Peter Attia MD Keypoints — Brain Health, Sleep & Alzheimer's

Peter Attia MD Keypoints

Episodes in this pack: 20

406 Migraine, cluster headache, and tension headache: symptoms, causes, prevention, and treatment

Guest: Brian Grosberg
Date: 2026-08-31 · Duration: 2:09:10
URL: https://www.youtube.com/watch?v=uiNEP8A34SE

KEYPOINTS

- **Headache has over 300 types and causes; the first split is primary versus secondary.**
  Grosberg, a headache neurologist, says the differential is one of the longest in medicine. Primary headaches (migraine, tension-type, cluster) are disorders in themselves; secondary headaches stem from something else, which is why red flags matter.
- **Migraine has specific diagnostic criteria, and it isn't always one-sided.**
  At least five lifetime attacks lasting 4–72 hours untreated, plus two of: one-sided, throbbing, moderate-to-severe, worse with activity—along with nausea or light and sound sensitivity. Up to 40% have pain on both sides. Tension-type headache lacks nausea and can last 30 minutes to a week.
- **Migraine is common, disproportionately female, and badly under-served.**
  About 45 million Americans, roughly 18% of women, with a female ratio of about 3:1. Only around 50 fellowship-trained headache neurologists graduate per year. Episodic migraine is under 15 headache days a month; chronic is 15+ and affects 1–2% of the population.
- **Hormones matter: the speed of estrogen decline is a key trigger.**
  Studies since the 1970s link migraine to the late-luteal estrogen drop; newer work shows it's the faster rate of decline that's distinctive in women with migraine. Pure menstrual migraine occurs in under 10% of women. Perimenopause often worsens it; about two-thirds improve after menopause, but 10–20% continue or worsen. Migraine without aura improves in about 47% of women in the first trimester and 80–87% in the second and third.
- **A migraine has phases, and aura is only in a minority.**
  Premonitory symptoms can precede the attack; aura evolves gradually over 5–60 minutes; then the headache and a postdrome. Some attacks build over hours, others wake people at 3 a.m. Light sensitivity is present in about two-thirds to 70%.
- **Cluster headache is among the most severe pains known and is often misdiagnosed.**
  Attacks peak in 5–15 minutes, last 15 minutes to 3 hours, and are stabbing or boring around one eye. About 97% have same-side eyelid droop, tearing, redness or nasal congestion—often mistaken for sinusitis or allergies—and about 90% are restless. One patient likened it to giving birth to 100 babies without an epidural. The male:female ratio is now about 3–4:1.
- **Migraine is a neurovascular disorder, not just a blood-vessel problem.**
  The 1940s vascular theory was too simple. Pain signals from the dura and its blood vessels travel along the first branch of the trigeminal nerve to the trigeminal nucleus caudalis in the brainstem—where C2–C3 neck nerves also converge, explaining neck pain in migraine. Neuropeptides such as CGRP and an inflammatory response are involved; serotonin was noted to fall in blood during attacks decades ago.
- **Many more people qualify for prevention than receive it.**
  About 40% of people with migraine are medically eligible for preventive therapy, but only 16–17% receive it. Low-dose amitriptyline or nortriptyline are used at doses well below those for depression, which Grosberg explains to reduce stigma.
- **CGRP drugs changed treatment, with roughly 60% responding.**
  Monthly CGRP monoclonal antibodies (and oral gepants) work in up to about 60% of patients, with response defined as at least a 50% drop in headache days; Grosberg also counts patients whose severity or acute-drug response improves. U.S. prices are often 3–10x what other countries pay.
- **Triptans transformed acute care; injections are fastest for cluster.**
  Ergotamines came first; triptans arrived in the mid-1990s, targeting 5-HT1B/1D receptors. For cluster, injectable sumatriptan has a median time to relief around 9 minutes. Botox for chronic migraine uses the PREEMPT protocol of injections in the forehead, sides and back of head, neck and shoulders; verapamil is used for cluster, sometimes at very high doses.
- **Tension-type headache is the most common primary headache, and neck pain is a shared feature.**
  Like migraine, it is split into episodic (under 15 days a month) and chronic (15+ days). Because neck nerves converge on the same brainstem nucleus as the trigeminal system, neck and shoulder pain can be referred pain rather than the cause. Peter asks whether responding to 1,000 mg of acetaminophen implies tension-type; Grosberg cautions that response to a simple analgesic doesn't by itself settle the diagnosis.

EXAMPLES

- **The patient who connected them**
  A woman in her late 50s or early 60s with menopausal migraine, whom Peter referred about 10 years ago, was among the first on a CGRP drug through a clinical trial—'a resounding success'.
- **Over 1,000 mg of verapamil**
  Grosberg recently saw a cluster patient who at one point needed more than 1,000 mg of verapamil a day, illustrating how aggressive cluster prevention can be.
- **The 15-page intake**
  His chronic patients complete about a 15-page questionnaire plus a headache diary, because patterns differ from person to person.
- **Weekend caffeine**
  Diaries reveal patterns like coffee at 6 a.m. on weekdays but 9 a.m. on Saturday—a classic weekend-headache trigger.
- **Obesity and inflammation**

Grosberg notes obesity is an identified risk factor for migraine progression, possibly via shared pro-inflammatory mechanisms, so addressing risk factors is part of preventing episodic migraine from becoming chronic.

OTHER RELEVANT

• Keep a headache diary for a month.

Grosberg calls it the most important thing patients can do: 10–20 minutes a day logging attacks, sleep, meals, caffeine, cycle and medications lets a primary-care doctor act in a 10-minute visit.

• Regularity is preventive.

Because the migraine brain is hypersensitive to change, consistent meals, hydration, exercise and sleep—plus morning light exposure—pay dividends.

• Know the red flags.

New headaches after age 50, a change in pattern, systemic symptoms, or new headaches in pregnancy warrant evaluation for secondary causes, though most headaches are benign.

• Don't assume 'sinus headache'.

One-sided eye pain with tearing, droop and restlessness that peaks within minutes may be cluster headache and deserves a neurologist.

• Cannabis and gray areas need a clinician's input.

Some patients use THC for headache, but Grosberg says evidence and drug-interaction data are limited, making it hard to advise—another reason to tell your doctor everything you take.

399 - The evolution of Alzheimer's disease and dementia care | Gayatri Devi, M.D.

Guest: Gayatri Devi
Date: 2026-07-13 · Duration: 1:58:42
URL: https://www.youtube.com/watch?v=x7NhqMOwdOM

KEYPOINTS

• Dementia is a spectrum, and most Alzheimer's brains have mixed pathology.
Devi, a memory-disorders neurologist practicing on Manhattan's Upper East Side for 26 years, says autopsy studies find 98–99% of Alzheimer's patients have some other concomitant brain pathology. About 40% of Alzheimer's patients eventually show Lewy body pathology and 30–40% of Lewy body patients have Alzheimer's pathology. Vascular disease is so intertwined that a 2002 Circulation paper asked, 'Is Alzheimer's stroke?'—every Alzheimer's risk factor is also a stroke risk factor.

• Prevention may need to start in the 30s and 40s.
Because the cascade begins decades before symptoms, she argues for building anti-inflammatory habits early to keep it from being triggered. Neuroinflammation and viral infections are emerging factors; she sees stronger data for shingles vaccination, relevant since virtually everyone over 50 has had varicella.

• Standard screening tests miss high-functioning patients.
Her patients often score 28–30 on the MMSE or MoCA 10–15 years into their condition because they compensate so well. She uses detailed neuropsychological testing: someone at the 99th percentile overall but the 10th in language or visuospatial skills has likely declined substantially.

• Forgetting names is usually normal; word-finding trouble is more concerning.
Peter describes taking a minute to recall the name of someone he's met 30 times. Devi notes we now meet far more people than 100 years ago—some speculate we're built to remember about 150 names. Difficulty finding ordinary words is a more meaningful signal.

• Women's higher risk is tied partly to longevity and menopause.
Life expectancy has risen from about 50 to the late 70s or early 80s; 150 years ago most women died before menopause, when estrogen production stops. Perimenopausal cognitive changes can start in the 40s unnoticed. She calls women denied HRT after the 2002 WHI a 'lost generation' now in their 70s. She prefers transdermal estrogen (gel or patch) for lower stroke and clot risk.

• Amyloid alone doesn't mean Alzheimer's; biomarkers need context.
About 25% of community-dwelling people in their 70s, 30%+ in their 80s and about 44% at 90 have amyloid without symptoms. Blood tests are mostly standardized against amyloid scans, and she thinks they should be standardized against both amyloid and tau. About 30% of participants in Alzheimer's drug trials didn't actually have Alzheimer's pathologically.

• APOE4 raises risk but isn't deterministic.
Devi estimates lifetime risk around 6% for a man and 10–12% for a woman with 3/3; one E4 raises it about 60% versus wild type, and 4/4 much more. PSEN1, PSEN2 and APP mutations are close to deterministic, with PSEN1 essentially 100% associated with early-onset disease.

• Slow titration of anti-amyloid antibodies may cut brain swelling and bleeding.
Aducanumab had a greater than 40% rate of ARIA, so Devi developed a very slow titration protocol. In published data on 4/4 patients she reports about 4% ARIA. The FDA has since approved a slower titration for donanemab (350, 700, 1,050, 1,400 mg), letting her hold patients at 350 mg for four or five infusions; lecanemab starts at 10 mg/kg and insurers won't reimburse slower starts, though some 4/4 patients have had severe ARIA on 3 mg/kg.

• ARIA in E4 carriers reflects blood-vessel amyloid.
E4 homozygotes have more cerebral amyloid angiopathy; removing amyloid from vessel walls creates 'little tears in the fabric of the blood vessels'. She monitors rigorously with MRI and treats refractory ARIA-E with steroids, as for inflammatory amyloid angiopathy.

• She favors multimodal treatment.
Off-label MRI-guided TMS since 2008 to maintain network connectivity, management of vascular risk, shunts for normal-pressure hydrocephalus, and for patients on blood thinners for atrial fibrillation, a Watchman device so they can become eligible for antibodies.

• The benefit of anti-amyloid drugs is modest on average, so patient selection matters.
Devi acknowledges the change on scales like the CDR sum of boxes is small, and early donanemab data showed little difference in some measures. Her approach targets high-risk people in their 50s or 60s—perhaps 5–10 years from symptoms—treated 'very low, very slow, very safe', asking whether the disease course bends. She'd still choose aducanumab despite its discontinuation and reports two exceptional responders, one stable for 17 years.

EXAMPLES

• A 51-year-old on lecanemab for prevention
A young 4/4 patient developed bilateral ARIA-E at 3 mg/kg, still present after six doses (about 3 months), illustrating the risk of treating early E4 homozygotes.

• ARIA before a trip to Europe
A man in his early 60s on slow-titrated aducanumab reached 8 mg/kg and at about month 18–19 developed significant ARIA-E, found a few weeks after onset. They dropped to 6 mg/kg, then went back up.

• Misdiagnosed Parkinson's
A woman with a negative DAT scan had been placed on carbidopa-levodopa 25/100, three tablets three times daily, at an academic center for presumed Parkinson's; Devi suspected Lewy body disease instead.

- **Brain fog at 21**
  A college student seen for migraines had six months of brain fog and no periods; her estradiol was 22 pg/mL—menopausal range.
- **Costs**
  Antibodies cost about $26,000 a year, with infusion fees from roughly $400 at an infusion center to as much as $10,000 in some institutions; aducanumab launched around $56,000 a year.

OTHER RELEVANT

- **Ask for detailed testing if you're high-functioning and worried.**
  A 'normal' MoCA can be falsely reassuring; percentile profiles across domains catch compensation.
- **Interpret positive biomarkers carefully.**
  Amyloid positivity is common with age; decisions should weigh tau, symptoms, genetics and overall risk.
- **E4/E4 carriers: ask about titration and monitoring.**
  If considering antibodies, ask about slow titration and MRI surveillance; the risk-benefit may not favor late, high-dose treatment.
- **Address vascular risk and hormones in midlife.**
  Blood pressure, metabolic health and, for appropriate women, transdermal HRT are levers she emphasizes.
- **Stratified trials are the goal.**
  Devi hopes within five years the field will identify and stratify risk better and tailor treatment, rather than applying one protocol to everyone—her open-label results need randomized testing.

395 – Brain lipidology: understanding APOE, cholesterol homeostasis, Alzheimer’s disease, & more

Guest: Dr. Tom Dayspring
Date: 2026-06-09 · Duration: 1:44:10
URL: https://www.youtube.com/watch?v=KWNgAyurXFY

KEYPOINTS

• The brain runs its own cholesterol system, almost completely separate from the blood.
Lipidologist Tom Dayspring's central point: apoB particles (LDL, VLDL) are far too big to cross the blood-brain barrier, so how much cholesterol is in plasma has 'zero to do with' brain cholesterol. A 2-year-old with LDL around 30 mg/dL is building brain tissue faster than at any other point in life, which shows that low circulating cholesterol doesn't starve the brain. That undercuts the common fear that drug-lowered LDL harms cognition.

• LDL's main job is bringing cholesterol back to the liver, not delivering it to cells.
Every cell can make all the cholesterol it needs. HDLs (about 90% of all lipoprotein particles) pick up excess cholesterol, then hand much of it to long-lived LDLs (3–5 day lifespan), which the liver clears through LDL receptors. This is indirect reverse cholesterol transport. When LDL falls, cells are simply in balance and less cholesterol needs returning.

• Plasma holds only a sliver of the body's cholesterol; the brain holds the most.
Of roughly 140 g of cholesterol in the body, the brain holds about 20–25 g versus 3–5 g in the liver, which is a transfer station rather than a vault. Brain cholesterol has a half-life of about five years, versus days in the periphery. Red blood cell membranes carry more blood cholesterol than lipoproteins do. Halving plasma cholesterol from 200 to 100 cuts total body cholesterol by only a couple of percent.

• Atherosclerosis comes from apoB particle number, mainly through poor clearance.
Above a threshold concentration, apoB particles diffuse into even healthy artery walls, get trapped, oxidize and are engulfed by macrophages that become foam cells. Every trial and Mendelian randomization study shows that lowering apoB lowers events. Insulin resistance, inflammation, blood pressure, smoking and autoimmune disease make entry easier. The rare 90-year-old smoker with high LDL and no plaque is genetically lucky, and Dayspring warns nobody can know in advance whether they're one of them.

• After about age 10, neurons stop making cholesterol and outsource it to astrocytes.
Building one cholesterol molecule takes 37 enzymatic steps and over 30 ATP, and neurons need their energy for firing. Oligodendrocytes make about 70% of brain cholesterol, mostly for myelin; astrocytes package cholesterol onto apoE into HDL-sized 'brain HDLs' that travel through the brain's tissue matrix. Neurons take them up mainly through LRP1 (which recognizes only apoE), plus LDL receptors and SR-B1. Dayspring suggests calling the LDL receptor the 'apoB/apoE receptor'.

• Plasma desmosterol tracks brain cholesterol synthesis; 24S-hydroxycholesterol signals neurons getting rid of excess.
The periphery mostly uses the lathosterol pathway, while astrocytes use the desmosterol (Bloch) pathway, so blood desmosterol correlates closely with levels in spinal fluid and brain. Neurons convert surplus cholesterol into water-soluble 24S-hydroxycholesterol, which crosses the barrier and goes to the liver for excretion. Rising plasma levels suggest a neuron under stress; only research labs measure it.

