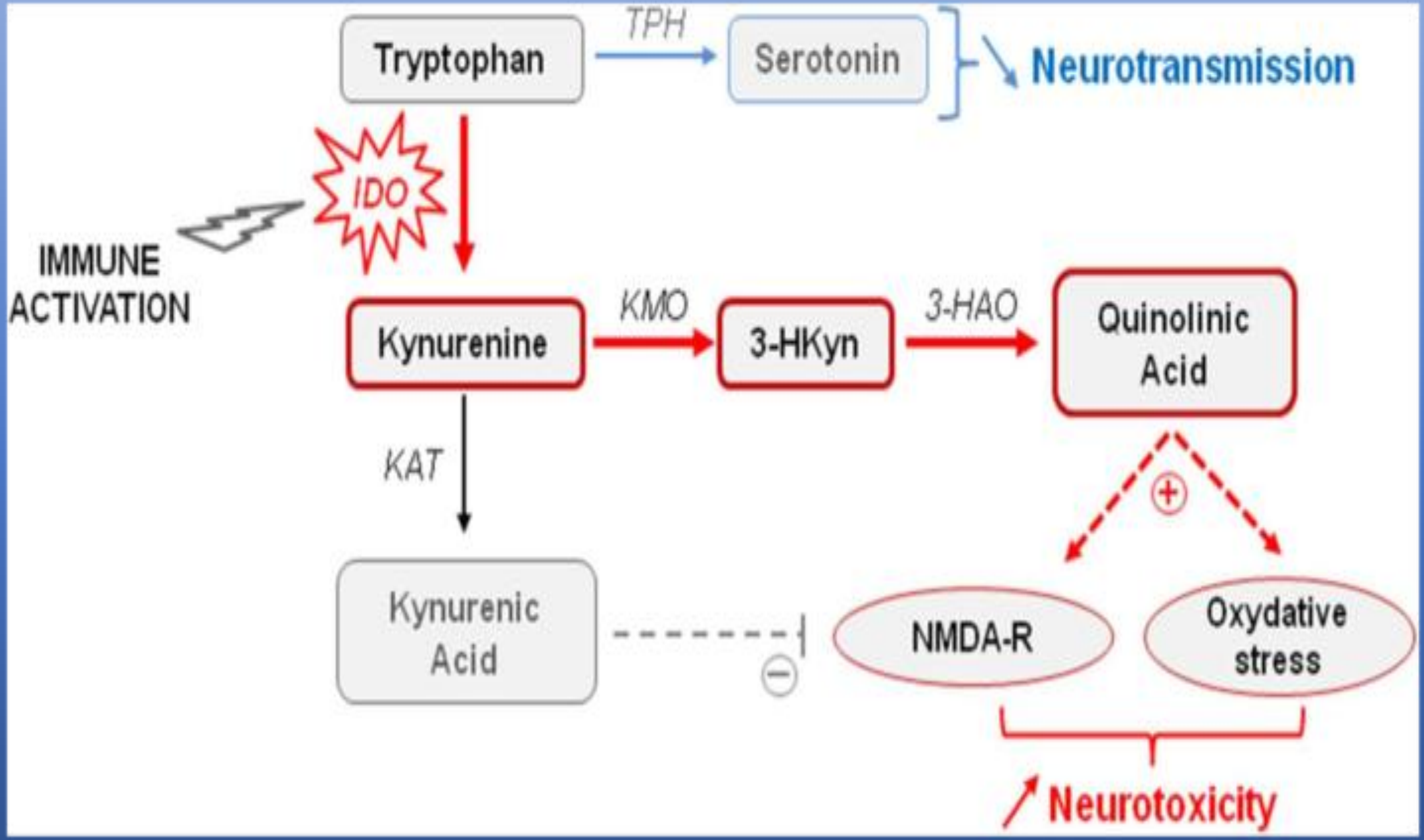

Sterile Inflammation
Cell swelling
Leukocyte infiltration
Tissue damage
Cytokine and chemokine production
Inflammation (i.e. redness, swelling, heat production)

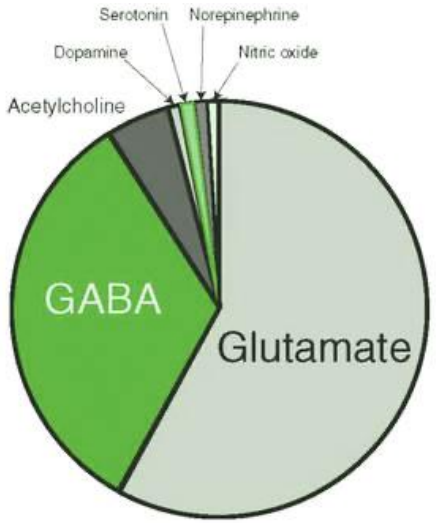

Aging
Damage
Inflammaging
Inflammation
Age
Trp
↓ NAD+ Energy homeostasis
↓ Indoles Metabolism and immunity
Age-related diseases
Reduced lifespan
Kyn
↑ Kyn metabolites Neurotoxicity
Age

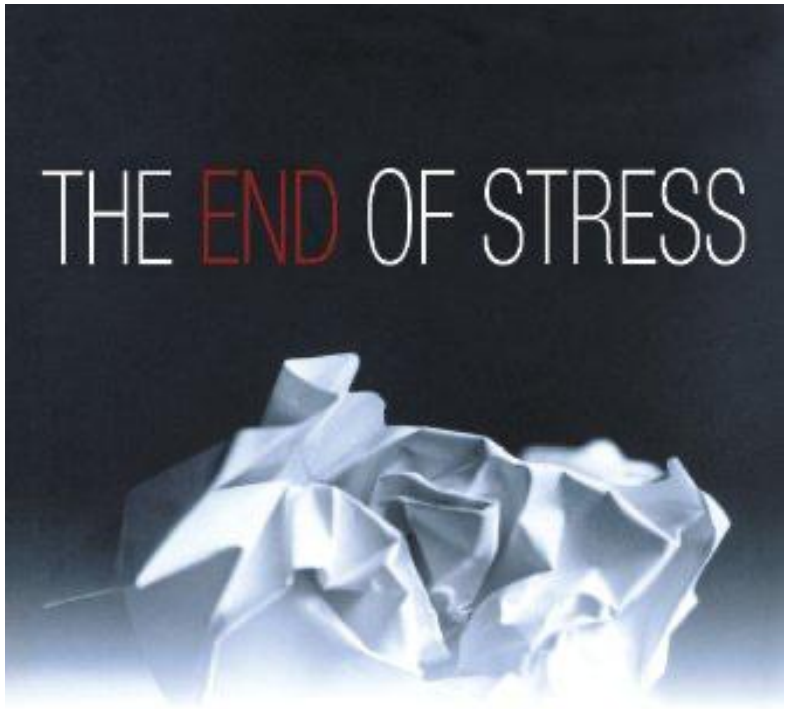

Innate immunity
Pathogen
PAMPS
PRR
(e.g., TLR)
APC
T cell
Macrophage
PMN
STRANGERS
Cytokines/chemokines
Immune cell recruitment
Inflammation
Adaptive immunity
Tissue repair
Stressed
DAMP
receptor
DAMPS
PRR
Healthy
DANGERS

Anorexia


Brain
Stress
CRH
↓
ACTH
↓
↑ Cortisol
Mood disorders
TRP
↑TDO/IDO
↑ KYN
↓5-HT
KAT
KYNA
QA
Dysbiosis
Digestive disorders
Gut


Tryptophan
TPH
Serotonin
Neurotransmission
IDO
IMMUNE ACTIVATION
Kynurenine
KMO
3-HKyn
3-HAO
Quinolinic Acid
KAT
Kynurenic Acid
NMDA-R
Oxydative stress
Neurotoxicity





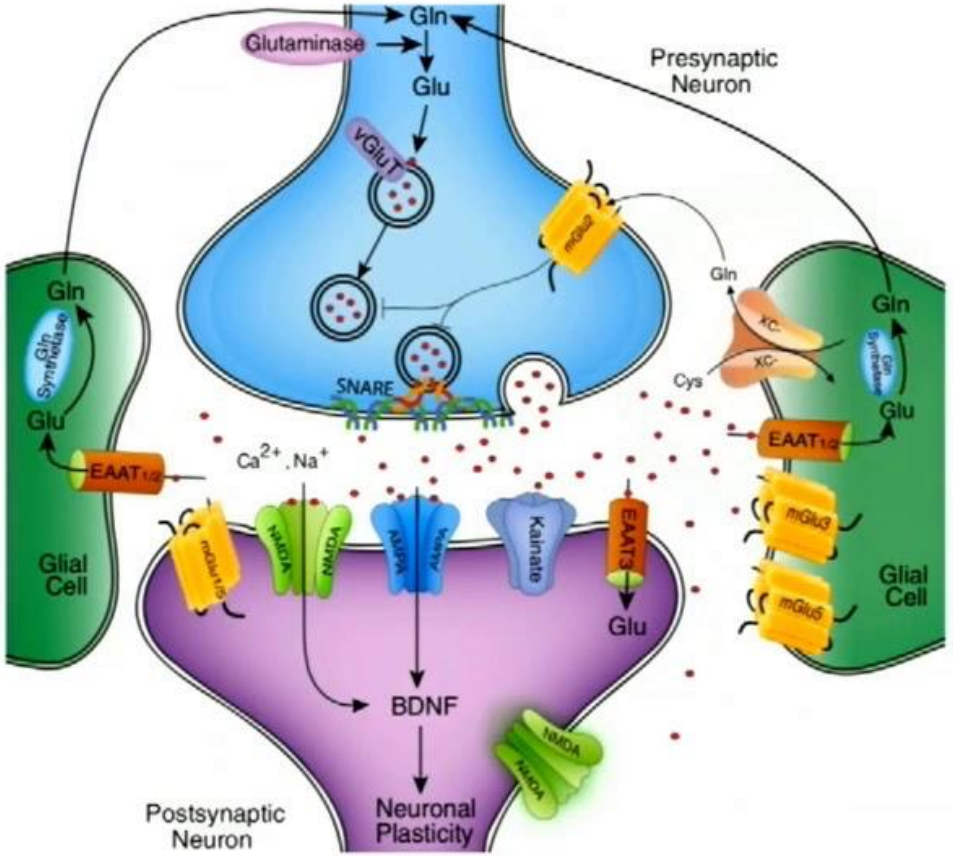
AS WE KNOW IT

Bruce McEwen

with Elizabeth Norton Lasley

Foreword by Robert Sapolsky

Putting It All Together… Glutamate's Complex Life Cycle



- Glutamate is packaged into presynaptic vesicles by VGLUT proteins and synaptically released in a voltage-dependent manner through vesicular interactions with SNARE proteins
- Synaptically-released Glutamate is recycled from the extracellular space by EAATs expressed predominantly on astroglia
- In astrocytes, Glutamate is converted to Glutamine by Glutamine synthetase and exported extracellularly to be taken up again by neurons
- Glutamate receptors are present on presynaptic and postsynaptic neurons as well as on glial cells
- These include both ionotropic receptors (NMDA, AMPA/KA) and metabotropic receptors (mGluRs). The effect of Glutamate is determined by the receptor subtype, localization (synaptic, peri-synaptic, and extrasynaptic), and interactions with various scaffolding and signaling proteins (not shown) in the postsynaptic density. Glutamate receptor stimulation results not only in rapid ionotropic effects but also in synaptic plasticity, eg, long-term potentiation and long-term depression, via cognate signal transduction cascades

VGLUT = vesicular glutamate transporter; EAATs = excitatory amino acid transporters; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; KA = kainite.

