Neurological Disorders

DR. DEBBY HAMILTON, MD, MPH

Mechanisms of Disease

- Neuroplasticity
- Neuroinflammation
- Oxidative Stress
- Glutathione Depletion
- Mitochondrial dysfunction
- Nutritional Deficiency
- Infections
- Toxicity

Neurological Disorders

- Neurodegenerative Diseases: Alzheimer's, Parkinson's disease, ALS
- Autism
- ADHD
- Mood disorders: depression, anxiety, bipolar disease, schizophrenia
- Traumatic Brain Injury
- Neurologic Lyme and tic borne infections

NEUROPLASTICITY

The Ability of the Brain to Reorganize Itself, Both in Structure and How It Functions

HOW THE BRAIN CHANGES

NEUROGENESIS

Continuous generation of new neurons in certain brain regions

NEW SYNAPSES

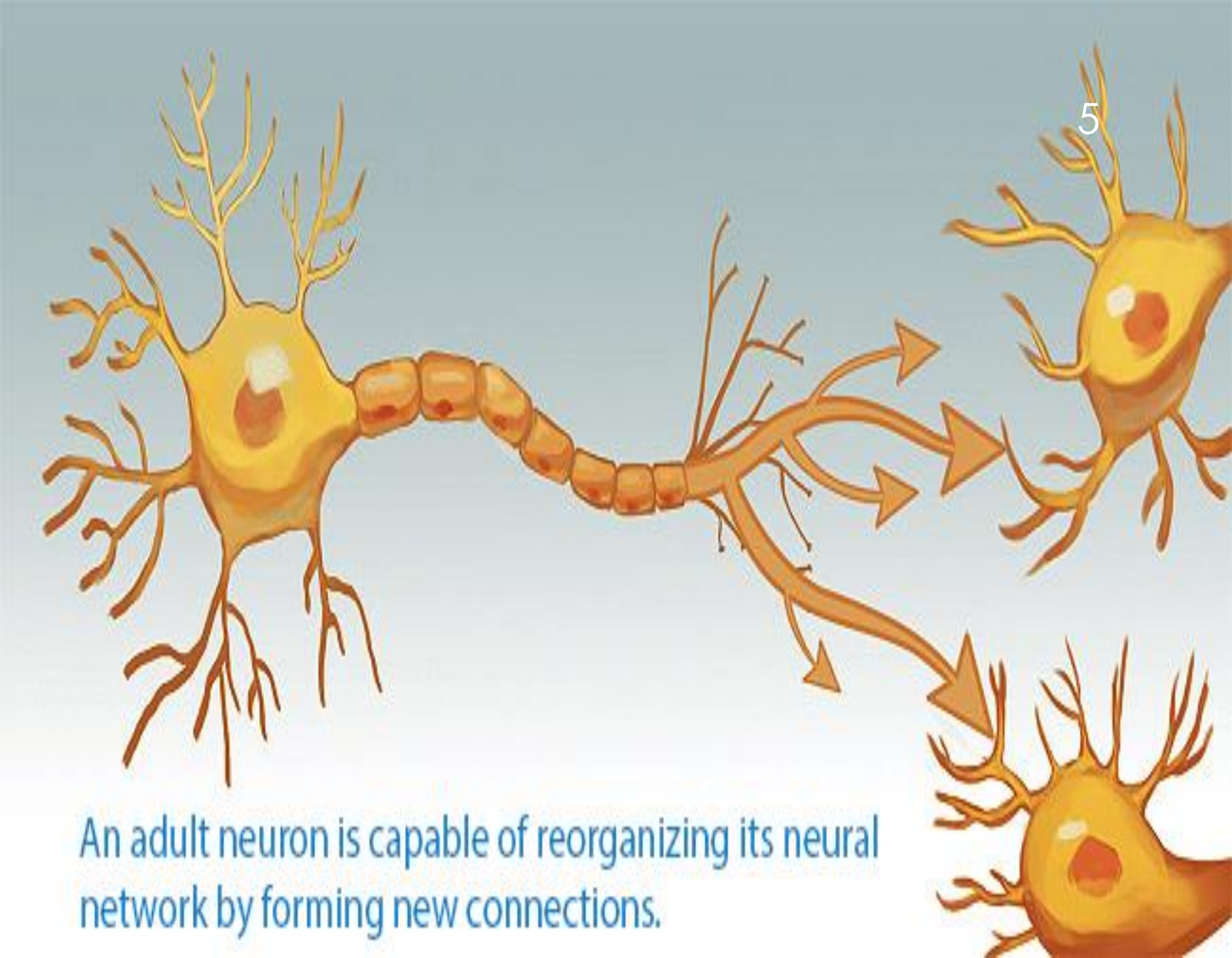
New skills and experiences create new neural connections

STRENGTHENED SYNAPSES

Repetition and practice strengthens neural connections

WEAKENED SYNAPSES

Connections in the brain that aren't used become weak



An adult neuron is capable of reorganizing its neural network by forming new connections.

Neurogenesis

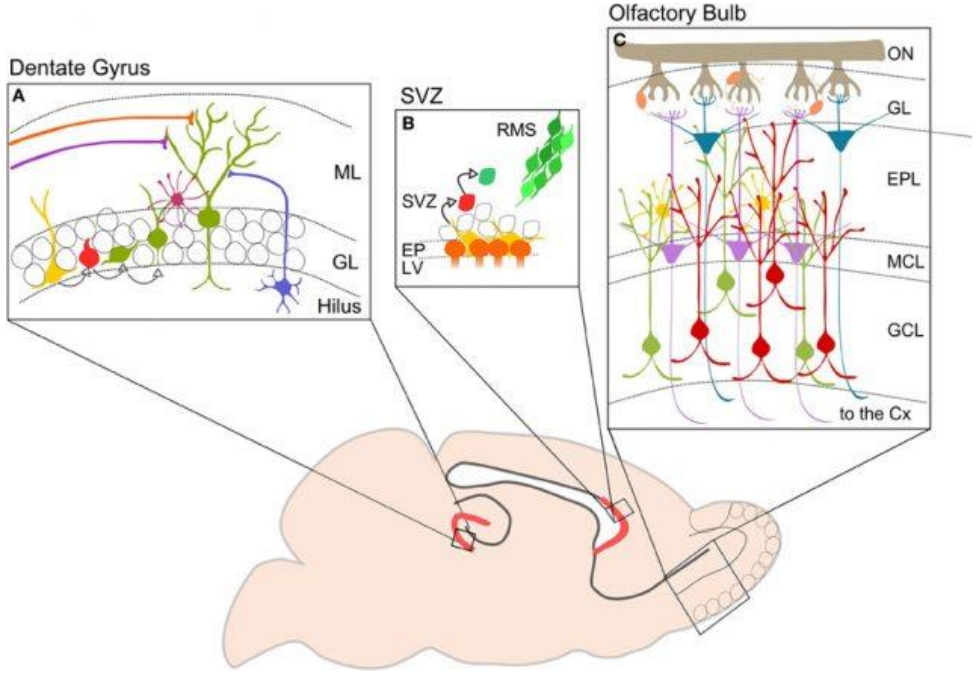
Only in 2 areas of the brain

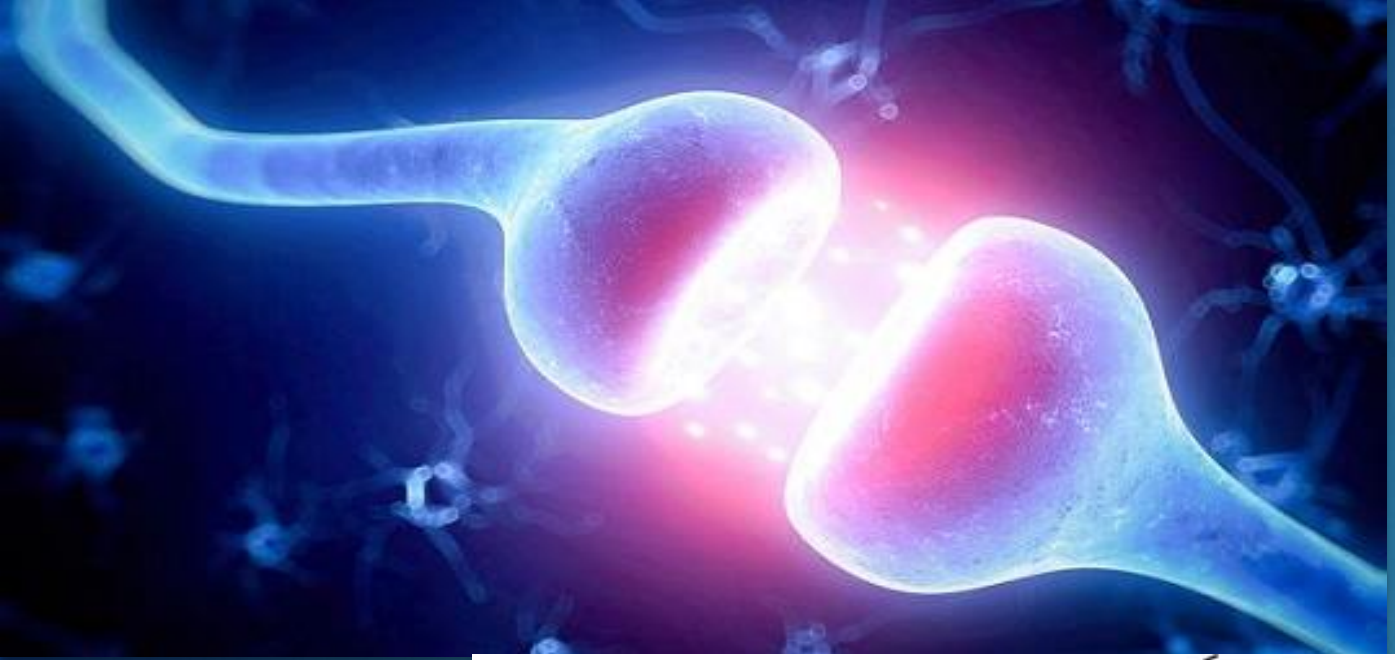
1. **Sub-ventricular zone(SVZ)**

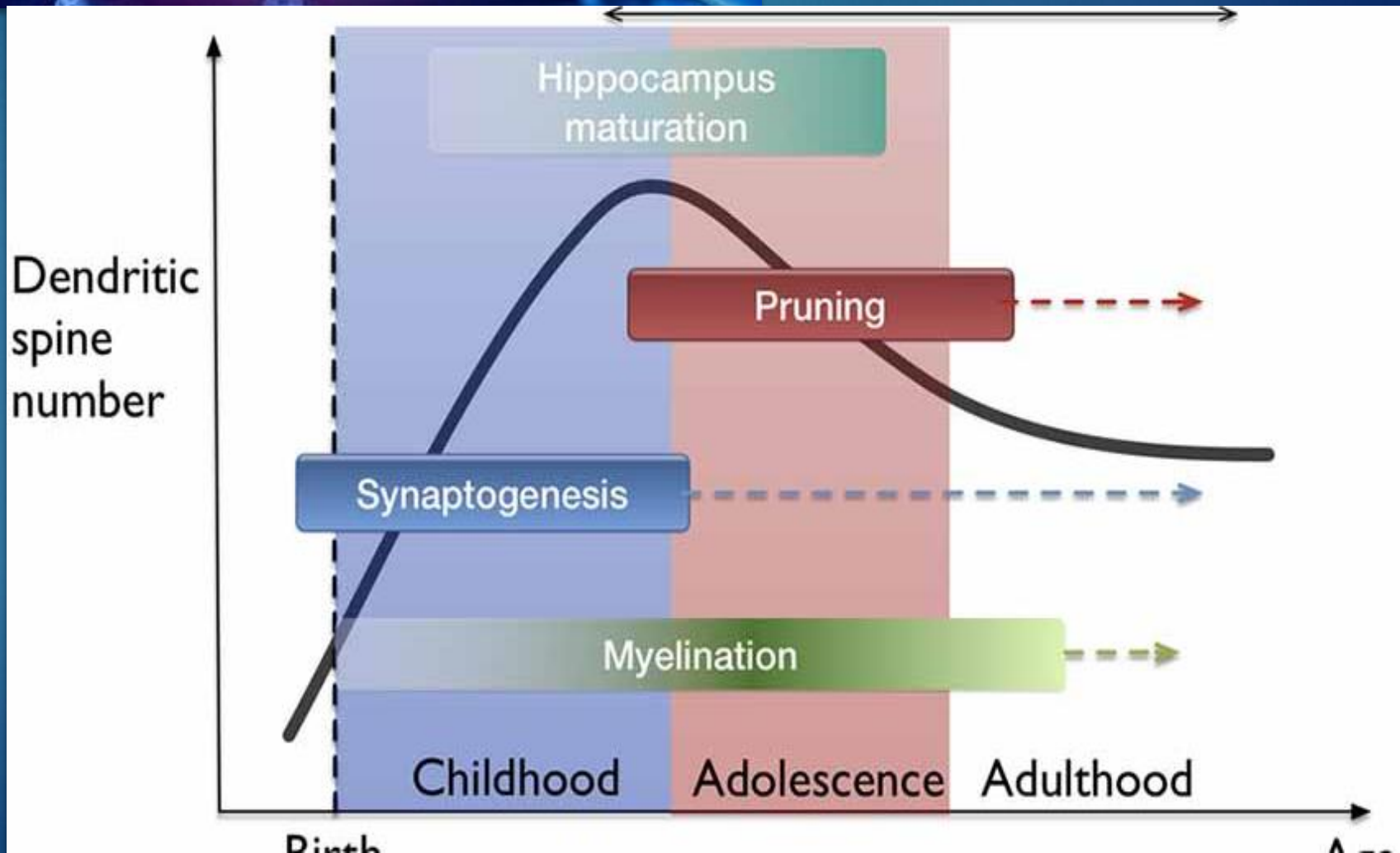
   Continuously generate neurons travel into olfactory bulb become interneurons

