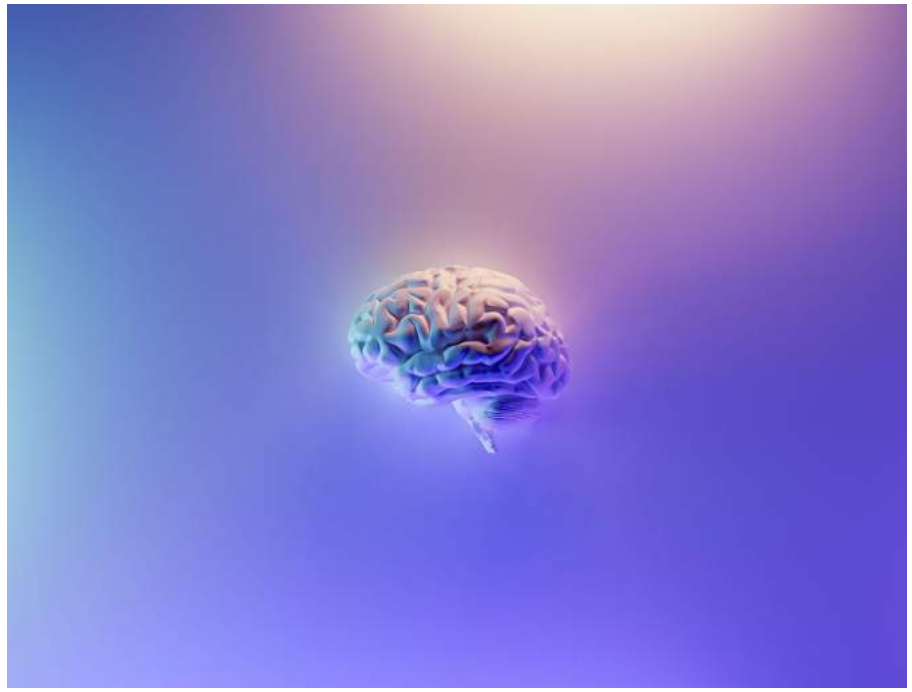

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Regulating the Stressed Brain with Integrative Nutrition and Lifestyle Modification

Dr. Jonathan Prousky, ND, MSc, MA, RP

Photo by Donald Giannatti on Unsplash

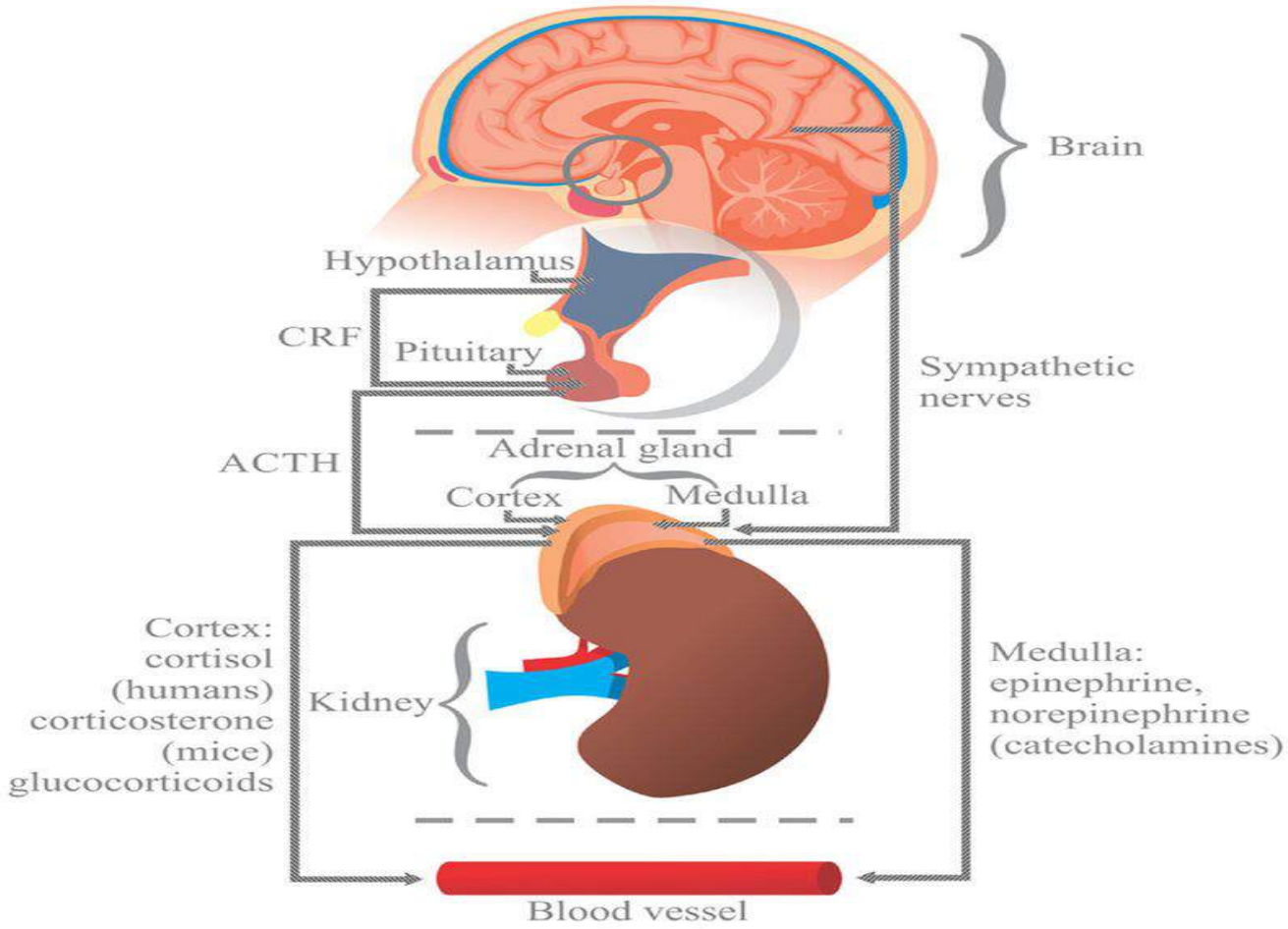
Chronic Stress[4,5]

