Exercise and Mental Health

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‘Mens sana in corpore sano’

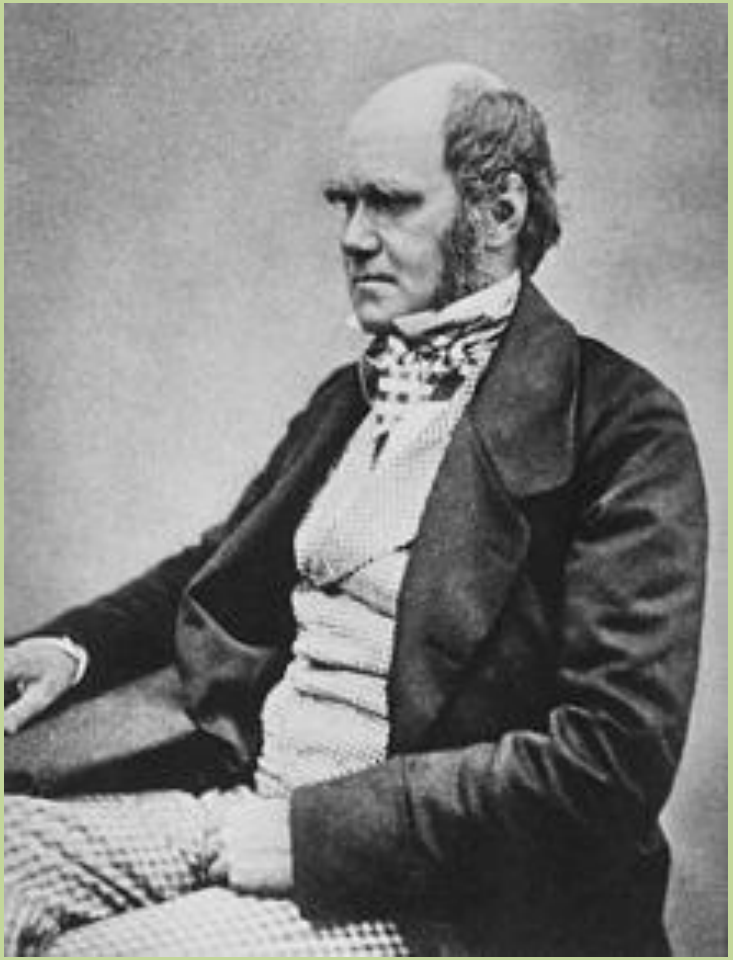
Juvenal circa 90 AD

(A healthy mind in a healthy body)

Is there a link between Physical and Mental Health ?

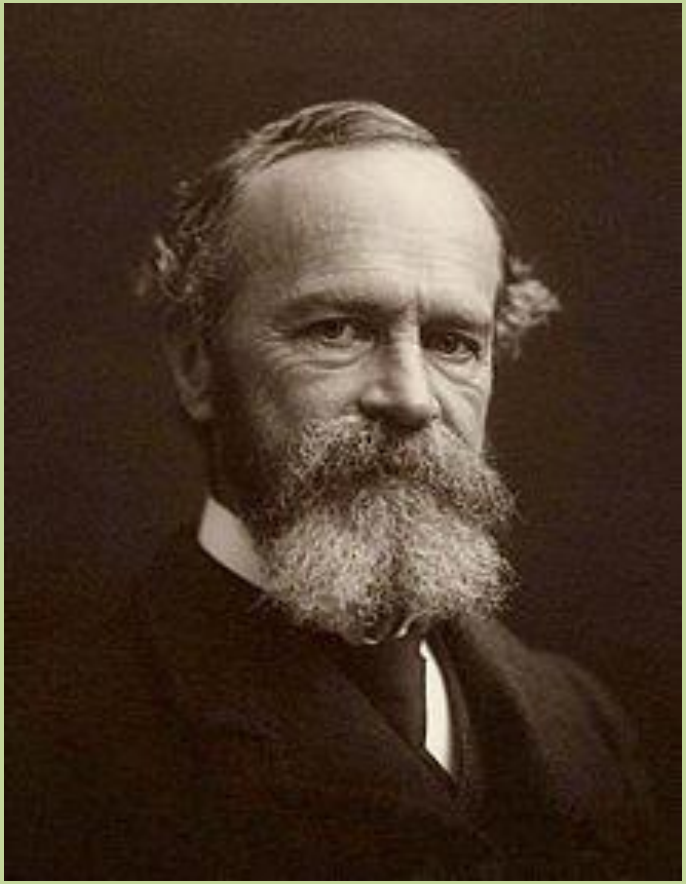
Lets look at the history of emotion research.

Charles Darwin



- In 1872, Darwin published "***The Expression of the Emotions in Man and Animals***"
- He believed that all mammals (including humans) show emotion through similar behaviours and facial expressions.
- Certain emotions were universal to all humans, regardless of culture: anger, fear, happiness and sadness.

William James



- Physician, physiologist and father of psychology

1884 Essay – " What is an Emotion?"

- Argued that emotion is the label or interpretation the brain puts onto the physiological response to different stimuli or sensory inputs.

- "If we fancy some strong emotion, and then try to abstract from our consciousness of it all the feelings of its characteristic bodily symptoms, we find we have nothing left behind… A purely disembodied human emotion is a nonentity. "

Walter Bradford Cannon

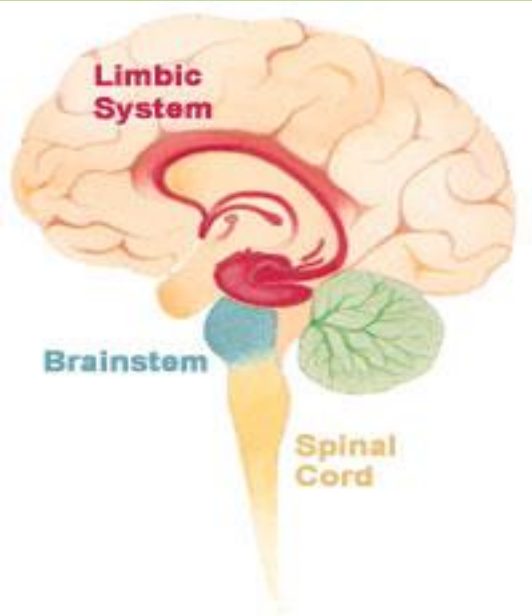
- American Physiologist – Coined “Flight or Fight response” and developed concept of “Homeostasis”

1915 - *Bodily Changes in Pain, Hunger, Fear and Rage:*

- Severed afferent sympathetic nerves removing sensory input from the viscera – emotion unchanged. Forced abandonment of the James model.

