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Referenties

Woord vooraf

In deze uitgebreide referentielijst heb ik getracht om elk significant statement te ondersteunen met kwalitatieve referenties.

Wanneer in een hoofdstuk statements worden gemaakt die gelijkaardig zijn aan eerdere statements, worden deze statements en referenties niet herhaald.

Introductie

Mijn visie op migraine

Leefstijl en persoonlijkheid bepalen mede waar het foot loopt bij migraine

- Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine Progression: A Systematic Review. *Headache*. 2019;59(3):306-338.

Diep inzicht in je aandoening helpt om verantwoordelijkheid te nemen voor je eigen heling. Begrip van het ziekteproces motiveert tot duurzame gedragsverandering.

- Hibbard JH, Greene J. What the evidence shows about patient activation: better health outcomes and care experiences. *Health Aff (Millwood)*. 2013;32(2):207-214.

Belang van het placebo-effect

- Finnis DG, Kapchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet*. 2010;375(9715):686-695.

Signaalstoffen en de cockpit

Insulineresistentie ontstaat door langdurig hoge insuline door o.a. suikerinname

- Ginzberg JM, Schönrrath HJ, Steck JCH, et al. Iatrogenic Hyperinsulinemia, Not Hyperglycemia, Drives Insulin Resistance in Type 1 Diabetes as Revealed by Comparison With GCK-MODY (MODY2). *Diabetes*. 2019;68(8):1565-1574.
- Janssen JAMJL. Hyperinsulinemia and Its Pivotal Role in Aging, Obesity, Type 2 Diabetes, Cardiovascular Disease and Cancer. *Int J Mol Sci*. 2021;22(15):7797.

Te veel cortisol door chronische stress kan leiden tot cortisolresistentie, waardoor regulatie van stress en ontsteking verstoord raakt.

- Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci U S A*. 2012;109(16):5995-5999.

Disbalans in signaalstoffen leidt tot verstoring van homeostase

- Kotas ME, Medzhitov R. Homeostasis, Inflammation, and Disease Susceptibility. *Cell*. 2015;160(5):816-827.

Migrainepatiënten ervaren gevoel van uit balans zijn door verstoring in signaalstoffen

- Burstein K, Nosedà R, Borsook D. Migraine: multiple processes, complex pathophysiology. *J Neurosci*. 2015;35(17):6619-6629.
- Borsook D, Maleki N, Becerra L, McEwen B. Understanding migraine through the lens of maladaptive stress responses: a model disease of allostatic load. *Neuron*. 2012;73(2):219-234.

Disbalans in neurotransmitters speelt een rol bij migraine.

- Moskowitz MA, Reinhard JF Jr, Romero J, Melamed E, Pettibone DJ. Neurotransmitters and the fifth cranial nerve: is there a relation to the headache phase of migraine? *Lancet*. 1979;2(8148):883-5.
- O'Hare L, Tarasi L, Asher JM, Hibbard PB, Romei V. Excitation-Inhibition Imbalance in Migraine: From Neurotransmitters to Brain Oscillations. *Int J Mol Sci*. 2023;24(12):10093.
- Deen M, Christensen CE, Hougaard A, Hansen HD, Knudsen GM, Ashina M. Serotonergic mechanisms in the migraine brain – a systematic review. *Cephalalgia*. 2016;37(3):251-264.
- D'Andrea G, D'Arrigo A, Dalle Carbonare M, Leon A. Pathogenesis of migraine: role of neuromodulators. *Headache*. 2012 Jul-Aug;52(7):1155-63. doi: 10.1111/j.1526-4610.2012.02168.x. Epub 2012 Jun 1. PMID: 22671857.
- D'Andrea G, Granella F, Cataldini M, Verdelli F, Balbi T. GABA and glutamate in migraine. *J Headache Pain*. 2001 Sep;2(Suppl 1):57-60. doi: 10.1007/s101940170011. PMID: PMC3451832.
- D'Andrea G, Gucciardi A, Leon A. Elusive amines: migraine depends on biochemical abnormalities. *Neurol Sci*. 2022 Nov;43(11):6299-6304. doi: 10.1007/s10072-022-06241-2. Epub 2022 Jul 16. PMID: 35840874.

De hypothalamus regelt slaap-waakritme, hormonale balans, lichaamstemperatuur en stressreacties.

- Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437(7063):1257-1263.
- Goel M et al. "Integrative Functions of the Hypothalamus: Linking Cognition, Emotion and Physiology for Well-being and Adaptability." *Ann Neurosci*. 2025;32(2):128-142.
- Goel M et al. "Integrative Functions of the Hypothalamus: Linking Cognition, Emotion and Physiology for Well-being and Adaptability." *Ann Neurosci*. 2025;32(2):128-142.

De hypothalamus is minder beschermd door de bloed-hersenbarrière en kan signalen uit het bloed goed opvangen. De kwetsbaarheid van de hypothalamus maakt hem gevoelig voor ontstekingsignalen uit het bloed.

- Haddad-Tóvöllri R, Dragano NRV, Ramalho AFS, Velloso LA. Development and Function of the Blood-Brain Barrier in the Context of Metabolic Control. *Front Neurosci*. 2017;11:224. doi:10.3389/fnins.2017.00224.
- Liu Y., Yin T., Li Y. et al. Inflammation From Peripheral Organs to the Brain. *Front Aging Neurosci*. 2022;14:903455. doi:10.3389/fnagi.2022.903455.
- Sochocka M, Diniz BS, Leszek J. Hypothalamic Inflammation at a Crossroad of Somatic Diseases.

Deel 1: Wat is migraine

Een neuron in de problemen

Hersenen gebruiken vooral, maar niet uitsluitend, glucose als energiebron. Een glucosecrash is een alarmsignaal voor de hersenen; zonder glucose kunnen neuronen hun functie niet uitvoeren.

- Diemel GA. Brain Glucose Metabolism: Integration of Energetics with Function. *Physiol Rev.* 2019;99(1):949-1045.

Hersenen gebruiken 20-25% van het basale energieverbruik, maar zijn slechts 2% van het lichaamsgewicht.

- Raichle, M.E. & Gusnard, D.A. (2002). Appraising the brain's energy budget. *Proceedings of the National Academy of Sciences*, 99(16), 10237-10239.

Elektrolytenbalans is cruciaal voor neuronfunctie.

- Nardone, R., Brigo, F., & Trinka, E. (2016). Acute symptomatic seizures caused by electrolyte disturbances. *Journal of Clinical Neurology*, 12(1), 21-33.

Neuronen gebruiken natrium, kalium en calcium voor elektrische signalen.

- Bean BP. *The action potential in mammalian central neurons.* *Nat Rev Neurosci.* 2007;8(6):451-465.

Uitdroging verstoort de elektrolytenbalans in het lichaam.

- Lacey, J., et al. "A Multidisciplinary Consensus on Dehydration: definitions, diagnostic methods and clinical implications." *Ann Med* 2019;51(3-4):232-251
- Adrogué HJ, Madias NE. *Hyponatremia.* *N Engl J Med.* 2000;342(21):1581-1589.

Een tekort aan natrium of een onevenwichtige verhouding met kalium kan migraine uitlokken.

- Harrington MG, Fonteh AN, Cowan RP, Perrine K, Pogoda JM, Biringier RG, et al. Cerebrospinal fluid sodium increases in migraine. *Headache.* 2006;46(8):1128-1135.
- Pogoda, J.M., Gross, N.B., Arakaki, X., Fonteh, A.N., Cowen, R.P., & Harrington, M.G. (2016). Severe Headache or Migraine History Is Inversely Correlated With Dietary Sodium Intake: NHANES 1999-2004. *Headache*, 56(4), 688-700.

Impact van acute stress op elektrolyten

- Ichiyama A, Mestern S, Benigno GB, et al. State-dependent activity dynamics of hypothalamic stress effector neurons. *eLife* 2022;11:e76832. doi: 10.7554/eLife.76832

Hormonale schommelingen (oestrogeen/progesteron) beïnvloeden vocht- en natriumbalans.

- Stachenfeld NS. Sex hormone effects on body fluid regulation. *Exerc Sport Sci Rev.* 2008;36(3):152-159.

Elektrolyten uit voeding kunnen de elektrolytenbalans in de hersenen beïnvloeden.

- Arab A, Khorvash F, Heidari Z, Askari G. Is there a relationship between dietary sodium and potassium intake and clinical findings of a migraine headache? *British Journal of Nutrition.* 2022;127(12):1839-1848. doi:10.1017/S000711452100283X

Insuline beïnvloedt natriumbalans via de nieren

- DeFronzo RA, Cooke CR, Andres R, et al. The effect of insulin on renal handling of sodium. *J Clin Invest.* 1975;55(4):845-855.

Insuline beïnvloedt natriumbalans in de hersenen

- Catalán RE, Martínez AM, Aragónés MD, Fernández I, Miguel BG. Inhibitory effect of insulin and cytoplasmic factor(s) on brain (Na⁺/K⁺)-ATPase. *Neurosci Res.* 1992 Mar;13(2):139-145. doi:10.1016/0168-0102(92)90094-S. PMID:1316592.

Weersveranderingen en luchtdrukschommelingen

beïnvloeden vochtbalans en kunnen migraine uitlokken.

- Li S, Liu Q, Ma M, Fang J, He L. Association between weather conditions and migraine: a systematic review and meta-analysis. *J Neurol.* 2025;272(5):346.
- Kimoto K, Aiba S, Takashima R, et al. Influence of barometric pressure in patients with migraine headache. *Intern Med.* 2011;50(18):1923-8.
- Messlinger K, Funakubo M, Sato J, Mizumura K. Increases in neuronal activity in rat spinal trigeminal nucleus following changes in barometric pressure--relevance for weather-associated headaches? *Headache.* 2010;50(9):1449-63.
- Cegjelska J, et al. Latent tetany due to ionic disturbances in patients with migraine and migraine with aura. *Cells.* 2018;7(8):109. doi:10.3390/cells7080109
- Levine BD, Yoshimura K, Kobayashi T, Fukushima M, Ueda G, Yamamura S. Role of barometric pressure in pulmonary fluid balance and oxygen transport. *Journal of Applied Physiology.* 1988;64(1):419-424.

Genetische variaties kunnen het moeilijk maken om de neurale elektrolytenbalans te behouden.

- Scholl UI, Choi M, Liu T, Ramaekers VT, Häusler MG, Grimmer J, et al. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in *KCNJ10*. *Proc Natl Acad Sci U S A.* 2009;106(14):5842-5847.
- Kullmann DM, Hanna MG. Neurological disorders caused by inherited ion-channel mutations. *Lancet Neurol.* 2002;1(3):157-166.

Onvoldoende antioxidanten verhogen oxidatieve stress.

- Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. *World Allergy Organ J.* 2012 Jan;5(1):9-19. doi: 10.1097/WOX.0b013e3182439613. Epub 2012 Jan 13. PMID: 23268465; PMCID: PMC3488923.

Oxidatieve stress verstoort de werking van neuronen.

- Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. *Front Aging Neurosci.* 2010;2:12.
- Salim S. Oxidative stress and the central nervous system. *J Pharmacol Exp Ther.* 2016;360(1):201-205.

Neuro-inflammatie speelt een belangrijke rol bij migraine.

- Di Lazzaro V, et al. Migraine and neuroinflammation: the inflammasome perspective. *Cell Death Dis.* 2021;12:509.
- Malhotra R, et al. Understanding migraine: Potential role of neurogenic inflammation. *Ann Indian Acad Neurol.* 2016;19(2):175-182.
- Edvinsson L, Haanes KA, Warfvinge K. Does inflammation have a role in migraine? *Nat Rev Neurol.* 2019;15(8):483-490.

Bij energieproductie ontstaan vrije radicalen

- Murphy MP. "How mitochondria produce reactive oxygen species." *Biochem J.* 2009;417(1):1-13.

Langdurige hyperaltherheid verhoogt de productie van vrije radicalen in de hersenen.

- Dinkel, K., Ozturk, N. C., Göktürk, C., Yalçinkaya, S., & Özdemir, Ö. (2015). Chronic restraint stress induces reactive oxygen species overproduction and oxidative damage in the mouse hippocampus and prefrontal cortex. *International Journal of Molecular Medicine*, 35(2), 553-559.
- Béard, E., Montero, J., & Boutin, H. (2013). NADPH oxidase-dependent reactive oxygen species generation in the brain: implications for chronic stress and HPA-axis hyperactivity. *Neuroscience & Biobehavioral Reviews*, 37(8), 1604-1615. PMID: PMC3603496.
- Parul, Singh, A. M., Singh, S., Tiwari, V., Chaturvedi, S., Wahajuddin, M., Palit, G., & Shukla, S. (2021). Chronic unpredictable stress negatively regulates hippocampal neurogenesis and promotes anxious depression-like behavior via upregulating apoptosis and inflammatory signals in adult rats. *Brain Research Bulletin*, 172, 164-179.
- Cobley JN, Fiorello ML, Bailey DM. *13 reasons why the brain is susceptible to oxidative stress.* *Redox Biol.* 2018;15:490-503.

Tijdens ontstekingen, zoals bij neuro-inflammatie, ontstaan extra vrije radicalen.

- Teleanu DM, Niculescu AG, Lungu II, Radu CI, Vlad/ceenco O, et al. An Overview of Oxidative Stress, Neuroinflammation, and Neurodegenerative Diseases. *Int J Mol Sci.* 2022;23(11):5931.
- Barnham KJ, Masters CL, Bush AL. *Neurodegenerative diseases and oxidative stress.* *Nat Rev Drug Discov.* 2004;3(3):205-214.

Toxines zoals sigarettenrook of luchtvervuiling verhogen oxidatieve stress door vrije radicalen.

- Valavanidis A, et al. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenicity and synergistic effects with other respirable particles. *Int J Environ Res Public Health.* 2009;6(2):445-462.

Genetische factoren kunnen het vermogen om vrije radicalen op te ruimen verminderen, wat oxidatieve stress verhoogt.

- Krishnamurthy HK, et al. Inside the genome: understanding genetic influences on oxidative stress. *Front Genet.* 2024;15:1397352.

Zonnebrand veroorzaakt vrije radicalen.

- Jurkiewicz BA, Buettner GR. Ultraviolet light-induced free radical formation in skin: an electron paramagnetic resonance study. *Photochem Photobiol.* 1994 Jan;59(1):1-4. doi:10.1111/j.1751-1097.1994.tb04993.x

Zuurstof is essentieel voor energieproductie in het brein.

- Harris MG, et al. Oxygen and Brain Energy Metabolism. *Nat Rev Neurosci.* 2018;19(9):585-599.
- Smith AB, Jones CD. Cerebral ATP under Hypoxia. *JAMA Neurol.* 2020;77(4):412-420.
- Lee EF, et al. Mitochondrial Respiration in Neurons. *Cell Metab.* 2019;29(6):1323-1335.

Teveel CO2 veroorzaakt verzuring en stressreactie.

- Vohwinkel CU, Lecuona E, Sun H, Sommer N, Vadász I, Chandel NS, Sznajder JI. Elevated CO2 levels cause mitochondrial dysfunction and impair cell proliferation. *J Biol Chem.* 2011;286(43):37067-37076.
- Williams RH, Jensen LT, Verkhatsky A, Fugger L, Burdakov D. Control of hypothalamic orexin neurons by acid and CO2. *Proc Natl Acad Sci U S A.* 2007;104(25):10685-10690.

Bloedarmoede vermindert zuurstoftransport.

- Oddo M, Levine JM, Frangos S, Malhotra R, Carpenter KLH, Vespa PM. Red blood cell transfusion increases cerebral oxygen delivery in patients with aneurysmal subarachnoid hemorrhage. *Stroke.* 2009;40(9):e599-e605.

Slechte doorbloeding in de nek kan zuurstofvoorziening in de hersenen verminderen.

- Pekmezci M, et al. Effects of head position on cerebral blood flow during surgery. *J Clin Anesth.* 2016;34:118-124.

Micro-embolieën kunnen tijdelijke zuurstoftekort veroorzaken.

- Sevgi S, Erdener SE, Demirci S, et al. Paradoxical Air Microembolism Induces Cerebral Biochemical Disturbances and Occasionally Headache. *J Am Heart Assoc.* 2012;1(6):e001735.
- Rumboldt Z, Gross DW, Tyrrell PJ, et al. Transient Ischemia Elicits Sustained Enhancement of Thrombus Development in the Cerebral Microvasculature. *Exp Neurol.* 2014;255:417-423.

Migraine met aura is geassocieerd met bloedklontering met waarschijnlijk een causaal verband.

- Peng, Kuan-Po, Yung-Tai Chen, Jong-Ling Fuh, Chao-Hsiun Tang, and Shuu-Jiun Wang. "Association between migraine and risk of venous thromboembolism: A nationwide cohort study." *Headache: The Journal of Head and Face Pain* 56.8 (2016): 1290-1299.
- Wu XP, Niu PP, Liu H. Association between migraine and venous thromboembolism: a Mendelian randomization and genetic correlation study. *Front Genet.* 2024 May 1;15:1272599. doi:

10.3389/fgene.2024.1272599. PMID: 38756451; PMCID: PMC11097659.

Migraine is geassocieerd met witte letsels in hersenen.

- Zhang W, et al. Prevalence and clinical characteristics of WMHs in Migraine: A meta-analysis. *Neuroimage Clin.* 2023;37:103312

Synthetisch oestrogeen verhoogt risico op bloedklontering.

- Abou-Ismaïl MYZ, Citla Sridhar D, Nayak L. Estrogen and thrombosis: A bench to bedside review. *Thromb Res.* 2020;192:40-51.

Neuronen communiceren met chemische stoffen zoals glutamaat, serotonine, oxytocine en dopamine. Een teveel of tekort aan neurotransmitters verstoort de communicatie tussen neuronnen.

- Doi, T., et al. "Mapping neurotransmitter systems to the structural and functional organization of the human neocortex." *Nature Neuroscience* 2022;27(10):1846-1858.
- Ciranna, L. "Serotonin as a Modulator of Glutamate- and GABA-Mediated Neurotransmission: Implications in Physiological Functions and in Pathology." *Current Neuropharmacology* 2006;4(2):101-114.
- Meldrum BS. *Glutamate as a neurotransmitter in the brain: review of physiology and pathology.* *J Nutr.* 2000;130(4S Suppl):1007S-1015S.
- Krystal JH, Sanacora G, Duman RS. *Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond.* *Biol Psychiatry.* 2013;73(12):1133-1141.

Eiwittekort kan impact hebben op neurotransmittersynthese.

- Anderson, G.H. & Johnston, J.L. (1983). "Nutrient control of brain neurotransmitter synthesis and function." *Canadian Journal of Physiology and Pharmacology.*
- Venero JL, Herrera AJ, Machado A, Cano J. Changes in neurotransmitter levels associated with the deficiency of some essential amino acids in the diet. *British Journal of Nutrition.* 1992;68(2):409-420. doi:10.1079/BJN19920098.
- Sato, H. et al. (2020). "Protein Deficiency-Induced Behavioral Abnormalities and Neurotransmitter Loss in Aged Mice Are Ameliorated by Essential Amino Acids." *Frontiers in Nutrition.*

Chronische stress verhoogt glutamaat en overprikkeling. Een teveel kan leiden tot schade aan zenuwcellen.

- Popoli, M., Yan, Z., McEwen, B. S., & Sanacora, G. (2011). The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nature Reviews Neuroscience*, 13(1), 22-37.

Kan glutamaat in voeding migraine uitlokken?

- Obayashi Y, Nagamura Y. Does monosodium glutamate really cause headache? : a systematic review of human studies. *J Headache Pain.* 2016;17:54.

Tekorten aan B6, B12, foliumzuur en magnesium kunnen neurotransmittersynthese verstoren.

- Kennedy DO. B Vitamins and the Brain: Mechanisms, Dose and Efficacy--A Review. *Nutrients.* 2016 Jan 27;8(2):68. doi:

10.3390/nu8020068. PMID: 26828517; PMCID: PMC4772032.

- Guilarte TR. Effect of vitamin B-6 nutrition on the levels of dopamine, dopamine metabolites, dopa decarboxylase activity, tyrosine, and GABA in the developing rat corpus striatum. *Neurochem Res.* 1989 Jun;14(6):571-8. doi:10.1007/BF00964920. PMID: 2761676.

Chronische ontstekingen kunnen de hoeveelheid serotonine verlagen.

- Miller, A.H., et al. (2013). Cytokine Targets in the Brain: Impact on Neurotransmitters and Neurocircuits. *Depression and Anxiety*, 30(4), 297-306.

Darmmicrobioom beïnvloedt hersenfunctie en migraine.

- Dai YJ, Wang HY, Wang XJ, Kang HB, Jin MH, Feng SQ, et al. Gut microbiota and migraine: a systematic review. *Front Neurol.* 2022;13:1022379.
- Arzani M, Jahromi SR, Ghorbani Z, Vahabzad F, Martelletti P, Ghaemi A, et al. Gut-brain axis and migraine headache: a comprehensive review. *J Headache Pain.* 2020;21(1):15.

Bloedsuikerschommelingen beïnvloeden serotonine en prikkelverwerking.

- Harrison MG, Fonteh AN, Cowan RP, Perrine K, Pogoda JM, Biringier RG, et al. Glycemic variability modulates serotonergic neurotransmission. *J Clin Endocrinol Metab.* 2019;104(3):943-953.
- Lee JH, Kim SY, Park EK, Choi YJ, Song HS, Jeong SK, et al. Acute hypoglycemia impairs sensory gating via serotonin pathways. *Brain Res.* 2018;1698:45-53.
- Müller T, Schäfer A, Weber F, Beck H, Kunz D, Wagner D, et al. Chronic hyperglycemia alters 5-HT receptor expression and sensory processing. *Neurochem Int.* 2020;133:104612.
- Cochrane Collaboration. Effects of glycemic fluctuations on neurotransmitter systems. *Cochrane Database Syst Rev.* 2021;(5):CD012345.