Stress-Vulnerability (Diathesis)

- When a person reaches their “breaking point” - this is the point at which they usually seek out assistance from a healthcare professional.
- This model was described decades ago in the context of schizophrenia and relapse.[1]

Concepts of allostasis, homeostasis, allostatic load, and allostatic overload

- ***Allostasis***.[2]
- Synchronous though non-linear activation of many different physiological processes.[3]
- Allostasis is initiated by the brain.
- Not the same as ***homeostasis***.



From: https://en.wikipedia.org/wiki/Stress_(biology)

For a description of the 4 types of allostatic responses see: McEwen[9]

Concepts of allostasis, homeostasis, allostatic load, and allostatic overload

- Allostatic load (AL), and allostatic overload (AO).[3,6,7]
- Psychological distress signals of AL and AO[8]

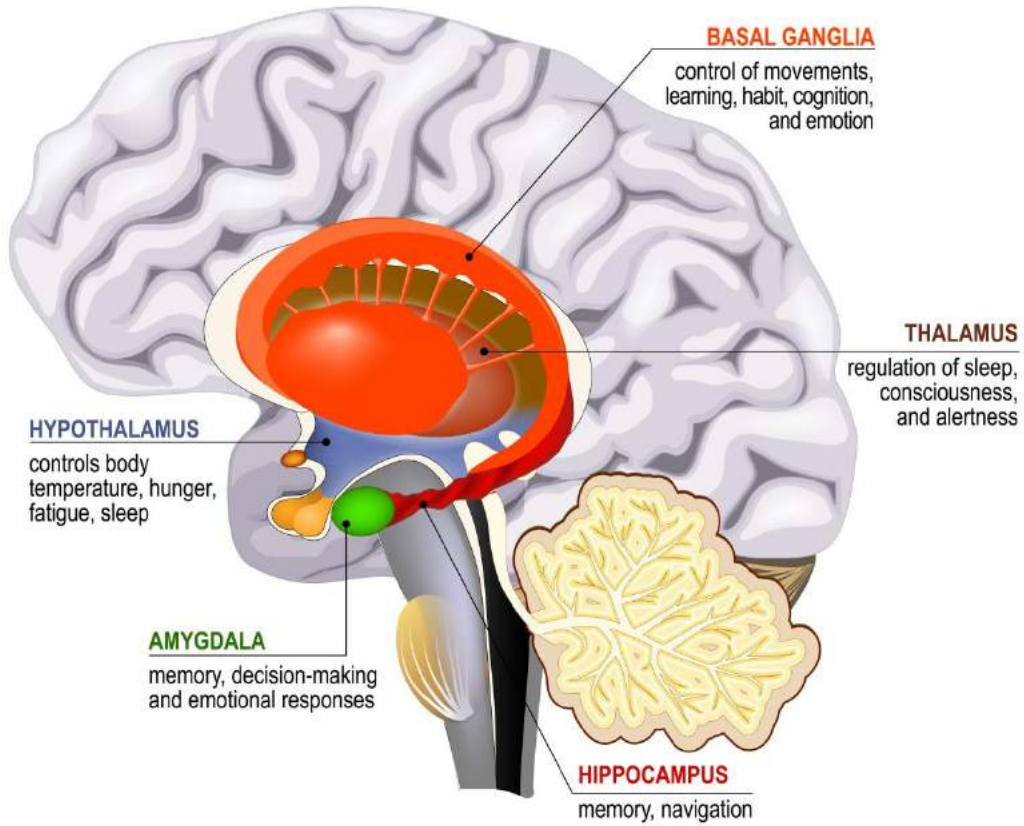
Specific brain regions and their associated stress-response mechanisms in general terms

- ***Hippocampus***, ***amygdala***, and ***prefrontal cortex*** (PFC) - have all been implicated in chronic stress and AL.