1927 : Cannon–Bard theory of emotional expression

- Using decorticated cats and ablating various brain regions, Cannon identified the thalamus as responsible for emotional responses
- Unilateral thalamus lesions cause excessive reactions to affective stimuli – loss of cortical inhibition.
- Argued physiological arousal did not have to precede emotional expression or experience.
- This has become the prevailing view since.



Papez –Maclean Theory

1937 – Papez proposed a neural circuit for the control of emotional expression.

1952 – Maclean redefined the circuit as the “visceral brain” and coined the term “Limbic System” because of the limbis shape

- Included connections to the hypothalamus, amygdala and the prefrontal cortex.
- Amygdala now thought to play a key role in emotion.

Magda Arnold - Richard Lazarus

1960 Arnold – Emotion as an Appraisal

- First step in emotion is an appraisal of the situation
- Physiological changes accompany, but do not initiate actions and experiences

1991 Lazarus - Cognitive Appraisal Theory

- Primary appraisal -establishes the meaning of the event
- Secondary appraisal - assesses the ability to cope with the consequences of the event.
- Cognition must precede the physiological arousal and emotion which happen simultaneously

Schachter–Singer theory

1962 – Two-factor theory of emotion,

- Emotion is based on two factors: physiological arousal and cognitive label.
- Physiological arousal occurs first, and then the individual must identify the reason for this arousal to experience and label it as an emotion.
- People use clues in their environment to explain physiological changes.

So the debate over the last 100 years has been whether physiology or cognitive appraisal drives emotion?

What is our Physiology?

- The biological mechanisms that maintain or alter our homeostatic steady state.
  - Autonomic Nervous System – SNS and PNS
  - The innate and adaptive immune systems
  - The HPA axis and other hormonal signalling

- Physiological response is a key component of emotion
- Exercise is the simplest and cheapest way to alter our physiology.
- What is the evidence?

Physiological Arousal in PTSD and Suicide

- Study of 2100 PTSD subjects with 222 suicide attempts.
- Physiological arousal most significant risk factor **OR 2.33 (1.33-4.08)**
- Perception of **defeat and entrapment** a key mechanism of suicidal behaviour. ***Johnson J[1] Psychol Psychother. 2008 Mar;81(Pt 1):55-77.***
- ***Autonomic hyperarousal results in a perception of ongoing threat of danger – which can result in "overwhelming feelings of defeat and entrapment" which may " in turn exacerbate the symptom of sensing a foreshortened future".***
- "In positive feedback, catastrophic cognitions are then amplified, leading to suicidal ideation. Suicide attempts can then be driven by the combination of both suicidal ideation and heightened arousal"

Selamen Z. Which symptoms of PTSD are associated with suicide attempts? J Anx Disord 2014 :28 : 246-251

Suicide and Physiological Arousal

- Panic symptoms in PTSD were significantly associated with suicidal ideation beyond effects of depression and traumas experienced.

Albanese BJ. Compr Psychiatry. 2015 Aug;61:42-8.

- Heightened arousal prospectively predicted death by suicide: as severity of arousal increased, the likelihood of suicide increased in those with high capability for suicide.

Ribeiro JD. J Affect Disord. 2015 Dec 1;188:53-9.

DEPRESSION AND ANXIETY 31:335–343 (2014)

Research Article

EFFECTS OF KETAMINE ON EXPLICIT AND IMPLICIT SUICIDAL COGNITION: A RANDOMIZED CONTROLLED TRIAL IN TREATMENT-RESISTANT DEPRESSION

Rebecca B. Price, Ph.D.,[1] Dan V. Iosifescu, M.D.,[2,3] James W. Murrough, M.D.,[2,3] Lee C. Chang, M.D.,[4] Rayan K. Al Jurdi, M.D.,[5,6] Syed Z. Iqbal, M.D.,[5,6] Laili Soleimani, M.D.,[2] Dennis S. Charney, M.D.,[2,3,7] Alexandra L. Foulkes, M.S.,[5,6] and Sanjay J. Mathew, M.D.[5,6]*

- ***Treatment-resistant major depression (No response to ≥3 antidepressants)***
- ***Ketamine [0.5mg/kg] (n = 36) or midazolam (0.045mg/kg) (n = 21), IV over 40 mins.***
- ***24 hours post-infusion,***
  - ***53% of ketamine group scored zero on all three explicit suicide measures,***
  - ***24% of the midazolam group ($\chi 2 = 4.6$; $P = .03$).***
- ***Ketamine-specific decreases in explicit suicidal cognition were large.***
- ***Implies that suicidal ideation is driven by glutaminergic transmission at the NMDA receptor.***

Panic Attacks

- Panic Attacks (PAs) comprise cognitive symptoms like catastrophic fear of dying alongside autonomic symptoms such as palpitations and sweating.

- DSM-V criteria , PA is >4 of 13 symptoms; 2 are cognitive/fear and 11 are physical.

Johnson PL. Neurosci Biobehav Rev. 2014 Oct; 46 Pt 3: 429–454.

- Klein proposed a CO_2 hypersensitivity theory of panic attacks where a “false suffocation alarm” produces respiratory distress followed by hyperventilation “to blow off” CO_2, and an urge to flee.

Klein DF. Arch Gen Psychiatry. 1993 Apr;50(4):306-17.

Inducing Panic Attacks (PA)

- Symptoms of Panic Attacks can be induced in healthy subjects by inhaling 7.5% CO_2 for 15 min.

Woods SW, Arch Gen Psychiatry. 1988 Jan;45(1):43-52.

- Acidosis from CO2 inhalation induces PAs in 40%-60% of Panic Disorder (PD) sufferers, compared to hyperventilation with PA rates ranging from 0–46%.

- PA vulnerability not simply a hypersensitivity to CO_2.

- IV infusion of 0.5M Na Lactate to 24 PD elicited PAs in 70% of males and 50% of females. Changes in pH seem to be trigger.

Johnson PL. Neurosci Biobehav Rev. 2014 Oct; 46 Pt 3: 429–454.

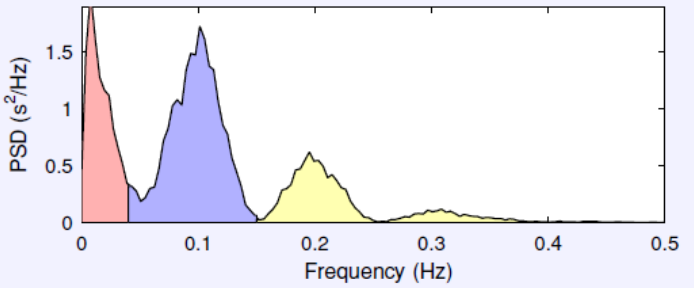
Heart Rate Variabiity (HRV)

- HRV is the R-R interval (msec) on the ECG.
- The High Frequency (HF) component HRV is a measure of parasympathic innervation to the myocardium and thought to reflect regulation of physiological arousal in response to environmental challenge.
- Low HRV represents either inadequate parasympathetic or excessive sympathetic activity.
- Rodent models of depression have found elevated sympathetic tone, decreased HRV and increased pro-inflammatory cytokines.

