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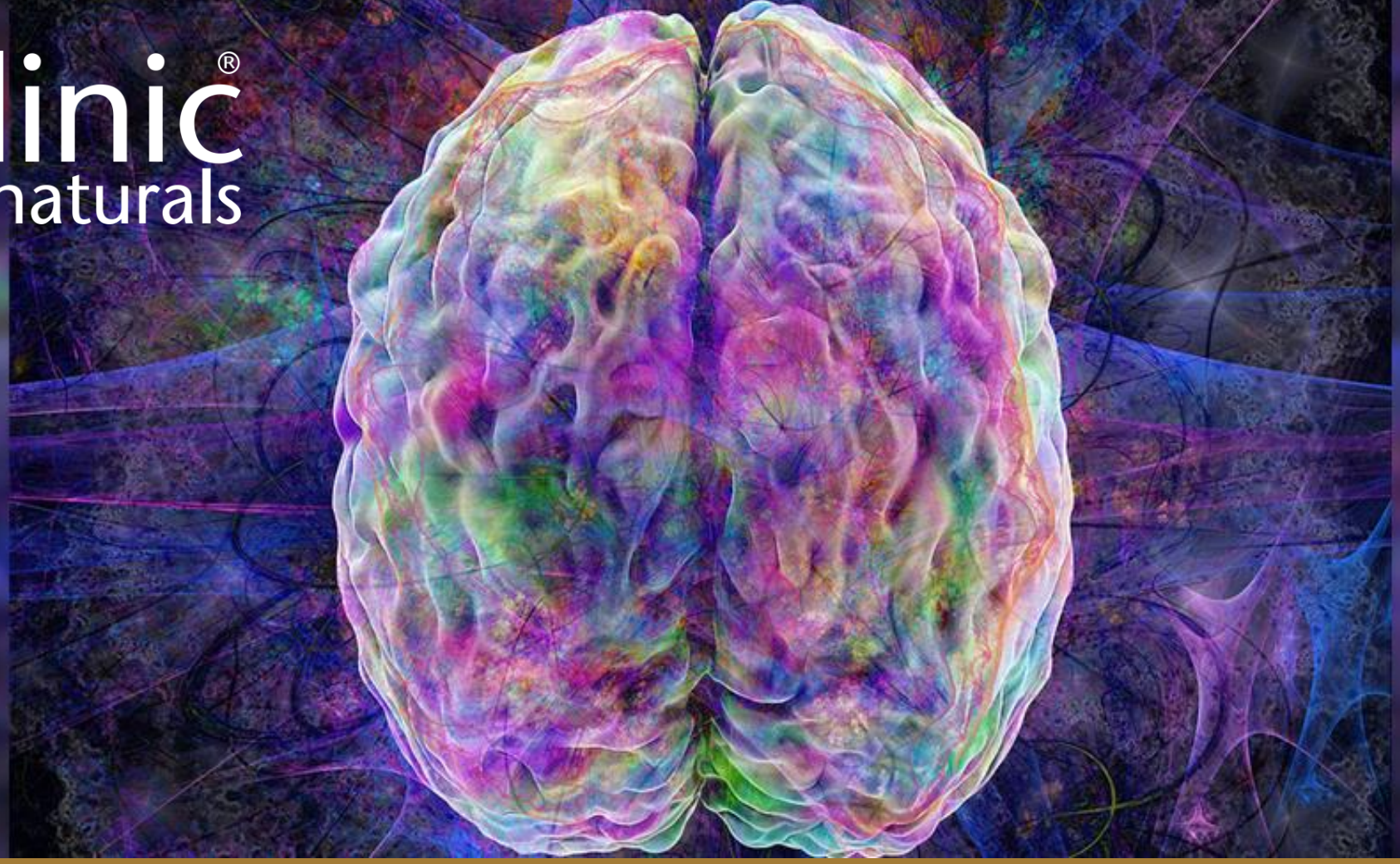
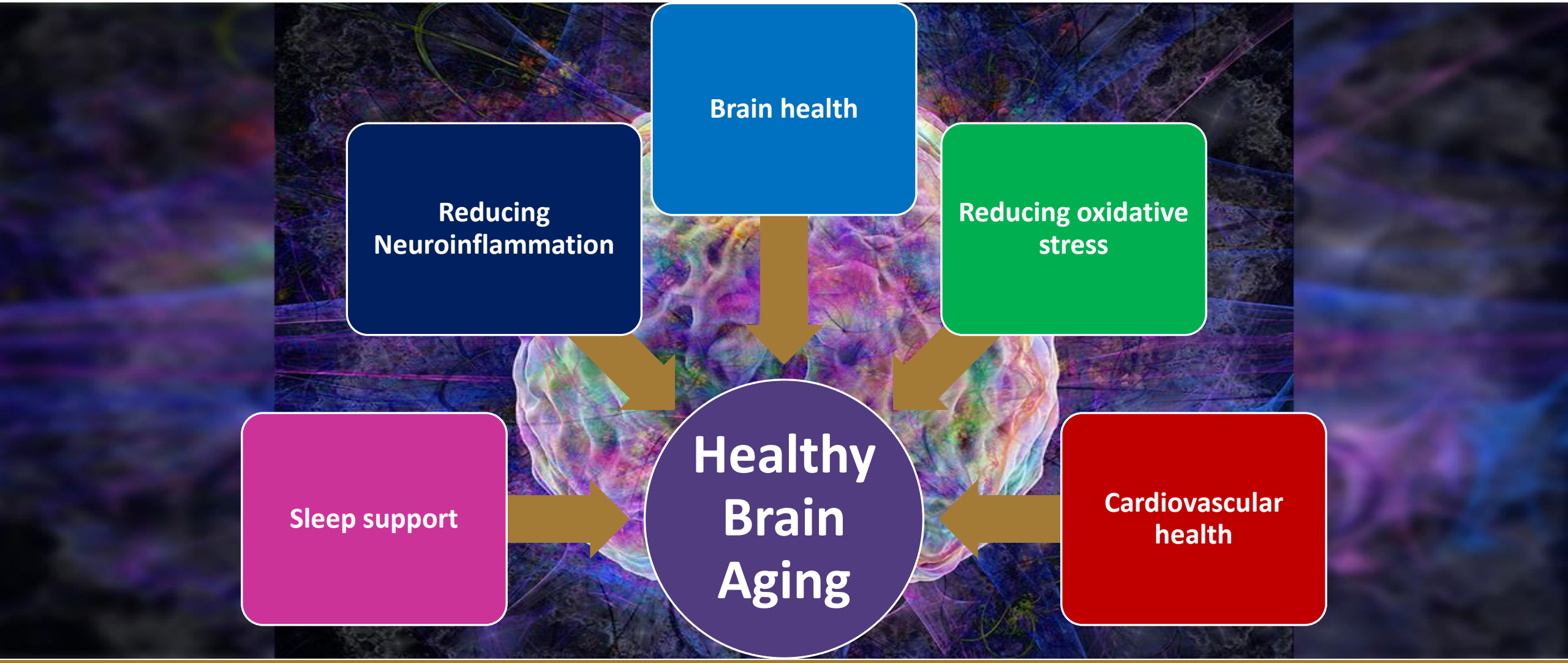


Unravelling the dynamic relationship between brain health, aging, memory and neuroinflammation.

Presented by Liesl Blott. Education and Training Manager

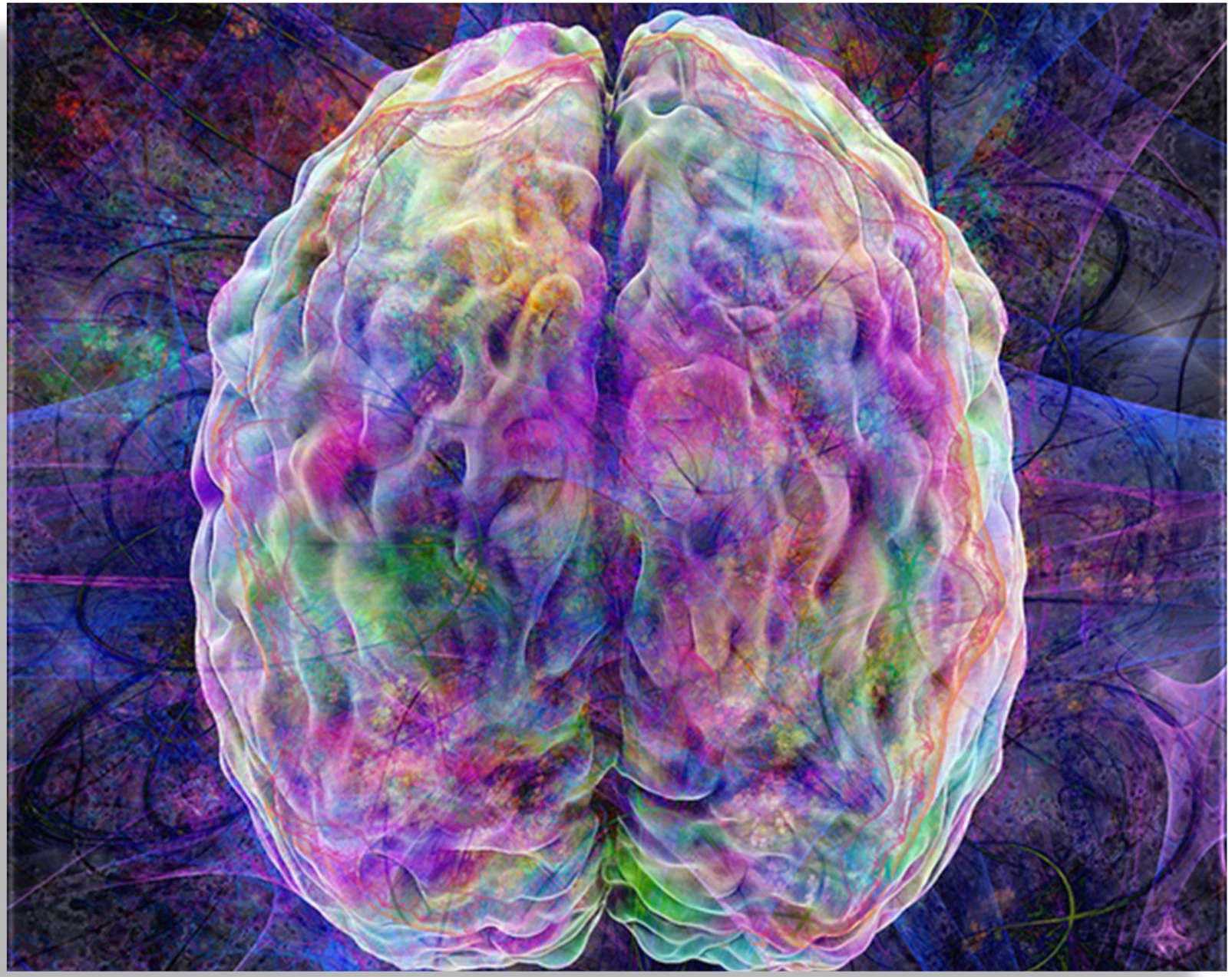
B.Pharm; BHSc (Western Herbal Medicine); AdvDip (Naturopathy); GradDip (Marketing Management); Cert IV (Assessment & Workplace Training)

Healthy brain aging needs a multi-faceted approach



BRAIN HEALTH

- Brain aging
- The brain's protective mechanisms
  - Blood-brain barrier function
  - Glymphatic system function
- Neuroinflammation
- Oxidative stress
- Sleep
- Memory and cognitive health
- Brain-heart connection



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Brain health and aging

- The brain is the most complex part of the human body.
- It is the source of the qualities that define our humanity.
- The brain controls many aspects of thinking:
  - Remembering.
  - Planning and organising.
  - Comprehending.
  - Making decisions.
  - And much more.
- These cognitive abilities affect how well we are able to perform everyday tasks, quality of life as well as the ability to continue to live independently as we age.

https://www.nia.nih.gov/health/brain-health/how-aging-brain-affects-thinking
https://www.ninds.nih.gov/health-information/public-education/brain-basics/brain-basics-know-your-brain

How the brain changes with aging

As we get older, the brain undergoes physiological changes which can affect mental function, even in healthy older people.

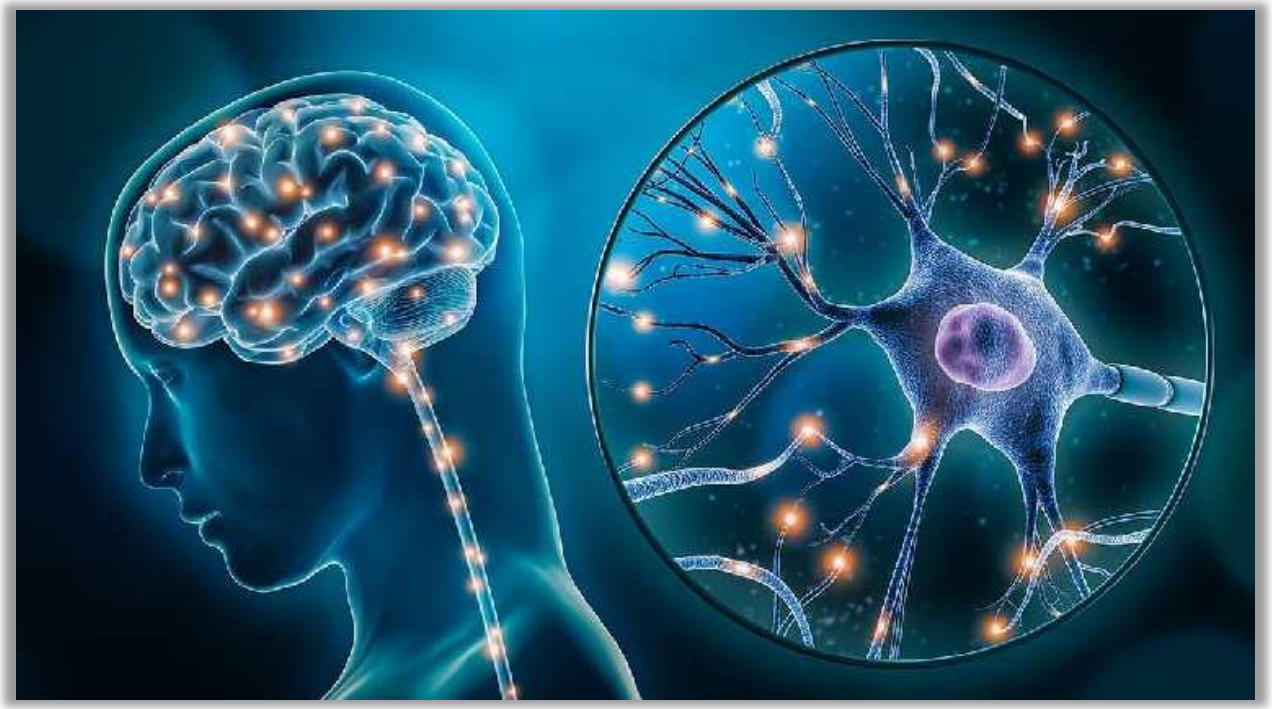
- Certain parts of the brain shrink, **including those important to learning** and other complex mental activities.
- Decrease in neuronal density, which means **processing speed gets slower.**
- **Reduced plasticity and ability to form new memories**.
- **Less effective communication** between neurons.
- **Decreased blood flow** in the brain.
- **Increased inflammation and neuroinflammation.**
- **Increased oxidative stress.**

https://healthdirectusa.com/blogs/latest-news-and-blog/brain-changes-as-we-age

Cognitive decline and aging

- There is a dynamic interplay between factors that lead to cognitive impairment and risk of neurodegeneration and the factors that lead to neuroplasticity and improved cognitive function.

- Emerging evidence suggests that healthy lifestyle choices improve the dynamic balance toward neuroplasticity and brain health and away from neurodegeneration.



https://hinjawadi.rubyhall.com/what-is-neuroplasticity/

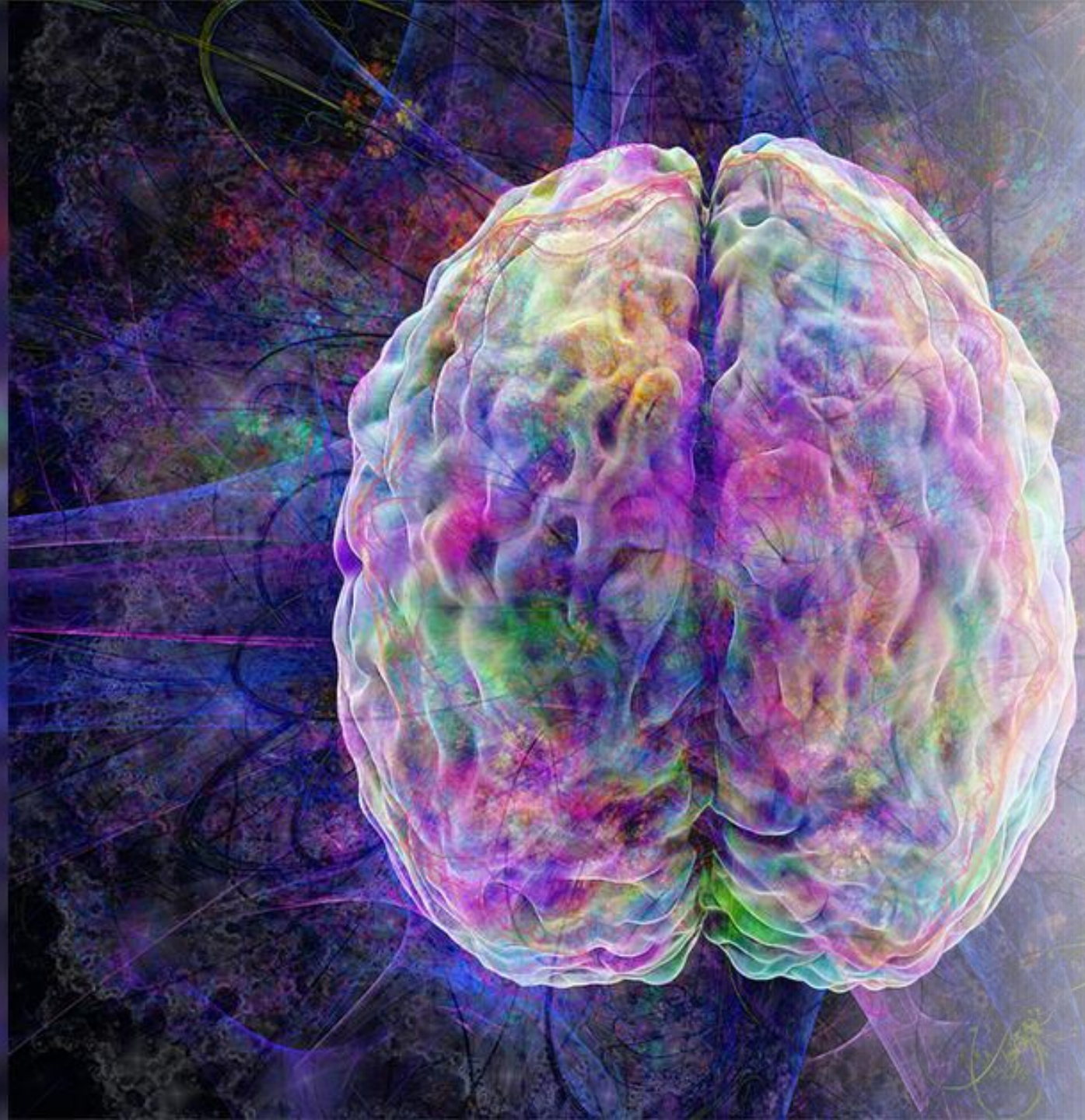
Murman et al 2015

Improving the balance towards brain health

Interventions that can promote healthy brain aging while reducing the detrimental impact of age on cognition and memory.