Specific brain regions and their associated stress-response mechanisms in general terms

- When something is deemed chronically stressful by context-driven emotional experience - i.e., when there was an initial strong reaction by the amygdala - the hippocampus undergoes specific neuroplastic changes that result in diminished coupling with the PFC.
- This results in increased stress-vulnerability to life experiences and consequently less top-down control.[13]

Limbic system



Specific brain regions and their associated stress-response mechanisms in general terms

- Top-down mechanisms.[10,11]
- Bottom-up mechanisms.[10,11]
- "...hostile takeover of consciousness by emotion" (p.226).[12]


AMYGDALA
CORTEX
HIPPOCAMPUS

Chronic stress, atrophy, and damage to specific brain structures

- ***Glucocorticoid cascade hypothesis (GCH)***.[3,7]
- Glucocorticoids potentiate the release of damaging extracellular levels of excitotoxic amino acids (EAA) under stress.[15]
- Glial cell depletion (or alterations) implicated in atrophy of brain regions like the hippocampus, amygdala and PFC.[15]
- These particular brain areas become targets of chronic stress and suggests that a ***common mechanism***.[15]

Chronic stress, atrophy, and damage to specific brain structures

- Glucose availability within the brain plays a role in mediating resilience or damage.[15,16]
- Lack of available glucose within the brain has even been proposed as a ***limiting factor in an individual's free will***.[17]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Social isolation, loneliness[31,32]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Social isolation, loneliness[31,32]

Personality factors[33-34]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Social isolation, loneliness[31,32]

Personality factors[33-34]

Employment/work[35]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Social isolation, loneliness[31,32]

Personality factors[33-34]

Employment/work[35]

Caregiving[36]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Social isolation, loneliness[31,32]

Personality factors[33-34]

Employment/work[35]

Caregiving[36]

Medical disease[37-39]

Biopsychosocial pressures or stressors

Chronic Stress

Prenatal and postnatal early life experiences[7,11,18,19]

Adverse childhood experiences[20-30]

Social isolation, loneliness[31,32]

Personality factors[33-34]

Employment/work[35]

Caregiving[36]

Medical disease[37-39]

Psychiatric illness[38,40-46]

Integrative Nutrition and Lifestyle Modification

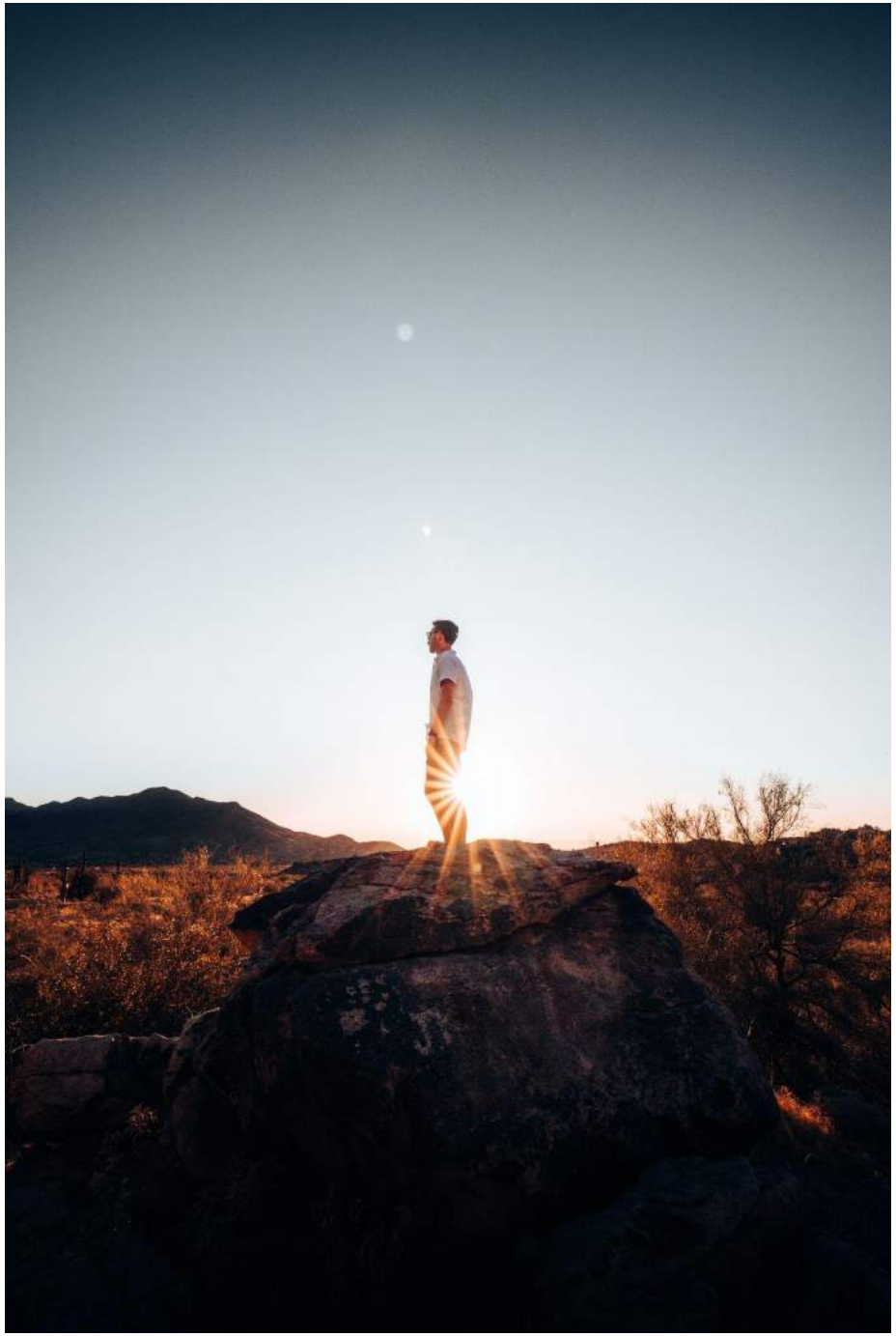
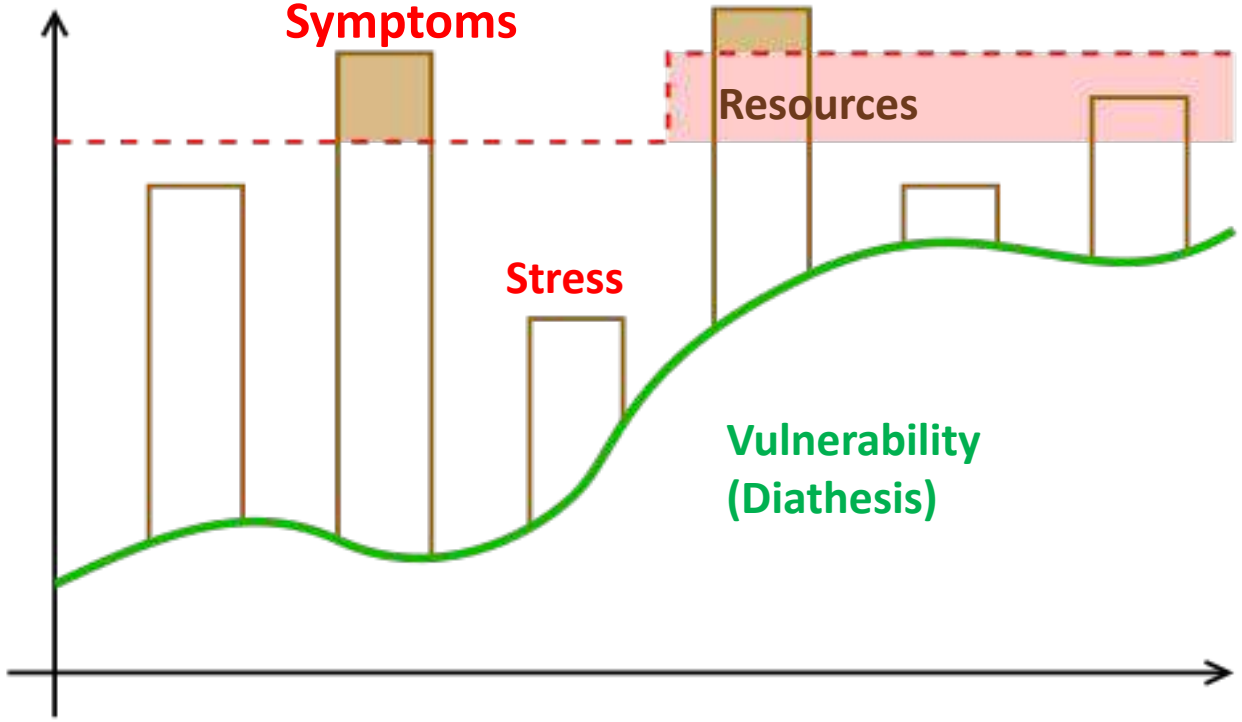