2. **Sub-granular zone(SGZ):** dendrate gyrus of the hippocampus

Stress has strong negative impact on hippocampal neurogenesis

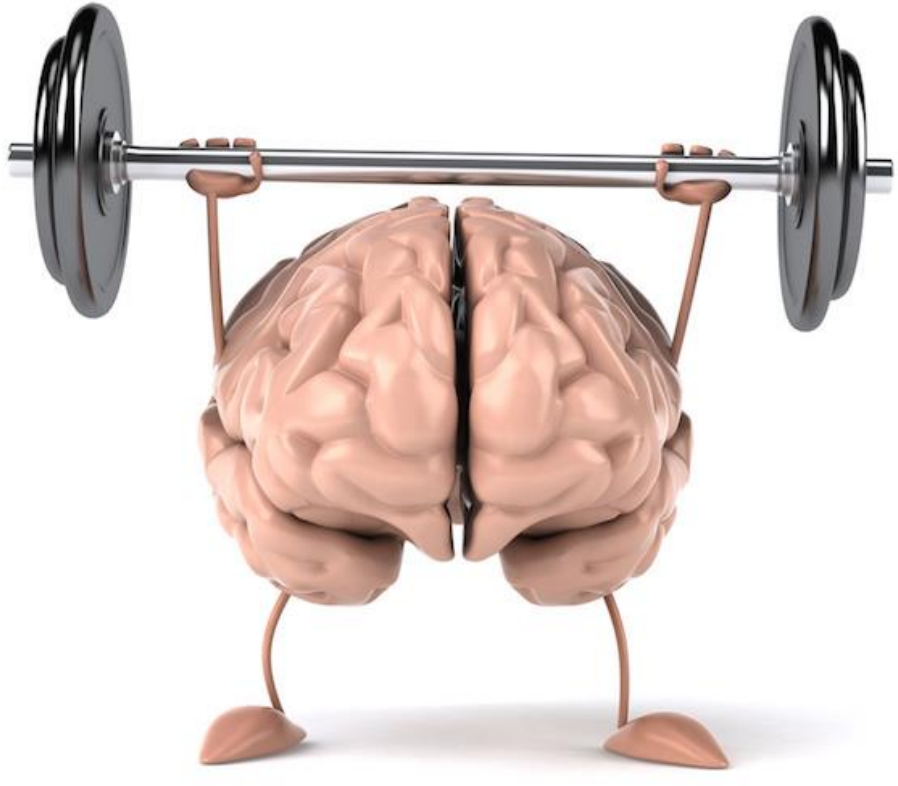





Hippocampus maturation
Pruning
Synaptogenesis
Myelination
Dendritic spine number
Childhood
Adolescence
Adulthood
Birth

Increase Neuroplasticity

- Physical Exercise
- Learning new skills
- Meditation
- Sleep
- Intermittent Fasting
- Increase BDNF(Brain Derived neurotrophic factor)
- Herbal supplements: (work by increasing BDNF, anti-oxidants, decreasing stress
- Good nutrition: omega three fatty acids

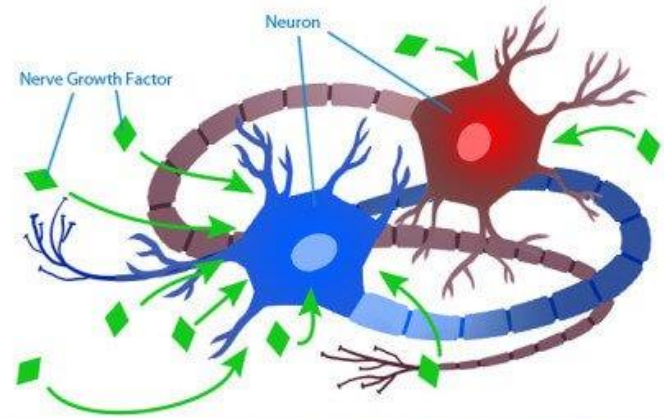


Decrease Neuroplasticity

- Stress: Increase cortisol, abnormal HPA axis
- Neurotoxins
- Physical and mental Inactivity
- Watching TV
- Poor nutrition
- Neuroinflammation from toxins, infections
- Traumatic brain injury
- Oxidative stress

Neurotrophic growth factors

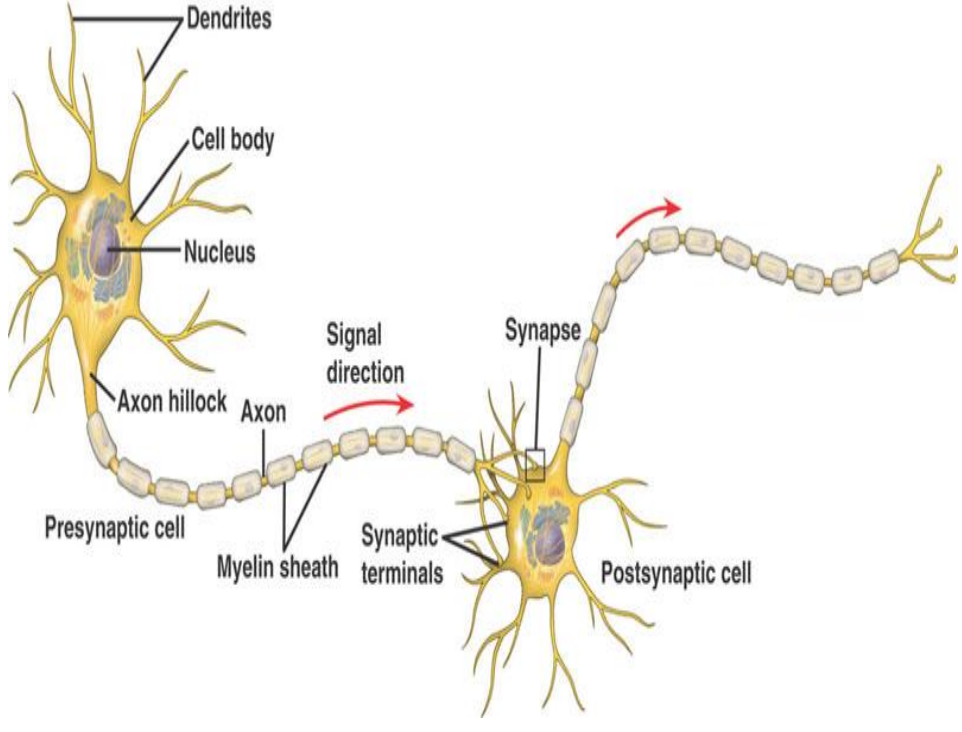
- Proteins that promote the survival, development, and function of neurons
  - Nerve Growth Factor (NGF): growth of sympathetic and sensory neurons
  - Brain Derived neurotrophic Factor (BDNF): primarily in the brain-central nervous system
  - NT-3, NT-4: peripheral and central nervous system



Nerve Growth Factors (shown in green) is required by neurons in order to survive. As they are a limited extracellular resource, some neurons (shown in blue) may uptake a disproportionate share of survival factors, leading to the eventual death of neighboring neurons (shown in red).

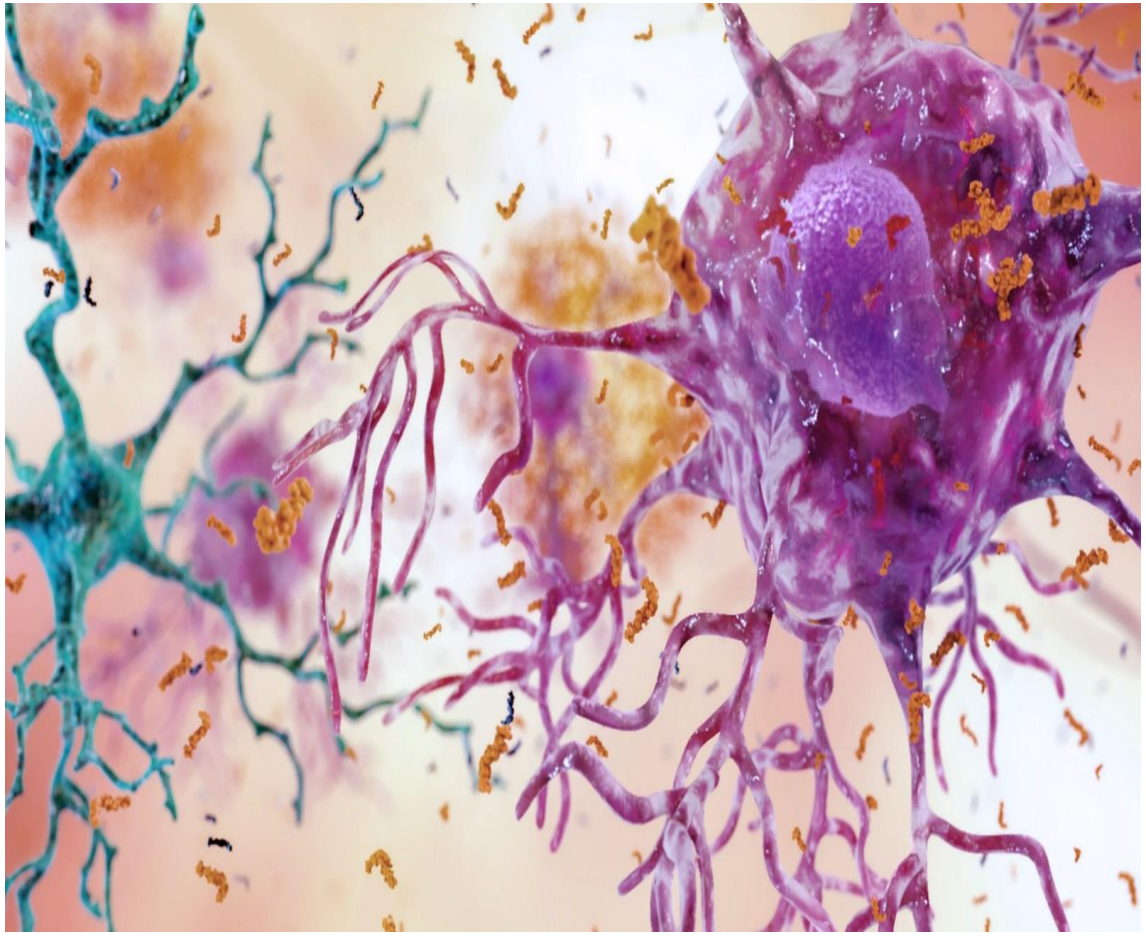
BDNF Functions

- Neuroplasticity:
  - Nervous system can change and adapt
- Neurogenesis:
  - New nerve cells
- Neuronal differentiation:
  - Nerve cells can change function
- Neuronal Repair
- Synaptogenesis:
  - Form new synapses
- Impact telomerase activity:
  - Stop breaking down telomeres so anti-aging



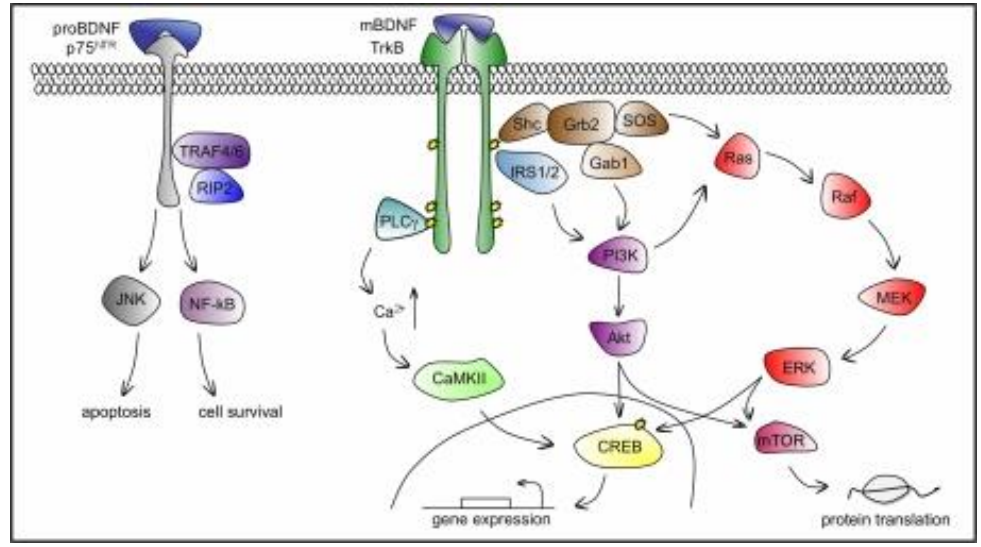
BDNF Functions

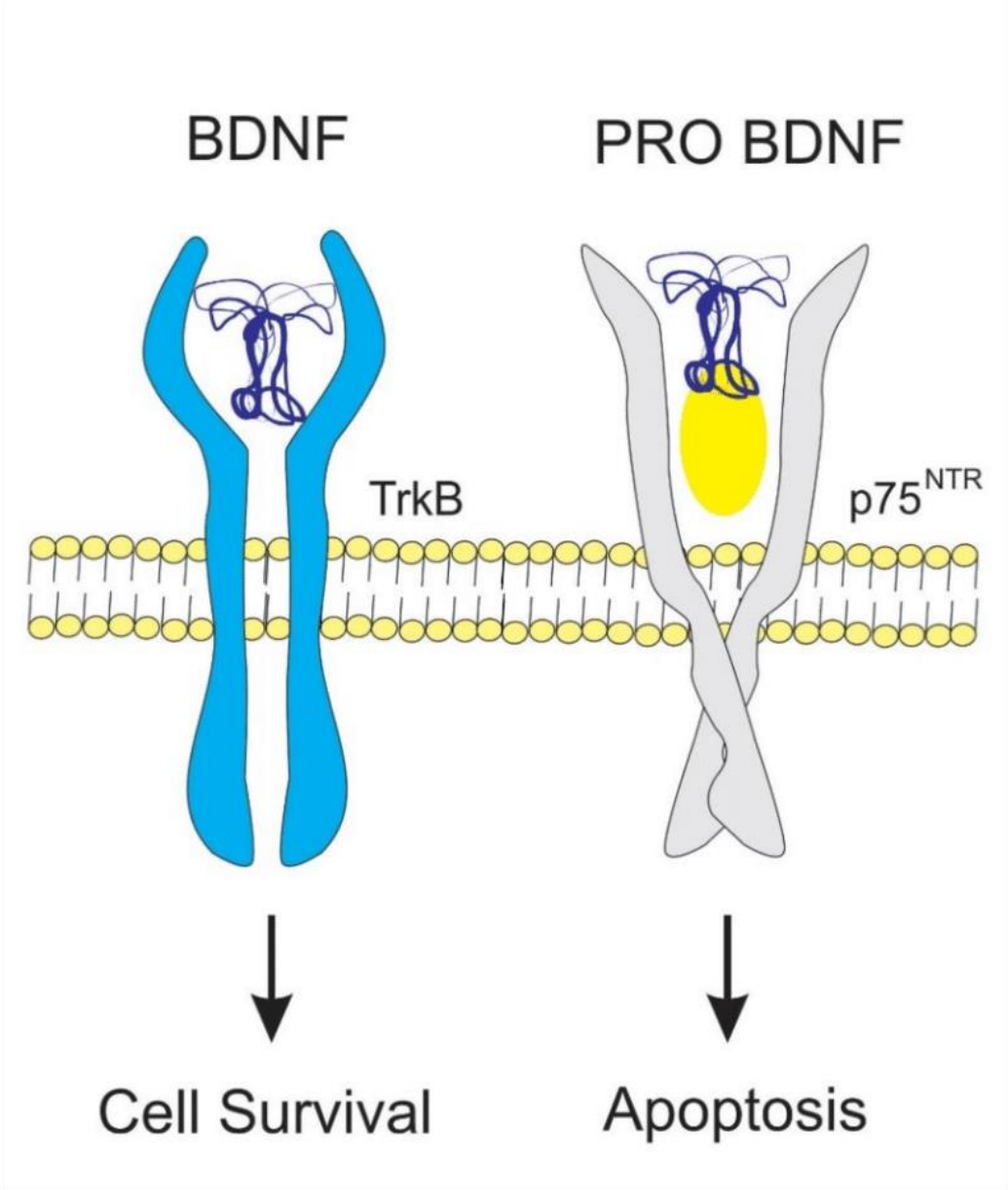
- Learning
- Memory
- Cognitive function
- Attention
- Resilience