• APOE4 makes dysfunctional brain HDLs, disturbing neuron membranes and tilting APP processing toward toxic amyloid-;#C"à
Peter's numbers: about 55% of people are E3/E3, 20–25% E3/E4, 1–2% E4/E4, and E2/E2 is under 0.5%. One E4 copy roughly doubles Alzheimer's risk (some series say triples); two copies are now usually put at 8–12x, down from older estimates of 20–25x. E4 particles bind neuron receptors poorly, so cholesterol lodges in membranes but doesn't reach the cell interior. Membrane cholesterol excess favors beta/gamma-secretase cleavage of APP into A;#C" ðver the alpha-secretase route; brains with Alzheimer's at autopsy are cholesterol-overloaded.

• Statins are the only lipid drugs that reach the brain, and randomized trials show neutral or beneficial cognitive effects.
Lipophilic statins enter faster, but at steady state hydrophilic ones like rosuvastatin get in too, so Dayspring doesn't pick a statin by solubility. Peter's earlier review of meta-analyses found neutrality or improvement for MCI and dementia, though dementia was always a secondary outcome. The hypothesis: modestly slowing brain synthesis may help, while oversuppression may explain the occasional statin 'brain fog' that clears when the drug stops.

• HDL's real value is its protein cargo and immune function, not its cholesterol count.
More than 200 proteins have been found on HDL particles, each particle carrying one or two. The tiniest, protein-laden apoA-I species can cross the blood-brain barrier and join apoE brain HDLs, possibly delivering anti-inflammatory and antioxidant proteins. No commercial test measures whether HDL is functional or dysfunctional.

EXAMPLES

• A study from about a decade ago: low desmosterol tracked with cognitive impairment.
Using mass spectrometry, researchers found plasma desmosterol closely matched spinal-fluid levels, and people with low desmosterol had more cognitive impairment and Alzheimer's. Dayspring proposes watching desmosterol in statin-treated patients, especially E4 carriers. If it's oversuppressed, lower the dose or switch to other apoB-lowering drugs.

• BROADWAY trial: obicetrapib moved Alzheimer's biomarkers.
NewAmsterdam Pharma's CETP inhibitor was tested to lower apoB and cardiovascular events, but biomarkers including phosphorylated tau and the amyloid 42/40 ratio moved favorably. People with genetic CETP loss of function have less Alzheimer's. The proposed mechanism: the liver overproduces apoA-I, which may enter the brain and 'rescue' E4 brain HDLs. It isn't FDA-approved; cognitive trials are expected, led by John Kastelein and Michael Davidson.

• Ezetimibe's metabolite may reach the brain.

Ezetimibe works in the gut and can't cross the barrier, but its glucuronide metabolite enters in small amounts and, in animals, reduces protein glycosylation and brain inflammation. Neurologists Richard Isaacson and Kellyann Niotis report anecdotal cognitive benefit. Dayspring suggests using banked serum from ezetimibe trials to check p-tau.

• PREDIMED as a model for trial design.

Peter expected a dietary primary-prevention trial to fail, yet Mediterranean versus low-fat was stopped early. Choosing people 'about to drive off the cliff' gives answers within a few years, which is how he thinks the obicetrapib and E4 cognition trials should be built.

OTHER RELEVANT

• Don't avoid low LDL out of fear for your brain.

Cholesterol in the brain is made locally. In Peter's practice they often combine a low-dose statin with ezetimibe, and use ezetimibe from day one in people who absorb a lot of dietary cholesterol, after testing synthesis and absorption markers.

• If you carry E4, consider tracking plasma desmosterol on a statin.

This is a plausible strategy but not trial-proven. A low value suggests possible oversuppression of brain synthesis. Statin brain fog that clears on stopping is a signal to adjust.

• Omega-3s: aim for an omega-3 index of about 8–9%; going higher is guesswork.

The brain takes up DHA and EPA mainly as lysophospholipids through a specific transporter at the barrier, so the supplement form matters less than checking the label is accurate. Brain evidence is observational (Bill Harris links the index to brain volume). Dayspring sees little downside.

363 A new frontier in neurosurgery: brain-computer interfaces, new hope for brain diseases, & more

Guest: Dr. Edward Chang
Date: 2025-09-08 · Duration: 2:09:14
URL: https://www.youtube.com/watch?v=y7LXTyUhSVM

KEYPOINTS

• Neurosurgery has steadily moved toward less collateral damage, though the craniotomy still has its place.
UCSF neurosurgeon Edward Chang traces modern neurosurgery to Harvey Cushing, who diagnosed early pituitary tumors and helped bring in electrocautery, and to Wilder Penfield, who popularized awake surgery and the homunculus map. Aneurysm repair used to mean a 7–9 inch incision and a microscope. Today about 90% are treated with coils through a catheter in the groin. Clot retrieval has turned many severe strokes into 'brain attacks' handled like heart attacks, and some patients go home the next day. Laser probes and focused ultrasound can now treat deep targets such as the nuclei behind tremor.

• Glioblastoma is still lethal, but molecular profiling and immune strategies are shifting the approach.
GBM arises from glial support cells and grows so fast it outstrips its blood supply, leaving necrosis. It isn't considered heritable, and each tumor has a different combination of mutations. Genetic profiling is now routine at academic centers, opening the door to targeted chemotherapy. GBMs also hide from the immune system, so 'unmasking' them is a major goal. For now, the more of the tumor surgeons remove, the longer patients survive, but microscopic cells beyond what MRI shows grow back. Focused ultrasound that temporarily opens the blood–brain barrier for drug delivery is being studied at UCSF. Chang's 2040 hope is to turn an average survival of about 18 months into a chronic condition.

• Awake surgery works because the brain itself feels no pain.
The scalp is numbed with lidocaine and epinephrine. Bone and brain tissue have no pain receptors, but the dura and some blood vessels do, so they're numbed too. Patients aren't intubated. The head is fixed in a holder and light propofol sedation is used at the start. The awake window is usually only 1–2 hours of a 6–8 hour operation, for mapping language or movement with electrical stimulation. The trade-off is resecting more tumor or seizure tissue against the risk of paralysis or aphasia.

• The '10% of the brain' myth has a grain of truth: some regions are redundant and plastic.
Roughly 10–15% is critical for basics like moving, speaking and seeing. Chang has removed an entire frontal lobe on one side many times. With slow-growing lesions, the other hemisphere, which was already sharing the work, takes over through synaptic plasticity. Language sits in the left hemisphere for about 99% of right-handers, about 2 cm above the left ear, and that real estate can't be sacrificed.

• Severing the corpus callosum stops seizures from spreading rather than curing them.
For drop attacks, where seizures spread so fast that patients collapse and may need to wear helmets, surgeons usually cut the front two-thirds of this heavily myelinated left–right highway. Chang compares a seizure to a whole stadium doing the wave instead of holding separate conversations. Cutting it fully risks a disconnection syndrome, with one hemisphere unaware of what the other is feeling, which is why partial cuts are preferred. The delicate step is protecting the pericallosal arteries, since injuring them can paralyze the legs.

• Recording from the brain's surface is the sweet spot for brain–computer interfaces.
Taking scalp EEG as 1, electrodes on the cortical surface (ECoG) give roughly 1,000x the resolution, because skull and scalp blur the signal. Penetrating single-neuron electrodes add perhaps another 5x, but scar tissue forms around them and their recordings drift from neuron to neuron within hours or days, so decoders must be recalibrated. Because ECoG doesn't break the brain's surface membrane, it avoids much of that reaction and can blanket a whole region, which absorbs individual variation in exactly where functions sit.

• The decoder translates attempted speech, not inner thoughts.
The array sits over the speech-motor cortex controlling the lips, jaw, tongue and larynx, so the patient must actually try to speak. Reading or imagining a sentence isn't enough. AI breaks the signal into 10–20 ms windows and maps them to statistically derived speech units, using an open-source speech-recognition model from Meta. A language model then infers the likeliest words, much as autocorrect does, and a synthesizer can recreate the person's pre-injury voice.

• Hearing loss deprives the brain and may accelerate cognitive decline.
Many older adults with normal hearing tests struggle in noisy restaurants because the problem is signal processing in the brain. Unrecognized hearing loss leads to social isolation and less stimulation, and Chang says many studies link it to accelerated memory loss. Peter's practice treats the link as causal, while noting that a recent trial suggesting otherwise had methodological problems. Chang thinks vision loss has less of this effect.

EXAMPLES

• Ann's story.
A vertebral artery stroke that damaged her pons while she was playing volleyball, months after her second daughter was born, left her quadriplegic and unable to speak. She communicated by eye-tracking letters. About 18 years later, after waiting until her daughter graduated, she joined the BRAVO trial and received a credit-card-sized array of 253 electrodes spaced 3 mm apart.

• From NATO code words to 80 words a minute.
Training started with the 26 NATO code words, chosen because they're easy to tell apart: about 50% accuracy after roughly 90 minutes of data on day one, and 95–100% within about a week. The 2023 Nature paper reached about 80 words a minute (conversation runs 150–160). A 2025 study streamed speech with under a second of delay using the same hardware and a new algorithm. Her face and jaw muscles also grew stronger from the constant practice.

• Fetal dopamine-cell grafts for Parkinson's.
These were tried 20–30 years ago. Some patients benefited, but unregulated dopamine caused severe dyskinesias. New stem-cell approaches aim for tuned dopamine output, better delivery and less immunogenic cells. Immunosuppression is still used for now as a precaution.

- **Neck manipulation and vertebral dissection.**
  Chang says it's 'not a wives' tale': certain chiropractic neck movements, and high-velocity sports injuries, are statistically linked to tears in the vertebral artery wall, though the incidence is very low.

OTHER RELEVANT

- **Get hearing checked and treated.**
  Unrecognized hearing loss is common, and both Chang and Peter see it as a modifiable contributor to cognitive decline.
- **Be cautious with aggressive neck adjustments.**
  The risk is rare but catastrophic. Chang advises against forceful, high-velocity neck manipulation.
- **Expect brain–computer interfaces outside the lab by about 2030.**
  Chang's stretch goal is fully implanted wireless arrays with about 4x more channels (his group is roughly a year from a wireless version), serving ALS, spinal cord injury, stroke and MS patients. He expects scalp-only systems to stay limited by physics.
- **Expect progress on Parkinson's sooner than on Alzheimer's.**
  Chang is more optimistic about movement disorders because the cell loss is concentrated in one small area that surgery can reach. Alzheimer's involves many brain systems at once, so he expects early detection and early treatment to bring the first gains there.

341 - Overcoming insomnia: improving sleep hygiene and treating disordered sleep with CBT-I

Guest: Ashley Mason
Date: 2025-03-24 · Duration: 2:21:18
URL: https://www.youtube.com/watch?v=NneZHMv7VBU

KEYPOINTS

- **Insomnia is common, clinical and episodic, and what keeps it going isn't what started it.**
  Mason, a UCSF psychologist who trained where CBT-I co-inventor Richard Bootzin worked, estimates that about 90% of adults struggle with insomnia at some point. At any moment, 5–10% meet the definition: roughly three months of bad sleep that is distressing and impairs life. Predisposing traits plus a trigger such as job loss, divorce or a crash start it. Coping behaviours—Benadryl or Ambien, naps, scrolling or reading in bed—keep it going after the trigger is gone.
- **CBT-I treats current behaviour, not the original cause, so one recipe fits most types.**
  Trouble falling asleep, waking at night and waking too early all get the same intervention; for night waking, the racing mind just shows up later. Mason doesn't ask what caused the insomnia until the end of the first session. Done well, about 50% reach remission and about 70% improve meaningfully. Failure mostly comes from not doing it—or from distressed natural short sleepers who may not need fixing.
- **Stimulus control: the bed is only for sleep and sex.**
  This descends from a 1970s study in which struggling students could study in only one library carrel. People with insomnia often 'camp out' in bed—snacking, TV, podcasts—hoping to catch sleep, and break the bed–sleep association. Dismantling studies show CBT-I fails without stimulus control or time-in-bed restriction.
- **Time-in-bed restriction matches time in bed to the sleep your body actually produces.**
  From a 7-day paper sleep diary, average sleep plus 30 minutes sets the time in bed, with a floor of about 5.5 hours. If someone sleeps about 6 hours with a 7 a.m. wake time, bedtime becomes 12:30 a.m. When sleep efficiency (time asleep ÷ time in bed) exceeds 85%, bedtime moves 15 minutes earlier each week. Patients get worse for the first couple of weeks.
- **Fix the wake time first—a consistent wake time alone helps 1–2 of every 8 patients.**
  In Mason's 'democracy within a dictatorship,' she sets the wake time from what the diary shows the person can actually do, not their aspirational 5 a.m. She runs one week with that wake time and no naps before calculating a bedtime. You can force a wake time with an alarm, but not a bedtime. During treatment, every day that ends in 'day' has the same wake time.
- **Scheduled worry time keeps worries from 'demanding attention' at night.**
  Saying 'stop worrying' doesn't work. Instead, book a non-negotiable hour a day and jot down intrusive worries until then. Mason also has patients track how much they believe a 1 a.m. or 7 a.m. thought at different times of day. A patient with MS believed 'I'll never make it through today' at 7 a.m., but 0% by 5:30 p.m. She turned 7–9 a.m. into Italian-learning time.
- **Keep the body cool and the hands and feet warm.**
  Mason swaps down comforters and duvets for cotton blankets ('if I had five cents...') and recommends a room in the mid-60s °F. Warm hands and feet help the core dump heat for sleep onset; socks or a small auto-off heating pad are fine. She's wary of heated settings on mattress-cooling devices, citing the electric-blanket era. Avoid a cold plunge before bed, and test whether a sauna helps or overstimulates you.
- **Caffeine, including decaf, ends by 11 a.m.—but don't cut the amount.**
  Caffeine's half-life is about 4–6 hours. Decaf can carry about 15% or more of regular caffeine, and one outside test found a tall Starbucks with about 310 mg against a stated 155 mg. Mason keeps the total the same to avoid withdrawal and just moves it before 11. She doubts truly caffeine-immune people exist.
- **Melatonin is the starter's pistol, not a car in the race.**
  Supplements often don't contain what the label says, and taking melatonin at the wrong time can push sleep before the body is ready, leading to night waking. Mason stops supplements during treatment. Exception: beta-blockers suppress melatonin, and one patient on metoprolol for 30 years needed only a small nightly melatonin dose.
- **Taper hypnotics slowly, and only after stabilising.**
  First come one drug, one dose, one time, with no middle-of-the-night top-ups and no 'rotating' Ambien, trazodone and Benadryl. After CBT-I, patients reduce in steps they rate as 1 out of 10 on a stress scale—say, 12.5 to 12 mg—weighed on a jewellery scale and held about three weeks, often over a year. The taper pauses during life crises, always alongside the prescriber. Mason worries least about low-dose trazodone.