Support blood brain barrier integrity	Support brain waste clearance	Reduce neuroinflammation and oxidative stress	Improve sleep duration and quality	Reduce cardiovascular risk
Eat a healthy diet	Avoid excessive alcohol consumption	Exercise regularly	Participate in cognitively stimulating activities	Manage emotional stress

Murman et al 2015



Aging and the brain's protective mechanisms

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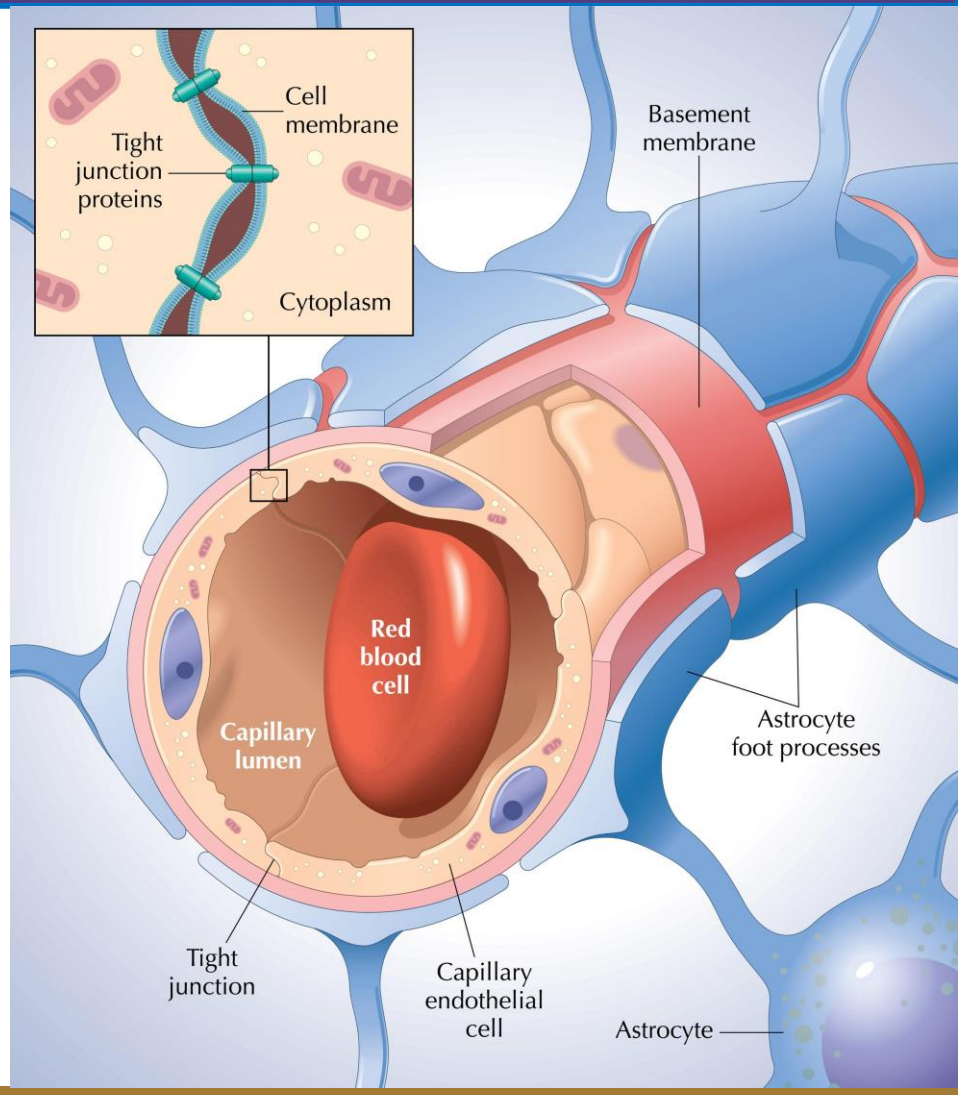
The brain's protective mechanisms: BBB

Control of <u>what flows into</u> the brain:

- The blood-brain barrier (BBB) is the interface between the brain and circulatory system and is essential for brain health.[1-5]
- The BBB protects the brain by controlling the influx of components from the peripheral circulation into the brain.[1-5]
- Without the BBB, the brain would be at risk of assault by toxins, pathogens and other compounds, which could lead to neuronal dysfunction and neurodegeneration.[3]
- The BBB is critical for proper CNS and neuronal function and serves to protect the brain and neural tissue.[1,2,5]

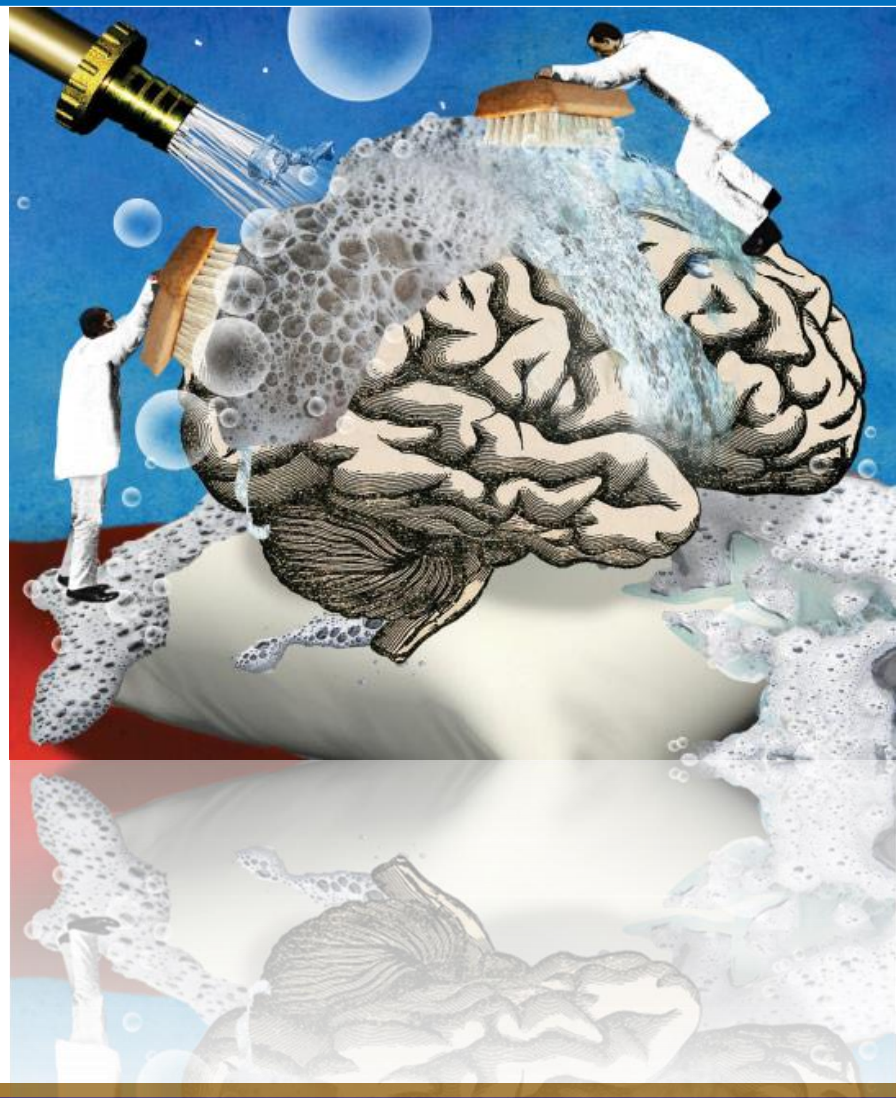


Morris et al 2018; Daneman et al 2015; Knox et al 2022; Małkiewicz et al 2019; Galea et al 2021

The brain's protective mechanisms: Glymphatic

Control of <u>what flows out</u> of the brain (waste clearance):

- The brain waste clearance system is a complex network of fluid channels and mechanisms within brain tissue known as the glymphatic system.[1,2]
- The glymphatic system is important for brain homeostasis and neurological health as it is responsible for the efficient clearance of neurotoxins and metabolic waste from the brain and brain tissue.
- This includes soluble proteins associated with neurodegenerative disease.[2-10]
- Brain waste clearance occurs when we sleep, mostly during deep slow-wave N3 sleep.[2]



Jessen et al 2015; Christensen et al 2021; Xie et al 2013; Verheggen et al 2018; Buccellato et al 2022; Rasmussen et al 2018; Voumvourakis et al 2023; Nedergaard et al 2020; Gao et al 2023

Effect of age on blood-brain barrier integrity

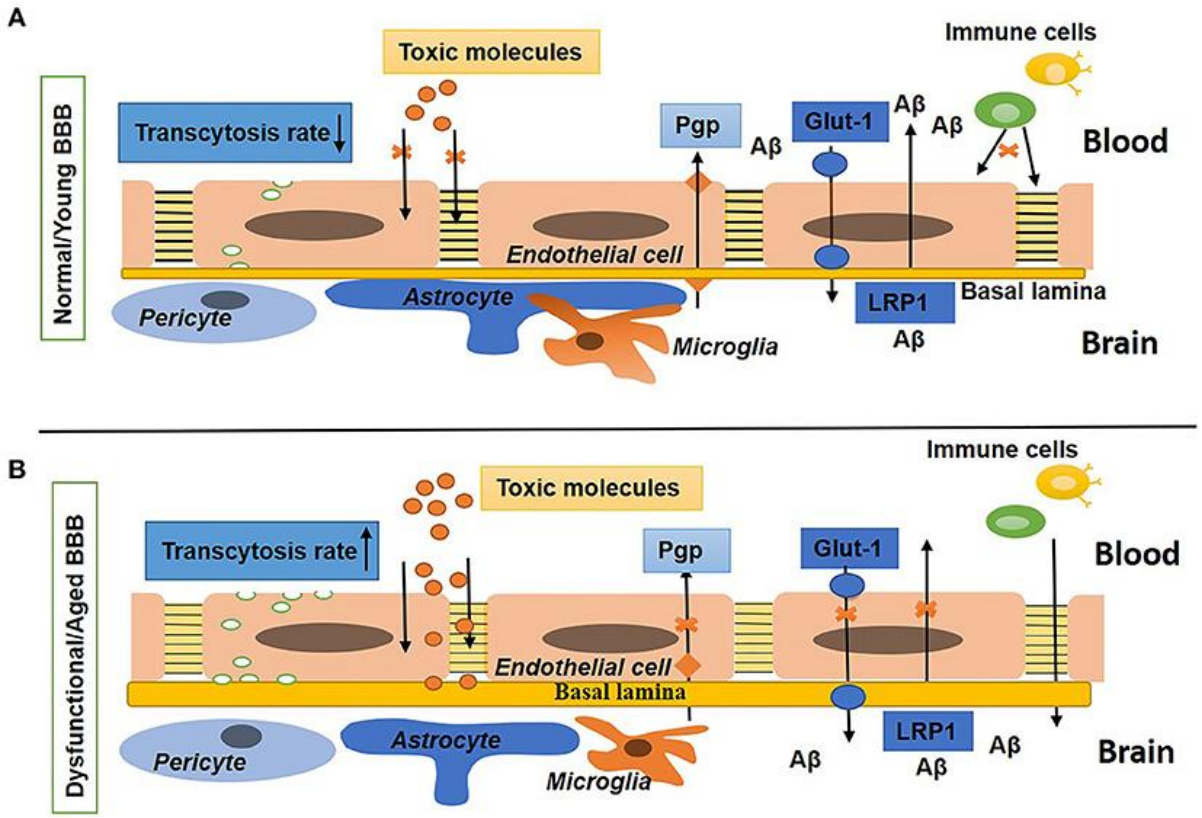
A meta-analysis of 31 human BBB permeability studies concluded that age-related increased BBB permeability may be involved in the initiation or worsening of cerebral microvascular disease.[1]

Contributing factors for age-related increased BBB permeability include:	
	Increased neuroinflammation and oxidative stress.[2] Age also moderates the BBB response to systemic inflammation.[2,3]
	Impaired brain waste clearance (glymphatic system)[5]
	Structural changes to the BBB.[2,4]
	Alterations in transporters (e.g. P-gp and LAT-1), enzymatic activity, receptors and signaling.[2,4]
	Genetic variations e.g. to ApoE4. ApoE4 is involved in tight-junction regulation.[4]
	Accumulation of neurodegenerative proteins.[5]

Large neutral amino acid transporter (LAT-1); P-glycoprotein (P-gp)

Farrall et al 2009; Galea et al 2021; Knox et al 2022; Banks et al 2021; Verheggen et al 2018.

BBB: Young vs older brain



(A) BBB in a young or normal state:

- Tight and adherens junctions.
- Low rate of transcytosis.
- No diffusion of toxins.
- Presence of influx (Glut-1) and efflux (P-gp) transporters.
- Basal lamina is thin and surrounded by pericytes, astrocyte endfeet, and microglia.

(B) BBB in an aged or disease state:

- Compromised tight and adherens junctions.
- High rate of transcytosis.
- Increased diffusion of toxins.
- Repressed activity of influx and efflux transporters.
- Pericytes, astrocytes, and microglia are not associated with the basal lamina.

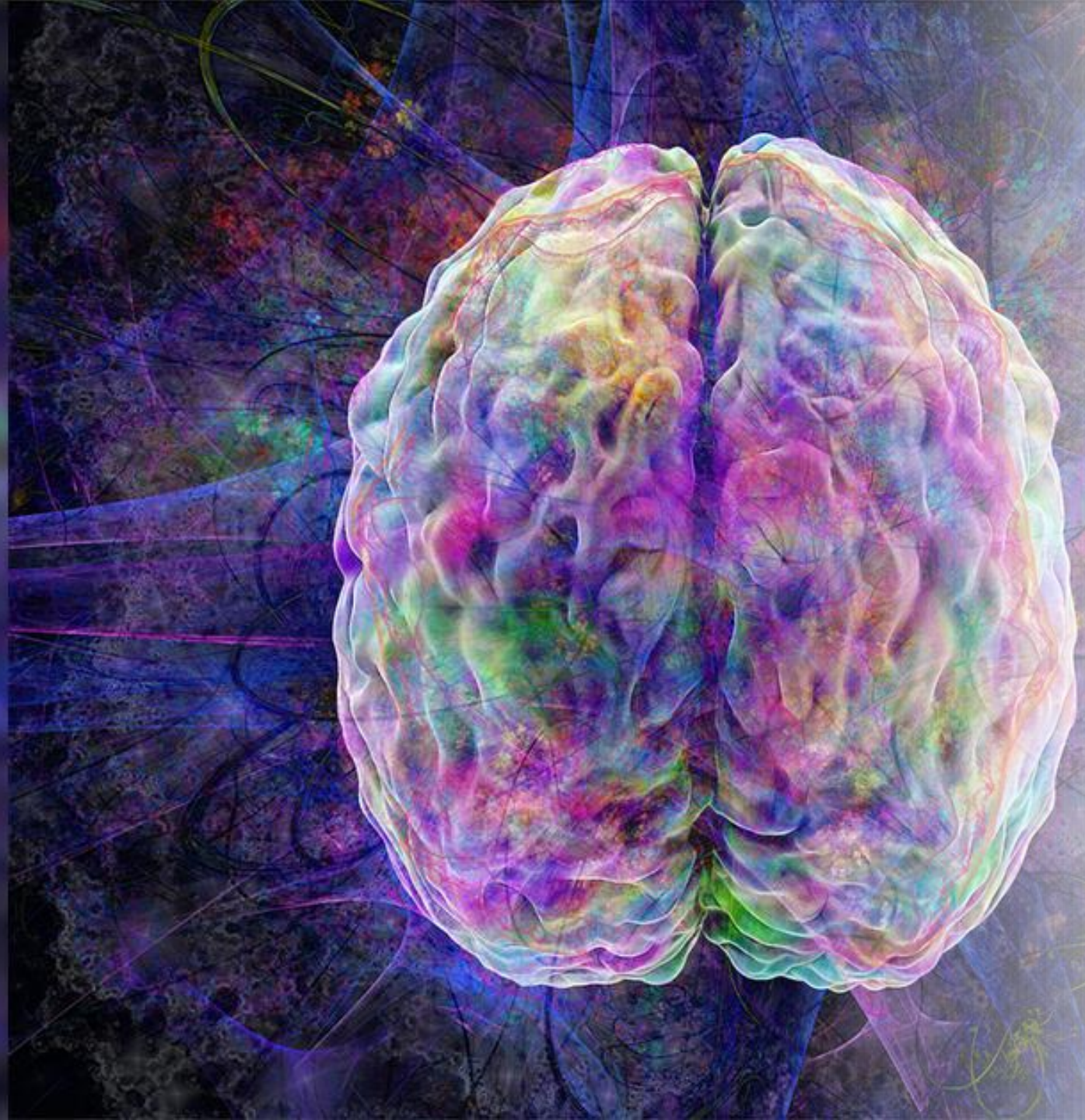
Transcytosis is a type of transcellular transport

Hussain et al 2021

Effect of age on glymphatic system clearance

Contributing factors for age-related decline in glymphatic function:	
	Sleep disruption and reduced sleep quality, especially deep sleep.[1-4]
	Increased neuroinflammation and oxidative stress.[5]
	Diminished cerebral blood flow, vessel wall elasticity and force of arterial pulsation.[2,4,6,7]
	Impaired BBB permeability.[7]
	Decline in cerebrospinal fluid (CSF) production, changes to CSF influx and AQP4 dysregulation.[8]
	Compromised lymphatic clearance due to age-related atrophy of lymph vessels.[3,9]
	Accelerated formation of neurodegenerative proteins.[7,8]

Buccellato et al 2022; Voumvourakis et al 2023; Nedergaard et al 2020; Reddy et al 2020; Christensen et al 2021; Jessen et al 2015; Verheggen et al 2018; Gao et al 2023; Yankova et al 2021.