Photo by Johanser Martinez on Unsplash



From:
https://en.wikipedia.org/wiki/Diathesis%E2%80%93stress_model

Integrative nutrition and lifestyle modification

B-complex vitamins+ (BCV+), Broad-spectrum mineral/vitamin formula (BSMV), and/or specific micronutrients

Stress and micronutrients

Photo by Adam Nieścioruk on Unsplash

- Stress can adversely impact micronutrient concentrations, leading to micronutrient depletion.[47]
  - Redistribution of micronutrients from tissues/organs to blood, or vice versa, due to increased metabolic demands.
  - Increased oxidative stress and inflammation may be associated with increased micronutrient utilization.
  - Increased micronutrient excretion (e.g., urine and sweat) may result in reduced bodily micronutrient stores.
  - Increased cortisol output via its impact on aldosterone may result in changes to the urinary excretion of electrolytes and minerals, and impact micronutrient status.
  - Appetite changes (i.e., reduced intake) could adversely impact micronutrient status.

Stress and micronutrients

Photo by Michał Parzuchowski on Unsplash

- Triage theory:[48] When a moderate shortage of vitamins and minerals (V/M) exists, the body will conserve the "V/M-dependent proteins/enzymes that are essential for survival and reproduction." As a result, the proteins/enzymes that are required to ensure long-term health are essentially rendered insufficient, which results in vulnerability toward disease, and likely vulnerability towards stress-related problems and brain dysfunction.

BCV+

- **The effects of an oral multivitamin combination with calcium, magnesium, and zinc on psychological well-being in healthy young male volunteers: a double-blind placebo-controlled trial**.[49]
  - 80 male volunteers given BCV+ (i.e., with 500 mg vitamin C, 100 mg calcium, 100 mg magnesium, and 10 mg zinc), or placebo.
  - The trial lasted 28 days.
  - In the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), there were statistically significant improvements (i.e., reduced from a mean of 5.2 to 4.1 on day 28 in the BCV+ group compared to 6.2 to 6.4 on day 28 in the placebo group).

BCV+

- **A double-blind, placebo-controlled, double-centre study of the effects of an oral multivitamin-mineral combination on stress**.[50]
  - The adult participants were included if they had high stress based on the study evaluations.
  - Group 1 (n=151) consisted of participants taking BCV+ (i.e., b-complex vitamins with 500 mg vitamin C, 100 mg calcium, 100 mg magnesium, and 10 mg zinc).
  - Group 2 (n=149) consisted of participants taking a matching placebo.
  - Both groups were evaluated at baseline and at day 30.
  - On all the measures used in the study, all showed that the BCV+ group (i.e., Group 1) had statistically significant results compared to the placebo group (i.e., Group 2) in terms of the pre- and post-assessments.