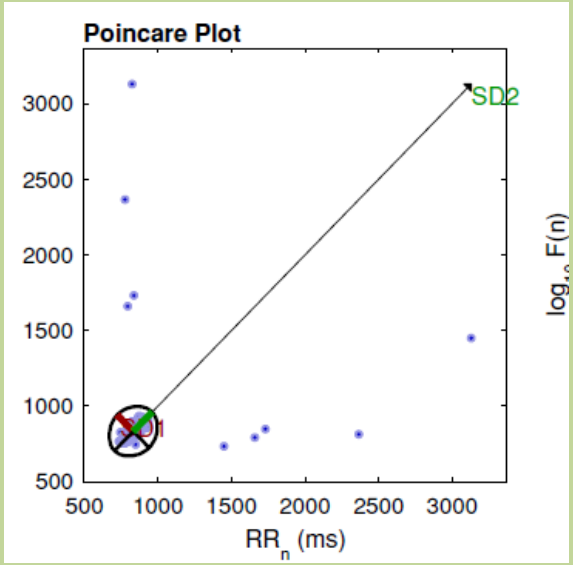
Grippo AJ. Stress. 2009 Jan;12(1):1-21.

Frequency–Domain Results

FFT spectrum (Welch's periodogram: 256 s window with 50% overlap)

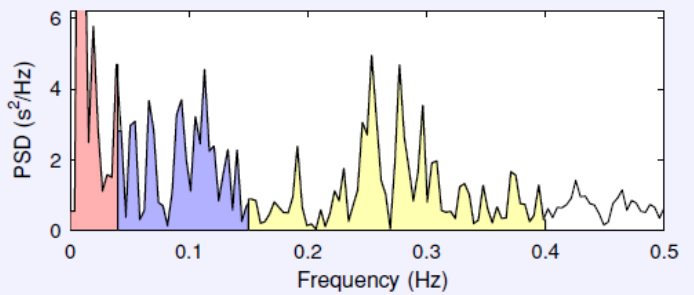


Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0–0.04 Hz)	0.0078	43460	26.7	
LF (0.04–0.15 Hz)	0.1016	84078	51.6	70.4
HF (0.15–0.4 Hz)	0.1953	35301	21.7	29.6
Total		162852		
LF/HF		2.382		

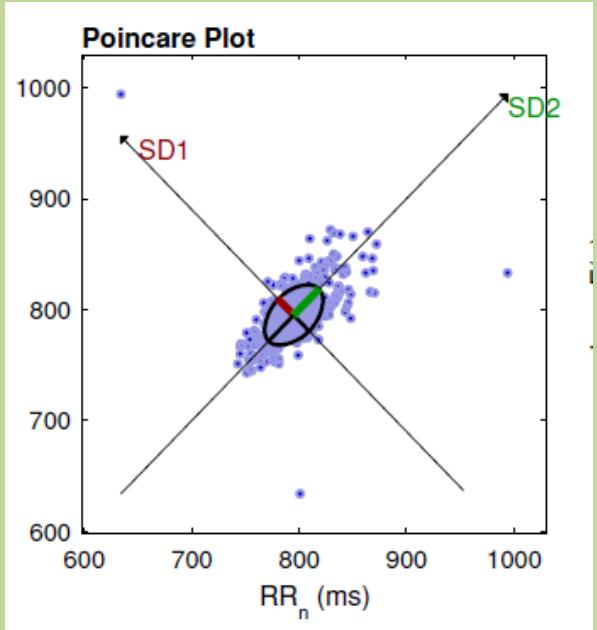


Frequency–Domain Results

FFT spectrum $\times 10^{-3}$ (Welch's periodogram: 256 s window with 50% overlap)



Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0–0.04 Hz)	0.0078	185	27.6	
LF (0.04–0.15 Hz)	0.1133	210	31.3	43.2
HF (0.15–0.4 Hz)	0.2539	275	41.0	56.6
Total		671		
LF/HF		0.764		



HF HRV predicts SI and Depression

- HF HRV predicted self-reported depressive symptoms across one year, controlling for age, puberty and sex. ($\beta = -0.391$ $p < 0.003$)
- HF HRV was most strongly associated with anhedonia one year later, after controlling for other facets of depression. ($p=0.002$, $R^2 = 0.12$)

Vazquez L J Affect Disord. 2016 May 15;196:243-7.

- 37 healthy students - Depression Screening and four questions concerning lifetime suicide ideation (SI).
- Significant correlation between the $\log_{10}$-transformed HF band of HRV and SI was found ($r=-.33$, $p<.05$).
- No change when controlling for depression.

Forkmann T. J Affect Disord. 2016 Apr;194:30-2. Resting vagal tone is negatively associated with suicide ideation.

Do traditional Antidepressants Work?

- <50% of patients respond within 3 mths .
- 10 to 30% remain unresponsive to 2 or more antidepressants and termed treatment resistant.
- Ketamine, an NMDA glutamate receptor blocker, induces a rapid antidepressant response in 60 to 70% of treatment resistant patients.
- Remission of depressive symptoms following a single IV bolus can last from 1 to 4 weeks.

Vasavada MM J Affect Disord. 2016 Jan 15;190:836-41.

Serotonin and Depression –The Marketing of a Myth

Professor David Healy ; Editorial BMJ April 21 2015.

- “drug companies marketed SSRIs for depression, even though they were weaker than older tricyclic antidepressants”

- “There was no correlation between serotonin reuptake inhibiting potency and antidepressant efficacy. No one knew if SSRIs raised or lowered serotonin levels; they still don’t know. There was no evidence that treatment corrected anything.”

Serotonin and Depression –The marketing of a Myth

- “The success of the SSRIs pushed older tricyclic antidepressants out of the market. This is a problem because SSRIs have never been shown to work for the depressions associated with a greatly increased risk of suicide (melancholia). The nervous states that SSRIs do treat are not associated with increased risk of suicide.”

- “The focus on SSRIs also coincided with the abandonment of the pursuit of research into established biological disturbances linked to melancholia (raised cortisol); the SSRIs are ineffective in mood disorders with raised cortisol.”

- “Meanwhile studies suggesting that ketamine, a drug acting on glutamate systems, is a more effective antidepressant than SSRIs for melancholia cast doubt on the link between serotonin and depression.”

Suicidality and Aggression with Antidepressants

- Reviewed 70 trials with 18,526 patients.

- For children and adolescents using AD
  - OR 2.39 (1.31 to 4.33) for suicidality, and
  - OR 2.79 (1.62 to 4.81) for aggression

- " we suggest minimal use of antidepressants in children, adolescents, and young adults, as the serious harms seem to be greater and their effect seems to be below what is clinically relevant. Alternative treatments such as exercise or psychotherapy may have some benefit and could be considered."