EXAMPLES

- **Middle-of-the-night reset**
  If you can't sleep, get up and do something 'embarrassing but boring'—trashy magazines, solitaire, a 20-minute sitcom. No email, news, social media or stressful trading, and don't make 3 a.m. into 'me time.'
- **Orange-lens glasses**
  For some patients with sleep-onset trouble who weren't using stimulating screens, wraparound orange glasses worn two hours before bed allowed them to quit Ambien. Attia finds that avoiding email matters more than filtering blue light.
- **Wine-glass swap**
  A patient drinking 16–20 oz of wine nightly moved to 2 oz plus a 'special' non-alcoholic drink in the same glass, keeping the routine consistent before treatment started.
- **Weekend rule**
  After a late Friday, sleep in by about an hour on only one day and hold your normal wake time the next. Attia's 2 a.m. flight return followed by sleeping until 8 pushed his bedtime late the following night.
- **The wearable-anxious 70-something**

An active volunteer was fine until her tracker kept warning her. The 'treatment' was taking the device away; Attia's clinic uses six-month tracker holidays.

OTHER RELEVANT

- **Low-hanging fixes to A/B test for two weeks**
  Older men waking to urinate can drink less at and after dinner (a light electrolyte tab may help). Use an eye mask for early waking, and take medications at consistent, appropriate times (not 450 mg bupropion at bedtime). Stop eating three hours before bed, and avoid podcasts in bed.
- **Do CBT-I yourself if you're stuck on a waitlist**
  Use 'Quiet Your Mind and Get to Sleep' (Manber and Carney) and a paper sleep diary. Find providers through the behavioural sleep medicine directory—telehealth makes access easier. Commit to weekly sessions over 5–8 weeks; four or more sessions predicts much better outcomes.
- **Rule out other sleep disorders**
  Snoring or gasping warrants evaluation, and if you have a CPAP, get it fitted and use it nightly.
- **Evening exercise depends on the person**
  Yoga or lifting late is usually fine. Late HIIT or hockey may keep heart rate up, especially in less fit people. A 5 a.m. class can cost sleep if your body won't sleep before 11.

303-A breakthrough in Alzheimer’s disease: potential of klotho for brain health & as a therapeutic

Guest: Dena Dubal
Date: 2024-05-27 · Duration: 2:23:23
URL: https://www.youtube.com/watch?v=qsA5MBLoeGI

KEYPOINTS

• Klotho was discovered by accident and behaves like a true longevity factor.

In 1997, Japanese scientist Makoto Kuro-o was studying hypertension. A transgene insertion disrupted a gene in one mouse line, and those mice aged prematurely from about two weeks old (osteoporosis, atherosclerosis, emphysema) and lived about three months instead of about 30. He mapped the disrupted gene and named it after Clotho, the Fate who spins the thread of life. The decisive test was the reverse: mice engineered to overexpress klotho lived about 30% longer.

• Most klotho circulates as a hormone cut from a membrane protein.

Klotho is a roughly 1,000-amino-acid (about 130 kDa) transmembrane protein, made mainly in the kidney and also in the brain's choroid plexus. Enzymes (ADAM10/17) clip off most of its outer portion into the blood or spinal fluid, where it acts on many organs. Dubal calls this the 'klotho hormone.'

• Levels fall with age, through the day, and with chronic stress; exercise raises them.

Cord blood has about six times adult levels, and levels can halve from age 40 onward. Fabrisia Ambrosio's lab linked the age-related decline to methylation of the klotho promoter. Levels also fall up to about 40% from morning to midnight. In Dubal's study with Elissa Epel and Aric Prather, highly stressed mothers of children with autism had lower klotho, which tracked shorter telomeres. Across about 12 studies, 12 weeks of regular exercise raised klotho about 30%. Rapamycin raises it in mice, and in mouse data a 45-minute treadmill run may nearly double it acutely.

• Extra klotho made mice smarter, which surprised Dubal.

Her lab crossed Alzheimer's-model mice with klotho overexpressers. The biggest surprise was in normal mice: those with more klotho learned and remembered better across many tasks and ages, with nearly non-overlapping data, not because they swam faster or saw better. The effect replicated in aging mice and Alzheimer's models. In a Parkinson's model (alpha-synuclein), klotho improved cognition by about 70% but did nothing for motor deficits.

• Klotho appears to protect brains despite Alzheimer's pathology.

In aggressive J20 amyloid mice, three- to fourfold klotho overexpression extended lifespan and normalized cognition, even though amyloid-beta and tau levels didn't change. Synapses were preserved, in work with Lennart Mucke and Eliezer Masliah. A colleague's analogy is 'a helmet for neurons' against amyloid, tau, alpha-synuclein and aging.

• It works through the GluN2B subunit of NMDA receptors.

Klotho mice looked like the 'Doogie Howser' GluN2B-overexpressing smart mouse. Klotho increased synaptic GluN2B and plasticity, and blocking GluN2B with drugs abolished the cognitive benefit.

• Klotho doesn't cross the blood–brain barrier, so a blood messenger was proposed—and platelets turned up.

Klotho injected into the belly or arm enhances cognition within 4 hours, and the effect lasts weeks. Plasma profiling after injection showed a surprising rise in platelet factors. A persistent postdoc showed klotho mildly activates platelets to release platelet factor 4 (PF4). PF4 crosses into the brain, acts via GluN2B in hippocampal slices, and enhances cognition in young and aging mice. Saul Villeda (young blood) and Tara Walker (exercise) found PF4 independently, and the three groups published together in Nature-family journals on the same day. Yet klotho still worked fully in PF4-knockout mice, so PF4 is 'sufficient but not necessary,' and other messengers are being sought.

• In old monkeys, one low physiological dose improved working memory for weeks; high doses didn't help.

With Unity Biotechnology and Yale (Graham Williams, Stacy Castner), 18 aged rhesus macaques did a largely blinded spatial delayed-response task: remembering which covered well held a treat. One subcutaneous low dose (within natural range) improved performance within 4 hours, lasting 14–21 days and in some cases tested to 28. Gains were largest on the harder, many-well version. Doses 10–20 times higher neither harmed nor helped, unlike in mice, where even far higher doses worked. Dubal concludes humans likely have a therapeutic window. She calls the study a 'burn your ships' risk she was willing to take.

• In humans, the KL-VS variant links higher klotho to better cognition and blunts APOE4 risk.

About 1 in 4–5 people carry one copy, with about 15–20% higher levels (for example, about 950 vs 800 pg/mL). Dubal and Jennifer Yokoyama found carriers scored better cognitively, by about as much as APOE4 carriers score worse. Michael Belloy and Michael Greicius analysed 22 cohorts and over 20,000 people: APOE4 carriers with KL-VS had near-normal Alzheimer's risk, less MCI-to-Alzheimer's conversion and less amyloid. Dubal says, from personal communication, protection also held for APOE4 homozygotes. Carriers also show less stroke and cardiovascular risk, but a worse prognosis in BRCA1-positive breast cancer. Rare KL-VS homozygotes have about 30% lower klotho and shorter lives.

EXAMPLES

• NHANES mortality signal

In about 10,000 US adults (mean age 56), serum klotho below about 666 pg/mL was associated with roughly 30% higher 5-year mortality, mainly from cancer and cardiovascular disease, and this replicated in another cohort. Attia stresses this is association, not proven causation.

• Mouse dosing

Even about 0.2–1 µg/kg, versus a usual 10 µg/kg, enhanced mouse cognition. Very high doses worked too, with no obvious problems in behaviour or basic blood work.

• Fasting caveat

A 24-hour fast raised klotho and BDNF in mouse brains. Attia warns a mouse fast that long is extreme and doesn't mean skipping breakfast equals a workout.

• A mentor's advice

As a resident, UCSF's neurology chair Stephen Hauser told her to do things 'big and important, not incremental,' because they take the same time.

OTHER RELEVANT

- **Testing is not yet practical**

  There's no standardized clinical klotho assay. Researchers draw samples in the morning while fasting. Attia says KL-VS status is hard to extract from consumer genetic tests.

- **Klotho as kidney marker**

  Klotho falls early in chronic kidney disease, so nephrologists are developing it as a more sensitive biomarker than current measures. Mouse studies also report anti-cancer effects.

- **Therapeutic vision**

  Dubal hopes klotho could be combined with anti-amyloid drugs like lecanemab or donanemab, perhaps as monthly or quarterly injections, but human trials are still needed. Attia disclosed he is an investor in Jocasta Neuroscience, which is developing klotho.

- **Exercise remains the accessible lever**

  Dubal emphasizes that regular exercise's roughly 30% increase in klotho exceeds the genetic KL-VS boost.

263 Concussions and head trauma: symptoms, treatment, and recovery | Micky Collins, Ph.D.

Guest: Micky Collins
Date: 2023-07-24 · Duration: 1:29:47
URL: https://www.youtube.com/watch?v=CBqBNCHOe2Q

KEYPOINTS

• A concussion is an energy crisis at the cellular level, not a structural injury.

Collins explains that when the brain shifts inside the skull, neuron membranes stretch. Potassium leaks out of the cell, raising demand for glucose so ATP can pump it back. At the same moment calcium floods in, causing vasoconstriction and reduced cerebral blood flow. Demand rises just as supply falls, a metabolic mismatch. The cells don't die; they run less efficiently. Standard imaging shows no structural change, and he says no reliable biomarker exists yet or is likely soon.

• There are six types of concussion, and treatment depends on which system is failing.

Collins lists cognitive fatigue, vestibular (the central brain pathways, not the inner ear), ocular (the eyes working as a team), migraine, anxiety/mood and, less often, cervical (neck). Patients can have one or all six. In his clinic's data the most common profile is anxiety, then migraine, vestibular, ocular and cognitive fatigue. His job, he says, is to find which system is 'decompensated' and target it.

• On-field dizziness predicts a slow recovery better than loss of consciousness.

Collins challenged Attia to name the strongest on-field predictor of long recovery. Attia guessed loss of consciousness, which was wrong. Dizziness was about six times more predictive of a recovery lasting a month or more, and fogginess ('feeling one step behind') came second. He notes that athletes who lose consciousness are always pulled from play, while dizzy athletes often keep playing.

• Playing through symptoms dramatically lengthens recovery.

In a retrospective study of about 300 kids, those removed from play right away recovered in an average of 18 days. Those who kept playing for just 15 minutes after symptoms began took 44 days. A follow-up dose-response analysis found that each minute played through the injury added roughly seven to eight days. He admits it wasn't randomized but says the gap is too large to ignore.

• Personal history shapes which pathway a concussion takes.

A history of migraine sends patients down the migraine pathway with less force. Car sickness predicts vestibular problems. Lazy eye or strabismus predicts ocular problems, and prior anxiety predicts the anxiety profile. Attia calls it 'concussive reserve.' Age matters too: high school athletes recover slowest, college athletes next and professionals fastest.

• Females are more vulnerable and recover more slowly.

Girls are more likely to be concussed than boys. Collins points to neck strength and hormones, and girls are about six times more likely to have migraine and car sickness. About 60% of his clinic's patients are female. His group has shown that menstrual cycles change after head injury and is starting a women's study on hormonal effects.

• Rest is the wrong treatment; targeted exposure is the right one.

The old advice was to rest an injured, energy-starved brain. Collins says that makes things worse. Anxiety is treated by exercise and regular sleep, which raise parasympathetic tone, and vestibular problems are treated by retraining. His clinic uses aggressive 'exertion therapy' plus exposure to busy environments. He stresses that this must be guided by a specialist, because the wrong approach can make patients worse.

• Early specialist care is the strongest predictor of good outcomes, but late cases are still treatable.

Across all the factors studied, being seen in the clinic within seven days best predicted recovery. Red flags such as an intracranial bleed must be ruled out first. Collins still says patients one to three years out can usually be treated effectively, and he follows patients every three to four weeks until they're normal.

• Medications are secondary and target the root problem, not downstream symptoms.

He tries behavioral treatment first. He avoids trazodone for sleep because the insomnia stems from nervous-system arousal. When drugs are needed, he says sertraline can help both vestibular and anxiety profiles, and he sometimes uses tricyclics, Wellbutrin, Effexor or escitalopram, often with an in-house psychiatrist. Untreated arousal can ripple outward. Attia asks about hypogonadism as one downstream example.

• Evidence on long-term brain disease is unsettled; the CTE picture suffers from selection bias.

Collins cites work from Grant Iverson's group, linked to Mass General, showing some relative increase in anxiety but no clear tendency toward dementia, Lewy body or other neurodegeneration after concussion. CTE brain-bank studies, he says, rely on people who donated brains because they had problems. UPMC is about two and a half years into a controlled study using neuropsych testing, imaging, lumbar punctures, CSF biomarkers and sleep studies. He also says there is no compelling evidence that APOE4 raises concussion risk.

EXAMPLES

• The race-car driver from Phoenix

Collins saw him the morning of the recording. He had a concussion in a crash, then a second crash with the same mechanism two weeks later. Two years on he had a vestibular profile with light and noise sensitivity, fog, dizziness with exercise and insomnia. He was no longer racing or working and had become reclusive. His plan: vestibular exercises morning and night, a 45-minute walk each morning, a 45–60-minute workout in the afternoon, fixed wake and bed times with no napping, and daily exposure to grocery stores, restaurants and parties.

• A cyclist who couldn't be in a room with a TV

Attia describes someone close to him riding at about 25 mph (40 km/h) who collided head-to-head with a runner who darted between cars. The runner fractured his face. The cyclist spent two years unable to tolerate a TV or noise, which Collins says is the classic vestibular-to-anxiety-to-migraine spiral.

• Equestrians, not boxers

Asked which sport carries the highest lifetime concussion risk, Attia guessed boxing. Collins says about 90% of equestrians suffer a concussion over their careers, from falls off a large animal. Football leads in raw numbers, women's soccer and basketball are also high, and the US sees about 1.8–3.6 million sports and recreation concussions a year.

• A 90-year-old who fainted

An elderly patient had a syncopal episode, likely from dehydration and stress, fell face-first off the toilet onto a linoleum floor and suffered a facial fracture, a small subdural bleed and a bad concussion. Eight weeks later the patient was highly motivated and was given walking plus balance and vestibular work after a fall-risk check.

• Nick Saban said yes

As a student, Collins asked Michigan State's medical staff about studying the football team and was sent to the head coach, Nick Saban, who approved it. The data fed a 1999 JAMA paper on college football. Collins started at UPMC in 2000 seeing two or three patients a week. The program now has about 20,000 visits a year and has trained 33 fellows.

OTHER RELEVANT

• Pull athletes at the first sign of dizziness or fog.

Teach kids and parents that sideline dizziness, fogginess, fatigue or blurred vision means stop now, because each extra minute may add days of recovery.

• Get seen early by a concussion specialist, not just any neurologist.

Collins says general neurologists and neurosurgeons often don't know this field. Specialty clinics now exist in most major areas, though rural access may be limited. Mild symptoms that are improving may not need a visit unless you risk another head hit soon.

• Expect an active plan: exercise, regular sleep, structured exposure.

Avoid prolonged dark-room rest and rumination. Treatments should be targeted to your profile and supervised.

• Be wary of unproven add-ons.

Collins won't prescribe hyperbaric oxygen because he sees no data showing it helps and says it feeds symptom-seeking. Attia adds the opportunity-cost argument: exercise time beats chamber time. Exogenous ketones at the time of injury are theoretically interesting, but neither knows of supporting human research.

257 Cognitive decline, neurodegeneration, and head injuries: mitigation and prevention strategies

Guest: Tommy Wood
Date: 2023-06-05 · Duration: 2:20:33
URL: https://www.youtube.com/watch?v=zKFEUV911Zw

KEYPOINTS

• Some cognitive slowing with age is normal; dementia is an accelerated departure from that curve.
Attia describes names that come back ten minutes late, something he didn't notice in his late 30s. Tommy Wood, a physician-scientist whose interests span lifestyle medicine, brain health and performance, separates this ordinary age-related drift in processing speed and recall from the steeper decline some people experience on the way to a dementia diagnosis. The goal of prevention is to stay on the gentle slope.