BCV+

- **A double-blind, placebo-controlled, double-centre study of the effects of an oral multivitamin-mineral combination on stress.**[50]
  - The measures included the Berocca Stress Index (BSI), Hamilton Anxiety Rating Scale (HARS), Visual Analog Scale (VAS), and Psychological Well-Being Scale (PGWA).
  - The between-group comparisons showed greater improvements among the participants in Group 1.
  - BSI - Group 1 (37.79%) and Group 2 (30.70%).
  - HARS - Group 1 (41.76%), and Group 2 (31.55%).
  - VAS - Group 1 (28.55%), and Group 2 (20.43%).
  - PGWS - Group 1 (27.16%), and Group 2 (17.81%).

BCV+

- **A double-blind, placebo-controlled, double-centre study of the effects of an oral multivitamin-mineral combination on stress**.[50]
  - "Given the interrelationship between stress and micronutrient requirements, restoration and maintenance of a normal micronutrient balance can help to avoid the deleterious physiological and psychological manifestations of excessive long-term stress."

BCV+

- **Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males.**[51]
  - The adult participants healthy males in full-time employment.
  - The BCV+ group (n=103; b-complex vitamins with 500 mg vitamin C, 100 mg calcium, 100 mg magnesium, and 10 mg zinc), or placebo (n=107).
  - The RCT last 33 days.

BCV+

- **Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males.**[51]
  - In terms or pre-treatment to post-treatment, the statistically significant results are shown below.
    - General Health Questionnaire-12 (GHQ-12): BCV+ (9.99 to 8.30) and placebo (9.86 to 9.14)
    - Profile of Mood States (POMS - vigour): BCV+ (24.0 to 26.3) and placebo (24.7 to 25.2)
    - Perceived Stress Scale (PSS): BCV+ (14.2 to 12.5) and placebo (13.0 to 12.9)

BCV+

- **Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males.**[51]
  - "Overall, these results suggest that improving nutritional status, by supplementation if necessary, may be beneficial to males within the general population as a whole."

BCV+

- **The effect of 90 day administration of a high dose vitamin B-complex on work stress.**[52]
  - 60 participants (19 men and 41 women) completed the 12 week trial.
  - Three groups were assessed - BCV+ (n=20), BCV+ sustained-release (n=22), and placebo (n=18).
  - Each capsule of the BCV+ (including the sustained-release form) consisted of b-complex vitamins plus vitamin E (50 IU), magnesium phosphate (140 mg), calcium phosphate (100 mg), potassium phosphate monobasic (117.3 mg), avena sativa (250 mg), passiflora incarnata (100 mg), lecithin (50 mg), choline bitartrate (25 mg) and inositol (25 mg). The participants took 2 capsules daily or placebo.

BCV+

- **The effect of 90 day administration of a high dose vitamin B-complex on work stress.**[52]
  - The data in this study supports changes in personal strain and depressed/dejected mood from BCV+.

BCV+

- **The effect of 90 day administration of a high dose vitamin B-complex on work stress.**[52]
  - Occupational Stress Inventory - Revised (OSI-R): psychological strain, i.e., BCV+ (including the sustained-release form) baseline (95.18) and 12 weeks (85.93), and placebo baseline (88.39) and 12 weeks (86.61)
  - POMS: depression-dejection, i.e.,BCV+ (including sustained-release form) baseline (11.41) and 12 weeks (8.85), and placebo (8.67) and 12 weeks (10.50).

BCV+

- **The effect of 90 day administration of a high dose vitamin B-complex on work stress.**[52]
  - "The results of this study are suggestive of significant decreases in the experience of workplace stress after 90-day supplementation of a B complex vitamin."

BCV

- **The Effect of Methylated Vitamin B Complex on Depressive and Anxiety Symptoms and Quality of Life in Adults with Depression**.[53]
  - 60 adults were randomly assigned - i.e., BCV (n=30) group and the placebo (n=30) group.
  - The participants were diagnosed with major depressive disorder (MDD) or a related depressive disorder.
  - The study duration was 60 days.
  - The BCV was a whole nutrient natural source extract from probiotic colonies and contained vitamins B1, B2, B3, B5, B6, and B12, and folate, PABA, biotin, inositol, puri□ed water, and certified organic alcohol.
  - Participants consumed 1 vial (i.e., equivalent to ½ teaspoon) of the BCV (or an identical looking placebo liquid) in at least 12 ounces of water over the course of each day.

BCV

- **The Effect of Methylated Vitamin B Complex on Depressive and Anxiety Symptoms and Quality of Life in Adults with Depression**.[53]
  - The results showed meaningful benefits on the mental health scale from the Medical Outcomes Study Short Form 36 (SF-36). On the other hand, the Beck Depression Inventory (BDI) results were not clinically meaningful.
  - The mental health scale of the SF-36: BCV baseline (46.7) and 60 days (61.6), and placebo baseline (57.1) and 60 days (62.2).
  - The BDI: The baseline and 60 day BDI results were not provided. For the BCV group, the BDI significantly decreased from baseline to 60 days (mean difference = 7.5), and the placebo group, the BDI significantly decreased from baseline to 60 days (mean difference = 7.9).

