Hopkins Study

- In the early 1980s, the Department of Energy commissioned a study on the effects of regular exposure to low levels of radiation on health. They compared two groups of nuclear shipyard workers from Baltimore whose jobs were very similar except for a single key difference: One group was exposed to radiation from the materials they were handling, and the other was not. The DOE wanted to quantify the ill effects of the radioactive toxins, and they tracked 28,000 workers exposed to radiation between 1980 and 1988.
- What they found shocked everyone involved. Instead of having worse health, the workers exposed to radiation had a 24 percent lower mortality rate than their counterparts—all 32,000 of them—who were not exposed to radiation. The toxins that everyone assumed and feared were ruining the workers' health were doing just the opposite. The low-grade cellular stressor of radiation activated their immune systems, and expanded their intracellullar clean up crews and made them stronger, more resilient.

Neurohormetic phytochemicals: low-dose toxins that induce adaptive neuronal stress responses

Mark P. Mattson and Aiwu Cheng

Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, Baltimore, MD 21224, USA

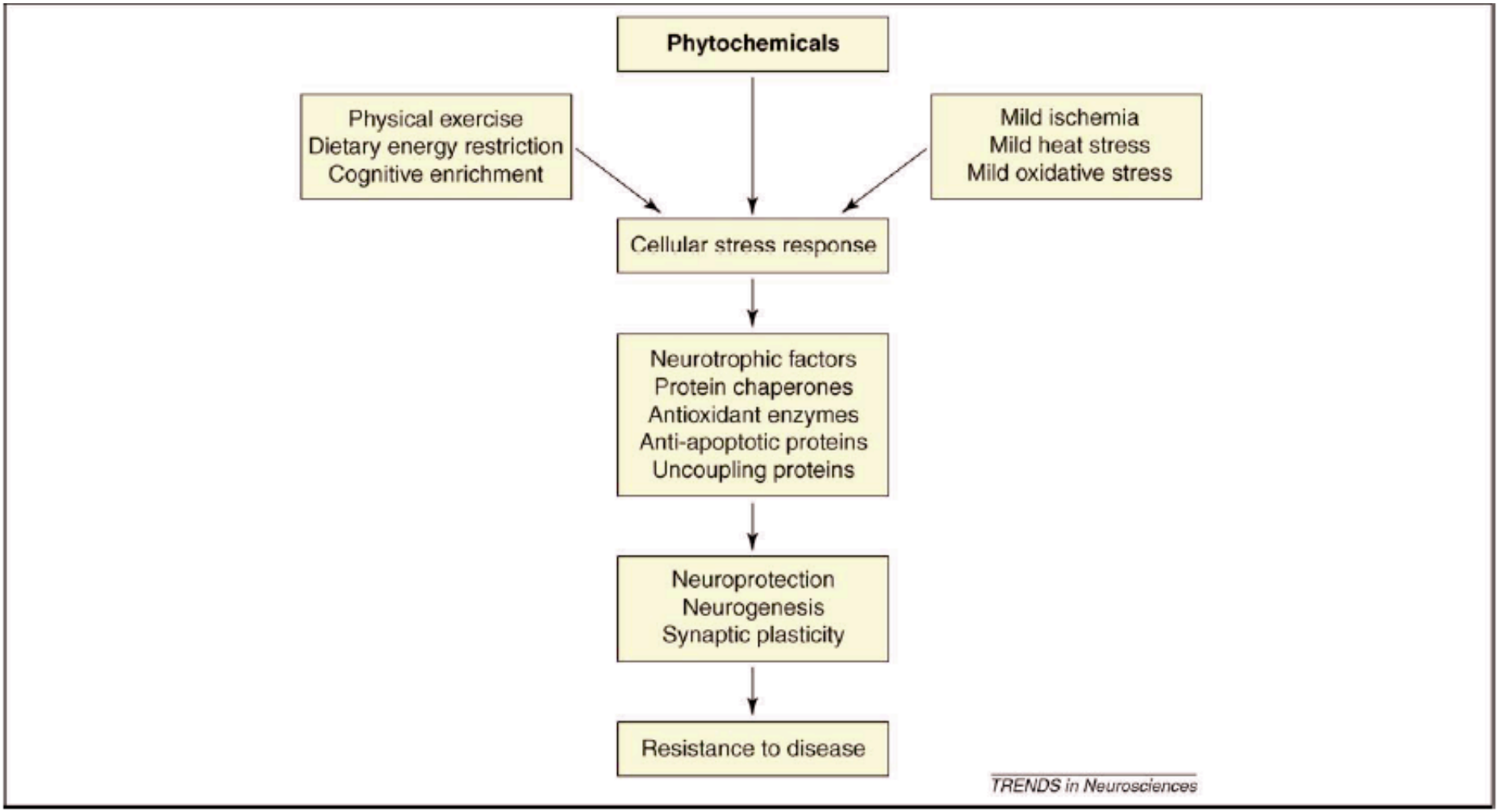


Figure 1. Disparate environmental and dietary factors activate common hormetic cellular stress-response pathways. Exercise, dietary energy restriction and cognitive stimulation are all known to enhance neurogenesis and synaptic plasticity, and can protect neurons against injury and neurodegenerative disorders. Exposure to one or more of these environmental factors induces the expression of neuroprotective proteins such as neurotrophic factors, protein chaperones, antioxidant enzymes, antiapoptotic proteins and mitochondrial uncoupling proteins. More direct exposure of neurons to sublethal levels of oxidative stress, heat stress or metabolic stress (e.g. mild ischemia) also induces the expression of multiple stress-resistance proteins. Phytochemicals might exert many of their beneficial actions by inducing a mild stress in neurons.