• The brain responds to the right kind and amount of demand.
Wood argues cognitive function is use-dependent: novel, effortful and complex tasks build capacity, while retiring from all demand ('I'm 65, I'm done with spreadsheets') removes a key stimulus. Much of the evidence is observational, though he notes some interventional trials in older adults. There is also a threshold: overload, like Attia's unproductive 10 minutes of distracted work, achieves nothing.

• Task-switching carries a real cost.
Refocusing after a switch takes on the order of 20-plus seconds, so someone changing focus every minute or two spends much of their time re-orienting. Wood suggests short blocks of single-task focus (perhaps 20–30 minutes) and walking breaks rather than constant juggling.

• Formula 1 is a model of performance under extreme cognitive load.
Drivers hit straight-line speeds of roughly 200–220 mph while managing dozens of settings on the steering-wheel computer, and the jump in car complexity from F3 to F2 to F1 is large. Wood, who works in this environment, says the demands make it a natural laboratory for multitasking capacity and recovery.

• Alzheimer's is probably many diseases leaving the same 'tombstone'.
Wood questions the amyloid-and-tau-centric view, noting that even Alois Alzheimer reportedly doubted whether his cases belonged together and that later genetic analyses of the original patient conflicted (one 2013 report claimed a PSEN1 mutation, another sample found none). His unifying view: homocysteine, poor omega-3 status, glucose hypometabolism and microvascular disease converge on a final common pathway of neuronal damage, with plaques and tangles as the residue.

• Research money is skewed away from modifiable risk.
Wood cites the 2020 Lancet Commission estimate that about 40% of dementia may be attributable to modifiable risk factors, yet funding concentrates on late-stage pathology. He also notes the factors interact, so population-attributable risks shouldn't simply be added up.

• Lowering homocysteine slows decline and brain atrophy, especially with good omega-3 status.
Elevated homocysteine has a suggested population-attributable risk around 20% for late-onset Alzheimer's. In the VITACOG trial (B12 and folic acid), lowering homocysteine slowed cognitive decline and atrophy, but atrophy slowed only in those in the top tertile of omega-3 status, and a Dutch study (B-PROOF) pointed the same way. Wood's evidence-based cutoff is 11 µmol/L; Attia's clinic targets 8–9 even though lab ranges call 13–14 normal.

• Poor omega-3 status may account for a similar share of risk.
Another roughly 20% attributable risk has been assigned to low marine omega-3 intake. Both homocysteine and the omega-3 index are cheap and easy to measure. Wood frames moving homocysteine from 13–14 down to 9–10 while taking about 1–2 g/day of DHA as a potential 'winning lottery ticket', while stating it's not certain.

• Strength is one of the strongest protective associations.
Comparing the strongest roughly 10% of people with the weakest 10%, Wood cites about a 70% lower incidence of and mortality from all-cause dementia. Grip strength is a proxy for whole-body strength, and resistance training in people in their 70s improves brain measures, likely through multiple pleiotropic effects.

• After a TBI, the first 24–72 hours are about preventing fever.
Fever worsens secondary injury. Therapeutic hypothermia (33.5°C for three days) is standard for newborns with birth asphyxia, but in adult TBI the benefit seems to come from keeping core temperature at or below about 36.5°C. Wood suspects the early neonatal trials partly looked good because control babies were warmed quickly and left feverish.

• Hyperbaric oxygen is risky early and unproven later.
Attia calls much of the hyperbaric industry 'a racket' outside indications like wound healing. Wood says that in the acute phase, extra oxygen in an inflamed, impaired brain may drive oxidative stress, and he has heard of unpublished work showing more adverse effects; any trial in the chronic phase would wait at least a couple of weeks, with only pilot data so far.

EXAMPLES

• A crash and a two-year concussion
Wood describes a cyclist colleague hit at about 40 km/h whose concussion was so severe he wasn't himself for about two years, which pushed Wood into head-injury research.

• Angry Birds vs. Mario 3D
In a training study, playing a 3D game (Super Mario 3D) improved working memory and some response inhibition more than a 2D game, which Wood uses to show that novelty and complexity matter.

• Creatine loading as neuroprotection
Pre-loading creatine in rodents (equivalent to about 0.2 g/kg, or roughly 20 g/day for a week in humans) was significantly neuroprotective before a TBI. In people, 20 g/day for a week raises brain creatine on magnetic resonance spectroscopy, while 5

g/day eventually gets similar levels.

- **'37 of them are garbage'**
  Attia says patients arrive with 40 supplements and usually only about three are worth it; Wood's evidence-backed short list covers folate, B12, B6, EPA and DHA.

- **F1 forces prioritization**
  With 23 races a season, a driver will do only a few interventions, so Wood must be sure each one is worth more than the 99 alternatives. Solo endurance athletes, by contrast, will do 'all 100 things'.

OTHER RELEVANT

- **Test homocysteine and the omega-3 index.**
  Aim for homocysteine below about 11 (Attia targets 8–9), using methylfolate, methyl-B12 and sometimes B6, and consider around 1–2 g/day of DHA. These are reasonable but not proven to prevent dementia.

- **Keep the brain under the right demand.**
  Pick novel, challenging tasks, work in focused single-task blocks and avoid constant switching. Don't retire your brain when you retire.

- **Build strength across life.**
  Resistance training works even in your 70s and ties to dementia risk and survival; you can't jump from the bottom to the top in a year, but you can climb.

- **After a head injury, prevent fever.**
  Keep core temperature at or below about 36.5°C in the first 24–72 hours; be skeptical of early hyperbaric oxygen.

- **Consider creatine for high-risk athletes.**
  Wood sees a case for prophylactic creatine (5 g/day or a 20 g/day loading week) and post-injury creatine, DHA and choline, while noting much of it is preclinical.

249 How the brain works, Andrew’s fascinating backstory, improving scientific literacy, and more

Guest: Andrew Huberman
Date: 2023-04-03 · Duration: 3:03:33
URL: https://www.youtube.com/watch?v=OGe1bTccCyg

KEYPOINTS

• Adrenaline briefly takes the forebrain offline, and getting familiar with that state makes you less likely to be hijacked by it.

Huberman says that after a jolt of adrenaline (an ice bath, a car crash, a troubling text), the forebrain quiets for about 20–30 seconds. Meanwhile heart rate and breathing rise, pupils dilate and vision tunnels. Glucose and lactate are shunted toward survival centers. The more often you practice these states, through deliberate cold or blood-flow-restriction training, the more you learn they pass. He frames this as stress inoculation.

• Lactate is a fuel, not a poison.

After putting Huberman through blood-flow-restriction cycling, Attia explains that repeated lactate exposure leads cells to make more MCT transporters, so they clear and use lactate more efficiently. The liver can also turn it back into glucose. Huberman adds that the hypothalamus and brainstem areas that control breathing appear to prefer lactate under high exertion or stress. BFR's appeal: growth hormone and metabolic stress with little soreness, but only with proper cuffs, not homemade tourniquets.

• The prefrontal cortex sets rules by context, and stress shrinks those rules.

Huberman uses the Stroop task (name the ink color, not the word) to show how the PFC switches rules. Under even mild stress, he says, everyone fails at novel rule-switching, 'Seal Team Six guy' or not. People fall back on what they've practiced. When calm, they can draw on far wider rule sets, which he links to creativity.

• Mood circuits run 'north to south' in health and 'south to north' in distress.

Huberman cites Nolan Williams's work, not his own. In calm, healthy states the prefrontal cortex drives the insula and amygdala from the top down. In depression, activity in the left dorsolateral PFC is weak, so thinking is driven bottom-up from the insula and amygdala. Williams's lab uses TMS to activate that region, and new ideas seem to emerge, partly by temporarily dampening interoception. The insula holds a map of the internal body and merges outside information, rules and internal state.

• The amygdala isn't the only seat of fear.

People or monkeys with damage to both amygdalae still panic when made to breathe CO2. Yet they lose learned fears such as snakes and behave inappropriately with food and sex, for example tasting a pen.

• Humans are visual animals, but other animals see better in specific ways.

About 40–42% of the human brain responds to visual input. With good vision, people resolve about 60 cycles per degree, meaning 60 black lines on a thumbnail at arm's length. A red-tailed hawk resolves about 120, enough to spot a gopher lift its head from a light pole. Huberman says color vision evolved late: dogs see roughly brown-red-orange tones, while a mantis shrimp distinguishes far more shades of red than we can.

• Belief changes physiology, not just how things feel.

Huberman describes Alia Crum's research, which separates mindset effects from placebo. Drinking the same milkshake labeled low- or high-calorie produced different hormonal and satiety responses. Hotel housekeepers told their work burns calories and lowers blood pressure lost about 8–11 pounds over three or four weeks. People told about stress's performance-enhancing effects responded differently from those told its harms. He relays her estimate that belief accounts for roughly 8–20% of the effects of things like a food or behavior.

• Teaching mechanisms changes people more than listing facts.

Huberman says 50 brain facts don't change anyone, but explaining the process behind a few daily experiences, like fatigue and stress, makes the tools stick. He warns against promising 'works the first time, every time' unless it truly does, such as morning sunlight viewing working within two or three days. Both agree the world would benefit more from freshman statistics and probability, especially standard deviation, than from calculus.

EXAMPLES

• From truancy to residential treatment

Huberman grew up near Stanford. His father, an Argentine physicist, worked at Xerox PARC. After his parents' high-conflict split around age 12–13, he fell into the underground skateboarding scene and stopped going to school. The school system placed him in a residential treatment program for truancy, not drugs or violence. He says it 'wasn't jail but it wasn't far off.' The conditions for release were a new high school and therapy.

• A therapist for more than 30 years

His therapist, trained mainly in psychoanalysis, was the first person who really paid attention to him. He still sees that person one to three times a week, and in graduate school he sometimes needed budget help to keep going.

• Ben Barres's lab

Huberman did his postdoc from 2005 to 2010 in Ben Barres's 32-person Stanford lab, which held four-hour lab meetings. Barres, who had taught Attia neuroscience in medical school, transitioned during Attia's year and had a mild face-recognition deficit. To pay Bay Area rent on a roughly $45k salary, Huberman wrote for Thrasher and Slap under a pen name, earning an extra $500–$1,000 a month.

• Losses that destabilized him

A close colleague with BRCA1 and BRCA2 mutations died of early-onset breast cancer. He says it felt like losing his mother. Barres died of pancreatic cancer in 2017. Huberman reacted by working twice as hard and taking risks again, including cage diving with great white sharks, and felt joyless despite tenure and a 2018 Nature paper.

• Hoffman, a SEAL and a seed question

In 2017 he did the week-long Hoffman Process (he notes it costs about $4–5k, with scholarships) and met Pat Dossett, who served 13 years in the SEAL Teams. Around the start of 2019 Dossett asked, 'What are you gonna do for the world?' That led to Instagram clips, about 30 podcast guest appearances in 2020 including Rogan and Lex Fridman, and the launch of the Huberman Lab podcast in 2021.

OTHER RELEVANT

- **Practice controlled stress.**
  Short, deliberate cold or hard intervals let you rehearse the adrenaline window and learn that it ends.
- **Do novel or creative work when calm.**
  Rule-switching collapses under stress, so protect relaxed time for hard thinking.
- **Frame your activity accurately and positively.**
  Mindset effects are real but limited; true beliefs about the benefits of exercise and stress may add to the physiological effects.
- **Learn statistics.**
  Understanding probability and standard deviation protects you from confusing health messaging.
- **Seek sustained help.**
  Huberman credits long-term therapy and deliberate inner work, not willpower alone, with turning his life around.

221 Understanding sleep and how to improve it

Guest: Matthew Walker
Date: 2022-09-05 · Duration: 1:37:11
URL: https://www.youtube.com/watch?v=APEwc0HjAqg

KEYPOINTS

• Modern society has cut sleep sharply in an evolutionary blink.
Walker argues evolution spent millions of years establishing an eight-hour night of sleep, and in about 70 years we've lopped off roughly 20–25% of it. He compares it to deciding to lower everyone's oxygen saturation by 20–25% for a century — no one would think that a good idea. Sleep deprivation likely degrades health faster than not eating or not exercising; Guinness stopped accepting sleep-deprivation record attempts.

• Sleep cycles every 90 minutes, but the mix changes across the night.
You descend from stage 1 through stages 2, 3 and 4 (deep, slow-wave sleep), rise back after about 70 minutes, then enter REM — repeating roughly every 90 minutes. Early cycles are dominated by deep non-REM sleep; later cycles by REM. Sleep is scored in 30-second epochs, using criteria in place for 60–70 years.

• Cutting sleep short disproportionately costs REM.
Someone sleeping six hours instead of eight loses 25% of total sleep but may lose up to 70% of their REM, because REM concentrates in the final hours. Waking at 5:30 to 'get a jump start' has a steeper price than it seems.

• Brainwaves slow dramatically as sleep deepens.
Awake, brain activity oscillates around 50–60 times per second; relaxing in bed, it drops toward 10 cycles per second; theta around 6–7. Stage 2 features sleep spindles of 10–15 cycles per second. Deep sleep's slow, high-amplitude waves looked so coma-like that it had a bad reputation for 20–30 years.

• Chronotype is largely genetic and shifts with age.
About 25–30% of people are morning types, 25–30% evening types, the rest in between; companies like 23andMe estimate it from genes. Teenagers' chronotype moves later, so a 15-year-old in bed at 10:30 for a 5:30 bus can't fall asleep — biology, not laziness. It drifts back in adulthood and earlier again in old age, hence Florida's early-bird dinner specials.

• Sleep efficiency means you need more time in bed than sleep.
A healthy person in their 40s has about 90% sleep efficiency. To get eight hours (480 minutes) of actual sleep, they need roughly 8 hours and 50 minutes in bed. Walker's 7–9 hour recommendation refers to sleep, not time in bed.

• Counterintuitively, insomnia is treated by restricting time in bed.
Compressing the sleep window builds sleep pressure and re-teaches the brain that bed is for sleep. Don't lie awake: after about 20 minutes, get up and return only when sleepy, to avoid a learned association between bed and wakefulness.

• Naps are a double-edged sword.
For people sleeping well, naps can be fine — hunter-gatherer tribes often nap in summer afternoons and sleep around 8:30–9 p.m. But for insomniacs, a late-afternoon nap releases sleep pressure needed at night.

• Cool room, warm bath.
Current data suggest about 65–67°F is optimal. A hot bath or shower helps not because you're toasty but because blood rushes to the skin and core temperature then plummets. A smart thermostat can warm the room in the final 15–20 minutes before waking.

• Walker has softened on blue light.
His book cited a Harvard study in which an hour of iPad reading delayed melatonin, reduced REM and impaired sleep for days. Work by Michael Gradisar at Flinders University changed his mind: he's less convinced device harm comes from blue light, though he believes it has some effect; engagement and displaced sleep matter too.

• Coffee's benefits may come from antioxidants, not caffeine.
A 2017 review found decaffeinated coffee — same antioxidants, no caffeine — shares many health associations. For Americans eating poor diets, morning coffee may be a main antioxidant source. Walker still advises avoiding caffeine in the afternoon.