Niciu MJ, et al. *Pharmacol Biochem Behav*. 2012;100(4):656-664.

Psychology Today Find Counselling Get Help Magazine

Emily Deans M.D.
Evolutionary Psychiatry

DEPRESSION

Magnesium for Depression

A controlled study of magnesium shows clinically significant improvement.

Posted Jan 28, 2018

10

Magnesium is one of the most important minerals in the body. Years ago, I wrote about the importance of magnesium for the brain; it remains my most read blog post to this day.

We get most of our magnesium from plants (almonds, black beans, cashews, pumpkin seeds, and dark chocolate are all good

Participants were given 2000mg (248mg of elemental magnesium) daily for 6 weeks on an immediate or delayed (until week 7, the crossover) schedule. Depression scores on average over the trial dropped by 6 points, which brought the mean from moderately depressed to mild or minimally depressed, a clinically important change. Anxiety scores also improved. Participants reported reduced muscle cramps, aches and pains, constipation, and decreased headaches during the magnesium trial (all of these are known already to improve with magnesium supplementation and are signs of magnesium depletion). When asked after the trial if they would continue magnesium, over 60% said yes. Those that didn't complained that magnesium didn't help or it caused diarrhea (n = 8).

Magnesium Research 2016; **29** (3): 112-9 REVIEW

Magnesium and depression*

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<anna.serefko@umlub.pl>

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Abstract. Magnesium is one of the most important elements in the human body and is involved in a number of biochemical processes crucial for the proper functioning of the cardiovascular, alimentary, endocrine, and osteoarticular systems. It also plays a vital modulatory role in brain biochemistry, influencing several neurotransmission pathways associated with the development of depression. Personality changes, including apathy, depression, agitation, confusion, anxiety, and delirium are observed when there is a deficiency of this element. Rodents receiving a diet deficient in magnesium displayed depressive behaviour that was reversed by antidepressant drugs. Poor nutrition, gastrointestinal and renal diseases, insulin resistance and/or type 2 diabetes, alcoholism, stress, and certain medications may lead to magnesium deficiency. Since the extracellular concentration of magnesium ions may not reflect their intracellular level, none of the current methods of evaluating magnesium status is regarded as satisfactory. The mood-improving potential of magnesium compounds have been confirmed by the results of numerous pre-clinical and clinical studies. It seems that magnesium supplementation is well-tolerated and enhances the efficacy of conventional antidepressant treatments, and as such could be a valuable addition to the standard treatments for depression, although differences in bioavailability between inorganic and organic compounds should be taken into consideration.

Key words: magnesium, depression, antidepressant therapy

Magnesium is one the most important elements in the human body. It regulates a number of biochemical processes and influences the functioning of the majority of organs. The adult human body contains approximately 24-35 g of magnesium, which is mainly deposited in bones (≈ 60%), muscles (≈ 20%) and other soft tissues. The extracellular fluid contains only 1% of the total body magnesium. Magnesium is a co-factor for hundreds of enzymes, it participates in the cell cycle, metabolism of carbohydrates, proteins, fats, nucleic acids, and is partially responsible for cell membrane permeability, cell signalling and migration, stability of nucleic acids, synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and glutathione, generation and utilisation of adenosine triphosphate (ATP), neuromuscular transmission, bone mineralisation, blood glucose control, and regulation of blood pressure. Magnesium metabolism is closely related to that of calcium and potassium, since it is required for the active transport of their ions through cell membranes. In addition, magnesium plays a vital modulatory role in the central nervous system (CNS) [1].

Magnesium homeostasis depends on magnesium intake and its secretion via urine and faeces. The Recommended Daily Allowance (RDA) of magnesium ranges between 310 and 420 mg, depending on age and sex [2]. Nuts, sunflower seeds, green leafy vegetables, and whole grains are all abundant sources of this element. Magnesium absorption via both facilitated transport and passive diffusion mostly takes place in the small

*Presented at The XIV International Magnesium Symposium, Magnesium and Health, Rome, Italy, June 23-24, 2016.

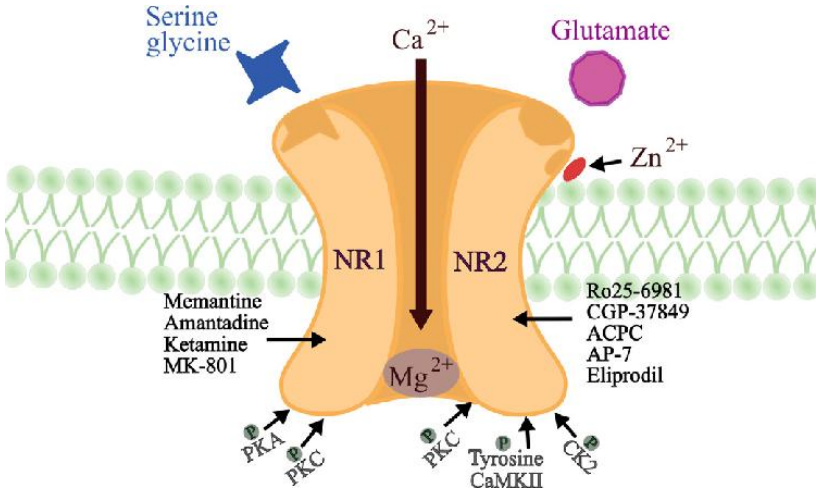
To cite this article: Serefko A, Szopa A, Poleszak E. Magnesium and depression. *Magnes Res* 2016; 29(3): 112-9 doi:10.1684/mrh.2016.0407

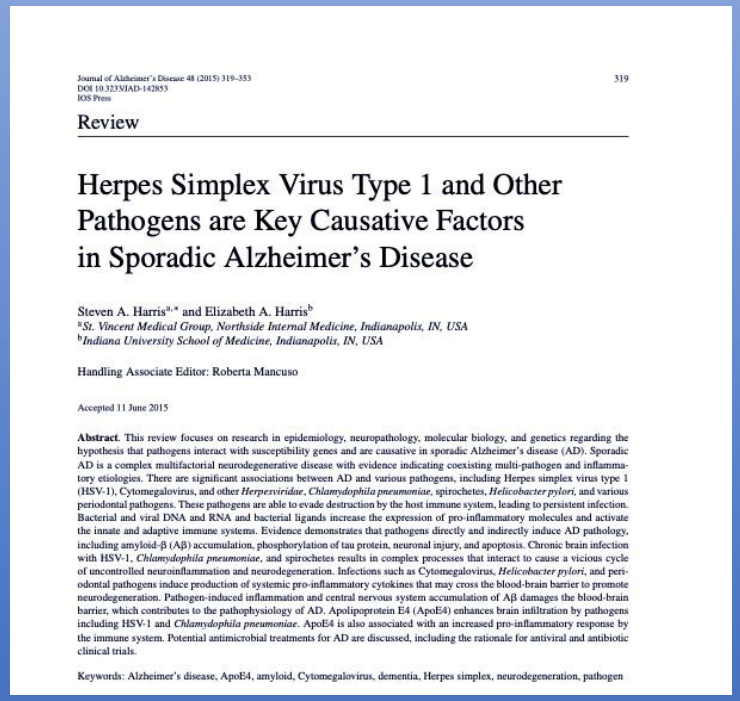
doi: 10.1684/mrh.2016.0407

Symptoms of Low Magnesium

Apathy
Confusion
Anxiety
Withdrawn social behavior
Dizziness
Headaches
Vomiting
Hallucinations
Insomnia
Tingling in hands and feet
Migraines
Parkinsonism
Concentration issues
Mood Swings
Compulsions
Heart skipping
Diarrhea
Muscle Cramps
Abdomen, Face, Neck, Back, Feet, Toes, Legs
Inattention
Nausea
Depression
Irritability
Numbness
Hyper excitability
Obsessions
Memory Loss/ Problems

- Magnesium is a cofactor in >300 enzymatic reactions.
- Mg acts as a counter ion for the energy-rich ATP.
- ATP is required universally for glucose utilization, synthesis of fat, proteins, nucleic acids and coenzymes, muscle contraction, methyl group transfer and many other processes.
- interference with magnesium metabolism influences these functions .





Journal of Alzheimer's Disease 48 (2015) 319–353
DOI 10.3233/JAD-142853
IOS Press

Review

Herpes Simplex Virus Type 1 and Other Pathogens are Key Causative Factors in Sporadic Alzheimer's Disease

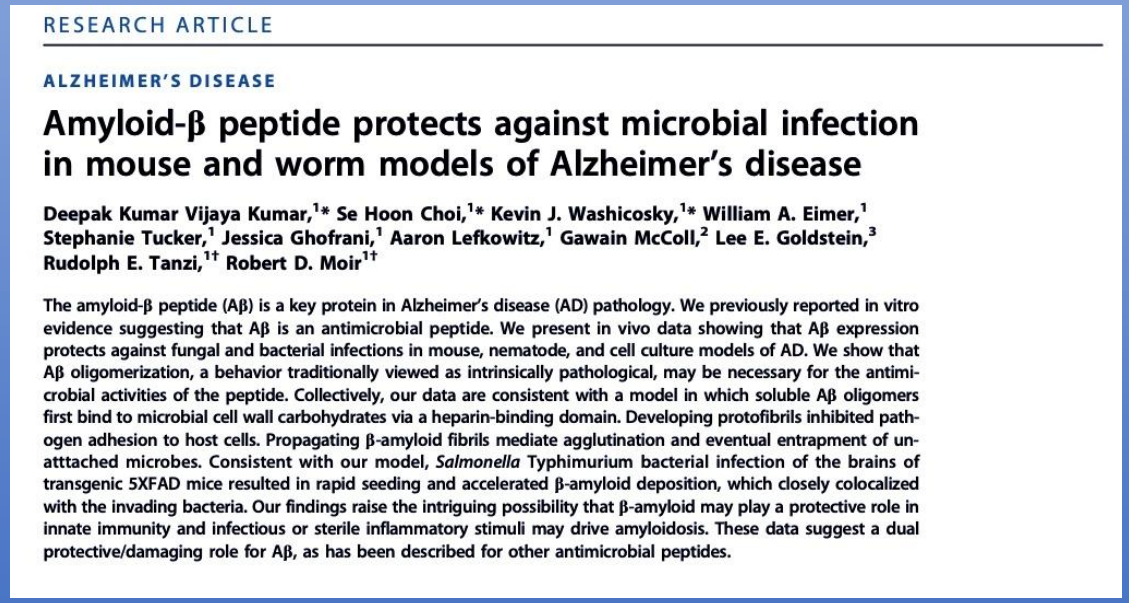
Steven A. Harris[a,*] and Elizabeth A. Harris[b]
[a]*St. Vincent Medical Group, Northside Internal Medicine, Indianapolis, IN, USA*
[b]*Indiana University School of Medicine, Indianapolis, IN, USA*