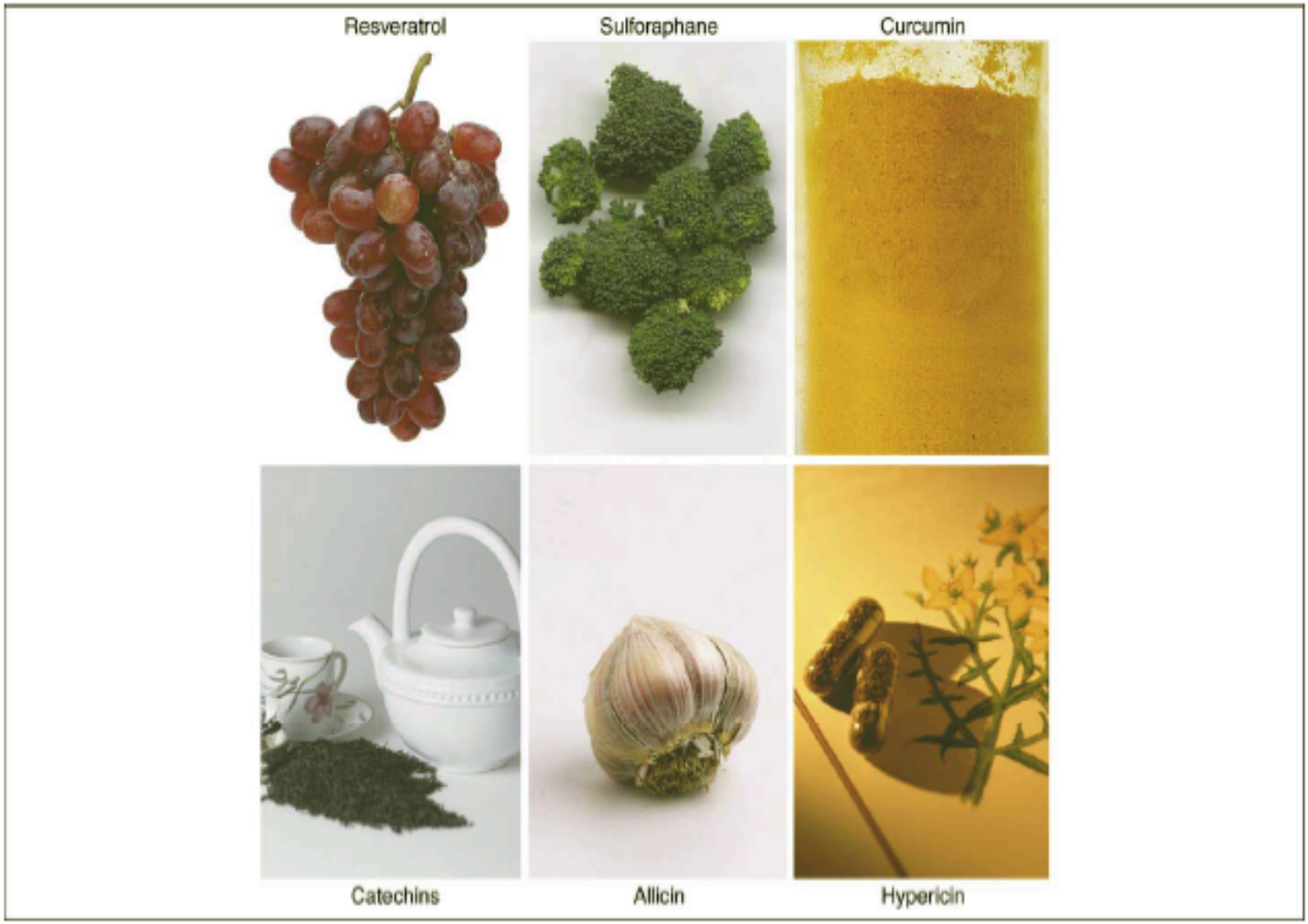
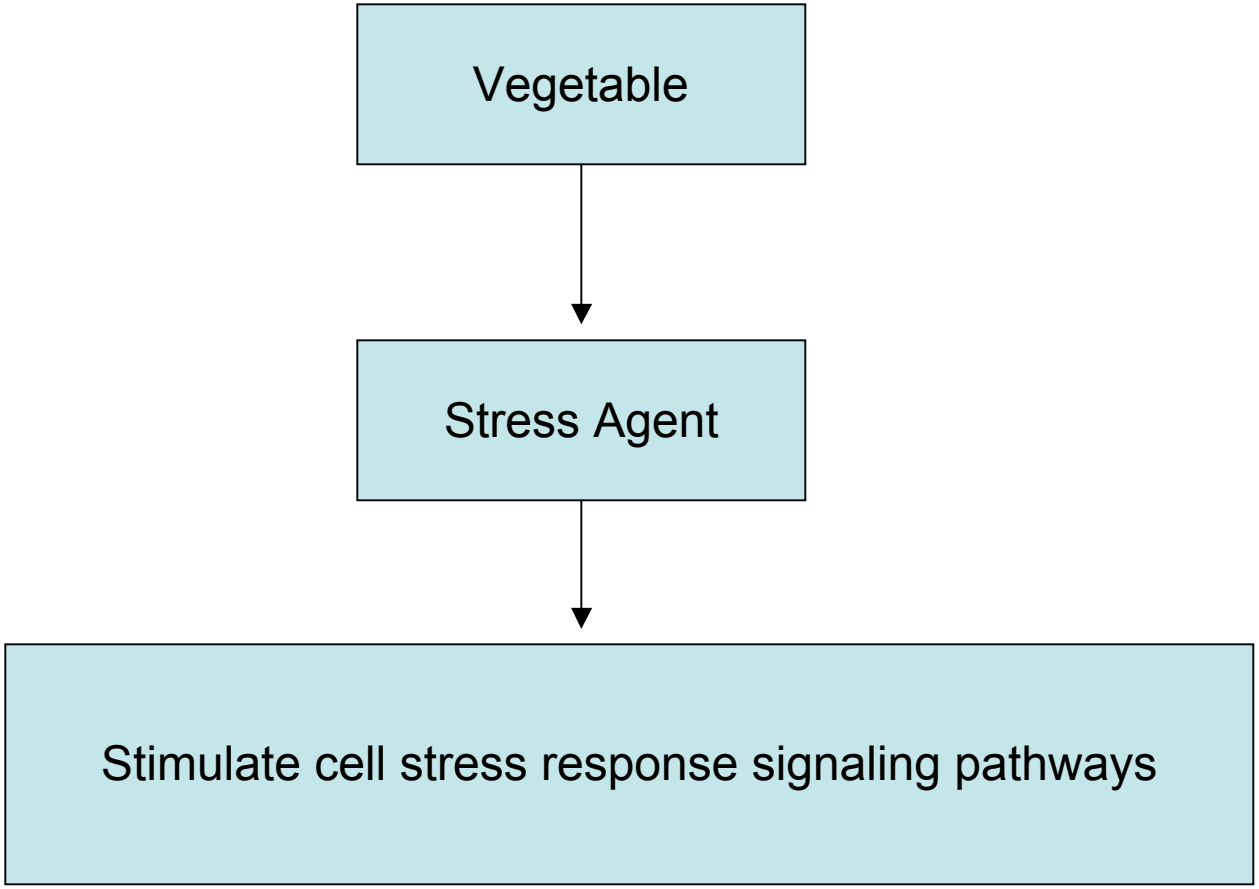