• Sleeping pills carry real risk; CBT-I is first line.
The FDA updated mortality warnings on sleeping pills. Dan Kripke's research found even three to 18 pills per year associated with statistically significant mortality increases. In 2016 the American College of Physicians said pills shouldn't be first line for insomnia; cognitive behavioural therapy for insomnia (CBT-I) should.

EXAMPLES

• Attia's residency sleep
During surgical residency, averaging about 114 hours a week at the hospital, Attia calculated he slept about 28 hours a week — none one night, eight another — and believed for years that sleep was optional.

• Survival without food vs. sleep
One person survived 382 days without food; even a lean person could last about 30 days. The last credible sleep-deprivation record attempt reached roughly 24 days, debatably.

• Phone-first mornings
Walker warns that checking your phone on waking floods you with anxiety. His rule: delay it, and try to push to 10 minutes after you sit down.

• Three-minute meditation
He argues three minutes daily beats 20 minutes once a week — consistency over dose.

• Sleep tracking blind spots
Walker notes that sleep quality is hard to sense because you are non-conscious during it, and current wrist-worn trackers

cannot reliably measure some of the metrics that matter, such as the depth of deep sleep. He treats them as rough guides rather than definitive scores.

OTHER RELEVANT

- **Protect the end of the night.**
  Waking early to gain time disproportionately sacrifices REM sleep.
- **Budget time in bed for sleep efficiency.**
  Plan roughly 8 hours 50 minutes in bed for eight hours' sleep.
- **Build a wind-down routine.**
  Sleep is like landing a plane: spend 15–30 minutes on stretching, meditation, and putting devices away.
- **Try CBT-I before pills.**
  Work with a therapist; use pills only as a short-term, last resort with your doctor.
- **Respect your chronotype.**
  Schedule demanding tasks around your biology where possible, and don't blame teenagers for late body clocks.
- **Keep the bedroom cool, not you.**
  Fall asleep more easily in a room that is too cold than too hot; warm up in bed or with a bath beforehand so core temperature can drop, and avoid alcohol in the evening and caffeine in the afternoon.

191 - Revolutionizing our understanding of mental illness with optogenetics

Guest: Karl Deisseroth
Date: 2022-01-17 · Duration: 2:42:06
URL: https://www.youtube.com/watch?v=anKrNnJDBZk

KEYPOINTS

• A psychiatry rotation changed his career.
Karl Deisseroth, a Stanford psychiatrist and bioengineer and Attia's former medical school classmate (he was in the highly selective MD-PhD Medical Scientist Training Program), planned on neurosurgery until a rotation on a locked psychiatric unit, with patients who were a danger to themselves or others, convinced him psychiatry was where the greatest need and mystery lay. He trained before 80-hour week limits, with a young son born in 1996.

• Psychiatry in 2004 lacked causal tools.
When he set up his lab in 2004, treatments like drugs, electroconvulsive therapy and vagus nerve stimulation worked for some patients but without precise understanding. The brain has about 90 billion neurons, each forming 10,000–100,000 synapses, and earlier tools (lesions, electrodes, drugs) couldn't control specific cell types with precise timing.

• Optogenetics borrows light-sensitive proteins from microbes.
Microbial opsins were discovered in 1971 by Dieter Oesterhelt and Walther Stoeckenius at UCSF; these single-component proteins pump or pass ions when light hits them. In principle someone could have put them into neurons in the late 1980s or 1990s, but the currents were thought far too small: neurons need about 100–200 picoamps to fire. Deisseroth's lab published its paper in summer 2005, and several other papers followed within six months.

• Viruses made targeting specific cells possible.
The opsin gene (such as channelrhodopsin) is packaged into a virus that delivers it, paired with cell-type-specific genetic elements, into neurons; it can even be given systemically in some settings, though focal injection is cheaper. Deisseroth says the method wasn't really 'solved' until about 2009, after years of work on light delivery, viral vectors and generalizable targeting.

• Optogenetics established causality for dopamine and reward.
In 2009, his group selectively fired dopamine neurons, not nearby GABA or serotonin cells, and showed it was sufficient to drive preference. With typical rewards like sugar water or social contact, animals prefer the stimulated side about 70–30 or 80–20; dopamine stimulation produced similar effects.

• Anxiety's components can be split apart.
In 2013, his lab found separate, nearby cell populations controlling distinct features of anxiety: breathing changes, risk-avoidance behavior (like avoiding exposed spaces) and the negative internal state. Too little anxiety is also dangerous, as people who don't perceive threat take extreme risks.

• Anxiety links autism and depression.
Deisseroth emphasizes that anxiety can be crushing and becomes pathological when it exceeds the normal range; it's a common thread in autism spectrum disorders, depression and other conditions. Optogenetics has been used to study social behavior and states like parenting (work at Harvard in 2018 used the same tools).

• Depression involves discounting effort.
Where a manic person thinks anything's possible, a depressed person thinks nothing is, devaluing effort and leading to hopelessness and sometimes suicidality. Anhedonia, the absence of pleasure, is so central that major depressive disorder can be diagnosed without depressed mood. In fish and mice, 'giving up' can be adaptive in truly hopeless situations, which suggests depression is a misfiring of a useful circuit.

• Severe psychiatric illnesses are highly heritable.
Genetic contributions run about 50% for depression and up to 50–80% for schizophrenia, autism and bipolar disorder. Hypomania may be unusually prevalent in North America, possibly because of who emigrated. Early-life trauma has clear, lasting psychiatric effects, including on personality disorders like borderline, seen in animals too.

• Optogenetics is a discovery tool first.
Deisseroth stresses that the immediate value of optogenetics is in identifying which cells and projections cause which behaviors, insights that can then guide treatments using other methods, such as drugs, brain stimulation or psychedelic-assisted therapy (ketamine, psilocybin, LSD and MDMA are all of interest to him and Attia). Psychiatrists grasped its importance quickly because they knew better than anyone how much specificity their field lacked.

• Projections uses patient stories to explain the science.
Deisseroth wrote Projections from about 2017 to 2020, blending clinical stories with circuit science and working with language in ways atypical for a scientist. He received the Lasker Award for optogenetics. Self-harm ranks among the 10 leading causes of death, and higher if overdoses are included, which is why the stakes are so high.

EXAMPLES

• Alexander's mania after 9/11
A patient with no personal or family psychiatric history, sailing in the Mediterranean with his wife on 9/11, became fully manic a couple of weeks after returning home, a case Deisseroth uses to show how stress can unmask latent vulnerability.

• The close call in 2005
Deisseroth's 2005 paper beat several competing groups by months; a scientist had even proposed in 1999 that light might someday control specific cells.

• Mice in exposed spaces
Like people on exposed boats, mice avoid open areas where predators strike; optogenetic manipulation could make mice more or less willing to enter them.

• Sugar water preference
Normal rewards shift mouse choices to roughly 70–30 or 80–20, a benchmark for judging whether dopamine stimulation is

meaningfully rewarding.

- **The ACE2 analogy**
  Attia compares viral targeting of neurons to how SARS-CoV-2 enters cells via the ACE2 receptor: knowing a surface receptor lets you aim a vector.

OTHER RELEVANT

- **Take anhedonia seriously.**
  Loss of pleasure is a core sign of depression even without obvious sadness; it deserves professional evaluation.
- **Recognize early-life trauma's long reach.**
  Trauma can shape mental health for life; early intervention matters. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Look for causal evidence.**
  Correlations in brain imaging are suggestive; optogenetics shows how causality can be tested in animals. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch for mania after stress.**
  Major stressors can trigger first manic episodes even in people without a history. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

164 - Diagnosing, preventing, & treating Alzheimer’s disease, & life lessons from dementia patients

Guest: Amanda Smith
Date: 2021-06-07 · Duration: 2:11:31
URL: https://www.youtube.com/watch?v=hf2ERS7MAws

KEYPOINTS

• Normal aging can be vibrant.
Amanda Smith, a geriatric psychiatrist and director of clinical research at the University of South Florida's memory center in Tampa, grew up around grandparents and their friends who led active lives into their 70s and 80s, which shaped her sense of what normal aging looks like. She came to USF in 1997 as an intern, trained under Eric Pfeiffer, who founded the center in 1980, and took over as principal investigator on many trials when he retired in 2008.

• Dementia is a syndrome; Alzheimer's is one cause.
Dementia means cognitive decline severe enough to impair daily function. In her clinic, roughly 50–60%+ of cases are Alzheimer's, about 20% vascular and about 20% Lewy body, with others such as frontotemporal dementia. Lewy body disease is often less protracted, while Alzheimer's averages 8–10 years from diagnosis and can last much longer.

• Amyloid builds for 10–20 years before symptoms.
Amyloid PET imaging showed plaques accumulate 10, 15 or 20 years before clinical decline. Before 2011, the FDA's definition of Alzheimer's required dementia, leaving no room to study prodromal patients; the 2011 redefinition introduced mild cognitive impairment (MCI) and preclinical Alzheimer's, enabling earlier intervention.

• The amyloid pathway has clear genetic clues.
People with Down syndrome have three copies of chromosome 21, where the amyloid precursor protein gene sits, make about a third more amyloid and almost inevitably develop Alzheimer's if they live long enough. Abnormal cleavage produces amyloid-beta peptides of 40 or 42 amino acids that clump; those fragments could theoretically be removed without consequence.

• APOE informs risk but isn't diagnostic.
E4 raises risk substantially, but you can carry E4 and never develop Alzheimer's, or have E2/E3 and develop it. Smith tells E2/E3 patients they have only about a 10% risk reduction relative to E3/E3 and are 'not off the hook', and tells E3/E4 or E4/E4 patients that risk is modifiable. Attia compares waiting for dementia to waiting for a heart attack: intervene on risk early.

• Behavioral symptoms affect nearly everyone with dementia.
About 90% of patients have a mood or behavioral issue at some point, such as depression, anxiety, agitation or psychosis, and caregivers need support too. Smith also spends a lot of time deprescribing: patients on 15–18 medications, like those still on three blood pressure drugs from age 50 who are now 90 and falling because their pressure is too low.

• The drug pipeline has shifted toward disease modification.
Of about 120 drugs in the pipeline at the time, roughly 29 were in phase 3, and about 80% targeted disease modification rather than symptoms, which Smith calls a watershed made possible by the 2011 redefinition. Developing one drug takes 10–15 years and about $1.3–1.4 billion. Twelve agents targeted cognitive enhancement and 12 neuropsychiatric symptoms.

• Trial design is a major challenge.
Alzheimer's trials traditionally run 18 months, because that's how long it takes for placebo patients to decline measurably; improvement rarely happens, so stability counts as success. Attia contrasts heart disease trials like FOURIER and ODYSSEY (PCSK9 inhibitors added to patients already at low LDL), arguing prevention trials in pre-symptomatic people are where the real wins will be.

• Anti-amyloid antibodies remove plaque.
Aducanumab and similar drugs clearly clear amyloid on PET; one of Smith's patients, after an anti-amyloid trial, failed screening for another trial because her scan had become amyloid negative. The aducanumab trial gave APOE4 carriers lower doses initially because of ARIA (amyloid-related imaging abnormalities) risk, later amended to allow 10 mg/kg. The FDA decision was due June 7, 2021, and families were pressing after nearly 20 years without new treatments.

• Healthy aging should be measured by function.
Smith argues outcomes should reflect what matters to patients and families, like independence and quality of life, not only test scores. She graduated from medical school in 1997, the year donepezil (Aricept) was approved, and has seen almost no new approved drugs since.

EXAMPLES

• Don't wait for the beach condo
Smith and her husband bought an old 1972 beach condo as soon as they could afford it, a lesson from patients: don't postpone the things you want to do until retirement, because cognitive decline can steal that time.

• The amyloid-negative patient
A patient whose amyloid cleared during one antibody trial was turned away from the next because she no longer had amyloid, an illustration of how effectively these drugs remove plaque, even if clinical benefit is debated.

• The over-medicated 90-year-old
Patients prescribed blood pressure drugs decades earlier keep taking them into frail old age, causing falls, a case for routinely reviewing medications.

• Attia's cardiology analogy
Waiting until someone has dementia to treat Alzheimer's is like waiting for multi-vessel coronary disease to start treating cholesterol, or waiting until 10-year risk exceeds 5%, which Attia calls equally nonsensical.

• Twenty years without new drugs
Smith notes families and patient advocates pushed hard for the aducanumab approval because, apart from symptomatic

drugs like donepezil, they had gone almost two decades without any new treatment; she sees that urgency alongside legitimate scientific debate over the drug's clinical benefit.

OTHER RELEVANT

- **Start prevention decades early.**
  Pathology begins 10–20 years before symptoms; address vascular and metabolic risk factors in midlife.
- **Use APOE as a risk tool, not a verdict.**
  Know your status if useful, but nobody is off the hook and nobody is doomed.
- **Review medications with age.**
  Ask whether every drug is still needed, especially blood pressure and sedating medications.
- **Support caregivers.**
  Behavioral symptoms are near-universal; families need help too. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Live now.**
  Don't defer meaningful experiences until later life. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#147-Hussein Yassine, M.D.: Deep dive into the “Alzheimer’s gene” (APOE), brain health, and omega-3s

Guest: Hussein Yassine
Date: 2021-02-01 · Duration: 2:06:30
URL: https://www.youtube.com/watch?v=2tH6P00RhFY

KEYPOINTS

• The brain is an energy-hungry, lipid-rich organ behind a tight barrier.
Yassine, a USC physician-scientist studying APOE and brain lipids, notes the brain is about 2% of body weight but uses roughly 20% of the body's energy. Astrocytes take up glucose and fat to fuel neurons, and microglia, immune cells, clear debris such as amyloid. About 40% of the brain's fatty acids are polyunsaturated—DHA, EPA and the omega-6 arachidonic acid.

• Brain glucose uptake runs through GLUT1, not insulin-driven GLUT4.
Muscle glucose uptake via GLUT4 responds to insulin, exercise and body weight, but the blood-brain barrier relies mainly on GLUT1, which the brain regulates to protect itself: it lowers GLUT1 in chronic high blood sugar such as type 2 diabetes and raises it in prolonged fasting. Yassine says APOE4 makes GLUT1 less effective at the barrier.

• APOE regulates the speed of lipid traffic.
Unlike apoB, a structural protein of lipoproteins, APOE and apoC3 regulate how quickly particles are processed and cleared, including remnants of dietary chylomicrons. APOE4 binds the LRP1 receptor, expressed at the blood-brain barrier, more tightly than E3 or E2. Its multiple roles in the periphery and the brain make it hard to study.

• APOE4 is the ancestral variant, shaped by diet and infection.
E4 is the oldest isoform; Attia cites E3 appearing roughly 50,000 years ago and E2 roughly 10,000 years ago. Yassine's view is that E4 was strongly protective against inflammation when humans faced parasites and sepsis, and thrived on a meat- and fish-rich diet in Africa. Migration to Europe and plant-based farming may have pressured it, favoring E3 and E2.

• The Alzheimer's link was found at Duke around 1988–89.
Allen Roses's group found Alzheimer's patients had substantially more APOE4, though the variant had been known since the 1960s. Two copies raise Alzheimer's risk about 12-fold; one copy raises it about two- to fourfold. E2 is protective, which makes E2/E4 carriers harder to classify.