BDNF Receptors

- Two receptors
  - TrkB: tropomyosin-related kinase
  - LNGFR: low affinity nerve growth factor receptor- also known as p75





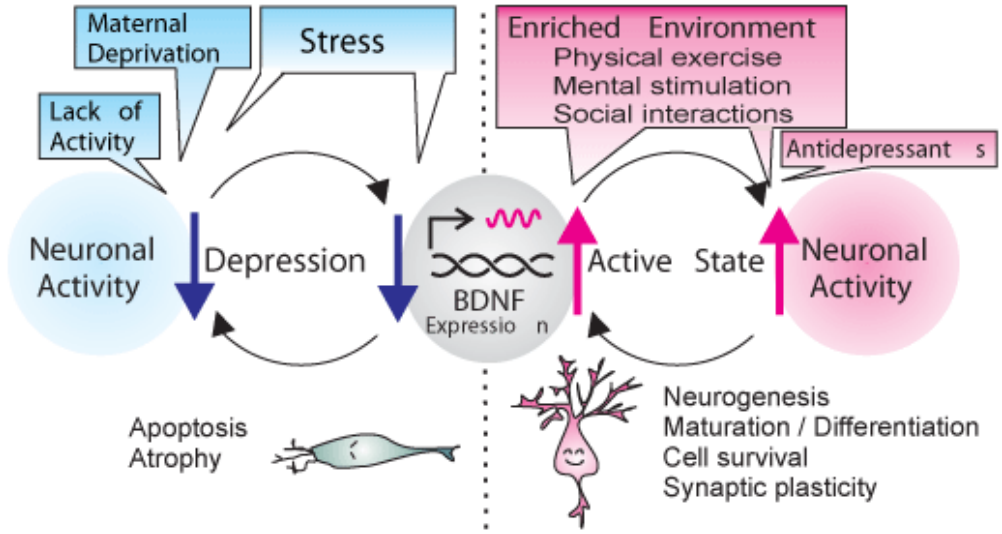
TrkB receptor:
BDNF

versus

p75 receptor:
Pro-BDNF

Brain Derived Neurotrophic Growth Factor

- Increased:
  - Exercise
  - Nutrition
  - Herbs
  - Learning
- Decreased
  - Stress
  - Poor diet
  - Depression
  - Low physical or mental activity



Neural Plasticity
Volume 2017, Article ID 7260130

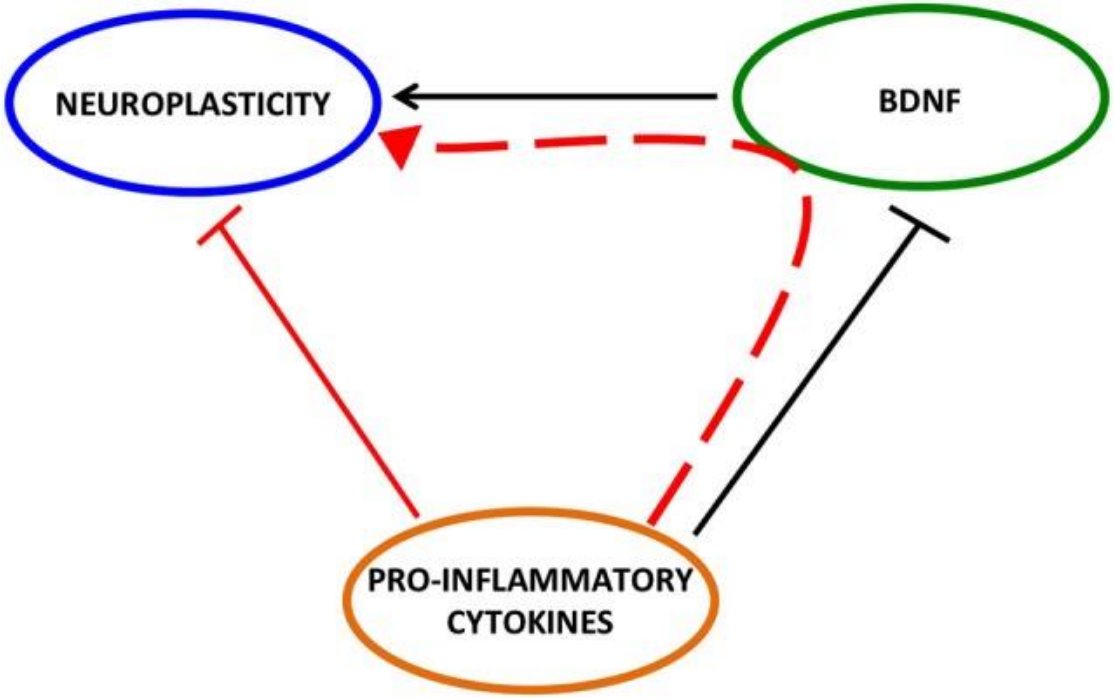
Review Article

Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection

Cristy Phillips

able 1: Effects of physical activity on brain-derived neurotrophic factor (BDNF).

Reference	Sample	Treatment	Assessment outcome
[233]	13 young, healthy men	Moderate-intensity aerobic PA 4 d/wk for 5 wks	↑ plasma BDNF
[234]	7 healthy, sedentary males	Aerobic PA 7 d/wk for 12 wks	↑ plasma BDNF
[238]	60 older adults	Aerobic PA 3 d/wk for 60 wks	↑ BDNF and ↑ hippocampal volume
[236]	47 healthy, sedentary males	Aerobic PA 3 d/wk for 5 wks	↑ serum BDNF following PA and ↑ memory on face name matching
[235]	62 healthy, sedentary males	Moderate-intensity aerobic PA for 2 wks	↑ serum BDNF following PA and ↑ memory on face name matching
[247]	104 persons with partial response to antidepressants	Add-on high (16 kcal/kg/week) or low (4 KKW) PA for 12 wks to standard depression care	Persons entering with ↑ BDNF levels exhibited ↑ rate of response to antidepressants
[248]	15 severely depressed adults	Add-on aerobic PA 16 kcal/kg/week for 3 d/wk for 3 wks to standard care for depression or medication-only group	Similar ↑ in BDNF in aerobic PA and medication-only group, but ↓ in oxidative stress markers seen only in PA group



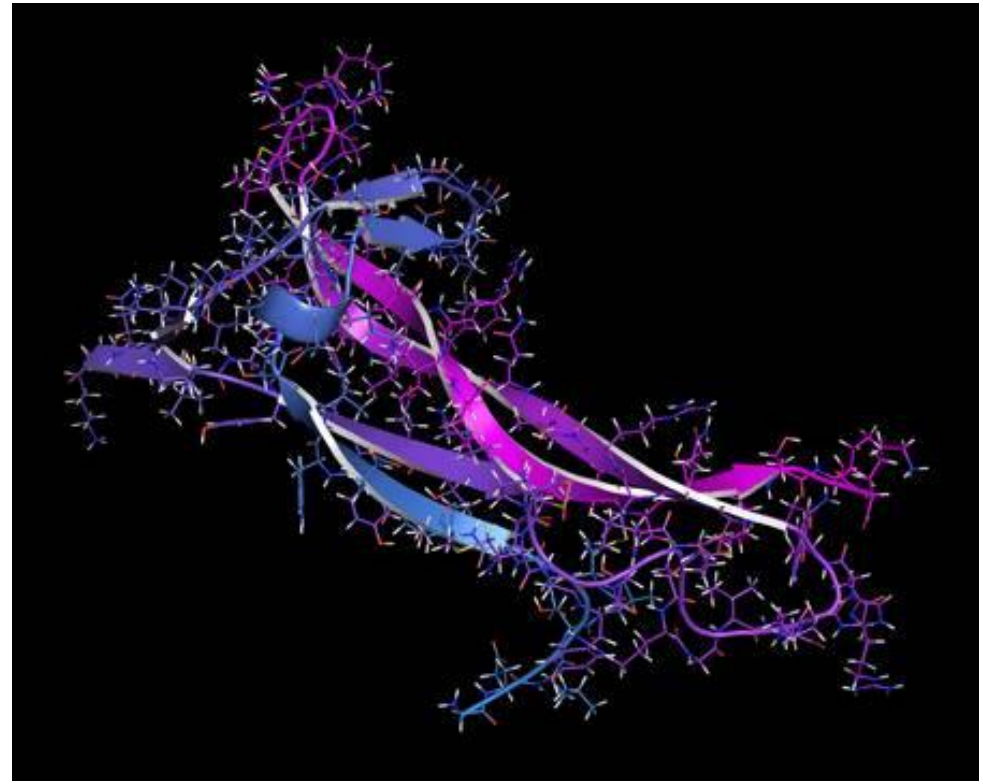
Calabrese F. et al. Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. Frontiers in Cellular Neuroscience. 2014;8:430.

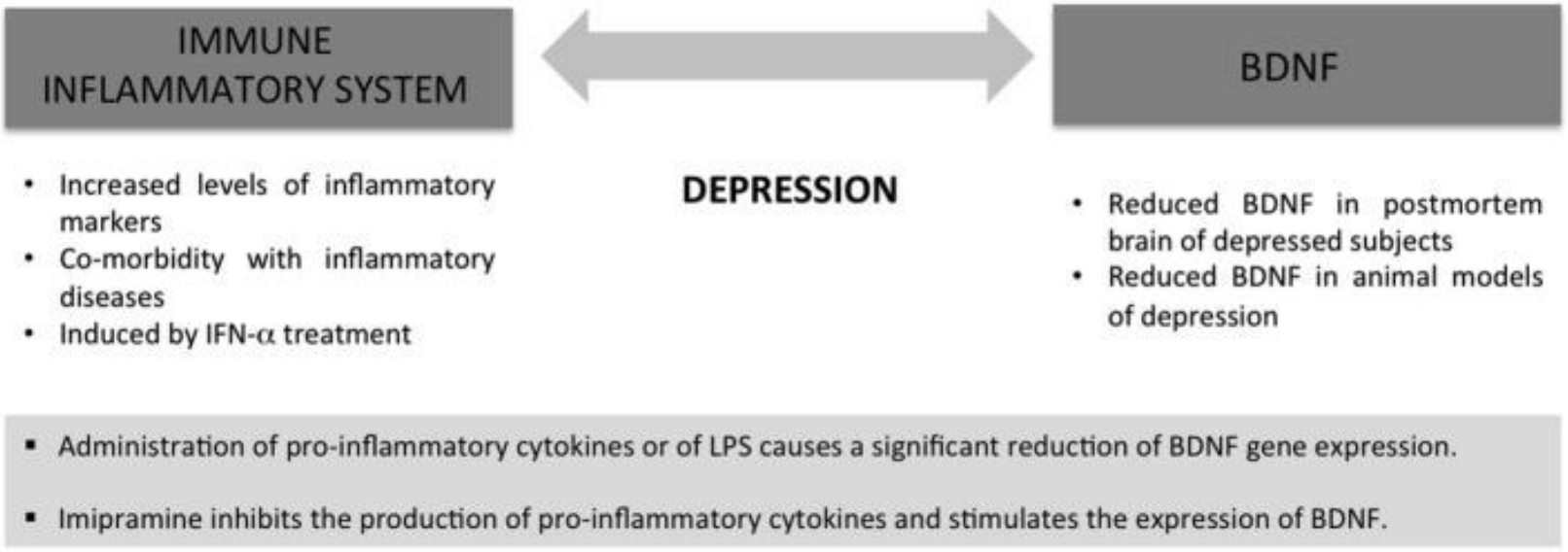
Brain Disorders and Related Neurotrophins

DISEASE	NEUROTROPHIN
Alzheimer's disease, Dementia, Rett syndrome	Nerve Growth Factor (NGF) Neurotrophin-3 (NT-3)
Addiction, Alzheimer's disease, Amytrophic lateral sclerosis (ALS), Anxiety, Depression, Huntington's disease, Parkinson's disease, Rett syndrome	Brain-Derived Neurotrophic Factor (BDNF)
Alzheimer's disease, Autism, Rett syndrome	Insulin-like growth factor 1 (IGF-1)
Addiction, Parkinson's disease	Glial-derived Neurotrophic Factor (GDNF), Neurturin
ALS, Huntington's disease	IGF-1, Ciliary Neurotrophic Factor (CNTF) Neurotrophin-4/5 (NT-4/5)

Disease States Associated with Low BDNF

- Depression and mood disorders
- Traumatic brain injury
- ADHD
- Autism Spectrum Disorders?
- Degenerative Disease
- Aging