Handling Associate Editor: Roberta Mancuso

Accepted 11 June 2015

Abstract. This review focuses on research in epidemiology, neuropathology, molecular biology, and genetics regarding the hypothesis that pathogens interact with susceptibility genes and are causative in sporadic Alzheimer's disease (AD). Sporadic AD is a complex multifactorial neurodegenerative disease with evidence indicating coexisting multi-pathogen and inflammatory etiologies. There are significant associations between AD and various pathogens, including Herpes simplex virus type 1 (HSV-1), Cytomegalovirus, and other *Herpesviridae*, *Chlamydophila pneumoniae*, spirochetes, *Helicobacter pylori*, and various periodontal pathogens. These pathogens are able to evade destruction by the host immune system, leading to persistent infection. Bacterial and viral DNA and RNA and bacterial ligands increase the expression of pro-inflammatory molecules and activate the innate and adaptive immune systems. Evidence demonstrates that pathogens directly and indirectly induce AD pathology, including amyloid-β (Aβ) accumulation, phosphorylation of tau protein, neuronal injury, and apoptosis. Chronic brain infection with HSV-1, *Chlamydophila pneumoniae*, and spirochetes results in complex processes that interact to cause a vicious cycle of uncontrolled neuroinflammation and neurodegeneration. Infections such as Cytomegalovirus, *Helicobacter pylori*, and periodontal pathogens induce production of systemic pro-inflammatory cytokines that may cross the blood-brain barrier to promote neurodegeneration. Pathogen-induced inflammation and central nervous system accumulation of Aβ damages the blood-brain barrier, which contributes to the pathophysiology of AD. Apolipoprotein E4 (ApoE4) enhances brain infiltration by pathogens including HSV-1 and *Chlamydophila pneumoniae*. ApoE4 is also associated with an increased pro-inflammatory response by the immune system. Potential antimicrobial treatments for AD are discussed, including the rationale for antiviral and antibiotic clinical trials.

Keywords: Alzheimer's disease, ApoE4, amyloid, Cytomegalovirus, dementia, Herpes simplex, neurodegeneration, pathogen



RESEARCH ARTICLE

ALZHEIMER'S DISEASE

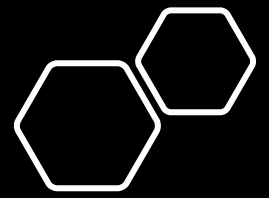
Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease

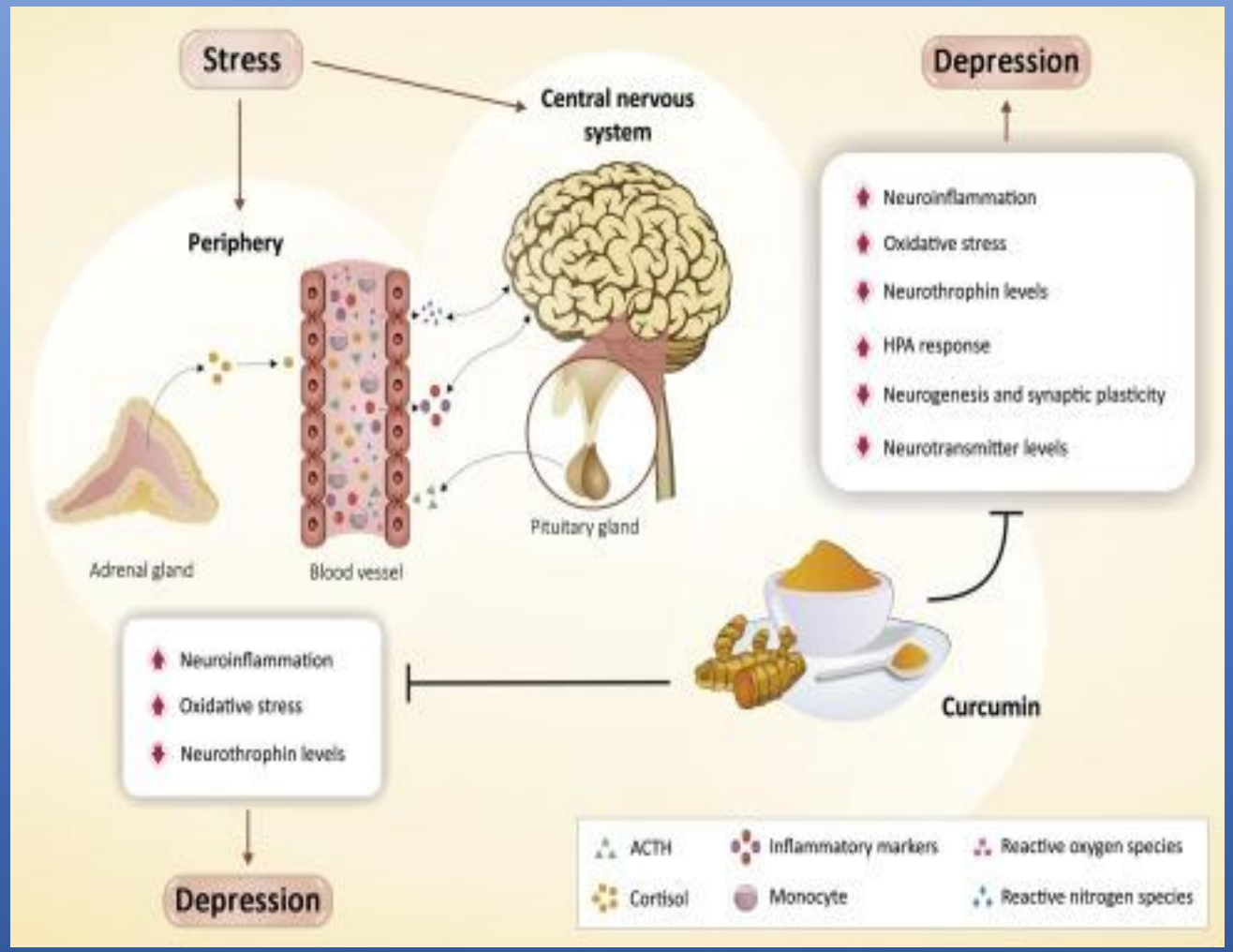
Deepak Kumar Vijaya Kumar,[1]* Se Hoon Choi,[1]* Kevin J. Washicosky,[1]* William A. Eimer,[1] Stephanie Tucker,[1] Jessica Ghofrani,[1] Aaron Lefkowitz,[1] Gawain McColl,[2] Lee E. Goldstein,[3] Rudolph E. Tanzi,[1†] Robert D. Moir[1†]

The amyloid-β peptide (Aβ) is a key protein in Alzheimer's disease (AD) pathology. We previously reported in vitro evidence suggesting that Aβ is an antimicrobial peptide. We present in vivo data showing that Aβ expression protects against fungal and bacterial infections in mouse, nematode, and cell culture models of AD. We show that Aβ oligomerization, a behavior traditionally viewed as intrinsically pathological, may be necessary for the antimicrobial activities of the peptide. Collectively, our data are consistent with a model in which soluble Aβ oligomers first bind to microbial cell wall carbohydrates via a heparin-binding domain. Developing protofibrils inhibited pathogen adhesion to host cells. Propagating β-amyloid fibrils mediate agglutination and eventual entrapment of unatttached microbes. Consistent with our model, *Salmonella* Typhimurium bacterial infection of the brains of transgenic 5XFAD mice resulted in rapid seeding and accelerated β-amyloid deposition, which closely colocalized with the invading bacteria. Our findings raise the intriguing possibility that β-amyloid may play a protective role in innate immunity and infectious or sterile inflammatory stimuli may drive amyloidosis. These data suggest a dual protective/damaging role for Aβ, as has been described for other antimicrobial peptides.

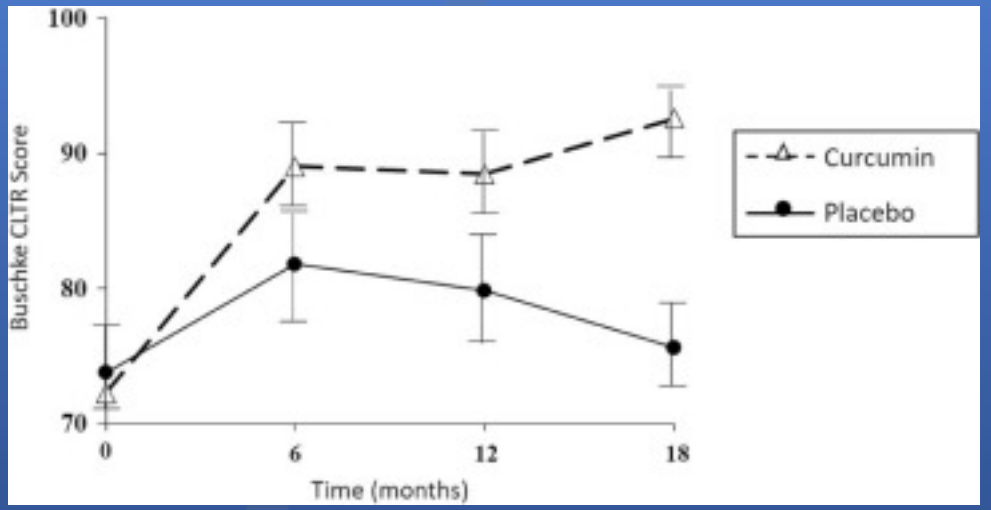
Findings:

- In AD brains 90% the plaques contain HSV-1 DNA
  - HSV-1 is a neurotropic virus that infects most humans
  - Attaining 90% prevalence by 6th decade of life
  - Infection by HSV-1 induces expression of cytokines and pro-inflammatory molecules,
  - Elevated levels of pro-inflammatory cytokines are consistently found in the brains of AD patients




Stress
Central nervous system
Depression
Periphery
Neuroinflammation
Oxidative stress
Neurothrophin levels
HPA response
Neurogenesis and synaptic plasticity
Neurotransmitter levels
Pituitary gland
Adrenal gland
Blood vessel
Curcumin
Neuroinflammation
Oxidative stress
Neurothrophin levels
Depression
ACTH
Inflammatory markers
Reactive oxygen species
Cortisol
Monocyte
Reactive nitrogen species