Neuroinflammation & Oxidative Stress

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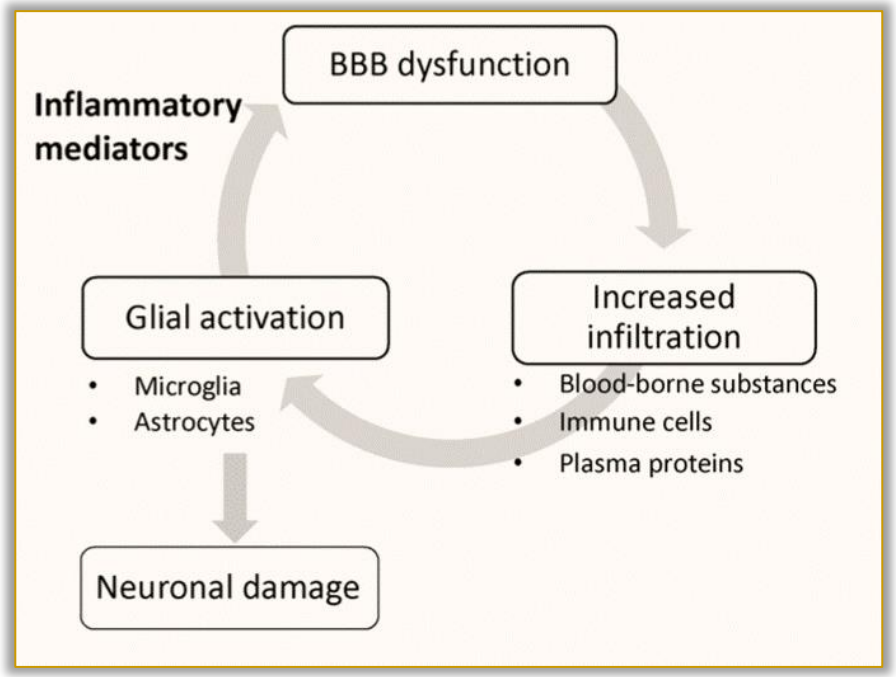
Neuroinflammation and BBB dysfunction



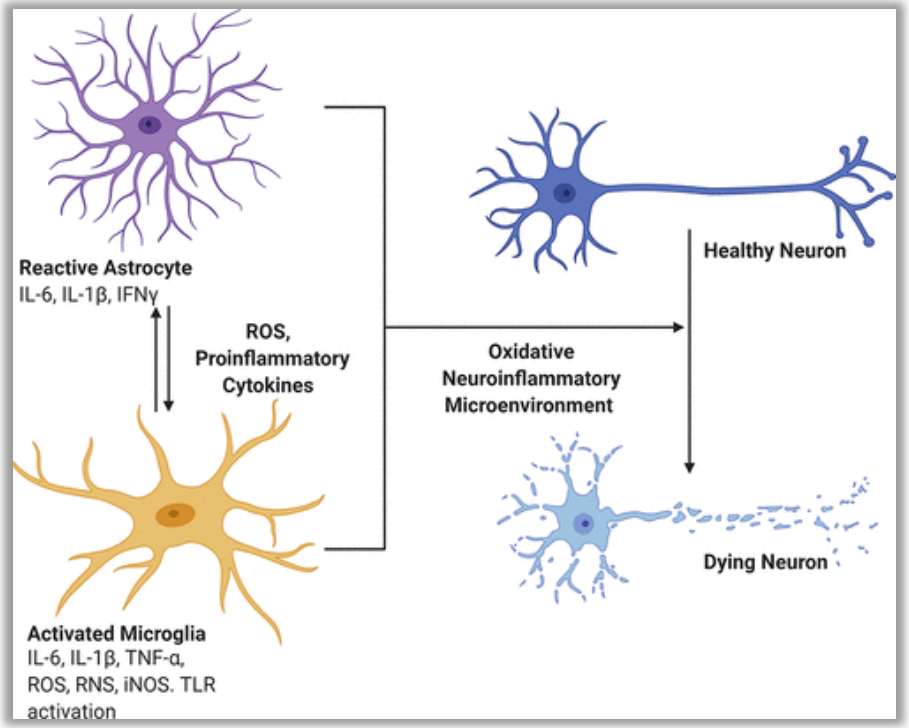
- Neuroinflammation changes BBB physiology and function.[1,2]
- This leads to increased infiltration of unwanted substances across the BBB including immune cells, neurotoxins and proteins.[1]
- Neuroinflammation amplifies glial cell activation which triggers recruitment of inflammatory mediators.[1,2]
  - Cytokines, chemokines, ROS, lipid mediators.
- The inflammatory response and glial activation can lead to neuronal damage.[1]
- Systemic lipopolysaccharides have also been shown to increase BBB permeability and to activate microglial cells.[1]

Glial cells=astrocytes and microglia

Takata et al 2021; Morris et al 2018

Neuroinflammation feeds neuroinflammation

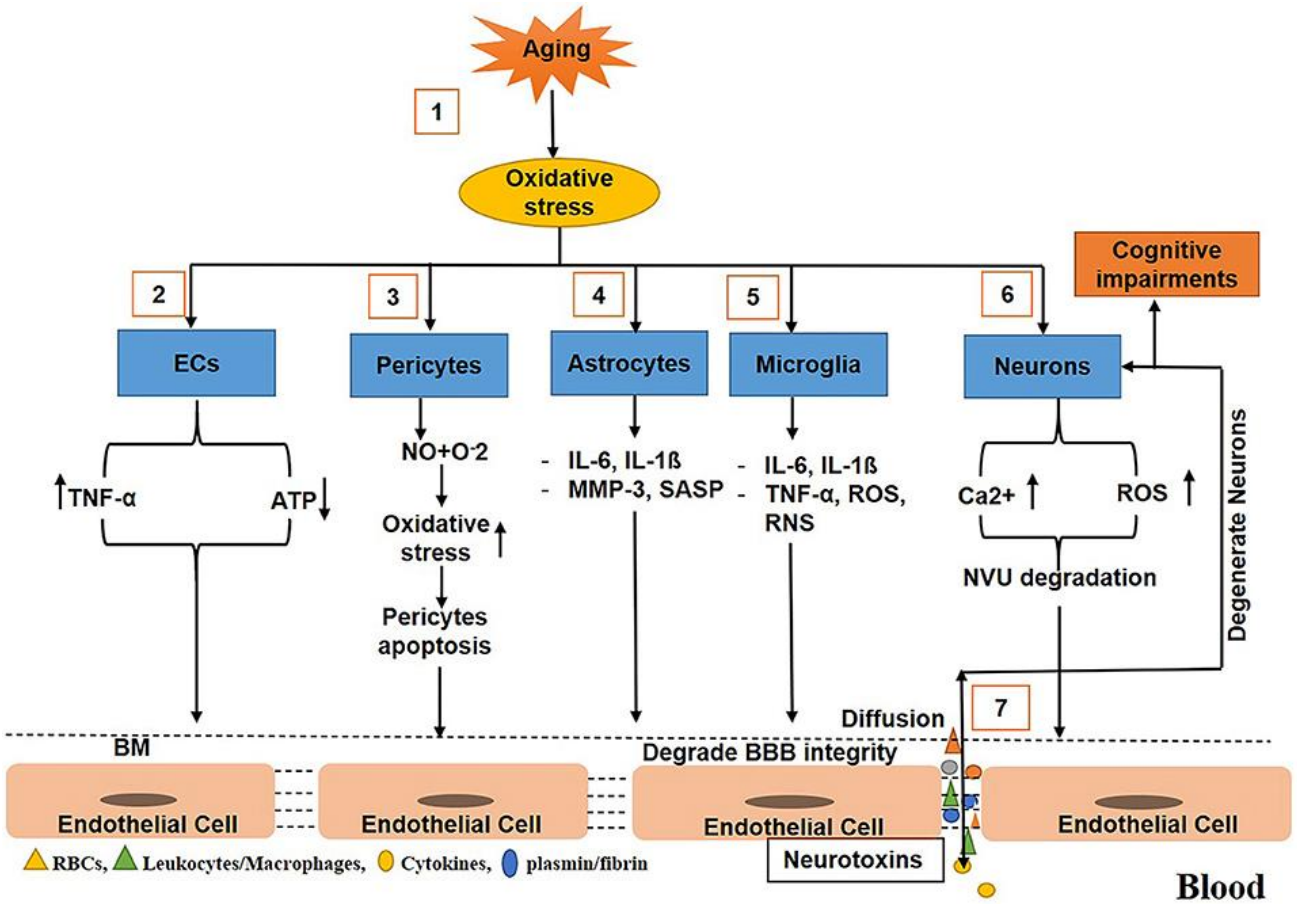
- Neuroinflammation triggers more neuroinflammation.[1-5]
- Neuroinflammation damages BBB integrity and impairs glymphatic waste clearance and causes neuronal damage.[1,2]
- It leads to activated microglia and reactive astrocytes which release neurotoxic compounds and free radicals.[3,4]
- It also impairs influx of nutrients and oxygen to brain tissue and neurons, which may cause hypoxia-associated inflammation.[4]
- In addition, neuroinflammation oamplifies production of proteins such as amyloid-β and α-synuclein.[2-4,6]
- Chronic peripheral inflammation can lead to neuroinflammation which increases BBB permability.[2]



Kaur et al 2020 [4]

Mogensen et al 2021; Hussain et al 2021; Buccellato et al 2022; Tokatly Latzer et al 2023; Takata et al 2021; Morris et al 2018; Kaur et al 2020.

Oxidative stress and BBB breakdown in aging



1. Oxidative stress increases with age.

Oxidative stress:

2. Triggers the release of TNF-α and increases ATP usage.
3. Induces pericytes to release nitric oxide that reacts with reactive oxygen to further upregulate oxidative stress, which damages pericytes and damages BBB integrity.
4. Activates astrocytes to release inflammatory mediators that degrade the basement membrane and tight junctions leading to BBB impairment.
5. Activates the microglia to secrete inflammatory mediators and free radicals, which also degrade BBB integrity.
6. Induces neurons to release ROS and calcium ion accumulation that degrades the neurovascular unit (NVU).
7. Toxins freely diffuse to and from the brain, causing neurodegeneration and decline in cognition.

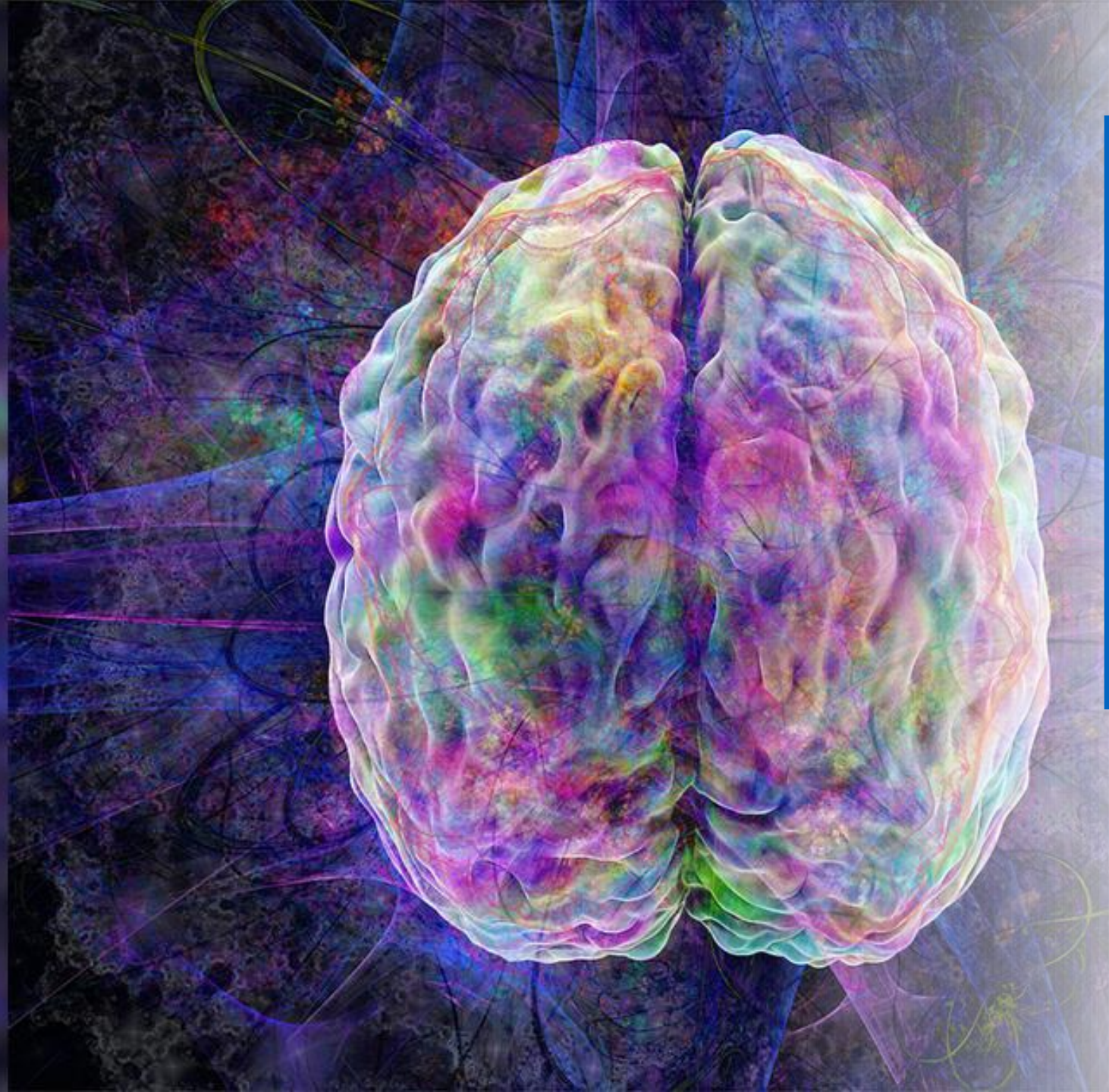
Hussain et al 2021

Summary: Neuroinflammation and oxidative stress

1. Neuroinflammation induces a series of changes to BBB physiology and compromises integrity and function of the BBB.[1-5]
2. Inflammation also triggers the release of ROS, which compromises BBB integrity.[1-3]
3. Neuroinflammation increases oxidative stress.[6,7]

   Oxidative stress increases neuroinflammation.[6,7]
4. Inflammation also contributes to glymphatic dysfunction and impairs glymphatic clearance.[3]
5. **Strategies to reduce inflammation, neuroinflammation and oxidative stress will help to support brain health.**

Verheggen et al 2018; Xuan et al 2022; Mestre et al 2020; Jessen et al 2015; Morris et al 2018; Hussain et al 2021