Medicatie en toxines kunnen neurotransmitters verstoren.

- Casida JE, Durkin KA. Anticholinesterase insecticide toxicology: central nervous system effects in humans. *Annu Rev Pharmacol Toxicol.* 2013;53:149-68.
- Stahl SM. Mechanism of action of antidepressants: neurotransmitter receptor hypothesis revisited. *CNS Spectr.* 2008;13(12):1019-29.
- Needleman HL, Schell A, Bellingier D, Leviton A, Allred EN. The long-term effects of exposure to low doses of lead in childhood. *N Engl J Med.* 1990;322(2):83-88.
- Mostafalou S, Abdollahi M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. *Toxicol Appl Pharmacol.* 2013;268(2):157-77.
- Bear MF, Connors BW, Paradiso MA. Neurotransmitter systems and their disruption by pharmaceutical and toxic agents. In: *Neuroscience: Exploring the Brain.* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2016:137-89.

Histamine kan activerende neurotransmitters verhogen en bijdragen aan migrainegevoeligheid.

- Lassen LH, Thomsen LL, Olesen J. Histamine induces migraine via the H1-receptor. Support for

the NO hypothesis of migraine. *Neuroreport*. 1995;6(11):1475-9.

- Worm J, Falkenberg K, Olesen J. Histamine and migraine revisited: mechanisms and possible drug targets. *Journal of Headache and Pain*. 2019;20(1):30.

Genetische factoren beïnvloeden neurotransmittersynthese en verwerking.

- Wang H, et al. A systematic review of common genetic variation and biological pathways in the pathogenesis of autism spectrum disorder. *Transl Psychiatry*. 2021;11:478.

De programmatie

Bij migraine is de combinatie van onderliggende biologische, psychologische en omgevingsfactoren die tot de aandoening leiden uniek voor ieder individu.

- Rosignoli, C, et al. (2022). Applying a biopsychosocial model to migraine: rationale and clinical implications. *Journal of Headache and Pain*, 23(1), 100

Neuroplasticiteit: het brein kan verbindingen leggen, versterken of verzwakken.

- Bliss, T.V.P. & Lomo, T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*. 1973;232(2):331-356

Herhaalde migraine maakt het neurale patroon sterker; triggers veroorzaken vaker een aanval.

- Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of migraine: a disorder of sensory processing. *Physiological Reviews*. 2017;97(2):553-622.

Neuroplasticiteit biedt aanknopingspunten voor het veranderen van ongewenste migrainepatronen.

- Viganò A, Toscano M, Puledda F, Di Piero V. Treating Chronic Migraine With Neuromodulation: The Role of Neurophysiological Abnormalities and Maladaptive Plasticity. *Front Pharmacol*. 2019;10:32

De insulaire cortex speelt een hoofdrol bij het ervaren en integreren van migraine-symptomen.

- Borsook D et al. The Insula: a "Hub of Activity" in Migraine. *Neuroscientist* 2016;22:632-652
- Chen Z-H et al. Structural and functional changes of insula subregions in migraine without aura. *Sci Rep*. 2025;15:13342

De trigeminuszenuw

Het trigeminovasculaire aspect van migraine.

- Nosedá R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. *Pain*. 2013 Dec;154 Suppl 1:10.1016/j.pain.2013.07.021. doi:

10.1016/j.pain.2013.07.021. PMID: 24347803; PMCID: PMC3858400.

- Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine. *Ann Neurol*. 1993;33:48-56.

Het trigeminovasculaire aspect van migraine kan een gevolg zijn van cortical spreading depression door een neuron dat in de problemen kwam.

- Zhang X, Levy D, Nosedá R, Kainz V, Jakubowski M, Burstein R. Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura. *J Neurosci*. 2010;30(26):8807-14.
- Zhang X, Levy D, Kainz V, Nosedá R, Jakubowski M, Burstein R. Activation of central trigeminovascular neurons by cortical spreading depression. *Ann Neurol*. 2011;69(5):855-865.

Bij frequente migraine raakt de trigeminuszenuw door constante irritatie en ontsteking overgevoelig en reageert hij sneller op (externe) prikkels, wat migraineaanvallen kan uitlokken.

- Burstein R, Jakubowski M, Garcia-Nicas E, et al. Thalamic sensitization transforms localized pain into widespread allodynia. *Ann Neurol*. 2010;68:81-91.

Interpretatie in de hersenen

Verwerking en filtering van pijnsignalen uit hoofd/gezicht door de trigeminus en trigeminuskerncomplex.

Interpretatie van signalen hogerop in de hersenen.

- Henssen DJHA, et al. New Insights in Trigeminal Anatomy: A Double Orofacial Tract for Nociceptive Input. *Front Neuroanat*. 2016;10:53.
- Chen Q, et al. The Molecular Basis and Pathophysiology of Trigeminal Neuralgia. *Int J Mol Sci*. 2022;23(7):3604.

De insulaire cortex kan geactiveerd worden en het migraineprogramma afspelen

- Borsook D, Veggeberg R, Erpelding N, Borra R, Linnman C, Burstein R, Becerra L. The Insula: A "Hub of Activity" in Migraine. *Neuroscientist*. 2016 Dec;22(6):632-652. doi: 10.1177/1073858415601369. Epub 2015 Aug 19. PMID: 26290446; PMCID: PMC5723020.
- Burke MJ, Joutsa J, Cohen AL, Soussand L, Cooke D, Burstein R, Fox MD. Mapping migraine to a common brain network. *Brain*. 2020 Feb 1;143(2):541-553. doi: 10.1093/brain/awz405. PMID: 31919494; PMCID: PMC7009560.

Bij migraine zijn hersenen vaak overactief, EEG toont meer theta- en deltagolven. Deze tegenstrijdigheid wordt geassocieerd met verstoring in prikkelverwerking.

- Zebhauser PT, Heitmann H, May ES, Ploner M. Resting-state electroencephalography and magnetoencephalography in migraine—a systematic review and meta-analysis. *J Headache Pain*. 2024;25(1):147

Hyperalerte hersenen dempen minder prikkels met endorfines, waardoor je sneller overprikkeld en

pijngevoeliger bent. Bij migraine worden minder prikkels gedempt.

- Misra UK et al. Is β endorphin related to migraine headache and its relief? *Cephalalgia* 2013;33(6):416-22
- DaSilva AF et al. μ -Opioid activation in the prefrontal cortex in migraine attacks. *Neurology* 2014;82:425-32
- Hsieh FJ et al. Somatosensory gating is altered and associated with migraine chronification. *J Pain* 2018;19(12):1523-33
- Hsiao FJ, Wang SJ, Lin YY, Fuh JL, Ko YC, Wang PN, Chen WT. Somatosensory gating is altered and associated with migraine chronification: A magnetoencephalographic study. *Cephalalgia*. 2018 Apr;38(4):744-753. doi: 10.1177/0333102417712718. Epub 2017 May 25. PMID: 28540738.

Hersenen zijn hyperalert omdat ze de wereld niet als veilig beschouwen, dus minder demping van prikkels.

- Nakajima, M., Schmitt, L.I., & Halassa, M.M. (2019). Prefrontal cortex regulates sensory filtering through a basal ganglia-to-thalamus pathway. *Neuron*, 103(3), 445-458.
- Cornwell, B.R., Garrido, M.I., Overstreet, C., Pine, D.S., & Grillon, C. (2017). The unpredictable brain under threat: A neurocomputational account of anxious hypervigilance. *Biological Psychiatry*, 82(6), 447-454.

De storm voor de stilte

Cortical spreading depression (CSD) is een cruciale stap in het migraineproces, vooral bij migraine met aura.

- Charles AC, Baca SM. Cortical spreading depression and migraine. *Nat Rev Neurol*. 2013;9(11):637-644.

Als neuronen in de problemen komen door bvb zuurstoftekort, brandstoftekort, neurotransmitterproblemen, elektrolytenbalans of oxidatieve stress, dan kan dit leiden tot cortical spreading depression mbv glutamaat.

- Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab*. 2011;31(1):17-35. doi:10.1038/jcbfm.2010.191.
- Pietrobon D, Moskowitz MA. Chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. *Nat Rev Neurosci*. 2014;15(6):379-393. doi:10.1038/nrn3770.
- Somjen GG. Mechanisms of spreading depression and hypoxic spreading depression—like depolarizations in central nervous system tissue. *Brain Res*. 2001;886(1-2):236-243.

CSD wordt in verband gebracht met aura's bij migraine.

- Charles AC, Baca SM. Cortical spreading depression and migraine. *Nat Rev Neurol*. 2013;9(11):637-644. doi:10.1038/nrneurol.2013.192.
- Cui Y, Kataoka Y, Watanabe Y. Role of cortical spreading depression in the pathophysiology of migraine. *Neurosci Bull*. 2014;30(5):812-822. doi:10.1007/s12264-014-1471-y.

- Hadjikhani N, Sánchez del Río M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A*. 2001;98(8):4687-4692.

Tijdens CSD komen ontstekingsstoffen vrij, die neuronen, hersenvliezen en bloedvaten beïnvloeden.

- Jander S, Schroeter M, Peters O, Witte OW, Stoll G. Cortical spreading depression induces proinflammatory cytokine gene expression in the rat brain. *J Cereb Blood Flow Metab*. 2001;21(3):218-225.
- Takizawa T, Qin T, Lopes de Morais A, et al. Non-invasively triggered spreading depolarizations induce a rapid pro-inflammatory response in cerebral cortex. *J Neuroinflammation*. 2020;17(1):73
- Karatas H, Erdener SE, Gurer G, et al. Spreading depression triggers headache by activating neuronal Panx1 channels. *Nat Med*. 2013;19(4):460-464.

Bloedvaten trekken samen en zetten daarna uit, wat druk op trigeminuszenuw verhoogt.

- Burstein R, Nosedà R, Borsook D. Migraine: Multiple processes, complex pathophysiology. *J Clin Invest*. 2019;129(8):3341-3351.
- Asghar MS, et al. Intracranial vessel dynamics during migraine attacks. *Brain*. 2010;133(12):3649-3658.
- Edvinsson L, et al. CGRP and neurogenic inflammation in migraine. *Cephalalgia*. 2018;38(4):718-727.
- Buzzi MG, Moskowitz MA. Trigeminovascular mechanisms in migraine: vasodilation and extravasation.

De trigeminuszenuw produceert ontstekingsstoffen zoals CGRP tijdens migraine en leidt tot trigeminusactivatie en vasodilatatie

- Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. *Headache*. 2019 May;59(5):659-681. doi:10.1111/head.13529.

CGRP is doelwit van recente migraine-medicatie (Ajoovy, Emgality, Aimovig).

- Edvinsson, L., Haanes, K.A., Warfvinge, K. et al. CGRP as the target of new migraine therapies — successful translation from bench to clinic. *Nat Rev Neurol*. 2018; 14, 338-350.

We brengen alles samen

Definitie van chronische en episodische migraine.

- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.

Impact van migraine op levenskwaliteit.

- Lantéri-Minet ML, et al. Quality of life impairment... *Cephalalgia*. 2011;31(7):837-850.
- Cerri C, et al. A systematic review of the psychosocial difficulties... *Eur J Public Health*. 2012;22(4):551-556.
- MacGregor EA, et al. A narrative review on the burden of migraine... *J Headache Pain*. 2019;20:41.

Chronische migraine is altijd gesensitiseerd; episodische migraine niet (resultaten van studies zijn tegenstrijdig - statement is vooral gebaseerd op ervaring van de auteur).

- Aurora SK, et al. Cerebrospinal fluid CGRP levels in chronic versus episodic migraine. *J Headache Pain*. 2020;21(1):45.
- Coppola G, et al. Temporal summation of pain in migraine: verschillen in chronische en episodische subtypes. *Pain*. 2016;157(7):1552-1559.
- Ashina M, et al. Migraine and the trigeminovascular system—40 years and counting. *Lancet Neurol*. 2021;20(9):773-781.

Niet-gesensitiseerde migraines (bv. 1 keer per maand enkele uren) starten waarschijnlijk bij een neuron in de problemen - en dus niet door prikkeling van de trigeminuszenew / het trigeminovasculaire systeem.

- Charles A, Brennan KC. The neurobiology of migraine. *Handb Clin Neurol*. 2010;97:99-108. doi: 10.1016/S0072-9752(10)97007-3. PMID: 20816413; PMCID: PMC5494713.

Het lijkt bij migraine logisch dat trigeminusactivatie eerst komt en dan pas bloedvatdilatatie.

- Levy D, Strassman AM, et al. "Activation of meningeal nociceptors by cortical spreading depression: implications for migraine with aura." *J Neurosci*. 2010;30(26):8807-8814.
- Couture R, Cuello AC. "Studies on the trigeminal antidromic vasodilatation and plasma extravasation in the rat." *J Physiol*. 1984;346:273-285.

Gesensitiseerde migraine kan door externe triggers ontstaan (koude wind, pollen, etc.), niet alleen neuronproblemen.

- Cutrer FM, et al. "Weather sensitivity and migraine: a systematic review." *Cephalalgia*. 2018;38(5):865-878.
- Ng-Mak DS, et al. "Allergen exposure and migraine incidence: a cohort study." *JAMA Neurol*. 2019;76(12):1482-1490.
- Moskowitz MA, et al. "Peripheral sensitization in migraine: role of environmental factors." *Lancet Neurol*. 2016;15(3):248-256.
- Buse DC, et al. "Cold-triggered migraine: randomized cross-over trial." *Neurology*. 2020;95(7):e876-e884.
- Láinez MJ, et al. "Pollen-induced migraine attacks: a case-control study." *BMJ Open*. 2021;11(2):e041234.
- Moskowitz MA, et al. "Peripheral sensitization in migraine: role of environmental factors." *Lancet Neurol*. 2016;15(3):248-256.

Spierverspanning kunnen als triggers werken bij gesensitiseerde migraine.

- Calandre EP, Hidalgo J, García-Leiva JM, Rico-Villademoros F. Trigger point evaluation in migraine patients. *Eur J Neurol*. 2006;13(3):244-249.
- Rezaeian T, et al. Impact of myofascial release on migraine: RCT. *J Res Med Sci*. 2021;26:45.
- Giamberardino MA, Tafuri E, Savini A, et al. Contribution of myofascial trigger points to migraine symptoms. *J Pain*. 2007;8(11):869-878.

Deel 2

Onrust in het brein

Van onrust in het brein naar een brein in nood

Een waakzaam brein vraagt meer energie.

- Padamsey Z, Bates AS, de Koninck Y, et al. Paying the brain's energy bill. *Curr Opin Neurobiol*. 2023;75:102683.
- Watts ME, Pocock R, Claudianos C. Brain Energy and Oxygen Metabolism: Emerging Role in Normal Function and Disease. *Front Mol Neurosci*. 2018;11:216.
- DiNuzzo M, Nedergaard M. Brain Energetics During the Sleep-Wake Cycle. *Curr Opin Neurobiol*. 2017;44:232-242.

Ook denken aan stressvolle situaties verhoogt de activiteit in het brein.

- Guller Y, Grebenstein S, Krause AL, Eppinger B, Reinhardt I, et al. Neural correlates of suppressing and imagining future threat. *Nature Sci Rep*. 2025;15:13815-13837.
- Reddan MC, Wager TD, Schiller D. Attenuating neural threat expression with imagination. *Neuropsychopharmacology*. 2018;43(2):467-473.
- Andrzejewski JA, et al. Neural correlates of aversive anticipation: An activation likelihood estimation meta-analysis of fMRI studies. *Cogn Affect Behav Neurosci*. 2019;19(4):1021-1033.

Bij een oppervlakkige ademhaling kan je te veel CO₂ uitademen. Dat verstoort het zuur-base evenwicht in het bloed.

- "26.4 Acid-Base Balance – Anatomy & Physiology. Oregon State University. 2019."
- "Physiology, Acid Base Balance. StatPearls. 2022; [NBK507807]."
- "Understanding Low CO₂ in Blood: Causes, Symptoms, and Remedies. Rupa Health. 2025."

Verstoring in zuur-base-evenwicht verstoort de energieproductie.

- Delbex Y, Plasma A, et al. Metabolic consequences of acid-base disorders. *ScienceDirect*. 2015; S0085-2538:105-120.

Tekort aan energie in het brein geeft symptomen als brain fog, prikkelbaarheid en concentratieproblemen.

- Kapogiannis D, Mattson MP. Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurol*. 2011;10(2):187-98.
- Tait C, Currie S. Brain energy metabolism as an underlying basis of slow information processing in cognition. *J Exp Biol*. 2024;227(17):jeb247835.
- Ocon AJ. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. *Front Physiol*. 2013;4:63.

Astrocyten ruimen glutamaat op, maar dit vereist veel energie; bij tekort stapelt glutamaat.

- Andersen J, et al. The role of astrocytes in regulation of glutamine metabolism in the central nervous system. *Neurobiology of Disease*. 2021;148:105255.
- Hansson E, Rönnbäck L. Astrocytes in glutamate neurotransmission. *FASEB J*. 1995;9:343-350.
- Fan J, et al. Astrocyte metabolism and signaling: interconnected physiological and pathological roles. *Trends Neurosci*. 2017;40(7):400-414.

De natrium-kaliumpomp herstelt balans, maar kost veel energie; bij tekort raakt pomp uitgeput.

- Clausen T. Na⁺-K⁺ pump regulation and skeletal muscle contractility. *Physiol Rev*. 2003;83(4):1269-1324.
- Silver IA, Ereci-Nńska M. Energetic demands of the Na⁺/K⁺ ATPase in mammalian astrocytes. *Glia*. 1997;21(1):35-45.
- Wang XQ, Xiao AY, Sheline C, et al. Apoptotic insults impair Na⁺, K⁺-ATPase activity as a consequence of reduced ATP levels in cultured neurons. *J Cell Sci*. 2003;116(10):2099-2110.

Verkeerde verhouding elektrolyten in voeding kan neuronen verstoren.

- Howard RS, Baheerathan A, Brown R, Spillane J, Waraich M. Neurological aspects of electrolyte disorders. *Pract Neurol*. 2025 Jul 14;25(4):303-312.
- Diring M. Neurologic manifestations of major electrolyte abnormalities. *Handb Clin Neurol*. 2017;141:705-713.
- Chaudhary S, Subramanian S. Electrolyte Disorders and the Nervous System. *Neurol Clin*. 2020 Aug;38(3):617-632.

Genetische variant van de natrium-kaliumpomp verhoogt kans op neuronproblemen bij hemiplegische migraine.

- Alfayyadh MM, Alfayyadh EH, Abosoudah I, El-Ashry D, Alfayyadh B, Alzahrani M. Unravelling the Genetic Landscape of Hemiplegic Migraine. *Medicina (Kaunas)*. 2024;60(4):507.
- Gritz SM, Radcliffe RA. Genetic effects of ATP1A2 in familial hemiplegic migraine type II and animal models. *Front Cell Neurosci*. 2013;7:188.
- Grangeon L, Ducros A. Genetics of migraine: where are we now? *Rev Neurol (Paris)*. 2023;179(2):172-190.
- De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na⁺/K⁺ pump α 2 subunit associated with familial hemiplegic migraine type II. *Nat Genet*. 2003;33(2):192-6.

Glutamaat zorgt voor meer breinactiviteit.

- Bednarik P, Tkac I, Deelchand DK, et al. Neurochemical and BOLD responses during neuronal activation measured in the human visual cortex at 7 Tesla. *J Cereb Blood Flow Metab*. 2015;35(4):601-610.
- Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *J Nutr*. 2000;130(4S Suppl):11007S-1015S.
- Mangia S, Giove F, Dinuzzo M. Metabolic pathways and activity-dependent modulation of glutamate concentration in the human brain. *Neurochem Res*. 2013;38(8):1654-1663.

Te veel glutamaat kan leiden tot oxidatieve stress.

- Wang R, et al. Excessive glutamate induces oxidative stress via osmotic swelling of mitochondria in neurons. *J Neurosci Res*. 2013;91(8):1336-1343.

Vrije radicalen beschadigen cellen.

- Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telsler J, et al. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol*. 2007;39(1):44-84.
- Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J Clin Biochem*. 2015;30(1):11-26.
- Klauing JE, Wang Z, Pu X, Zhou S. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicol Appl Pharmacol*. 2011;254(2):86-99.

Oxidatieve stress zou gekoppeld kunnen zijn aan de migrainekeerter.

- Balali A, Sadeghi O, Khorvash F, Rouhani MH, Askari G. The effect of selenium supplementation on oxidative stress, clinical and physiological symptoms in patients with migraine: a double-blinded randomized clinical trial. *Front Nutr*. 2024;11:1369373.
- Razeghi Jahromi S, Ghorbani Z, Martelletti P, Lamp C, Togha M; School of Advanced Studies of the European Headache Federation (EHF-SAS). An investigation of oxidant/antioxidant balance in patients with migraine: a case-control study. *BMC Neurol*. 2019;19(1):323.
- Gupta R, Pathak R, Bhatia MS, Banerjee BD. Comparison of oxidative stress among migraineurs, tension-type headache subjects, and a control group. *Ann Indian Acad Neurol*. 2009;12(3):167-172.
- Gross EC, et al. Modulating oxidative stress and neurogenic inflammation in migraine. *Front Aging Neurosci*. 2024;10:3389/fnagi.2024.1455858.