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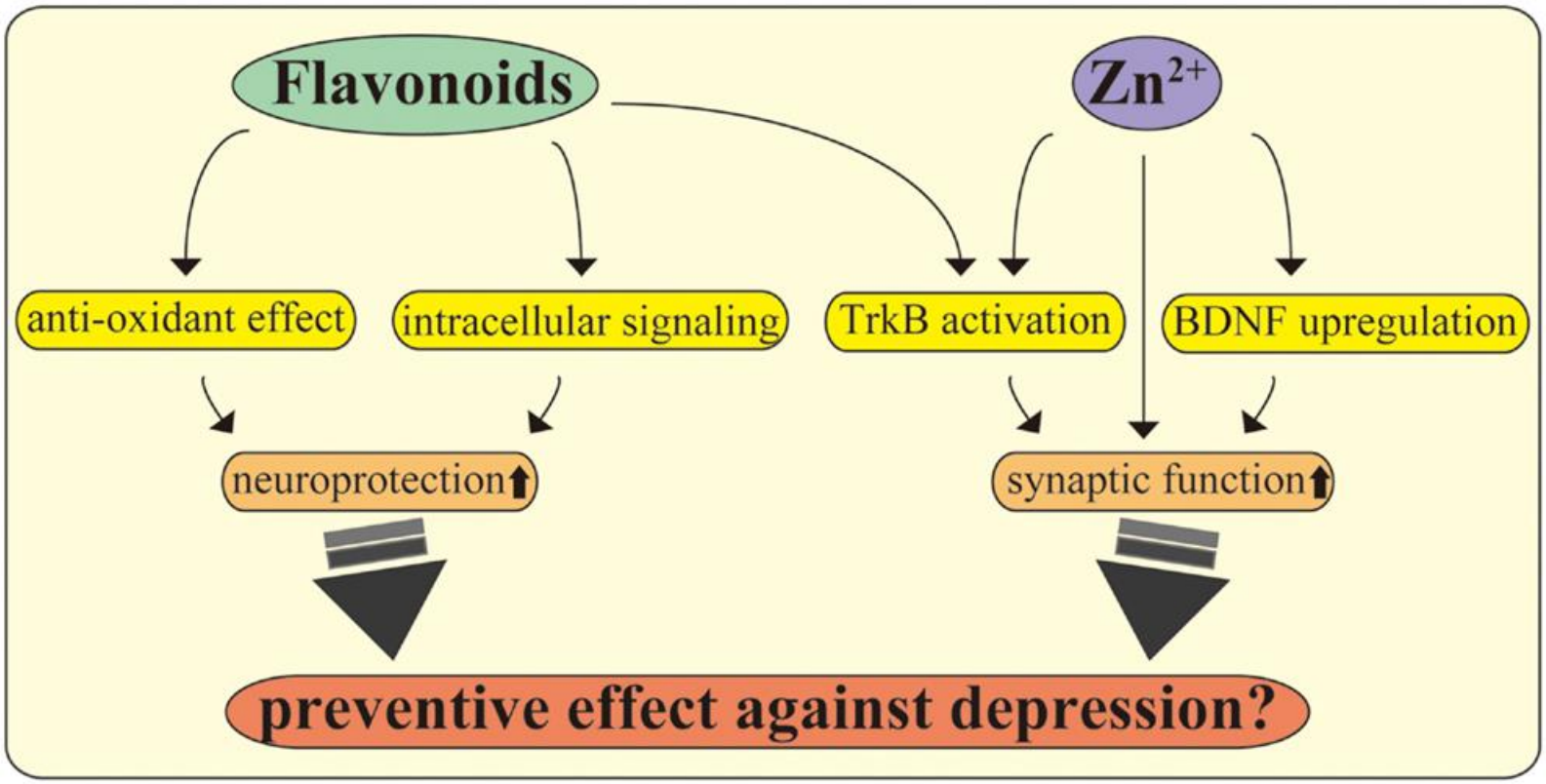
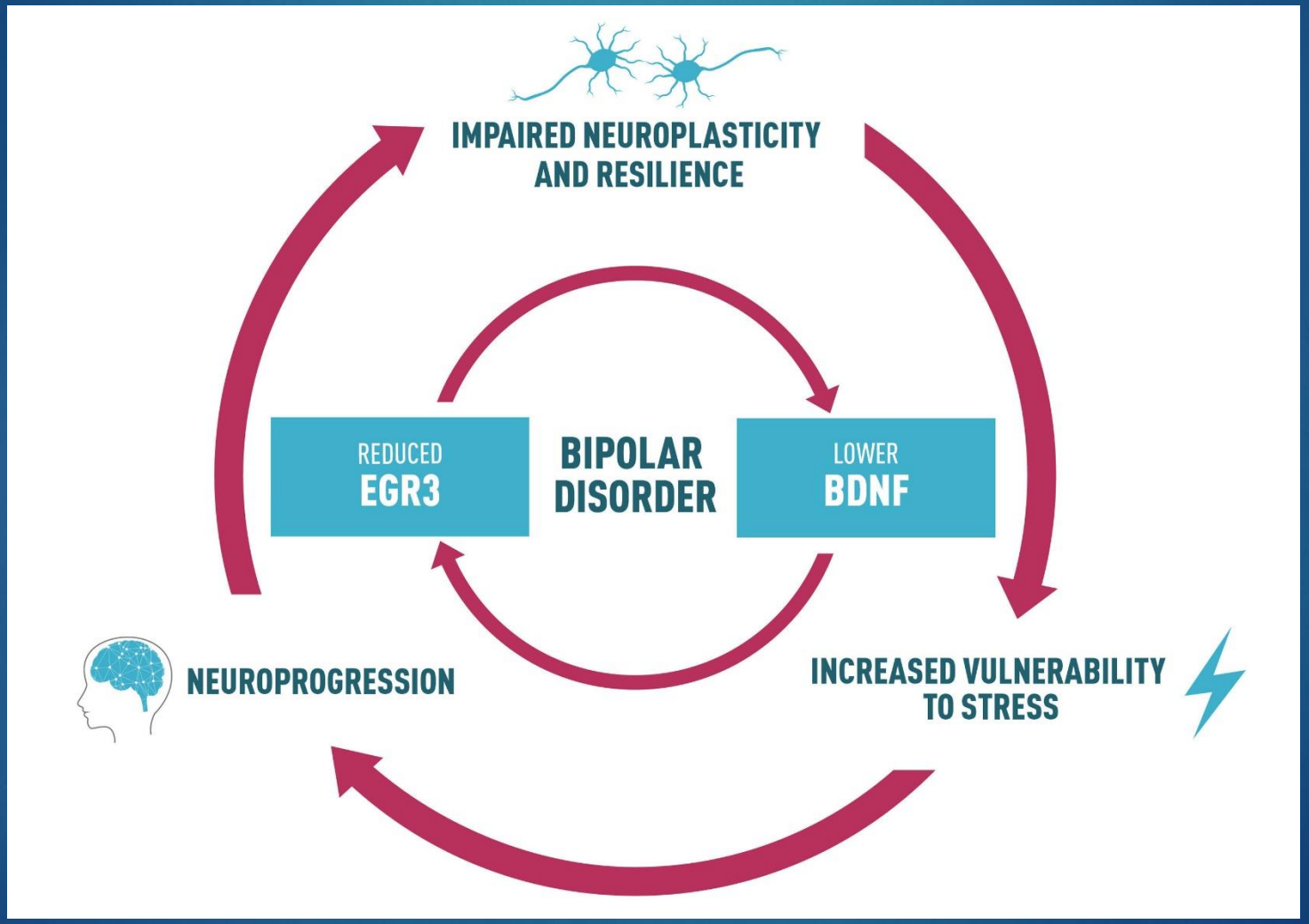


The role of BDNF in comorbid depression: possible linkage with steroid hormones, cytokines and nutrition.
Numakawa T. et al. Frontiers in Psychiatry. 2014 Vol 5(136)

Bipolar Disorder and Low BDNF



Genetic SNP's in BDNF

Val66 Met polymorphism

20 to 30% of Caucasians

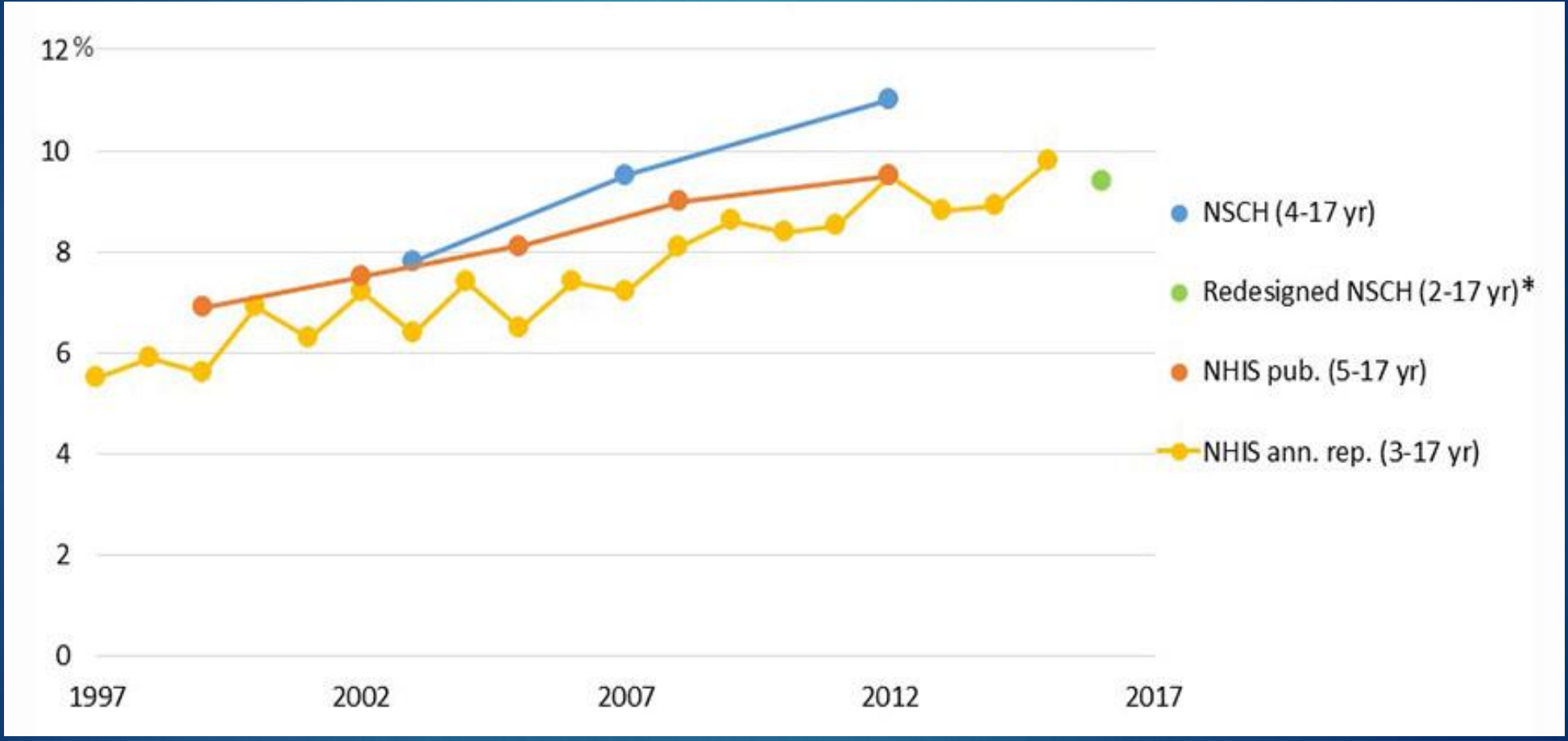
The association between *BDNF* Val66Met polymorphism and emotional symptoms after mild traumatic brain injury. *BMC Medical Genetics*. 2018. Wang Y-J, Chen K-Y, Kuo L-N, et al. ;19:13. doi:10.1186/s12881-017-0518-0.

- Patients with the BDNF Val66Met allele
  - Higher anxiety scores
  - Higher depression scores
  - Following traumatic brain injury

Prevalence of ADHD

https://www.cdc.gov/ncbddd/adhd/timeline.html

(Percent of children with a parent-reported ADHD diagnosis)



Mechanisms of Disease in ADHD

- Poor Neuroplasticity: low BDNF
- Neuroinflammation
- Mitochondrial dysfunction
- Oxidative stress
- Low glutathione
- Nutritional deficiency
- Toxicity

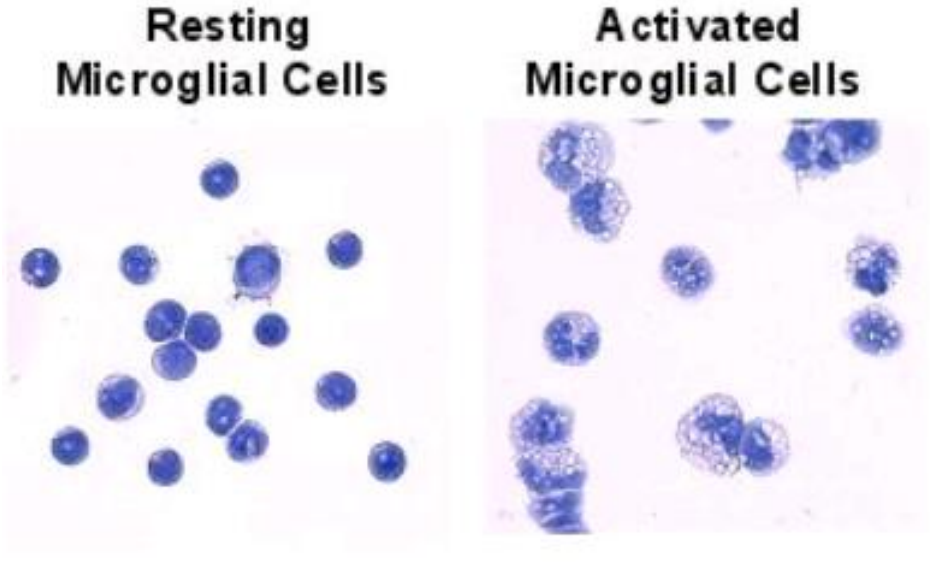
Prevalence of ASD

- About 1 in 68 children in 2012:CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network. From 1 in 150 children in 2000
- ASD is about 4.5 times more common among boys (1 in 42) than among girls (1 in 189).
- Studies in Asia, Europe, and North America have identified individuals with ASD with an average prevalence of between 1% and 2%.
- About 1 in 6 children in the United States had a developmental disability in 2006-2008, ranging from mild disabilities such as speech and language impairments to serious developmental disabilities, such as intellectual disabilities, cerebral palsy, and autism.

- https://www.cdc.gov/ncbddd/autism/data.html

Microglia: Functions

- Phagocytosis
- Synaptic Pruning
- Development of CNS
- Maintenance of CNS cells
- Instigate inflammation
- Repair and regeneration in CNS inflammation



Activated Microglia: Cycle of inflammation and repair

1. Rapid proliferation of microglial cells
2. Migrate to site of insult or infection
3. M1 activated microglia: neurotoxic with release of pro-inflammatory cytokines including TNF-alpha, IL-1B, IL-6, COX, Reactive oxygen species (ROS), Nitric oxide
4. Engulf dying cells, infectious agents, toxic proteins, and cell debris
5. M2 activated microglia: secrete anti-inflammatory cytokines for repair including: IL-10, TGF-B, enzymes to inhibit ROS production (arginase), proteins to maintain extra-cellular matrix

Inflammation in ADHD

METHODS: Sixty children were studied: 34 consecutive drug-naïve children with ADHD (30 males and 4 females; mean age of 10.10 years, sd=2.43 age) and 26 healthy control children (22 males and 4 females; mean age of 10.70 years, sd=1.81).

RESULTS: Data reveal higher IL-6 and IL-10 levels in ADHD patients than in the control group (p= .03).