UCLA STUDY
CURCUMIN'S SIGNIFICANT EFFECT ON MEMORY AND MOOD*


Buschke CLTR Score
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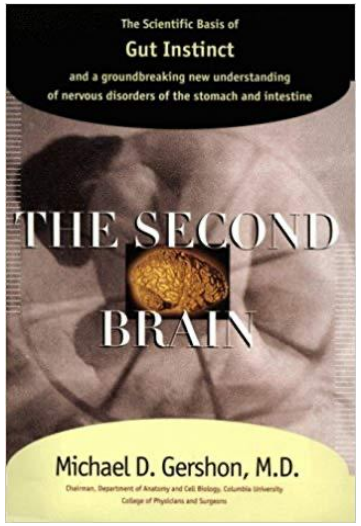
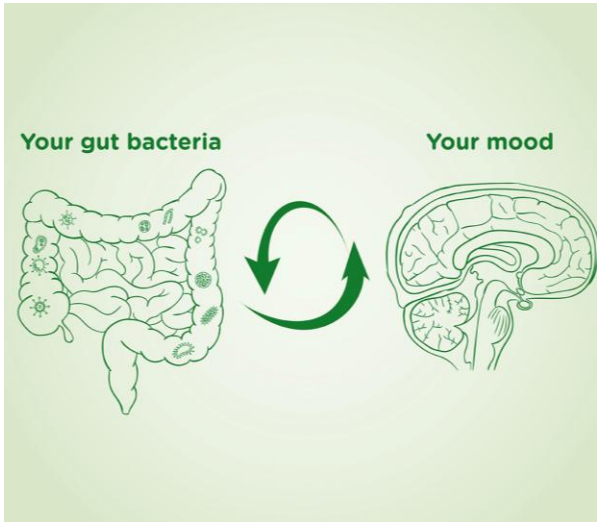
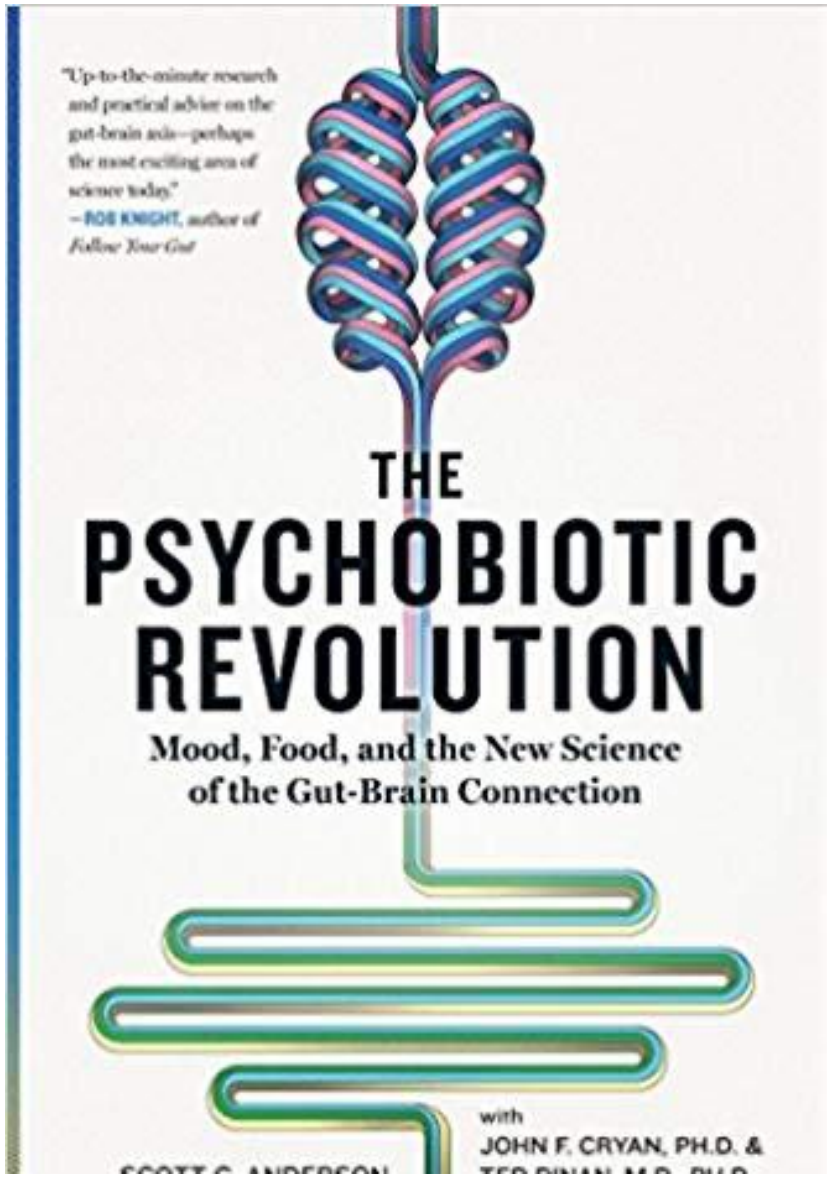
90
80
70
0
6
12
18
Time (months)
Curcumin
Placebo


The Scientific Basis of
Gut Instinct
and a groundbreaking new understanding
of nervous disorders of the stomach and intestine
THE SECOND
BRAIN
Michael D. Gershon, M.D.


Your gut bacteria
Your mood


"Up-to-the-minute research
and practical advice on the
gut-brain axis—perhaps
the most exciting area of
science today."
—ROB KNIGHT, author of
Follow Your Gut
THE
PSYCHOBIOTIC
REVOLUTION
Mood, Food, and the New Science
of the Gut-Brain Connection
with
JOHN F. CRYAN, PH.D. &

frontiers in Neurology

MINI REVIEW
published: 04 June 2019
doi: 10.3389/fneur.2019.00574

The Gut and Parkinson's Disease—A Bidirectional Pathway

Susanne Fonseca Santos[1], *Hadassa Loth de Oliveira*[2], *Elizabeth Sumi Yamada*[1], *Bianca Cruz Neves*[2] *and Antonio Pereira Jr.*[1,3]*

[1] Graduate Program in Neuroscience and Cell Biology, Institute of Biology, Federal University of Pará, Belém, Brazil, [2] Department of Biochemistry, Institute of Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [3] Department of Electrical and Biomedical Engineering, Institute of Technology, Federal University of Pará, Belém, Brazil

Humans evolved a symbiotic relationship with their gut microbiome, a complex microbial community composed of bacteria, archaea, protists, and viruses, including bacteriophages. The enteric nervous system (ENS) is a gateway for the bidirectional communication between the brain and the gut, mostly through the vagus nerve (VN). Environmental exposure plays a pivotal role in both the composition and functionality of the gut microbiome and may contribute to susceptibility to neurodegenerative disorders, such as Parkinson's disease (PD). The neuropathological hallmark of PD is the widespread appearance of alpha-synuclein aggregates in both the central and peripheral nervous systems, including the ENS. Many studies suggest that gut toxins can induce the formation of α-syn aggregates in the ENS, which may then be transmitted in a prion-like manner to the CNS through the VN. PD is strongly associated with aging and its negative effects on homeostatic mechanisms protecting from inflammation, oxidative stress, and protein malfunction. In this mini-review, we revisit some landmark discoveries in the field of Parkinson's research and focus on the gut-brain axis. In the process, we highlight evidence showing gut-associated dysbiosis and related microbial-derived components as important players and risk factors for PD. Therefore, the gut microbiome emerges as a potential target for protective measures aiming to prevent PD onset.

Keywords: Parkinson's disease, enteric nervous system, microbiome, neurotoxicants, probiotics

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neurodegeneration, a section of the journal Frontiers in Neurology

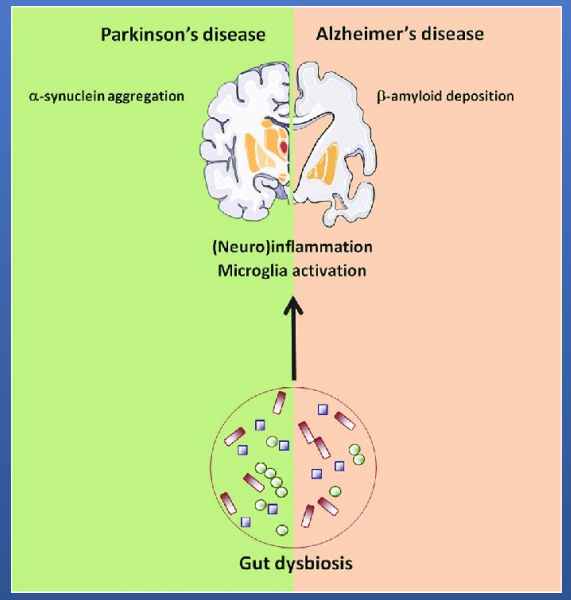
Received: 26 January 2019
Accepted: 16 May 2019
Published: 04 June 2019

Citation:
Santos SF, de Oliveira HL, Yamada ES, Neves BC and Pereira A Jr (2019)