BCV

- **The Effect of Methylated Vitamin B Complex on Depressive and Anxiety Symptoms and Quality of Life in Adults with Depression.**[53]
  - BCV "...offers utility for improving the overall mental health quality of life of adults with MDD or another depressive disorder with no side effects."

Micronutrient Comparison Study

- **Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses.**[54]
  - All 91 participants experienced an earthquake and had heightened anxiety or stress for 2-3 months post-earthquake.
  - The RCT duration was 4 weeks (28 days).
  - 30 participants were assigned the BCV+ at 1 capsule/day (i.e., providing b-complex vitamins with 500 mg vitamin C, 100 mg calcium, 100 mg magnesium, and 10 mg zinc).
  - 31 participants were assigned to the BSMV at 4 capsules/day.
  - 30 participants were assigned to the BSMV at 8 capsules/day.
  - 25 participants served as nonrandomized controls.

Micronutrient Comparison Study

- **Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses.**[54]
  - With respect to changes from baseline to 4 weeks, the BSMV group (4 capsules/day) had the more notable clinical benefits on the various clinical rating scales than the other groups despite what was noted in the paper (will address later).
  - In terms of subjective improvements (i.e., self-rated changes), participants taking the higher dose of BSMV (8 capsules/day) subjectively reported significantly greater improvement in mood, anxiety, and energy over the 4 weeks as compared with those taking BCV+ (1 capsule/day). For example, at 4 weeks, 52% of those taking BSMV (8 capsules/day) reported their anxiety levels as “much” to “very much” improved since baseline compared to only 17% of those taking the BCV+.

Percent of participants with at least a 50% reduction in outcomes compared to nonrandomized controls[54]

	BCV+ (1 capsule/day); n=30	BSMV (4 capsules/day); n=31	BSMV (8 capsules/day); n=30	Nonrandomized controls; n=25
Depression and Anxiety Stress Scale (DASS)				
Depression	50%	**61%**	43%	36%
Anxiety	47%	**74%**	57%	28%
Stress	43%	**58%**	50%	20%
Total	43%	**74%**	60%	20%
Impact of Event Scale-Revised (IES-R)				
Avoid	47%	**61%**	43%	8%
Intrusion	37%	45%	**47%**	24%
Arousal	37%	**45%**	43%	16%
Total	37%	48%	**53%**	12%
Perceived Stress Scale (PSS)	17%	**29%**	20%	8%

Percent change of the three treatments from baseline[54]

	BCV+ (1 capsule/day); n=30	BSMV (4 capsules/day); n=31	BSMV (8 capsules/day); n=30
Depression and Anxiety Stress Scale (DASS)			
Depression	-51%	**-52%**	-44%
Anxiety	-51%	**-69%**	-58%
Stress	-41%	**-55%**	-49%
Total	-47%	**-57%**	-50%
Impact of Event Scale-Revised (IES-R)			
Avoid	-49%	**-60%**	-51%
Intrusion	-31%	-40%	**-42%**
Arousal	-33%	**-49%**	-43%
Total	-37%	**-49%**	-45%
Perceived Stress Scale (PSS)	-21%	**-34%**	-27%

Micronutrient Comparison Study

- **Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses.**[54]
  - "This study is consistent with a growing body of literature supporting nutrients as important for improving psychological functioning."

Micronutrient Comparison Study

- **A randomised trial of nutrient supplements to minimise psychological stress after a natural disaster.**[55]
  - RCT involving three groups.
  - Vitamin D3 group (n=17) at 1000 IU/day.
  - BCV group (n=21) at 1 capsule/day.
  - BSMV group (n=18) at 4 capsules/day.
  - Followed for 6 weeks.

Percent change compared to baseline[55]

	Vitamin D3 (1000 IU/day); n=17	BCV (1 capsule/day); n=21	BSMV (4 capsules/day); n=18
Depression and Anxiety Stress Scale (DASS)			
Depression	-24%	-52%	**-53%**
Anxiety	-20%	-61%	**-70%**
Stress	-27%	-54%	**-59%**
Total	-24%	-55%	**-59%**
Impact of Event Scale-Revised (IES-R)			
Avoid	-33%	**-42%**	-33%
Intrusion	-22%	-41%	**-43%**
Arousal	-24%	-43%	**-46%**
Total	-27%	**-43%**	-40%

Micronutrient Comparison Study

- **A randomised trial of nutrient supplements to minimise psychological stress after a natural disaster.**[55]
  - "The findings reported here are also consistent with other studies showing that nutrient treatment with B-Complex or broad-spectrum formulas has a positive impact on mental health."

Specific Micronutrients

- Antidepressants:
  - Increase the availability of serotonin and other monoamines between the synapses of neurons.[56]
  - Increase BDNF expression, and may help to compensate for the altered levels of BDNF in specific brain areas .[57]
  - Reverse this core psychological process, known as ***negative affective bias***, by increasing the processing of positive affective information.[56]
  - Function as glutamatergic modulators, which attenuates excitotoxic damage.[58]

Specific micronutrients that putatively possess therapeutic effects similar to antidepressant medication		
Treatment	***Suggested Daily Dose***	***References***
5-Hydroxytryptophan (timed- or sustained-release formulations)	400-1200 mg	59,60
Acetyl-L-carnitine	1000-4000 mg	61,62
S-Adenosylmethionine	1600-3200 mg	63, 64
L-Theanine	250 mg at bedtime	65