Figure 2. Neurohormetic phytochemicals include compounds from a range of botanical sources and chemical classes. Resveratrol is a polyphenolic compound present in high amounts in red grapes and wine, and in peanuts and soy. Broccoli and other cruciferous vegetables contain high amounts of the isothiocyanate sulforaphanes. Curcumin is the yellow pigment in the roots of turmeric. Green tea contains high amounts of catechins. Garlic is rich in allicin, allium and other organosulfur compounds. St John's wort contains the phenanthroperylene quinone hypericin.



The issue is how much & how often the phytochemical is ingested becomes very Important.

Mattson

- It is the case that the stress response at ANY level includes these damaging mechanism (oxidative, metabolic, and excitotoxic), but at the lower levels, they're effect is outweighed by repair mechanisms, and at certain point if it turns into chronic stress, the damaging mechanisms overwhelm the protective mechanisms.
- Moderate exercise, CR, toxins, learning are good because the cells respond adaptively and enhance their ability to cope with more stress and resist disease.
- Over threshold stress- impairs ability of cells to respond to stress. MR receptors in the hippocampus are filled and then depleted and GR are used by Cortisol and they

Mattson II

- EXCITOTOXICITY- related to Glutamate activity. Demands more energy. Makes Free Radicals. Reduced glucose levels and increased free radicals decreases resilience. Exercise and other stress Inoculators build resilience. Initially activity and stress of all sorts activate BDNF and friends. Then too much churning reach the Tipping Point- no recovery period. Just like the muscles- stretch, strain, break- need recovery or get damage; with recovery get growth. Too much activate proteases that during excitotoxicity that actually chew up various molecules in the cell.
- However, major drive to growth is activity and recovery

Mattson III

- Many of the beneficial chemicals in plants—vegetables and fruits—have evolved as toxins to dissuade insects and other animals from eating them," Mattson explains. "And what they're doing is inducing a mild, adaptive stress response in the cells. For example, in broccoli, there's a chemical called sulforaphane, and it clearly, in a very specific manner, activates stress response pathways in cells that upregulate antioxidant enzymes. Another example is cumin. They have anti-oxidants, but at the level you can possibly get in your diet, they're not going to function as anti-oxidants."

Humans: Fish out of Water

- Genes from 15,000 years ago. Paleolithic Man had to walk five to ten miles on an average day, just to be able to eat.
- The average energy expenditure per unit of body mass is about 40 percent of our Stone Age ancestors. Even you followed the most demanding governmental recommendations for exercise and logged 30 minutes of physical activity a day, you'd still be at less than half the energy expenditure for which your genes demand.

STRESS

- Malleable term, Continuum
- Drives us to act
- Triggered by a primitive call to survive, your body's response to stress is a built-in gift of evolution without which you wouldn't be here today.
- Any level of activity in your brain cells generates molecular byproducts that can cause them damage, but under normal circumstances, a recovery process follows that leaves the cells hardier for future challenges. Your neurons get broken down and built up just like your muscles—stressing them makes them more resilient
- aging is caused by a breakdown of neurons' ability to bounce back after stress.