Sharma T BMJ. 2016 Jan 27;352:i65.

Does exercise improve Depression?

- Exercise is an effective treatment strategy for depression

Conn VS. Depressive symptom outcomes of physical activity interventions: meta-analysis findings. Ann Behav Med. 2010;39:128–138

- Regular exercise protects against new depressive illnesses. For each standard deviation increase in physical activity score, there was a 50% decreased risk of developing depressive or anxiety disorders.

Pasco JA. Habitual physical activity and the risk for depressive and anxiety disorders among older men and women. Int Psychogeriatr. 2011;23:292–298

- Low PA in childhood associated with increased risk of reporting depression in adulthood (OR=1.70, $p<0.001$).

Jacka FN J Sci Med Sport. 2011 May;14(3):222-6. Lower levels of physical activity in childhood associated with adult depression.

Exercise and Depression

- Higher emotional well-being found among physically active youths, independent of social class and health status .

Steptoe A . J Psychosom Res. 1996 Aug;41(2):171-80. Stress, social support and health-related behaviour: a study of smoking, alcohol consumption and physical exercise.

- High levels of adulthood physical activity associated with lower levels of depressive symptoms ($p < 0.001$).

Kaisa Kaseva. 2016. J Sports Med . Trajectories of Physical Activity Predict the Onset of Depressive Symptoms but Not Their Progression: A Prospective Cohort Study.

- Assessed prospectively over 2-years, a 1 SD unit increase in leisure-time physical activity was associated with a 0.25 SD unit decrease in depressive symptoms in adolescents.

Motl RW Psychosom Med. 2004 May-Jun;66(3):336-42. Naturally occurring changes in physical activity are inversely related to depressive symptoms during early adolescence.

Impact of exercise on depression and anxiety

- Non exercisers twice as likely to have depressive symptoms (OR: 2.1) and anxiety (OR: 2.5) than those with regular physical activity

Mello MT. J Affect Disord. 2013 Jul;149(1-3):241-6. Relationship between physical activity and depression and anxiety symptoms: a population study.

- Activity associated with fewer depressive symptoms from 23 to 50 years of age - estimated reduced risk of depression by 19%.

Pinto Pereira SM 2014 JAMA Psychiatry. 2014;71(12):1373-1380. Depressive symptoms and physical activity during 3 decades in adult life: bidirectional associations in a prospective cohort study.

- 8-week , 3/week interval cycle training post AMI increased HF HRV
- Initial depression severity ($p<0.01$) and state anxiety decreased significantly ($p<0.01$).

Korzeniowska-Kubacka. Eur J Cardiovasc Nurs. 2016 Nov 29. The impact of exercise-only-based rehabilitation on depression and anxiety in patients after myocardial infarction.

What is the most effective type of exercise?

- Higher intensity exercise is more effective at reducing anxiety levels than lower intensity exercise.
- Greater aerobic fitness associated with lower state anxiety during acutely stressful situations

***Steptoe 1989 J Psychosom Res. 1989; 33(5):537-47. The effects of exercise training on mood and perceived coping ability in anxious adults from the general population*.**

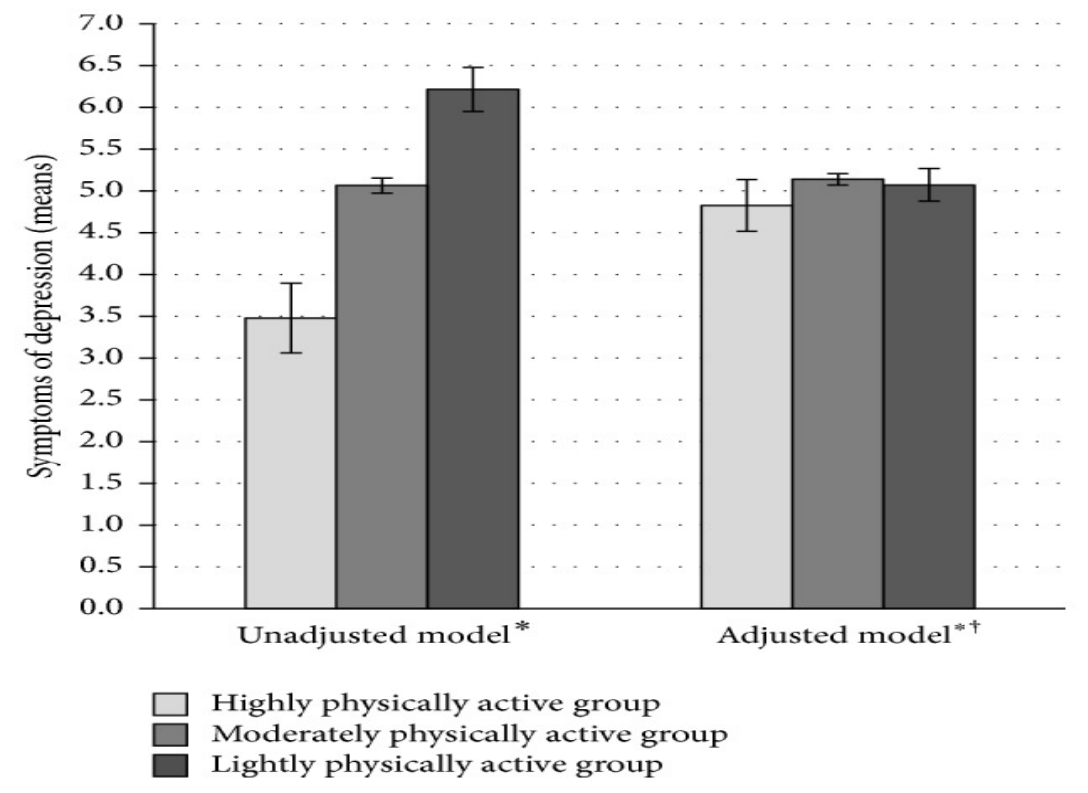
- Anxiety sensitivity can be reduced by repeated exercise and this reduction is more rapid in high intensity exercise.

Broman-Fulks JJ. Effects of aerobic exercise on anxiety sensitivity. Behav Res Ther. 2004 Feb;42(2):125-36.

- Permitting patients to select exercise intensity did not maximize improvements in mood, as they usually chose a lower intensity than prescribed

Meyer JD. Med Sci Sports Exerc. 2016 Nov;48(11):2207-2215. Psychobiological Responses to Preferred and Prescribed Intensity Exercise in Major Depressive Disorder.

Exercise Intensity predicts onset of depression



Kaisa Kaseva. 2016. J Sports Med . Trajectories of Physical Activity Predict the Onset of Depressive Symptoms but Not Their Progression: A Prospective Cohort Study.