Specific Micronutrients

- Benzodiazepines target the benzodiazepine-binding site in the brain located on the chloride channel.
  - Boost the effects of gamma-aminobutyric acid (GABA) on the frequency of the opening of the chloride channel.[66]
  - Modulate the activity of the HPA axis by mitigating the effects of CRH,[67] and reduce the limbic response to anxiety.[68]

Specific micronutrients that putatively possess therapeutic effects similar to benzodiazepine medication		
Treatment	***Suggested Daily Dose***	***References***
Niacinamide/Nicotinamide (i.e., amide form of vitamin B3)	500-2500 mg	69,70
Theanine	200-400 mg	71-73

Integrative nutrition and lifestyle modification

B-complex vitamins+ (BCV+), Broad-spectrum mineral/vitamin formula (BSMV), and/or specific micronutrients

Breathing

Breathing

- **Neural correlates of mindfulness meditation-related anxiety relief.**[74]
  - "...is premised on stabilizing attention, acknowledging discursive sensory events as 'momentary' and 'releasing' them without affective reaction."
  - Just 4 sessions of mindfulness meditation (i.e., 20 minutes/session) over 4 consecutive days modulated areas of the brain responsible for state anxiety. The changes in the PFC were presumably reflective of changes in cognitive reappraisal processes, and in down-regulating negative emotions, such as amygdala activity.

Breathing

- **The Effectiveness of Diaphragmatic Breathing Relaxation Training for Reducing Anxiety.**[75]
  - Patients randomized to diaphragmatic breathing (DBR) experienced clinically meaningful reductions in their Beck Anxiety Inventory (BAI) scores, heart rate, and breathing rate.
  - All participants participated in an 8-week course on DBR.
  - The experimental group did DBR twice daily at home (i.e., at least 10 DBR exercises/session), and kept a diary.

The Effectiveness of Diaphragmatic Breathing Relaxation Training for Reducing Anxiety[75]	
Experimental Group (N=15; from baseline to 8 weeks)	**Control Group (N=15; from baseline to 8 weeks)**
BAI Score: 19.13 ± 7.52 to 5.33 ± 4.52	BAI: 19.87 ± 10.75 to 18.20 ± 9.87
Heart Rate (number/minutes): 85.52 ± 8.02 to 76.97 ± 7.14	Heart Rate (number/minutes): 82.82 ± 5.50 to 83.63 ± 6.17
Breath Rate (number/minute): 16.24 ± 2.27 to 12.59 ± 2.40	Breath Rate (number/minute): 16.04 ± 1.43 to 16.16 ± 1.81

Integrative nutrition and lifestyle modification

B-complex vitamins+ (BCV+), Broad-spectrum mineral/vitamin formula (BSMV), and/or specific micronutrients

Breathing

Exercise

Exercise[76]

- Is an often neglected as part of regular mental health care.
  - Improvements mediated by the communication with the HPA axis and brain regions, such as the limbic system, amygdala, and hippocampus.
  - Provides a healthy distraction; reduces anxiety, depression, and negative mood; increases self-efficacy and self-esteem; augments cognitive function and mental alertness; provides stress relief; reduces tiredness; and assists with social interaction.
  - Thirty minutes of moderate intensity exercise, such as brisk (power) walking for 3 days/week is sufficient for these health benefits. The 30 minutes do not need to be continuous.

Exercise[77]

- The biological factors associated with the improvements from regular exercise include increased levels of monoamine neurotransmitters, beta-endorphins, opioids, endocannabinoids, neurotrophic factors, and even specific (yet helpful) pro-inflammatory processes.
    - Other benefits from exercise include: Transient hypofrontality; flow, and self-efficacy.
    - Different types of exercise have been studied (e.g., yoga, walking, weight-lifting, and running), and all of them produce benefits when they are done consistently, and for adequate durations of time (i.e., at least 90 minutes each week).
    - Exercise that is of moderate to high-intensity has been shown to produce greater therapeutic effects at attenuating psychiatric symptoms.

Exercise[78]

- 6 months of regular aerobic exercise was shown to increase the size of the anterior hippocampus, resulting in spatial memory improvements.
- Exercise increased hippocampal volume by 2%, which reversed age-related loss in volume by 1-2 years.
- The increased hippocampal volume was also associated with increased serum levels of brain-derived neurotrophic factor (BDNF).