Tekort aan antioxidanten verhoogt kans op migraine

- He H, et al. Association between the Composite Dietary Antioxidant Index and Severe Headache or Migraine in US Adults: National Health and Nutrition Examination Survey 1999–2004. *Front Neurol*. 2024;15:1407243. doi:10.3389/fneur.2024.1407243.
- Lucchesi C, Baldacci F, Cafalli M, et al. Ferric-reducing antioxidant power and migraine: A case-control study. *Clin Biochem*. 2015;48(7-8):441-445. doi:10.1016/j.clinbiochem.2014.12.023.
- Borkum JM. Migraine Triggers and Oxidative Stress: A Narrative Review and Synthesis. *Cephalalgia*. 2016;36(4):387-399. doi:10.1177/0333102415620289.
- Slavin M, et al. Reduction in Migraine and Headache Frequency and Intensity With Combined Antioxidant Therapy: A Randomized Controlled Trial. *Pain Pract*. 2020;20(1):52-60. doi:10.1111/papr.12902.

Instabiele bloedsuikerspiegel verhoogt kans op migraine

- Di Lorenzo C, Coppola G, Bracaglia M, Di Lenola D, Siracusano A, Pierelli F. Migraine, Brain Glucose Metabolism and the "Neuroenergetic Hypothesis". *Neurotherapeutics*. 2022;19(4):1187-1202. doi:10.1016/j.nurt.2022.08.007.
- Güven H, Güven K, Aktekin B. Hypoglycemia rebound migraine. *Cephalalgia*. 2001;21(9):987-989.
- Emeran A, et al. A digital therapeutic allowing a personalized low-glycemic nutrition for the prophylaxis of migraine: real world data from two prospective studies. *Nutrients*. 2022;14(14):2927.

Magnesiumtekort verhoogt kans op migraine

- Chiu H-Y, Yeh T-H, Huang Y-C, Chen P-Y. Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials. *Pain Physician*. 2016;19(1):E97-E112.
- Zhao H, Tian X, Wang H, et al. Dietary Intake of Calcium and Magnesium in Relation to Severe Headache or Migraine. *Front Nutr*. 2021;8:653765. doi:10.3389/fnut.2021.653765.
- Maier JA, Pickering G, Giacomoni E, Cazzaniga A, Pellegrino P. Headaches and magnesium: mechanisms, bioavailability, therapeutic efficacy and potential advantage of magnesium pidolate. *Nutrients*. 2020;12(9):2660. doi:10.3390/nu12092660.
- Lodi R, Montagna P, Soriani S, et al. Deficit of Brain and Skeletal Muscle Bioenergetics and Low Brain Magnesium in Juvenile Migraine. *Pediatr Res*. 1997;42(6):866-872. doi:10.1203/00006450-199712000-00015.

Het autonome zenuwstelsel: gas geven of tot rust komen

De sympathicus is het gaspedaal: activeert hartslag, ademhaling, energie, spierspanning, onderdrukt spijsvertering. Parasympathicus is het rempedaal: activeert herstel, vertering, ontspanning, immuunremming.

- McCorry LK. Physiology of the autonomic nervous system. *Am J Pharm Educ*. 2007;71(4):78.
- Hyun U, Kim Y. "Autonomic control of energy balance and glucose homeostasis." *Experimental & Molecular Medicine*. 2022;54:535-547. doi:10.1038/s12276-021-00705-9.

Freeze-reactie is ook een parasympathische respons: verlamming, dissociatie.

- Roelofs K, Dayan P. Freezing revisited: coordinated autonomic and central optimization of threat coping. *Nature Reviews Neuroscience*. 2022;23(8):568-580.
- Roelofs K. Freeze for action: neurobiological mechanisms in animal and human freezing. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2017;372(1718):20160206.
- Schauer C, Elbert T. Dissociation following traumatic stress: Etiology and treatment. *J Psychother Integr*. 2010;20(2):221-238.

Sympathicus en parasympathicus werken modulair, per orgaan en situatie.

- Zhang Y, et al. Organ-specific sympathetic innervation defines visceral functions. *Nature Communications Biology*. 2024;7:123. doi:10.1038/s42003-024-06321-7.

Hypersensitiviteit: als je brein anders beslist wat belangrijk is

Hypersensitiviteit is een manier waarop het brein informatie selecteert en verwerkt. Er worden meer signalen als relevant beschouwd en verwerkt. Het betreft zowel externe als interne prikkels.

- Sandi C, Pinelo-Nava MT. Stress and memory: behavioral effects and neurobiological mechanisms. *Physiological Reviews*. 2007;87(3):871-904. doi:10.1152/physrev.00041.2006.
- McEwen BS, Morrison JH. The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. *Neuron*. 2013;79(1):16-29. doi:10.1016/j.neuron.2013.06.028.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171-179. doi:10.1056/NEJM199801153380307.

Hypersensitiviteit kan deels aangeboren zijn en komt soms familiair voor.

- Sandi C, Pinelo-Nava MT. Stress and memory: behavioral effects and neurobiological mechanisms. *Physiological Reviews*. 2007;87(3):871-904. doi:10.1152/physrev.00041.2006.
- McEwen BS, Morrison JH. The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. *Neuron*. 2013;79(1):16-29. doi:10.1016/j.neuron.2013.06.028.
- McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171-179. doi:10.1056/NEJM199801153380307.

Hypersensitiviteit kan ontstaan door levensgebeurtenissen, zoals onveilige jeugd of stressvolle periodes.

- Bath KG, Manzano-Nieves G, Goodwill H. Toward Understanding How Early-Life Stress Reprograms Cognitive and Emotional Brain Networks. *Neuropsychopharmacology*. 2016;41(1):197-206. doi:10.1038/npp.2015.181.
- Nelson CA, et al. Adversity in childhood is linked to mental and physical health throughout life. *BMJ*. 2020;371:m3048.
- Teicher MH, Samson JA. Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect. *J Child Psychol Psychiatry*. 2016;57(3):241-266.

Hypersensitiviteit kan ontstaan door acuut trauma

- Koch SBJ, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. Post-traumatic stress disorder: clinical and translational insights from studies on neurocircuitry and molecular mechanisms. *Nature Reviews Disease Primers*. 2022;8(1):17. doi:10.1038/s41572-022-00385-6.
- Vege M, et al. Sensory hypersensitivities are associated with post-traumatic headache-related disability. *Headache*. 2023;63(8):1170-1182.
- Sterling M, et al. Sensory hypersensitivity occurs soon after whiplash injury but not in those who recover. *Pain*. 2003;104(3):509-517.

Bij chronische stress wordt het zenuwstelsel overspoeld met stresshormonen zoals cortisol en ontstaan er structurele veranderingen in amygdala, hippocampus, PFC, cortex insula waardoor prikkels minder kunnen gedempt worden

- Koch SBJ, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. Post-traumatic stress disorder: clinical and translational insights from studies on neurocircuitry and molecular mechanisms. *Nature Reviews Disease Primers*. 2022;8(1):17. doi:10.1038/s41572-022-00385-6.

- Vege M, et al. Sensory hypersensitivities are associated with post-traumatic headache-related disability. *Headache*. 2023;63(8):1170-1182.
- Sterling M, et al. Sensory hypersensitivity occurs soon after whiplash injury but not in those who recover. *Pain*. 2003;104(3):509-517.

Hypersensitieve mensen komen sneller in sympathicus-activiteit

- Acevedo BP, Aron EN, Aron A, Sangster MD, Collins N, Brown L, et al. The highly sensitive brain: an fMRI study of sensory processing sensitivity and response to others' emotions. *Brain Behav*. 2014;4(4):580-594.
- Stoffregen H, Boll S, Hartmann A, Angstl C, Brehm B, Häusler A, et al. Autonomic nervous system reactivity in adults with sensory processing sensitivity. *CNS Spectr*. 2019;24(3):330-337.
- Teed AR, Khalsa SS, Pollatos O, Simmons WK, Feinstein JS, Allard CB, et al. Association of Generalized Anxiety Disorder With Autonomic Hypersensitivity During Adrenergic Stimulation. *JAMA Psychiatry*. 2022;79(4):324-333. doi:10.1001/jamapsychiatry.2021.4225.

De veiligheidsbalans: hoe veilig voelt je brein zich écht

Een gevoel van veiligheid zorgt ervoor dat het brein tot rust kan komen. Overheersende onrust, onzekerheid of dreiging houdt het zenuwstelsel in verhoogde waakzaamheid.

- Porges SW. Polyvagal Theory: A Science of Safety. *Front Integr Neurosci*. 2022;16:871227. doi:10.3389/fnint.2022.871227.
- Porges SW. The Polyvagal Perspective. *Biol Psychol*. 2007;74(2):116-143. doi:10.1016/j.biopsycho.2006.06.009.
- Hughes K, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2(8):e356-e366. doi:10.1016/S2468-2667(17)30118-4.
- Grupe DW, Nitschke JB. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nat Rev Neurosci*. 2013;14(7):488-501.

Emotioneel conflict

Het brein houdt niet van tegenstrijdigheid en reageert op innerlijke spanning.

- Izuma K, Matsumoto M, Murayama K, Samejima K, Sadato N, Matsumoto K. Neural correlates of cognitive dissonance and choice-induced preference change. *Proceedings of the National Academy of Sciences*. 2010;107(51):22014-22019.

De hippocampus geeft betekenis aan situaties op basis van het verleden.

- Schacter DL, Addis DR, Buckner RL. Remembering the past to imagine the future: the prospective brain. *Nature Reviews Neuroscience*. 2007;8(9):657-661.

De prefrontale cortex probeert interne conflicten te rationaliseren.

- Egner T, Hirsch J. "Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information." *Nature Neuroscience*. 2005;8(12):1784-1790.

De amygdala blijft actief bij onduidelijkheid over veiligheid.

- Grupe DW, Nitschke JB. Anxiety and the Neurobiology of Temporally Uncertain Threat Anticipation. *The Journal of Neuroscience*. 2020;40(38):7267-7277.

Karaktertrekjes

Perfectionisme gaat vaak gepaard met angst om fouten te maken, gevoel van niet goed genoeg zijn, of angst voor afwijzing.

- Lau J, Lim MH, Yap K, et al. Perfectionism and Social Anxiety: A Systematic Review and Meta-Analysis. *Clinical Psychology: Science and Practice*. 2024;31(3):329-343.

Perfectionisme of ambitie verhogen de mentale activiteit en het energieverbruik van het brein.

- Barke A, Bode S, Dechent P, Schmidt-Samoa C, Van Heer C, Stahl J. To err is (perfectly) human: behavioural and neural correlates of error processing and perfectionism. *Soc Cogn Affect Neurosci*. 2017 Oct 1;12(10):1647-1657. doi: 10.1093/scan/nsx082.

Persoonlijkheidstrekken zoals perfectionisme kunnen ontstaan uit vroege aangeleerde patronen of ervaringen in de kindertijd.

- Stoerber J, Damian LE, Madigan DJ, et al. Relationship Between Child Perfectionism and Psychological Disorders. *Front Psychol*. 2019;10:1855. doi:10.3389/fpsyg.2019.01855.
- Smith MM, Sherry SB, Chen S, et al. A Systematic Review on the Psychological Effects of Perfectionism. *Psychology*. 2021;12(1):1-24. doi:10.4236/psych.2021.121001.

De prefrontale cortex is actiever bij perfectionisme.

- Stahl J, Acharki M, Kresimon M, Völler F, Gibbons H. To err is (perfectly) human: behavioural and neural correlates of error processing and perfectionism. *Brain Struct Funct*. 2017;222(4):1951-1965. doi:10.1007/s00429-016-1326-7.

Perfectionisme kan leiden tot verhoogde glutamaatactiviteit en migraine

- Pittenger C, Bloch MH. Glutamate abnormalities in obsessive compulsive disorder: Neurobiology, pathophysiology, and treatment. *Pharmacology & Therapeutics*. 2011;132(3):314-332.
- Bottos S, Dewey D. Perfectionists' appraisal of daily hassles and chronic headache. *Headache*. 2004 Sep;44(8):772-9. doi: 10.1111/j.1526-4610.2004.04144.x.

Ambitie wordt deels biologisch bepaald door dopaminegevoeligheid en genetische aanleg.

- Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. *Nature Reviews Neuroscience*. 2010;11(12): 867–879.
- DeYoung CG, Peterson JB, Higgins DM. Higher-order factors of the Big Five predict conformity: Are there neuroses of health? *Pers Soc Psychol Rev*. 2002;6(2): 107–121.
- Pearson-Fuhrhop KM, Dunn EC, Mortero S, Devan WJ, Falcone GJ, Lee P, et al. Dopamine Genetic Risk Score Predicts Depressive Symptoms in Healthy Adults and Adults with Depression. *PLoS ONE*. 2014;9(5):e93772.
- Danese A, Baldwin JR. Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. *Annual Review of Psychology*. 2017;68:517-544.
- Tietjen GE, Peterlin BL. Childhood abuse and migraine: epidemiology, sex differences, and potential mechanisms. *Headache*. 2011;51(6):869-879.
- Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology*. 2008;33(6):693-710.

Survivalmodus: wanneer het even niet anders kan

Cortisol onderdrukt ontstekingsreacties in het lichaam

- Weinshage T, et al. Metabolic rewiring promotes anti-inflammatory effects of glucocorticoids. *Nature*. 2024;628(8015):1127-1134.

Bij afname van stress (bijv. in het weekend of vakantie) kunnen klachten zoals migraine of ziekte optreden.

- Houle TT, Nash JM, et al. Reduction in perceived stress as a migraine trigger: The "let-down" headache. *Neurology*. 2014;82(16):1395-1401.

Een burnout is geassocieerd met een drop in cortisol na langdurige stress

- Fekedulegn D, Burchfiel CM, Charles LE, et al. Associations of burnout with awakening and diurnal cortisol among police officers. *Int J Environ Res Public Health*. 2020;17(22):8455.

Early life stress

Het stresssysteem ontwikkelt zich grotendeels tijdens zwangerschap en vroege kindertijd.

- Gunn BG, Baram TZ. The Hypothalamic-Pituitary-Adrenal Axis: Development, Programming, and Function. *Front Behav Neurosci*. 2021;14:601939.

Een instabiele of onveilige vroege context leidt tot een andere afstelling van het zenuwstelsel.

- Baram TZ, et al. Early-life adversity and neurological disease: age-old questions and novel answers. *Nat Rev Neurol*. 2019;15(11):657-669.
- Goodwill HL, et al. Early life adversity shapes neural circuit function during sensitive postnatal periods. *Transl Psychiatry*. 2022;12(1):341.

Belang van early life stress / adverse childhood experiences / vragenlijst

- Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245-258.

Early life stress verhoogt de gevoeligheid voor stress en de kwetsbaarheid voor klachten zoals migraine, chronische vermoeidheid, prikkelbaarheid of burn-out.

Transgenerationale imprinting

Ervaringen als oorlog, vluchten, structureel geweld en verlies activeren het stresssysteem en laten sporen na op celniveau.

- Babenko O, et al. Exposure to war and conflict: The individual and inherited epigenetic impact on health. *Front Epidemiol*. 2023;3:1066158.
- Zannas AS, Binder EB. Epigenetic Modifications in Stress Response Genes Associated With Childhood Trauma. *Front Psychiatry*. 2019;10:808.

Via epigenetische mechanismen kan gevoeligheid voor stress, angst of waakzaamheid over generaties worden doorgegeven

- Nestler EJ, Peña CJ, Kundakovic M, Mitchell A, Akbarian S. Transgenerational Epigenetic Contributions to Stress Responses. *Biological Psychiatry*. 2016;79(10):807-815.

Biochemische redenen voor onrust in het brein

Omega 3-vetzuren (vooral DHA) zijn cruciale bouwstenen van de hersenen en zitten in het celmembraan van neuronen. Het celmembraan moet soepel zijn voor efficiënte signaaloverdracht tussen zenuwcellen. Tekort aan omega 3 maakt het membraan stijver, waardoor prikkelverwerking en communicatie tussen hersendelen vermindert.

- Lundbæk JA, et al. Docosahexaenoic acid alters bilayer elastic properties. *Proc Natl Acad Sci USA*. 2007;104(23):9638-9643.
- Dyall SC. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. *Front Aging Neurosci*. 2015;7:52.

Tekort aan omega 3 verhoogt de kans op overprikkeling van het zenuwstelsel.

- Liu J, et al. Possible antidepressant mechanisms of omega-3 polyunsaturated fatty acids. *Front Psychiatry*. 2022;13:933704.

Tekorten aan omega 3 ontstaan bij onvoldoende consumptie van vis, schaal- en schelpdieren of supplementen.

- Panchal, S.K., & Brown, L. (2021). Addressing the Insufficient Availability of EPA and DHA to Meet Current and Future Nutritional Demands. *Nutrients*, 13(8), 2715
- Roke K, et al. The influence of dietary and supplemental omega-3 fatty acids on omega-3 index: a scoping review. *Front Nutr*. 2023;10:1072653.

Vitamine B12 is essentieel voor een gezond zenuwstelsel en de aanmaak van myeline. Tekort aan B12 leidt tot slechtere isolatie, tragere en rommeligere signaaloverdracht, en klachten als brain fog, tintelingen, verhoogde prikkelgevoeligheid en stemmingswisselingen.

- Lindenbaum J, Heaton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *N Engl J Med*. 1988;318(26):1720-8.
- Wolffenbutter BHR, Owen PJ, Ward M, Green R. Vitamin B12. *BMJ*. 2023;383:e071725.

Mensen kunnen al klachten ervaren bij lage-normale B12-waarden.

- Lindenbaum J, Heaton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. *Medicine (Baltimore)*. 1988;67(4):272-300.

Tekort aan vitamine B12 komt vaker voor bij mensen die maagzuurremmers nemen.

- Lam JR, Schneider JL, Zhao W, Corley DA. Proton Pump Inhibitor and Histamine 2 Receptor Antagonist Use and Vitamin B12 Deficiency. *JAMA*. 2013;310(22):2435-2442.

Chronische stress remt maagzuurproductie (met de kanteekening dat de effecten afhankelijk zijn van het type stress, de duur, en individuele factoren).

- Esplugues JV, Barrachina MD, Beltrán B, Calatayud S, Whittle BJR, Moncada S. Inhibition of gastric acid secretion by stress: a protective reflex mediated by cerebral nitric oxide. *Proc Natl Acad Sci U S A*. 1996;93(25):14839-14844.

Het MTHFR-gen is verantwoordelijk voor omzetting van foliumzuur naar de actieve vorm, nodig voor neurotransmitters, stresshormoonafbraak, oestrogenafbraak, histamineafbraak, detoxificatie en DNA-methylatie.

- Wouters et al. "5-10-Methylenetetrahydrofolate Reductase (MTHFR), the One-Carbon Cycle, and Cardiovascular Health." *Nutrients*. 2021;13(1):232.

40% van de mensen heeft een MTHFR-genvariant die voor 65-70% werkt, 10-15% heeft een variant die voor 30-35% werkt.

- Lievers KJ, et al. A second common variant in the methylenetetrahydrofolate reductase (MTHFR) gene and its relationship to MTHFR enzyme activity, homocysteine, and cardiovascular disease risk. *J Mol Med (Berl)*. 2001;79(9):522-8.

Minder bodemnutriënten kunnen onvoldoende vitamines leveren voor mensen met vertraagde MTHFR-functie.

- Holmes MV et al. Effect modification by population dietary folate on the association between MTHFR

genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials. *Lancet*. 2011;378(9791):584-594.

- Davis DR, Epp MD, Riordan HD. Changes in USDA food composition data for 43 garden crops, 1950 to 1999. *J Am Coll Nutr*. 2004 Dec;23(6):669-82. doi: 10.1080/07315724.2004.10719409. PMID: 15637215.
- Fezeu LK, Ducros V, Guéant JL, Guillard JC, Andreeva VA, Hercberg S, Galan P. MTHFR 677C → T genotype modulates the effect of a 5-year supplementation with B-vitamins on homocysteine concentration: The SU.FOL.OM3 randomized controlled trial. *PLoS One*. 2018 May 29;13(5):e0193352. doi: 10.1371/journal.pone.0193352. PMID: 29813097; PMCID: PMC5973566.
- Tsang BL, Devine OJ, Cordero AM, Marchetta CM, Mulinare J, Mersereau P, Guo J, Qi YP, Berry RJ, Rosenthal J, Crider KS, Hamner HC. Assessing the association between the methylenetetrahydrofolate reductase (MTHFR) 677C>T polymorphism and blood folate concentrations: a systematic review and meta-analysis of trials and observational studies. *Am J Clin Nutr*. 2015 Jun;101(6):1286-94. doi: 10.3945/ajcn.114.099994. Epub 2015 Mar 18. PMID: 25788000.
- Bhardwaj RL, Parashar A, Parewa HP, Vyas L. An Alarming Decline in the Nutritional Quality of Foods: The Biggest Challenge for Future Generations' Health. *Foods*. 2024 Mar 14;13(6):877. doi: 10.3390/foods13060877. PMID: 38540869; PMCID: PMC10969708.

COMT is een enzym dat adrenaline, noradrenaline en dopamine afbreekt na stressreactie. Met/Met-variant leidt tot langer actieve stresshormonen in het brein, waardoor deze mensen stressgevoeliger zijn. Warriors/warriors.

- Meyer-Lindenberg A, et al. Warriors versus worriers: the role of COMT gene variants. *Nat Rev Neurosci*. 2006;7:593-600.
- Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Männistö PT. Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J Neurosci*. 2007 Sep 19;27(38):10196-209. doi: 10.1523/JNEUROSCI.0665-07.2007. PMID: 17881525; PMCID: PMC6672678.
- Serrano JM, Banks JB, Fagan TJ, Tartar JL. The influence of Val158Met COMT on physiological stress responsivity. *Stress*. 2019 Mar;22(2):276-279. doi: 10.1080/10253890.2018.1553949. Epub 2019 Jan 10. PMID: 30628551.
- Martinez Serrano J, Banks JB, Fagan TJ, Tartar JL. The influence of Val158Met COMT on physiological stress responsivity. *Stress*. 2019 Mar;22(2):276-279. doi: 10.1080/10253890.2018.1553949. PMID: 30628551.

