



A Sound Mind in a Sound Body: The Link between Diet and Cognition

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Objectives

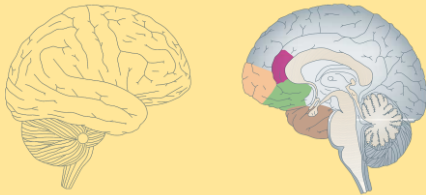
- Define neurogenesis and neuroplasticity
- Define and describe the role of BDNF in cognitive function and homeostasis
- Describe the roles of dietary components in influencing neuroplasticity
- Describe the role of gut bacteria and gut peptides in neuroplasticity
- Describe the similarities between diabetes, Alzheimer's disease and mental disorders
- Describe the role that epigenetics might play in the cognitive process
- State why dietitians must, and how they can leverage the scientific research on nutrition and cognitive function to get their patients to eat healthfully

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Hippocampus: Seat of learning and memory

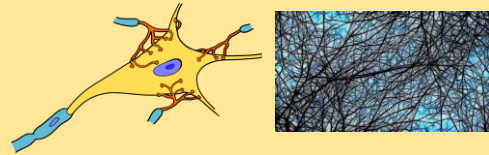


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What is neuroplasticity and neurogenesis?

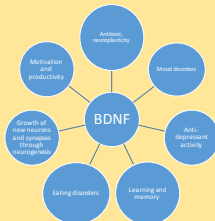


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BDNF : The Master Mind behind neuroplasticity!



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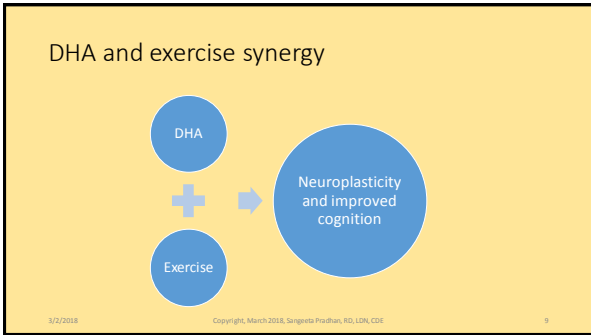
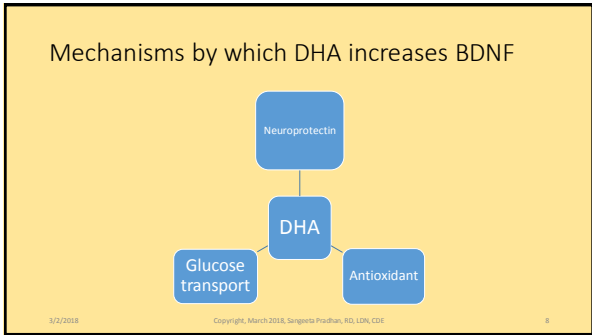
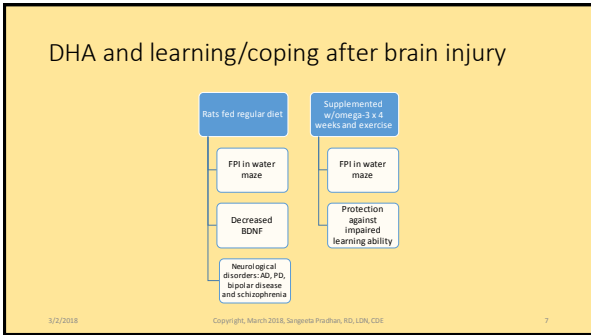
DHA and risk of Alzheimer's disease

- Prospective study 1993-2000
- Total 815 residents unaffected by AD initially
- Participants consuming fish 1x/week of more had 60% decreased chance of developing AD
- Strong correlation between DHA and decreased AD risk, but not EPA

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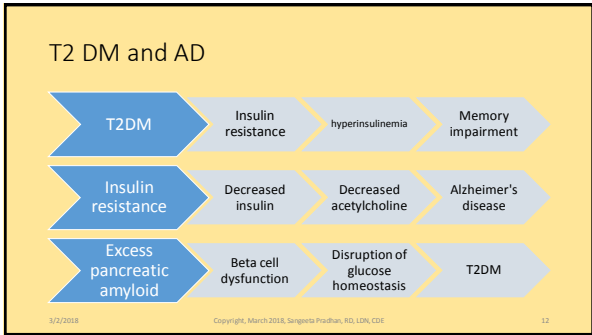
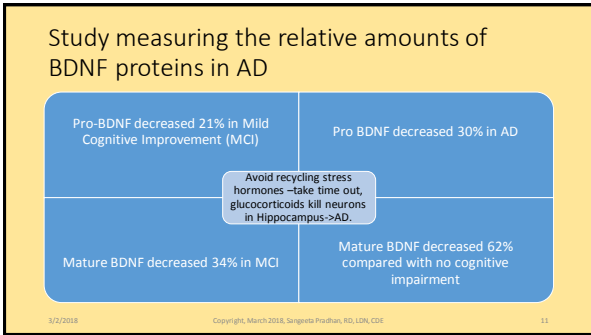
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Folate