Stress Response

- Activity at low level- CR, Ex, Learning- metabolic stress- free radicals, calcium
- Freeze-Flight-Fight : SNS to HPA- Norepinephrine, CRF, Endorphins (Body & Brain), Serotonin, Dopamine, then Cortisol
- While your muscles are ready to fire immediately upon sensing a threat, cortisol levels peak 30 minutes to an hour later, which is why the stress response lingers and can causes longer-term effects.
- Cortisol and stress leads to movement to obtain glucose and remember how and where. So it drives us to food and wisdom. Fat and Sugar are quick stress reducers.

Stress and the Brain

- Stress demands adaptation: mechanisms evolved to help our plastic brain grow to meet these challenges. Neurotransmitters, Growth Factors (HGH included), adding to blood supply.
- Three major types of stressors: what we call COGNITIVE OPERATIONS (thinking and feeling), DIETARY RESTRICTION and EXERCISE. They stress nerve cells and if a RECOVERY period follows: then we see brain and nerve cell growth. Just like our muscles.

Exercise and Aggression

- Acutely and chronically raises Serotonin and GABA levels
- Reduces stress and anxiety responsiveness
- Decreases hyperaroused state
- Decreases muscle tension
- Improves mood, motivation, self-efficacy

OMEGA-3 BORDERLINE AGGRESSION

Measure and Time	Score: E-EPA group (N=20)[b] Mean	SD	Placebo group (N=10)[c] Mean	SD
Modified Overt Aggression Scale				
Baseline	22.7	38.1	27.6	23.6
Week 2	11.6	7.8	26.1	27.7
Week 3	7.9	7.2	19.5	23.1
Week 4	7.5	7.3	10.7	8.9
Week 6	8.9	7.4	18.7	24.4
Week 8	7.2	8.1	12.9	17.1
Montgomery-Åsberg Depression Rating Scale				
Baseline	17.7	8.4	18.0	3.1
Week 2	11.6	7.4	15.2	8.1
Week 3	10.7	7.6	13.5	8.1
Week 4	8.2	8.1	13.0	7.6
Week 6	6.6	7.1	8.8	6.6
Week 8	6.2	4.9	8.0	5.5

20 subjects were randomly assigned to 1 g of eicosapentaenoic Acid EPA; 10 subjects were given placebo. 90% completed the study. Significantly less aggressive episodes $p < 0.0001$ as well as lower depressive scores $p<0.0001$.

Study over a 10 week period.

Zanarini, M Frankenburg F. *Am J Psychiatry 160:1, January 2003*

TABLE 1. Aggression and Depression in Women With Borderline Personality Disorder Randomly Assigned to 8 Weeks of Double-Blind Treatment With Ethyl-Eicosapentaenoic Acid (E-EPA) or Placebo

	Score				Random Effects Regression Analysis[a]		
	E-EPA group (N=20)[b]		Placebo group (N=10)[c]				
Measure and Time	Mean	SD	Mean	SD	Independent Variable	z	p
Modified Overt Aggression Scale					Individual baseline score	5.699	<0.001
					Treatment group	2.717	0.007
					Time	−8.534	<0.001
Baseline	22.7	38.1	27.6	23.6			
Week 2	11.6	7.8	26.1	27.7			
Week 3	7.9	7.2	19.5	23.1			
Week 4	7.5	7.3	10.7	8.9			
Week 6	8.9	7.4	18.7	24.4			
Week 8	7.2	8.1	12.9	17.1			
Montgomery-Åsberg Depression Rating Scale					Individual baseline score	4.852	<0.001
					Treatment group	2.091	0.04
					Time	−11.805	<0.001
Baseline	17.7	8.4	18.0	3.1			
Week 2	11.6	7.4	15.2	8.1			
Week 3	10.7	7.6	13.5	8.1			
Week 4	8.2	8.1	13.0	7.6			
Week 6	6.6	7.1	8.8	6.6			
Week 8	6.2	4.9	8.0	5.5			

[a] Overall models assessing between-group differences in symptom improvement over the course of the study were significant for both outcome measures (Modified Overt Aggression Scale: $\chi^2=118.0$, df=3, $p<0.0001$; Montgomery-Åsberg Depression Rating Scale: $\chi^2=167.1$, df=3, $p<0.0001$).

[b] N=19 at week 4, and N=18 at weeks 6 and 8.

[c] N=9 at weeks 6 and 8.

Dose: 1 gm EPA per day

Ninety percent of those taking this compound were able to complete the entire 8-week trial and reported no clinically relevant side effects. Those treated with this compound also experienced a significantly greater reduction in their overall aggression as well as their depressive symptoms than those treated with placebo. These results are consistent with the findings of recent reports concerning omega-3 fatty acids as an effective adjunctive treatment for bipolar disorder and recurrent depression.

Omega-3s and Aggression 1

- Important components of phospholipids which are integral to neuron membranes, especially dendrites and synapses
- Shift in Western Diet to high w-6 EFAs (Essential Fatty Acids) versus w-3 EFAs
- Estimates are optimum 4:1 ratio where we are 17:1
- May be responsible for large rise in psychiatric disorders as a whole and impulsivity and aggression in particular.
- Finnish and Japanese studies show less suicidal ideation and deaths from suicide in frequent fish consumers..

