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How Running Give Us a High Expectations to Overcome Neurological Disorders

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ABSTRACT

Whether chasing down dinner, pushing a stroller up a hill or running errands for a neighbor, we can take joy in the effort. And the more physically active you are, the more rewarding these experiences become. One of the ways that regular exercise changes your brain is by increasing the density of binding sites for endocannabinoids. Spring-like leg behavior is a general feature of mammalian bouncing gaits, such as running and hopping. Although increases in step frequency at a given running speed are known to increase the stiffness of the leg spring (kleg) in non-amputees, little is known about stiffness regulation in unilateral transfemoral amputees. Thus Consequently, the unilateral transfemoral amputees attained the desired step frequency in the unaffected limb, but were unable to match the three highest step frequencies using their affected limbs.

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The runner's high is often held up as a lure for reluctant exercisers, described in terms that can strain credulity. In 1855, Scottish philosopher Alexander Bain described the pleasure of a fast walk or run as "a species of mechanical intoxication" that produces an exhilaration akin to the ancient ecstatic worship of Bacchus, the Roman god of wine. Trail runner and triathlete Scott Dunlap sums up his running high this way: "I would equate it to two Red Bulls and vodka, three ibuprofen, plus a $50 winning Lotto ticket in your pocket." Others liken it to a spiritual experience. In The Runner's High, Dan Sturn describes tears streaming down his face during mile seven of his morning jog. "I flew closer and closer to the place mystics and shamans and acidheads all try to describe. Each moment became precious. I felt simultaneously all alone and completely connected." But this side effect is not exclusive to running. Bliss can be found in any sustained physical activity, whether that's hiking, swimming, cycling, dancing or yoga. However, the high emerges only after a significant effort. It seems to be the brain's way of rewarding you for working hard. Why does such a reward exist? The latest theory about the runner's high makes a bold claim: Our ability to experience it is linked to our earliest ancestors' lives as hunters, scavengers and foragers. Researchers like biologist Dennis Bramble and paleoanthropologist Daniel Lieberman (watch his TEDxWilmingtonWomen Talk on dopamine) have hypothesized that the neurochemical state which makes running gratifying may have originally served as a reward to keep early humans hunting and gathering. David Raichlen, an anthropologist at the University of Southern California, was familiar with the idea that natural selection favored traits that allowed humans to run. His own work in graduate school helped establish the theory (including a 2005 academic paper title "Why is the human gluteus so maximus?") Still, he was stymied by the problem of motivation. A skeleton that makes running easier is not enough to create an endurance athlete. What would make early humans willing to exert so much effort? If anything, humans seem predisposed to conserve energy. It's a caloric risk to travel all day, using up energy reserves in the hopes of catching something big.

Raichlen, a recreational runner, began to think about the runner's high. Maybe early humans got high when they ran so they wouldn't starve. Such a neuro-reward would have to do two things: Relieve pain and induce pleasure. Scientists have speculated that endorphins are behind the runner's high, and studies show that high-intensity exercise causes an endorphin rush. But Raichlen had in mind another candidate, a class of brain chemicals called endocannabinoids. These are the same chemicals mimicked by cannabis or marijuana. Endocannabinoids alleviate pain and boost mood, which fit Raichlen's requirements for rewarding physical labor. And many of the effects of cannabis are consistent with descriptions of exercise-induced highs, including the disappearance of worries or stress, a reduction in pain, the slowing of time and a heightening of the senses.

Earlier research hinted that exercise might trigger a release of these chemicals, but no one had ever documented it during running. So Raichlen put regular runners through treadmill workouts of differing intensities. Before and after each run, he drew blood to measure endocannabinoid levels. Walking slowly for 30 minutes had no effect, nor did running at maximum effort. Jogging,

however, tripled the runners' levels of endocannabinoids and the elevation in endocannabinoids correlated with the runners' self-reported high.