- Study examined whether total intake (diet plus supplements) of antioxidant vitamins (E, C, carotenoids) and B vitamins (folate, B6, and B12) is associated with a reduced risk of AD.
- 579 nondemented elderly volunteers from the Baltimore Longitudinal Study of Aging. After a mean follow-up of 9.3 years, AD developed in 57 participants. Only total intake of folate at or above the RDA was associated with a significant decreased risk of AD. No association was found between total intake of vitamins C, carotenoids, or vitamin B12 and risk of AD.
- Additional studies are necessary to further investigate whether folate or other unmeasured factor(s) may be responsible for this reduction in risk.

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BDNF and hyperglycemia

- BDNF administration in rats
- Intracerebroventricular administration
- Hepatic glucose suppression
- Decreased glucagon
- Decreased glucose levels
- Independent of insulin and tissue glucose uptake

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High fat, high sugar

- HFS diet : direct effect → Decreased BDNF → Decreased Synapsin I
- HFS diet → Oxidative stress and inflammation → Decreased BDNF → Decreased neuroplasticity
- Antioxidants curcumin → Dramatic decrease in oxidative stress → Normalized BDNF, synapsin I → Curcumin counter acted cognitive dysfunction caused by TBI

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High saturated fat and BDNF

Vitamin E supplementati on of high fat diet → Reduced oxidative damage → Normalized levels of BDNF, synapsin I → Reversed HF induced impaired cognition

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BDNF and energy homeostasis?

- BDNF
 - Hippocampal
 - Neural plasticity
 - Neurogenesis, learning and memory
 - Hypothalamic
 - Inhibit food intake, energy metabolism
 - Obesity, eating disorders

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BDNF

- BDNF, an important mediator of synaptic plasticity; memory and learning
- Energy homeostasis
- Genetic deletion of the *Bdnf* gene in animals: hyperphagic and develop obesity
- Infusion of BDNF reduces body weight, normalizes glucose levels, increases insulin sensitivity

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Caloric restriction and intermittent fasting

- Rodent studies
- Calorie restriction
 - Decreased oxidative stress
 - Improved learning, water maze
 - Increased BDNF
 - Decreased cognitive deficits

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Aerobic exercise improves learning.

- Aerobic exercise
- In 27 subjects

Compared to anaerobic sprints or rest

Randomized cross over design

- Vocabulary learning 20% higher
- In the aerobic group

- Strongest increase in BDNF and catecholamines
- BDNF – short term learning success

Catecholamines correlated to long term learning success

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Flavonols and Exercise

Epicatechin upregulation of genes

+

Exercise

Retention of spatial memory in water maze

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polyphenols

- 7 week supplementation
- Blueberry rich diet

Young healthy animals

Animals were 2 months old

- Improved spatial learning performance
- Faster rate of learning

- Increased BDNF in hippocampus

Increase of BDNF in the dentate gyrus of blueberry fed animals

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Curcumin

Neurotrophic state

Synaptic

Free radical scavenger/antioxidant

The adverse effects with chronic DM2018 in beta cell dysfunction

HDAC inhibitor

Reduced beta amyloid hyperphosphorylation

Curcumin

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Curcumin: May combat oxidative damage and low BDNF levels in DM and obesity

Lipid peroxidation, protein oxidation and BDNF were measured

Curcumin

- Diabetic mice, 50mg/kg of curcumin x 8 weeks
- Obese humans, 500 and 750 mg x 12 weeks

Partial effects noted

- Restored BDNF levels
- Did not decrease oxidative damage in HC and FC of mice
- Decreased oxidative damage, but did not restore BDNF

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Mediterranean diet and BDNF, depression

Mediterranean diet

- (1) Predimed randomized trial, n=243, control (low fat), Med + evoo, Med + nuts
- (2) Chicago Health and Aging Project, n= 3502

- Non significant increases in BDNF in both test groups
- Significant increase in BDNF in Med + nuts diet in folks with depression
- 98.6% lower rate of depressive symptoms

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BDNF and learning: Learning deficit in BDNF mutant mice.

```

    graph LR
      A[BDNF mutant mice] --> B[Aged mice]
      B --> C[Decreased BDNF]
      B --> D[Impaired learning]
    
```

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BDNF and learning: Learning deficit in BDNF mutant mice

```

    graph LR
      A[Mutation in BDNF receptor] --> B[Hyperphagic obesity]
      A --> C[Impaired learning]
    
```

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Insulin and ghrelin: peripheral hormones modulating memory and hippocampal function.