- DonFrancesco. R. et al. Serum cytokines in paediatric neuropsychiatric syndromes: focus on Attention Deficit Hyperactivity Disorder. Minerva Pediatrica. 2016 Dec.

Summary of Neuroinflammation markers in ASD

- Microglial activation
- Astrocytic activation with elevated levels of GFAP(glial fibrillary acidic protein)
- Proinflammatory profile of cytokines in the brain, CSF and blood
- Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation

ADHD in adults and low BDNF

International Journal of Neuropsychopharmacology (2013), **16**, 1267–1275. © CINP 2013
doi:10.1017/S1461145712001629

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Decreased serum levels of brain-derived neurotrophic factor in adults with attention-deficit hyperactivity disorder

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Abstract

It has been hypothesized that brain-derived neurotrophic factor (BDNF) is involved in the pathogenesis of attention-deficit hyperactivity disorder (ADHD), although experimental data regarding the contribution of *BDNF* gene polymorphisms to this psychiatric disorder are controversial. Recently, changes in BDNF serum levels have been reported in children with ADHD, but there are no studies about the possible role of this neurotrophin in adults. A total of 54 Caucasoid ADHD adults, including the predominantly inattentive and combined types (aged 33.43 ± 8.99 yr) and 59 Caucasoid unrelated healthy controls (aged 35.52 ± 9.37 yr) were included in a study to evaluate BDNF levels in serum. Medical, neurological and psychiatric co-morbidities were excluded. Clinical data concerning ADHD diagnosis and blood samples for patients and controls were collected. BDNF serum levels were significantly lower in adults with ADHD compared to healthy controls ($p < 0.0001$). Although the combined type of ADHD subgroup displayed lower BDNF serum levels than the inattentive type, the differences did not reach statistical significance. No significant correlations were found between serum BDNF levels and scores on the Conners' Adult ADHD Rating Subscales. These results suggest a role for BDNF in ADHD, at least in those patients whose disorder persists throughout life. Low BDNF levels may contribute to the neurodevelopmental deficits of ADHD and to the persistence of the disorder into adulthood. BDNF differences between ADHD subtypes should be further studied.

Received 21 May 2012; Reviewed 3 August 2012; Revised 3 November 2012; Accepted 10 December 2012; First published online 3 January 2013

Key words: ADHD, BDNF, brain-derived neurotrophic factor, epigenetics, neurodevelopment.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a psychiatric condition that is defined by the core symptoms of inattention, hyperactivity and impulsivity and that begins in childhood, before the age of 7 yr, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised (DSM-IV-TR). Symptom intensity, especially hyperactivity, has been shown to decrease over time (Hart et al., 1995; Mick et al., 2004); however, for many patients the disorder persists into adulthood, although in some of them only some impairing symptoms remain (Rasmussen and Gillberg, 2000). The estimated prevalence of ADHD in adults ranges from 2.9% (Faraone and Biederman, 2005) to 4.4% (Kessler et al., 2006).

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Although the underlying pathogenesis of ADHD is still not well established, it is already accepted that it has a multi-factorial neurodevelopmental origin with a strong genetic component, with an estimated heritability of approximately 60% (Biederman and Faraone, 2005). Environmental risk factors also play a role in ADHD, especially if they are present in the pre- and early postnatal periods during the development of the brain (Galéra et al., 2011; Sagiv et al., 2012). From a neurobiological point of view, different lines of evidence suggest the involvement of the dopaminergic and serotoninergic systems (Solanto, 2002; Ribasés et al., 2009; Landaas et al., 2010; Nijmeijer et al., 2010) in the pathogenesis of ADHD. Experimental studies have shown a strong relationship between these monoamergic systems and a member of the neurotrophin family, brain-derived neurotrophic factor (BDNF; Küppers and Beyer, 2001; Dluzen et al., 2002; Goggi et al., 2003), which is widely expressed in the mammalian brain (Leibrock et al., 1989). BDNF has an important role in the development of the dopamine system (Yurek et al., 1996; Küppers and

ADHD in children and low BDNF

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ORIGINAL ARTICLE

Brain-Derived Neurotrophic Factor as a Biomarker in Children wi on Deficit-Hyperactivity Disorder

Farshid Saadat[1], Maryam Kosha[2], Ali Amiry[2], Gholamreza Torabi[2]*

[1]Department of Immunology, School of Medicine, Guilan University of Medical Sciences, Rasht-3477 Iran, [2]Department of Psychiatry, Shafa Hospital, Rasht, Iran

Abstract :

Background: Evidence suggests that Brain-Derived Neurotrophic Factor (BDNF) is involved in the pathogenesis of Attention-Deficit Hyperactivity Disorder (ADHD), although experimental data regarding the contribution of BDNF concentration to this psychiatric disorder are controversial. *Aim:* To evaluate the plasma levels of BDNF in patients with ADHD. *Material and Methods*: In this cross sectional study, ADHD and controls were recruited from the outpatient clinic of the Shafa Hospital, Rasht; between March 2012 and April 2013. Clinical data concerning ADHD diagnosis and blood samples for patients were collected before treatment. Medical, neurological and psychiatric co-morbidities were excluded. The mean of BDNF concentration measured and compared with healthy controls. BDNF assay was determined using ELISA kits according to manufacturer's instructions. Descriptive statistical analysis was used with analysis of variance to find the significance of data. *Results*: Statistical analyses showed that the mean BDNF levels were significantly lower in ADHD patients and its subgroups as compared with normal control subjects ($p<0.001$). *Conclusion*: This study showed a dramatically lower BDNF plasma levels in untreated patients with ADHD, which might be useful adjunct method for diagnosis of ADHD in society.

Keywords: Brain-Derived Neurotrophic Factor (BDNF), Attention-Deficit Hyperactivity Disorder (ADHD), BDNF Blood Level

Introduction:

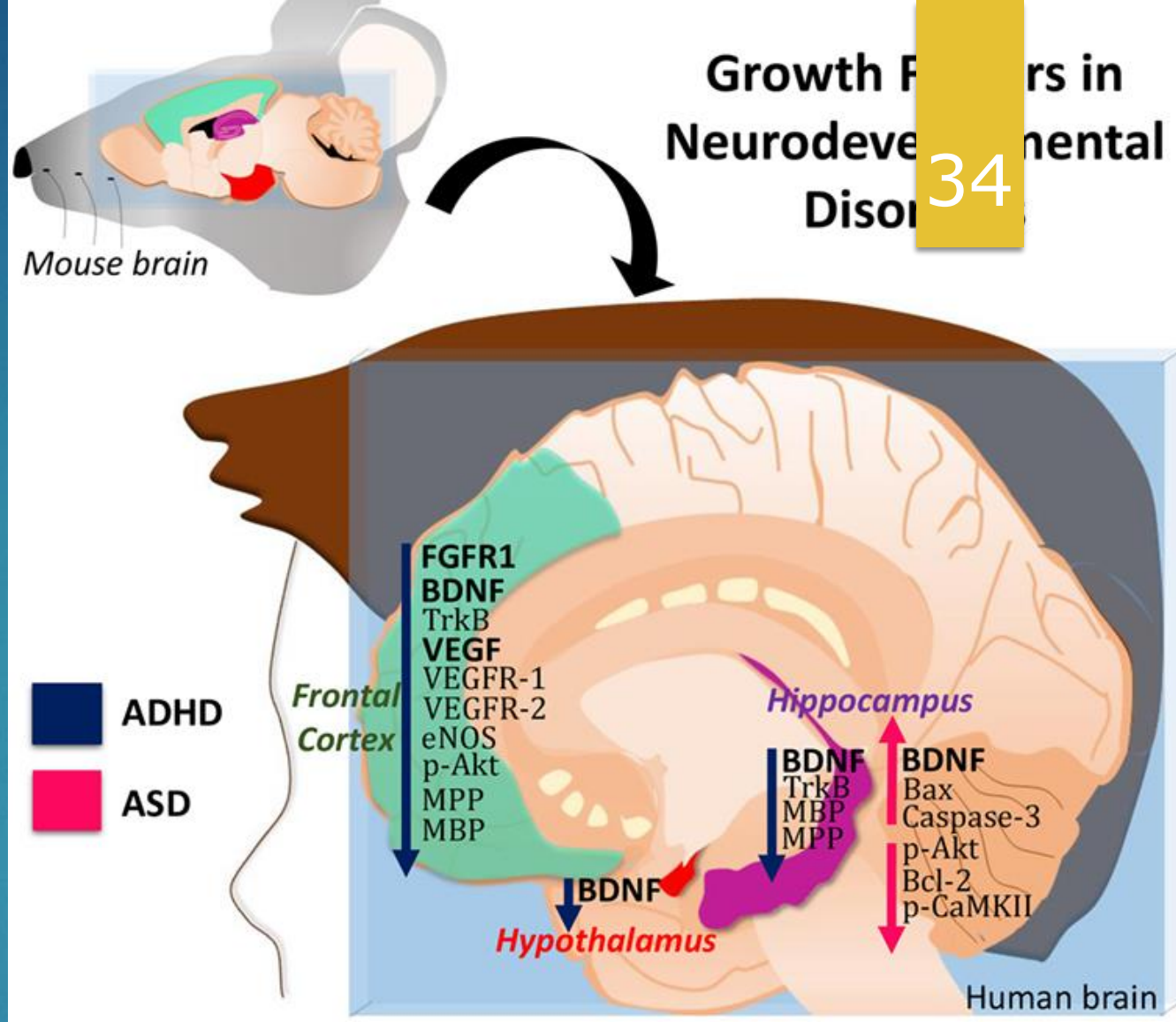
Attention deficit-hyperactivity disorder (ADHD) is a mental and neurobehavioral disorder characterized by inattention, impulsivity and hyperactivity. Diagnosing ADHD is based on its symptoms to inattention (ADHD-I), hyperactivity-impulsiveness (ADHD-H) or a combination of inattention and hyperactivity (ADHD-C) [1]. ADHD affects children globally and is diagnosed about twelve percent of Iranian kindergartens and school-aged children [2]. Moreover, its symptoms can be difficult to differentiate from other disorders, increasing the likelihood that the diagnosis of ADHD would be missed.

Although, the definite causes of ADHD are ambiguous, some factors such as genetics, dietary and the social environmental factors might be important to contributors in this disorder [3, 4]. Recently, there is evidence, which suggests that brain-derived neurotrophic factor, is involved in the pathogenesis of ADHD [5].

Brain-derived neurotrophic factor (BDNF) is a 25-kDa member of the neurotrophin family and highly expressed in cortical and hippocampal structures. It enhances the growth and maintenance of several neuronal systems as well

BDNF and other growth factors in Autism and ADHD

- Galvez-Contreras AY. Et al. Alterations of Growth Factors in autism and ADHD. Front Psychiatry.13 July 2017.



Expression levels of GF in blood

ADHD	ASD
↓ BDNF	BDNF ↑
↑ GDNF	TGF-β1 ↓
↑ NGF	EGF ↓
↑ NT3	NT4 ↓
↑ IGF2	HGF ↓

Autism and BDNF: mixed results

- Measurement of ProBDNF versus BDNF
- Different receptors with different actions

DOI 10.1007/s10571-016-0415-7

BRIEF COMMUNICATION

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Meta-Analysis of BDNF Levels in Autism

Raluca Armeanu[1] · Mikael Mokkonen[1,2] · Bernard Crespi[1]

Received: 18 May 2016 / Accepted: 3 August 2016

Abstract Brain-derived neurotrophic factor (BDNF) centrally mediates growth, differentiation and survival of neurons, and the synaptic plasticity that underlies learning and memory. Recent meta-analyses have reported significantly lower peripheral BDNF among individuals with schizophrenia, bipolar disorder, and depression, compared with controls. To evaluate the role of BDNF in autism, and to compare autism to psychotic-affective disorders with regard to BDNF, we conducted a meta-analysis of BDNF levels in autism. Inclusion criteria were met by 15 studies, which included 1242 participants. The meta-analysis estimated a significant summary effect size of 0.33 (95 % CI 0.21–0.45, $P < 0.001$), suggesting higher BDNF in autism than in controls. The studies showed notable heterogeneity, but no evidence of publication biases. Higher peripheral BDNF in autism is concordant with several neurological and psychological theories on the causes and symptoms of this condition, and it contrasts notably with the lower levels of BDNF found in schizophrenia, bipolar disorder, and depression.

Keywords Autism · BDNF · Meta-analysis · Schizophrenia · Bipolar disorder · Depression

Electronic supplementary material The online version of this article (doi:10.1007/s10571-016-0415-7) contains supplementary material, which is available to authorized users.

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Published online: 08 August 2016

Introduction

Brain-derived neurotrophic factor (BDNF) is a protein that belongs to the family of neurotrophins (Brigadski and Lessmann 2014). BDNF regulates dendritic spine maturation and pruning and plays important roles in promoting growth, differentiation, and survival of neurons (Binder and Scharfman 2004; Orefice et al. 2016). Expression of BDNF is regulated in part by neuronal activity induced by sensory stimulation (Woo and Lu 2009), and local protein synthesis at dendrites is mediated by BDNF, whereby it contributes to synaptic plasticity, learning, and memory (Lu et al. 2013; Bowling et al. 2016).

Given the considerable importance of BDNF, levels of this factor have been investigated among individuals with a range of psychiatric conditions. In particular, recent meta-analyses have demonstrated that BDNF levels in serum or plasma are significantly lower in subjects with schizophrenia (Ahmed et al. 2015), bipolar disorder (Fernandes et al. 2015), and depression (Molendijk et al. 2013) than in matched controls. The similar results across these three psychotic-affective disorders are not unexpected, given the strong overlap between them in their causes, phenotypic manifestations, and risk factors (e.g., Konstantareas and Hewitt 2001).