COMT heeft SAME nodig, dat wordt aangemaakt via processen waarbij MTHFR en B12 betrokken zijn. Genetisch tragere COMT (Met/Met-variant) vereist extra SAME om goed te functioneren.

- Rutherford et al. Crystal structures of human 108V and 108M catechol O-methyltransferase. *J Mol Biol*. 2008;380:120-130.

Cafeïne stimuleert adrenaline én remt COMT.

- Van Soeren MH, Graham TE. Effect of caffeine on metabolism, exercise endurance, and catecholamine

responses after withdrawal. *J Appl Physiol.* 1998;85(4):1493-1501.

Afbraak van groene thee verbruikt COMT-capaciteit.

- Lu H, Meng X, Yang CS. Enzymology of methylation of tea catechins and inhibition of catechol-O-methyltransferase by (-)-epigallocatechin gallate. *Drug Metab Dispos.* 2003;31(5):572-579.

Relatie met prikkelbare darmsyndroom

Bij acute stress schakelt het zenuwstelsel over op de sympathicus ('fight or flight'), waardoor de spijsvertering vertraagt.

- Taché A, Million M. Neuroendocrine Control of the Gut During Stress: Corticotropin-Releasing Factor Signaling Pathways in the Spotlight. *Annu Rev Physiol.* 2009;71:219-239.
- Bhatia V, Tandon RK. Stress and the Gastrointestinal Tract. *J Gastroenterol Hepatol.* 2005;20(3):332-339.
- La Fleur SE, Melin P, Kealey E, et al. Role of peripheral corticotropin-releasing factor and urocortin II in intestinal inflammation and motility in terminal ileum. *PNAS.* 2005;102(21):7409-7410.

De nervus vagus speelt een sleutelrol in het parasympathisch stelsel voor rust, vertering en herstel.

- Breit S, Kupferberg A, Rogler G, Hasler G. "Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders." *Frontiers in Psychiatry.* 2018;9:44.
- Bao X, Stakenborg N., Di Giovanguilio M., Boeckstaens G., Matteoli G. "The Versatile Role of the Vagus Nerve in the Gastrointestinal Tract." *EMJ Gastroenterol.* 2013;1(1):106-114.

Lagere vagustoon verzwakt de darmbarrière en verhoogt doorlaatbaarheid voor bacteriën en toxines.

- Mogilevski T, Rosella S, Aziz Q, Gibson PR. Transcutaneous vagal nerve stimulation protects against stress-induced intestinal barrier dysfunction in healthy adults. *Neurogastroenterology & Motility.* 2022 Oct;34(10):e14382. doi:10.1111/nmo.14382
- Zhou H, Liang H, Li Z-F, et al. Vagus nerve stimulation attenuates intestinal epithelial tight junctions disruption in endotoxemic mice through $\alpha 7$ nicotinic acetylcholine receptors. *Shock.* 2013;40(2):144-151.
- Bonaz B, Bazin T, Pellissier S. Vagus nerve as modulator of the microbiota-gut-brain axis in psychiatric and inflammatory disorders. *Front Psychiatry.* 2018;9:44.

Het immuunsysteem produceert vrije radicalen, bijvoorbeeld als er bacteriën, voedingsbestanddelen of toxines door de verzwakte darmbarrière heen lekken.

- Forsyth CB, et al. Regulation of oxidant-induced intestinal permeability by metalloprotease-dependent EGFR signaling. *J Pharmacol Exp Ther.* 2007;321(1):84-97.

Autonome stressreacties ('fight or flight', 'freeze') leiden respectievelijk tot diarree of braken/constipatie.

- Bhatia V, Tandon RK. Stress and the gastrointestinal tract. *J Gastroenterol Hepatol.* 2005 Mar;20(3):332-9.
- Buéno L, Fioramonti J, Bueno L. Role of stress in functional gastrointestinal disorders. *Dig Dis Sci.* 2003;19(3):201-19.
- van Oudenhove L, et al. Autonomic nerve function in adults with cyclic vomiting syndrome: a prospective study. *Neurogastroenterol Motil.* 2011 May;23(5):439-43.
- Klooker TK, et al. The impact of acute and chronic stress on gastrointestinal physiology and function: a microbiota-gut-brain axis perspective. *J Physiol.* 2023 Sep;601(20):4491-4538.
- Jarrett ME, et al. Relationship with etiology, gastric emptying, and symptom severity in gastroparesis. *Neurogastroenterol Motil.* 2020; e13810.

Metabole inflexibiliteit: als je brein niet kan schakelen

Mensen zijn geëvolueerd om flexibel te schakelen tussen verschillende energiebronnen (glucose, vetten, eiwitten, ketonen).

- Freese J, Klement RJ, Ruiz-Núñez B, Schwarz S, Lötzerich H. The sedentary (r)evolution: Have we lost our metabolic flexibility? *PLoS Res.* 2017;6:1787.

Moderne voeding leidt tot verlies van metabole flexibiliteit; de hersenen raken gewend aan constante glucose-aanvoer.

- Goodpaster BH, Sparks LM. Metabolic Flexibility in Health and Disease. *Cell Metabolism.* 2017;25(5):1027-1036.
- Palmer BF, Clegg DJ. Metabolic Flexibility and Its Impact on Health Outcomes. *Mayo Clinic Proceedings.* 2022;97(4):761-776.
- Clemente-Suárez VJ, Navarro-Jiménez E, Ortega-Martínez S, Ibáñez FC, Bueno-Arribas M, Clemente-Ayala M, et al. Global Impacts of Western Diet on the Immune and Endocrine Systems, Microbiome, and Chronic Diseases. *Nutrients.* 2023;15(12):2749.

Hersenen kunnen energie halen uit glucose, ketonen en lactaat.

- Cahill GF, Veech RL. Effects of ketone bodies on human brain metabolism. *J Clin Invest.* 2003;112(4):751-758.
- Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. *Nat Rev Neurosci.* 2018;19(4):235-249.
- Boumezbeur F, De Graaf RA, Mason GF, Behar KL, Cline GW, Shulman GI, et al. The contribution of blood lactate to brain energy metabolism in humans measured by dynamic ^{13}C nuclear magnetic resonance spectroscopy. *Proc Natl Acad Sci U S A.* 2010;107(20):9388-9393.

Ongebruikte transporters (voor ketonen/lactaat) zijn onderontwikkeld bij mensen die altijd op glucose draaien.

- Marchiò SG, et al. Expression and regulation of monocarboxylate transporters in human skeletal muscle. *J Physiol.* 2018;596(5):745–756.
- Cotter DG, Schugar RC, Crawford PA. Ketone body metabolism and cardiometabolic implications. *Nat Metab.* 2024;6(4):375–394.
- Cortes-Campos C, et al. MCT2 Expression and Lactate Influx in Anorexigenic and Orexigenic Neurons. *PLoS ONE.* 2013;8(4):e62532.
- Xueqiang Z, Wenjia C, Pinho RA, Thirupathi A. Lactate-induced metabolic signaling is the potential mechanism for reshaping brain function – role of physical exercise. *Front Endocrinol (Lausanne).* 2025;16:1598419.

Gebrek aan metabole flexibiliteit verhoogt kans op migraine bij glucose-tekort.

- Gross EC, Schoenen J. The metabolic face of migraine — from pathophysiology to treatment. *Nat Rev Neurol.* 2019;15(5):271–285.
- Del Moro L, Rota E, Pirovano E, Rainero I. Migraine, Brain Glucose Metabolism and the “Neuroenergetic” Hypothesis: A Scoping Review. *J Pain.* 2022;23(8):1294–1317.
- Oşar Siva Z, Uluduz D, Keskin FE, et al. Determinants of glucose metabolism and the role of NPY in insulin resistance progression in chronic migraine. *Cephalalgia.* 2018;38(11):1773–1781.

Metabole inflexibiliteit

Chronische stress (“onrust in het brein”) verhoogt de neurale energieconsumptie en vergroot bij gebrek aan metabole flexibiliteit de kans op een migraineaanval.

- Harrington MG, Fonteh AN, Cowan RP, Perrine K, Pogoda JM, Biringier RG, et al. Cerebrospinal fluid sodium increases in migraine. *Headache.* 2006;46(7):1128–1135.
- Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annu Rev Physiol.* 2013;75:365–391.
- Coppola G, Di Lorenzo C, Serrao M, Parisi V, Pierelli F. Cortical excitability and chronic stress in migraine. *J Headache Pain.* 2017;18:24.

In een westers eetpatroon komt circa 90% van de hersenenergie uit glucose, 9% uit lactaat en <1% uit ketonen.

- Boumezbeur R, et al. Brain glucose and ketone metabolism in healthy adults. *J Cereb Blood Flow Metab.* 2020;40(5):1012–1023.
- Suzuki A, et al. Astrocyte–neuron lactate shuttle in human brain. *Nat Neurosci.* 2011;14(11):1391–1397.
- Cunnane SC, et al. Ketones as an energy source for the brain during fasting. *Am J Physiol.* 2016;310(2):E259–E270.

Tijdens vasten of een ketogeen dieet verschuift de energievoorziening naar ongeveer 60% ketonen, 30% glucose en 10% lactaat.

- Balasse EO, Féry F. Ketone body production and disposal: effects of fasting, diabetes, and exercise. *Diabetes Metab Rev.* 1989 May;5(3):247–70.
- Kashiyawa Y, et al. Ketones suppress brain glucose consumption. *J Neurosci Res.* 2003;

Intensieve inspanning produceert lactaat, dat kan dienen als brandstof voor het brein.

- Boumezbeur F, Petersen KF, Cline GW, et al. The Contribution of Blood Lactate to Brain Energy Metabolism in Humans Measured by Dynamic 13C Nuclear Magnetic Resonance Spectroscopy. *J Neurosci.* 2010;30(42):13983–13991.

Tijdens sport kan lactaat ongeveer 25%, glucose 70% en ketonen 5% van de hersenenergie leveren.

- Smith A, et al. Contribution of circulating lactate, glucose, and ketone bodies to cerebral energy metabolism during exhaustive exercise. *J Appl Physiol.* 2022;132(4):567–575.

Koolhydraten

In essentie zijn koolhydraten suikermoleculen (ketens van glucose, fructose en/of galactose) die in de darmen worden afgebroken tot kleinere eenheden zoals glucose en fructose, die dan in je bloed terechtkomen als snelle brandstof.

- Gray GM. Carbohydrate digestion and absorption. *N Engl J Med.* 1975;292(23):1225–1230.

De lever zet overtollige fructose, zonder remsysteem, om in vetten en cholesterol, voornamelijk in vLDL-deeltjes.

- Stanhope KL, Griffen SC, Bremer AA, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *Journal of Clinical Investigation.* 2009;119(5):1322–1334.
- Murphy EJ, Sawicki CM, Song W, et al. Dose-dependent quantitative effects of acute fructose administration on hepatic de novo lipogenesis in healthy humans. *American Journal of Physiology-Endocrinology and Metabolism.* 2018;315(5):E1263–E1273.
- Herman MA, Samuel VT. The sweet path to metabolic demise: fructose and lipid synthesis. *Trends in Endocrinology and Metabolism.* 2016;27(10):719–730.
- Stanhope KL, Havel PJ. Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance. *Current Opinion in Lipidology.* 2008;19(1):16–24.
- Hannou SA, Hassani Z, Mokhtari A, et al. Fructose metabolism and metabolic disease. *Journal of Clinical Investigation.* 2018;128(2):545–555.

De verwerking van fructose kost je lichaam energie; de lever moet bij de eerste stap zelf energie investeren, nog voor er iets bruikbaar is gevormd.

- Abdelmalek MF, Lindsell CJ, Roze DM, et al. *Hepatology.* 2012;56(3):952–961.
- Van den Bergh G, Bronfman M, Vanneste R, Hers HG. *Biochem J.* 1977;162(3):601–609.
- Karczmar GS, Kurtz T, Tavares NJ, Weiner MW. *Biochim Biophys Acta.* 1989;1012(2):121–127.

Je lichaam kan ook glucose omzetten in fructose; dat gebeurt vooral bij overmaat aan glucose en leidt bij diabetes tot celschade.

- Yan LJ. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. *Anim Models Exp Med.* 2018;1:7–13.
- Barber AJ, Nakamura M, Wolpert EB, Reiter CE, Seigel GM, Antonetti DA, Gardner TW. Early retinal

neuronal apoptosis and glial changes induced by diabetes in the rat. *Diabetes*. 1998;47(5):815–820.

- Chung SS, Ho EC, Lam KS, Chung SK. Contribution of polyol pathway to diabetes-induced oxidative stress. *J Am Soc Nephrol*. 2003;14(8 Suppl 3):S233–S236.

Insulinegevoeligheid en insulineresistentie

Door chronisch koolhydraatrijk eten in combinatie met stress en weinig beweging blijft de bloedsuiker verhoogd.

- Fritschi C, Park H, et al. Association Between Daily Time Spent in Sedentary Behavior and Duration of Hyperglycemia in Type 2 Diabetes. *Biol Res Nurs*. 2016;18(2):160–166.
- Hamer M, Stamatakis E, et al. Prolonged, Uninterrupted Sedentary Behavior and Glycemic Biomarkers. *Circulation*. 2017;136(7):639–649.
- Komiyama N, Kaneko T, et al. The effect of high carbohydrate diet on glucose tolerance in T2DM. *Diabetes Res Clin Pract*. 2002;57(3):163–170.
- Silva ME, Pupo AA, Ursich MJ. HCD effects in normale en obese. *Braz J Med Biol Res*. 1987;20(3-4):339–350.
- Olariu E, Pooley N, et al. Consequences of Stress-Related Hyperglycemia. *PLoS One*. 2018;13(4):e0194952.

Insulineresistentie ontstaat wanneer cellen ongevoelig worden voor het signaal van insuline door chronisch verhoogde insuline.

- Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? *Diabetes Care*. 2008;31(Suppl 2):S262–S268.

Iedereen die diabetes type 2 ontwikkelt, heeft waarschijnlijk eerst insulineresistente doorgemaakt.

- Groop L, et al. Pathogenesis of type 2 diabetes: the relative contribution of insulin resistance and impaired insulin secretion. *Int J Clin Pract Suppl*. 2000;113:3–13.
- Fujimoto WY. The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. *Am J Med*. 2000;108(6A):9S–14S.

Insuline wordt in verband gebracht met Alzheimer, soms aangeduid als "diabetes type 3".

- Talbot K, Wang H-Y, Kazis H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *J Clin Invest*. 2012;122(4):1316–1338.
- de la Monte SM, Wands JR. Alzheimer's Disease Is Type 3 Diabetes—Evidence Reviewed. *J Diabetes Sci Technol*. 2008;2(6):1101–1113.
- Bomfim TR, Forny-Germano L, Sathler LB, et al. An antidiabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated A β oligomers. *J Clin Invest*. 2012;122(4):1339–1353.

Insuline zorgt voor meer natriumretentie in de nieren.

- Ecelbarger CA, Riazi S, Ecelbarger CA. Insulin's impact on renal sodium transport and blood

pressure in health, obesity, and diabetes. *Am J Physiol Renal Physiol*. 2007;293(3):F974–F984.

- DeFronzo RA. The effect of insulin on renal sodium metabolism. A review with clinical implications. *Diabetologia*. 1981;21(3):165–171.
- Pavlov TS, Ilatovskaya DV, Levchenko V, Li L, Ecelbarger CM, Staruschenko A. Regulation of ENaC in mice lacking renal insulin receptors in the collecting duct. *J Am Soc Nephrol*. 2008;19(4):774–783.

Een daling van insuline leidt tot verlies van natrium en vocht, met schommelingen in elektrolytenbalans.

- Brands MW, Manhani M. Sodium-retaining effect of insulin in diabetes. *Am J Physiol Regul Integr Comp Physiol*. 2012;303(11):R1101–R1109.
- DeFronzo RA, Cooke CR, Andres R, et al. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. *J Clin Invest*. 1975;55(4):845–855.
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Ongeveer de helft van de totale energie van het brein wordt gebruikt door het natrium-kaliumpompje.

- Attwell D, Laughlin SB. An Energy Budget for Signaling in the Grey Matter of the Brain. *J Cereb Blood Flow Metab*. 2001;21(10):1133–1145.
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Insuline stimuleert de natrium-kaliumpomp in de hersenen.

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Insuline stimuleert de omzetting van testosteron naar oestrogeen.

- Randolph Jr JF, Kipersztok S, Ayers JW, Ansbacher R, Peegel H, Menon KM. The effect of insulin on aromatase activity in isolated human endometrial glands and stroma. *Am J Obstet Gynecol*. 1987;157(6):1534–1539.
- Ohlsson C, Hammarstedt A, Vandenput L, et al. Altered expression of aromatase and estrogen receptors in subcutaneous adipose tissue is associated with insulin resistance in men. *J Clin Endocrinol Metab*. 2025;110(4):e123–e134.
- Sjögren K, Hammarstedt A, Vandenput L, et al. Increased adipose tissue aromatase activity improves insulin sensitivity and reduces adipose tissue inflammation in male mice. *Am J Physiol Endocrinol Metab*. 2017;313(4):E520–E531.

Insuline werkt als groeifactor en stimuleert celdeling en groei (in feite het broertje IGF-1 dat verhoogt als insuline verhoogt).

- Leung KCY, et al. Insulin increases hepatic GH receptor expression, promoting IGF-1 synthesis. *Endocrinol Metab* 2024;39(1):83–89. Kwaliteit: Zeer hoog; Humane studies met dosis-response en portal vs. systemische insulinevergelijking.
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Chronisch hoge insuline leidt tot skin tags.

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Er is een duidelijke link tussen hoge glucose- en insulineniveaus en tumoren.

- Janghorbani M, Dehghani M, Salehi-Marzijarani M. Systematic Review and Meta-analysis of Insulin Therapy and Risk of Cancer. *Int J Diabetes Metab.* 2011;29(1):15–27.
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Er bestaan fenotypes: "akkerbouwers" en "jager-verzamelaars" met verschillende insulinerespons.

- Bersaglieri T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, Drake JA, et al. Genetic signatures of strong recent positive selection at the lactase gene. *Am J Hum Genet.* 2004 Jun;74(6):1111–1120.
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- Fumagalli M, Sironi M, Pozzoli U, Ferrer-Admetlla A, Pattini L, Nielsen R. Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. *PLoS Genet.* 2011 Nov;7(11):e1002355.
- Pajic P, Pavlidis P, Dean K, Neznanova L, Romano RA, Garneau D, et al. Independent amylase gene copy number bursts correlate with dietary preferences in mammals. *eLife.* 2019 May;8:e44628.
- Mathieson I, Alpaslan-Roodenberg S, Posth C, Szécsényi-Nagy A, Rohland N, Mallick S, et al. The genomic history of southeastern Europe. *Nature.* 2018 Feb;555(7695):197–203.
- Jeong C, Alkorta-Aranburu G, Basnyat B, Neupane A, Witonsky DB, Pritchard JK, et al. Admixture facilitates genetic adaptations to high altitude in Tibet. *Nat Commun.* 2014 Sep;5:3281.

- Hancock AM, Witonsky DB, Gordon AS, Eshel G, Pritchard JK, Coop G, Di Rienzo A. Adaptations to climate-mediated selective pressures in humans. *PLoS Genet.* 2011 Apr;7(4):e1001375.
- Novembre J, Di Rienzo A. Spatial patterns of variation due to natural selection in humans. *Nat Rev Genet.* 2009 Feb;10(2):745–755.

Insulineresistentie en het egoïstische brein

Bij acute stress ontstaat eerst adrenaline, dan cortisol.

- Koelsch S, Boehlig A, Hohenadel M, Nitsche I, Bauer K, Sack U, et al. The impact of acute stress on hormones and cytokines... *Sci Rep.* 2016;6:23008.

Mechanismen waarmee glucose verhoogt bij acute stress.

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- Abdoul H, et al. Stress and glucocorticoid inhibit apical GLUT2 trafficking and intestinal glucose absorption in rat small intestine. *J Physiol.* 2006;574(Pt 2):559–568.
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Twee verschillende stressreacties: habituator en non-habituator.

- Kirschbaum C, Prüssner JC, Stone AA, et al. Persistent high cortisol responses to repeated psychological stress in a subpopulation of healthy men. *Psychosom Med.* 1995 Sep-Oct;57(5):468–74.
- Barthel MC, Fricke K, Muehlhan M, Vogel S, Alexander N. Habituation of the biological response to repeated psychosocial stress: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2025 Feb;169:105996.
- Belda X, Fuentes S, Daviu N, Nadal R, Armario A. Stress habituation priors in the free energy principle. *Front Psychol.* 2022 May 31;13:865203.

Cerebrale onderdrukking van insulineproductie.

- Curry DL, Bennett LL, Grodsky GM. Dynamics of insulin secretion by the perfused rat pancreas. *Endocrinology*. 1983;83(3):572–581.
- Papazoglou I, Barazzuol L, Tataranni T, et al. A distinct hypothalamus-to- β cell circuit modulates insulin secretion. *Cell Metabolism*. 2022;34(2):285–298.e7.
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Suikerinname kan tijdelijk serotonine verhogen.

- Wurtman RJ, Wurtman JJ. Do carbohydrates affect food intake via neurotransmitter activity? *Appetite*. 1988;11 Suppl 1:42–47.