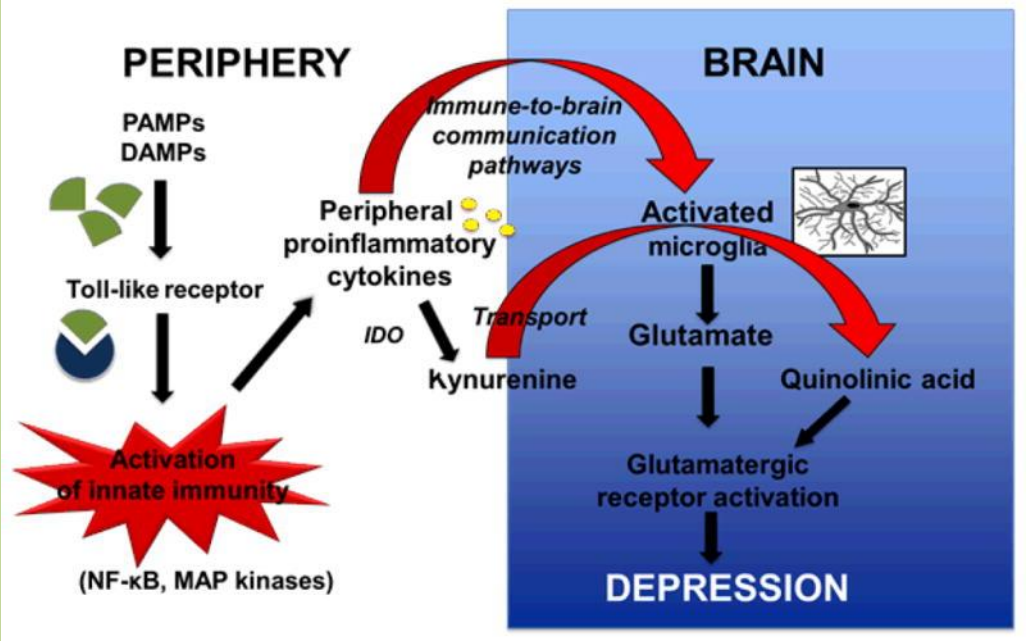
Is Depression an Inflammatory Disorder?

- Chronic inflammation in physically ill patients associated with depression.
- Sickness behaviour is mediated by pro-inflammatory cytokines.
- Adaptive response that enhances recovery by conserving energy to combat acute inflammation.
- Considerable similarities between sickness behaviour and depression
- In depression, central sensitization and progressive damage by oxidative and nitrosative stress to lipids, proteins, and DNA.
- Acute Inflammation is protective (sickness behaviour) but chronic inflammation is not, with neurodegeneration and depression.

Maes M 2012 BMC Medicine, 10:66. Is depression is a form or a consequence of sickness behaviour?

The Pathophysiology of Inflammation-induced Depression

Dantzer R J Neural Transm. 2014 Aug; 121(8): 925–932.



Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate Toll-like receptors in innate immune cells.

These immune cells release pro-inflammatory cytokines that produce kynurenine from tryptophan catalyzed by indoleamine 2,3 dioxygenase (IDO).

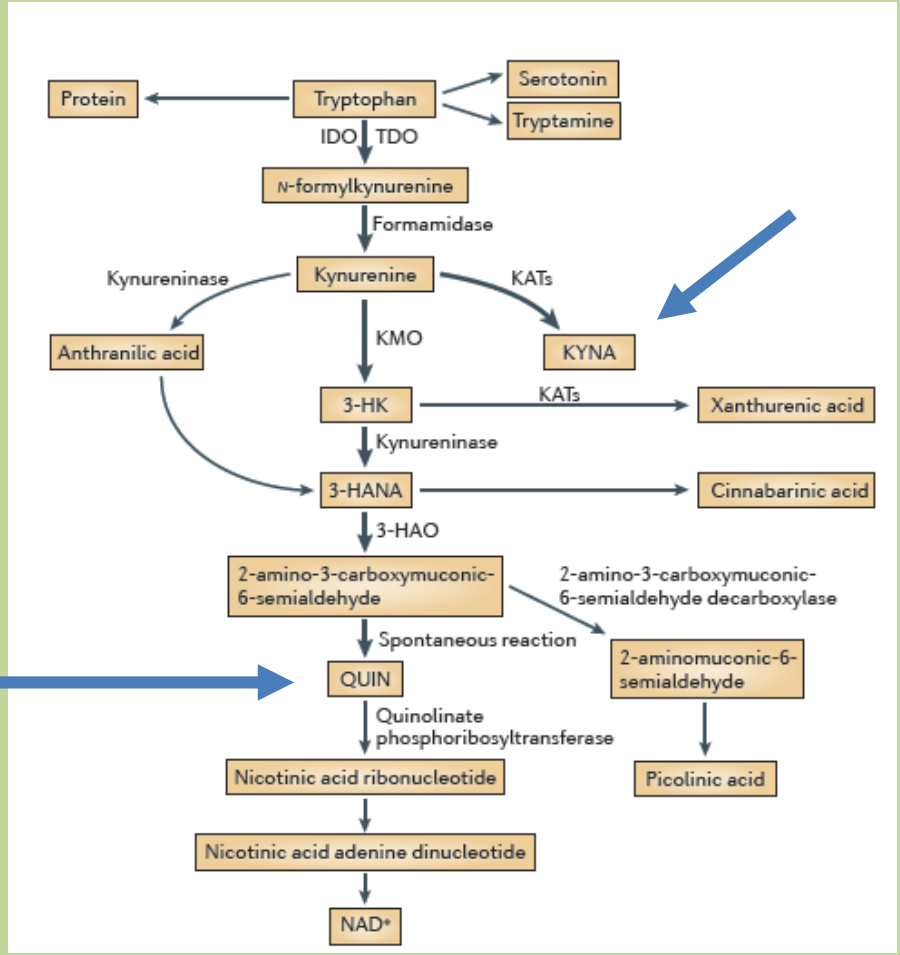
Cytokine signaling to the brain activates microglia that metabolize kynurenine into quinolinic acid.

Activated microglia also release glutamate.

Increased glutamatergic neurotransmission is thought to result in symptoms of depression.

Tryptophan-Kynurenine Pathway

(normally occurs in muscle)



Kynurenic acid (KYNA),

- Depression is associated with elevated kynurenine levels.
- The Kynurenine pathway in muscle is a source of the coenzyme NAD+, crucial for mitochondrial function.
- Two main metabolites: Kynurenic acid (KYNA) and Quinolinic Acid (QUIN)
- KYNA is an antagonist of glutamate receptors, inhibiting all three excitatory receptors — NMDA receptors (NMDARs), kainate receptors and AMPA receptors (AMPARs)
- KYNA also has antioxidant properties and is able to scavenge free radicals
- In rodent forebrain, increases in KYNA cause prompt reductions in extracellular glutamate and dopamine levels.