Insulin	Ghrelin
Receptors in hippocampus	Receptors in hippocampus
Hippocampal memory	Hippocampal memory
Synaptic plasticity	Anxiety

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Leptin, ghrelin and GLP1

- Leptin receptors in brain areas, the hypothalamus, the cerebral cortex and the hippocampus.
- Dysfunctional leptin receptors and impairment in LTP, spatial learning
- Hippocampal plasticity
- Peripheral administration of ghrelin increases food intake in normal rodents and humans whereas chronic administration: adiposity
- Ghrelin: LTP? enhanced spatial learning and memory formation.
- GLP1:
 - pancreatic insulin secretion and subsequent glucose uptake by muscle cells,
 - suppressing food intake through actions on the hypothalamus.
 - spatial memory

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BDNF and eating disorders

```

    graph TD
      A[Leptin] --> D((Anorexigenic effect via BDNF - low levels: eating disorders))
      B[Insulin] --> D
      C[Pancreatic polypeptide] --> D
    
```

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? Link between disruption in energy homeostasis and mental disease

Abnormal metabolism (T2DM, metabolic syndrome)	<ul style="list-style-type: none"> • Psychiatric disorders, Depression • Role for MNT
Difficult to establish cause-effect	<ul style="list-style-type: none"> • Poor quality of life • Anti-psychotic medications

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Metabolic dysfunction, oxidative stress and synaptic dysfunction

Common feature of neurodegenerative disorders

Reactive oxygen species

Metabolic dysfunction, subsequent synaptic dysfunction

Oxidative damage

Chronic inflammation

Membrane damage

High ROS

High content of ROS, high O2 consumption makes the brain vulnerable

Free radicals w/ double bonds = peroxide, aldehydes and chronic inflammation

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Epigenetics

- Epigenetics is essentially additional information layered on top of the sequence of letters (A, C, G, and T, nucleotide bases in DNA) that makes up DNA.
- DNA sequence is the text, epigenetics is a pack of highlighters
- Different types of epigenetic marks
- Methyl groups: associated with inactivation.

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Short chain fatty acids (SCFA) from gut bacteria, and gene expression

HATs: Transfer of acetyl group to histone residues
Neutralizes + charge
Decreases bond w/DNA

HDACs

- Loosens chromatin
- Increased access for gene transcription

Removal of acetyl groups
Transcription repressed

Altered host genome in liver, muscle and brain

- Allows transcriptions
- SCFA: Butyrate is an HDAC inhibitor

HDAC inhibitors

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Altered histone acetylation is associated with age-dependent memory impairment in mice.

HATs and HDAC inhibitors

Aged mice : deregulation of histone acetylation

Failure to express gene associated with memory

Restoration of HAT

Bacterial butyrate acts as a HDAC inhibitor

Recovery of cognition

Reinstates learning induced gene

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Butyrate and histone acetylation

Histone: spool around which DNA winds

Histone acetylation

Gene transcribed or repressed

HDAC: removal of an acetyl group

Gene silenced

Neurodegenerative disorders

HDAC inhibitors increase histone acetylation

Expression of pro-regenerative genes, allows gene transcription again

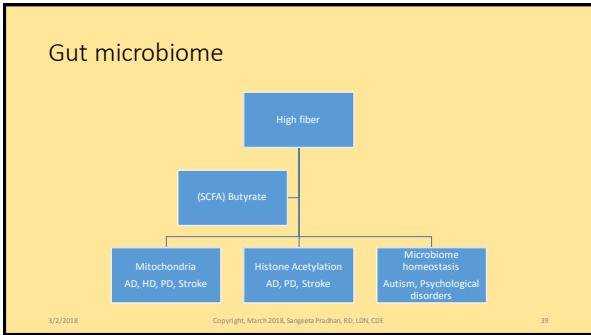
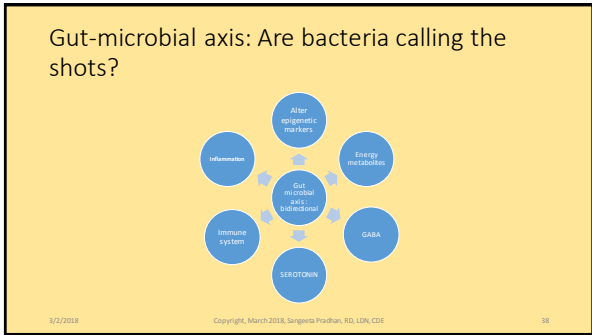
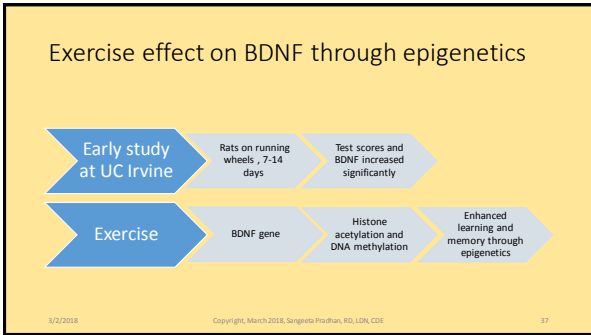
Bacterial butyrate (derived from fiber) is an HDAC inhibitor