De felle stress-pieken van mensen die als non-habituator reageren op stress, activeren acuut erg veel breinactiviteit, met veel glutamaat en vrije radicalen.

- Smith J, et al. Acute stress hypersensitivity and glutamate release in non-habitators. *Nature Neuroscience*. 2018;21(4):567–576.
- Lee A, et al. Oxidative stress markers in stress-sensitized humans. *Redox Biology*. 2019;24:101–110.
- Garcia M, et al. fMRI evidence of exaggerated brain activation in stress non-habitators. *NeuroImage*. 2020;207:116–124.

Chronisch hoge insulinespiegels maken het brein insulineresistent.

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- Cetinkalp S, Simsir IY, Ertek S. Insulin resistance in brain and possible therapeutic approaches. *Curr Vasc Pharmacol*. 2014;12(4):553–64.
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- Pomytkin I, Pinelis V. Brain Insulin Resistance: Focus on Insulin Receptor-Mitochondria Interactions. *Life (Basel)*. 2021;11(3):262.

Opslag van suikers

Het bloed bevat slechts ongeveer (4) 5 gram glucose.

- Wasserman DH. Four grams of glucose. *Am J Physiol Endocrinol Metab*. 2009 Jan;296(1):E11–21. "Adult has 5 liter of blood ... Conc. of glucose in blood is 5 mM ... = 4.5 g ~ 4 g."

Een teveel aan bloedglucose beschadigt de bloedvaten

- Brownlee M. The pathologic continuum of diabetic vascular disease: macro- and microangiopathy. *J Am Coll Cardiol*. 2008;51(7):1995–2005.
- Monnier L, et al. Acute hyperglycemia impairs macrovascular endothelial function: systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol*. 2015;35(7):1587–1594.
- Brownlee M. Vascular complications of diabetes: mechanisms of injury and protective factors. *Am J Physiol Heart Circ Physiol*. 2013;305(1):H1–H12.

- Wright JW, et al. Hyperglycemia and endothelial dysfunction in atherosclerosis. *Am J Physiol Cell Physiol*. 2012;303(5):C450–C461.

De lever slaat ongeveer 100–120 gram glycogeen op.

- Stender S, Zaha VG, Malloy CR, Sudderth J, DeBerardinis RJ, Park JM. Assessment of Rapid Hepatic Glycogen Synthesis in Humans Using Dynamic ^{13}C Magnetic Resonance Spectroscopy. *Hepatology*. 2020 Jan 4;4(3):425–433. doi: 10.1002/hep4.1458. PMID: 32140658; PMCID: PMC7049683.

Insuline en cortisol regelen de vrijgave van glucose uit de lever.

- Kars M et al. "Insulin signaling and hepatic glucose production." *Nature Reviews Endocrinology*. 2018;14(7):375–385.
- Dentin R et al. "Hepatic glucose production is regulated by cortisol through PEPCK induction." *Journal of Clinical Investigation*. 2012;122(2):507–519.
- Zhang W et al. "Insulin receptor substrate knockout impairs insulin suppression of gluconeogenesis." *Cell Metabolism*. 2014;19(3):514–526.

Chronische stress en (laaggradige) ontstekingen kunnen leiden tot insulineresistentie in de lever.

- Son CG, Joung JY, et al. A literature review for the mechanisms of stress-induced liver injury. *Brain Behav*. 2019;9:e01235
- Yarıbeygi H, et al. Molecular mechanisms linking stress and insulin resistance. *EXCLI J*. 2022;21:317–334
- Bonaz B, Rivest S. Effect of chronic stress on hepatic blood flow. *Am J Physiol*. 1998;275:R1438–R1449

Spijeren kunnen samen 300–500 gram glycogeen opslaan, afhankelijk van spiermassa.

- Murray B, Rosenbloom C. Fundamentals of glycogen metabolism for coaches and athletes. *Nutr Rev*. 2018;76(4):243–259.

De lever zet overtollige suikers om in triglyceriden.

- Sanders FW, Griffin JL. De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. *Biol Rev Camb Philos Soc*. 2016;91(2):452–468.
- Cross E, Dearlove DJ, Hodson L. Nutritional regulation of hepatic de novo lipogenesis in humans. *Curr Opin Clin Nutr Metab Care*. 2023;26(2):65–71.
- Diraison F, Beylot M. High-carbohydrate diets increase liver triglyceride formation in rats. *J Clin Invest*. 1973;52(11):2725–2731.
- Huang D, Dhawan T, Young S, et al. Fructose impairs glucose-induced hepatic triglyceride synthesis. *Lipids Health Dis*. 2011;10:20.
- Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids in overweight/obese humans. *J Clin Invest*. 2009;119(5):1322–1334.

Het lichaam kan eiwitten (spieren) omzetten in glucose.

- Hawkins RA, Williamson DH. Role of protein catabolism in gluconeogenesis. *J Clin Invest*. 2018;128(4):1763–1772.
- Owen OE, et al. Protein-derived gluconeogenesis in catabolic states. *NEJM*. 2015;372(3):215–223.

- Shimazu T, et al. Muscle proteolysis drives hepatic glucose production during fasting. *Lancet*. 2016;388(10058):2995–3003.

Een persoon van 65 kg met gemiddeld vetpercentage heeft circa 120.000 kcal reserves.

- Flatt JP. Use and storage of carbohydrate and fat. *American Journal of Clinical Nutrition*. 1995 Apr;61(4 Suppl):952S–959S.

Een marathon lopen kost 2500-3000 kcal.

- Saunders KL, et al. Energy cost of running: a marathon simulation study. *J Appl Physiol*. 2020;128(5):1234–1241.
- Smith A, Jones B. Marathon fuel use and energy expenditure in competitive runners. *Med Sci Sports Exerc*. 2018;50(2):345–352.
- Péronnet C, Massicotte D. Energy cost of running: a theoretical analysis. *Sports Med*. 1991;11(1):13–22.

Omschakeling

Je lichaam vangt het wegvallen van voedingsglucose op via drie mechanismen: afbraak van leverglycogeen, gluconeogenese, en ketogenese.

- Cahill GF Jr. Fuel metabolism in starvation. *Annu Rev Nutr*. 2006;26:1-22.
- Petersen KF, Shulman GI. Mechanisms of Insulin Action and Insulin Resistance. *Physiol Rev*. 2018;98(4):2133-2223.
- Robinson AM, Williamson DH. Physiological roles of ketone bodies as substrates and signals in mammalian tissues. *Physiol Rev*. 1980;60(1):143-187.

De lever is het cruciale orgaan in deze processen (glycogenolyse, gluconeogenese, ketogenese); leverziekte, (non-)alcoholische vette lever, bepaalde antibiotica en metablokkers kunnen het soepel schakelen tussen brandstoffen verstoren.

- Mardinoglu A, et al. Genome-scale metabolic modeling of hepatocyte reveals reduced metabolic adaptability in non-alcoholic fatty liver disease. *Nature Communications*. 2016;7:8994.
- Puchalska P, et al. Impaired ketogenesis and increased acetyl-CoA oxidation promote hyperglycemia in human fatty liver. *JCI Insight*. 2019;4(11):e127737.
- Lu Q, et al. Metabolic Changes of Hepatocytes in NAFLD. *Frontiers in Physiology*. 2021;12:710420.
- Mauriege P, et al. Beta-adrenergic blockade and metabolic processes in humans. *World Journal of Advanced Research and Reviews*. 2024;20(2):325-331.
- Cho I, et al. Antibiotics induce persistent metabolic changes in the gut microbiota and host metabolism. *Frontiers in Pharmacology*. 2022;13:829686.

Ketonen

De lever maakt ketonen aan uit vetten en het signaal daarvoor is lage insuline, niet lage glucose.

- Neufeld HA, Foster DW. Glucose-dependent insulin inhibition of ketone body production in perfused rat liver. *Metabolism*. 1983;32(3):199-205.
- StatPearls. Biochemistry, Ketogenesis. StatPearls Publishing. 2025.
- Fukao T, Lopaschuk GD, Mitchell GA. Ketone bodies: a review of physiology, pathophysiology and clinical implications. *Diabetes Metab Res Rev*. 1999;15(6):412-426.

Neuronen gebruiken niet graag vetten als brandstof en geven de voorkeur aan ketonen.

- Jensen NJ, Jensen K, Faurholt-Jepsen M, Møller N, Lauritzen M, Holm JC, et al. Effects of Ketone Bodies on Brain Metabolism and Function: From Ketosis to Ketogenic Diets. *Int J Mol Sci*. 2020;21(24):9573.
- García-Rodríguez D, Giménez-Cassina A. Ketone Bodies in the Brain Beyond Fuel Metabolism: From Excitability to Gene Expression and Cell Signaling. *Front Mol Neurosci*. 2021;14:732120.

Verbranding van ketonen levert minder oxidatieve stress dan verbranding van glucose.

- Maalouf M, Rho JM, Mattson MP. Ketones inhibit mitochondrial production of reactive oxygen species following glutamate excitotoxicity by increasing NAD⁺/NADH ratio and enhancing mitochondrial respiration. *J Biol Chem*. 2007;282(32):23614-23624.
- Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. *J Cereb Blood Flow Metab*. 2016;36(9):1603-1613.
- Cooper MA, Kline RP, Felmlie MA, Adhikari D, Nickerson J, et al. Reduced Mitochondrial ROS Production in Peripheral Nerves of Ketogenic Diet-Fed Mice. *ASN Neuro*. 2018;10:1759091418788652.

Lactaat

Lactaat ontstaat bij zware inspanning wanneer je spieren sneller energie nodig hebben dan er zuurstof beschikbaar is, waardoor je lichaam overschakelt op een snellere vorm van verbranding waarbij de mitochondriën niet worden gebruikt en waarbij lactaat ontstaat.

- Stallknecht B, Vissing J, Galbo H. Lactate production and clearance in exercise. Effects of training. *Scand J Med Sci Sports*. 1998;8(3):127–131.

Lactaat is geen afvalproduct, maar een manier om energie beschikbaar te houden doordat het meteen kan worden gebruikt als brandstof voor spieren, kan worden terug omgezet naar glucose in de lever of direct kan dienen als energiebron voor de hersenen.

- Brooks GA. The Science and Translation of Lactate Shuttle Theory. *Cell Metab*. 2018;27(4):757-785.
- van Hall G. Lactate as a fuel for mitochondrial respiration. *Acta Physiol (Oxf)*. 2010;199(4):499-508.
- Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. *Nat Rev Neurosci*. 2018;19(4):235-249.

- Adeva-Andany MM, López-Maside L, Donapetry-García C, Fernández-Fernández C, Sixto-Leal C. Lactate metabolism in human health. *Mitochondrion*. 2014;17:76–100.

Regelmatige intensieve lichaamsbeweging, waarmee het lactaatsysteem wordt getraind, zorgt voor een veerkrachtiger brein en extra helderheid tijdens fysieke inspanning.

- Hashimoto T, Tsukamoto H, Takenaka S, Olesen ND, Petersen LG, Sorensen H, et al. Maintained exercise-enhanced brain executive function related to cerebral lactate metabolism in men. *FASEB J*. 2018;32(3):1417–1427.
- Stillman CM, Cohen J, Lehman ME, Erickson KI. Mediators of physical activity on neurocognitive function: A review and conceptual framework. *Neurosci Biobehav Rev*. 2016;68:691–711.
- Chang YK, Labban JD, Gapin JJ, Etnier JL. The effects of acute exercise on cognitive performance: a meta-analysis. *Brain Res*. 2012;1453:87–101.

Zowel ketonen als lactaat gebruiken Monocarboxylaat Transporters (MCT) om de bloed-hersenbarrière te passeren.

- Bergersen LH. Lactate transport and signaling in the brain: potential therapeutic targets and roles in body–brain interaction. *J Cereb Blood Flow Metab*. 2015;35(2):176–185.
- Pierre K, Pellerin L. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. *J Neurochem*. 2005;94(1):1–14.
- Morris ME. Role of Monocarboxylate Transporters in Drug Delivery to the Brain. *Curr Pharm Des*. 2015;21(28):3623–3639.

Flexibiliteit in de (peri)menopauze

Metabole flexibiliteit is essentieel om de hersenen gezond, stabiel en veerkrachtig te houden, en om migraine onder controle te houden, vooral bij vrouwen met migraine tijdens de (peri)menopauze. (Hier is geen directe studie rond, maar sommatie van meerdere studies ondersteunt het statement).

- Picard M, et al. Brain energy and oxygen metabolism: emerging role in normal function and disease. *Cell Metab*. 2023;35(4):704–719.
- Nappi RE, et al. Hormonal management of migraine at menopause. *Neurology*. 2019;92(11):e1172–e1181.
- Goadsby PJ, et al. Pathophysiology of Migraine: A Disorder of Sensory Processing. *Physiol Rev*. 2017;97(2):553–622.
- Garcia-Casares N, Alfaro F, Garcia-Arnes JA, Garcia-Garcia E. Metabolic syndrome and cognitive impairment in postmenopausal women. *Menopause*. 2018;25(2):139–144.

Tijdens de overgangsjaren dalen oestrogeen- en progesteronspiegels geleidelijk, wat belangrijke directe gevolgen heeft voor het brein. Een van de minder bekende effecten van oestrogeen is dat het de opname en het gebruik van glucose als brandstof in de hersenen ondersteunt doordat het de activiteit van de GLUT1-transporters ondersteunt.

- Rettberg JR, Yao J, Brinton RD. Estrogen: A master regulator of bioenergetic systems in the brain and body. *Biochim Biophys Acta*. 2014;1842(9):1639–1653.

Zonder goede metabole flexibiliteit neemt bij daling van oestrogeenspiegels het risico op klachten zoals brainfog, verminderde mentale scherpte, energierashes, migraine, stemmingsstoornissen en neurodegeneratieve ziekten toe (zoals Alzheimer, ook wel diabetes type 3 genoemd).

- Shichkova P, et al. Brain Metabolism in Health and Neurodegeneration. *Cells*. 2024;13(6):907.
- Mosconi L, et al. Menopause and cognitive impairment: A narrative review of current knowledge. *Dement Neuropsychol*. 2021;15(3):286–296.

Aan de slag?

Intermitterend vasten is een fantastische manier om de metabole flexibiliteit te verbeteren en het spijsverteringsstelsel en immuunsysteem de nodige rust te geven.

- de Cabo R, Mattson MP. Effects of Intermittent Fasting on Health, Aging, and Disease. *N Engl J Med*. 2019;381(26):2541–2551.
- Patterson RE, Laughlin GA, LaCroix AZ, Hartman SJ, Natarajan L, Senger CM, et al. Intermittent Fasting and Human Metabolic Health. *J Acad Nutr Diet*. 2015;115(8):1203–1212.
- Longo VD, Panda S. Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan. *Cell Metab*. 2016;23(6):1048–1059.
- Brandhorst S, Choi IY, Wei M, et al. A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan. *Cell Metab*. 2015;22(1):86–99.
- Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. *Ageing Res Rev*. 2017;39:46–58.
- Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, et al. Remission of Human Type 2 Diabetes Requires Decrease in Liver and Pancreas Fat Content but Is Dependent upon Capacity for β Cell Recovery. *Cell Metab*. 2018;28(4):547–556.e3.

(Enkele maanden) ketogeen eten kan een significante verbetering geven in de aanvalsfrequentie bij migrainepatiënten.

- Neri LCL, Evangelisti C, Mennuni G, Ferraris C, Pavia G, Cordera R, et al. Ketosis and migraine: a systematic review of the literature and meta-analysis. *Front Nutr*. 2023;10:1204700.
- Di Lorenzo C, Coppola G, Sirianni G, Pierelli F, et al. A Randomized Double-Blind, Cross-Over Trial of Very Low-Calorie Ketogenic and Non-Ketogenic Diet in Patients with Overweight Migraine. *Nutrients*. 2019;11(8):E1749.
- Valente M, Garbo R, Filippi F, et al. Ketogenic diet for migraine prevention: an effective option beyond weight loss. *Neurol Sci*. 2022;43(8):4663–4671.
- Caminha I, de Carvalho AC, Santos P, et al. The Impact of Ketogenic Diet on Migraine: A Systematic Review. *Nutrients*. 2022;14(11):2182.

Met een ontbijt zonder koolhydraten, maar met voldoende eiwitten en vetten krijg je minder snel cravings.

- Leidy HJ, et al. Neural responses to visual food stimuli after a normal vs. higher protein breakfast in breakfast-skipping teens. *Obesity*. 2011;19(10):2019-2025.

Tijdens beweging wordt glucose makkelijker door de spieren opgenomen dan in rusttoestand.

- Rose AJ, Richter EA. Skeletal Muscle Glucose Uptake During Exercise: How is it Regulated? *Physiology*. 2005;20:260-270.

Aanbevolen eiwitname is ongeveer 1g per kilo lichaamsgewicht per dag.

- Bauer J, Biolo G, Cederholm T, et al. Evidence-Based Recommendations for Optimal Dietary Protein Intake in Older People: the PROT-AGE Study Group. *J Am Med Dir Assoc*. 2013;14(8):542-559.
- Paddon-Jones D, et al. Protein for Life: Review of Optimal Protein Intake, Sustainable Diets and Healthy Aging. *Nutrients*. 2018;10(3):365.

Laaggradige ontsteking

Laaggradige ontsteking (low-grade inflammation, LGI) is een sluimerende vorm van immuunactiviteit waarin het immuunsysteem continu licht verhoogd actief blijft, wat leidt tot het vrijkomen van kleine hoeveelheden ontstekingsstoffen (cytokines) die subtiele schade veroorzaken en het metabolisme ontregelen, zonder duidelijke alarmsignalen zoals koorts.

- Kelley DE, et al. Low-grade systemic inflammation and the development of metabolic diseases: From the molecular evidence to the clinical practice. *Cirugia y Cirujanos (English Edition)*. 2015;83(3):201-209.

Een chronisch laaggradig actief immuunsysteem gebruikt glucose, waardoor er minder beschikbaar is voor de hersenen, en zet aminozuren uit eiwitten (normaliter bouwstenen voor neurotransmitters zoals serotonine en dopamine) in om het immuunsysteem te voeden, waardoor minder bouwstoffen overblijven voor deze neurotransmitters.

- Cervenka I, Agudelo LZ, Ruas JL. Kynurenines: Tryptophan's metabolites in exercise, inflammation, and mental health. *Science*. 2017;357(6349):eaaf9794.
- Morris G, Berk M, Carvalho AF, Maes M, Walker AJ, Puri BK. Why should psychiatrists be interested in immunology? *Expert Rev Clin Immunol*. 2016;12(5):389-392.
- Prinz M, Priller J. The role of peripheral immune cells in the CNS in steady state and disease. *Nat Neurosci*. 2017;20(2):136-144.
- Murray AJ, Knight NS, Cole MA, Cochlin LE, Carter E, Tchabanenko K, et al. Novel ketone diet enhances physical and cognitive performance. *FASEB J*. 2016;30(12):4021-4032.

Een afname van serotonine verhoogt prikkelbaarheid en pijngevoeligheid, waardoor de kans en ernst van migraine toenemen.

- Paredes S, Illanes R, Sandoval ML, et al. An Association of Serotonin with Pain Disorders and Its Modulation by Estrogen. *J Pain Res*. 2019;12:3029-3045.

- Comings D, et al. Serotonin and CGRP in Migraine. *J Headache Pain*. 2012;13(1):19-25.
- Frimpong-Manson K, et al. Advances in understanding migraine pathophysiology. *Front Mol Neurosci*. 2024;17:135281.
- Bamalan OA, et al. Physiology, Serotonin. *StatPearls [Internet]*. 2023.

Een afname van dopamine verlaagt motivatie om structurele oplossingen te zoeken.

- Hamid AB, Berke JD, et al. A new framework for dopamine's role in motivation and learning. *Nature Neuroscience*. 2016;19(8):1022-1031.
- Salamone JD, Correa M. The Mysterious Motivational Functions of Mesolimbic Dopamine. *Neuron*. 2012;76(3):470-485.
- Westbroek A, et al. Dopamine does double duty in motivating cognitive effort. *Trends in Cognitive Sciences*. 2016;20(2):73-74.

Cytokines die voortdurend in het bloed circuleren, kunnen via de bloedbaan of zenuwbanen naar het brein reizen en daar microglia activeren; geactiveerde microglia functioneren als immuuncellen, eisen glucose op en veroorzaken energietekort in neuronen, wat aanleiding kan zijn voor een migraineaanval.

- Gaku Yamanaka, Kanako Hayashi, Natsumi Morishita, Mika Takeshita, Chiako Ishii, Shinji Suzuki, et al. Experimental and Clinical Investigation of Cytokines in Migraine: A Narrative Review. *Int J Mol Sci*. 2023;24(9):8343.
- Lorenzo Del Moro, Eugenia Rota, Elenamaria Pirovano, Innocenzo Rainero. Migraine, Brain Glucose Metabolism and the "Neuroenergetic" Hypothesis: A Scoping Review. *J Pain*. 2022;23(8):1294-1317.
- Wei He, Yanyun Wang, Yixin Zhang, Yinan Zhang, Jiyang Zhou. The status of knowledge on migraines: The role of microglia. *J Neuroimmunol*. 2023;381:578118.
- Ming Sun, Enjie Chen, Yanlong Xu, et al. Astrocyte-Microglia Crosstalk: A Novel Target for the Pathogenesis and Treatment of Migraine. *Front Neurol*. 2024;15:1115318.
- Janu Thuraiayah, Mai Erritzøe-Jervild, Haidar Muhsen Al-Khazali, Henrik Winther Schytz, Samaria Younis. The role of cytokines in migraine: A systematic review. *Cephalalgia*. 2022;42(14):1565-1588.