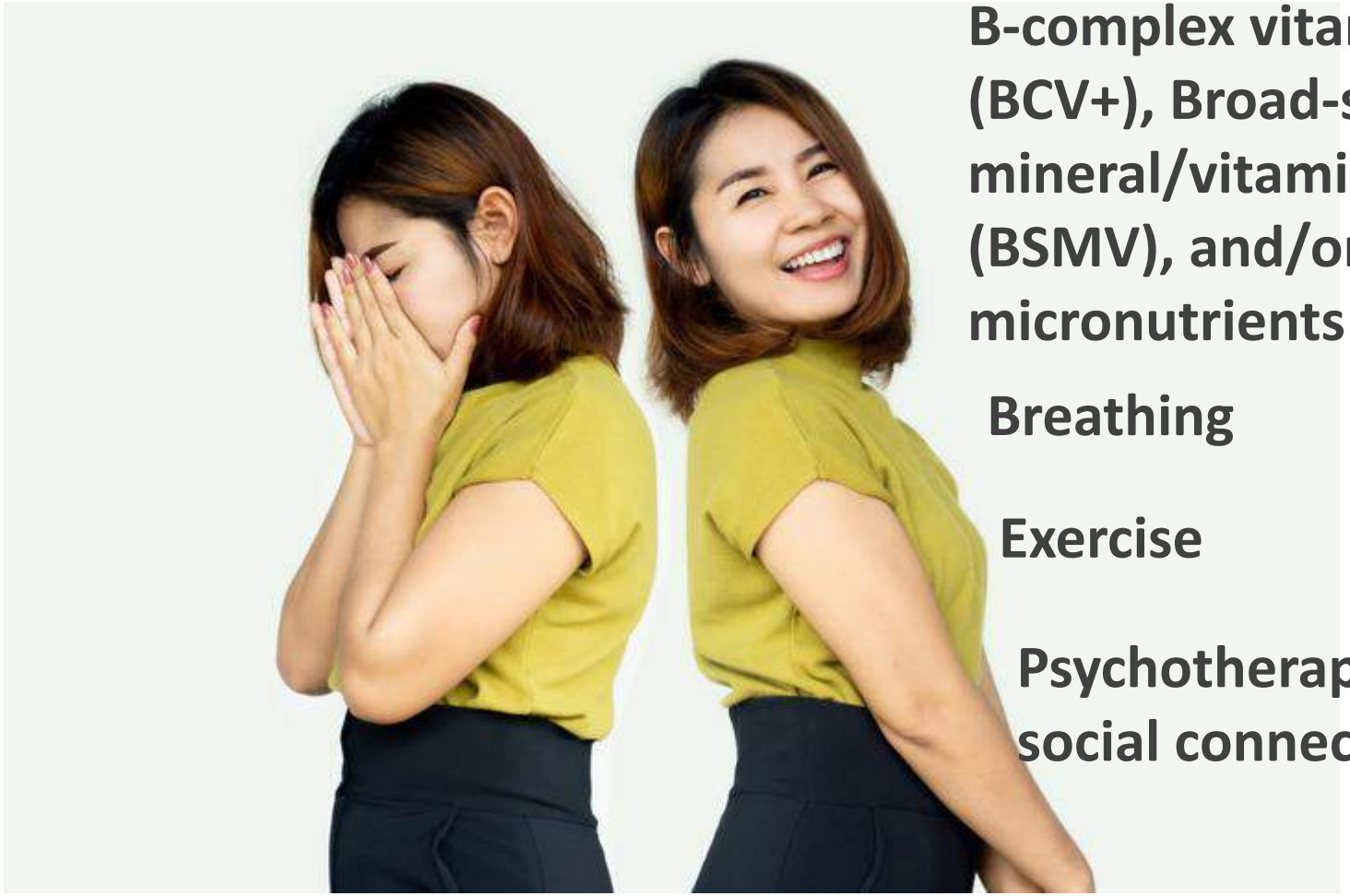
Exercise[79]

- Running has been used as interoceptive exposure to reduce anxiety sensitivity (AS).
- Participants included 18 participants that were assessed to be high in AS and 10 assessed to be low in AS.
- Participants (i.e., female undergraduate students) were encouraged to "...run at an intensity that induced physiological arousal sensations (e.g., rapid breathing, increased heart rate), to focus on these sensations while running, and to compare these to anxiety-related sensations."
- Though the participants were encouraged to complete 42 running trials, 28 participants completed at least 20 running trials. One running trial refers to a 10-minute run.

Exercise[79]

- **High AS participants:**
  - Experienced “decreases in cognitive, affective, and somatic reactions to running over time” (p.264).
  - The “decreases in cognitive and affective, but not in somatic, reactions to running were related to decreases in AS levels.”
  - The decrease in AS (i.e., among high AS participants) was not related to decreasing the experience of somatic sensations, but from alterations in cognitive and affective reactions to these sensations.

Integrative nutrition and lifestyle modification



B-complex vitamins+ (BCV+), Broad-spectrum mineral/vitamin formula (BSMV), and/or specific micronutrients

Breathing

Exercise

Psychotherapy and/or social connections

Psychotherapy and/or Social Connections

- Psychotherapy has been articulated as an ***epigenetic drug*** by inducing "changes in brain circuits that can enhance the efficiency of information processing in malfunctioning neurons to improve symptoms in psychiatric disorders, just like drugs."[80] Some examples.[81-84]
- In terms of ***social support***, it would seem reasonable to conclude that similar therapeutic changes would result when people are more socially engaged in meaningful ways. An example is that of the Experience Corps©.[85,86]

Psychotherapy and/or Social Connections

- The brain also expects social relationships to happen. This is the premise of the ***social baseline theory***.[87]
  - An interesting and more widespread example of fostering social integration includes the Blue Zones Project (https://www.bluezonesproject.com/), which supports communities by promoting the same principles as described in the book (i.e., The Blue Zones Solution by Dan Buettner).

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Conclusions

- Chronic stress, as noted earlier, is pathological and happens when allostatic mechanisms fail to adapt because resources have been exhausted.
- The brain, the principal organ that mediates how an individual responds to the world, is subject to multiple stressful and chronic insults that increase the risks of body and brain damage, disease, psychiatric illness, and other health outcomes.
- That is why several pragmatic integrative treatments were recommended as viable options that target, regulate, and potentially optimize allostatic mechanisms.
- Integrative approaches, such as those mentioned in this presentation, should serve as models of the kinds of interventions that can realistically and dramatically affect the course of chronic stress and prevalent medical diseases via allostatic brain mechanisms.