Schwarcz R. Kynurenines in the mammalian brain: when physiology meets pathology. NATURE REVIEWS | NEUROSCIENCE (13): 465-477

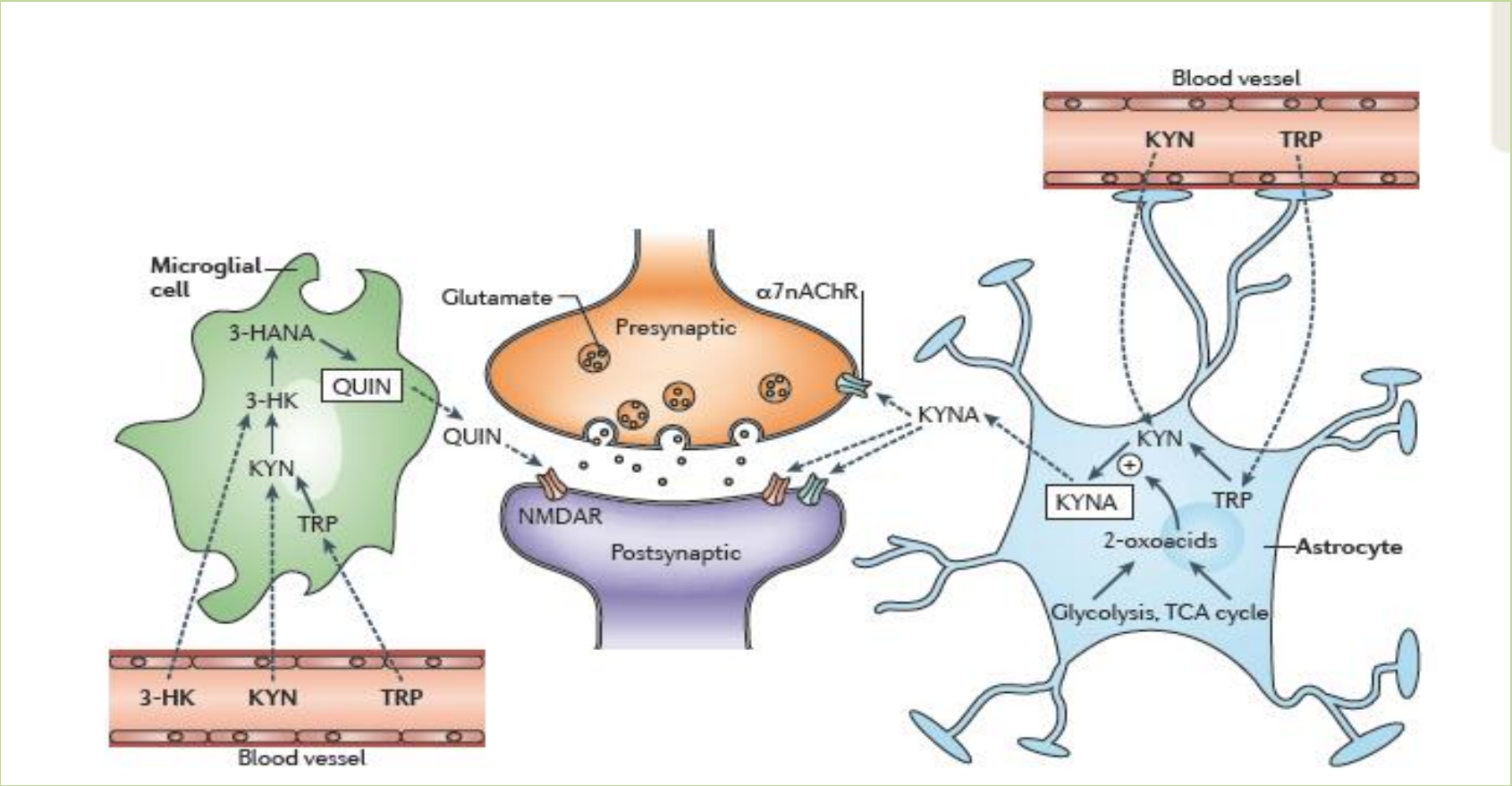
Quinolinic acid (QUIN)

- Depressed patients have significantly increased QUIN-positive cells.
- Upregulation of microglial QUIN in brain regions associated with depression.
- Subsyndromal inflammation thought to cause increased QUIN and glutamatergic activity.
- QUIN has a >tenfold greater affinity for the NR2B NMDAR subunit in the forebrain compared to the hindbrain-specific NR2C subunit.

de Carvalho LP. Neurochem Int. 1996 Apr;28(4):445-52. The endogenous agonist quinolinic acid and the non endogenous homoquinolinic acid discriminate between NMDAR2 receptor subunits.

- QUIN also stimulates lipid peroxidation and generation of reactive oxygen and nitrogen species.

Dantzer R. J Neural Transm (Vienna). 2014 Aug;121(8):925-32. Is there a role for glutamate-mediated excitotoxicity in inflammation-induced depression?



Metabolism is driven by levels of tryptophan (TRP), kynurenine (KYN) or 3-hydroxykynurenine (3-HK).

Pathway is physically separated in the brain ;

- Astrocytes contain kynurenine aminotransferases (KATs) and produce kynurenic acid (KYNA)
- Microglia contain kynurenine 3-monooxygenase (KMO) and produce quinolinic acid (QUIN)

Exercise can modulate Inflammation

- Acute exercise generates *reactive oxygen species* (ROS) and inflammatory cytokines that cause inflammation.

Sachdev S, Production, detection, and adaptive responses to free radicals in exercise. Free Radic Biol Med. 2008;44:215–223.

- During acute exercise, a rapid increase in IL-6 is quickly followed by induction of anti-inflammatory IL-1ra and IL-10

Ostrowski K, Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. J Physiol. 1999;515:287–291.

Exercise can modulate Inflammation

- Recovery after exercise-induced IL-6 spike dampens the inflammatory response and oxidative burst activity.

Walsh NP. Exerc Immunol Rev. 2011;17:6–63. Position statement. Part one: Immune function and exercise.

- Regular exercise down-regulates systemic inflammation via homeostatic adaptation.

Teixeira de Lemos E. Mediators Inflamm. 2011;2011:253061. Differential effects of acute (extenuating) and chronic (training) exercise on inflammation and oxidative stress status in an animal model of type 2 diabetes mellitus.

- Exercise modulates oxidative stress and neurotrophins, with positive effects on neuroplasticity and normal neuronal functions.

Moylan S Neurosci Biobehav Rev. 2013 May;37(4):573-84. Exercising the worry away: how inflammation, oxidative and nitrogen stress mediates the beneficial effect of physical activity on anxiety disorder symptoms and behaviours.