Sleep and other causes of BBB disruption

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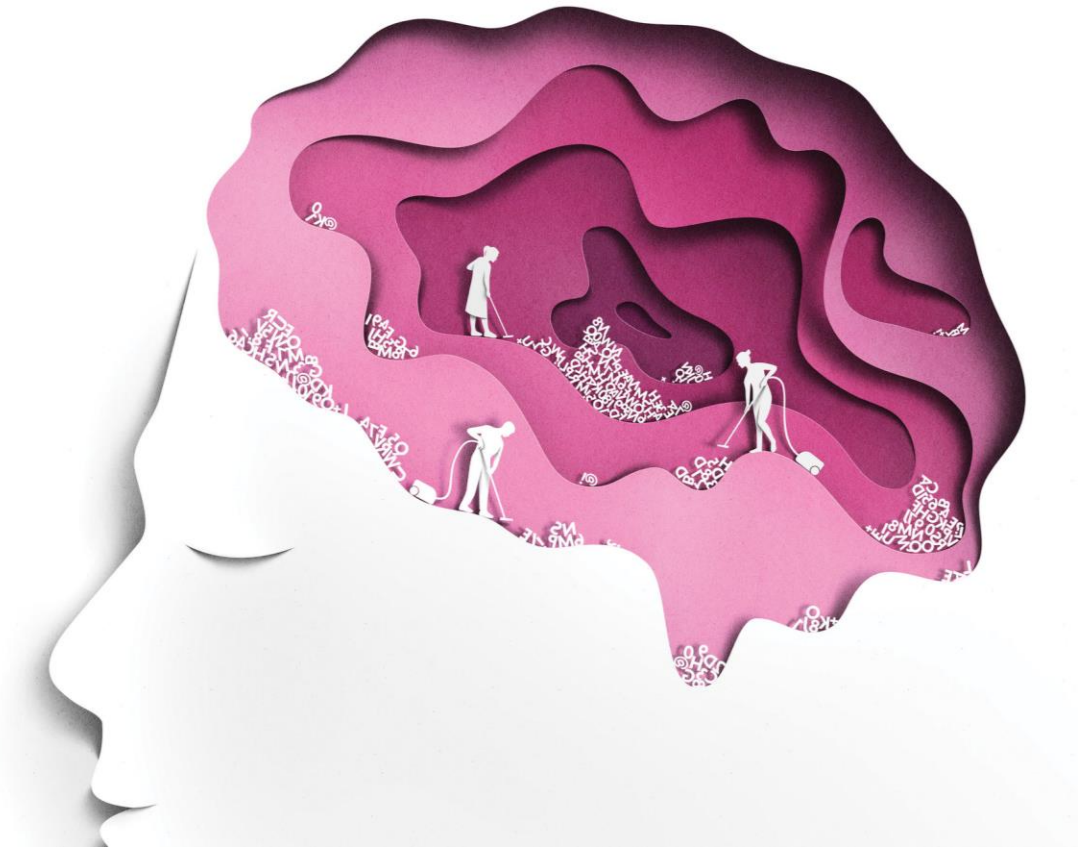
Sleep and brain health

- The glymphatic brain waste clearance system appears to be 90% more active during sleep, especially deep N3 sleep.[1,2]
- Chronic lack of sleep impairs glymphatic system function and clearance of toxins and brain waste from the brain. This in turn can exacerbate BBB dysfunction.[1,2]

Sleep architecture and age

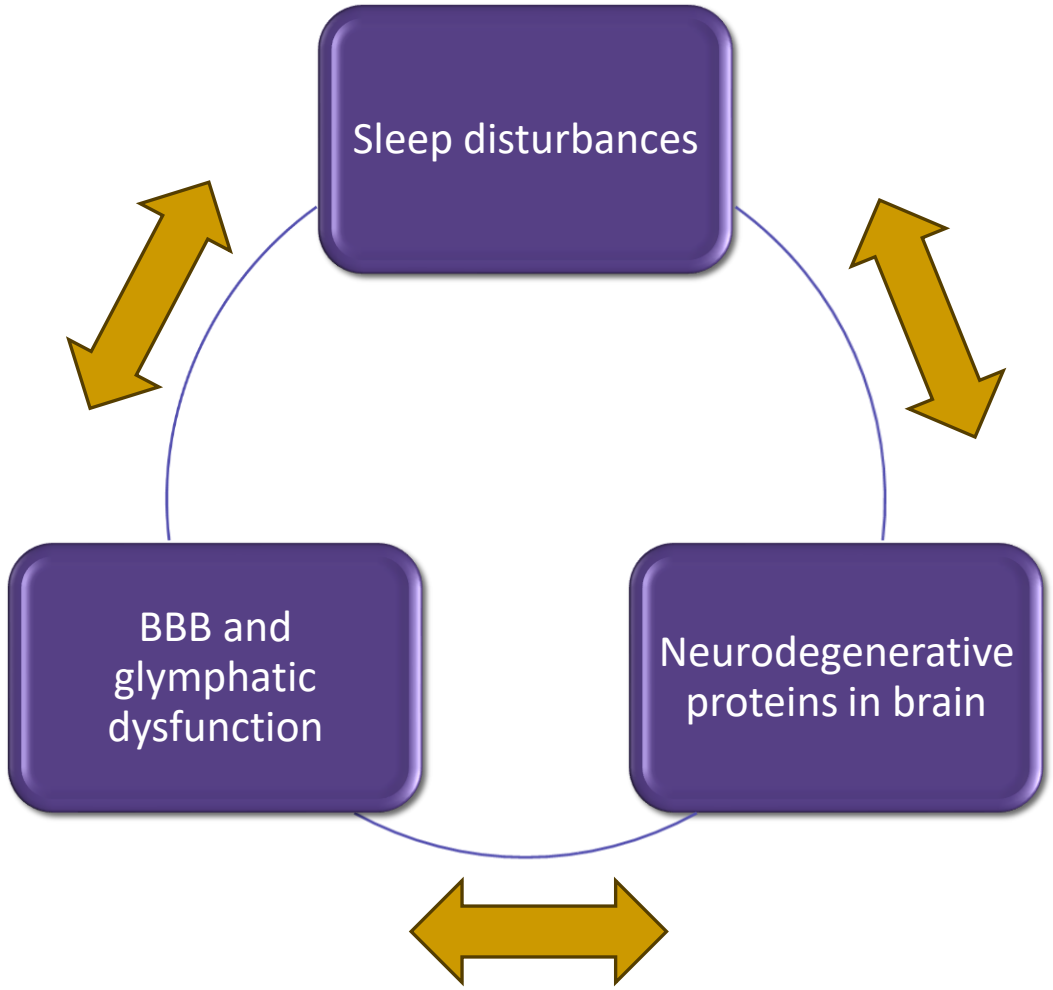
- In young adults, slow-wave sleep makes up between 10 and 25% of total sleep time.[3]
- The amount of time spent in N3 deep sleep declines with age and may be very limited in the elderly.[3,4]
- This gradual deterioration of N3 sleep may be a contributing factor for the increased incidence of neurodegenerative disease reported in the elderly population.[4-6]



Christensen et al 2021; Xie et al 2013; Reddy et al 2020; Voumvourakis et al 2023; Buccellato et al 2022; Nedergaard et al 2020.

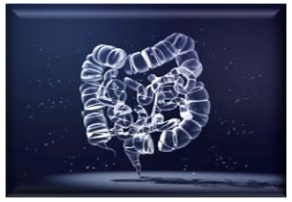
Sleep and neurological disease: A common pathway

- There appears to be a causal relationship between sleep disturbance and the increased occurrence and progression of neurodegenerative disorders.[1,2]
- The BBB and glymphatic system degrade with age – as does sleep quality.[3,4]
- Neurodegenerative disease also causes sleep disturbances – and the incidence increases with age.[2,5]



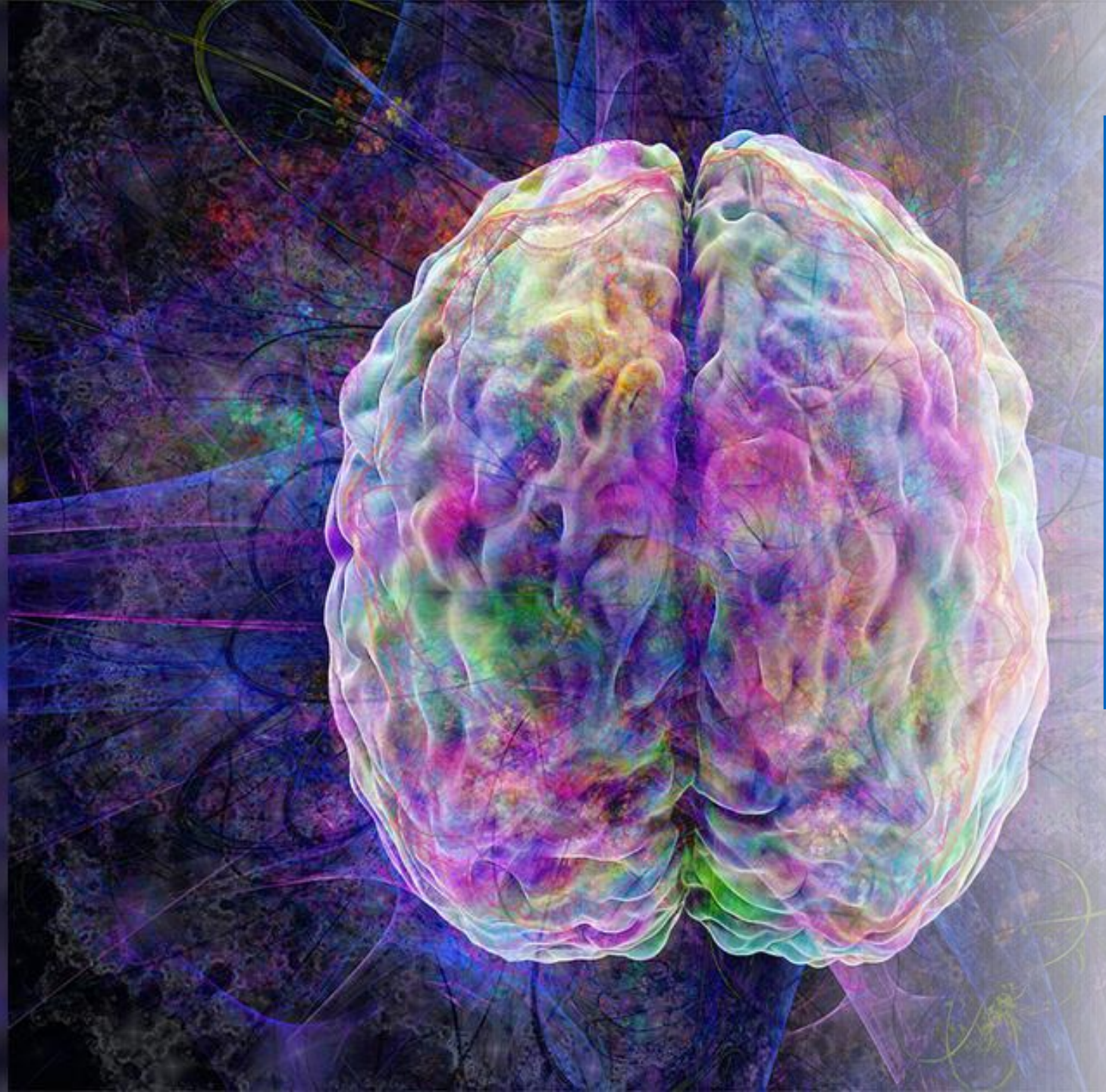
Voumvourakis et al 2023; Nedergaard et al 2020; verheggen et al 2018; Scott-Massey et al 2022; Christensen at al 2021

Other causes of BBB disruption



Other contributing factors for increased brain-barrier permeability include:	
Gut dysbiosis & intestinal gut permeability	• BBB integrity, CNS homeostasis, inflammation and neuroinflammation are linked to the integrity of the intestinal barrier and gut microbiota composition.[3-5]
Elevated circulating lipopolysaccharides (LPS)	• Elevated systemic LPS levels induce changes to the astrocytes of the BBB, which increases BBB permeability.[6,7]
Stress	• Evidence suggest that acute stress damages the BBB, while chronic stress triggers neuroinflammation which leads to an increased risk of barrier permeability.[8,9]
High environmental toxicity **Genetic factors** **Dietary factors**	• These factors have all been identified as triggers for an increased risk of BBB dysfunction and BBB permeability.[1,2,6.10]

Obrenovich 2018; Main et al 2017; Ghezzi et al 2022; Morris et al 2018; Esposito et al 2001; Gárate et al 2013; Galea et al 2021.



Memory, cognition, neurodegenerative decline

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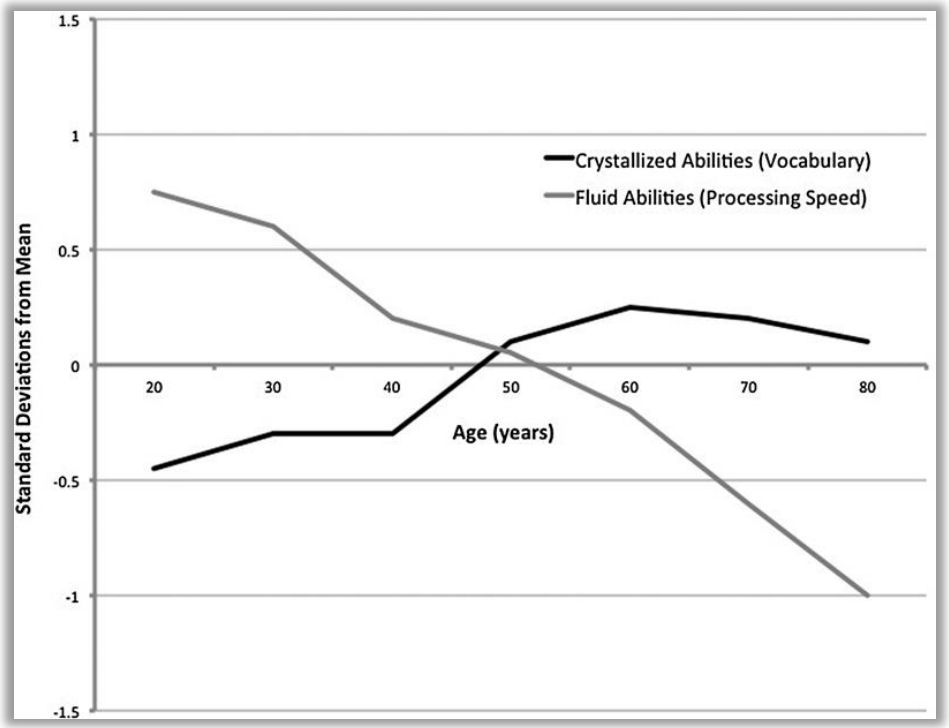
Cognitive decline and aging

The most important cognitive changes with aging are affect cognitive tasks that require one to quickly process or transform information to make a decision.



- **Crystallised abilities** includes acquired knowledge, cumulative skills and memories.
- Tests of general knowledge, reading comprehension, math, science, historical information and vocabulary would reflect crystallized abilities.
- These generally do not decline until over the age of 60.

- **Fluid abilities** require cognitive processing and reflect the ability to manipulate and transform information such as problem solving.
- There is a clear steady decline in fluid abilities and processing speed between the ages of 20-80 years.

Murman et al 2015

Cognitive decline and dementia in Australia

- Dementia is when cognitive impairment and changes to brain function has become severe enough to compromise social or working life.[1,2]
- Alzheimer's disease is the most common form of dementia.[2]

In Australia, statistics report that dementia:

- Affects 10% of people over the age of 65 years.[2]
- Affects 30% of people over the age of 85 years.[2]
- Is the second leading cause of death of all Australians and the leading cause of death in women.[3]

It is estimated that:

- More than 421,000 Australians are living with all forms of dementia (2024).[4]
- More than 1.6 million people in Australia are involved in the care of someone living with dementia (2024).[5]

Hugo et al 2014; Dementia.org.au; AIHW; Dementia Australia; Dept Health and Aged Care

BBB and cognitive/neurological health

BRAIN FOG

Difficulty concentrating

MEMORY LOSS

Headache

FATIGUE

Some mood disorders

www.123rf.com/photo_89251834_blue-brain-human-background.html

BBB and cognitive/neurological health

Alzheimer's disease

Parkinson's disease

Multiple sclerosis

ALS

www.123rf.com/photo_89251834_blue-brain-human-background.html

Blood-brain barrier: Health impact

JEM

Review

Alzheimer's disease: A matter of blood–brain barrier dysfunction?

Axel Montagne,[1,2]* Zhen Zhao,[1,2]* and Berislav V. Zlokovic[1,2]

[1]Zilkha Neurogenetic Institute, Keck School of Medicine and [2]Department of Physiology and Neuroscience, Keck School of Medicine, University of Southern California, Los Angeles, Los Angeles, CA

REVIEW
published: 19 August 2021
doi: 10.3389/fnins.2021.688090

Blood–Brain Barrier Breakdown: An Emerging Biomarker of Cognitive Impairment in Normal Aging and Dementia

Basharat Hussain [1,2†], Cheng Fang [1†] and Junlei Chang [1*]

Molecular Psychiatry
www.nature.com/mp

REVIEW ARTICLE OPEN

The blood-brain barrier in aging and neurodegeneration

Emily G. Knox [1,2], Maria R. Aburto[2,3], Gerard Clarke [2,4], John F. Cryan [2,3] and Caitriona M. O'Driscoll [1]

Microvascular and blood-brain barrier dysfunction in Alzheimer's disease

New insights from
quantitative magnetic resonance imaging

Epub 2007 Sep 14.

Blood-brain barrier: ageing and microvascular disease--systematic review and meta-analysis

Andrew J Farrall [1], Joanna M Wardlaw

Affiliations

PMID: 17869382 DOI: 10.1016/j.neurobiolaging.2007.07.015

Leaky brain in neurological and psychiatric disorders: Drivers and consequences

Australian & New Zealand Journal of Psychiatry
2018, Vol. 52(10) 924–948
DOI: 10.1177/0004867418796955

Gerwyn Morris[1], Brisa S Fernandes[1,2], Basant K Puri[3], Adam J Walker[1], Andre F Carvalho[2] and Michael Berk[1,4]

ANZJP

A leaky blood–brain barrier, fibrinogen infiltration and microglial reactivity in inflamed Alzheimer's disease brain

Jae K. Ryu, James G. McLarnon *

International Journal of Molecular Sciences
MDPI

Review

Blood–Brain Barrier Dysfunction and Astrocyte Senescence as Reciprocal Drivers of Neuropathology in Aging

Marcela K. Preininger [1,2] and Daniela Kaufer [1,3,*]

SPECIAL ISSUE REVIEW
EJN European Journal of Neuroscience FENS WILEY

Inflammation-driven brain and gut barrier dysfunction in stress and mood disorders

Ellen Doney | Alice Cadoret | Laurence Dion-Albert | Manon Lebel | Caroline Menard

Review Neurobiol Dis. 2004 Jun;16(1):1-13. doi: 10.1016/j.nbd.2003.12.016.