A. Tanskanen, J.R. Hibbeln et al., J Fish consumption and depression and suicidal in a general population, Arch. Gen. Psychiatry 58 (2001) 512–513. T. Hirayama, Life Style and Mortality, A Large Consus-Based Cohort Study in Japan, Karger, Basal, 1990

Omega-3s and Aggression 2

Higher homicide rates across 26 countries in those with lower rates of seafood consumption, $p<0.0005$

EFAs Supplementation studies in Aggression

Author	*n*	Population	Supplement	Outcome	Significance
Gesch et al. [31]	231	Prisoners	Efamol Marine 1260 mg LA 160 mg γLA 80 mg EPA 44 mg DHA Mean = 142 days RCT	Fewer violent offences (26.3%); supplements for ⩾2 weeks (35.1%)	$P = 0.03$ (95% CI 8.3–44.33%); supplements for ⩾2 weeks $P<0.001$ (95% CI 16.3–53.9%)
Hamazaki et al. [29]	41	University students	1.5 g DHA 200 mg EPA 100 mg AA 3 months RCT	Extra-agression at exam time in control group	$P = 0.002$ (95% CI 16.8–3%)
Hamazaki et al. [30]	40	University employees and farmers. Age 50–60 years	1.5 g DHA or plant oils 2 months RCT	Decreased hostility in University employees but not farmers	$P = 0.04$

B. Hallahan et al Prostaglandins, Leukotrienes and Essential Fatty Acids 71 (2004) 211–216

Omega-3s and ADHD

- ADHD - inverse relationship between total o-3 EFA concentrations in plasma and behavioural assessment scores (Conner's Parent Rating Scale and teacher scores of academic abilities) L.J. Stevens, S.S. Zentall, et al. Omega-3 fatty acids in boys with behaviour, learning, and health problems, Physiol. Behav. 59 (1996) 915–920.
- Mean serum levels are lower ADHD than controls $p<0.00$. M. Bekaroglu et al. J. Child Psychol. Psychiatry 37 (1996)
- 225–227.
- Supplementation with Omega-3s has promising effect on impulsive behavior

OMEGA-3s Aggression

Table 2
EFAs Supplementation studies in Aggression

Author	*n*	Population	Supplement	Outcome	Significance
Gesch et al. [31]	231	Prisoners	Efamol Marine 1260 mg LA 160 mg γLA 80 mg EPA 44 mg DHA Mean = 142 days RCT	Fewer violent offences (26.3%); supplements for ⩾2 weeks (35.1%)	$P = 0.03$ (95% CI 8.3–44.33%); supplements for ⩾2 weeks $P < 0.001$ (95% CI 16.3–53.9%)
Hamazaki et al. [29]	41	University students	1.5 g DHA 200 mg EPA 100 mg AA 3 months RCT	Extra-agression at exam time in control group	$P = 0.002$ (95% CI 16.8–3%)
Hamazaki et al. [30]	40	University employees and farmers. Age 50–60 years	1.5 g DHA or plant oils 2 months RCT	Decreased hostility in University employees but not farmers	$P = 0.04$

Action maybe the effect of Omega-3s on raising concentrations of Serotonin in the Frontal Cortex and decreasing metabolism, similar effects of the SSRIs

B. Hallahan et al Prostaglandins,Leukotrienes and Essential Fatty Acids
71 (2004) 211–216

For anxiety:

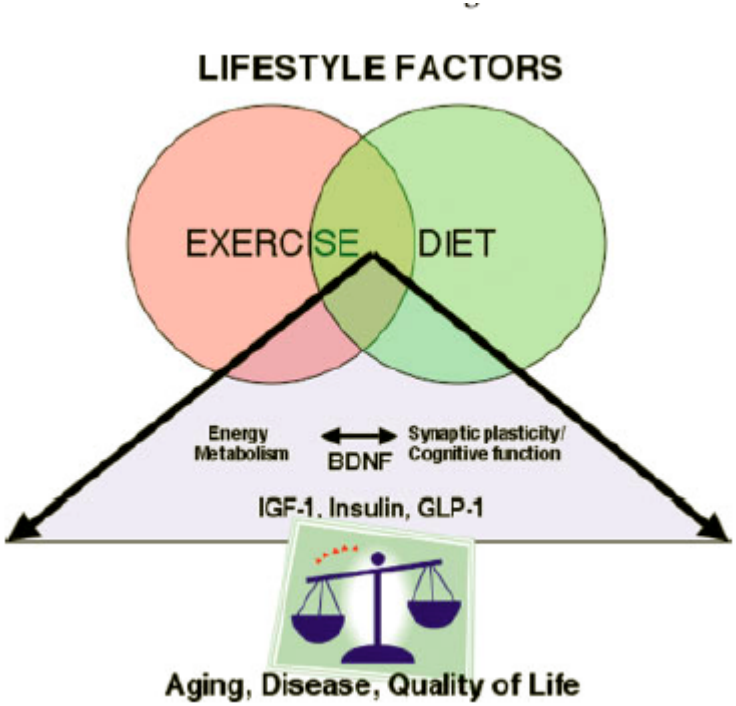
- Transient interruption-a distraction. Treating your own anxiety or acute stressed out state is very reinforcing.
- Boosting self-mastery. Get a hobby.
- No drugs, no TV, no alcohol, see reduction in tension,
- Reduce muscle tension. One will see a drop of electrical activity in the muscles after exercising.
- Thermogenic effect. Raise core heat to retool the inside. This leads to the general relaxation response
- Neurotransmitters: increase serotonin, norepinephrine, dopamine, GABA effect (rod dishman).