• APOE4 alone may not be sufficient for disease.
APOE sits on chromosome 19 in a region with about 20–30 co-inherited genes, such as TOMM40 and apoC1, which can modify risk. In one dataset Attia examined, healthy E4 carriers had risk barely above non-carriers, while E4 with diabetes was much higher. Yassine cautions that APOE4 itself promotes insulin resistance with age, so it may help cause the diabetes rather than simply interact with it.

• Americans eat little DHA, but supplement trials are inconsistent.
US intake of DHA averages about 100 mg a day, which may not supply enough to the brain. Yet supplement studies conflict, products vary in production, concentration and quality, and most trials last only three months to a year, too short for brain outcomes.

• REDUCE-IT versus STRENGTH shows how trial design shapes answers.
REDUCE-IT gave 4 grams of pure EPA to high-risk people with high triglycerides, inspired by Japanese data, and cut cardiovascular events, but its mineral-oil placebo drew criticism that the placebo may have raised risk. STRENGTH used a mostly EPA mix with some DHA versus corn oil and found no difference. Possible explanations include placebo, dose, EPA:DHA ratio, or participants without a deficiency; almost 80% had type 2 diabetes.

• Young E4 brains crave DHA; older ones lose access.
When Yassine's team infused labeled DHA into 35-year-old E4 carriers, their brains took up omega-3s avidly. But somewhere between 55 and 70, E4 brains' ability to capture DHA from blood declines—alongside GLUT1 failure and blood-brain-barrier breakdown—suggesting a critical window for prevention.

• DHA failed in mild Alzheimer's, especially for E4 carriers.
In a large 2010 JAMA trial led by Joseph Quinn, 2 grams of DHA for 18 months in patients aged 65–80 with mild Alzheimer's had no overall effect. On reanalysis, E4 carriers showed no response while non-carriers appeared to improve on cognitive scores. DHA builds synapses; EPA acts more as an anti-inflammatory signal.

• Early-life DHA matters most while the brain is growing.
Yassine notes that large studies in the 1990s linked low DHA in infancy—via formula or diet—to poorer school outcomes, prompting the FDA around 2001–2002 to allow DHA in infant formula. Brain growth slows considerably between ages 6 and 12–13, after which lipid pools are relatively stable. What happens between 6 and 60 is elusive: no large study shows that 35-year-olds eating no omega-3s are in a disease state.

EXAMPLES

• The PreventE4 trial
Begun in 2019 and slowed by COVID, it gives high-dose DHA (about 2 grams, based on pilot data that E4 carriers need more) to cognitively healthy 55–70-year-olds; results were expected around 2024–2025. Yassine admits that age range may already be too late, but trials in 35-year-olds would take decades.

• DHA kinetics
Blood levels plateau after three to six weeks of maximal supplementation and clear within three to six weeks of stopping, while DHA stays in neuronal membranes far longer, consistent with the brain's need for stable lipid pools.

• The cPLA2 enzyme
Yassine's lab found cPLA2, which strips fatty acids from membrane phospholipids, hyperactivated in E4 brains with Alzheimer's compared with E4 carriers who died without it.

- **Exercise and amyloid**

A PET imaging study from John Morris's team at Washington University found E4 carriers who exercised had less amyloid plaque than sedentary carriers—epidemiology, not proof.

OTHER RELEVANT

- **Eat fatty fish at least once a week.**

Yassine doesn't think evidence supports supplements yet; epidemiology suggests E4 carriers eating one serving of fatty fish weekly may supply enough omega-3s to the brain.

- **Control blood pressure.**

A Swedish analysis found education and hypertension control protected E4 carriers from dementia; much of E4's risk runs through blood vessels.

- **Exercise throughout life.**

Even modest activity is a modifiable lever on E4 risk. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Know your genotype in context.**

APOE4 raises risk but isn't destiny; neighboring genes, diabetes and lifestyle shape outcomes.

#138-Lauren Rogen & Richard Isaacson MD: Alzheimer’s disease prevention—patient & doctor perspective

Guest: Lauren Miller Rogen & Richard Isaacson
Date: 2020-11-23 · Duration: 2:11:50
URL: https://www.youtube.com/watch?v=AJmf1ZLwCuA

KEYPOINTS

• Lauren's mother developed symptoms at about 52

Lauren Miller Rogen's maternal grandfather had Alzheimer's, with symptoms in his late 50s or early 60s. He was in a nursing home for most of her childhood. At Lauren's college graduation, when she was 22 and her mother was 52, her mother repeated the same story several times. Her mother had been a sharp, vibrant first-grade teacher. By Lauren's wedding, when her mother had just turned 60, she couldn't stand with the family at the ceremony. Lauren's father, who was in denial at first, became an exhausted full-time carer.

• Most Alzheimer's is late-onset, and true genetic early-onset is rare

Isaacson has seen roughly 1,500–2,000 patients. He says he can count on two hands those with deterministic early-onset mutations, such as amyloid precursor protein mutations, which cause disease in the 40s or 50s. These account for well under 1% of cases. Lauren's family didn't fit that pattern. Theirs was late-onset Alzheimer's that had been pushed earlier.

• APOE sets a baseline risk, and the genes around it matter too

E3 is neutral, E2 is protective and E4 raises risk, more so with two copies. Isaacson sees E4 as increasing vascular risk and the build-up of harmful proteins. He says E4 carriers may even have smaller brains at birth. He adds that 'not all APOE4s are created equal': nearby genes such as TOMM40 may change how an E4 behaves. He describes that point as his belief, not a certainty. Every patient in his clinic gets an APOE test.

• Alzheimer's has three stages, and the first is silent

Stage one is preclinical: the disease has started in the brain but there are no symptoms. Isaacson cites a figure of about 46 million Americans in this stage while admitting the exact number is uncertain. Stage two is mild cognitive impairment due to Alzheimer's. Stage three is dementia. He says roughly 12–16% of people with MCI progress to dementia each year, depending on the study. He sees the preclinical stage as the most important target for prevention.

• Women with E4 face a distinct, compounded risk

Alzheimer's disproportionately affects women, and Attia argues that women's longer lifespan doesn't fully explain the gap. Isaacson credits Maria Shriver with pushing him to study it. Lauren's mother was E4/E4. She also had a hysterectomy with removal of her ovaries at about 46, an abrupt surgical menopause. She didn't exercise, and the household ate dessert most nights. Isaacson calls it 'the perfect storm' of genetics, sex, loss of hormones and lifestyle.

• Her uncle was also E4/E4 but became ill about 15 years later

Lauren's uncle, her mother's older brother, also carried two copies of E4. He was a lifelong athlete and an obsessive cyclist, and his symptoms began in his late 60s or early 70s. Because both siblings had the same genotype, Isaacson attributes the gap to sex, the hormone loss and lifestyle, probably in combination.

• Body fat, especially belly fat, matters more for women

Isaacson says that as waist size grows, the brain's memory centre gets smaller. He cites a 39% higher risk of dementia in women with enlarged waist circumference. For women he tracks body-fat percentage and where the fat sits, not weight. He also flags widowhood as a major risk factor for cognitive decline.

• Prevention runs on the ABCs, rechecked every six months

A is anthropometrics: body composition, fat and muscle. B is blood biomarkers: lipids, inflammation, metabolism, nutrition and genetics. C is cognitive function. Repeating them on a schedule shows whether the plan is working.

• Hearing loss may be the largest modifiable risk factor

Isaacson cites the Lancet Commission's 2020 report, which found hearing loss to be the most impactful modifiable risk factor. Attia raises the question of whether it actually causes dementia or simply rises with age alongside it. Isaacson says he doesn't have a perfect answer, but he is considering referring high-risk patients for hearing checks. He blames short 10–15 minute appointments for the lack of screening.

EXAMPLES

• Lauren's supplement and lab protocol

Lauren is APOE3/4. Isaacson's view is that E4 carriers need more omega-3, so she takes at least about 2 g of combined EPA/DHA a day, adjusted to a red-blood-cell omega-3 index of at least 12–14. She also takes purified cocoa flavanols, a specific curcumin formulation and low-dose B vitamins to keep homocysteine down. High homocysteine is linked to brain shrinkage. Isaacson aims for vitamin D around 50 (50–70) ng/mL rather than the 'normal' 30, while noting that the exact optimum isn't known.

• Her cognitive scores went from below average to the top tier

Lauren has done Isaacson's test battery six or seven times. Her memory started 0.87 standard deviations below the mean. It is now about one standard deviation above it, and she is above the 90th percentile on many tests. Isaacson cautions that the results include practice effects and good and bad days. One visit went badly when she had let her habits slip, and she calls it 'a good kick in the behind'.

• Better smell scores turned out to be learning

Loss of smell can be an early sign of Parkinson's, and odour identification is being studied for Alzheimer's. Lauren's score improved, but she points out that she had simply learned to tell apart the coffee and gasoline cards. Isaacson uses it as an example of subjectivity creeping into an 'objective' test.

• Testing a couple's teenage children

Attia describes an E4/E4 husband and wife whose children would each have a 25% chance of being E4/E4, 50% of E3/E4

and 25% of E3/E3. He suggested testing the children in their 20s, and sooner if a boy wanted to play football, given that head trauma and E4 may interact. The family's GP called him, furious about the testing.

• Hilarity for Charity

Lauren and her husband Seth started the charity with a comedy fundraiser in January 2012. It became its own 501(c)(3) in 2017. It focuses on families: paying for care so carers like her father get a break, and support groups organised by age. At 26, she had found little in common with a 56-year-old in a support group.

OTHER RELEVANT

• Know your APOE status, with context

A commercial test can tell you your status. Isaacson's point is that a 3/4 result is not a sentence: it is a reason to act. Lauren's brother panicked over an early 23andMe 'Alzheimer's risk' report before he understood it.

• Treat cannabis as an individual experiment

Isaacson is not against THC or CBD. He thinks the CBD-to-THC ratio matters and prefers edibles to smoking, but he admits this isn't grounded in solid science. He suggests changing one thing at a time and tracking cognition and sleep over three to six months.

• Start prevention early

Isaacson would start omega-3s for E4 carriers 'as early as possible'. Lauren started in her 20s. The underlying point is that Alzheimer's pathology begins decades before symptoms.

• Support the carer, not just the patient

Many carers are with a loved one 24/7 with no relief. Respite care, peer support from people at a similar stage of life, and sharing the load protect the carer's health as well.

#126–Matthew Walker, Ph.D.: Sleep & immune function, chronotypes, hygiene tips, & his book

Guest: Matthew Walker
Date: 2020-08-31 · Duration: 1:41:52
URL: https://www.youtube.com/watch?v=5stcuh065Vk

KEYPOINTS

• The pandemic changed sleep in three ways: how much, when, and dreaming

Walker, a UC Berkeley neuroscientist, cites a sleep-tracking company's data on about 68,000 Americans claiming total sleep rose 20%. He is skeptical of that figure. More cautious peer-reviewed papers in Current Biology found a gain of about 15 minutes. On average, people went to bed about 30 minutes later and woke about 50 minutes later. He expects the data to split into two groups: people sleeping longer and better, and people sleeping less and worse because of job loss or anxiety.

• Lockdown shrank 'social jet lag'

Social jet lag is the gap between weekday and weekend sleep timing. Walker says sleeping until 10 or 11 a.m. on weekends and then dragging the clock back two or three hours on Sunday night is 'like flying back and forth from San Francisco to New York every weekend.' Without commutes and school runs, sleep times became more uniform across the week. He calls it the 'revenge of the night owls,' who could finally sleep in line with their chronotype.

• There are two likely reasons people dreamed more

First, sleeping in extends time in the late-night window where REM sleep is concentrated, so people get more REM cycles and vivid dreams. Second, Walker says REM sleep provides 'overnight therapy.' It isn't time that heals all wounds but 'time during REM sleep.' Because sleep responds to the day before, more emotionally difficult days can produce more REM. That may explain why Peter's dreams intensified even though his schedule didn't change.

• Alcohol can create an anxiety–REM spiral

Walker says alcohol sedates rather than producing natural sleep, fragments sleep by stimulating fight-or-flight activity, and suppresses REM in the later hours. If wine numbs anxiety but removes the REM that processes emotions, the next day starts more anxious, which invites another glass. He stresses he isn't judging. Both men agree responses vary: fast metabolizers may clear an early drink before bedtime, while for others even a glass with a late lunch could crush their REM.

• Short sleep weakens immune defenses and vaccine response

Walker cites a study finding that people sleeping under seven hours were almost three times as likely to be infected with a rhinovirus. In a prospective study of more than 70,000 women, those sleeping five hours or less were 70% more likely to develop pneumonia. Too little sleep in the week before a flu shot led to less than half the normal antibody response. Antibodies remained low 20–30 days later, so the response wasn't just delayed. He says whether this applies to COVID vaccines is unknown and should be tracked.

• Deep sleep depends on time awake; REM depends more on circadian timing

Deep non-REM sleep, front-loaded in the first cycles, is driven mainly by adenosine sleep pressure. Higher cortisol typically means less deep sleep, and melatonin plays a smaller role. REM depends less on how long you've been awake and more on the circadian clock. Walker admits 'we have no idea why' sleep is organized with deep sleep early and REM late.

• Naps are a double-edged sword

In Walker's studies, naps as short as 17 minutes improve learning and memory, and naps have shown cardiovascular benefits too. But naps release sleep pressure. His rule: if you struggle with sleep at night, avoid naps; if you sleep well, regular naps are fine. Some hunter-gatherer groups sleep six to six and a half hours at night plus a summer afternoon siesta. He calls this biphasic pattern different from the historical 'first and second sleep,' which he doesn't think reflects how our physiology is designed.

• Chronotype is largely genetic and shifts with age

About 25–30% of people are morning types, 25–30% are evening types, and the rest are in between. Data from 23andMe and UK Biobank point to about nine contributing genes, mostly clock genes. Teenagers' rhythms shift later, so a 15-year-old who can't fall asleep at 10:30 isn't at fault. Older adults shift earlier, hence Florida's early-bird specials. A validated morningness–eveningness questionnaire works without genetic testing.

• Walker publicly corrected errors in Why We Sleep

Examples he gives: a study described as 'over half a million' people actually analyzed 474,684. Another said to involve over 4,000 people analyzed 2,282 and measured 'cardiac events,' including angina requiring bypass, not 'cardiac arrests.' He also wrote that short sleep doubles cancer risk; he now says it is linked to doubling for specific cancers such as ovarian or lung, and calls the original phrasing 'poor judgment.' The figure of 30–40% of depressed patients responding to sleep deprivation was 45% in a later meta-analysis of prospective studies. Corrections went to a second edition, plus a blog post of more than 8,000 words.

EXAMPLES

• Peter's wearable data after alcohol

Peter says that whenever he reaches two drinks, heart rate variability is 'crushed,' resting heart rate rises 10 to 25 beats, respiratory rate rises two breaths a minute and core temperature rises half a degree. He admits drinking more during the pandemic. One drink around 6 p.m. doesn't seem to affect him.

• Long sleep and mortality, reinterpreted

Walker's book argued that long sleepers die sooner because undetected illness drives extra sleep. He has updated that view: poor-quality sleep, which itself predicts mortality, leads people to stay in bed longer, so it can look like 'long sleep'.

• The 'WHO vs IARC' correction

Critics said it was the IARC, not the WHO, that classified night shift work as a probable carcinogen in 2007, reaffirmed in 2019. Walker notes the IARC is part of the WHO, but says he should have named both.