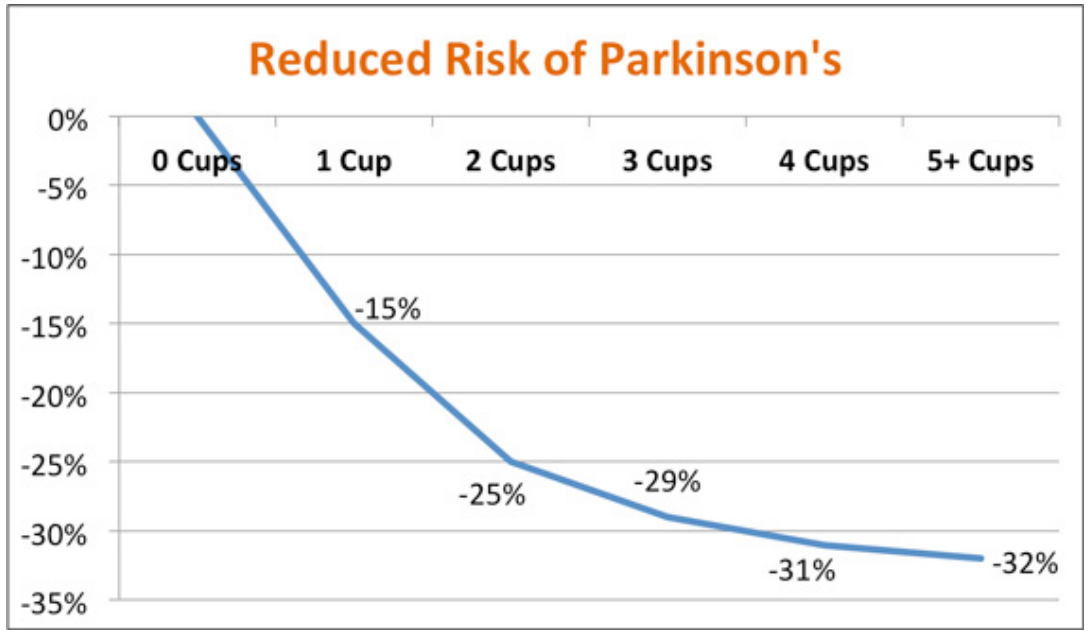
INTRODUCTION

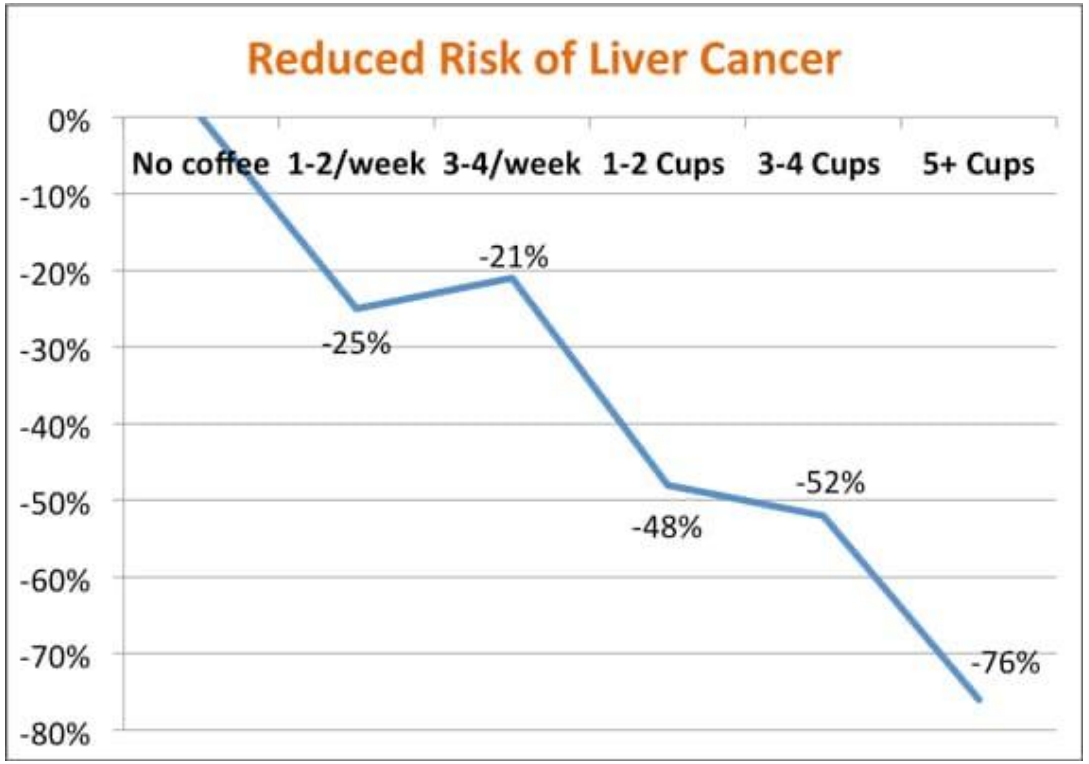
Parkinson's Disease (PD) is a common neurodegenerative disorder typically associated with the progressive loss of dopaminergic neurons located in the midbrain nucleus substantia nigra pars compacta (SNpc) (1). Although the cardinal symptoms of PD are motor impairments attributed to the depletion of the neurotransmitter dopamine in the striatum, a major target of the SNpc (2), it has been long recognized [for review, see (3)] that other non-motor symptoms, including olfactory (4–6) and gastrointestinal (GI) dysfunction (4), appear during the so-called premotor phase of the disease.

The neuropathological hallmark of PD is the presence of cytoplasmic inclusions, called Lewy bodies (LB) or Lewy neurites (7–9), in SNpc neurons (10). LBs are composed mostly of α-synuclein (α-syn) aggregates (11–13), whose aberrant soluble oligomeric conformations are thought to



- The microbiota of PD patients exhibits a pro-inflammatory profile due to increased intestinal permeability to endotoxins (lipopolysaccharide)


Reduced Risk of Parkinson's
0%
-5%
-10%
-15%
-20%
-25%
-30%
-35%
0 Cups
1 Cup
2 Cups
3 Cups
4 Cups
5+ Cups
-15%
-25%
-29%
-31%
-32%


Reduced Risk of Liver Cancer
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
-80%
No coffee
1-2/week
3-4/week
1-2 Cups
3-4 Cups
5+ Cups
-25%
-21%
-48%
-52%
-76%

nutrients

MDPI

Article

Coffee Consumption and the Risk of Depression in a Middle-Aged Cohort: The SUN Project

Adela M. Navarro [1,2], Daria Abasheva [1], Miguel Á. Martínez-González [1,3,4,5], Liz Ruiz-Estigarribia [1,4], Nerea Martín-Calvo [1,3,4], Almudena Sánchez-Villegas [6] and Estefanía Toledo [1,3,4,*]

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* Correspondence: etoledo@unav.es; Tel.: +34-948425600 (ext. 806224)

Received: 30 August 2018; Accepted: 16 September 2018; Published: 19 September 2018

check for updates

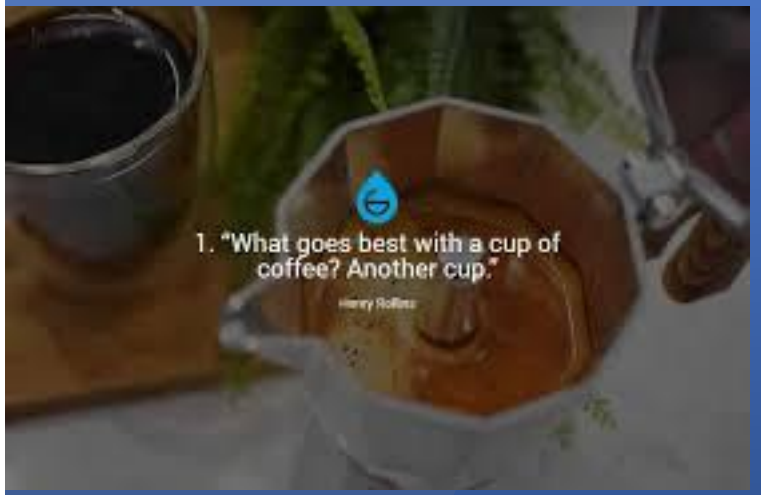
Abstract: Coffee is one of the most widely consumed drinks around the world, while depression is considered the major contributor to the overall global burden of disease. However, the investigation on coffee consumption and depression is limited and results may be confounded by the overall dietary pattern. We assessed the relationship between coffee intake and the risk of depression, controlling for adherence to the Mediterranean diet. We studied 14,413 university graduates of the 'Seguimiento Universidad de Navarra' (SUN) cohort, initially free of depression. We evaluated coffee consumption using a validated food-frequency questionnaire (FFQ). Incident depression cases were adjudicated only if the participant met two criteria simultaneously: (a) validated physician-diagnosed depression together with (b) new onset of habitual antidepressant use. Both criteria were needed; participants meeting only one of them were not classified as cases. Participants who drank at least four cups of coffee per day showed a significantly lower risk of depression than participants who drank less than one cup of coffee per day (HR: 0.37 (95% CI 0.15–0.95)). However, overall, we did not observe an inverse linear dose–response association between coffee consumption and the incidence of depression (p for trend = 0.22).

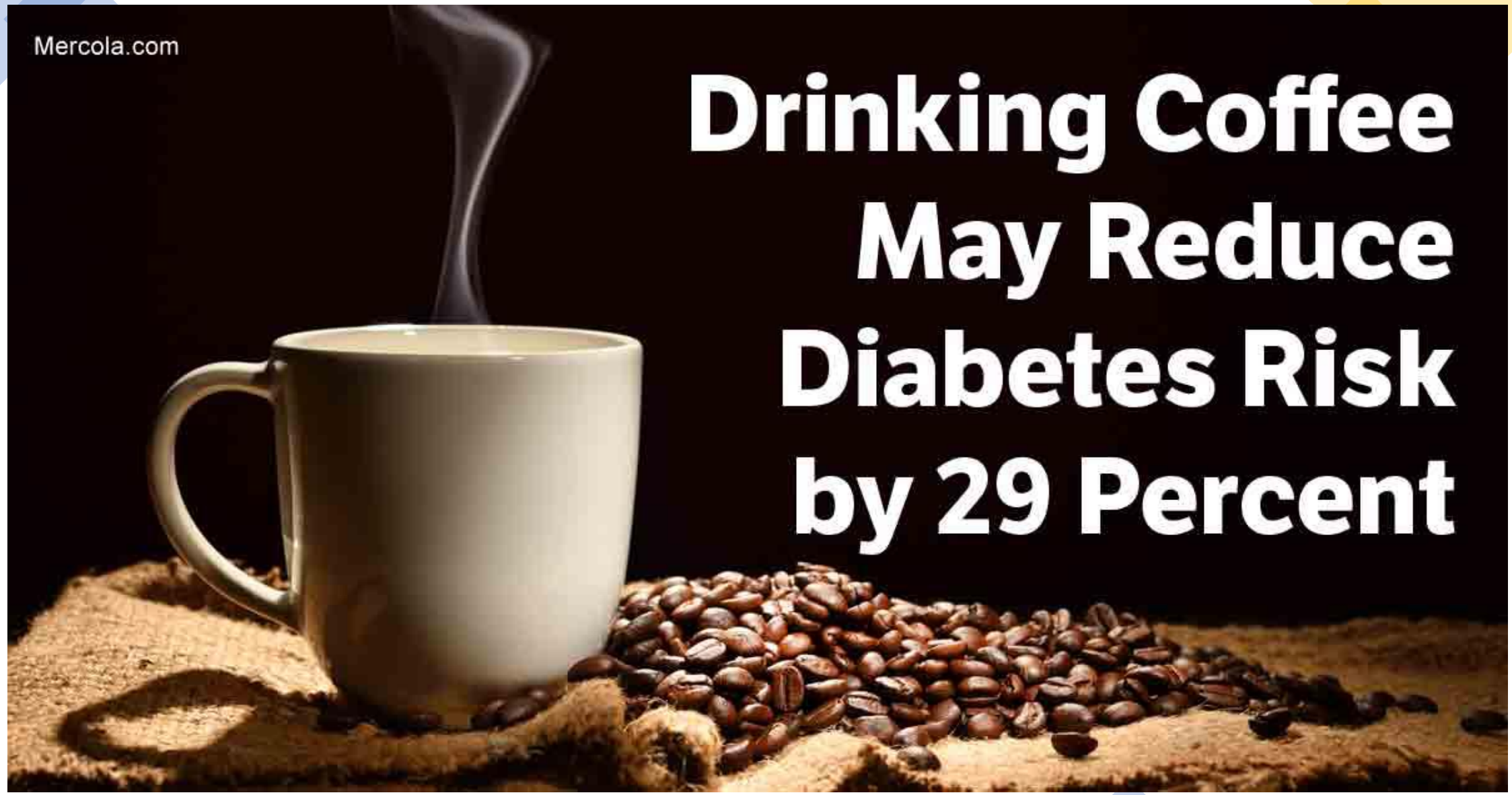
Keywords: coffee; depression; cohort study

1. Introduction

Depression is considered the major contributor to the overall global burden of disease and a common cause of disability worldwide, with more than 300 million people affected [1]. Severe forms of depression can lead to suicide, which is the second leading cause of death in people aged 15–29 years, accounting for 800,000 deaths every year [2]. The lifetime prevalence of depression and the distribution of suicide rates are not uniform. Within Europe, both depression prevalence and suicide rates are higher in northern countries than in southern ones [3]. Nowadays, the prevention of depression represents a public health priority due to its huge social and economic burden.