The pattern of association of BDNF levels with autism has been unclear (Tsai 2005; Halepoto et al. 2014). Serum or plasma BDNF is higher among individuals with autism compared with controls in some studies (e.g., Connolly et al. 2006; Ricci et al. 2013), but other studies have reported lower levels (e.g., Nelson et al. 2001; Hashimoto et al. 2007), or nonsignificant differences (e.g., Croen et al. 2008). The overall pattern of association between BDNF and autism has thus remained unresolved, and the causes of

Circulating brain-derived neurotrophic factor has diagnostic and prognostic value in traumatic brain injury. *Journal of Neurotrauma*, Korley, F. et al. (2016). *33*(2), 215-225. DOI: 10.1089/neu.2015.3949

- The found that levels of (BDNF), taken within 24 hours of someone's head injury, could predict the severity of a TBI and how a patient would fare.
  - Healthy BDNF: 60
  - Average head trauma: 20
  - Most severe head trauma: 4
- patients with high levels of BDNF had mostly recovered from their injuries 6 months later.
- patients with the lowest levels of BDNF, symptoms still lingered at follow-up 6 months later

Neurodegenerative diseases

- 5 million Americans suffer from Alzheimer's disease
- 1 million from Parkinson's
- 400,000 from multiple sclerosis (MS)
- 30,000 from amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease)
- 30,000 from Huntington's

- **If left unchecked 30 years from now, more than 12 million Americans will suffer from neurodegenerative diseases**.

http://neurodiscovery.harvard.edu/challenge

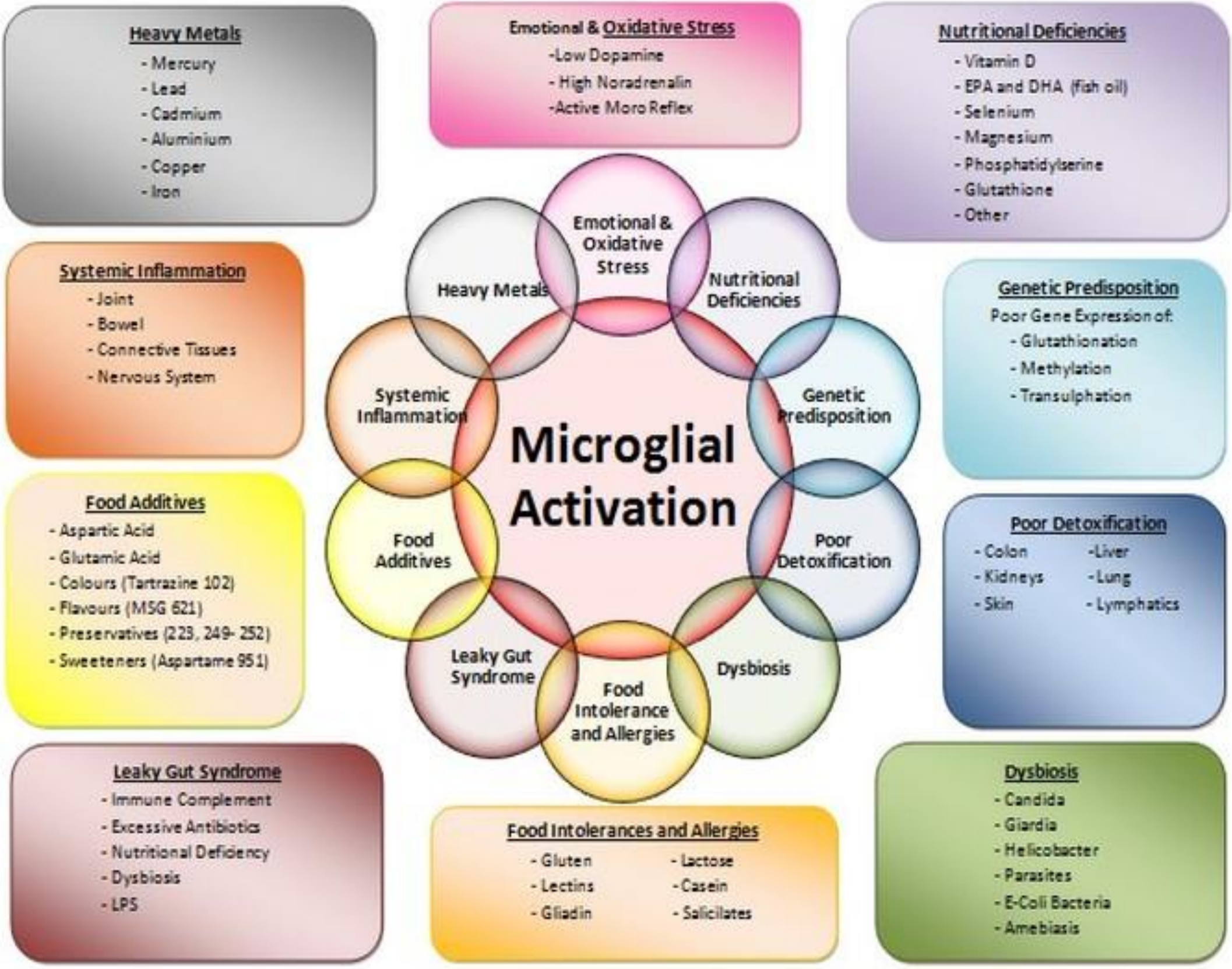
Alzheimer's Neuroinflammation

- Accumulation of protein aggregates
  - Extracellular: B-amyloid plaques
  - Intracellular: Neurofibrillary tangles (NFT)
  - Cause loss of synaptic function leading to neuronal death
- Microglial activation
- Astrocyte activation
- Pro-inflammatory cytokines near B-amyloid protein deposits and NFT

Parkinson's Neuroinflammation

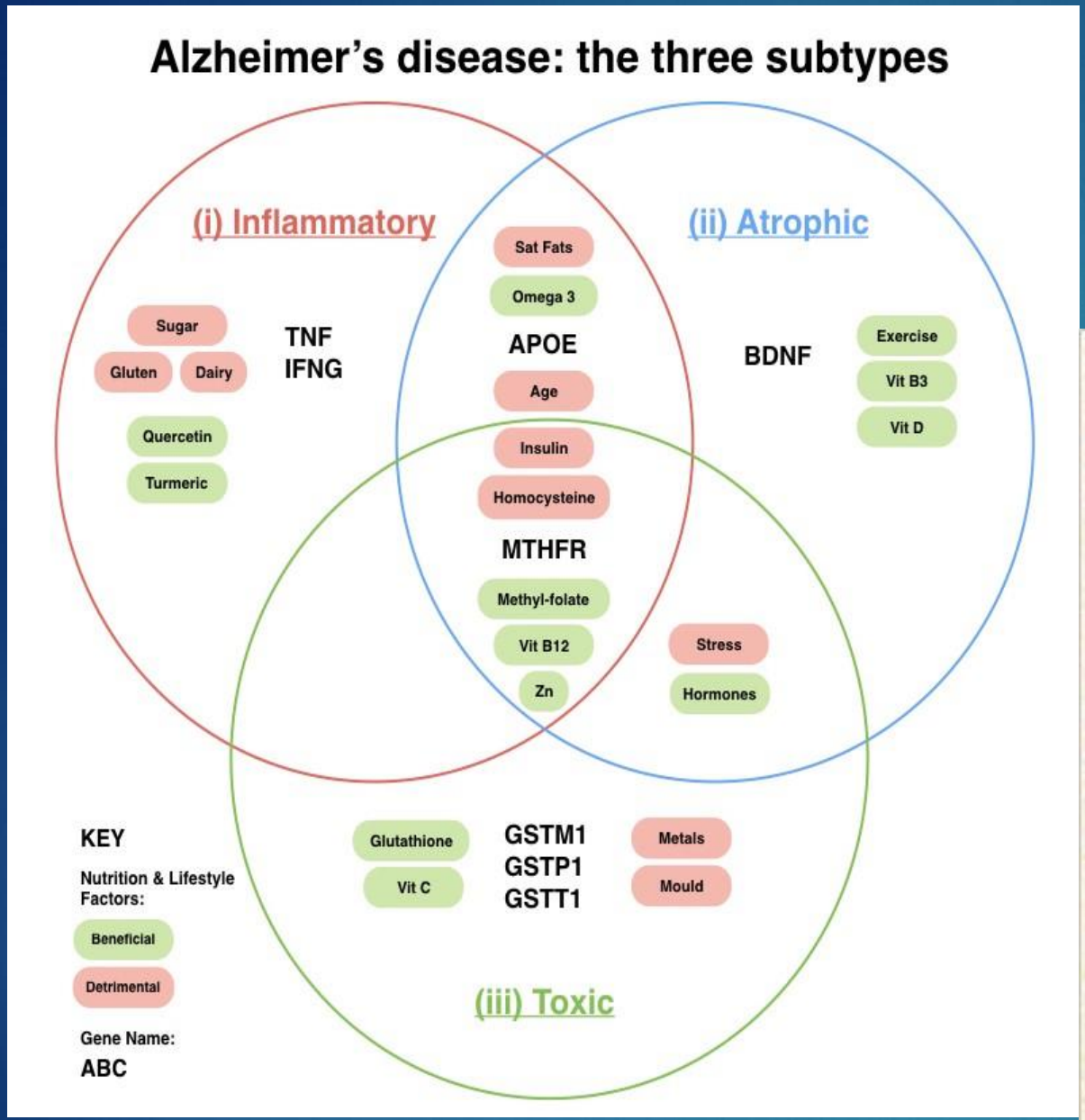
- Loss of dopamine neurons in the substantia nigra
- Alpha-synuclein (Lewy body) protein inclusions in the nervous system
- Microglial activation
- Increase in pro-inflammatory cytokines

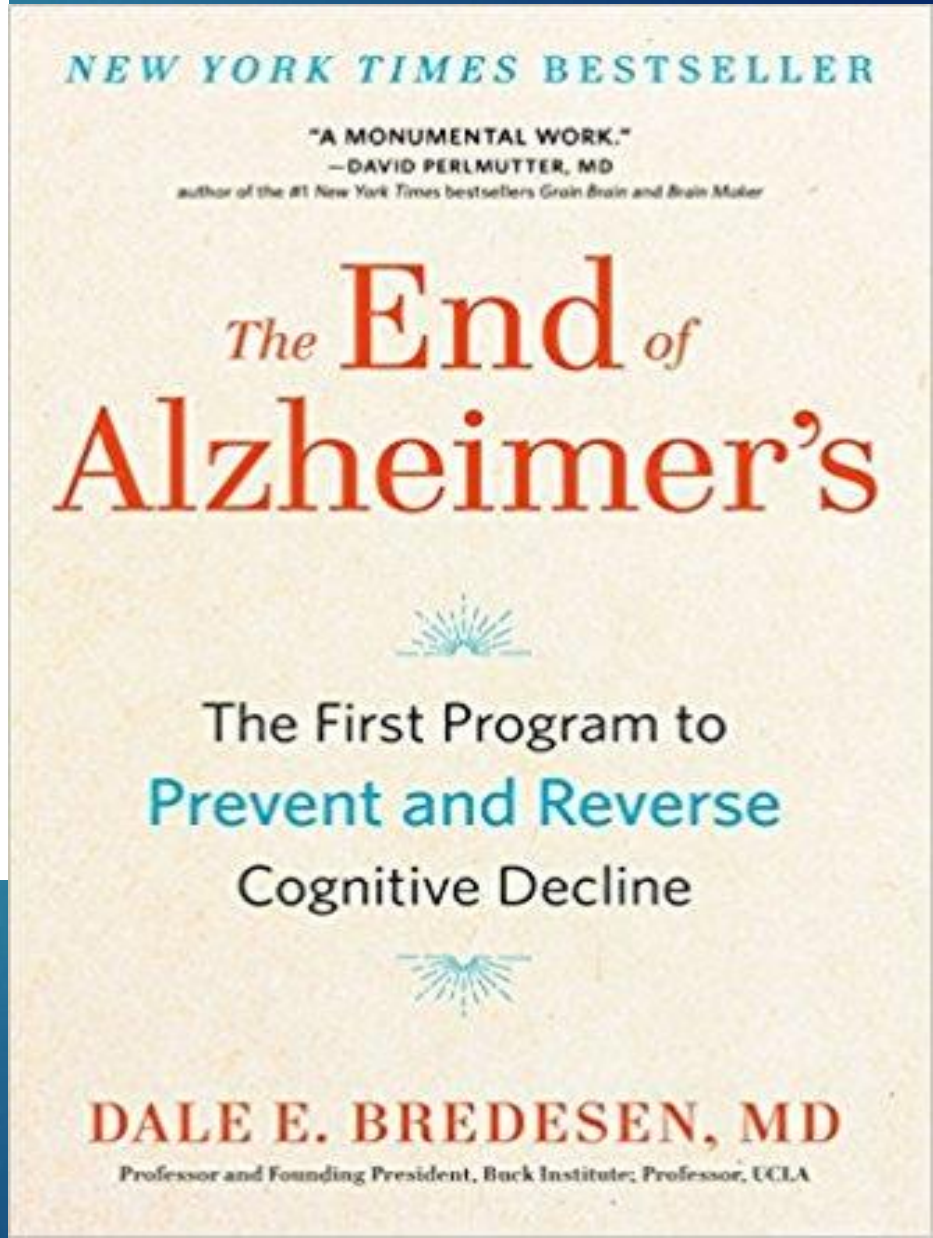
- Subramaniam SR et al. Targeting microglial activation states as a therapeutic avenue in Parkinson's disease. Frontiers Aging Neurosci. 2017. June


Heavy Metals
- Mercury
- Lead
- Cadmium
- Aluminium
- Copper
- Iron
Emotional & Oxidative Stress
-Low Dopamine
- High Noradrenalin
-Active Moro Reflex
Nutritional Deficiencies
- Vitamin D
- EPA and DHA (fish oil)
- Selenium
- Magnesium
- Phosphatidylserine
- Glutathione
- Other
Systemic Inflammation
- Joint
- Bowel
- Connective Tissues
- Nervous System
Genetic Predisposition
Poor Gene Expression of:
- Glutathionation
- Methylation
- Transulphation
Food Additives
- Aspartic Acid
- Glutamic Acid
- Colours (Tartrazine 102)
- Flavours (MSG 621)
- Preservatives (223, 249- 252)
- Sweeteners (Aspartame 951)
Poor Detoxification
- Colon
- Liver
- Kidneys
- Lung
- Skin
- Lymphatics
Leaky Gut Syndrome
- Immune Complement
- Excessive Antibiotics
- Nutritional Deficiency
- Dysbiosis
- LPS
Food Intolerances and Allergies
- Gluten
- Lactose
- Lectins
- Casein
- Gliadin
- Salicilates
Dysbiosis
- Candida
- Giardia
- Helicobacter
- Parasites
- E-Coli Bacteria
- Amebiasis
Microglial Activation
Emotional & Oxidative Stress
Heavy Metals
Nutritional Deficiencies
Systemic Inflammation
Genetic Predisposition
Food Additives
Poor Detoxification
Leaky Gut Syndrome
Dysbiosis
Food Intolerance and Allergies

HIGHER BDNF

LESS DEMENTIA


Alzheimer's disease: the three subtypes
(i) Inflammatory
(ii) Atrophic
(iii) Toxic
Sugar
Gluten
Dairy
Quercetin
Turmeric
TNF
IFNG
Sat Fats
Omega 3
APOE
Age
Insulin
Homocysteine
MTHFR
Methyl-folate
Vit B12
Zn
BDNF
Exercise
Vit B3
Vit D
Stress
Hormones
Glutathione
Vit C
GSTM1
GSTP1
GSTT1
Metals
Mould
KEY
Nutrition & Lifestyle Factors:
Beneficial
Detrimental
Gene Name:
ABC


NEW YORK TIMES BESTSELLER
"A MONUMENTAL WORK."
—DAVID PERLMUTTER, MD
author of the #1 New York Times bestsellers Grain Brain and Brain Maker
The End of Alzheimer's
The First Program to Prevent and Reverse Cognitive Decline
DALE E. BREDESEN, MD
Professor and Founding President, Buck Institute; Professor, UCLA

BDNF Essentials™

Supplement Facts

Serving Size: 2 Capsules Servings Per Container: 60

Amount Per Serving		%Daily Value
Choline (as Cytidine Diphosphate Choline Sodium Salt)**	25 mg	5%
Sodium (as Cytidine Diphosphate Choline Sodium Salt)**	5 mg	<1%
NeuroCyto Protect™ Blend	1175 mg	†
Lions Mane Mushroom (*Hericium erinaceus*) mycelium Powder, Skullcap (*Scutellaria lateriflora*) Herb Powder, Bilberry (*Vaccinium myrtillus*) Fruit Extract, Bacopa (*Bacopa monnieri*) Herb Powder, Sensoril® Ashwagandha (*Withania somnifera*) Root and Leaf Extract		
Cognition Blend	175 mg	†
CDP Choline Sodium Salt, Sharp-PS® Phosphatidylserine		

† Daily Value not established.