• Night terrors in children

Night terrors usually arise from deep, dreamless non-REM sleep, so people recall little. Children have more intense deep sleep, which raises the odds. Walker stresses he isn't a pediatric sleep specialist or an MD.

OTHER RELEVANT

- **Build a wind-down routine**

  Sleep is 'not a light switch' but more like landing a plane. Give yourself 15–30 minutes of light stretching or meditation, with phones away. Keep the room cool, get daylight in the first half of the day, and if you've been awake 20 minutes, get up and return only when sleepy.

- **Consider CBT-I sleep restriction for insomnia**

  A six-hour window of solid sleep beats eight hours in bed with two spent tossing and turning. Walker notes he is a scientist, not a clinician, and suggests seeing a doctor if problems persist.

- **Use your chronotype, don't fight it**

  Knowing you are an owl explains the struggle of a 7:15 start on your fourth coffee. It helps couples with mismatched schedules and removes self-blame: 'it's not your fault.'

#49–Matt Walker, Ph.D., on Sleep (Part 3 of 3): Effects of poor sleep on metabolism & performance...

Guest: Matthew Walker
Date: 2020-01-09 · Duration: 2:01:06
URL: https://www.youtube.com/watch?v=K5utMfG1rSg

KEYPOINTS

• Short sleep halves muscle glucose uptake in a clamp study

Attia recalls a small but tightly controlled University of Chicago study. As he remembers it, healthy subjects slept four hours a night for about two weeks and then repeated a euglycemic clamp, the gold-standard test of insulin sensitivity. Their ability to move glucose into muscle fell by about 50%. Walker notes the finding has been replicated with four, five or six hours a night for one week.

• Attia now credits residency sleep loss for his own metabolic decline

Looking back, Attia believes sleep deprivation, not just cafeteria food, drove his weight gain, insulin resistance and hypogonadism at the end of residency. He says his testosterone was about 200–220 ng/dL, against a cutoff of about 350 for two standard deviations below the mean, even though he kept exercising hard throughout.

• One week of six-hour nights changed the activity of 711 genes

Walker describes a PNAS study in which healthy adults were limited to six hours a night for a week and compared with themselves on eight hours. Blood samples showed 711 genes with altered activity, roughly 3% of the genome. About half went up, including genes linked to tumor promotion, chronic inflammation, stress and cardiovascular disease. The other half went down, including many immune genes. Walker argues six hours is an everyday amount of sleep, not an extreme lab condition.

• Lost sleep can't be banked back, but sleeping better still helps

Walker says sleep is not like a bank: damage done while under-slept doesn't seem reversible, so weekend catch-up doesn't erase it. But improving sleep from now on is still worthwhile. Attia compares it to quitting smoking, where risk falls steadily the longer someone stays off cigarettes.

• Sleep loss pushes appetite hormones in the wrong direction

After a week of four to six hours a night, leptin (the fullness signal) falls and ghrelin (the hunger signal) rises. Walker says people sleeping six hours on weeknights eat about 300 extra calories a day. He estimates that adds up to about 70,000 calories a year, while acknowledging the arithmetic is complicated by compensation.

• Six hours of sleep cuts time to physical exhaustion by about 30%

In healthy, active people restricted to six hours, Walker cites roughly a 30% drop in time to exhaustion. Force, aerobic output and motivation to train all fall too. His illustration: someone trained to hold out for a 10K could fail at about 7K. Attia raises the caveat that sleep may partly work indirectly, through better food choices and more activity.

• Caffeine has a quarter-life of about 12 hours

Caffeine's half-life is about six hours, so a midday coffee leaves about a quarter of the dose in the brain at midnight. A 200 mg dose in the evening reduced deep sleep by about 20% in Walker's studies, even in people who said they slept fine. He says matching that loss through aging would take 20 to 30 years. Genetic differences in caffeine metabolism exist, though Attia finds the link to how people feel imperfect.

• Alcohol sedates, fragments sleep and suppresses REM

Walker separates sedation from sleep: a nightcap knocks you unconscious faster but doesn't help you fall asleep naturally. Alcohol also causes many brief awakenings you don't remember and is a strong REM blocker, leaving people unrefreshed and reaching for caffeine. Attia adds that ethanol inhibits antidiuretic hormone, causing extra night-time urination. Its warming effect works against the 2–3°F drop in core temperature needed to start sleep.

• THC helps you fall asleep faster but costs REM and causes dependence

Walker says acute THC shortens the time it takes to fall asleep, but that is its only benefit. It robustly blocks REM sleep, tolerance builds, and stopping brings a harsh rebound insomnia that often drives people back to it. For the developing teenage brain, both men consider the answer clearly no.

• CBD looks more promising, but the evidence is thin

The early data suggest CBD may help people fall asleep faster. One small study even hinted at more deep sleep, which Walker refuses to rely on. He suspects a sweet-spot dose and two possible mechanisms: lowering core body temperature and reducing anxiety, where he thinks CBD's evidence is strongest. He says the research is hard to fund.

• Sleep and mental health run both ways

Walker sees the causes of insomnia shifting from biological to psychological, and says the rise in anxiety has moved in lockstep with the rise in insomnia. He says the two are probably significantly interrelated, but stops short of claiming more.

EXAMPLES

• CPAP users delayed Alzheimer's by about 10 years

In a group of middle-aged and older adults with sleep apnea, about half used CPAP consistently. Those who did staved off Alzheimer's disease by about 10 years. Walker calls it a causal demonstration, though Attia notes that people who stick with CPAP may also stick with other healthy habits.

• Five ways short-sleeping employees underperform

Walker cites work by his group and Christopher Barnes on employees sleeping six hours or less. They choose easier tasks such as email, produce fewer creative solutions, coast on teammates' work, and behave less ethically, for example falsifying data or expense claims. Employees also rated leaders as less charismatic after the leaders' short nights, without knowing how much they had slept.

• Attia's ring data on alcohol

Attia notes that he invests in and advises Oura. On his own data, one drink four to five hours before bed seems harmless. More than that, or one drink closer to bed, raises his resting heart rate by 6–8 beats, cuts heart-rate variability by about 20%, adds 1–2 breaths per minute and raises temperature by 0.3–0.6°F. He says patients who wear the ring report the same pattern.

- **An MDMA-assisted therapy case fixed a patient's insomnia**

  Attia describes a patient who had done everything: temperature, light, no alcohol or caffeine, an hour of daily meditation. Even 50 mg of Thorazine for rumination helped only intermittently. Clinical, therapist-guided MDMA therapy for underlying trauma resolved his sleep for months. Attia calls it an outlier, not a recommendation.

- **Using deep-sleep waves to support memory**

  Walker describes a head-worn device from one of his startups that reads deep-sleep brain waves and adds electrical stimulation in time with them, 'like a choir' backing a flagging lead singer. The aim is to boost deep sleep, learning and memory in older adults and people with dementia.

OTHER RELEVANT

- **Set a caffeine curfew**

  Given the 12-hour quarter-life, cut off caffeine well before afternoon. Walker also asks why you need caffeine before midday, if it's to cover poor sleep.

- **Treat snoring as a medical issue**

  Walker urges anyone who snores to get a sleep test and treat apnea, given its links to cognitive decline.

- **Use your own data to set an alcohol limit**

  Attia sees most people's limit somewhere between zero and two drinks, with timing mattering as much as quantity.

- **Keep the bedroom cool**

  Since sleep onset needs a drop in core temperature, a cold room helps. Alcohol, a hot room or a big late meal work against it; Attia says late binges of poor-quality carbohydrates hit his sleep much like two drinks.

#47–Matt Walker, Ph.D. on Sleep (Part 1 of 3): Dangers of poor sleep, dementia risk, mental health..

Guest: Matthew Walker
Date: 2020-01-09 · Duration: 1:43:19
URL: https://www.youtube.com/watch?v=VkX3nYpMr2g

KEYPOINTS

• Walker found his field by recording dementia patients asleep, not awake

As a PhD student in London, Walker spent two years failing to tell dementia types apart from waking brainwaves. Reading journals one Sunday, he noticed that some dementias attack the brain's sleep-generating centres while others spare them until late in the disease. He set up a sleep lab, got results, and began asking whether disrupted sleep is a symptom, a predictor or a cause of Alzheimer's. He now believes the evidence points to a causal role.

• Deep sleep powers the brain's 'sewage system'

The glymphatic system is a cleaning network run by glial cells. In deep sleep, Walker says, those cells shrink dramatically, giving cerebrospinal fluid room to flush out the day's metabolic waste. He compares it to Manhattan's buildings shrinking so a flood can wash the streets. That waste includes beta-amyloid, one of the two core proteins in Alzheimer's, so skimping on sleep lets it build up 'like compound interest on a loan'.

• The evidence chain runs from brain scans to spinal taps

In people in their 70s and 80s, PET scans show visibly more amyloid in those sleeping seven hours or less than in those sleeping more. That is associational, he notes. Rats deprived specifically of deep sleep, or with fragmented sleep, show immediate amyloid build-up. In humans, cerebrospinal fluid taken after one night of selectively disrupted deep sleep shows significant rises in amyloid and tau. That last finding is what led Walker to say publicly that sleep is a critical part of preventing Alzheimer's.

• Sleep has four pillars

Walker proposes regularity (avoiding 'social jet lag' from shifting bedtimes), continuity (unfragmented sleep), quantity (total hours and hours in each stage) and quality, meaning the electrical signature of sleep. He stresses that eight hours in bed doesn't guarantee eight hours of good-quality deep sleep, especially with caffeine or alcohol. He expects different sleep features to predict different subtypes of Alzheimer's.

• Non-REM and REM battle in 90-minute cycles

Non-REM sleep has four stages; stages 3 and 4 are the deep, restorative ones. REM is dream sleep, with rapid side-to-side eye movements. Awake, brainwaves are fast, at about 50–60 cycles per second, and small, like a stadium crowd chattering before the game. With eyes closed, the visual cortex at the back of the brain slows to an alpha rhythm of about 10 cycles per second. The two types of sleep alternate in cycles of about 90 minutes all night.

• Deep sleep dominates early in the night, REM late

Walker likens the night to a buffet. From about 9 p.m. to 3 a.m. the brain preferentially takes deep non-REM sleep; after about 3 a.m., REM and stage 2. So sleeping 9 p.m. to 3 a.m. preserves deep sleep but cuts most REM, while very late sleepers get the reverse. Attia sees this on his ring: more deep sleep after early nights back in California, more REM in New York.

• Memory needs sleep both after and before learning

Deep non-REM sleep after learning 'hits the save button' on new memories, so getting the first half of the night protects them. Stage 2 sleep, rich in brief bursts of activity called sleep spindles, peaks in the last two hours of the night and prepares the brain to take in new memories the next day. Cutting the morning short reduces that capacity.

• Lack of REM sleep hits mental health hardest

Walker calls sleep 'emotional first aid'. He links REM loss most strongly to depression, anxiety and suicidality. In young teenagers, he says, insufficient sleep is one of the strongest predictors of suicidal thoughts, attempts and deaths. Sleep problems and anxiety feed each other, but a four-year-old's meltdown after one bad night suggests sleep can drive the problem.

• Drowsy driving can be deadlier than drunk driving

Microsleeps, brief lapses when the eyelids partly close, become common on six or seven hours of sleep. Walker says drowsy driving causes more crashes than drugs and alcohol combined. Drunk drivers usually react, but too late. During a microsleep there's no braking or steering at all, just 'a two-ton missile' at 65 mph.

EXAMPLES

• A family killed after someone's 5.5-hour nights

A reader emailed Walker that his wife and 18-month-old daughter had died in a head-on crash. The other driver had averaged about five and a half hours of sleep for two months and had a microsleep at 60 mph. The man was left to raise his four-year-old son alone.

• Leaders who boasted about short sleep

Walker cites two heads of state who bragged about sleeping four to five hours, then developed Alzheimer's; he names Margaret Thatcher. He doesn't think it's coincidental, while noting that public figures face pressure to boast this way.

• Guinness stopped certifying sleep-deprivation records

Guinness allowed sleep-deprivation records, the last real attempt reaching about 24 days, until links to mental illness, cancer, heart disease and suicide led it to stop. Yet it certified Felix Baumgartner's supersonic skydive from the edge of space. Attia jokes that you can jump off Niagara Falls 12 times but not skip sleep.

• Rats die of sleep loss as fast as starvation

Rats totally deprived of sleep died as quickly as, or about 20% quicker than, rats deprived of food. In humans, fatal familial insomnia, an inherited prion-gene disorder, starts like ordinary insomnia and progresses to death in about 18–24 months.

• Sleep loss on a societal scale

Walker says nature took about 3.6 million years to build an eight-hour night, and in roughly 70 years societies have cut 20–25% of it. Meanwhile, sleep is stigmatised as laziness once children grow up.

OTHER RELEVANT

• Protect sleep as Alzheimer's prevention

With no strong drugs available, Walker considers sleep one of the best preventive steps backed by current science. Attia adds that almost all his patients rank preserving cognition as their top priority.

• Shift gradually before flying east

Before an eight-hour shift to London, Walker starts waking about 10 minutes earlier each day for about five days. The conversation also stresses that both deep and REM sleep matter, with REM described as arguably even more important for mortality risk.

• Never drive drowsy

If you are surviving on six or seven hours, assume microsleeps are possible and treat drowsiness behind the wheel as seriously as alcohol.

#48–Matt Walker, Ph.D., on Sleep (Part 2 of 3): Heart disease, cancer, causes of sleep disruption...

Guest: Matthew Walker
Date: 2020-01-09 · Duration: 2:04:32
URL: https://www.youtube.com/watch?v=pv7i22DHiVE

KEYPOINTS

• Daylight saving time shows how much one hour of sleep matters to the heart.

Walker describes the twice-yearly time change, affecting about 1.6 billion people in 70 countries, as a global experiment. He says the spring shift, which costs an hour of sleep, is followed by a 24% relative rise in heart attacks the next day, and the autumn shift by a 21% drop. The effect fades over about three to four days. Attia points out that this happens despite the mood boost of spring, which should push the other way.

• Short sleepers developed more coronary artery calcification.

Walker cites a five-year study of healthy middle-aged adults with no calcium in their coronary arteries at the start. Those sleeping five hours or less had a two- to three-fold higher risk of developing it. He stresses that the study shows association, not causation, but notes it adjusted for exercise, BMI, neck circumference, smoking and snoring history to rule out sleep apnea.

• Walker sees fight-or-flight overdrive as the common thread behind sleep loss's harms.

Cutting sleep to about five hours for a single night raises sympathetic tone, blood pressure, heart rate and cortisol, and blunts growth hormone. Walker compares chronic short sleep to revving a car engine in neutral, his example being a Mezger Porsche GT3 engine, until the gaskets blow. He says he is writing a paper arguing that this autonomic imbalance underlies most of the damage from insufficient sleep.

• Dieting while sleep-deprived means losing muscle instead of fat.

Walker cites a study in which dieters sleeping six hours or less lost about 70% of their weight from lean mass rather than fat. Attia links this to worse fuel partitioning: higher cortisol, catecholamines and insulin, lower testosterone, and a likely shift toward burning glycogen rather than fat. Attia also says sleep is his own single best tool for eating well.

• Short sleep impairs fertility in both men and women.