Participants who drank at least four cups of coffee per day showed a significantly lower risk of depression than participants who drank less than one cup of coffee per day




Mercola.com
Drinking Coffee May Reduce Diabetes Risk by 29 Percent

ORIGINAL CONTRIBUTION

Effect of DHA Supplementation During Pregnancy on Maternal Depression and Neurodevelopment of Young Children

A Randomized Controlled Trial

Maria Makrides, BSc, BND, PhD
Robert A. Gibson, BSc, PhD
Andrew J. McPhee, MBBS
Lisa Yelland, BSc
Julie Quinlivan, MBBS, PhD
Philip Ryan, MBBS, BSc
and the DOMInO Investigative Team

Context Uncertainty about the benefits of dietary docosahexaenoic acid (DHA) for pregnant women and their children exists, despite international recommendations that pregnant women increase their DHA intakes.

Objective To determine whether increasing DHA during the last half of pregnancy will result in fewer women with high levels of depressive symptoms and enhance the neurodevelopmental outcome of their children.

Design, Setting, and Participants A double-blind, multicenter, randomized controlled trial (DHA to Optimize Mother Infant Outcome [DOMInO] trial) in 5 Australian maternity hospitals of 2399 women who were less than 21 weeks' gestation with singleton pregnancies and who were recruited between October 31, 2005, and January 11, 2008. Follow-up of children (n=726) was completed December 16, 2009.

Intervention Docosahexaenoic acid–rich fish oil capsules (providing 800 mg/d of DHA) or matched vegetable oil capsules without DHA from study entry to birth.

Main Outcome Measures High levels of depressive symptoms in mothers as indicated by a score of more than 12 on the Edinburgh Postnatal Depression Scale at 6 weeks or 6 months postpartum. Cognitive and language development in children as assessed by the Bayley Scales of Infant and Toddler Development, Third Edition, at 18 months.

Results Of 2399 women enrolled, 96.7% completed the trial. The percentage of women with high levels of depressive symptoms during the first 6 months postpartum did not differ between the DHA and control groups (9.67% vs 11.19%; adjusted relative risk, 0.85; 95% confidence interval [CI], 0.70-1.02; *P*=.09). Mean cognitive composite scores (adjusted mean difference, 0.01; 95% CI, −1.36 to 1.37; *P*=.99) and mean language composite scores (adjusted mean difference, −1.42; 95% CI, −3.07 to 0.22; *P*=.09) of children in the DHA group did not differ from children in the control group.

Conclusion The use of DHA-rich fish oil capsules compared with vegetable oil capsules during pregnancy did not result in lower levels of postpartum depression in mothers or improved cognitive and language development in their offspring during early childhood.

Trial Registration anzctr.org.au Identifier: ACTRN12605000569606

JAMA. 2010;304(15):1675-1683 www.jama.com

Author Affiliations: Child Nutrition Research Centre, Women's and Children's Hospital, Flinders Medical Centre, and Women's and Children's Health Research Institute, Adelaide (Drs Makrides and Gibson); Schools of Pediatrics and Reproductive Health (Dr Makrides), Agriculture, Food and Wine (Dr Gibson), and Population Health and Clinical Practice (Dr Ryan and Ms Yelland), University of Adelaide, Adelaide; Department of Neonatal Medicine, Women's and Children's Hospital, Adelaide (Dr McPhee); and School of Medicine, University of Notre Dame Australia, and Sunshine Hospital, Melbourne (Dr Quinlivan), Australia.
The DOMInO Investigative Team members and their author affiliations are listed at the end of this article.
Corresponding Author: Maria Makrides, BSc, BND, PhD, Child Nutrition Research Centre, Women's and Children's Health Research Institute, Women's and Children's Hospital, 72 King William Rd, North Adelaide SA 5006, Australia (maria.makrides@health.sa.gov.au).

See also p 1717 and Patient Page.

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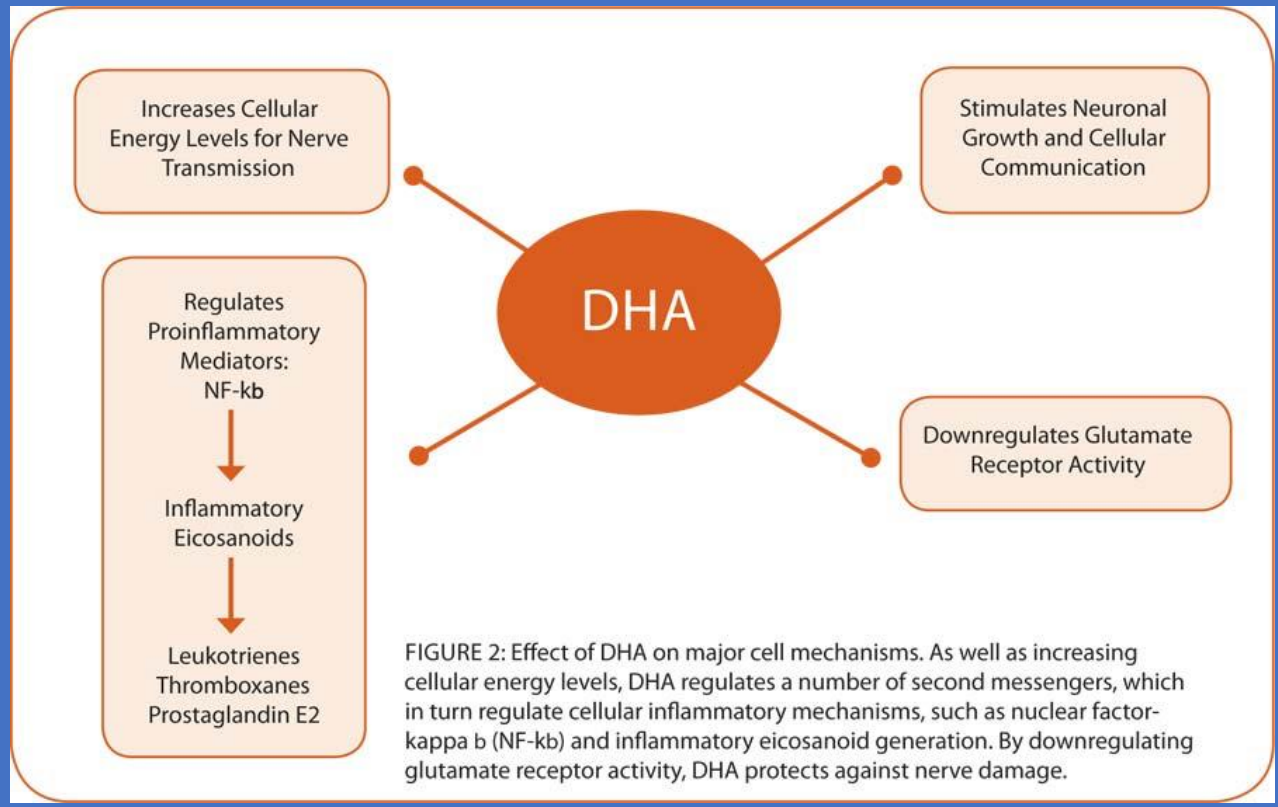

FIGURE 2: Effect of DHA on major cell mechanisms. As well as increasing cellular energy levels, DHA regulates a number of second messengers, which in turn regulate cellular inflammatory mechanisms, such as nuclear factor-kappa b (NF-kb) and inflammatory eicosanoid generation. By downregulating glutamate receptor activity, DHA protects against nerve damage.

Hindawi
Journal of Aging Research
Volume 2019, Article ID 5198402, 11 pages
https://doi.org/10.1155/2019/5198402

Research Article

The Effects of Lutein and Zeaxanthin Supplementation on Brain Morphology in Older Adults: A Randomized, Controlled Trial

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Received 27 July 2019; Accepted 29 October 2019; Published 1 December 2019

Academic Editor: Carmela R. Balistreri

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A growing literature emphasizes the importance of lifestyle factors such as nutrition in successful aging. The current study examined if one year of supplementation with lutein (L) and zeaxanthin (Z), two nutrients with known antioxidative properties and cognitive benefits, impacted structural brain outcomes in older adults using a double-blind, randomized, placebo-controlled trial design. Community-dwelling older adults (38 males and 27 females) aged 65–87 years (*M* = 71.8 years, *SD* = 6.06 years) were randomized into supplement (*N* = 33) and placebo groups (*N* = 14) using simple randomization. The supplement group received 10 mg L + 2 mg Z daily for 12 months while the placebo group received a visually identical, inert placebo. L and Z were measured via retinal concentrations (macular pigment optical density or MPOD). Structural brain outcomes, focusing on global and frontal-temporal lobe regions, were acquired using both T1-weighted and DTI MRI sequences. We hypothesized that the supplement group would increase, maintain, or show attenuated loss in hypothesized regions-of-interest (ROIs) while the placebo group would show age-related declines in brain structural integrity over the course of the trial. While results showed age-related declines for frontal and temporal gray and white matter volumes, as well as ferritin white matter microstructure across both groups, only minimal differences were found between the supplement and placebo groups. However, exploratory analysis showed that individuals who responded better to supplementation (i.e., showed greater increases in MPOD) showed less decline in global and prefrontal gray matter volume than supplement "nonresponders." While results suggest that one year of L and Z supplementation may have limited effects on structural brain outcomes overall, there may be a subsample of individuals for whom supplementation of L and Z provides greater benefits. ClinicalTrials.gov number, NCT02023943.

1. Introduction

Aging is associated with many changes, both cognitive and neural, that contribute to negative outcomes such as decreased functional independence, significant personal and societal economic burden, and psychological distress for both aging individuals and their caregivers [1, 2]. One of the more common theories of biological aging is the Free Radical/Oxidative Stress Theory of Aging [3], which states that oxidative stress causes damage to DNA and proteins. In turn, oxidation leads to neural inflammation, neurotoxicity, reduced cerebral perfusion, and disruption of neural structure and cognitive functioning [4]. To combat the negative effects of oxidation, researchers have studied nutrients such as vitamins, flavonoids, and carotenoids for their potential in preventing and treating age-related cognitive and neural decline. Intake of these nutrients, along with healthy fatty acids and adherence to a balanced healthy diet, has been associated with positive neural effects, including preserved gray and white matter volume, white matter microstructure, and lower risk of cerebral infarcts, even after controlling for demographics and vascular risk factors [5–7].

Lutein (L) and zeaxanthin (Z) are two nutrients in the xanthophyll carotenoid family that have been suggested to

Foods **2015**, *4*, 1-x manuscripts; doi:10.3390/foods40x000x

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foods

ISSN 2304-8158

www.mdpi.com/journal/foods

Article

Lutein and Brain Function

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Academic Editor:

Received: / Accepted: / Published:

Abstract: Lutein is one of the most prevalent carotenoids in nature and in the human diet. Together with zeaxanthin, it is highly concentrated as macular pigment in the foveal retina of primates, attenuating blue light exposure, providing protection from photo-oxidation and enhancing visual performance. Recently, interest in lutein has expanded beyond the retina to its possible contributions to brain development and function. Only primates accumulate lutein within the brain, but little is known about its distribution or physiological role. Our team has begun to utilize the rhesus macaque (*Macaca mulatta*) model to study the uptake and bio-localization of lutein in the brain. Our overall goal has been to assess the association of lutein localization with brain function. In this review, we will first cover the evolution of the non-human primate model for lutein and brain studies, discuss prior association studies of lutein with retina and brain function, and review approaches that can be used to localize brain lutein. We also describe our approach to the biosynthesis of ^{13}C-lutein, which will allow investigation of lutein flux, localization, metabolism and pharmacokinetics. Lastly, we describe potential future research opportunities.