Anxiety

- THE ANXIOUS PERSON-DIFFERENTIATE STRESS AND ANXIETY

- Believe that stressors are everywhere
- Chronically overactive stress response
- NOT usually CORTISOL excess
- Too much SYMPATHETIC NERVOUS SYSTEM activation
- Anxiety and fear conditioning: managed by the amygdala.
- Tells the hypothalamus to release GCs and activate SNS

"How many times have I told you—no coffee after September!"



The influence of lifestyle choices, exercise & diet, on metabolism, & Neuro-cognitive health. Energy metabolism & aspects of brain function are shown to interface through common factors, BDNF, & IGF-1, insulin & FLP-1.
A lack of exercise & an unhealthy diet may tip the scales, leading to accelerated aging, diseases of the body & brain.

Comparison of Aerobic Exercise, Clomipramine, and Placebo in the Treatment of Panic Disorder

Andreas Broocks, M.D., Borwin Bandelow, M.D., Gunda Pekrun, M.A., Annette George, M.D., Tim Meyer, M.D., Uwe Bartmann, M.A., Ursula Hillmer-Vogel, M.D., and Eckart Rüther, M.D.

Broocks, A., Et al. AMJ Psychiatry : 155:5, May 5, 1998

TABLE 1. Demographic Characteristics of 46 Patients With Panic Disorder With or Without Agoraphobia in a Study of Treatment With Exercise, Clomipramine, or Placebo

	Exercise Group (N=16)			Clomipramine Group (N=15)			Placebo Group (N=15)		
Variable	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sex									
Male	6			11			6		
Female	10			4			9		
Panic disorder									
With agoraphobia	15			13			14		
Without agoraphobia	1			2			1		
Age (years)		31.8	9.5		33.9	9.2		34.8	6.8
Duration of illness (years)		3.1	2.1		4.1	4.6		6.9	7.9

TABLE 2. Baseline Scores and Change Scores at Week 10 on Primary Outcome Measures

Measure	Exercise Group (N=16) Mean	Exercise Group (N=16) SD	Clomipramine Group (N=15) Mean	Clomipramine Group (N=15) SD
Hamilton Anxiety Rating Scale score				
Baseline	24.4	8.0	22.5	6.4
Change				
Completer analysis[b]	–13.1	9.5	–14.0	7.3
Last-observation-carried-forward analysis	–12.9	8.4	–14.0	7.3
Clinical Global Impression score (observer rating)				
Baseline	4.4	0.9	4.7	0.6
Change				
Completer analysis[b]	–2.0	0.9	–3.1	0.7
Last-observation-carried-forward analysis	–1.7	1.0	–3.1	0.7
Panic and Agoraphobia Scale score (observer rating)				
Baseline	28.5	9.1	24.4	6.4
Change				
Completer analysis[b]	–13.7	7.5	–16.8	8.5
Last-observation-carried-forward analysis	–12.5	7.7	–16.8	8.5
Panic and Agoraphobia Scale score (patient rating)				
Baseline	27.0	10.2	23.1	5.1
Change				
Completer analysis[b]	–9.8	6.8	–13.4	7.4
Last-observation-carried-forward analysis	–8.8	6.9	–13.4	7.4

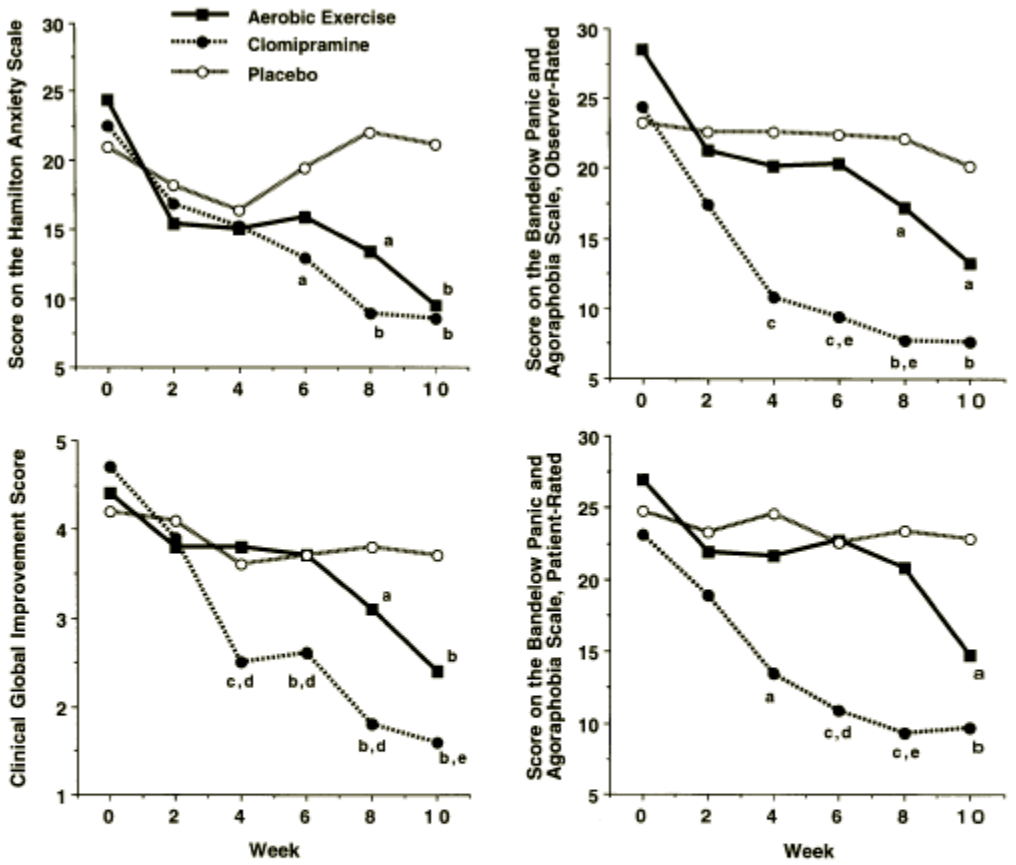
[a]Greenhouse-Geisser adjustments were used in the overall ANOVA. Main treatment effects were compared by repeated measures ANOVA using all six time points (baseline and 2, 4, 6, 8, and 10 weeks); p values of these post hoc tests were corrected by the Bonferroni-Holm method.