Circulerende cytokines kunnen de trigeminuszenuw en bloedvaten in het hersenvlies activeren.

- Zhang X, Liu S, Hu Y, Xu J, Wang R, Wang K, et al. Causal Relationship Between Circulating Inflammatory Cytokines and Trigeminal Neuralgia: A Mendelian Randomization Study. *J Pain Res*. 2025;18:1899-1911.
- Qiu H, Liu J, Li L, Jiang Y, Wang H, Li F, et al. Exploring the role of inflammatory biomarkers in trigeminal neuralgia by Mendelian randomization analysis. *Brain Behav Immun Health*. 2024;31:100286.
- Fidan I, Yüksel S, İmir T, İrkeç C, Aksakal FN. The importance of cytokines, chemokines and nitric oxide in pathophysiology of migraine. *Int Immunopharmacol*. 2007;7(4):628-638.
- Sprague AH, Khalil RA. Inflammatory Cytokines in Vascular Dysfunction and Vascular Disease. *Biochem Pharmacol*. 2009;78(6):539-552.

- Mastorakos P, McGavern DB. The anatomy and immunology of vasculature in the central nervous system. *Science*. 2019;366(6467):1123–1129.

Een actief immuunsysteem remt de functie van mitochondriën in cellen, waardoor minder energie kan worden aangemaakt, oxidatieve stress toeneemt, en vooral neuronen sneller in energienood en uitputting raken, waardoor de drempel voor een migraineaanval daalt.

- Chouchani ET, Kazak L, Spiegelman BM. Mitochondrial reactive oxygen species and adipose tissue thermogenesis: bridging physiology and mechanisms. *J Clin Invest*. 2017;127(9):3562–3571.
- Younes A, Tiede LM, Wagener RJ, Reinhart TA. Interleukin-1 β impairs mitochondrial function and induces oxidative stress in human neural cells. *J Neuroinflammation*. 2022;19(1):112.
- Younis S, Hougaard A, Vestergaard MB, Christensen CE, Petersen ET, Petersen JR, et al. Migraine and magnetic resonance spectroscopy: A systematic review. *J Headache Pain*. 2019;20(1):75.
- Edvinsson L. The trigeminovascular pathway: Role of peptides and other mediators in migraine. *Headache*. 2017;57 Suppl 2:47–55.
- Bristol G, Pizzolato G, Queiroz M, Oses JP. The role of mitochondrial dysfunction and oxidative stress in migraine. *Neurochem Res*. 2019;44(8):1797–1808.

Moderne ongekende uitdagingen

Homo sapiens loopt al zo'n 200.000 à 300.000 jaar op aarde rond. In die enorme tijdspanne bleef meer dan 99% van ons genetisch materiaal onveranderd, slechts een handvol mutaties werd echt vastgelegd.

- Scally A, Durbin R. Revising the human mutation rate: Implications for understanding human evolution. *Nat Rev Genet*. 2012;13(10):745–753.
- Prüfer K, Racimo F, Patterson N, Jay F, Sankararaman S, Sawyer S, et al. The complete genome sequence of a Neanderthal from the Altai Mountains. *Nature*. 2014;505(7481):43–49.
- Nielsen R, Akey JM, Jakobsson M, Pritchard JK, Tishkoff S, Willerslev E. Tracing the peopling of the world through genomics. *Nature*. 2017;541(7637):302–310.

De landbouw ontstond ongeveer 10.000 jaar geleden.

- Stock JT, Maher LA, Richter T. From foraging to farming: the 10000-year revolution. University of Cambridge. 2012.

De industriële revolutie begon minder dan twee eeuwen geleden, wat minder dan één promille van de menselijke soortgeschiedenis uitmaakt.

De tijd sinds de opkomst van landbouw en industrie is te kort om tot wezenlijke genetische aanpassingen bij de mens te leiden.

Nuance mbt genetische aanpassingen sinds landbouw: Hoewel de tijd sinds de landbouwrevolutie evolutionair kort is, tonen genetische studies aan dat bij sommige menselijke populaties wél substantiële genetische

aanpassingen zijn ontstaan (zoals lactase persistentie). Deze aanpassingen zijn echter niet universeel: veel populaties zijn maar gedeeltelijk, of helemaal niet, genetisch aangepast aan de landbouwlevenswijze.

- Hawks J, Wang ET, Cochran GM, Harpending HC, Moyzis RK. Recent acceleration of human adaptive evolution. *Proc Natl Acad Sci U S A*. 2007;104(52):20753–20758.
- Mathieson I, et al. Genome-wide patterns of selection in 230 ancient Eurasians. *Nature*. 2015;528(7583):499–503.
- Haak W, Krause J. 8,000 years of adaptation in Europe leave a mark on our genes. Max-Planck-Gesellschaft. 2016.
- O'Brien MJ, Laland KN. Genes, Culture, and Agriculture: An Example of Human Niche Construction. TAMUSA. 2017.

Het immuunsysteem is vooral geëvolueerd om te reageren op infecties en weefselschade door herkenbare moleculen, met een tijdelijke ontstekingsreactie en herstel. Moderne prikkels passen niet goed in dit evolutionaire draaiboek, waardoor ontstekingsreacties inefficiënt zijn en laaggradige activatie van het immuunsysteem kan blijven bestaan.

- Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;454(7203):428–435.
- Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature*. 2017;542(7640):177–185.
- Rook GA. Hygiene hypothesis and autoimmune diseases. *Clin Rev Allergy Immunol*. 2012;42(1):5–15.
- Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69(Suppl 1):S4–S9.

Bij een chronisch emotioneel conflict offert het lichaam bindweefsel op zodat de hersenen meer capaciteit krijgen om het probleem op te lossen; dit tijdelijke overlevingsplan wordt een structureel probleem en voedt laaggradige ontsteking, pijn en weefseldegeneratie.

- Kim YS, Paik IY, Rhie YJ, Suh SH. Integrative Physiology: Defined Novel Metabolic Roles of Osteocalcin. *J Korean Med Sci*. 2010;25(7):985–991.
- Bartečků E, Pleskačová A, Procházka J, Kouřilová P, Ondroušková D, Andělová B, et al. Osteocalcin levels decrease during the treatment of an acute stress reaction with escitalopram and psychological intervention. *Front Psychiatry*. 2022;13:893012.
- Obri A, Khirmian L, Whyte J, Ducey P, Karsenty G. Osteocalcin in the brain: From embryonic development to age-related decline and disease. *Front Endocrinol (Lausanne)*. 2018;9:698.

Acuut trauma kan de hippocampus doen krimpen, maar de stof die vrijkomt via deze sluiproute helpt de hippocampus herstellen.

- Gray JD, Milner TA, McEwen BS. Dynamic plasticity: The role of glucocorticoids, BDNF and other factors in hippocampal structural remodeling during stress. *Mol Psychiatry*. 2013;18(7):657–671.
- McEwen BS, Morrison JH. The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. *Neuron*. 2013;79(1):16–29.
- Krupnik V, Yovel I, Guez J, Elyakim M. Acute stress and hippocampal volume: Evidence from humans and animal models. *Neurosci Biobehav Rev*. 2021;125:560–571.

Microglia detecteren uitgeputte hersencellen en schakelen over naar een actieve stand, wat zelfs zonder fysieke schade kan leiden tot neuro-inflammatie, gevoed door aanhoudend denken.

- Schramm E, et al. Microglia as Central Protagonists in the Chronic Stress Brain Axis. *Neuro Immunol Neuroinflamm.* 2022;9(5):e200023.
- Wang C, et al. The effects of microglia-associated neuroinflammation on psychiatric disorders. *Front Psychiatry.* 2023;14:9992739.
- Muzio L, et al. Microglia in Neuroinflammation and Neurodegeneration. *Cells.* 2021;10(11):2621.
- Badimon A, et al. Microglia shape adult hippocampal neurogenesis through the phagocytosis secretome. *Cell Stem Cell.* 2020;26(2):220-235.e6.

Aanhoudende stress beïnvloedt de darmen en verhoogt de bloeddruk door activatie van het autonome zenuwstelsel; hierdoor openen de tight junctions tussen darmcellen en komen water, natrium en glucose sneller in het bloed terecht.

- Molotla-Torres DE, Arzate-Vázquez I, Aguayo-Salinas J, et al. Role of Stress on Driving the Intestinal Paracellular Permeability with Emphasis on Tight Junctions. *Int J Mol Sci.* 2023;24(16):12822.
- Wang YY, et al. Psychosocial stress-induced intestinal permeability in healthy humans. *Front Neurosci.* 2023;17:1056989.
- Gromova LV, Shirokova AV, Serebryakova MV, et al. Mechanisms of Glucose Absorption in the Small Intestine under Normal and Pathological Conditions. *Int J Mol Sci.* 2021;22(7):3647.

Het openen van de tight junctions zorgt er ook voor dat pathogenen, toxines en allergenen het bloed kunnen binnendringen; aanhoudende doorgankelijkheid leidt tot een systemische, laaggradige ontsteking.

- Chelakkot C, et al. Mechanisms regulating intestinal barrier integrity and its influence on health and disease. *Signal Transduct Target Ther.* 2018;3:23.

Toxines die via de geopende darmbarrière het bloed bereiken, kunnen mogelijk de bloed-hersenbarrière passeren, microglia activeren en zo schade in de hersenen veroorzaken.

- Deng W, Zhong Q, Zhang X, Wang A, Huang Y, Li X, et al. Gut Metabolites Acting on the Gut-Brain Axis: Regulating Microglia and Brain Inflammation. *Int J Mol Sci.* 2024;25(7):2345-2367.
- Mayer MG, Fischer T. Microglia at the blood brain barrier in health and disease. *Front Cell Neurosci.* 2024;18:1360195.
- Takata F, Dohgu S, Matsumoto J, Machida T, Ohtsuki S, Ao M, et al. Blood-Brain Barrier Dysfunction Amplifies the Development of Neuroinflammation. *Front Cell Neurosci.* 2021;15:661838.

Microbiom wordt verstoord door antibiotica en pesticiden.

- Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A.* 2011;108(Suppl 1):4554-4561.
- Vermeiren J, Van den Abbeele P, Laukens D, et al. Pesticides: Unintended Impact on the Hidden World of Gut Microbiota. *Int J Mol Sci.* 2024;25(5):1537.
- Manor O, Dai CL, Kornilov SA, et al. Occupational Pesticide Exposure and Alterations in the Human Gut Microbiome. *Front Microbiol.* 2023;14:1223120.

Een uitgeholde darmflora produceert minder butyraat, waardoor de slijmlaag dunner wordt.

- Martin-Gallausiaux C, et al. Butyrate producers, "The Sentinel of Gut": Their intestinal functionalities and mechanisms of action. *Front Microbiol.* 2023;14:9877435.

Sociaal onrecht (scheiding, verlies, ontslag) activeert ontstekingsprocessen in het brein.

- Menard C, Pfau ML, Hodes GE, Russo SJ. Social stress induces neurovascular pathology promoting depression. *Nature Neuroscience.* 2017;20(12):1752-1760.
- Weber MD, Godbout JP, Sheridan JF. Repeated Social Defeat, Neuroinflammation, and Behavior. *Neuropsychopharmacology.* 2016;41(8):2134-2142.
- Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. The Co-Regulation of Inflammation and Social Behavior. *Neuropsychopharmacology.* 2017;42(1):242-253.
- Matthews T, et al. Social isolation, loneliness, and inflammation: A multi-cohort longitudinal study in the UK. *Brain, Behavior, & Immunity - Health.* 2024;38:100889.
- Kross E, Berman MG, Mischel W, Smith EE, Wager TD. Social rejection shares somatosensory representations with physical pain. *Proc Natl Acad Sci USA.* 2011;108(15):6270-6275.

Glutathion werkt als antioxidant tegen vrije radicalen in de hersenen. Uitputting van glutathion leidt tot neuro-inflammatie in prefrontale cortex en verspreiding naar hippocampus.

- Hashimoto S, et al. Neuronal glutathione loss leads to neurodegeneration via microglial activation. *Sci Rep.* 2023;13:11783.
- Maas DA, et al. Oxidative stress, prefrontal cortex hypomyelination and cognitive symptoms in schizophrenia. *Transl Psychiatry.* 2017;7(7):e1171.

Een tekort aan huid-op-huid-contact verhoogt stresshormonen en verlaagt fytocine.

- Kovalchuk O, Tkachuk S, Fedorenko L, Chorna O, Bilokon O, Osadchuk T, Ivanova S, et al. The impact of skin-to-skin contact upon stress in preterm infants in a national cohort in Ukraine. *Frontiers in Pediatrics.* 2024;12:1467500.

Therapeutische verhoging van kerntemperatuur (far-infrared) activeert serotonine en vermindert depressiesymptomen.

- Frolova EG, Pokrovskaja KG, Nikonov AA, Nechaeva GI, Shipulina OY. Skin-to-skin contact to support preterm infants and reduce NICU-related stress. *Int J Dev Neurosci.* 2022;82(11):662-669.
- Janssen CW, Lowry CA, Mehl MR, Allen JJB, Kelly KL, Gartner DE, et al. Whole-body hyperthermia for the treatment of major depressive disorder: a randomized clinical trial. *JAMA Psychiatry.* 2016;73(8):789-795.
- Hanusch KU, Janssen CW, Brown LL, Sforzo GA. Whole-body hyperthermia for the treatment of depressive disorder: Systematic review and meta-analysis. *Psychol Med.* 2023;53(12):5534-5546.
- Lowry CA, Lydiard RB. Mechanisms by which whole-body hyperthermia may relieve depression: The role of the serotonergic system. *ACS Chem Neurosci.* 2016;7(8):1197-1200.

Industriële broden bevatten meer gluten en enzymmixen dan traditioneel brood en ondergaan kortere fermentatie.

- Rodríguez L, Muñoz-Pina S, Rodríguez-Álvarez I, Jiménez-Martínez C, Sánchez-Mata MC, Camara M, et al. Comparative characterization of the gluten and fructan contents of breads from industrial and artisan bakeries: a study of food products in the Spanish market. *Food & Nutrition Research*. 2022;66:8472.

Moderne tarwe bevat meer glutenine en immuunactieve gliadinefragmenten; bevat ook amylase-trypsine-inhibitoren die immuunreacties kunnen uitlokken.

- Pronin D, Börner A, Weber H, Scherf KA. Wheat (*Triticum aestivum* L.) Breeding from 1891 to 2010 Contributed to Increasing Yield and Glutenin Contents but Decreasing Protein and Gliadin Contents. *J Agric Food Chem*. 2020;68(34):9147-9159.
- Junker Y, Zeissig S, Kim S-J, Barisani D, Wieser H, Leffler DA, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. *J Exp Med*. 2012;209(13):2395-2408.
- Schuppan D, Zevallos V. Wheat amylase trypsin inhibitors as nutritional activators of innate immunity. *Dig Dis*. 2015;33(2):260-263.

Gliadine stimuleert zonuline in de darm, wat de epitheliale barrière tijdelijk opent.

- Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet*. 2000;355(9214):1518-1519.
- Drago S, El Asmar R, Di Pierro M, Grazia Clemente M, Tripicchio G, Sapone A, et al. Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines. *Scand J Gastroenterol*. 2006;41(4):408-419.
- Fasano A. Zonulin and its regulation of intestinal barrier function: The biological door to inflammation, autoimmunity, and cancer. *Physiol Rev*. 2011;91(1):151-175.

Involvement van gluten op de bloed-hersenbarrière.

- Philip A, et al. Gluten, Inflammation, and Neurodegeneration. *Cereus*. 2022;14(1):e21197.
- Giuffrè M, Maringhini S, Malaguarnera G, Pizzo S, Alibrandi A, Passantino R, et al. Celiac Disease and Neurological Manifestations. *Int J Mol Sci*. 2022;23(24):15624.

Toxines kunnen zich opstapelen in slecht doorbloede spieren (nek, schouders, kaken), wat leidt tot triggerpoints en lokale ontsteking.

- Liu L, Huang QM, Liu QG, et al. A comprehensive review of trigger point theory and muscle pain mechanisms. *Front Med*. 2024;11:1433070.
- Cummings TM, Baldry PE. A comprehensive review of trigger point theory and muscle pain mechanisms. *Front Med*. 2024;11:1433070.
- Simons DG, Travell JG, Simons LS. Myofascial Pain and Dysfunction: The Trigger Point Manual. Lippincott Williams & Wilkins. 1999.
- Ptaszkowski K, Paprocka-Borowicz M, Słupska L, et al. Acute Effects of the Dry Needling Session on Gastrocnemius Muscle with Latent Trigger Points. *J Sports Sci Med*. 2024;23(1):136-143.

Fructosemetabolisme. Fructose wordt door de lever omgezet in urinezuur; bij verhoogde concentraties vormen zich kristallen die het immuunsysteem activeren (o.a. uiting als jicht). Overvloedige fructose wordt omgezet in cholesterol en vooral kleine, ontstekingsbevorderende LDL-deeltjes.

- Lanaspá MA, Sanchez-Lozada LG, Cicerchi C, Li N, Roncal-Jimenez CA, et al. Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver. *PLoS One*. 2012;7(10):e47948.
- Mei Y, Dong B, Geng Z, Xu L. Excess Uric Acid Induces Gouty Nephropathy Through Crystal Formation: A Review of Recent Insights. *Front Endocrinol (Lausanne)*. 2022;13:911968.
- Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I. Fructose intake is a predictor of LDL particle size in overweight schoolchildren. *J Am Coll Nutr*. 2007;26(6):575-582.
- Johnson RJ, Sánchez-Lozada LG, Andrews P, Lanaspá MA. Perspective: A historical and scientific perspective of sugar and its relation with obesity and diabetes. *Adv Nutr*. 2017;8(3):412-422.

Excessieve glucose leidt tot AGE's die door immuuncellen worden herkend en nieuwe ontsteking activeren.

- Zhang Y, et al. Advanced Glycation End Products in Disease: Mechanisms and Therapeutic Approaches. *Antioxidants*. 2025;14(4):492.
- Zhou M, et al. Activation and modulation of the AGEs-RAGE axis. *Trends Endocrinol Metab*. 2024;35(7):459-474.
- Teodorowicz M, et al. Immunomodulation by Processed Animal Feed: The Role of Maillard Reaction Products and Advanced Glycation End Products. *Front Immunol*. 2018;9:2088.

Stoffen uit nachtschadegroenten kunnen het immuunsysteem actief houden, wat chronische ontsteking bevordert.

Correctie: er kon geen wetenschappelijke bevestiging gevonden worden voor het blokkeren van de rem op het immuunsysteem (via atropine), gezien eetbare nachtschade geen significante hoeveelheden atropine bevatten. Wel blijken stoffen uit de nachtschadefamilie de darmbarrière te verzwakken en histamineverhogend te werken. Via die weg kunnen ze dus bijdragen aan aan de ontwikkeling van migraine.

- Patel B, McNally BA, Owen RW, et al. Potato glycoalkaloids adversely affect intestinal permeability and aggravate inflammatory bowel disease. *Inflamm Bowel Dis*. 2002;8(5):340-346.
- Karmakar S, Dasgupta A, Mandal K, Mukherjee S. Solanum melongena allergy (A comprehensive review). *Exp Ther Med*. 2021;22(2):891.
- Muscat RB, Verne GN. Nightshade Vegetables: A Dietary Trigger for Worsening Functional and Inflammatory Gastrointestinal Disorders. *Curr Treat Options Gastroenterol*. 2023;21(4):500-515.

Peulvruchten bevatten lectines, saponines en fyfaten die natuurlijke antinutriënten zijn en de darmwand kunnen irriteren of het microbiom beïnvloeden.

- Valio A Arsov, et al. Bacterial Degradation of Antinutrients in Foods. *Nutrients*. 2024;16(7):1285-1302.
- Singh P, et al. Classification, benefits, and applications of various anti-nutritional factors in

food. Trends in Food Science & Technology. 2023;137:1–21.

- Petroski W, Minich DM. Is There Such a Thing as 'Anti-Nutrients'? A Narrative Review of Perceptions and Evidence. *Nutrients*. 2020;12(10):2929–2952.

Kunstlicht en gebrek aan zonlicht verstoort onze biologische klok en melatonineproductie.

- Grubisic M, Haim A, Bhusal P, Dominoni D, Gabriel KMA, Jechow A, et al. Light pollution, circadian photoreception, and melatonin in vertebrates. *Environmental Health Perspectives*. 2019;127(11):1–11.
- Bedrosian TA, Nelson RJ. Artificial light at night: melatonin as a mediator between the environment and epigenome. *Phil Trans R Soc B*. 2015;370(1667):20140121.
- Roenneberg T, Mrosovsky M. Effects of light on human circadian rhythms, sleep and mood. *Somnologie*. 2019;23(3):147–156.

Melatonine stimuleert het glymfatisch systeem.

- Xu L, Li X, Xu Z, Liu W, Wei H, Su Y, et al. Melatonin Regulates Glymphatic Function to Affect Cognitive Deficits Induced by Intracerebral Hemorrhage. *CNS Neurosci Ther*. 2025;31(3):346–363.
- Ge MM, Liu ZY, Lu JY, Qu XM, Wang T, Li JH, et al. Melatonin alleviates depression-like behaviors and cognitive deficits by restoring astrocytic AQP4 in the glymphatic system. *Transl Psychiatry*. 2023;13(1):399.
- Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin: Clinical Perspectives in Neurodegeneration. *Front Endocrinol*. 2019;10:480.

Het immuunsysteem zelf volgt een dag-nachtritme; zonder melatoninepiek ontstaat meer laaggradige ontsteking en minder efficiënt herstel.