The blood-brain barrier: an overview: structure, regulation, and clinical implications

Praveen Ballabh [1], Alex Braun, Maiken Nedergaard

microorganisms

Review

Leaky Gut, Leaky Brain?

Mark E. M. Obrenovich [1,2,3,4,5]

Sci Transl Med. 2019 Dec 4;11(521):eaaw8283. doi: 10.1126/scitranslmed.aaw8283.

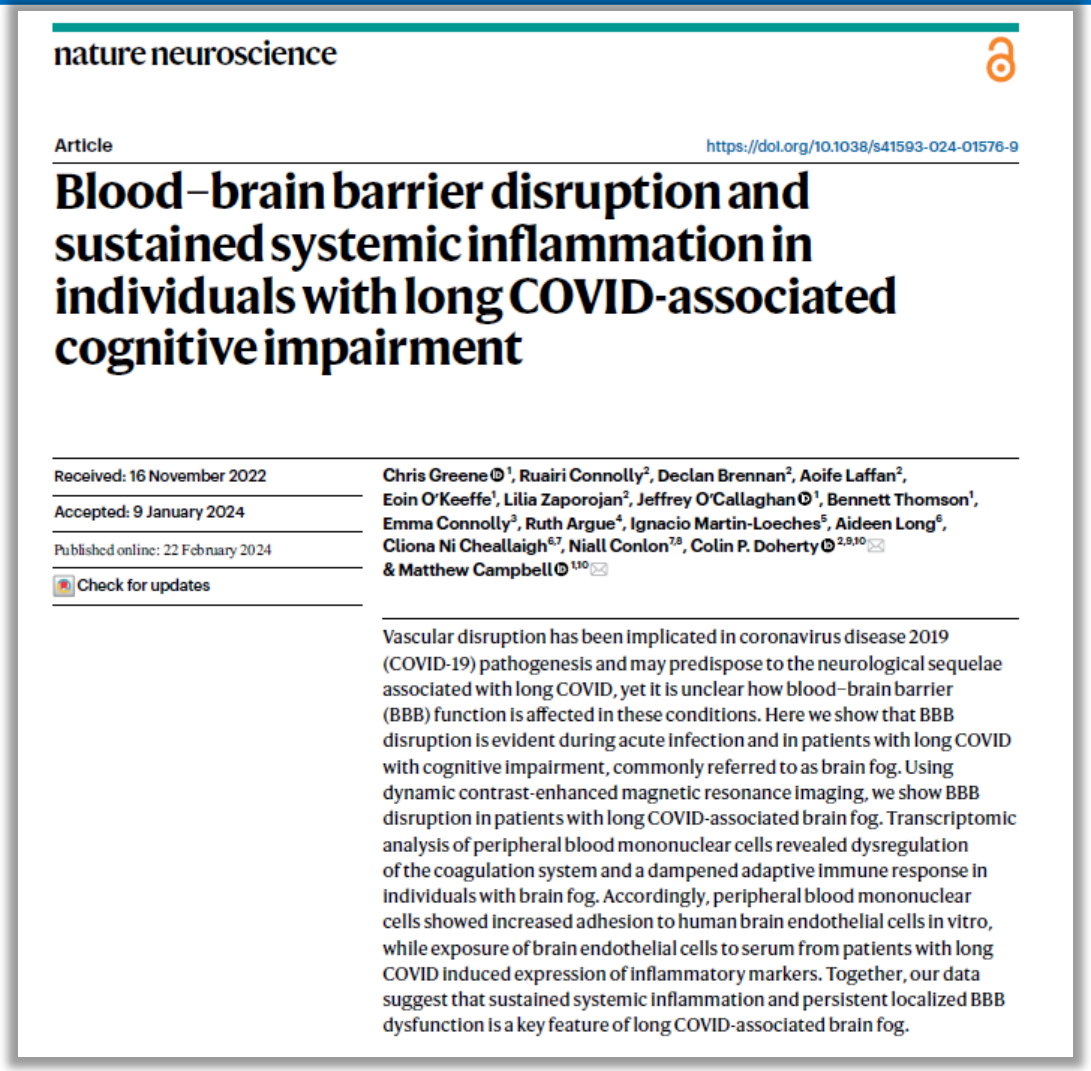
Blood-brain barrier dysfunction in aging induces hyperactivation of TGFβ signaling and chronic yet reversible neural dysfunction

Review Article

Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation

BBB disruption and long-COVID brain fog

A recent study concluded that sustained systemic inflammation and persistent localised BBB dysfunction were a key feature of long COVID-associated brain fog.[1]



nature neuroscience

Article

https://doi.org/10.1038/s41593-024-01576-9

Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment

Received: 16 November 2022

Accepted: 9 January 2024

Published online: 22 February 2024

Check for updates

Chris Greene[1], Ruairi Connolly[2], Declan Brennan[2], Aoife Laffan[2], Eoin O'Keeffe[1], Lilia Zaporojan[2], Jeffrey O'Callaghan[1], Bennett Thomson[1], Emma Connolly[3], Ruth Argue[4], Ignacio Martin-Loeches[5], Aideen Long[6], Cliona Ni Cheallaigh[6,7], Niall Conlon[7,8], Colin P. Doherty[2,9,10] & Matthew Campbell[1,10]

Vascular disruption has been implicated in coronavirus disease 2019 (COVID-19) pathogenesis and may predispose to the neurological sequelae associated with long COVID, yet it is unclear how blood–brain barrier (BBB) function is affected in these conditions. Here we show that BBB disruption is evident during acute infection and in patients with long COVID with cognitive impairment, commonly referred to as brain fog. Using dynamic contrast-enhanced magnetic resonance imaging, we show BBB disruption in patients with long COVID-associated brain fog. Transcriptomic analysis of peripheral blood mononuclear cells revealed dysregulation of the coagulation system and a dampened adaptive immune response in individuals with brain fog. Accordingly, peripheral blood mononuclear cells showed increased adhesion to human brain endothelial cells in vitro, while exposure of brain endothelial cells to serum from patients with long COVID induced expression of inflammatory markers. Together, our data suggest that sustained systemic inflammation and persistent localized BBB dysfunction is a key feature of long COVID-associated brain fog.

Greene et al 2024

Glymphatic system research – Health impact

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Review

The Role of Glymphatic System in Alzheimer's and Parkinson's Disease Pathogenesis

Francesca R. Buccellato [1,2,*], Marianna D'Anca [2], Maria Serpente [2], Andrea Arighi [2] and Daniela Galimberti [1,2]

Glymphatic Dysfunction: A Bridge Between Sleep Disturbance and Mood Disorders

Tao Yan [1], Yuefeng Qiu [2], Xinfeng Yu [3] and Linglin Yang [4]**

[1] Department of Psychiatry, Changxing People's Hospital, Huzhou, China, [2] Department of Psychiatry, Zhejiang Hospital, Hangzhou, China, [3] Department of Radiology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [4] Department of Psychiatry, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

biomedicines

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Review

The Dynamic Relationship between the Glymphatic System, Aging, Memory, and Sleep

Konstantinos I. Voumvourakis [1,†], Eleni Sideri [1,2,†], Georgios N. Papadimitropoulos [1], Ioanna Tsantzali [1], Paul Hewlett [2], Dimitrios Kitsos [1], Marianna Stefanou [1], Anastasios Bonakis [1], Sotirios Giannopoulos [1], Georgios Tsivgoulis [1] and George P. Paraskevas [1,*]

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REVIEWED BY
Ruisheng Duan,
Shandong University, China
Jose Vicente Lafuente,

Glymphatic system: an emerging therapeutic approach for neurological disorders

Ying Gao[1], Kangding Liu[1] and Jie Zhu[1,2]*

[1]Department of Neurology, Neuroscience Centre, The First Hospital of Jilin University, Changchun, China, [2]Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Karolinska

Science. 2020 October 0

Glymphatic failure as a final common pathway to dementia

Maiken Nedergaard, Steven A. Goldman

Center for Translational Neuromedicine, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark; Center for Translational Neuromedicine, University of Rochester Medical Center, Rochester, NY 14642, USA

The glymphatic pathway in neurological disorders.

Martin Kaag Rasmussen[#1], Humberto Mestre[#2,3], and Maiken Nedergaard[1,2,3,*]

ELSEVIER FULL-TEXT ARTICLE

Review Brain Res Bull. 2018 Jan:136:118-129. doi: 10.1016/j.brainresbull.2017.02.011. Epub 2017 Mar 6.

The role of aquaporin-4 in synaptic plasticity, memory and disease

Jacqueline A Hubbard [1], Jenny I Szu [1], Devin K Binder [2]

Neurobiology of Disease

Cortical Spreading Depression Closes Paravascular Space and Impairs Glymphatic Flow: Implications for Migraine Headache

Aaron J. Schain, Agustin Melo-Carrillo, Andrew M. Strassman, and Rami Burstein

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Review

Glymphatic System Dysfunction and Sleep Disturbance May Contribute to the Pathogenesis and Progression of Parkinson's Disease

Andie Massey [1], Matthew K. Boag [1], Annie Magnier [1], Dharah P. C. F. Bispo [1], Tien K. Khoo [2,3] and Dean L. Pountney [1,*]

ELSEVIER

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties

Jennaya Christensen, Glenn R. Yamakawa, Sandy R. Shultz, Richelle Mychasiuk *

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The emerging relationship between interstitial fluid-cerebrospinal fluid exchange, amyloid β and sleep

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Effect of sleep on overnight CSF amyloid-β kinetics

Brendan P. Lucey, MD[1,2,*], Terry J. Hicks[1], Jennifer S. McLeland[1], Cristina D. Toedebusch[1], Jill Boyd[1], Donald L. Elbert, PhD[3], Bruce W. Patterson, PhD[4], Jack Baty[5], John C. Morris, MD[1,2,6], Vitaliy Ovod, MS[1], Kwasi G. Mawuenyega, PhD[1], and Randall J. Bateman, MD[1,2,6]

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Annual Review of Pathology: Mechanisms of Disease

The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future

Benjamin A. Plog[1,2] and Maiken Nedergaard[1]

Review

The Glymphatic System: A Novel Component of Fundamental Neurobiology

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Author manuscript

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Establishing a framework for neuropathological correlate glymphatic system functioning in Parkinson's disease

Saranya Sundaram[a,b,1], Rachel L. Hughes[a,1], Eric Peterson[b], Eva M. Müller-Oehri Helen M. Bronté-Stewart[d,e], Kathleen L. Poston[d,e], Afik Faerman[a], Chloe Bhowm Tilman Schulte[a,b,*]

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HHS Public Access

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Sleep, Cerebrospinal Fluid, and the Glymphatic System: A Systematic Review

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Aquaporin 4 beyond a water channel; participation in motor, sensory, cognitive and psychological performances, a comprehensive review

Review

Seyede Zohreh Jazaeri[a,b], Ghorban Taghizadeh[c], Javad Fahanik Babaei[d], Sepideh Goudarzi[e], Pegah Saadatmand[f], Mohammad Taghi Joghataei[a,b,g,h], Zohreh Khanahmadi[i]

Brain-heart connection

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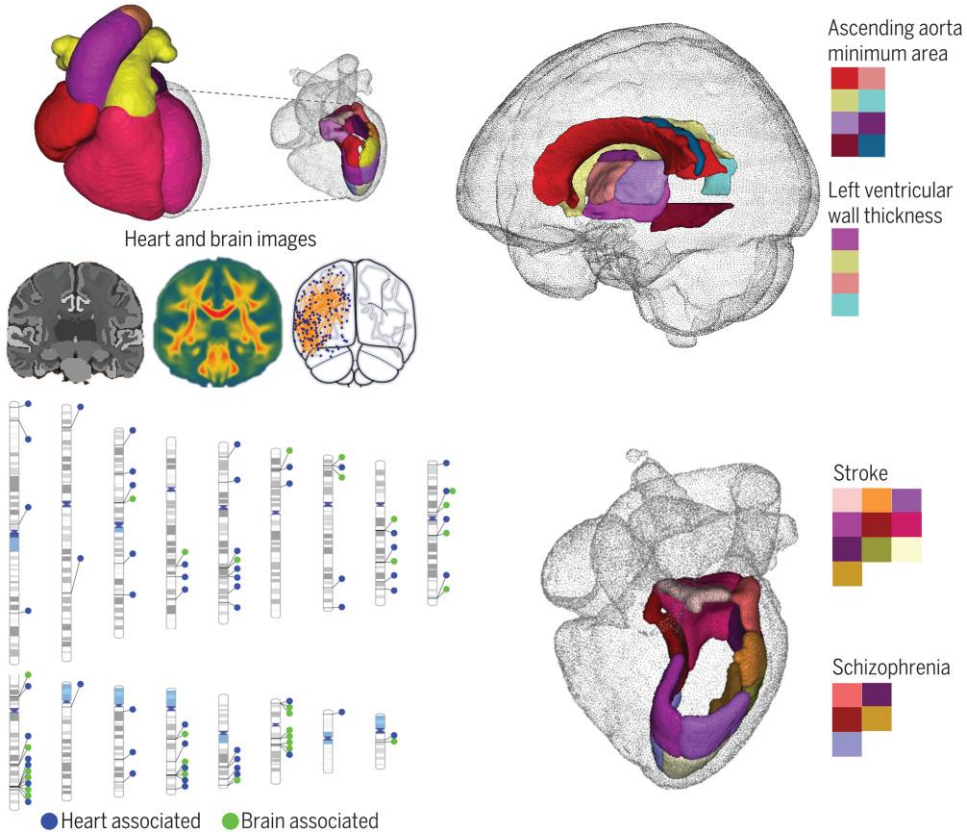
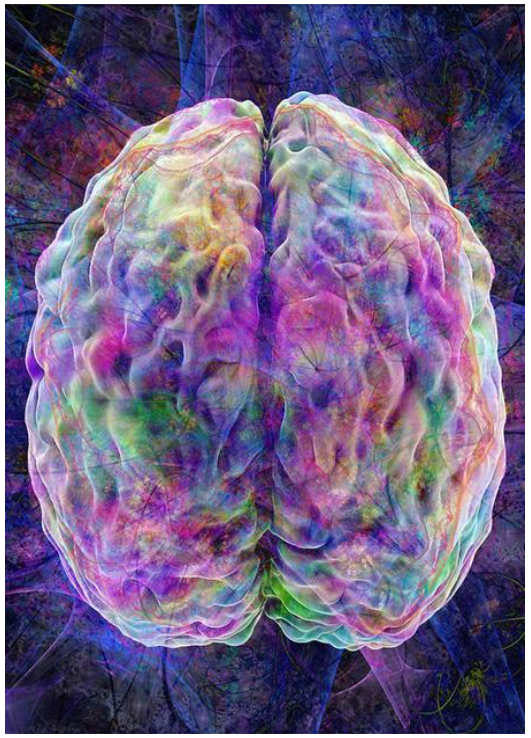
Heart-brain connection

A growing body of evidence shows a correlation between heart health and brain health. Cardiovascular disease potentially increases the risk of brain diseases such as stroke, dementia and cognitive impairment.[1]

- A recent study involving more than 40 000 subjects quantified this heart-brain connection using both MRI and genetic data.[1]
- Genetic correlations were observed between heart MRI traits and brain-related traits and disorders.[1]
- These results highlight the importance of managing a multi-organ approach to health management to reduce disease risk and progression.[1]



Aging: Common denominators for brain and heart



Inflammation

Oxidative stress

Sleep disturbances

Sleep: brain health and heart health

1

Chronically impaired sleep time or quality compromises glymphatic clearance of waste and toxins from the brain, including neurodegenerative proteins.[1-4]

2

Chronic sleep disturbances increase the risk of cardiovascular health conditions.[5]

Sleep deprivation increases sympathetic nervous system activity.[5]

3

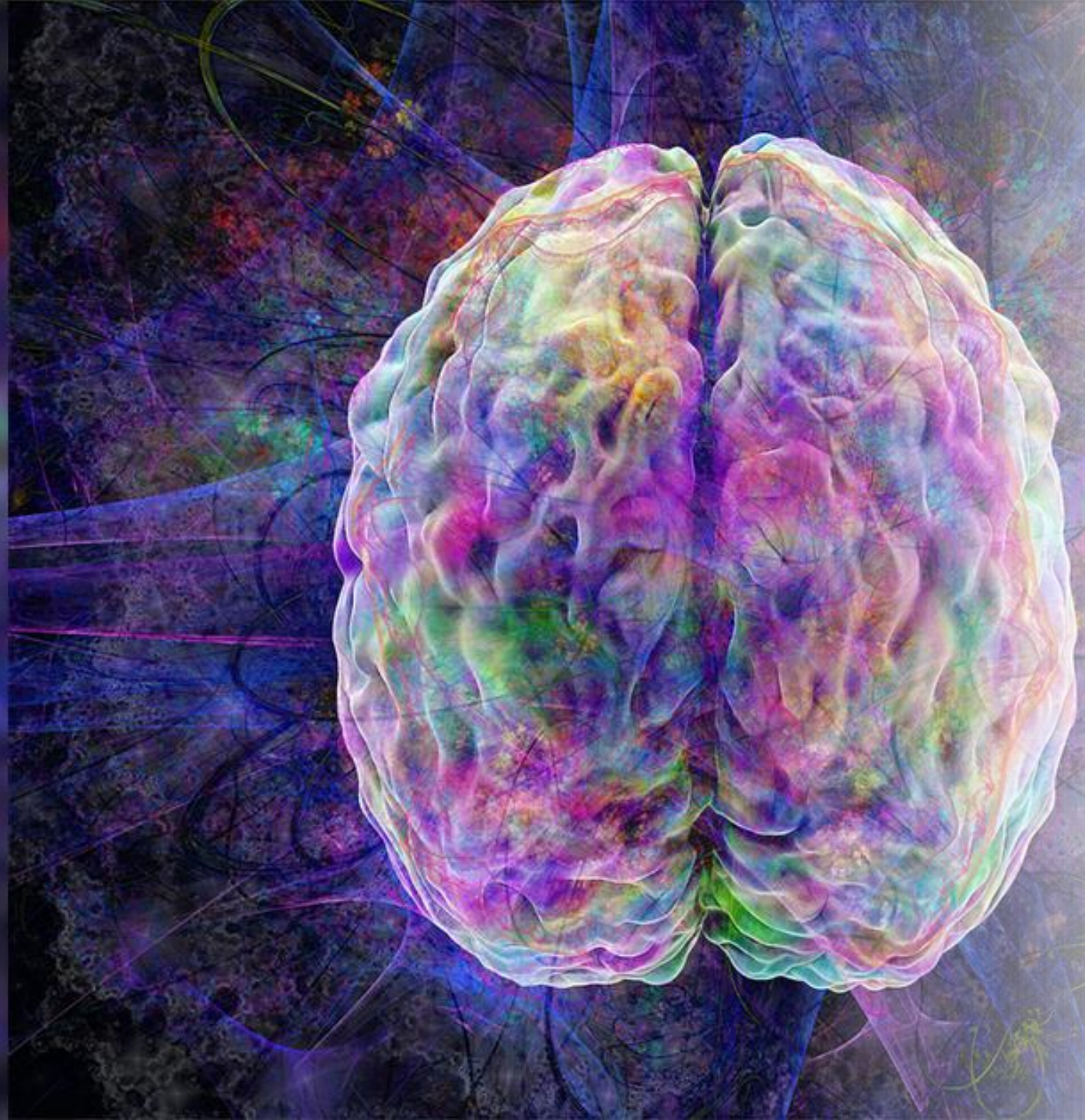
A study over 8-10 years, with >4800 participants reported an increased risk of hypertension in those with ≤ 5 hours sleep.[5]

A study of almost 72 000 women reported increased CHD in those with inadequate sleep duration.[5]

4

Strategies to support healthy sleep and to restore healthy circadian rhythms help support brain health and heart health.