of Patients With Panic Disorder With or Without Agoraphobia Treated With Exercise, Clomipramine, or Placebo

Placebo Group (N=15)		Repeated Measures ANOVA[a]											
		Group-by-Time Interaction			Exercise Versus Placebo			Clomipramine Versus Placebo			Clomipramine Versus Exercise		
Mean	SD	F	df	p	F	df	p	F	df	p	F	df	p
20.9	8.5												
0.8	6.9	6.14	10, 165	0.0001	6.47	1, 33	0.02	11.82	1, 33	0.003	0.51	1, 33	n.s.
1.9	7.0	8.08	10, 205	0.0001	13.36	1, 41	0.0007	18.35	1, 41	0.0002	0.33	1, 41	n.s.
4.2	0.8												
–0.4	1.1	7.16	10, 165	0.0001	7.96	1, 33	0.008	62.43	1, 33	0.0002	26.92	1, 33	0.0002
–0.3	1.0	9.55	10, 205	0.0001	9.70	1, 41	0.003	83.82	1, 41	0.0002	39.04	1, 41	0.0002
23.2	7.4												
–2.1	9.0	3.70	10, 165	0.0005	4.93	1, 33	0.03	23.27	1, 33	0.0002	5.63	1, 33	0.02
0.5	9.4	5.78	10, 205	0.0001	11.22	1, 41	0.002	38.30	1, 41	0.0002	6.99	1, 41	0.01
24.8	6.7												
–1.1	5.7	4.47	10, 165	0.0001	2.02	1, 33	n.s.	15.50	1, 33	0.0008	5.90	1, 33	0.02
0.5	7.7	6.20	10, 205	0.0001	5.15	1, 41	0.03	25.80	1, 41	0.0002	7.58	1, 41	0.009

[b]For the exercise and placebo groups in the completer analysis, N=11; for the clomipramine group, N=15.

FIGURE 1. Change in Primary Outcome Measures of Patients' Anxiety During 10 Weeks of Treatment With Aerobic Exercise (N=11), Clomipramine (N=15), or Placebo (N=11) (Completer Analysis)



[a]Significantly different from placebo: p<0.05 (ANOVA followed by Tukey-Kramer adjustments for multiple comparisons).
[b]Significantly different from placebo: p<0.001 (ANOVA followed by Tukey-Kramer adjustments for multiple comparisons).
[c]Significantly different from placebo: p<0.01 (ANOVA followed by Tukey-Kramer adjustments for multiple comparisons).
[d]Significantly different from exercise: p<0.01 (ANOVA, followed by Tukey-Kramer adjustments for multiple comparisons).
[e]Significantly different from exercise: p<0.05 (ANOVA, followed by Tukey-Kramer adjustments for multiple comparisons).

TABLE 3. Baseline Scores and Change Scores at Week 10 on Secondary Outcome Measures

	Exercise Group (N=11)		Clomipramine Group (N=15)	
Measure	Mean	SD	Mean	SD
Beck Anxiety Inventory score				
Baseline	32.9	12.8	30.2	10.8
Change	–18.0	13.3	–14.6	15.8
Fear Questionnaire score				
Baseline	65.3	28.2	60.5	27.1
Change	–24.1	12.6	–30.3	23.2
Montgomery-Åsberg Depression Rating Scale score				
Baseline	17.5	8.1	17.5	7.8
Change	–9.7	6.8	–11.4	6.1
Beck Depression Inventory score				
Baseline	15.2	8.9	14.7	6.8
Change	–8.4	8.8	–7.5	6.6
Clinical Global Impression score (patient rating)				
Baseline	4.6	1.0	4.4	0.7
Change	–1.8	1.0	–2.6	1.4

[a]Greenhouse-Geisser adjustments were used in the overall ANOVA. Main treatment

of Patients With Panic Disorder With or Without Agoraphobia Treated With Exercise, Clomipramine, or Placebo