OTHER INGREDIENTS: Hypromellose (Capsule), Leucine.

**Choline and Sodium are from Cognition Blend
Sensoril® is a registered trademark of NutraGenesis, LLC.
Sharp-PS® is a registered trademark of Enzymotec USA, Inc.

Research area	Specifics	Skullcap	Lion's Mane	Bacopa	Ashwagandha	Blueberry	Citicoline	PS
Neuroplasticity	Increase BDNF	x	x	x	x	x		
	increase learning	x	x	x	x	x	x	x
	increase memory	x	x	x	x	x	x	x
	improve cognitive fxn	x	x	x	x	x	x	x
	increase executive fxn				x			
	improve psychomotor				x			
	improved acetylcholine						x	x
	improved attention			x	x		x	x
	improved processing speed			x	x		x	
	improved hippocampal fxn				x			
	improved telomerase activity				x			
Neurologic	Decrease glutamate		x					
	decrease seizures	x						
	improve mood	x			x			x
	decrease anxiety	x			x			x
	decrease depression					x		x
	decrease b-amyloid	x	x	x	x		x	
	improved optic fxn							
	improved sleep	x			x			x
	decrease synuclein protein	x	x					
Inflammation	Decrease oxidative stress	x	x	x		x	x	x
	decrease inflammation	x	x	x	x	x	x	x
	inhibit NF-KB				x			
	activate nrf2			x		x		
	increase antioxidants	x			x	x		
stress	decrease cortisol				x			x
	decrease stress symptoms				x			
	increased blood flow							
	formation of cell membranes						x	x
neurogenesis	stimulate brain regeneration	x	x					

Lion's Mane Mushroom (Hericium erinaceus)

- Increase BDNF*
- Increase neurogenesis*
- Decrease glutamate*
- Increase memory, learning, cognitive fxn
- Decrease b-amyloid protein(Alzheimer's)
- Decrease synuclein protein(Parkinson's)
- Decrease oxidative stress
- Anti-inflammatory

Lion's Mane (Hericium)

Lion's Mane Mushroom strongly stimulates the synthesis of nerve growth factor (NGF)

In this study, 6 months of taking Lion's Mane mushroom, 6 out of 7 dementia patients demonstrated improvements in their perceptual capacaties, and all 7 had improvements in their dressing, bathing and eating scores.

Scientists believe that Lion's Mane may be a powerful reducer of brain inflammation and a strong inducer of brain tissue regeneration.

Alzheimers Issue. Phytotherapy Research. Volume 23, Issue 3, pages 367-372, March 2009

Skullcap: American

Scutellaria Lateriflora

Skullcap Functions

- Increase BDNF*
- Increase neurogenesis*
- Decrease seizures*
- Increase memory, learning, cognitive fxn
- Improved sleep
- Decrease anxiety
- Decrease b-amyloid protein(Alzheimer's)
- Decrease synuclein protein(Parkinson's)
- Decrease oxidative stress
- Anti-inflammatory

Skullcap (*Scutellaria lateriflora*) (also known as Virginia Skullcap)

- **Scutellarin:**
  - Shown protective effect for cerebral injury via regulating expression of NOS isoforms & angiogenic molecules (Hu XM et al)
  - Protection against ConA-induced immunological liver injury in mice; mechanism: effect on pro-inflammatory cytokines (inhibition NF-kappaB-TNF-alpha-iNOS transduction pathway) (Tan ZH et al)
  - Study showed neuroprotective effects on brain ischemic injury-iinhibition of the apoptosis-inducing factor pathway in rats (Zhang HF et al)
  - Anti-inflammatory activity in microglial cell (Wang S et al)

Bilberry: Vaccinium myritillus

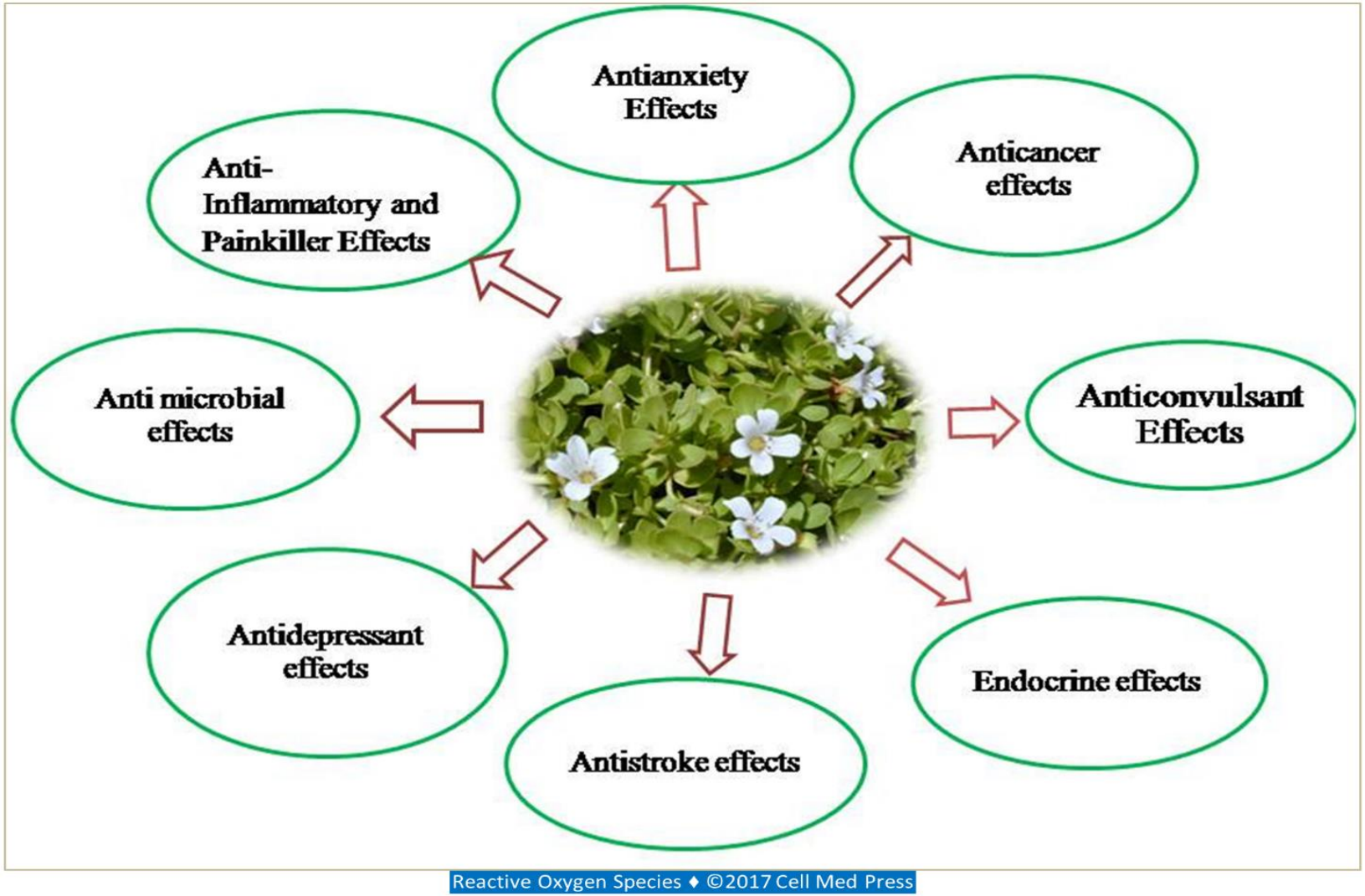
Blueberry/Bilberry

- Increase BDNF*
- Increase neurogenesis*
- Activate Nrf2*: Brain anti-oxidant*
- Increase attention
- Increase processing speed
- Increase memory, learning, cognitive function
- Improved sleep
- Decrease seizures
- Decrease depression
- Decrease oxidative stress
- Anti-inflammatory

Bacopa:

Bacopa Monnieri

Bacopa: Functions



Ashwagandha

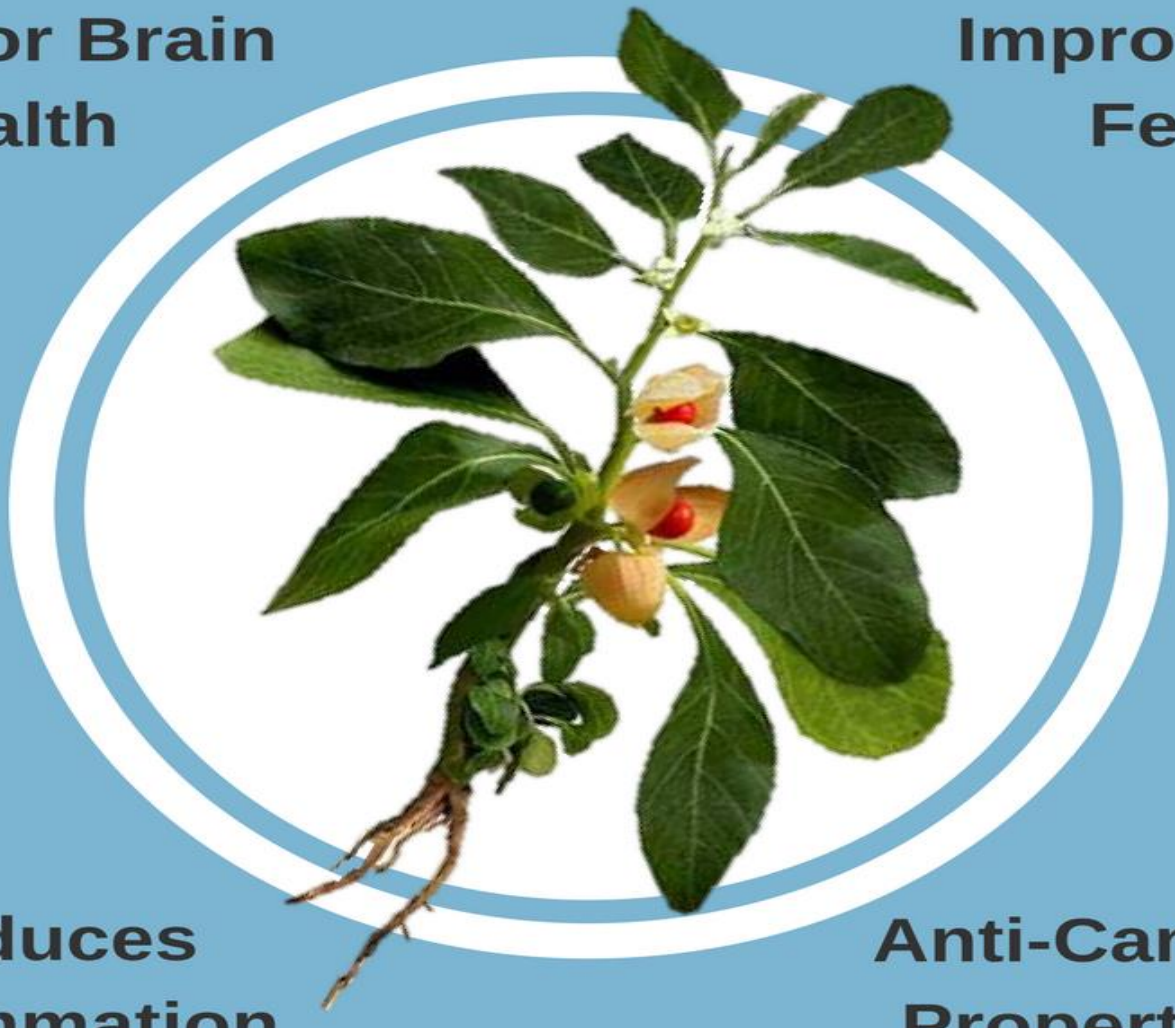
Withania Somnifera

Benefits of Ashwagandha

Great for Brain Health

Improves Male Fertility

Boosts Immune System



Increases Energy Naturally

Lowers Blood Sugar

Reduces Stress & Anxiety

Reduces Inflammation

Anti-Cancer Properties

STRESSRX

Neurologic Benefits of Ashwagandha

- Increase BDNF*
- Increase neurogenesis*
- Decrease cortisol and stress*- adaptogen
- Increase memory, learning, cognition
- Improved sleep
- Increase telomerase activity
- Decrease anxiety, depression
- Improve mood
- Decrease b-amyloid protein(Alzheimer's)
- Decrease synuclein protein(Parkinson's)
- Decrease oxidative stress
- Anti-inflammatory