Exercise can modulate Inflammation

- Rats subjected to Chronic Variable Stress (CVS)[which induces depression] developed oxidative damage.
- Exercise prevented oxidative damage, but was unable to reverse all enzyme changes .

Santos TM. Int J Dev Neurosci. 2016 Dec 27. (16)30223-4. Effects of previous physical exercise to chronic stress on long-term aversive memory and oxidative stress in amygdala and hippocampus of rats.

- Exercise increases KAT 1, 3, and 4 in the muscle of mice.
- Shifts kynurenine metabolism to kynurenic acid (KYNA).
- KAT gene and protein expression increased in muscles of endurance-trained subjects.

Schlittler M. Am J Physiol Cell Physiol. 2016 May 15;310(10) Endurance exercise increases skeletal muscle kynurenine aminotransferases and plasma kynurenic acid in humans.

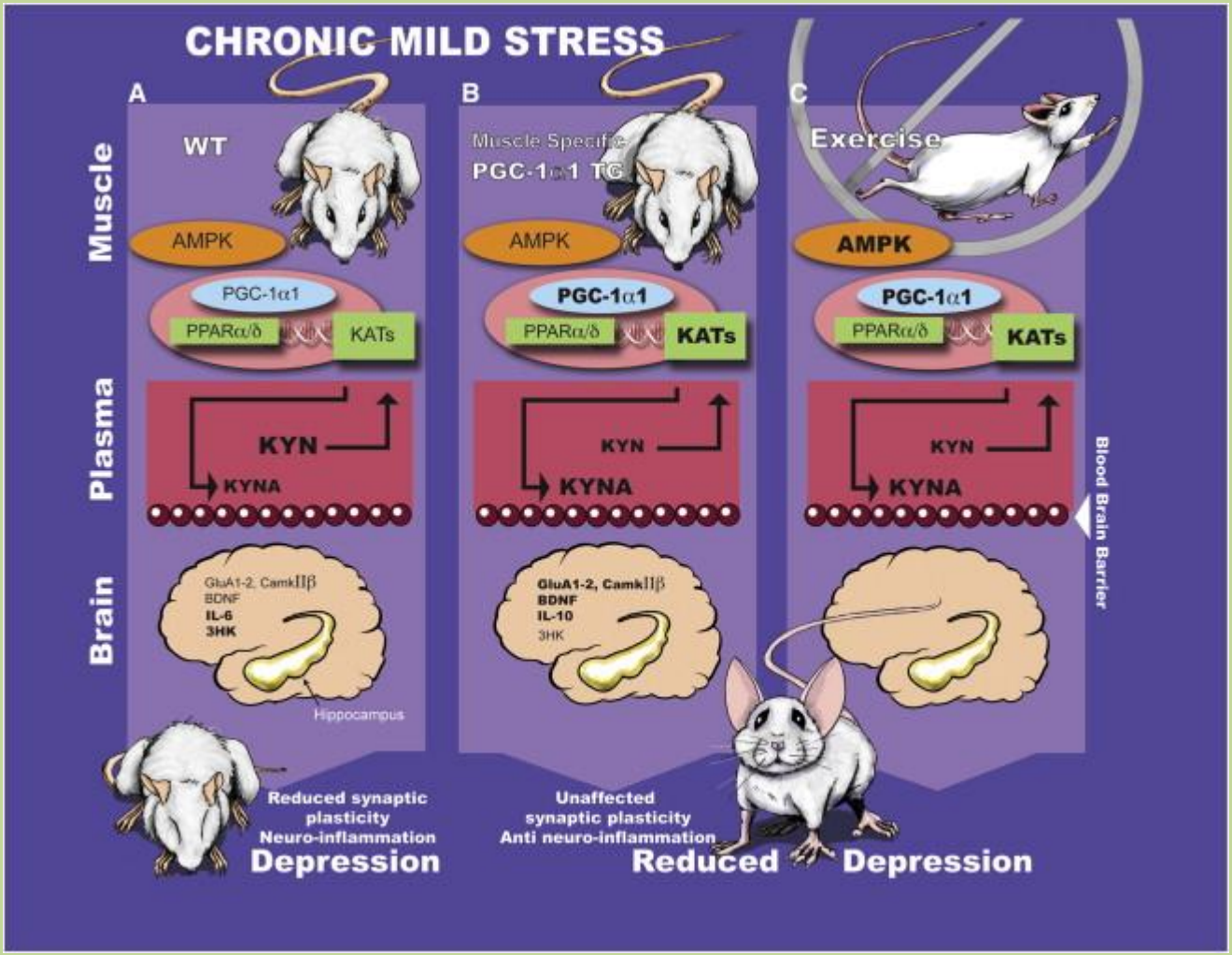
Effect of Exercise on Kynurenine (KYN) metabolism

- Peroxisome proliferator-activated receptor-gamma co-activator (PGC-1α1) promotes KAT expression, reducing circulating kyenurine (KYN).
- Mice with gene deletion had reduced KAT expression and displayed depressive behaviour following KYN administration.
- Mice that overexpress PGC-1α1 (mck-PGC-1α1) were subjected to 5-weeks of chronic mild unpredictable stress (CMS).
- Mice were resistant to stress and protected from pro-inflammatory changes.
- Cytokines induced by CMS (IL-6, TNFα, and IL-1β) were unchanged in hippocampus, but anti-inflammatory IL-10 was significantly increased.
- Resilience of mck-PGC-1α1 mice to depression “may be due to reduction of stress-induced neuro-inflammation”.