Verheggen et al 2018; Xuan et al 2022; Mestre et al 2020; Jessen et al 2015; Nagai et al 2010.



Interventions to support brain health

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Improving the balance towards brain health

Interventions that can promote healthy brain aging while reducing the detrimental impact of age on cognition and memory.

Support blood brain barrier integrity	Support brain waste clearance	Reduce neuroinflammation and oxidative stress	Improve sleep duration and quality	Reduce cardiovascular risk
Eat a healthy diet	Avoid excessive alcohol consumption	Exercise regularly	Participate in cognitively stimulating activities	Manage emotional stress

Murman et al 2015

Supporting BBB health and integrity

STOP

- Consuming gluten and foods that the individual cannot tolerate.
- Including sugar and processed foods in meals.
- Ignoring stress.
- Drinking alcohol in excess.
- Exposure to environmental toxins in air, water and food.

START

- Detoxifying the body of pesticides, heavy metals and other environmental toxins.
- Taking in probiotic foods to keep the gut balanced.
- Increasing intake of dietary essential fatty acids, which are vital for the brain.
- Reducing inflammation through the diet.
- Making quality sleep a priority.
- Reducing psychological and emotional stress.

SEEK

- Supplements that may support blood-brain barrier health and integrity.

Acknowledged to https://mindd.org/leaky-brain/

Therapeutic goals to support BBB health

Reduce modifiable causative factors of blood-brain barrier disruption

Reduce inflammation and neuroinflammation

- BBB disruption = inflamed brain
- Key contributing factor for BBB disruption and contributes to glymphatic dysfunction.

Reduce oxidative stress

- Key contributing factor for BBB disruption.
- Also affects glymphatic function.

Support sleep

- Impaired sleep quality compromises clearance of brain waste.

Support gut health and reduce intestinal permeability

- 'Leaky gut-brain leak connection'
- Increased gut-barrier permeability and dysbiosis are linked to neuroinflammation.

Support BBB repair (direct & indirect)

- Addressing key causes of BBB disruption facilitates repair and removes ongoing triggers.

Therapeutic goals to support BBB health

Address the clinical effects associated with increased blood-brain barrier permeability

Support brain health

Increased BBB permeability results in:

- Loss of normal protective mechanisms
- May compromise brain health and function.

Support nervous system health

Increased BBB permeability may result in:

- Neuronal loss
- Neuronal dysfunction
- Neuroinflammation
- Neurodegeneration.

- BBB dysfunction may also present as headaches.

Support cognitive health

- Increased BBB permeability may affect cognitive health and function.

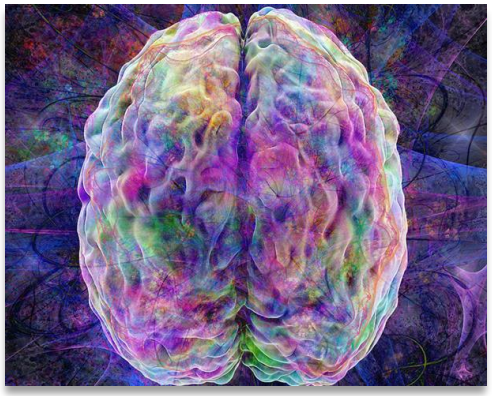
- It may manifest as brain fog, difficulty in concentrating and memory loss.

- Also contributes to an increased risk of neurocognitive disorders.

Support mood

- Impaired BBB integrity may affect mood or manifest as mood disorders.

Interventions to support brain and heart health



- Omega-3 fatty acids (EPA/DHA)
- Specialised pro-resolving mediators (SPMs)
- Cocoa
- Vitamin D
- Vitamin K2
- Magnesium
- Curcumin

https://www.istockphoto.com/photo/overmind-brain-activity-colored-human-overbrain-model-view-top-3d-illustration-gm1251284579-365120652

Ingredient summary

Reduce inflammation/ neuro-inflammation

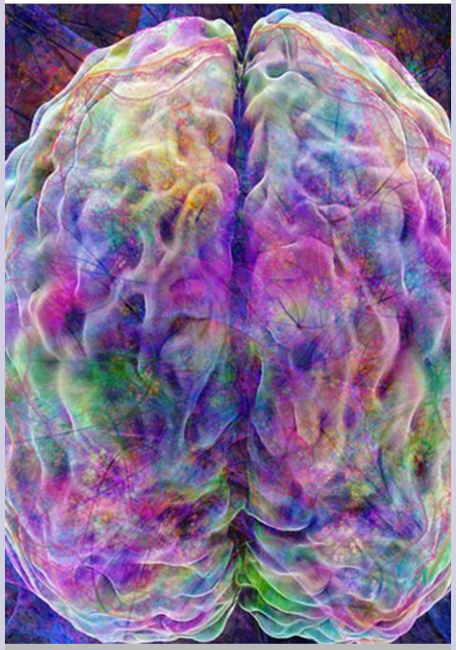
- Omega-3 fatty acids
- SPMs
- Cocoa
- Vitamin D
- Vitamin K2
- Magnesium
- Curcumin

Antioxidant

- Omega-3 fatty acids
- Cocoa
- Magnesium
- Curcumin
- Green tea

Support sleep

- Cocoa
- Phyto-melatonin
- Hops
- Lemon balm



Support brain health/BBB repair

- Omega-3 fatty acids
- Cocoa
- Vitamin D
- Magnesium
- Curcumin
- Green tea

Support cognitive health

- Omega-3 fatty acids
- Cocoa
- Magnesium
- Vitamin D
- Curcumin

Support cardiovascular health

- Omega-3 fatty acids
- SPMs
- Magnesium
- Vitamin D

https://www.istockphoto.com/photo/overmind-brain-activity-colored-human-overbrain-model-view-top-3d-illustration-gm1251284579-365120652

Omega-3 fatty acids: Brain health

DHA is recognised as the most important omega-3 fatty acids for brain and cognitive health:[1,2]

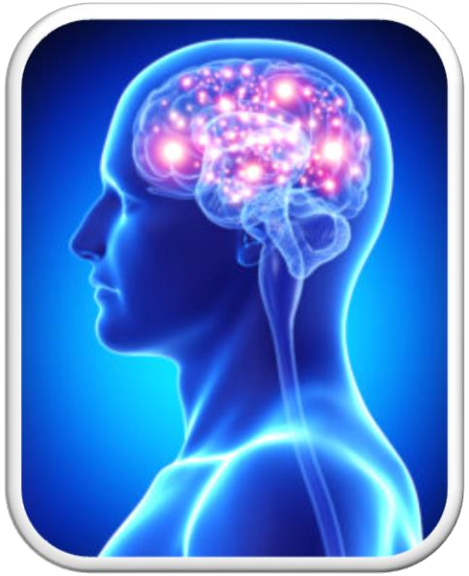
- Supports neurological function, learning, cognition.
- Counteracts neuroinflammatory processes.
- Facilitates neurotransmission.
- Influences synthesis and function of neurotransmitters.
- Involved in neuronal membrane and receptor function.

Braun & Cohen 2015, Natural Medicines Database 2024

DHA: Brain health

- There is a correlation between DHA deficiency and increased risk for development of several types of dementia and aged-related cognitive decline.[1]

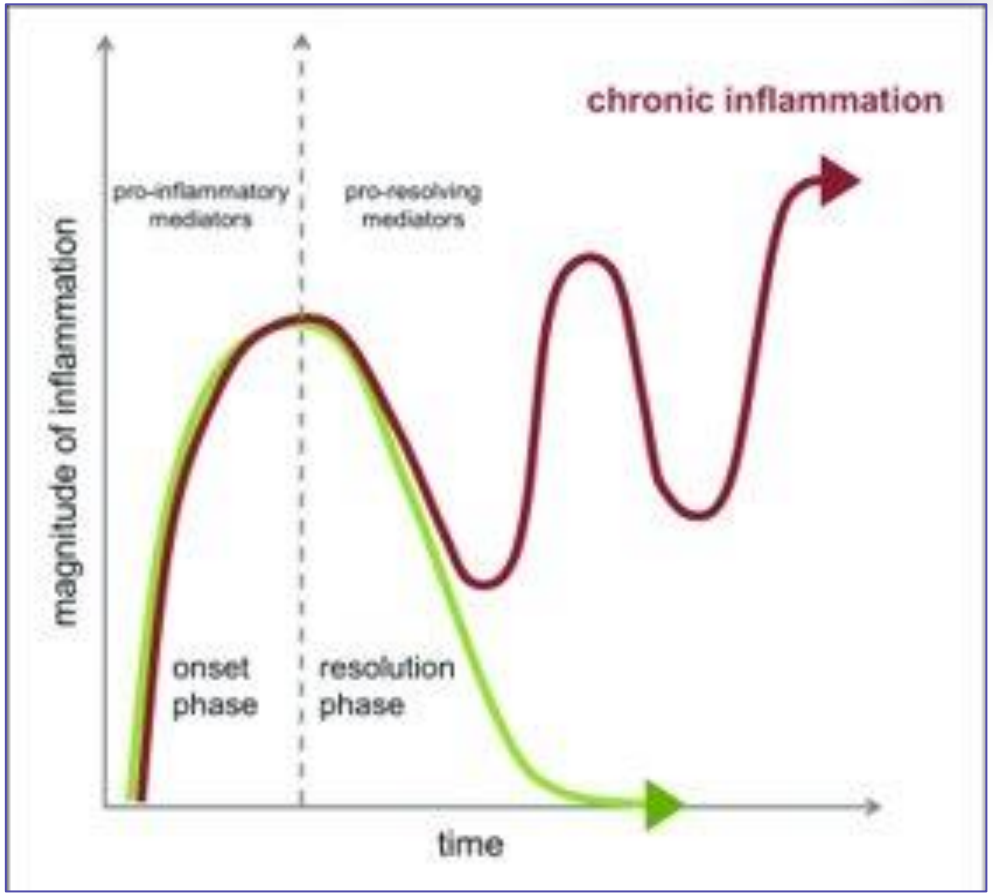
- Research suggests omega-3 fatty acids, especially DHA, may have protective benefits against age-related cognitive decline.[1-6]
  - Enhanced clearance of neurotoxic proteins such as amyloid-β peptides.
  - Decreased synthesis of pro-inflammatory cytokines.
  - Increased production of neurotrophic and neuroprotective factors.



Loef et al 2013; Yanai et al 2017; Ammann et al 2017; Conquer et al 2000; Lopez et al 2011; Schaefer et al 2006.

SPMs Specialised Pro-resolving Mediators

- SPMs are a class of endogenously produced lipid mediators and include resolvins, protectins, and maresins.[1]
- In the body, SPMs:[1-4]
  - Facilitate resolution or 'ending' of inflammation and promoting a return to homeostasis.
  - Inhibit additional inflammation and regulate the immune response.
  - Clear away damaging by-products of inflammation.
  - Promote clearance of dead cells, debris, blood clots and bacteria by macrophages.
  - Aid in tissue repair, remodelling and protection.



Barnig et al. Activation of resolution pathways to prevent and fight chronic inflammation: Front Immunol. 2019 Jul 23;10:1699.

Fredman et al 2017; Al-Shaer et al 2021; Gudernatsch et al 2020; Perretti et al 2017; Barnig et al 2019.

SPMs: Brain health and neuroinflammation

SPMs play an important role in modulating and resolving CNS neuroinflammation and supporting neural and brain tissue repair.[1-3]

Evidence suggests SPMs:

- Help resolve age-related low-grade neuroinflammation. Neuroinflammation is associated with cognitive decline.[3]
- Can ameliorate hyperreactive inflammation.[1]
- Shorten inflammatory resolution time.[1]
- Accelerate CNS tissue regeneration and repair.[1,2]
- Maintain brain homeostasis.[2]

Shang et al 2019; Tiberi et al 2021; Joffre et al 2020

SPMs

- Inadequate SPM bioactivity may result in unresolved inflammation.[1,2]
- Chronic inflammation underpins several disease states, including neurological, cardiovascular and joint conditions.[1-3]

Factors that limit endogenous production of SPMs include:[1-3]			
	Inadequate intake of dietary omega-3 fatty acids to meet physiological needs.		Aging, with SPM production decreasing with age.
	Pre-existing health conditions which both increase physiological demand and compromise biosynthesis.		Physical stressors: Overexertion as well as a sedentary lifestyle.
	Environmental toxin overload.		Dietary factors.
	Genetic predisposition.		Insufficient, or poor-quality sleep.

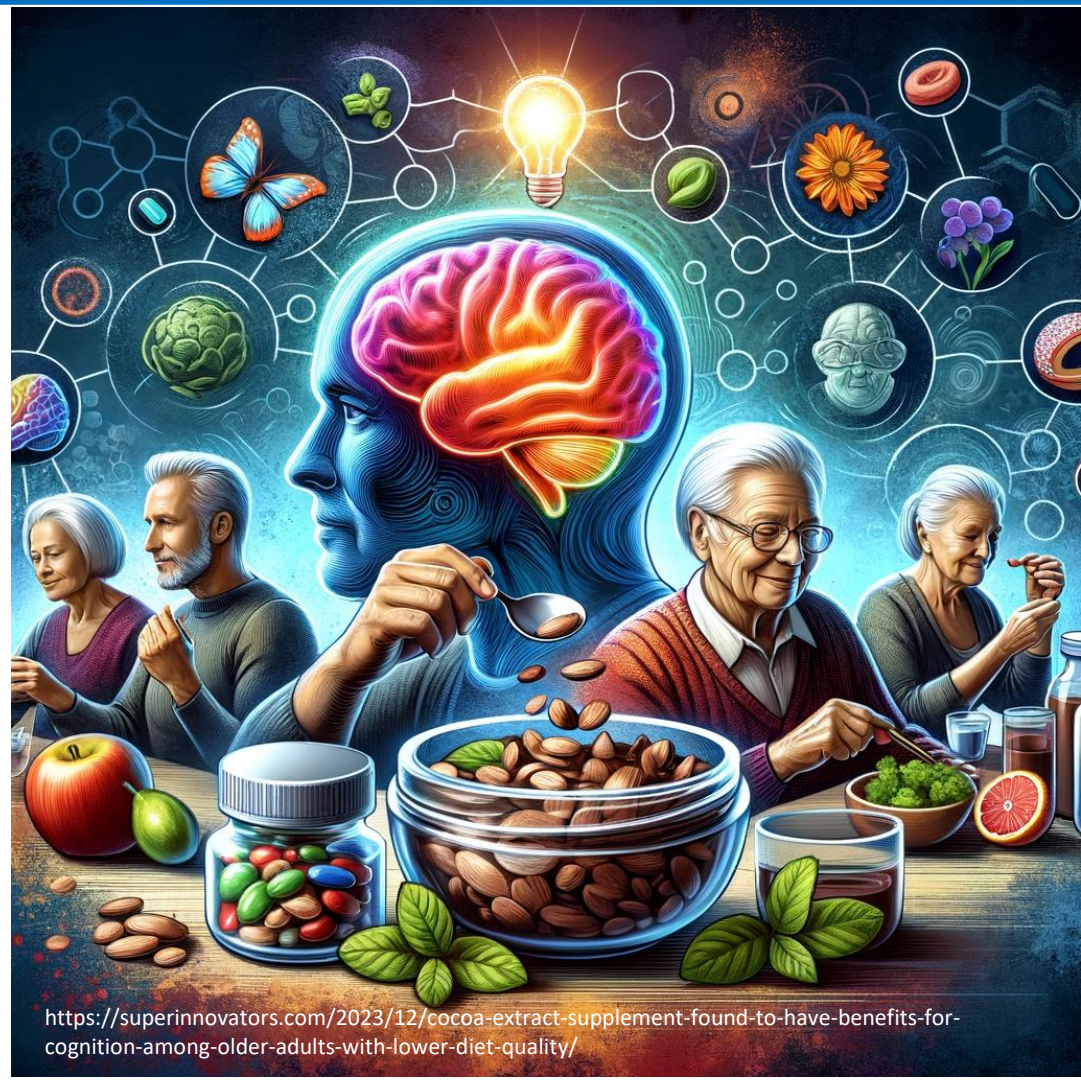
Cocoa: Brain health

Brain health:	• Cocoa consumption has been shown to improve brain blood flow, induce cerebral vasodilation and increase cerebral blood oxygenation in clinical studies. [1-4] • Neuro-modulatory effects have been reported in human studies.[1-4] • Cocoa is reported to be neuroprotective and to stimulate neuro-regeneration.[5]
Neuroinflammation:	• Consumption of cocoa polyphenols and flavonoids has been shown to reduce neuroinflammation.[1,5]
Antioxidant:	• Cocoa polyphenols are antioxidant.[1-4]