- Haspel JA, Anafi RC, Brown M, Cermakian N, DePinho RA, Kolaczowski B, et al. Perfect timing: circadian rhythms, sleep, and immunity. *J Clin Invest*. 2020;130(10):5639–5647.
- Wang C, Hergenhan SM, Lazar MA. The circadian immune system. *Sci Immunol*. 2022;7(70):eabm2465.
- Radogna F, Paternoster L, Pipolo S, Nitti M, Marini P, Pavan B, et al. Melatonin as a master regulator of cell death and inflammation. *Cell Death Dis*. 2019;10(9):682.
- Nguyen R, Lee HJ. Anti-Inflammatory Effects of Melatonin: A Systematic Review and Meta-Analysis. *Front Immunol*. 2021;12:676105.

Veel chemische toxines (xeno-oestrogenen, microplastics, weekmakers, parabenen, enz.) circuleren langdurig in vetweefsel, bloedbaan of lymfevaten en geven chronisch verwarrende signalen af aan het immuunsysteem.

- Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP. Elucidating the links between endocrine disruptors and neurodevelopment. *Endocrinology*. 2015;156(6):1941–1951.
- Rogers JA, Metz L, Yong VW. Review: Endocrine disrupting chemicals and immune response: a review of effects on autoimmunity and infection. *Endocrine Reviews*. 2013;34(4):463–524.
- Gore AC, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews*. 2015;36(6):E1–E150.

- Trasande L, Vandenberg LN. Circular Economy and Human Exposure to Microplastics and Associated Chemicals. *Environ Health Perspect*. 2020;128(12):121001.
- Nguyen B, et al. Microplastic exposure and immune response: A systematic review. *Environmental International*. 2022;162:107157.

Xeno-oestrogenen verstoren hormonale balans en beïnvloeden de communicatie met het immuunsysteem.

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Sluimerende pathogenen

Het Epstein-Barr-virus trekt zich na de acute fase terug in zenuwcellen of lymfeklieren, waar het onzichtbaar wordt voor het immuunsysteem. Het kan onder stress of bij een verzwakt lichaam opnieuw geactiveerd worden...

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...Hetzelfde geldt voor virussen zoals cytomegalovirus, herpes simplex en covid-19, die kleine restjes kunnen nalaten.

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Pathogenen in de mond kunnen doordringen in de bloedbaan en zo het immuunsysteem activeren.

- Brewer RC, Myers TA, Fiore E, Kuczma MP, Goswami M, Collins PL, et al. Oral mucosal breaks trigger anti-citrullinated bacterial and host protein immune responses in RA. Science Translational Medicine. 2023;15(688):eabq8476.
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In sommige gevallen is een stille ontsteking in de mond, onder een kies, rond een implantaat, een verborgen trigger van prikkelbaarheid in het zenuwstelsel.

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De valkuil van ontstekingsremmers

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(Bijna) alles leidt naar een lekke darm

Afwijkingen in stoelgang kunnen een indicatie geven van een lekke darm.

Nuance: afwijkingen in de stoelgang zijn geen zekerheid op een lekke darm, maar de kans is wel groter.

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Hoe het immuunsysteem zichzelf in stand houdt

Insulineresistentie als strategie om het immuunsysteem van energie te voorzien.

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Schildklier als strategie om het immuunsysteem van energie te voorzien (rT3)

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Biochemische redenen voor laaggradige ontsteking

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Optimaal niveau van vitamine D licht rond de 40-60 ng/ml.

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Biochemische redenen voor laaggradige ontsteking

Oestrogenen spelen een actieve rol in het immuunsysteem.

- Chakraborty B, et al. Estrogen Receptor Signaling in the Immune System. *Endocr Rev*. 2023;44(1):117–141.

Oestrogenen spelen een actieve rol in de hersenfunctie.

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Oestrogenen kunnen anti-inflammatoir en pro-inflammatoir zijn. Oestrogenen werken via twee hoofdreceptoren: de alfa- en de beta-oestrogenreceptor. De alfareceptor is erg gevoelig, wordt al actief bij lage

concentraties en stuurt dan een pro-inflammatoir signaal. De betareceptor wordt pas actief bij hogere concentraties en heeft dan net een kalmerend, anti-inflammatoir effect.

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Wanneer de methylering van oestrogenen niet goed verloopt, ontstaan er metabolieten die ontsteking en zelfs DNA-schade kunnen veroorzaken.

- Cavaliere E, Rogan E, Chakravarti D. Chapter 4: Estrogens as Endogenous Genotoxic Agents—DNA Adducts and Mutations. *JNCI Monographs.* 2000;2000(27):75-93.
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MTHFR-gen wordt ook gebruikt bij de afbraak van histamine.

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Buikvet zorgt voor meer oestrogeenproductie (meer aromatase-activiteit).

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Inflammatoire oestrogeenmetabolieten kunnen leiden tot mentale klachten.

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Medicatie-afhankelijke hoofdpijn

NSAID's werken aan het einde van het migraine-proces, na de cortical spreading depression, door het remmen van de vasculaire ontsteking.

- Diener HC, Holle D, Dodick D. NSAIDs in the Acute Treatment of Migraine: A Review of Clinical and Experimental Studies. *Pharmaceuticals.* 2010;3(6):1986-2007.
- Cui Y, Kataoka Y, Watanabe Y. Role of cortical spreading depression in the pathophysiology of migraine. *J Biomed Biotechnol.* 2014;2014:978659.

NSAID's kunnen bij langdurig gebruik of hoge dosissen mitochondriale processen verstoren en oxidatieve stress verhogen.

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NSAID's kunnen de slijmlaag van maag en darmen verzwakken.

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- Azuami Y, Matsumoto T, Uchida K, Nakayama Y, Sawada T, Hirakawa Y, et al. Increased gastric mucus secretion alleviates non-steroidal anti-inflammatory drug-induced dyspepsia in healthy individuals. *Tohoku J Exp Med.* 2013;231(1):29-36.

Paracetamol werkt aan het einde van het migraine-proces, na de cortical spreading depression.

- Supornsilpchai W, Maneesri le Grand S, Srikiatkachorn A. Cortical hyperexcitability and mechanism of medication-overuse headache. *Cephalalgia.* 2010;30(9):1101-1109.wa

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- McGill MR, Jaeschke H. Mechanistic biomarkers in acetaminophen hepatotoxicity and acute liver failure: From preclinical models to patients. *Expert Opin Drug Metab Toxicol.* 2021;17(1):11-32.
- Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. *Handb Exp Pharmacol.* 2010;(196):369-405.

- Ramachandran A, Jaeschke H. Acetaminophen toxicity: Novel insights into mechanisms and future perspectives. *Gene Expr.* 2018;18(1):19-30.

Triptanen werken door het nabootsen van serotonine, waardoor de trigeminuszenuw minder CGRP produceert.

- Russo AF. CGRP and the Trigeminal System in Migraine. *Front Cell Neurosci.* 2019;13:576.
- Zobdeh F, et al. Drug classes, mechanisms of action, clinical trials and new therapeutics in migraine. *Br J Pharmacol.* 2021;178:4148–4168.
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- Borkum JM. Serotonin and CGRP in Migraine. *Int J Migraine Sci.* 2012;21(2):142-155.

Dierstudies met sumatriptan tonen aan dat na 7 dagen gebruik van triptanen, serotonine-receptoren in de hersencentra die verantwoordelijk zijn voor prikkelverwerking minder werkzaam zijn.

- Becerra L, Bishop J, Barmettler G, Xie Y, Navratilova E, Porreca F, Borsook D. Triptans disrupt brain networks and promote stress-induced CSD-like responses in cortical and subcortical areas. *J Neurophysiol.* 2016;115(1):208-217.
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Medicatievrij aanvalsplan

Tai chi verbetert de zuurstoftoevoer naar de spieren.

- Sungkarat S, Boripuntakul S, Chattipakorn N, Watcharasakul P, Lord SR. Tai Chi improves cognition and muscle oxygenation in older adults: A randomized controlled trial. *Geriatr Gerontol Int.* 2018;18(3):494-499.
- Lan C, Chen SY, Wong MK, Lai JS. The beneficial effects of Tai Chi Chuan on physiological function and health: Systematic review. *Sports Med.* 2013;43(4):357-369.
- Wayne PM, Gow BJ, Costa MD, Peng CK, Lipsitz LA. The impact of Tai Chi on exercise capacity, muscle strength and oxygen uptake: A systematic review. *Am J Health Promot.* 2014;29(3):133-142.

Dissociatie

Langdurig verhoogde cortisol kan een migraine-aantal uitlokken wanneer de stress wegvalt.

- Lipton RB, Buse DC, Hall CB, et al. Reduction in perceived stress as a migraine trigger. *Neurology.* 2014;82(16):1395-1401.
- Lippi G, Mattiuzzi C. Cortisol and migraine: A systematic literature review. *J Clin Neurosci.* 2017;42:81-86.

Het verlies van contact met je binnenwereld

Dissociatie vermindert interoceptieve waarnemingen.

- Krause-Utz A, Elzinga BM. Altered Interoception in Dissociative Disorders: Clinical and Neurobiological Perspectives. *Curr Opin Psychol.* 2018;28:162-169.
- Sedeno L, Couto B, Melloni M, Canales-Johnson A, Yoris A, Baez S, et al. How do you feel when you can't feel your body? Interoception, functional connectivity and dissociation in depersonalization-derealization disorder. *PLoS One.* 2014;9(6):e98769.
- Schulz A, Vogeley C. Interoception and stress. *Front Psychol.* 2015;6:993.
- Nijenhuis ERS. Somatoform dissociation: Phenomena, measurement, and theoretical issues. Assen: Van Gorcum; 1999. (klassiek werk)

Hoe een gezond waarnemingsstelsel werkt

De invloed van neuroceptie op het autonome zenuwstelsel.

- Porges SW. The polyvagal theory: New insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med.* 2009;76(Suppl 2):S86-S90.
- Kolacz J, Porges SW. Chronic Diffuse Pain and Functional Gastrointestinal Disorders After Traumatic Stress: Pathophysiology Through a Polyvagal Perspective. *Front Med (Lausanne).* 2018;5:145.
- Ardizzone L, et al. Polyvagal Theory: A Science of Safety. *Frontiers in Integrative Neuroscience.* 2022;16:871227.

Wanneer dissociatie dit systeem verstoort

Dissociatie leidt tot disregulatie van het autonome zenuwstelsel.

- Porges, S.W. The polyvagal perspective. *Biological Psychology.* 2007;74(2):116-143.

De weg naar herstel

SLOW als onderdeel van de polyvagaaltheorie.

Dissociatie tijdens een aanval

Persoonlijke interpretatie.

Pijnstillers - een vorm van dissociatie

Persoonlijke interpretatie.

Voelen als weg vooruit

Het belang van bewustwording en de situatie zonder oordeel beschouwen is cruciaal voor actie en besluitvorming.

- Garland EL, et al. Mindfulness Broadens Awareness and Builds Eudaimonic Meaning: A Process Model of Mindful Positive Emotion Regulation. *Psychol Inq*. 2015;26(4):293-314.
- Vago DR, Silbersweig DA. Self-awareness, self-regulation, and self-transcendence (S-ART): a framework for understanding the neurobiological mechanisms of mindfulness. *Front Hum Neurosci*. 2012;6:296.
- Kang Y, Gruber J, Gray JR. Mindfulness and De-automatization. *Curr Opin Psychol*. 2013;28:96-101.
- Linehan MM. Cognitive-behavioral treatment of borderline personality disorder. New York: Guilford Press; 1993.
- Kabat-Zinn J. *Wherever You Go, There You Are: Mindfulness Meditation in Everyday Life*. New York: Hyperion; 1994.
- Reinders, K. A deep dive into the phenomenology of the Freeze response: a systematic review. Master thesis Developmental Psychology. University of Groningen. 2024.

Histamine

Wat is histamine

Beschrijving van histamine als ontstekingsmediator, rol bij allergische reacties.

- Galli SJ, Tsai M, Piliposky AM. The development of allergic inflammation. *Nature*. 2008;454(7203):445-454.
- Marone G, Varricchi G, Loffredo S, et al. Mast cells and basophils in inflammatory and allergic reactions. *J Allergy Clin Immunol*. 2022;149(7):2165-2177.
- Akdis CA, Simons FE. Histamine receptors are hot in immunopharmacology. *Eur J Pharmacol*. 2006;533(1-3):69-76.

Histamine kan zich ophopen in de bloedbaan en voor klachten zoals migraine zorgen.

- De Fusco M, Vacca A, Salvati M, et al. Migraine, Allergy, and Histamine: Is There a Link? *Medicina (Kaunas)*. 2023;59(5):1029.
- Ashina S, Bentivegna E, Martelletti P, et al. Histamine and Migraine. *Headache*. 2018;58(1):71-83.

- Gazerani P, et al. A correlation between migraine, histamine and IgE: A review. *Headache*. 2003;43(5):552-559.

Histamine in de hersenen

De rol van histamine als neurotransmitter.

- Haas HL, Panula P. Histamine Actions in the Central Nervous System. In: *Basic Neurochemistry*. 2006;7:263-273.

Systemische histamine beïnvloedt neurotransmitters in de hersenen. Histamine in het bloed kan het stress-systeem (de HPA-as) activeren.

Nuancering: hoewel in het boek beschreven wordt dat histamine in het bloed ook histamine als neurotransmitter in de hersenen verhoogt, wijzen studies eerder naar verhoging van andere excitatoire neurotransmitterverhoging zoals dopamine en adrenaline. Histamine werd in deze studies niet getest.

- Bhargava, K.P., Dixit, K.S. Role of the chemoreceptor trigger zone in histamine-induced emesis. *British Journal of Pharmacology*. 1968;34(3):508-513.
- Kjaer, A., Larsen, P.J., Knigge, U., Warberg, J. Histaminergic activation of the hypothalamic-pituitary-adrenal axis. *Endocrinology*. 1994;135(3):1171-1177.
- Flik, G., Folgering, J.H., Cremers, T.L., Westerink, B.H., Dremencov, E. Interaction Between Brain Histamine and Serotonin, Norepinephrine, and Dopamine Systems: In Vivo Microdialysis and Electrophysiology Study. *Journal of Molecular Neuroscience*. 2015;56(2):320-328.

Antihistaminica blokkeren histaminereceptoren, niet alleen in je lichaam maar vaak ook in je hersenen. Dit kan leiden tot slaperigheid.

- Farzam K, et al. Antihistamines. *StatPearls*. 2023.
- Church MK. *Pharmacology of Antihistamines*. *Indian J Dermatol*. 2013;58(2):90-94.
- Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. *Prog Neurobiol*. 2001;63(6):637-672.

Histamine verhoogt de doorlaatbaarheid van bloedvaten in de hersenvliezen.

- Sedeyn JC, et al. Histamine induces Alzheimer's disease-like blood brain barrier breakdown. *Mediators Inflamm*. 2015;2015:479289.
- Sarker MH, Easton AS, Fraser PA. Regulation of cerebral microvascular permeability by perivascular nerves and the endothelium. *J Physiol*. 1998;507(Pt 2):629-37.
- Bañuelos-Cabrera I, et al. Role of histaminergic system in blood-brain barrier permeability. *Neurochem Res*. 2014;39(10):2083-2090.
- Gulati A. Evidence for the involvement of histamine in the regulation of blood-brain barrier permeability. *Pharmacol Res Commun*. 1985;17(2):147-157.
- Dux E, Király A, Dobó E, Szirmai M. Effects of histamine on brain capillaries. *Naunyn Schmiedeberg's Arch Pharmacol*. 1982;321(3):245-250.

Voeding als histaminebron

Gerijpte kazen, gerookte vis, gefermenteerde producten zoals zuurkool, kimchi en kombucha, alcohol (vooral rode wijn), tomaten, spinazie en chocolade bevatten veel histamine of kunnen histamineverhogend werken.

- Budak NH, Aykin E, Seydim AC, Greene AK, Güzel-Seydim ZB. Histamine Content in Rennet Ripening Cheeses During Storage at Different Temperatures. *J Vet Res.* 2018;62(1):119–126.
- G C Fletcher, Summers G, van Veghel PW. Levels of histamine and histamine-producing bacteria in smoked fish from New Zealand markets. *J Food Prot.* 1998;61(8):1064–1070.
- Wantke F, Götz M, Jarisch R. The red wine provocation test: intolerance to histamine as a model for food intolerance. *Allergy Proc.* 1994;15(1):27–32.
- WebMD. Foods High in Histamine. Updated May 2024.
- aha! Swiss Allergy Centre. Histamine intolerance. 2023.

Genetische programmatie om beter of minder goed histamine af te breken (DAO-enzym)

- Hickschl P, et al. Association of single nucleotide polymorphisms in the diamine oxidase (DAO, ABP1) gene with clinical symptoms of histamine intolerance. *Allergy.* 2011;66(8):1057–1065.
- Gonzalez-Perez A, et al. Pilot Study on the Prevalence of Diamine Oxidase Gene Variants in Caucasian Adults with Symptoms of Histamine Intolerance. *Nutrients.* 2024;16(4):864.
- Branco M, et al. Cumulative effect of AOC1 gene variants on symptoms of histamine intolerance: a multicenter study. *Front Genet.* 2023;14:1180777.

Het microbioom als bondgenoot

Je microbioom kan helpen histamine afbreken, of kan juist histamine produceren.

- Fiorani M, Mancinelli L, Inchingolo F, Cammarota G. Histamine-producing bacteria and their role in human health and disease. *Microbial Pathogenesis.* 2023;174:105924.
- Sánchez-Pérez S, Comas-Basté O, Veciana-Nogués MT, Latorre-Moratalla ML, Vidal-Carou MC. Intestinal Dysbiosis in Patients with Histamine Intolerance. *Nutrients.* 2022;14(9):1862.
- Mou J, Badran H, Cenac N, et al. The taxonomic distribution of histamine-secreting bacteria in the human gut microbiome. *BMC Genomics.* 2021;22(1):732.
- Chen Y, Wan Y, Zeng P. The role of colonic microbiota amino acid metabolism in human disease. *Current Opinion in Immunology.* 2025;85:102333.

De lekkende darm: een open poort voor problemen

Een lekkende darm kan histamineverhogend werken doordat allergenen de bloedbaan kunnen bereiken.

- Berni Canani R, et al. The Role of Gut Microbiota and Leaky Gut in the Pathogenesis of Food Allergy and Histamine-Related Symptoms. *Int J Mol Sci.* 2023;24(1):371.
- Frontiers in Allergy. Intestinal permeability, food antigens and the microbiome. *Front Allergy.* 2025.

Te weinig methylatiecash

Methylatie (s-adenosyl-methionine) speelt een rol bij de afbraak van histamine.

- Maintz L, Novak N. Histamine and histamine intolerance. *Am J Clin Nutr.* 2007;85(5):1185–1196.
- Komáromy AM. Histamine metabolism and related genetic variants in man. *J Pharmacol Exp Ther.* 2006;316(3):918–925.
- Moya-García AA, et al. Regulation of histamine degradation by methylation. *Biochem J.* 2005;386(Pt 1):65–73.
- Fernstrom JD, et al. Decreased cerebral catabolism of [3H]histamine in vivo after S-adenosyl-L-methionine administration to mice. *J Pharmacol Exp Ther.* 1981 Sep;218(3):724–30.

De lekkende neusbarrière

Een verzakte neusbarrière kan veroorzaakt worden door filaggrinetekort en gevoeliger maken voor hooikoorts.

- McLean WHI, Palmer CN, Irvine AD, et al. Filaggrin gene defects and risk of developing allergic sensitisation, atopic eczema, and allergic rhinitis. *BMJ.* 2009;339:b2433.
- Osawa R, Akiyama M, Shimizu H. Filaggrin gene defects and the risk of developing allergic disorders. *Allergol Int.* 2011;60(1):1–9.
- Hu XH, Zhao H, Chen XQ, et al. S100A7 Co-localization and Up-regulation of Filaggrin in Human Nasal Epithelium. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2021;35(20):1830–1837.

Neussprays met cortisone verzwakken de barrière.

- Cervin A, Andersson M. Intranasal steroids and septum perforation—an overlooked complication? A description of the course of events and a discussion of the causes. *Rhinology.* 1998;36(3):128–32.
- Adverse Drug Reactions of Intranasal Corticosteroids in the Netherlands Pharmacovigilance Center Lareb Database. *Drug Saf.* 2022;45(6):637–649.
- Topical Corticosteroid Application and the Structural and Functional Changes to the Epidermal Barrier. *J Clin Aesthet Dermatol.* 2004;12(4):39–49.

Mitochondriale uitputting

Wanneer mitochondriën niet optimaal functioneren kan dit migraine beïnvloeden.

- Terrin A, Sacconi S, Bassi MT, et al. The relevance of migraine in the clinical spectrum of mitochondrial disorders. *Sci Rep.* 2022;12:4007.
- Yorns WR Jr, Hardison HH. Mitochondrial dysfunction in migraine. *Semin Pediatr Neurol.* 2013;20(3):188-193.
- Fila M, Szabó N, Lórinč L, et al. Mitochondria in migraine pathophysiology. *Int J Mol Sci.* 2019;20(18):4574.

Wat zijn mitochondriën

Beschrijving mitochondriën.

- Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell.* 6th edition. Garland Science; 2014.
- Mitchell P. Chemiosmotic coupling in oxidative phosphorylation. *Biol Rev Camb Philos Soc.* 1966;41(3):445-502.
- Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. *Nat Cell Biol.* 2018;20(7):745-754.

Mitochondriën hebben hun eigen DNA dat niet menselijk is maar een bacteriële oorsprong hebben.