DOI 10.3233/JAD-142265
IOS Press

The Impact of Supplemental Macular Carotenoids in Alzheimer's Disease: A Randomized Clinical Trial

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Accepted 15 October 2014

Abstract.
Background: Patients with Alzheimer's disease (AD) exhibit significantly less macular pigment (MP) and poorer vision when compared to control subjects.
Objective: To investigate supplementation with the macular carotenoids on MP, vision, and cognitive function in patients with AD versus controls.
Methods: A randomized, double-blind clinical trial with placebo and active arms. 31 AD patients and 31 age-similar control subjects were supplemented for six months with either Macushield (10 mg meso-zeaxanthin [MZ]; 10 mg lutein [L]; 2 mg zeaxanthin [Z]) or placebo (sunflower oil). MP was measured using dual-wavelength autofluorescence (Heidelberg Spectralis®). Serum L, Z, and MZ were quantified by high performance liquid chromatography. Visual function was assessed by best corrected visual acuity and contrast sensitivity (CS). Cognitive function was assessed using a battery of cognition tests, including the Cambridge Neuropsychological Test Automated Battery (CANTAB)).
Results: Subjects on the active supplement (for both AD and non-AD controls) exhibited statistically significant improvement in serum concentrations of L, Z, MZ, and MP ($p < 0.001$, for all) and also CS at 1.2 cpd ($p < 0.039$). Also, for subjects on the active supplement, paired samples *t*-tests exhibited four significant results (from five spatial frequencies tested) in the AD group, and two for the non-AD group, and all indicating improvements in CS. We found no significant changes in any of the cognitive function outcome variables measured ($p > 0.05$, for all).
Conclusion: Supplementation with the macular carotenoids (MZ, Z, and L) benefits patients with AD, in terms of clinically meaningful improvements in visual function and in terms of MP augmentation.

Keywords: Age-related macular degeneration, Alzheimer's disease, cognitive function, contrast sensitivity, lutein, meso-zeaxanthin, randomized clinical trial, visual function, zeaxanthin

INTRODUCTION

We have recently reported in the Carotenoids and Age-Related Dementia Study (CARDS, report 1) that patients with mild to moderate AD exhibit significantly

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Molecular Psychiatry (2013), 1–8
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www.nature.com/mp

ORIGINAL ARTICLE

Omega-3 fatty acid supplementation changes intracellular phospholipase A_2 activity and membrane fatty acid profiles in individuals at ultra-high risk for psychosis

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The identification of an ultra-high risk (UHR) profile for psychosis and a greater understanding of its prodrome have led to increasing interest in early intervention to delay or prevent the onset of psychotic illness. In a randomized placebo-controlled trial, we have identified long-chain ω-3 (ω-3) polyunsaturated fatty acid (PUFA) supplementation as potentially useful, as it reduced the rate of transition to psychosis by 22.6% 1 year after baseline in a cohort of 81 young people at UHR of transition to psychosis. However, the mechanisms whereby the ω-3 PUFAs might be neuroprotective are incompletely understood. Here, we report on the effects of ω-3 PUFA supplementation on intracellular phospholipase A_2 (*in*PLA_2) activity, the main enzymes regulating phospholipid metabolism, as well as on peripheral membrane lipid profiles in the individuals who participated in this randomized placebo-controlled trial. Patients were studied cross-sectionally ($n = 80$) and longitudinally ($n = 65$) before and after a 12-week intervention with 1.2 g per day ω-3 PUFAs or placebo, followed by a 40-week observation period to establish the rates of transition to psychosis. We investigated *in*PLA_2 and erythrocyte membrane FAs in the treatment groups (ω-3 PUFAs vs placebo) and the outcome groups (psychotic vs non-psychotic). The levels of membrane ω-3 and ω-6 PUFAs and *in*PLA_2 were significantly related. Some of the significant associations (that is, long-chain ω-6 PUFAs, arachidonic acid) with *in*PLA_2 activity were in opposite directions in individuals who did (a positive correlation) and who did not (a negative correlation) transition to psychosis. Supplementation with ω-3 PUFA resulted in a significant decrease in *in*PLA_2 activity. We conclude that ω-3 PUFA supplementation may act by normalizing *in*PLA_2 activity and δ-6-desaturase-mediated metabolism of ω-3 and ω-6 PUFAs, suggesting their role in neuroprogression of psychosis.

Molecular Psychiatry advance online publication, 12 March 2013; doi:10.1038/mp.2013.7

Keywords: calcium-independent phospholipase A_2; ω-3 fatty acids; neuroprogression; psychosis; schizophrenia; ultra-high risk

INTRODUCTION

In the 1990s, criteria for identifying[1] individuals at 'ultra-high risk' (UHR) of psychotic disorder—that is, in the putatively prodromal phase of psychosis—were introduced and validated in a series of prospective studies.[2–4] Individuals at UHR were identified by one or more of the following characteristics: (1) subthreshold, attenuated forms of positive psychotic symptoms over the past year; (2) episodes of frank psychotic symptoms that did not last longer than a week and had spontaneously abated; and/or (3) having a first-degree relative with a psychotic disorder or a schizotypal personality disorder, in addition to a significant decrease in functioning over the previous year.[4] An age range of 15–30 years was also included in the identification approach, as this age group has been found to have the highest risk for psychosis. These UHR criteria have been adopted, and adapted, by various international groups.[5]

Several interventions, both pharmacological as well as psychological, have been proposed to delay or even prevent the onset of psychosis in UHR populations.[6] While antipsychotics may be of value, they appear to have an unclear risk-benefit profile.[7] Our recent randomized placebo-controlled trial[1] found a 4.9% rate of transition to acute psychosis in UHR patients treated with long-chain ω-3 (ω-3) polyunsaturated fatty acids (PUFAs) as compared with a psychosis transition rate of 27.5% in individuals who received placebo in addition to standard care, indicating that supplementation with ω-3 PUFAs may reduce the risk of transition to psychosis. More recently, we have made other discoveries that underpin the importance of lipid biology to the onset of psychosis. We showed that lower levels of ω-3 PUFAs correlate with more severe negative symptoms in UHR patients,[8] and that decreased levels of FAs (that is, nervonic acid, ω-3 PUFAs) may serve as biomarkers predicting the conversion to psychosis in UHR subjects.[9] However, the pharmacological and neurochemical mechanisms of ω-3 PUFA action remain incompletely understood.

In the present study, we aimed to examine one putative mechanism underlying the effect of ω-3 PUFA supplementation using a prospective longitudinal design. This mechanism is hypothesized to include changes in the levels of different PUFAs,

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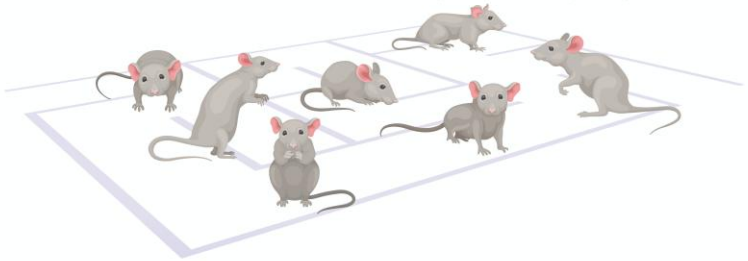
Received 28 November 2011; revised 10 December 2012; accepted 2 January 2013

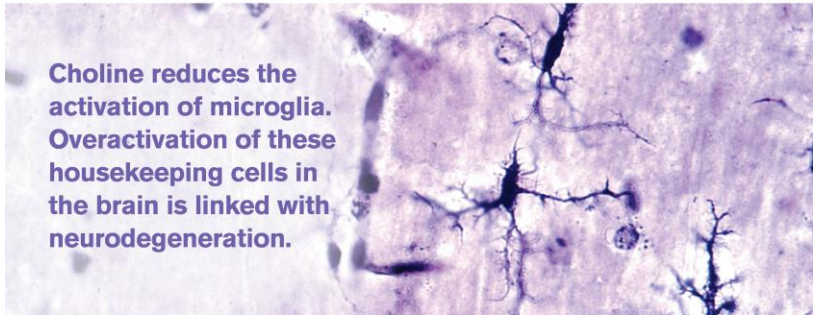
- *In summary the present results clearly show an effect of N3 PUFA supplementation on membrane PUFA profile and inPLA2 activity in UHR patients. Together with the clinical effects observed in this trial N3 PUFA supplementation appears to provide promising neuroprotective treatment strategy related to the reduction of neuroprogression mediated by excitotoxicity and oxidative damage while providing resources for phospholipid based neural membrane plasticity.*

Lifelong Choline diet improves Alzheimer's symptoms

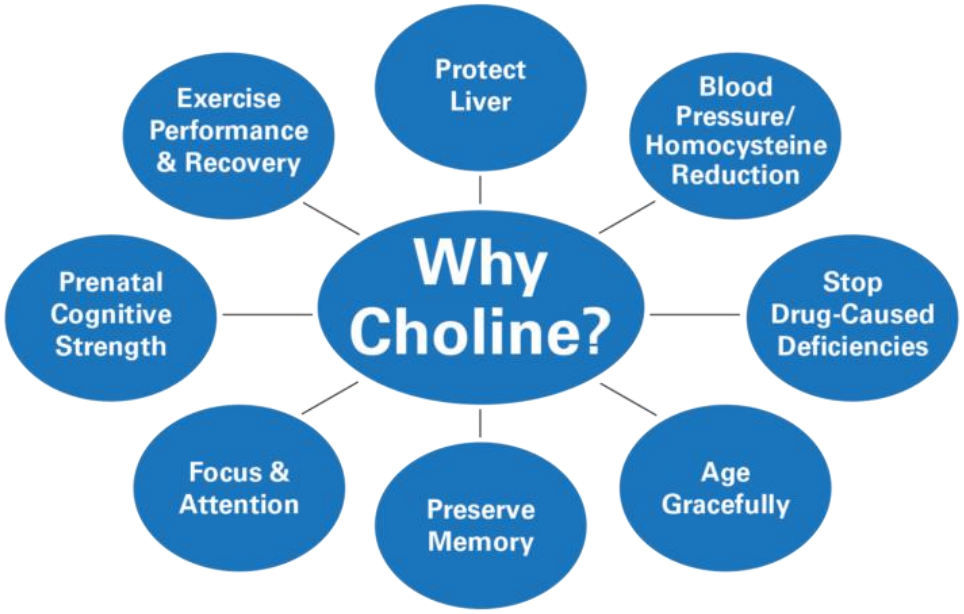
Female mice bred to display Alzheimer's-like symptoms develop progressive cognitive decline.