Placebo Group (N=11)		Repeated Measures ANOVA[a]											
		Group-by-Time Interaction			Exercise Versus Placebo			Clomipramine Versus Placebo			Clomipramine Versus Exercise		
Mean	SD	F	df	p	F	df	p	F	df	p	F	df	p
35.8	18.8												
–0.4	10.7	10.35	1, 32	0.0003	16.31	1, 32	0.0006	15.28	1, 33	0.001	0.12	1, 32	n.s.
74.0	26.5												
–8.2	19.7	2.93	10, 160	0.006	0.25	1, 32	n.s.	7.86	1, 33	0.03	5.02	1, 32	0.03
17.7	7.9												
–1.8	7.5	18.26	1, 32	0.0001	23.55	1, 32	0.0002	32.00	1, 33	0.0001	0.16	1, 33	n.s.
18.3	10.7												
–2.5	5.2	5.49	1, 32	0.009	9.16	1, 32	0.01	7.72	1, 33	0.02	0.19	1, 32	n.s.
4.9	1.1												
–1.0	1.4	4.40	10, 160	0.0001	0.24	1, 32	n.s.	12.28	1, 33	0.003	9.32	1, 32	0.005

effects were compared by repeated measures ANOVA; p values of these post hoc tests were corrected by the Bonferroni-Holm method.

Effects of aerobic exercise on anxiety sensitivity

Broman-Fulks Joshua J., Berman Mitchell E., Rabian Brain A., Webster Michael J. Behavior Research and Therapy. 42 (2004); 125-136

Hypothesis

- Participants in the high and low intensity exercise conditions would both show improvement on all anxiety measures from pre to post-treatment and gains would be maintained at follow up.
- It was expected that the high intensity exercise group would show significantly more improvement on these measure in comparison with the low intensity caparison group.

Broman-Fulks Joshua J., Berman Mitchell E., Rabian Brain A., Webster Michael J. Behavior Research and Therapy. 42 (2004); 125-136

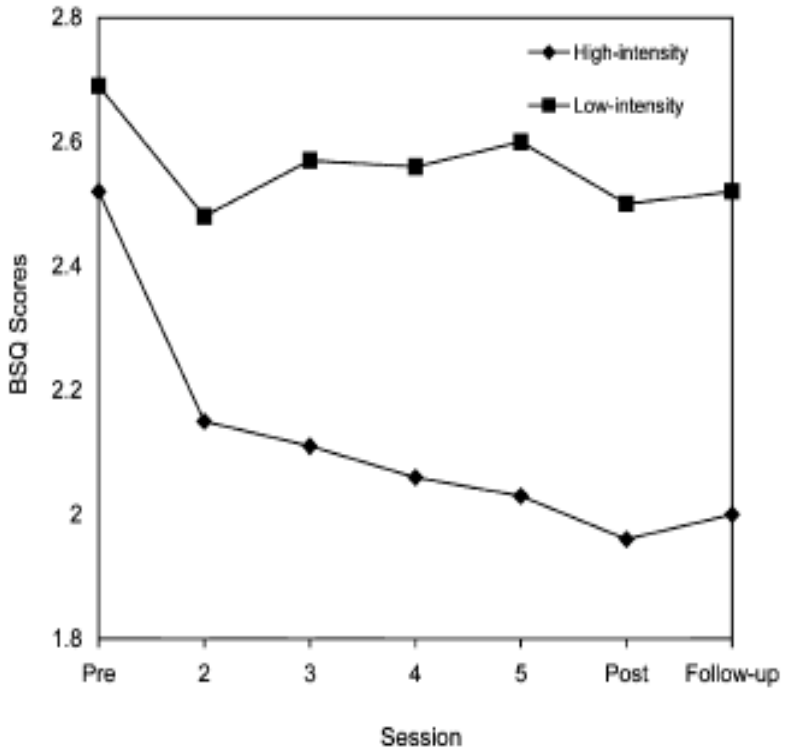


Fig. 1. Mean BSQ scores for high- and low-intensity exercise groups at pre-intervention, before each exercise session, post-intervention, and at a one-week follow-up session.

What do the results say?

- Both high and low intensity exercise are successful on average.
- High intensity exercise had severval distinct advantages over low-intensity exercise.
  - Produced more rapid reductions in ASI scores.
  - Yielded more than twice as many “treatment” responders.

Broman-Fulks Joshua J., Berman Mitchell E., Rabian Brain A., Webster Michael J. Behavior Research and Therapy. 42 (2004); 125-136

High-intensity exercise may be especially effective in the rapid reduction of fear of physiological arousal in high anxiety sensitivity individuals.

Broman-Fulks Joshua J., Berman Mitchell E., Rabian Brain A., Webster Michael J. Behavior Research and Therapy. 42 (2004); 125-136

What does this mean?

- For the client who refuses more traditional means of treatment, high intensity exercise is best option for them.
- All individuals need to get out and move.

Broman-Fulks Joshua J., Berman Mitchell E., Rabian Brain A., Webster Michael J. Behavior Research and Therapy. 42 (2004); 125-136

Association between physical activity and metal disorders among adults in the United States

Goodwin Renee D. Prevention Medicine 36 (2003); 698-703

Objective

- To determine the association between regular physical activity and mental disorders among adults in the United States.

Goodwin Renee D. Prevention Medicine 36 (2003); 698-703

Results

- After adjusting for all co-morbid mental disorders, current major depression, panic attacks , social phobia, specific phobia and agoraphobia were significantly less common among those who reported regular physical activity.
- The data shows the link between regular physical activity and lower prevalence of current depression and anxiety disorder sin the general population and are consistent with the previous studies showing an association between exercise and decreased likelihood of anxiety and depression

Goodwin Renee D. Prevention Medicine 36 (2003); 698-703