Citicoline: CDP-choline Metabolic Pathway

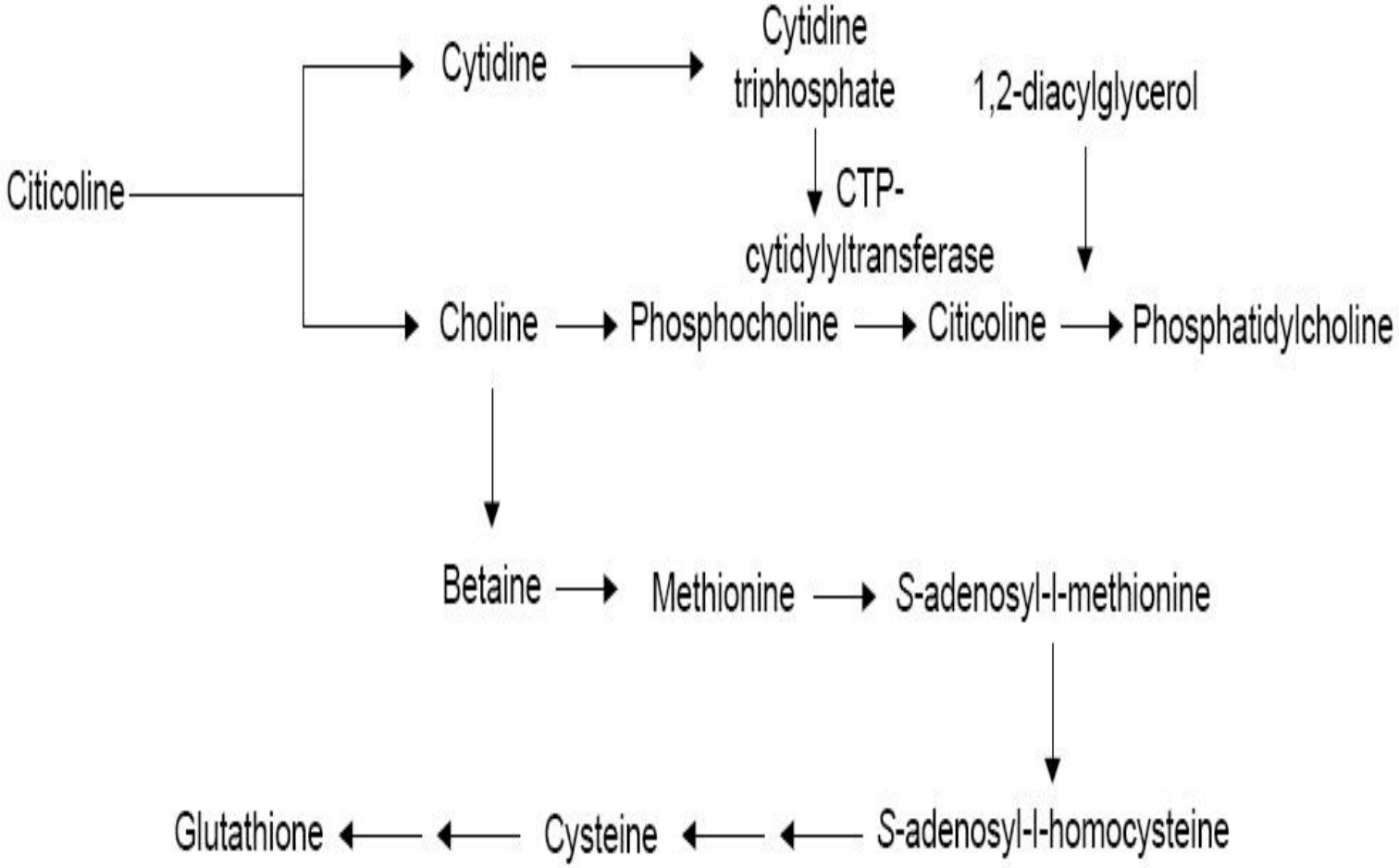


Figure 2 Citicoline's metabolic pathways.
Abbreviation: CTP, cytidine triphosphate.

Citicoline Benefits

- Improved cell membranes*
- Increase acetylcholine*
- Increase learning, memory, cognitive function
- Improve attention
- Decrease b-amyloid

NCBI Resources How To

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Advanced

Abstract

Send to:

Methods Find Exp Clin Pharmacol. 1997 Apr;19(3):201-10.

Citicoline improves memory performance in elderly subjects.

Alvarez XA[1], Laredo M, Corzo D, Fernández-Novoa L, Mouzo R, Perea JE, Daniele D, Cacabelos R.

Author information

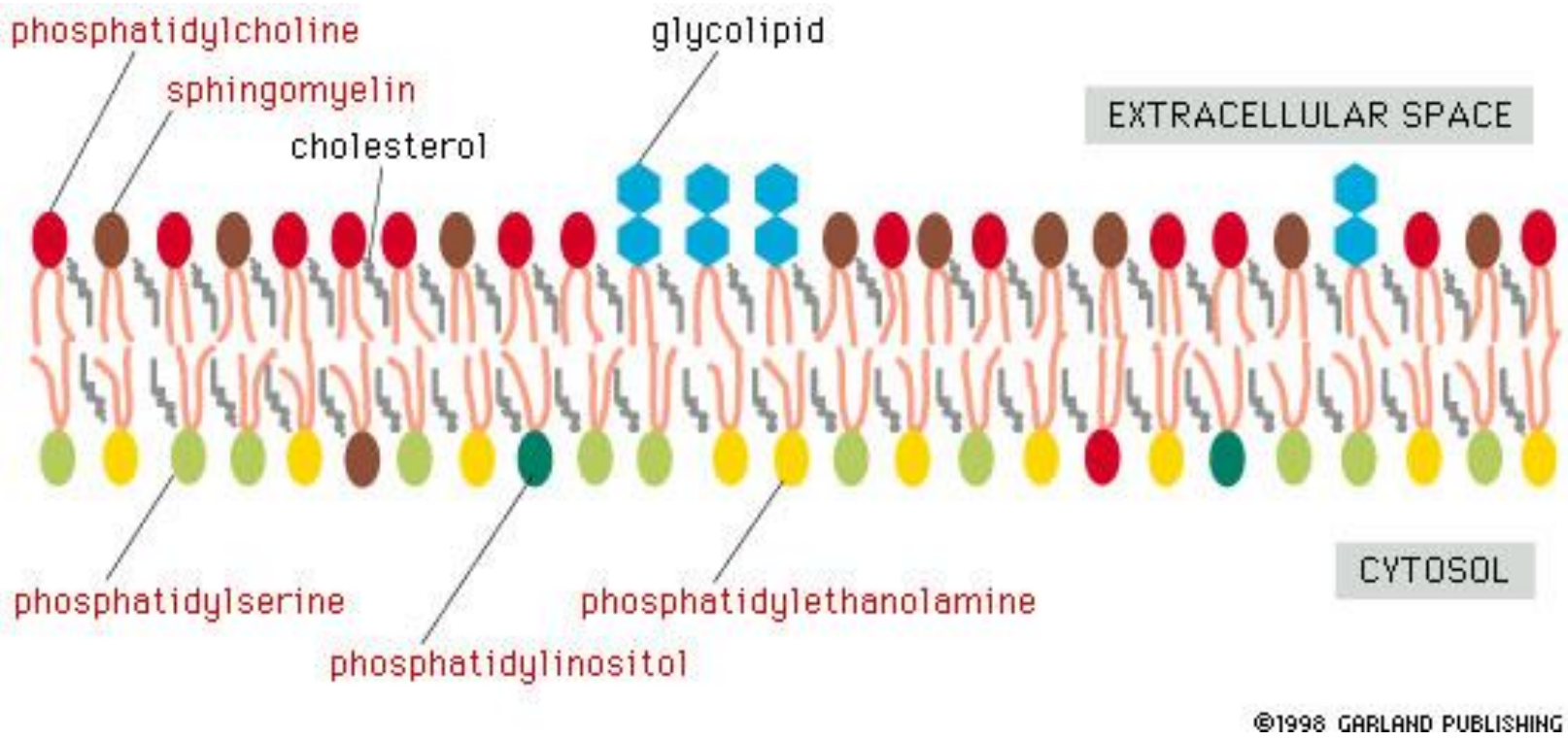
[1]EuroEspes Biomedical Research Center, La Coruña, Spain.

Abstract

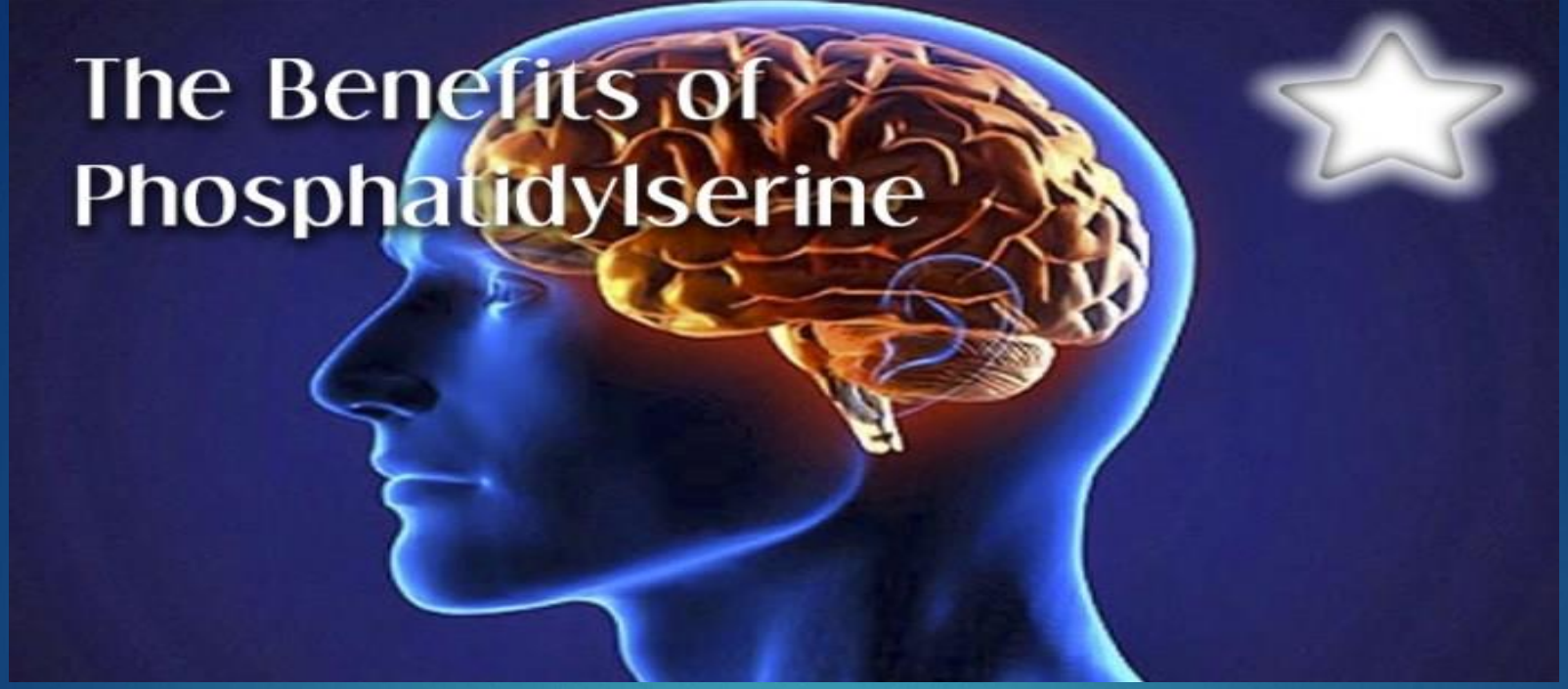
Citicoline is a choline donor involved in the biosynthesis of brain phospholipids and acetylcholine extensively used in the treatment of neurodegenerative diseases. In this study we investigated the effects of the oral administration of citicoline alone (C1000:1000 mg/day; C500:500 mg/day) or in combination with nimodipine (C +NI:300 + 90 mg/day) during 4 weeks on memory performance in elderly subjects with memory deficits and without dementia (N = 24; age = 66.12 +/- 10.78 years; MMS score = 31.69 +/- 2.76). Results indicated that citicoline in comparison with placebo improves memory in free recall tasks, but not in recognition tests. A significant improvement in word recall (5.17 +/- 1.1 vs. 3.95 +/- 1.2 omissions; $p < 0.005$), immediate object recall (6.5 +/- 1.6 vs. 5.5 +/- 1.2 omission; $p < 0.05$) and delayed object recall (8.5 +/- 2.1 vs. 6.7 +/- 2.4 omissions; $p < 0.005$) was observed after citicoline treatment. Similar results were found in the three subgroups of treatment (8 subjects per group), suggesting that citicoline possesses memory-enhancing activity at doses of 300-1000 mg/day. A decrease in systolic blood pressure and minor changes in lymphocyte cell counting were also observed in old subjects after receiving citicoline. These effects are consistent with the vasoregulatory and neuroimmune actions of citicoline and suggest that this compound may improve memory by acting on mechanisms of brain neurotropism and cerebrovascular regulation. According to the present results, showing that citicoline improves memory performance in elderly subjects, we concluded that this molecule is suitable for the treatment of memory deficits in old people.

Ischemic cascade level	Citicoline putative mode of action	Main effects	References
Cell energy balance	Stimulation/restoration of Na^+/K^+ ATPase activity	Cell energy deficiency correction Preservation/restoration of neuronal ionic balance	Plataris et al[45]
	Restoration/prevention of loss of neuronal ATP levels	Preservation/restoration of membrane integrity	Hurtado et al[34]
Glutamate exitotoxicity	Delay/prevention in the reversal of neuronal glutamate transporters	Decreased/delayed neuronal glutamate efflux	Hurtado et al[34]
	Increase in the surface fraction of EAAT2 transporter	Increased glutamate uptake by astrocytes	Hurtado et al[31]
Oxidative cascade	Prevention of PLA2 activation	Decreased FFA release	Adibhatla and Hatcher[46]
	Induction of glutathione reductase activity	Glutathione synthesis stimulation	Adibhatla et al[48]
Apoptosis	Increase in the Bcl-2 expression	Attenuation/neutralization of Bad/Bax family proteins	Sobrado et al[72]
	Upregulation of SIRT1 protein	Attenuation/prevention of caspase-3 activation	Hurtado et al[78]
	Downregulation of procaspase and caspase expression	Attenuation/prevention of PARP cleavage and DNA damage	Krupinski et al[69]
Endothelial barrier disruption	TJ protein regulation	Reduction of brain edema	Schabitz et al[30]
		Decrease in permeability of endothelial barrier and restoration of TJ proteins linear structure	Ma et al[49]

Citicoline research



Cell Membrane



- Improved cell membranes*
- Increase acetylcholine*
- Decrease cortisol and stress*
- Increase learning, memory, cognitive function
- Improved sleep
- Decrease anxiety, depression
- Improve attention
- Decrease b-amyloid

Key concepts
BDNF Essentials™

- Increases BDNF
- Increases Neuroplasticity
- Supports cognitive functioning: memory, attention, learning
- Decreases cortisol and stress: helps increase BDNF
- Anti-inflammatory and anti-oxidant
- **NOT** activating

Key concepts *Neuroplasticity*

- Exercise both body and brain
- Low glycemic diet with good fats
- Supportive herbs and nutrition
- Decrease stress so normalize HPA axis
- Decrease inflammation
- Decrease oxidative stress
- Minimize and remove neurotoxins

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