When mice received additional choline in their diet, they showed marked improvement in cognitive performance.





Choline reduces the activation of microglia. Overactivation of these housekeeping cells in the brain is linked with neurodegeneration.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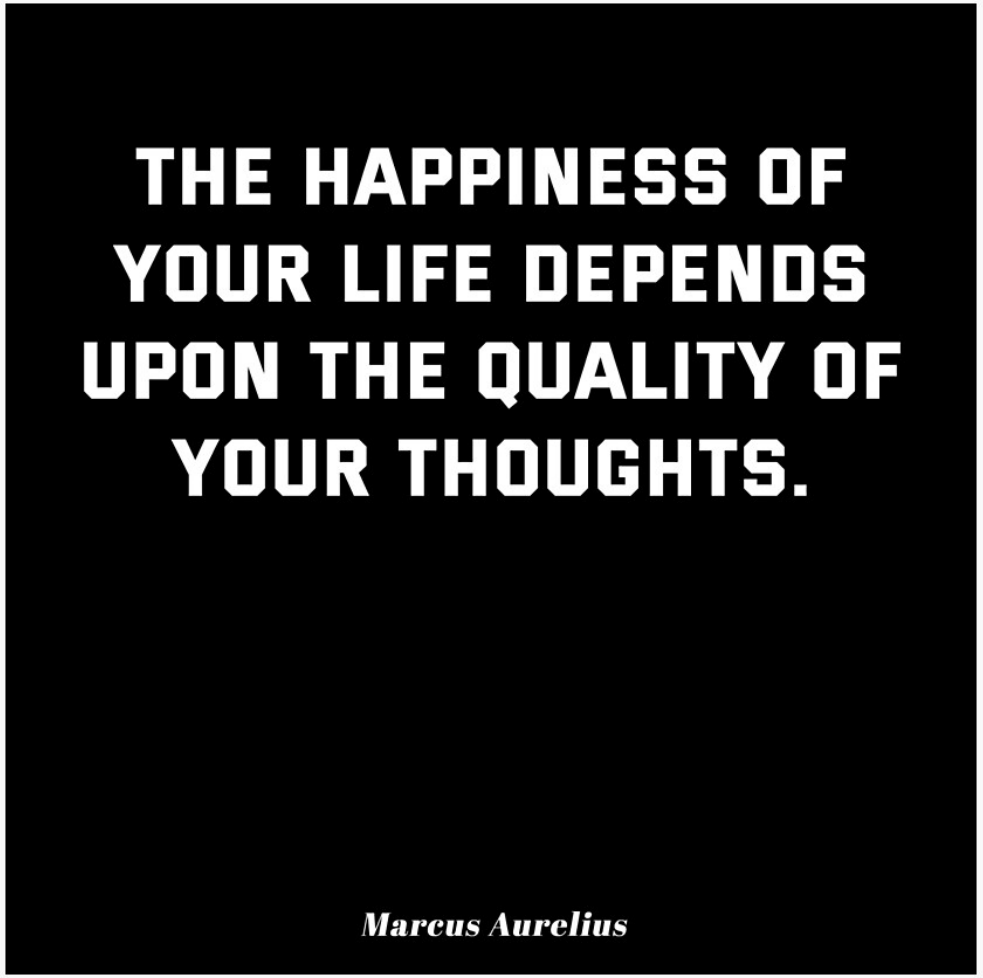
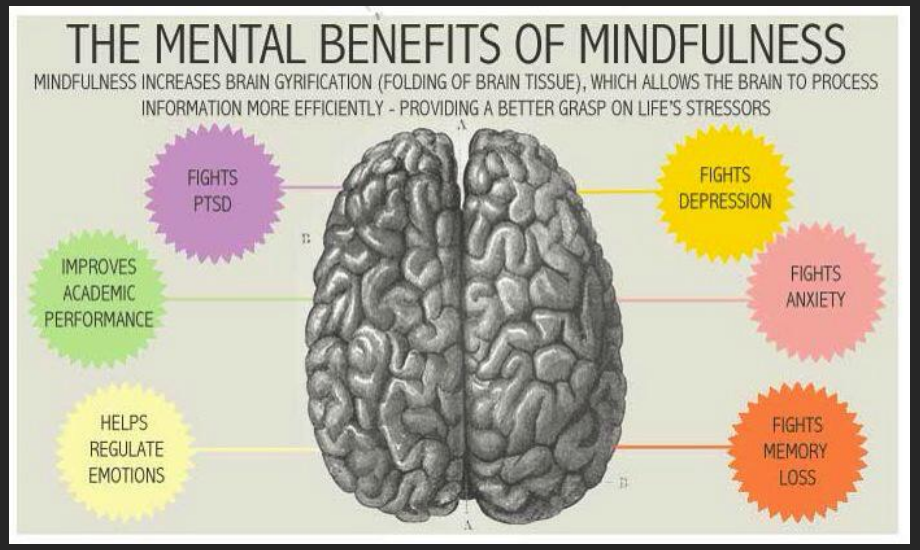
Preserve Memory
Focus & Attention
Prenatal Cognitive Strength
Exercise Performance & Recovery


THE HAPPINESS OF YOUR LIFE DEPENDS UPON THE QUALITY OF YOUR THOUGHTS.
Marcus Aurelius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FIGHTS ANXIETY
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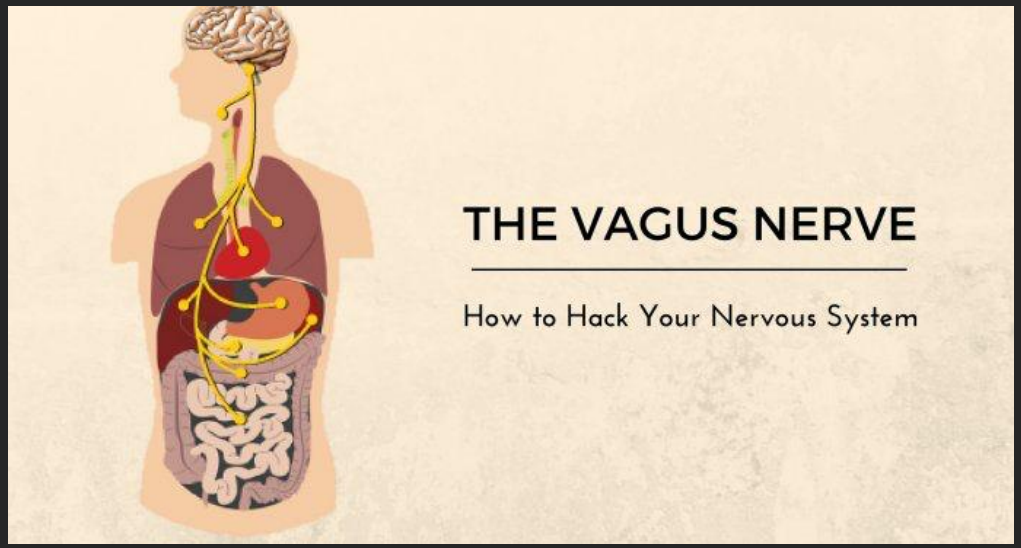
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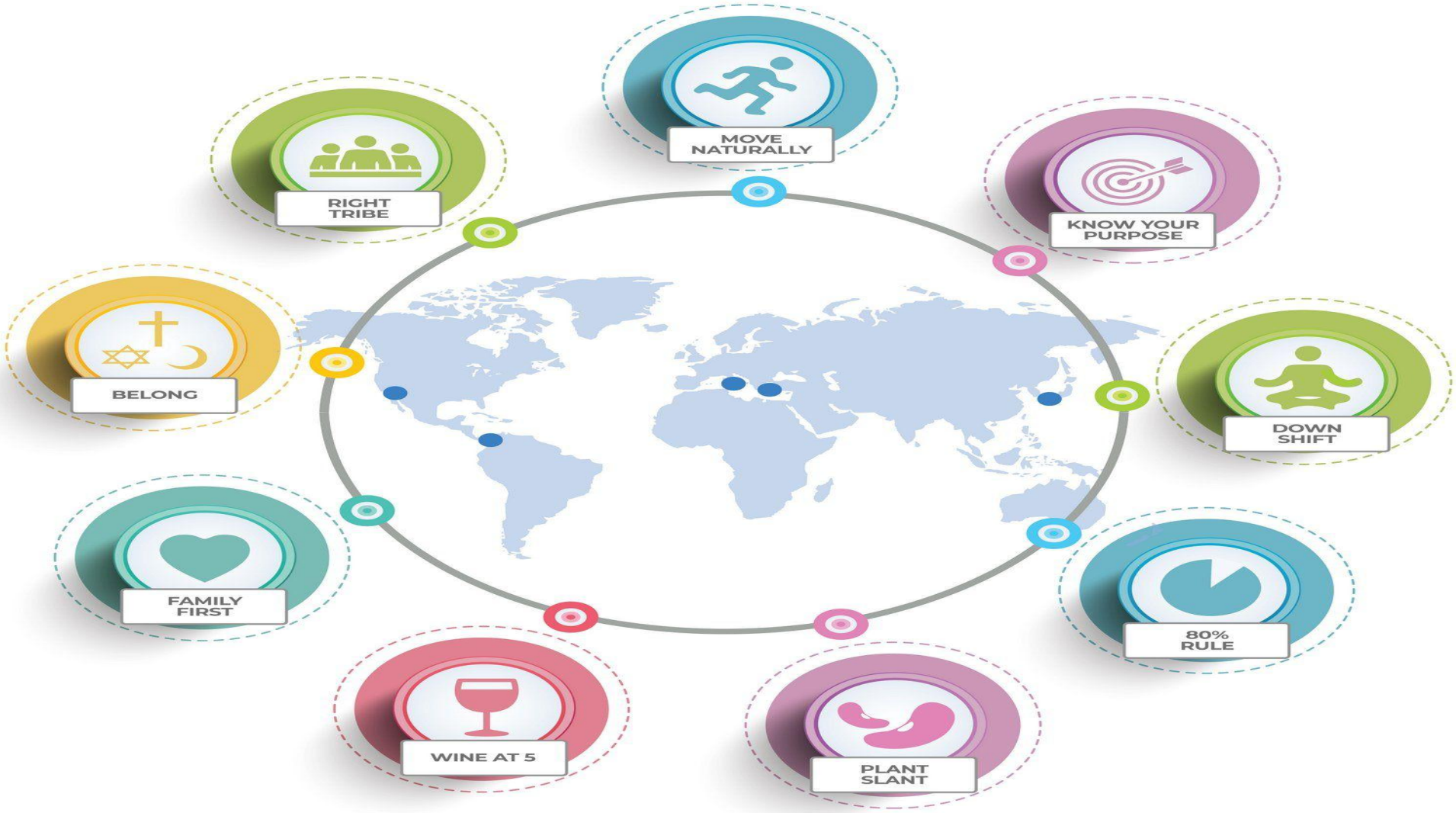

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