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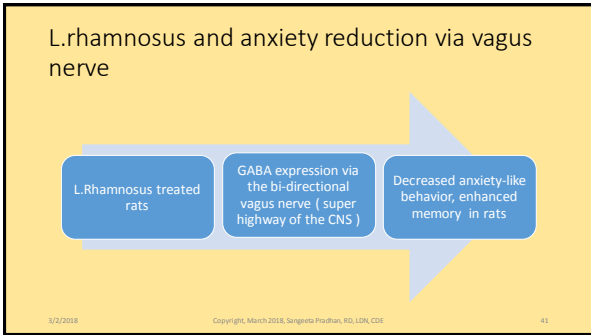
BDNF: Miracle Grow for the brain!

- The King of all nerve growth factors
- Evolution's greatest gift: you increase it just by using your brain!!
 - Be a life long leaner!
 - Antitoxic and antidepressant
- Intelligence and memory
- Lessens AD risk
- Improves scores at any age
- Improves mood, motivation and energy
- Exercise has one of the most potent impacts: 10,000 steps per day

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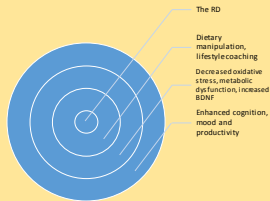


- ### Fiber and butyrate
- Bacteria produce butyrate as an end point in the gut lumen
 - Fermentation intermediates: lactate, succinate or formate, which are used by the bacteria themselves to proliferate and survive
 - Primary energy source of colonocytes, mutually beneficial relationship.
 - High fiber foods: resistant starches and fructo-oligosaccharides (FOS)
 - Butyrate production in rats fed 2 weeks of a high FOS diet and starch free wheat bran
 - Different strokes for different folks: Butyrate level depends upon type of fiber
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- ### Mind-Altering take-aways
- Healthy weight (Note relation between metabolic dysfunction and mental health)
 - Mediterranean style diet
 - Antioxidant rich fruits veggies, fatty fish, whole grains, limited sugars and unhealthy fats
 - DHA
 - Probiotics
 - Ace card: Exercise
 - Become a Life long learner
 - Reduce stress/cortisol levels: Mindfulness and meditation
 - Tap into the power of neuroplasticity and epigenetics
 - Remind your patients that cognitive function can be largely influenced by *modifiable* risk factors
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The RD: Ripple effects from what we can do!



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Appendix A: Glossary of terms and abbreviations

- AD: Alzheimer's disease
- BDNF: Brain derived neurotrophic factor
- FPI: Fluid percussion injury
- HC: Hippocampus
- HD: Huntington's disease
- PD: Parkinson's disease
- TBI: Traumatic brain injury
- GABA: is an inhibitory neurotransmitter, which means that it weakens or slows down signals and reduces anxiety
- HATs: Histone Acetyl Transferases transfer acetyl groups to highly conserved N-terminal L-lysine residues, thereby loosening the chromatin structure and allowing gene transcription
- (HDACs): Histone deacetylases remove acetyl groups and repress gene transcription
- Histone: They are the chief protein components of chromatin, acting as spools around which DNA winds, playing a role in gene regulation.

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Appendix B: Glossary of terms and abbreviations :

- Acetylcholine: Acetylcholine is a neurotransmitter—a chemical released by nerve cells to send signals to other cells. Low insulin levels and low insulin sensitivity can contribute to a decrease in acetylcholine synthesis, leading to AD.
- Adipogenesis: The process of cell differentiation by which pre-adipocytes become adipocytes
- Beta-amyloid: Peptides that are the main components of the plaques found in the brain of patients with AD
- Dentate gyrus: The dentate gyrus is part of the hippocampus and is thought to contribute to the formation of new episodic memories
- Epigenetics literally means "above" or "on top of" genetics. It refers to external modifications to DNA that turn genes "on" or "off." These modifications do not change the DNA sequence, but instead, they affect how cells "read" genes
- Neuroprotectin: A DHA derived mediator that protects the brain against oxidative stress
- Synapses: A family of proteins that have been known to regulate neurotransmitter release at synapses
- Synapse: is a junction between neurons, consisting of a minute gap across which impulses pass by diffusion of a neurotransmitter
- SCFA: Short chain fatty acids produced by bacterial fermentation such as butyrate

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