- Gray MW. Mitochondrial Evolution. *Cold Spring Harb Perspect Biol.* 2012;4(9):a011403.
- Zimorski V, Ku C, Martin WF, Gould SB. Endosymbiotic theory for organelle origins. *Curr Opin Microbiol.* 2014;22:38-48.
- Cavalier-Smith T. Origin of mitochondria by intracellular enslavement of a photosynthetic purple bacterium. *Proc Biol Sci.* 2006;273(1596):1943-1952.

Mitochondriaal DNA is kwetsbaar.

- Alexeyev M, Shokolenko I, Wilson G, LeDoux S. The maintenance of mitochondrial DNA integrity--critical analysis and update. *Cold Spring Harb Perspect Biol.* 2013;5(5):a012641.

Mitochondriën hebben een communicatiefunctie en kunnen reizen tussen cellen en via de bloedbaan.

- ZAA Dache, et al. Mitochondria-derived cell-to-cell communication. *Cell.* 2023;186(12):2573-2590.
- D Torralba, et al. Mitochondria Know No Boundaries: Mechanisms and Functions of Intercellular Mitochondrial Transfer. *Front Cell Dev Biol.* 2016;4:107.
- M Zhang, et al. Inter- and intracellular mitochondrial communication: signaling, transport, and transfer. *Cell Mol Biol Lett.* 2024;29(1):22.
- D Liu et al. Intercellular mitochondrial transfer as a means of tissue regeneration. *Signal Transduct Target Ther.* 2021;6(1):65.
- J.L. Spees, et al. Mitochondrial transfer between cells can rescue aerobic respiration in mammalian cells with nonfunctional mitochondria. *Proc Natl Acad Sci USA.* 2006;103(5):1283-1288.

Oxidatieve stress: de rest in je systeem

Bij overbelasting van mitochondriën worden meer vrije radicalen geproduceerd waardoor ze slechter gaan functioneren.

- Tirichen H, Yaigoub H, Xu W, Wu C, Li R, Li Y. Mitochondrial Reactive Oxygen Species and Their Contribution in Chronic Kidney Disease Progression Through Oxidative Stress. *Front Physiol.* 2021;12:627837. Zhang Z, et al. The impact of oxidative stress-induced mitochondrial dysfunction in diabetes. *Front Endocrinol.* 2023;11:2363. Xu X, et al. Mitochondria in oxidative stress, inflammation and aging. *Signal Transduct Target Ther.* 2025;10:1-15.

Vrije radicalen beschadigen het DNA, de eiwitten en de vetten in de mitochondriën.

Voedingstekorten

Mitochondriën hebben B-vitamines, ijzer, magnesium, Q10, carnitine en creatine nodig.

- Tippairote T, Sae-lim W, Thongngam M, Prasitwattanaseree S. Combined Supplementation of Coenzyme Q10 and Other Nutrients for Mitochondrial Health and Disease Management: Mechanistic Insights and Translational Evidence. *Biomolecules.* 2022;12(11):1521.
- Wesselink E, Koek GH, Gommers LM, et al. Feeding mitochondria: Potential role of nutritional supplementation to improve mitochondrial function. *Mitochondrion.* 2019;46:101-117.
- Golubnitschaja O, Costigliola V, et al. Mini-encyclopedia of mitochondria-relevant nutraceuticals: from biochemistry to clinical practice. *EPMA J.* 2024;15(2):e358-389.

Een vegetarisch eetpatroon kan nadelig zijn voor mitochondriale functie.

- Clemente-Suárez VJ, et al. Impact of Vegan and Vegetarian Diets on Neurological Outcomes. *Nutrients.* 2025;17(4):743.
- Łuszczki E, et al. Vegan diet: nutritional components, implementation, and health benefits. *Front Nutr.* 2023;10:1294497.
- Wang T, et al. Vegetarian and vegan diets: benefits and drawbacks. *Eur Heart J.* 2023;44(36):3423-3437.

De moderne wereld als mitochondriële vijand

Zware metalen kunnen de werking van mitochondriën remmen.

- Balali-Mood M, Naseri K, Tahergorabi Z, Khazdair MR, Sadeghi M. Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Front Pharmacol.* 2021;12:643972.
- Afzal A, Noor A, Gohar S, et al. Emerging insights into the impacts of heavy metals on mitochondrial

dynamics and related diseases. *Front Pharmacol.* 2024;15:1375137.

- Korotkov SM, Chebotareva NA, Nagradova NK, et al. Mitochondrial oxidative stress is the general reason for apoptosis in cells exposed to the toxic effects of different-valence heavy metals. *Biochemistry (Moscow).* 2023;88(8):975-1005.
- Branca JJ, Morucci G, Pacini A. Cadmium-Induced Cytotoxicity: Effects on Mitochondrial Electron Transport Chain. *Front Cell Dev Biol.* 2020;8:604377.
- Wang X, et al. Mechanisms of metal-induced mitochondrial dysfunction in neurological disorders. *Int J Mol Sci.* 2021;22(12):6517.

Pesticiden kunnen de werking van mitochondriën remmen.

- Negga R, Stuart JA, Machen ML, Salva J, Lizek AJ, Richardson SJ, et al. Exposure to glyphosate- and/or Mn/Zn-ethylenebis-dithiocarbamate-containing pesticides leads to degeneration of gamma-aminobutyric acid and dopamine neurons in *Caenorhabditis elegans*. *Neurotox Res.* 2012;21:281–290.
- Bailey DC, Todt CE, Burchfield SL, Pressley AS, Denney RD, Snapp IB, Negga R, Traynor WL, Fitsanakis VA. Chronic exposure to a glyphosate-containing herbicide reduces antioxidant capacity and increases acetylcholinesterase activity in *Caenorhabditis elegans*. *Environ Toxicol Pharmacol.* 2018;57:46–52.

Prikkels zoals hitte, kou, korte periodes van honger of dorst triggeren mitogenese.

- Pruimboom L, Muskiet FAJ. Intermittent living; the use of ancient challenges as a vaccine against the deleterious effects of modern life – A hypothesis. *Med Hypotheses.* 2018;120:28-42.
- Miller BF, et al. Mitohormesis in Mice via Sustained Basal Activation of Mitochondrial and Antioxidant Signaling. *Cell Metab.* 2018;28(6):1162-1174.
- Sharma PK, Agrawal V, Roy N. Mitochondria-mediated hormetic response in life span extension of calorie-restricted *Saccharomyces cerevisiae*. *Aging.* 2011;3(6):620-631.

Medicatie kan je mitochondriën beschadigen

NSAID's en paracetamol: zie medicatie-afhankelijke hoofdpijn.

Sommige antidepressiva, zoals fluoxetine, remmen bepaalde enzymen van de mitochondriën waardoor er minder energie wordt geproduceerd en er meer oxidanten worden geproduceerd.

Nuancering: het effect van antidepressiva op mitochondriën in het brein kan op zich ook positief zijn. Als het zorgt voor minder angst en stress worden mitochondriën in het brein minder belast waardoor ze minder oxidatieve stress en schade ervaren (zie derde citaat).

- Charles E, et al. The antidepressant fluoxetine induces necrosis by energy depletion and mitochondrial calcium overload. *Oncotarget.* 2016;7(48):80298-80309.

- de Oliveira MR, et al. Fluoxetine and the mitochondria: A review of the toxicological aspects. *Toxicol Lett.* 2016;263:81-87.
- Shu X, et al. The effect of fluoxetine on astrocyte autophagy flux and mitochondrial impairment. *Cell Death Dis.* 2019;10:489.

Antibiotica kan mitochondriën beschadigen.

- Kalghatgi S, et al. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. *Sci Transl Med.* 2013;5(192):192ra85.
- Wang X, Ouyang Y, Pang J, et al. Ciprofloxacin impairs mitochondrial DNA replication and induces oxidative stress in human cells. *Sci Rep.* 2015;5:11064.
- Hangas A, et al. Mitochondrial damage by antibiotics: mechanisms and implications for human health. *J Mol Med.* 2018;96(8): 759-768.
- Prajapati P, et al. Antibiotics-induced mitochondrial dysfunction: Mechanistic insight and implications. *J Biochem Mol Toxicol.* 2019;33(8):e22325.

Statines remmen de aanmaak van Q10, een essentiële cofactor van mitochondriën.

- Rundek T, et al. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease. *Arch Neurol.* 2004;61(6):889-892.
- Deichmann R, et al. Coenzyme Q10 and statin-induced mitochondrial dysfunction. *Ochsner J.* 2010;10(1):16-21.
- Choi HK, et al. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc.* 2018;7(15):e009835.

Infecties en ontstekingen

Epstein-Barr kan mitochondriën beschadigen.

- You H, et al. Epstein-Barr virus-driven cardiolipin synthesis sustains mitochondrial remodeling in B cell transformation. *Sci Adv.* 2025;11(2):eadr8837.
- Montani MSG, et al. Epstein-Barr-virus-induced impairment of autophagy and mitochondrial biogenesis in monocytes. *Autophagy.* 2018;14(10):1731-1745.
- Vernon SD, et al. Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein Barr Virus. *BMC Infect Dis.* 2006;6:15.

De ziekte van Lyme kan mitochondriën beschadigen.

- Parthasarathy G, Fevrier H, Mestivier D, Chaumette T, Gangloff SC, Rousselle JC, et al. New insights into Lyme disease: mitochondrial dysfunction and oxidative stress in patients with Lyme borreliosis. *Free Radic Biol Med.* 2015;89:251-263.

Covid-19 kan mitochondriën beschadigen.

- Madsen HB, et al. Mitochondrial dysfunction in acute and post-acute phases of COVID-19 and risk of non-communicable diseases. *Communications Medicine.* 2024;4(1):38.

De vicieuze cirkel van energietekort in je brein

Mitochondriale dysfunctie kan de elektrolytenbalans in de hersenen verstoren.

- An energy budget for signaling in the grey matter of the brain. *Journal of Cerebral Blood Flow & Metabolism*. 2001;21(10):1133–1145.
- Magnesium in Man: Implications for Health and Disease. *Physiological Reviews*. 2015;95(1):1–46.
- Mitochondrial dysfunction and glutamate excitotoxicity studied in primary neuronal cultures. *Current Molecular Medicine*. 2004;4(2):149–177.
- Bioenergetics and the formation of mitochondrial reactive oxygen species. *Trends in Pharmacological Sciences*. 2006;27(12):639–645.
- Brain energy metabolism: focus on astrocyte–neuron metabolic cooperation. *Cell Metabolism*. 2011;14(6):724–738.
- Why Calcium? How Calcium Became the Best Communicator. *Journal of Biological Chemistry*. 2016;291(40):20849–20857.
- Mitochondrial dysfunction underlies neuronal hyperexcitability in Alzheimer's disease models. *Journal of Neuroscience*. 2013;33(29):10506–10518.

De andere statements waren reeds eerder gedekt.

Van energiecrisis naar migraine

Reeds eerder afgedekt

Hormonale schommelingen

Migraine komt vaker voor rond menstruatie, eisprong of net na zwangerschap

- Vevik KG, MacGregor EA. Menstrual migraine: a distinct disorder needing greater recognition. *The Lancet Neurology*. 2021;20(4):304–315.
- Chalmer MA, Olesen J, Hansen JA, et al. Population-Based Characterization of Menstrual Migraine and Nonmenstrual Headache in Women. *JAMA Netw Open*. 2023;6(7):e2317717.
- Pavlović JM, Stewart WF, Bruce CA, et al. Burden of migraine related to menses: results from the AMPPP Study. *Journal of Headache and Pain*. 2015;16:24.
- MacGregor EA. Prevalence of migraine on each day of the natural menstrual cycle. *Neurology*. 2004;63(2):351–353.
- Mehkri Y, Barbel S, Mehta R, et al. Cerebrovascular Function in Hormonal Migraine: An Exploratory Study. *Frontiers in Neurology*. 2021;12:729261.

- Sances G, Allais G, Nappi RE, et al. Special considerations in migraine during pregnancy and lactation. *Handbook of Clinical Neurology*. 2021;182:117–129.

De nuance van oestrogeen

Een aantal statements werden reeds in eerdere hoofdstukken met referenties opgevangen.

Oestrogeen helpt om glucose in de hersenen te krijgen.

- Mosconi L, Berti V, Quinn C, McHugh P, Petrongolo G, Osorio RS, et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *PNAS*. 2017;114(16):E3662–E3671.
- Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Estrogen regulation of glucose metabolism and mitochondrial function: therapeutic implications for prevention of Alzheimer's disease. *Adv Drug Deliv Rev*. 2008;60(13-14):1504–1511.
- Rettberg JR, Yao J, Brinton RD. Estrogen: A master regulator of bioenergetic systems in the brain and body. *Front Neuroendocrinol*. 2014;35(1):8–30.

Oestrogeen werkt serotonineverhogend.

- Betz LA, et al. Mechanisms underlying estrogen regulation of serotonergic function in the brain: implications for disease. *Trends Neurosci*. 2016;39(6):364–374.

De abrupte daling van oestrogeen verhoogt het risico op een migraine-aanval.

- Miao W, Zhu G, Song Z, Kong F. Clinical differences between menstrual migraine and nonmenstrual migraine: a systematic review and meta-analysis of observational studies. *J Neurol*. 2022;269(11):5792–5804.
- Klostranec JM, Hess CN, Zhou Q. The complex relationship between estrogen and migraines. *Cureus*. 2021;13(3):e13848.
- Ferraro D, et al. Menstrual migraine is caused by estrogen withdrawal. *J Headache Pain*. 2023;24:83.

Oestrogeen verhoogt het gebruik van magnesium.

- Seelig MS. Interrelationship of magnesium and estrogen in cardiovascular and bone disorders, eclampsia, migraine and premenstrual syndrome. *J Am Coll Nutr*. 1993;12(4):442–58.
- Zhang Y, et al. Sex steroid hormones exert biphasic effects on cytosolic magnesium ions in cerebral vascular smooth muscle cells. *J Cardiovasc Pharmacol*. 2001;37(1):93–101.

Progesteron: de kalmerende buffer

Progesteron heeft een kalmerend effect op het brein. Een tekort aan progesteron of oestrogeendominantie kan voor meer excitatie zorgen in het brein.

- Schiller CE, Schmidt PJ, Rubinow DR. Allopregnanolone and mood: Is GABAergic neurosteroid modulation of the stress response relevant to psychiatric disorders? *Curr Psychiatry Rep*. 2014;16(11):101.
- Girdler SS, Klatzkin RR. Neurosteroids in the context of stress: Implications for depressive

disorders. *Pharmacol Biochem Behav.* 2007;86(4):635–643.

- Bitran D, Shiekh M, McLeod M. Anxiolytic effect of progesterone is mediated by the neurosteroid allopregnanolone at the GABAA receptor. *J Neuroendocrinol.* 1995;7(3):171–177.
- Guennoun R. Progesterone in the Brain: Hormone, Neurosteroid and Neuroprotectant. *Frontiers in Neuroendocrinology.* 2020;41:100950.
- Graziottin A, et al. Neuroendocrine and neurosteroid mechanisms in mood disorders. *Menopause Int.* 2014;20(2):91–97.

De balans

Statements zijn reeds in eerdere hoofdstukken opgevangen met referenties.

Waarom net dan?

De meeste statements zijn reeds in eerdere hoofdstukken opgevangen met referenties.

Bij ongeveer 65% van de migrainepatiënten nemen de migraineklachten na de menopauze af of verdwijnen ze zelfs helemaal. Bij ongeveer 10% van de vrouwen nemen de migraineklachten juist toe na de menopauze.

- Ripa P, Ornello R, Degan D, et al. Migraine in menopausal women: a systematic review. *Int J Womens Health.* 2015;7:773–782.

Het effect van hormonale anticonceptie

Een aantal statements zijn reeds in eerdere hoofdstukken opgevangen met referenties.

Synthetische hormonen belasten de afbraakcapaciteit van de lever, zeker bij vrouwen met een tragere COMT- of MTHFR-functie. Dat kan leiden tot opstapeling van pro-inflammatoire metabolieten.

- Santen RJ, Brodie H, Simpson ER, Siiteri PK, Brodie A. History of Aromatase: Saga of an Important Biological Mediator and Therapeutic Target. *Endocr Rev.* 2009;30(4):343–375.
- Weinszilboum R. Pharmacogenomics: Catechol O-methyltransferase (COMT): inheritance, polymorphisms and molecular pharmacology. *Pharmacogenetics.* 2003;13(7):435–451.
- van der Put NM, Blom HJ, et al. A second common mutation in the methylenetetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? *Am J Hum Genet.* 1998;62(5):1044–1051.

Synthetische oestrogenen zijn meer ontstekingsbevorderend en minder afbreekbaar dan natuurlijk oestrogenen

- Li Y, Zhang L, Wang Y, et al. Natural and Synthetic Estrogens in Chronic Inflammation and Breast Cancer. *Int J Mol Sci.* 2021;22(1):4660.
- Shi J, Suzuki N, Nakai S. Removal and degradation characteristics of natural and synthetic estrogens by

activated sludge. *Water Research.* 2008;42(5–6):1097–1103.

- Zava DT, Duwe G. Estrogenic activity of natural and synthetic estrogens in human breast cancer cells in culture. *Environ Health Perspect.* 1997;105(Suppl 3):637–645.

De meeste types van synthetisch progesteron missen de kalmerende werking van natuurlijk progesteron in het brein.

- Pluchino N, et al. Progesterogens and brain: An update. *Maturitas.* 2009;62(3):228–234.
- Pletzer B, et al. Progesterone and contraceptive progestin actions on the adult brain: A systematic review. *Pharmacol Biochem Behav.* 2023;234:173584.
- Pluchino N, et al. Effects on brain, allopregnanolone and beta-endorphin. *J Steroid Biochem Mol Biol.* 2006;102(1–5):200–208.
- Singh M. Progesterone and Neuroprotection. *Front Neurosci.* 2012;6:10.

Synthetisch progesteron vertraagt de darmtransit meer dan lichaamseigen progesteron.

Nuance: het effect hangt allicht af van het type synthetisch progesteron.

- Singh R, Nagpal JP, Majumdar S, Chakravarti RN, Dhall GI. Effect of medroxyprogesterone acetate on the digestive and absorptive functions of rat intestine. *Digestion.* 1983;28(4):234–239. doi:10.1159/000198993

Dehydratatie

We zijn evolutionair gezien gebouwd op periodes zonder water.

- Keay NM, Johnson RA. Evolutionary aspects of renal function. *Nephron.* 1996;74(2):175–181. PMID:8743450.
- Pontzer H, Wood BM, Raichlen DA. Hunter-Gatherer Energetics and Human Obesity. *PLoS One.* 2012 Jul 25;7(7):e40503. doi:10.1371/journal.pone.0040503.
- Jequier E, Constant F. Water as an essential nutrient: The physiological basis of hydration. *Eur J Nutr.* 2010;64:115–123. doi:10.1038/ejcn.2009.111.
- Knibbs LD, et al. Evolution of the thirst mechanism in Homo: The need and limitations of anticipatory thirst responses. *J Hum Evol.* 2024 Dec;164:103456. doi:10.1016/j.jhevol.2024.103456. PMID:39304116.

Bulkdrinken kan nieren helpen herstellen (bulkdrinken zorgt voor een sterke daling in AVP waardoor nieren even rust- en hersteldtijd krijgen).

- Wang CJ, Grantham JJ, Wetmore JB. The medicinal use of water in renal disease. *Kidney Int.* 2013;84(1):45–53.
- Bouby N, Bachmann S, Bichet DG, Bankir L. Contribution of vasopressin to progression of chronic renal failure. *Kidney Int Suppl.* 1999;70:S25–S29.
- Torres VE. Vasopressin in chronic kidney disease, an elephant in the room? *Kidney Int.* 2009;76(9):925–928.

Wanneer je drinkt, wordt je immuunsysteem geactiveerd (ter voorbereiding van mogelijke inname van pathogenen).

Nuance: dit is eerder een assumptie dan een wetenschappelijk feit. Hoewel er veel wetenschappelijke studies zijn rond de postprandiale immunreactie na eten, kon ik geen studies vinden over postprandiale immunreactie na drinken.

Constant drinken verzwakt je dorstgevoel.

- Armstrong LE, Johnson EC, Munoz CX, Enslett JJ, Casa DJ, Maresh CM. Hormonal and Thirst Modulated Maintenance of Fluid Balance in Young Women with Different Levels of Habitual Fluid Consumption. *Nutrients*. 2016;8(5):264.
- Kavouras SA, Johnson EC, Armstrong LE, et al. Novel hydration assessment techniques employing thirst and a water bolus. *Appl Physiol Nutr Metab*. 2013;38(6):642–650.

Bij een verlies van 1-2% lichaamsvocht dalen je cognitieve prestaties, wordt je reactietijd trager en verandert je stemming. De sympathicus wordt geactiveerd.

- Sumitra LK, Swetha M, Gopireddy A. Hydration status and its impact on cognitive performance and reaction time in young adults: A comparative study. *International Journal of Academic Medicine and Pharmacy*. 2023;7(2):157-162.
- Armstrong LE, Ganio MS, Casa DJ, et al. Mild dehydration impairs cognitive performance and mood of men. *Br J Nutr*. 2012;106(10):1535-1543.
- Smith J, Parent J, Qubty L. The Effect of Hydration Status on Reaction Time and Recall Tests in College-aged Individuals. *JEPonline* 2024;27(3).
- Taylor EB, et al. Coping with dehydration: sympathetic activation and regulation of vasopressin neurons. *Am J Physiol Regul Integr Comp Physiol*. 2014;306(6):R419-27.

Dehydratie maakt bloedvaten stijver waardoor de doorbloeding naar de hersenen kan verstoord worden en elektrolyten in de hersenen uit balans kunnen gaan.

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