Zeli et al 2022; Socci et al 2017; Gratton et al 2020; Sokolov et al 2013

Cocoa: Cognitive health

- Cocoa promotes memory, cognitive function and synaptic plasticity.[1]
- Evidence suggests:
  - Cocoa enhances and sustains cognitive function in both younger and older adults.[1-8]
  - May help reduce the risk of age-related cognitive decline.[1-4]
- A review of 9 observational studies and 10 interventional studies reported:[2]
  - Cocoa may help manage cognitive decline in aged people.
  - May help improve or aid recovery of neurovascular connectivity.
  - Greatest benefits reported in studies with 500-900 mg cocoa flavanols daily for ≥ 8 weeks.



https://superinnovators.com/2023/12/cocoa-extract-supplement-found-to-have-benefits-for-cognition-among-older-adults-with-lower-diet-quality/

Zeli et al 2022; Socci et al 2017; Gratton et al 2020; Sokolov et al 2013; Martin et al 2020; Desideri et al 2012; Mastroiacovo et al 2015; Nehlig et al 2013

Vitamin D: Brain and cognitive health

Brain health:	• Circulating calcifediol crosses the BBB and enters glial and neuronal cells to be converted into the active calcitriol form, where it supports brain health and function.[1,2]
Neuroinflammation:	• Vitamin D has anti-inflammatory and neuroprotective actions.[1-3] • Preliminary research suggests that vitamin D protects endothelial cells and ameliorates BBB disruption, mainly by reducing inflammation.[4-6]
Cognitive health:	• Vitamin D supports normal cognitive and neurological function. • Vitamin D deficiency has been associated with cognitive decline and an increased risk of some cognitive disorders.[1,7-9]

Anjum et al 2018; Sultan et al 2020; Harms et al 2011; Won et al 2015; Dehghani et al 2013; Enkjargal et al 2017; Charoenngam et al 2020; Soni et al 2012; Annweiler et al 2016; Llewellyn et al 2010

Vitamin K2: CV and inflammation

Bone health

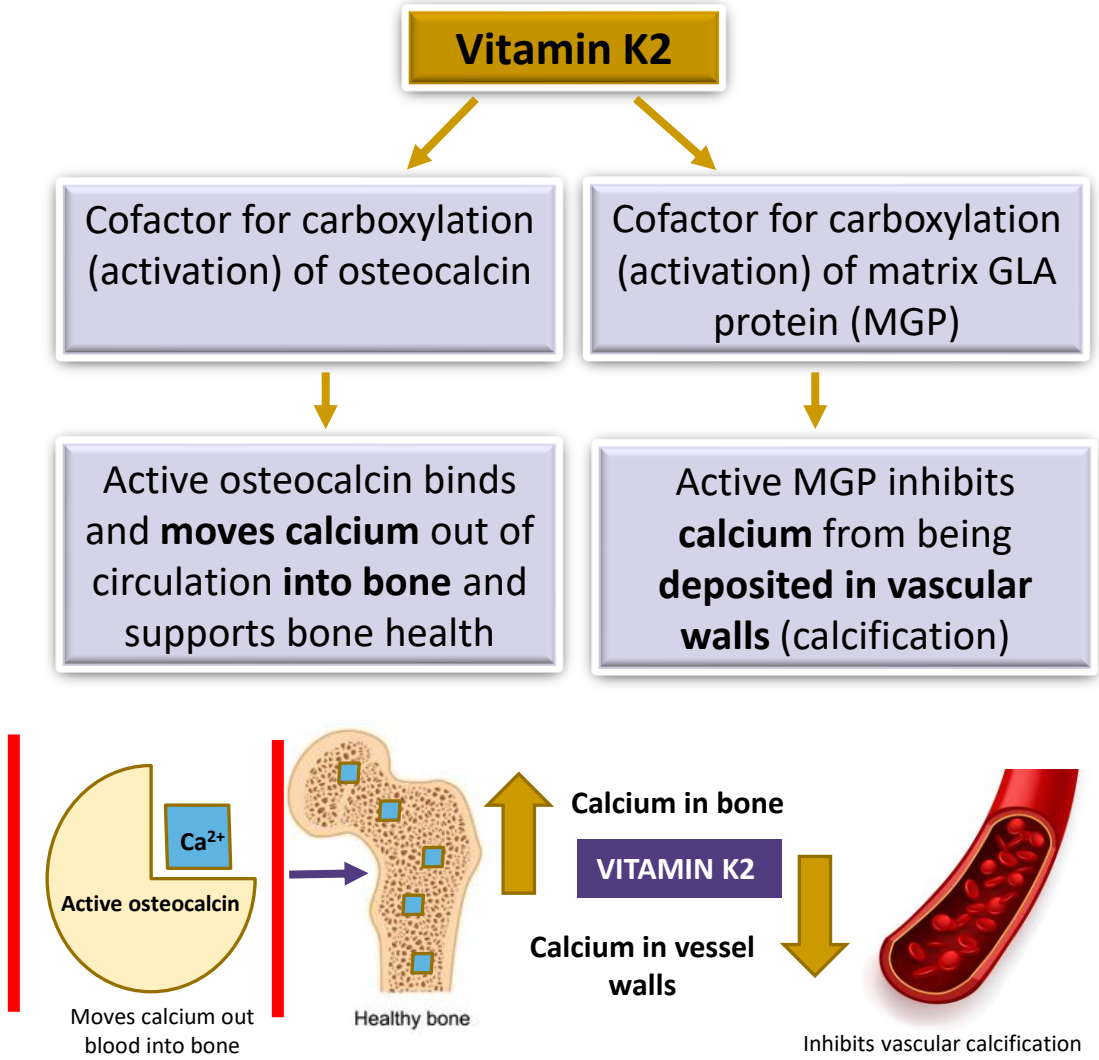
- Vitamin K2 activates osteocalcin, which then binds to calcium, leading to calcium being deposited into bones.[1-4]

Cardiovascular health

- Vitamin K2 also activates (stimulates carboxylation) of matrix GLA protein (MGP), which inhibits calcification of blood vessels.[3,4]

Inflammation

- Emerging evidence suggests vitamin K is a protective nutrient in aging and 'inflammaging'.
- It has been shown to exert a protective role in the inflammatory and mineralization processes associated with the onset and progression of age-related diseases.[5]



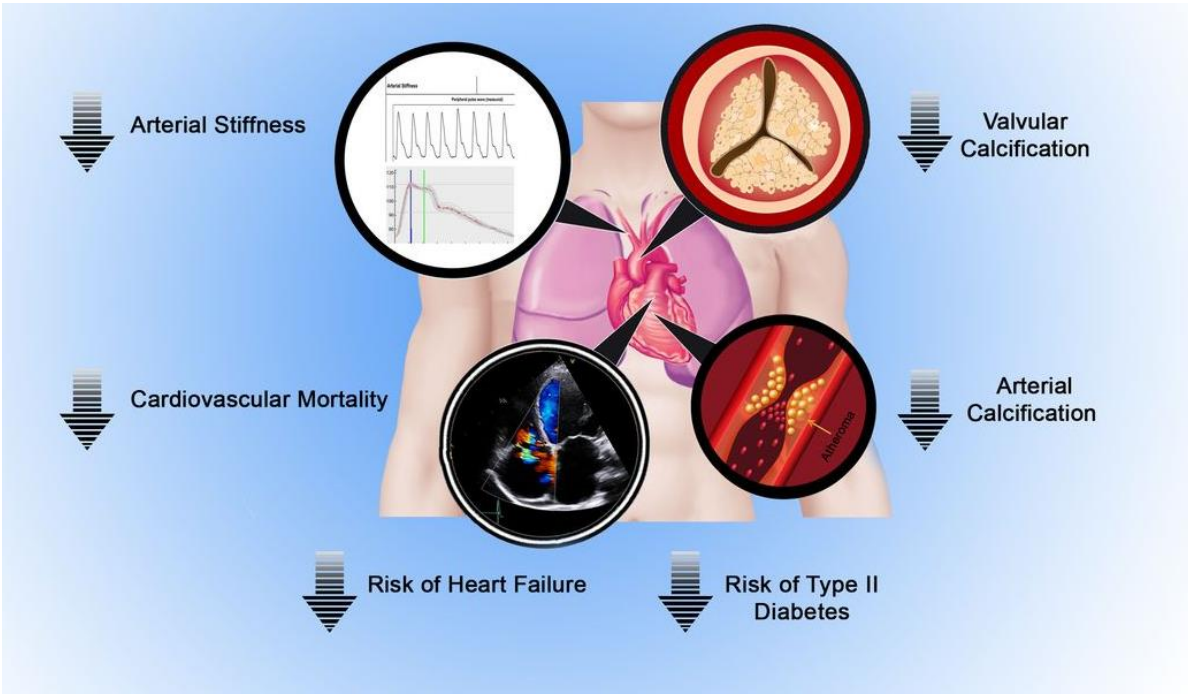
Knapen et al 2013; Rodríguez-Olleros et al 2019; Hariri et al 2021; Maresz et al 2015; Simes et al 2019

Vitamin K2 – Brain health

- Vitamin K deficiency is strongly associated with arterial stiffness, vascular and valvular calcification, heart failure and cardiovascular mortality.[1]

Link to brain health:

- Impaired cerebral blood flow is a contributing factor for age-related cognitive deterioration and an increased risk of dementia.[2]
- Arterial pulsation is a key driver for glymphatic system clearance.[2] Compromised cerebral blood flow may impede brain waste clearance.[2]



Vitamin K2 supports cardiovascular health.[1]

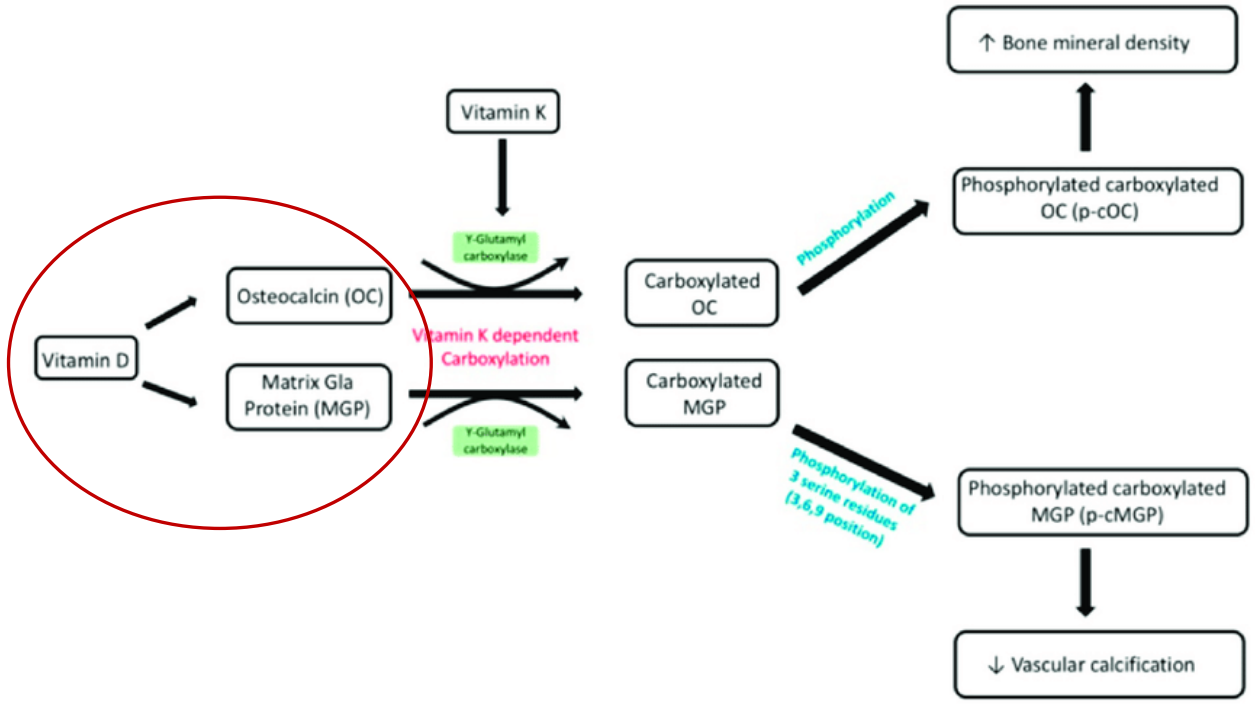
Hariri et al 2021;Nedergaard et al 2020

Synergy between vitamin D and K2

The synergy between vitamin D and vitamin K2 is reported in multiple studies.[1]

This synergy is due to biological mechanisms as well as different complementary effects on bone and CV health.[1]

- **Vitamin D (as calcitriol) is needed for the synthesis of the vitamin K-dependent proteins, osteocalcin and matrix GLA protein (MGP).[1]**
- Vitamin K2 is an essential co-factor for the carboxylation of these proteins to their active forms.[1]
  - Carboxylated osteocalcin results in ↑ bone mineral density.[1]
  - Carboxylated MGP results in ↓ vascular calcification.[1]



Adequate intake of both vitamin D and vitamin K are necessary to support bone and vascular health.[1,2]

Khalil et al 2023; Hou et al 2019

Magnesium: Brain and nervous system health

12
Mg
24.31

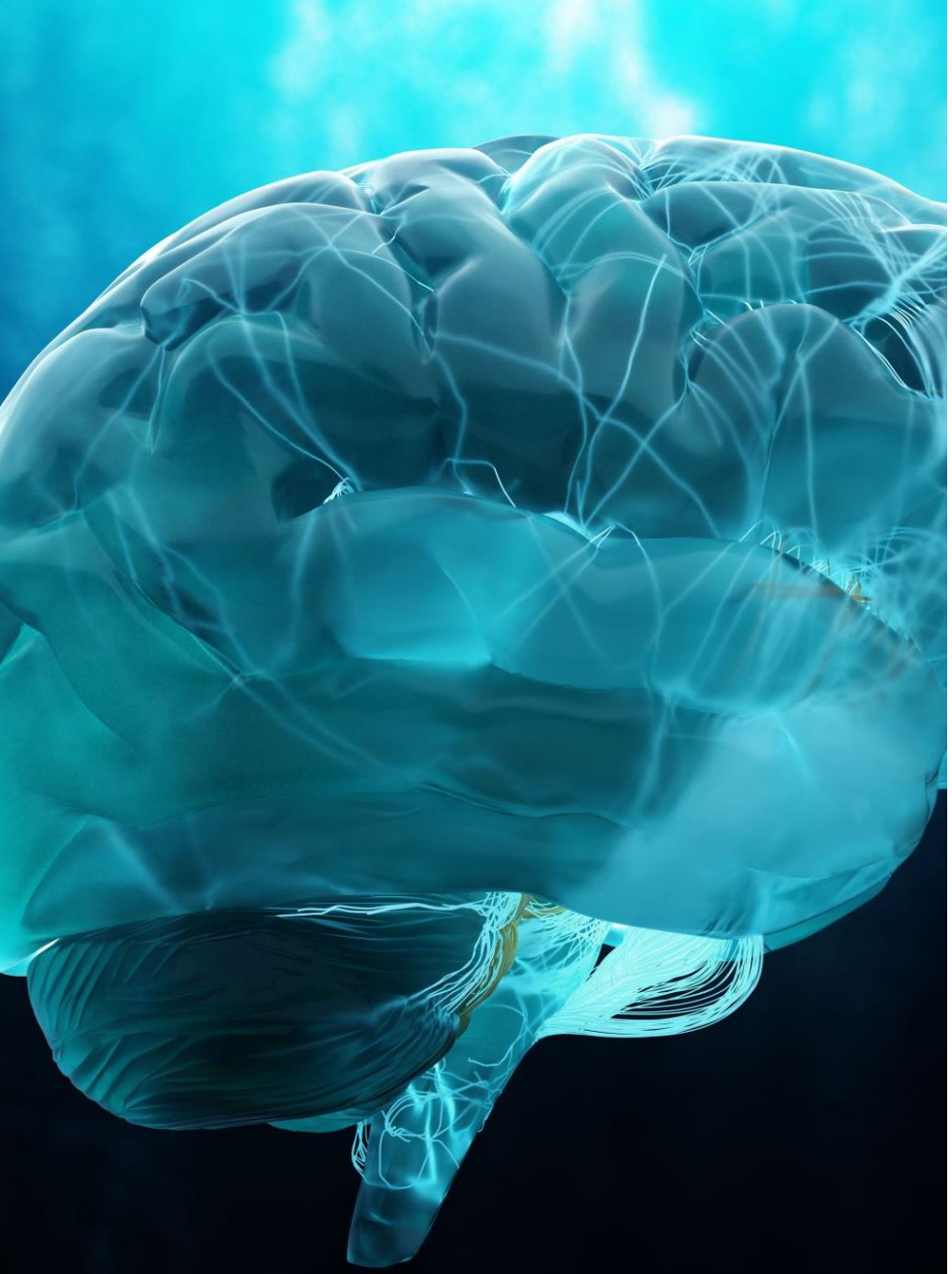
Brain health:	• Magnesium directly influences BBB properties. • Evidence suggests magnesium prevents BBB disruption, reduces hyperpermeability and supports BBB integrity and repair.[1-7]
Neuroinflammation:	• Magnesium deficiency is linked to low-grade inflammation and neuroinflammation.[1] • Neuroinflammation compromises BBB integrity.[1]
Antioxidant:	• Magnesium upregulates antioxidant enzyme activity and inhibits production of ROS.[4] • It may be protective to brain tissue due to these antioxidant actions.[4]
Nervous system health and sleep:	• Magnesium supports nervous system health and helps regulate the stress response.[8-10] • Stress appears to be a contributing factor for triggering neuroinflammation, which can lead to impaired BBB and glymphatic system function.[11-15] • Low magnesium status has been linked to poor sleep quality, altered circadian rhythms and low melatonin levels.[16]

Maier et al 2022; Kaya et al 2011; Euser et al 2008; Shadman et al 2019; Esen et al 2005; Kaya et al 2004; Kaya et al 2001; Hechtman et al 2019; Boyla et al 2017; Esposito et al 2001; Garate et al 2013; Wei et al 2019; Xie et al 2013; Reddy et al 2020

Curcumin: Brain and nervous system health

Brain and cognitive health:	• Curcumin reduces inflammation and has antioxidant properties.[1-4] • Curcumin has been shown to improve memory and attention in adults without dementia. Preliminary evidence also suggests curcumin decreases amyloid and tau accumulation in brain regions that modulate mood and memory.[5]
Neuroinflammation:	• Curcumin has significant anti-inflammatory actions and downregulates the synthesis of multiple pro-inflammatory mediators, including inhibition of NF-kβ and TNF-α.[1,2,6]
Antioxidant:	• Curcumin has significant antioxidant activity and has been shown to improve systemic markers of oxidative stress in clinical trials.[3,7]

Aggarwal et al 2013; Aggerwal et al 2009; He et al 2015; Di Meo et al 2019; Hewlings et al 2017; Goozee et al 2016; Small et al 2018



Verheggen et al 2018; https://www.ntu.edu.sg/engineering/research/research-focus

In Summary.....