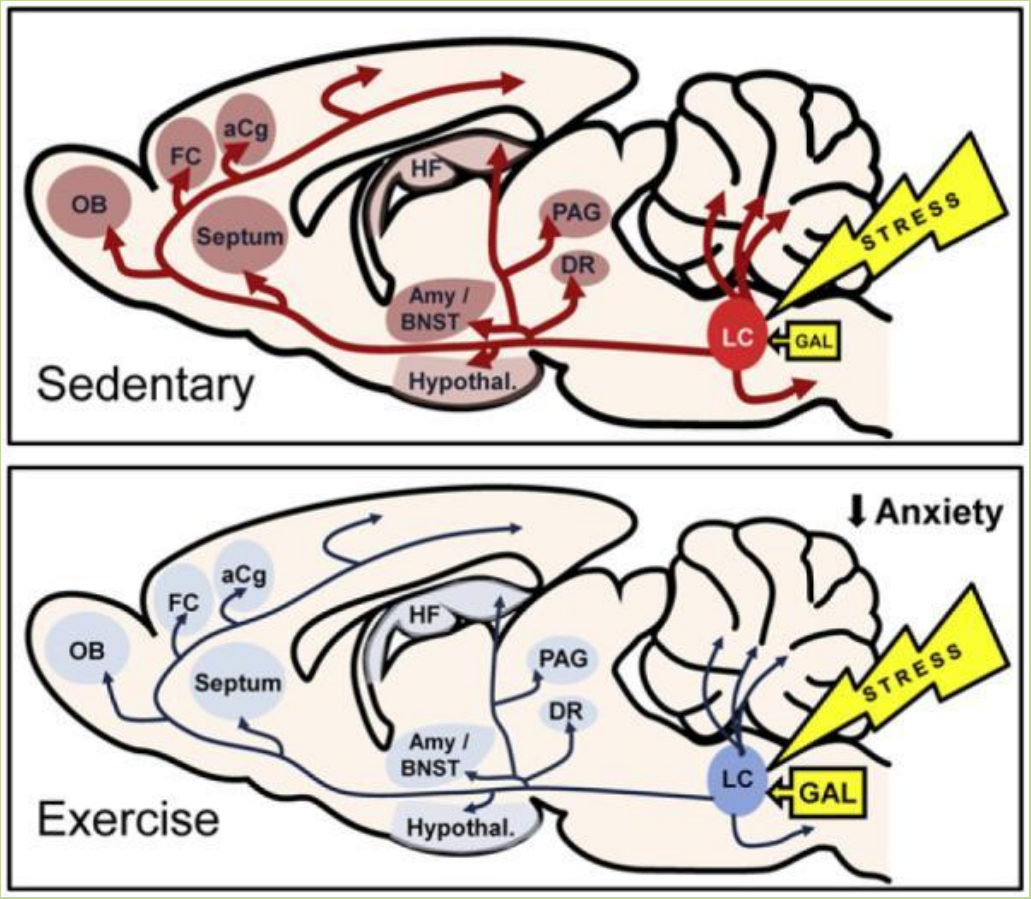
Agudelo LZ. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. Cell. 2014 Sep 25;159(1):33-45

Plasma kynurenine (KYN) levels are elevated by chronic mild stress.

GM Mice that overexpress KATs are protected from exhibiting depressive-like behaviour through upregulation of Kynurenic Acid (KYNA) pathway.



Exercise also helps to reduce Anxiety

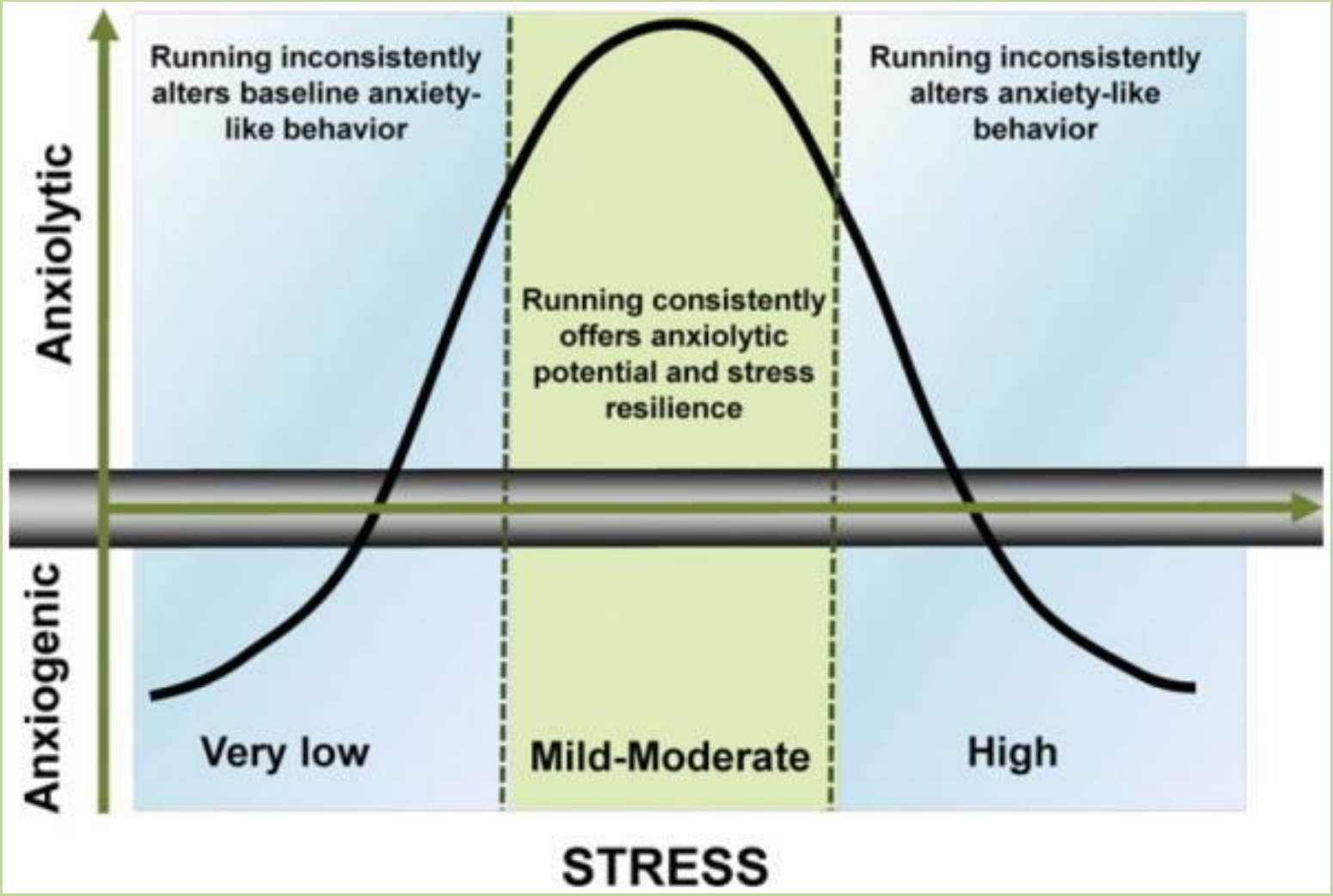


Greenwood BN. Eur J Neurosci. 2013;37(3): 469-478. Exercise-induced stress resistance is independent of exercise controllability and the medial prefrontal cortex.

Stress increases Noradrenaline (NA) output from the Locus Coeruleus to brain circuits that control anxiety.

Rats that exercise increase expression of the peptide galanin which decreases NA output.

Exercise is most effective in mild to moderate Stress/Anxiety



Greenwood BN, Eur J Neurosci. 2013;37(3): 469-478.

Conclusion

- There is increasing evidence that physiology does influence emotion and mood.
- Perhaps it's time to stop talking about mental health and instead focus on creating "healthy minds".
- Encouraging and facilitating our children and patients to exercise is an investment in their healthy mind.