According to Walker, men sleeping five to six hours have testosterone levels like men ten years older, and those sleeping six hours or less have fewer, more misshapen sperm with more chromosomal abnormalities. Men sleeping five hours have smaller testicles, though he notes this is associational. Women sleeping five to six hours have about 20% lower FSH and roughly 30% more abnormal menstrual cycles.

• The body has no way to bank sleep.

Walker argues that evolution gave us fat cells to store energy for famine but no equivalent for sleep, because humans are the only species that routinely deprive themselves of it. Sleeping in on weekends, which he calls social jet lag, doesn't repay a weekday debt. Shifting your schedule by about three hours each weekend is, in his comparison, like flying from San Francisco to New York and back every week.

• One short night sharply weakens anti-cancer immune cells.

Walker cites a UCLA study in which four hours of sleep for one night cut natural killer cell activity by about 70%. He notes the WHO classifies night shift work as a probable carcinogen. Attia, who trained in an immunotherapy lab, describes how the adaptive immune system constantly suppresses cancer cells. Walker adds worsening sleep as another reason cancer rises with age.

• Teenagers' late body clocks clash with early school start times.

Walker says teens need 9–10 hours of sleep because the brain keeps developing until about 25, yet only about 11% get enough and the average is around 7 hours. Meanwhile 72% of parents believe their teen sleeps enough. A teenager's circadian rhythm naturally shifts later, so a 7:30 a.m. start, with buses at 5:30, works against their biology.

• Screens at night delay and suppress melatonin.

Walker cites studies in which an hour of iPad reading before bed cut melatonin release by about 50% and delayed its peak by about three hours. It also reduced REM sleep and left people feeling less rested, with effects lasting two to three days. He says television affects melatonin less, but watching in bed teaches the brain to treat the bedroom as a place for being awake.

• Walker says sleeping pills sedate you rather than produce real sleep.

He describes Ambien-type sedative-hypnotics as knocking out the cortex, producing shallower and electrically different deep sleep. He cites associations with higher mortality and higher cancer risk, while noting causation isn't proven. He finds the cancer link especially telling, since real sleep should lower that risk. He favors CBT-I, which works but takes effort.

EXAMPLES

• Teton County, Wyoming

Moving school start from 7:35 to 8:55 a.m. gave students about an extra hour of sleep and, Walker says, cut car crashes among 16- to 18-year-olds by about 70% the following year. He compares this with anti-lock brakes, which cut accident rates by 20–25%.

• Attia's nap in Patterson Park

During residency, with call every third night, Attia stayed awake from Monday morning to Wednesday evening after volunteering for an extra ER shift. He kept stalling his car at stoplights, wisely avoided the freeway, then unwisely napped in the park with a one-hour alarm. He woke at 2 a.m. with rat bites on his arms.

• Ambien as a 'chemical baseball bat'

On a weekly 26-hour round trip from San Francisco to Atlanta during his McKinsey years, Attia used Ambien on the red-eye. He later found emails and phone calls he didn't remember. Kirk Parsley told him that unconsciousness isn't sleep, any more than being knocked out by a bat.

• Judges after the spring time change

Walker says federal judges hand down harsher sentences on the Monday after the spring shift and more lenient ones after the autumn shift. Car accidents and suicide attempts show the same spring pattern.

OTHER RELEVANT

• If you struggle to sleep at night, skip naps.

Walker compares a nap to a pressure valve releasing the adenosine-driven sleepiness you need at bedtime. For people who sleep well and can nap regularly, naps are fine and benefit learning and immune and cardiovascular health. Insomniacs should stay awake and build up sleep pressure.

• Weigh school start times when choosing a school.

Walker would factor start time into any school decision. He says later starts are linked to better grades, less truancy, fewer behavioral and psychiatric problems, fewer dropouts and fewer car crashes.

• Keep the bed for sleep and intimacy, and dim the lights after sundown.

Avoiding screens and bright light in the evening protects melatonin timing, which Walker says matters for adults as well as children.

• Look at cortisol and nighttime glucose.

Attia's working model is that adenosine has to build while cortisol falls before melatonin can start sleep. From his continuous glucose monitor he sees a strong link between high nighttime glucose and poor sleep, which he suspects reflects cortisol. He offers this as a personal hypothesis, not established fact.

#38–Francisco Gonzalez-Lima, Ph.D.: Alzheimer’s disease & the vascular hypothesis

Guest: Francisco Gonzalez-Lima
Date: 2020-01-07 · Duration: 2:32:08
URL: https://www.youtube.com/watch?v=zCjMFuFv9Gg

KEYPOINTS

• Late-onset Alzheimer's as a neuronal energy crisis

Gonzalez-Lima, a UT Austin neuroscientist working in pharmacology, toxicology and psychology for about 27 years, was introduced to the field by Jack de la Torre about 25 years earlier. Their vascular hypothesis holds that the core problem in late-onset Alzheimer's is a progressive shortfall of energy to neurons, driven by reduced blood flow. In this view, plaques and tangles are not the primary cause. Attia presents it as a credible alternative to the dominant amyloid view, not a settled answer.

• Alzheimer's original patient was not typical

Alois Alzheimer's 1907 report described a woman of about 51 who died in 1906 after years of dementia. Attia notes she likely had a rare early-onset genetic form, such as a PSEN1 or PSEN2 mutation, which accounts for under 1% of cases, though this has never been confirmed. Meanwhile Oskar Fischer's group in Prague studied 'senile dementia' in people in their 60s–80s, the common late-onset form.

• Blood flow to the brain falls with age

Gonzalez-Lima says brain blood supply drops by about 20% between ages 22 and 60, roughly half a percent a year. Arterial stiffening and atherosclerosis in the large arteries, such as the carotids, show up as rising blood pressure. Guidelines now aim for under 120/80, compared with about 135/90 that used to be accepted. He calls atherosclerosis a major risk factor.

• Function matters more than structure

Structural scans show anatomy. Functional imaging such as FDG-PET, which grew out of earlier metabolic-mapping work, shows how hard brain regions are working. Attia says many patients don't understand the difference because doctors rarely explain it. Much of Gonzalez-Lima's career has been spent mapping brain metabolism and function.

• The brain is uniquely vulnerable to energy shortfalls

At about 2% of body weight, the brain uses about 20% of the body's energy. Its circuits are highly convergent and redundant, which hides early losses until function visibly fails.

• Cytochrome oxidase is reduced in Alzheimer's brains

His 2001 study used brains collected within about three hours of death, a very short post-mortem interval, through the Sun City Health Center in Arizona. It found reduced activity of cytochrome oxidase (complex IV), the final, rate-limiting enzyme of the electron transport chain that reduces oxygen to water and drives ATP production. Regions connected to damaged areas also declined, a functional change that standard pathology misses.

• Partial inhibition of complex IV mimics hypoperfusion

Inhibiting cytochrome oxidase by more than about 40% kills an organism, which is how cyanide works. His lab used very low doses to create 'functional hypoperfusion' without killing animals. Attia notes duration matters as well as degree: 40% for seconds differs from 40% for minutes.

• Methylene blue can boost mitochondrial respiration at low doses

Paul Ehrlich studied it in the 1880s and developed the 'magic bullet' idea, because it concentrates in nerve tissue. The first synthetic medicines, including chlorpromazine around 1950, derived from it. At low doses it shuttles electrons and helps respiration. At high doses it becomes a pro-oxidant, a 'hormetic', two-phase dose response. It treats methaemoglobinaemia at low doses but can cause it at high ones. It was once used for bladder infections, and its half-life is about 12 hours.

• Near-infrared light also targets cytochrome oxidase

Cytochrome oxidase absorbs near-infrared photons. His group delivers 1,064 nm laser light through the forehead, a wavelength that penetrates deeper but is rarely studied in biochemistry. He says this improves mitochondrial respiration in the targeted brain tissue. Studies are ongoing with NIH BRAIN Initiative and aging-related funding.

EXAMPLES

• The LMTM trial

A Scottish company tested LMTM, a methylene-blue derivative, in early Alzheimer's. The primary result failed. The benefit was seen in a subset of about 15% who took it alone, without standard Alzheimer's drugs, and the lowest dose worked best. Attia notes the problem with parsing subsets after the fact. The guests note that a low dose working best would fit methylene blue's two-phase dose response, though the trial wasn't designed to show that.

• Stroke rescue in animals

Infusing low-dose methylene blue (about 1 mg/kg) protected animal brains from much of the damage after stroke, as shown with longitudinal fMRI. He argues ambulances and emergency rooms should consider it for any acute insult to brain energy supply, and a trial for traumatic injury is plausible. These are animal and early human data.

• Don't buy lab-grade methylene blue

Chemical-supply grade can contain about 15% impurities, and industrial dye grades more. Gonzalez-Lima warns against giving it to animals or people. Because it predates the FDA, it was grandfathered in and has never gone through modern approval.

• Head trauma

Blows to the head cause rapid twisting and bending forces, which links head injury to later Alzheimer's and Parkinson's risk. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• A classroom demonstration

Methylene blue turns water blue, then clear when a reducing agent like vitamin C is added, a visible demonstration of its redox cycling.

OTHER RELEVANT

- **Protect your vasculature to protect your brain**

  Blood pressure under 120/80 and preventing atherosclerosis are among the most plausible ways to protect brain energy supply over decades.

- **Use metabolic flexibility**

  After 12–14 hours without food, the body starts producing ketones, an alternative fuel for the brain. Both guests see this as relevant to insulin resistance, which impairs glucose delivery.

- **Everyone with a brain is at risk**

  Gonzalez-Lima suggests preventive measures for everyone rather than only high-risk groups. Attia agrees prevention should start early. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Treat methylene blue as experimental**

  Despite the long history, clinical evidence for Alzheimer's is preliminary, dose-dependent and easy to misuse. Only use pharmaceutical-grade methylene blue, under medical supervision.

#18 – Richard Isaacson, M.D.: Alzheimer’s prevention

Guest: Richard Isaacson
Date: 2020-01-01 · Duration: 2:24:31
URL: https://www.youtube.com/watch?v=Vq_hAXQsB78

KEYPOINTS

• A clinical diagnosis of Alzheimer's is often wrong

Isaacson, who directs the Alzheimer's Prevention Clinic at Weill Cornell, explains that Alzheimer's has traditionally been diagnosed clinically: progressive short-term memory loss plus other changes that impair daily activities. It accounts for about 60–70% of dementia. Ordinary cognitive aging, such as misplacing keys or a word on the tip of the tongue, doesn't disrupt independent living. He cites a study in which 40% of patients clinically diagnosed with Alzheimer's, and receiving anti-amyloid drugs, had no amyloid in the brain.

• 'A-G-E': age, genetics, environment

Isaacson's mnemonic captures the constant tug of war between genes and environment. Age is the top risk factor. Genes such as APOE4, along with others, can make the disease unavoidable for some people despite doing everything right. For others, changing their environment changes how their genes play out.

• About one in three cases may be preventable, and delay matters too

Based on conservative population risk models, Isaacson says one in three Alzheimer's cases may be preventable. For the rest, the goal is delay of two, five, seven or 10 years, long enough that many people die of something else first. Attia frames it as optionality: getting the disease at 78 instead of 69 buys nine years in which much can change.

• APOE4 risk estimates have been revised down

Everyone inherits two APOE copies, making six combinations. About 55–60% of people are 3/3, the neutral baseline. Isaacson has seen only one or two 2/2 patients, a genotype carrying about 20% lower risk. 3/4 covers about 20–25% of the population, with risk once quoted as three to four times higher, now perhaps two. For 4/4, early-2010s literature said about 25-fold. Recent papers say eight to 10-fold, which Isaacson believes overestimates the risk, and Attia unofficially guesses four to six times. Two copies don't guarantee the disease.

• Women may be in the 'express lane' because of menopause

Attia doubts that women's higher risk is explained only by living longer. Isaacson believes Alzheimer's is fundamentally mitochondrial, with amyloid as the garbage that accumulates. He thinks the bioenergetic shifts of the perimenopause transition 'fast-forward' women toward the disease. His group studies women around menopause and, with a small grant, men aged 40–65 (15 a year for four years).

• Many roads lead to Alzheimer's

Isaacson describes several routes into the disease. Diabetes 'will put you in the fast lane', and hormonal change and mitochondrial dysfunction are others. MTHFR, a gene in folate metabolism, is another road. He says it matters mainly for people with high homocysteine.

• The 'ABCs' of prevention

In his precision-medicine programme, patients are stratified by APOE and MTHFR genes, then by A: anthropometrics such as body fat, lean mass and visceral fat (not BMI), B: blood biomarkers and C: cognitive testing. Attia praises Isaacson for running deeper lipid panels, including apoB, LDL particle number and particle subtypes, than most cardiologists.

• Pro-statin, but not one-size-fits-all

Isaacson thinks different statins work differently in different people, that there is a sex difference, and that low dose is better when in doubt. He cites atorvastatin slowing hippocampal shrinkage in men. He urges real caution in APOE4 carriers, especially 4/4, and has seen men switched to a high-potency statin whose cholesterol numbers looked great but whose memory got worse.

• Exercise has the strongest evidence for risk reduction

When Attia's team checked about 200 references in a review by Dale Bredesen, they couldn't verify about a third. One resveratrol citation had nothing to do with Alzheimer's. Starting again from first principles, the only intervention with top-level evidence was exercise. Isaacson adds it is the only thing shown to reduce or slow amyloid build-up in people who already have it.

EXAMPLES

• B vitamins work only alongside omega-3s

Isaacson cites evidence that B vitamins can slow brain shrinkage and improve memory in people with high homocysteine, but only if omega-3 levels are good. If standard folic acid and cyanocobalamin don't lower homocysteine, he switches to methylated forms of folate and B12. He names a brand Attia introduced him to, a combined lozenge.

• Theracurmin and amyloid

Regular curcumin trials failed partly because it wasn't absorbed into the blood. In a study by Gary Small and colleagues, a nanoparticle form called Theracurmin led to less amyloid on PET scans after 18 months. Isaacson says he sells nothing and doesn't think everyone needs it. He considers it for some higher-risk patients, such as families with both APOE4 and TNF-alpha gene variants.

• Uncle Bob

Isaacson's uncle, who introduced his parents and pulled him from a pool when he was three, was diagnosed with Alzheimer's when Isaacson was in high school. Seeing 'the life of the party' decline and the toll on his children set Isaacson's career path.

• A 0.4% drug success rate

Attia urges donors to fund prevention: 99.6% of Alzheimer's drugs fail. He says $100,000 barely buys five animals for a drug study but goes much further in a prevention clinic.

• Real intensity versus elliptical TV time

Isaacson averages about 155 beats per minute in spin classes, peaking around 180, but admits lifting weights only about once a week. Attia says he should be lifting two or three times a week. Isaacson thinks muscle mass may matter more for men's

brain health and body fat for women's.

OTHER RELEVANT

- **Learn about brain health early**
  Isaacson's first 'no-regret' step is education; his free public site is alzu.org, with a free accredited course for clinicians. Changes made at 30, 40 or 50 add up.
- **Know your numbers**
  Isaacson's second step is to track blood pressure, resting pulse, body fat, weight, cholesterol, blood sugar, sleep and exercise output; he calls himself a data junkie. Both men use an Oura ring, with an investment in and advisory role with Oura disclosed on air.
- **Exercise hard and mix it up**
  Most evidence is for aerobic exercise. Include interval training, without overdoing it, and strength work, since muscle and body composition both appear to matter.