- BBB dysfunction leads to compromised influx of unwanted compounds into the brain.
- It also contributes to glymphatic system dysfunction, which compromises the clearance of brain waste and neurotoxins out of the brain.[1]
- Dysfunction of one, or both, may result in accumulation of neurotoxins, proteins and metabolites in the brain, which increase the risk of neurodegenerative diseases, as well as having shorter term effects.[1]
- **Therapeutic interventions for disrupted BBB integrity should address:**
  - **Key causative factors, such as neuroinflammation and oxidative stress.**
  - **Key clinical consequences.**

The combination of these strategies may help protect the brain from damage, promote repair, support cognition, reduce the risk of neurocognitive decline and help to counteract the effects of aging on the brain.

Summary of key actions and ingredients

Reduce inflammation/ neuro-inflammation

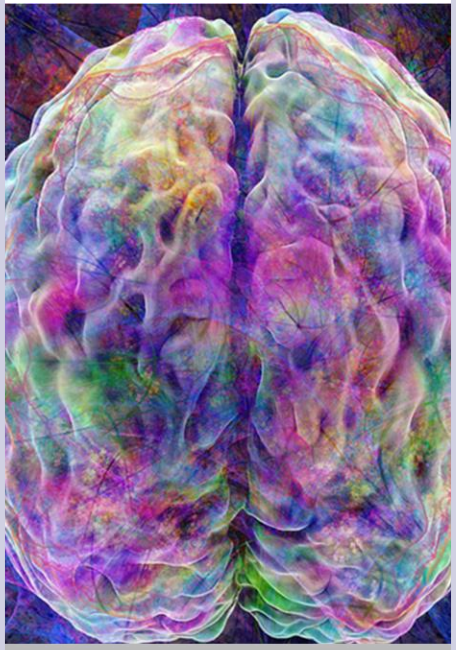
- Omega-3 fatty acids
- SPMs
- Cocoa
- Vitamin D
- Vitamin K2
- Magnesium
- Curcumin

Antioxidant

- Omega-3 fatty acids
- Cocoa
- Magnesium
- Curcumin
- Green tea

Support sleep

- Cocoa
- Phyto-melatonin
- Hops
- Lemon balm



Support brain health/BBB repair

- Omega-3 fatty acids
- Cocoa
- Vitamin D
- Magnesium
- Curcumin
- Green tea

Support cognitive health

- Omega-3 fatty acids
- Cocoa
- Magnesium
- Vitamin D
- Curcumin

Support cardiovascular health

- Omega-3 fatty acids
- SPMs
- Magnesium
- Vitamin D

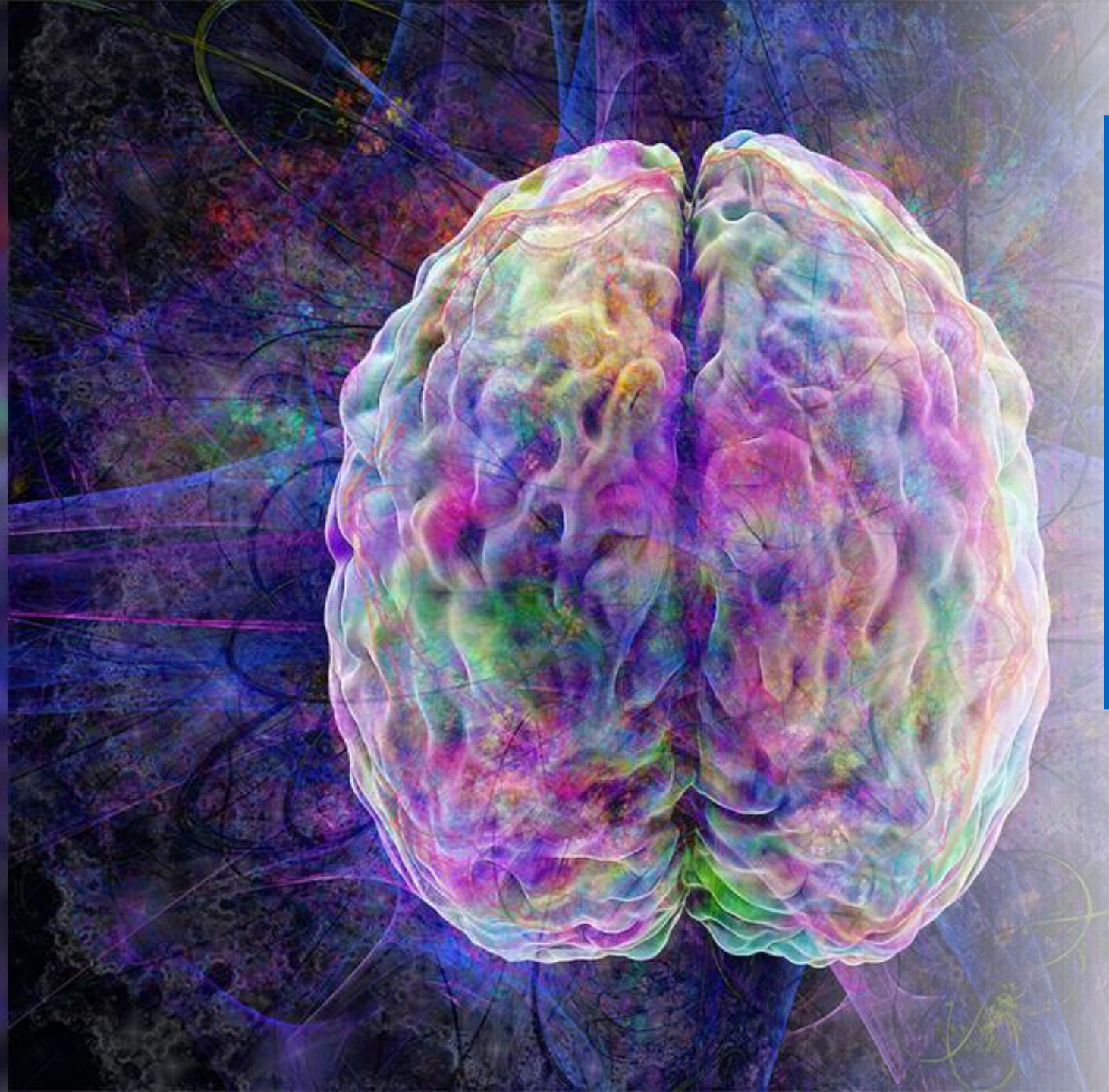
https://www.istockphoto.com/photo/overmind-brain-activity-colored-human-overbrain-model-view-top-3d-illustration-gm1251284579-365120652

Support brain health with lifestyle interventions

Interventions that can promote healthy brain aging

Support blood brain barrier integrity	**Support brain waste clearance**	**Reduce neuroinflammation and oxidative stress**	**Improve sleep duration and quality**	**Reduce cardiovascular risk**
Eat a healthy diet	**Avoid excessive alcohol consumption**	**Exercise regularly**	**Participate in cognitively stimulating activities**	**Manage emotional stress**

Murman et al 2015



Brain health and supporting patient care

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Brain health: key populations

- **Aging population.**
- **Those at higher risk of neurodegenerative decline.**
- **Preventative to support long term brain health and function.**
- Chronic inflammation or high risk of oxidative stress (adjunct).
- Chronic low-quality sleep or high stress (adjunct).
- Concomitant cardiovascular disease
- ‘Brain fog’ or needing cognitive support.
- Gut dysbiosis / compromised gut permeability (strong correlation).
- High exposure to environmental toxins including moulds (adjunct).

Patient support for brain health

- As we age, we have:
  - An increased number of health problems.
  - An increased number of pills and potions to take.
  - Increased cost associated with staying healthy.
  - Decreased resources to pay for health.

- The are several common contributing factors for brain and heart conditions – and with that, the opportunity to select supplements that support a shift in balance towards brain and heart health.

- Some of these ingredients also support other systems, such as bone health, metabolic health, mood, joint health and help inflammation and oxidative stress.

Multi-functional complementary ingredients include:

- Omega-3 fish oils
- SPMs
- Cocoa
- Vitamin D
- Vitamin K2
- Magnesium
- Curcumin
- Green tea

Patient support for inflammation / neuroinflammation

- Neuroinflammation has been identified as key contributing factor for BBB disruption and impaired glymphatic clearance.
- Vascular inflammation has been identified as a key contributing factor for heart disease, especially atherosclerosis.
- Peripheral inflammation exacerbates neuroinflammation and vascular inflammation.
- Inflammation and oxidative stress exacerbate each other.

Complementary ingredients shown to reduce neuroinflammation / inflammation include:

- Omega-3 fish oils
- SPMs
- Vitamin D
- Magnesium
- Curcumin

Patient support for sleep disturbances

- Our quality of sleep naturally declines with age.
- Women often experience poor sleep quality due to menopause.
- Sleep disturbances occur due to conditions like sleep apnoea or snoring, which increase with age (self or partner).
- Sleep disturbances can occur due to other age-related health conditions, including pain and inflammation.

Lifestyle interventions to support sleep are the first-line approach.

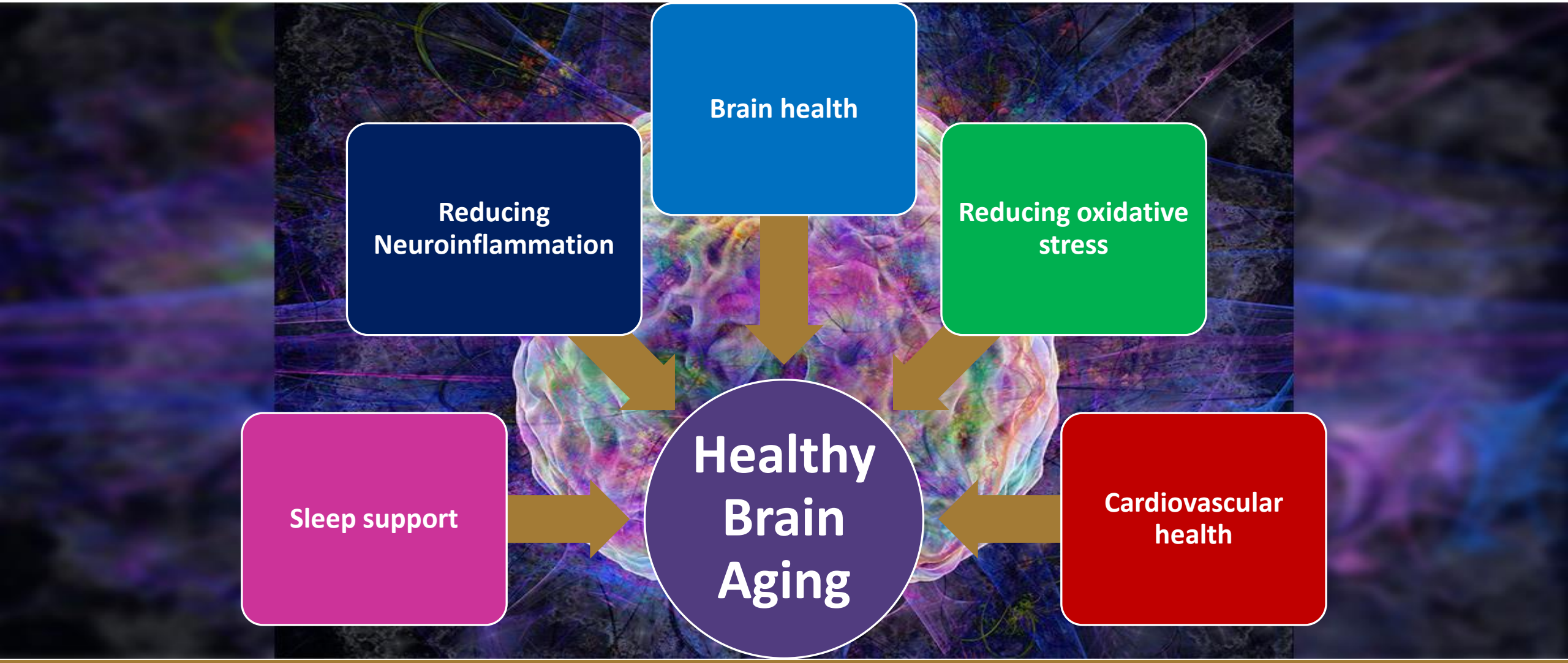
In addition, naturopathic support for sleep includes:

- Cocoa
- Phytomelatonin
- Hops
- Lemon balm

Potential problems

- Sleep is needed for neurological, cognitive and physical health.
- Brain waste clearance occurs at night. Chronic lack of sleep may affect ability to clear toxins and brain waste.
- Hypnotic drug therapies should be used with caution in the elderly – disorientation; dependence; increased risk of risk falls and fractures.

Healthy brain aging needs a multi-faceted approach



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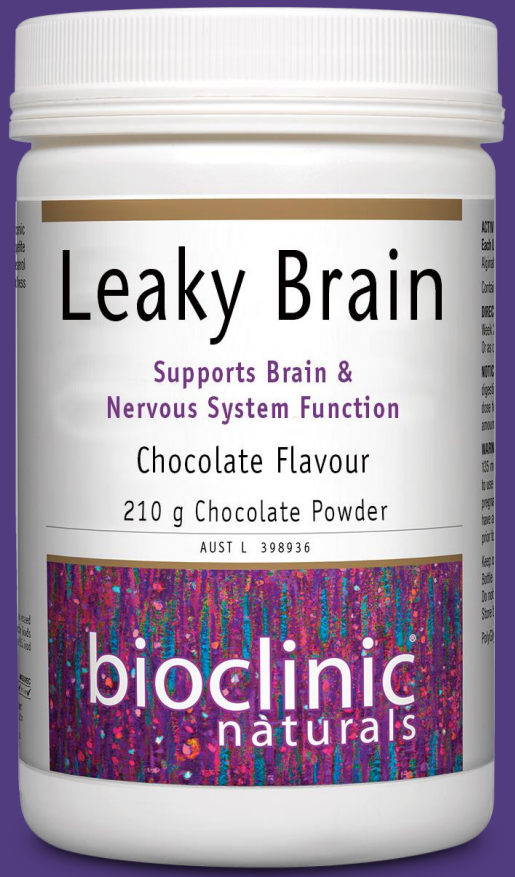

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Bioclinic Naturals Leaky Brain

Leaky Brain includes a unique blend of anti-inflammatory, antioxidant, brain, cognitive and gut supportive nutrients and herbs.

It has been formulated with ingredients that:

- Reduce the key underlying causes of BBB disruption.
- Support repair of BBB integrity.
- Help address the consequences of increased BBB permeability.

Chocolate flavoured powder. Vegetarian-friendly

Key actions

Support brain & nervous system

- Cocoa
- Magnesium
- Vitamin D
- Acetyl-L-carnitine
- Leucine
- Inositol
- B vitamins
- Holy basil
- Green tea
- Lavender

Support cognitive health

- Cocoa
- Green tea
- Acetyl-L-carnitine
- Vitamin D
- B vitamins

Reduce inflammation

- Cocoa
- Curcumin
- Holy basil
- Green tea
- Feverfew

Antioxidant

- Cocoa
- Curcumin
- Green tea
- Holy basil
- Acetyl-L-carnitine

Support GI health and beneficial flora

- Cocoa
- Curcumin
- Green tea
- Vitamin D
- B vitamins

Patients with chronic inflammation or neuro-inflammation.

Inflammation is a key contributing factor for BBB disruption.

Patients looking to support bone health, cardiovascular health

Secondary action to support brain health.

Patients with chronic sleep disturbances or dysregulated circadian rhythms.

Toxins and waste are cleared from the brain during deep sleep.

Chronic sleep disturbances may increase CV risk

Patients with conditions associated with inflammation including mild osteoarthritis.

Patients looking for occasional 'top-up' support for cognition and focus.

BBB disruption affects cognitive health.

Thank you

Please email any queries to

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