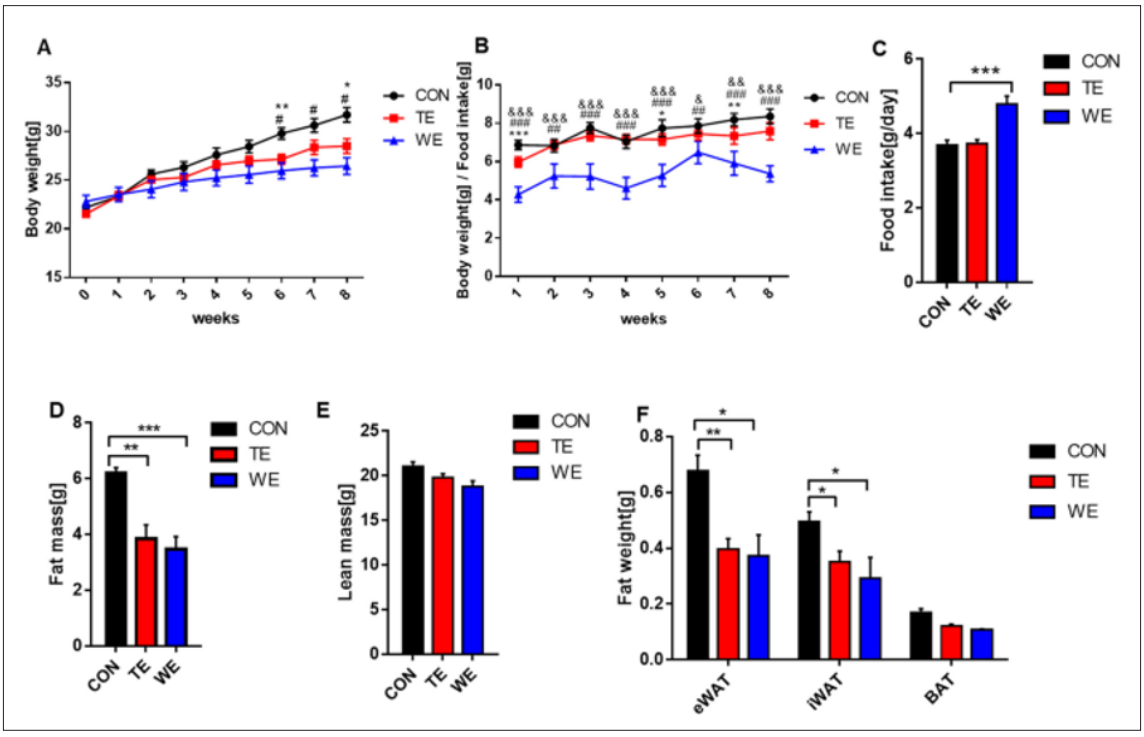
Raichlen's hunch was correct: The runner's high is a buzz. Why did jogging increase endocannabinoids, but walking slowly and running at an exhausting pace did not? Raichlen speculates that our brains reward us for exercising at intensities similar to those used for hunting and foraging two million years ago. If that is true, then natural selection should have rewarded other animals who hunt or scavenge in similar ways. Canines, for example, evolved to chase prey over large distances. Raichlen put pet dogs on the treadmill, too, to see if they got a high. As a comparison group, Raichlen used pet ferrets. Wild ferrets are nocturnal, hunting sleeping mammals but also toads, bird eggs and other sources unlikely or unable to lead them in a wearying chase.

Natural selection had no reason to reward ferrets for physical endurance and apparently it didn't. After 30 minutes of jogging, the dogs showed increased blood levels of endocannabinoids. The ferrets, despite trotting on the treadmill at an impressive speed of 1.9 miles per hour, did not. What does all this mean for today's recreational exerciser? For one, it suggests that the key to unlocking the runner's high is not the physical action of running but its continuous moderate intensity. Scientists have documented a similar increase in endocannabinoids from cycling, walking on a treadmill at an incline, and outdoor hiking. If you want the high, you just have to put in time and effort.

There's no objective measure of performance you must achieve, no pace or distance you need to reach that determines whether you experience an exercise-induced euphoria — you just have to do something that is moderately difficult for you and stick with it for at least 20 minutes. That's because the runner's high isn't a running high; it's a persistence high. Persistence is key to experiencing a high while exercising, but maybe that's not the best way to think about it. We don't persist so we can get a neurochemical reward; the high is built into our biology so that we can persist. Natural selection has endowed us with a way to chase our goals and keep going even when it's hard.

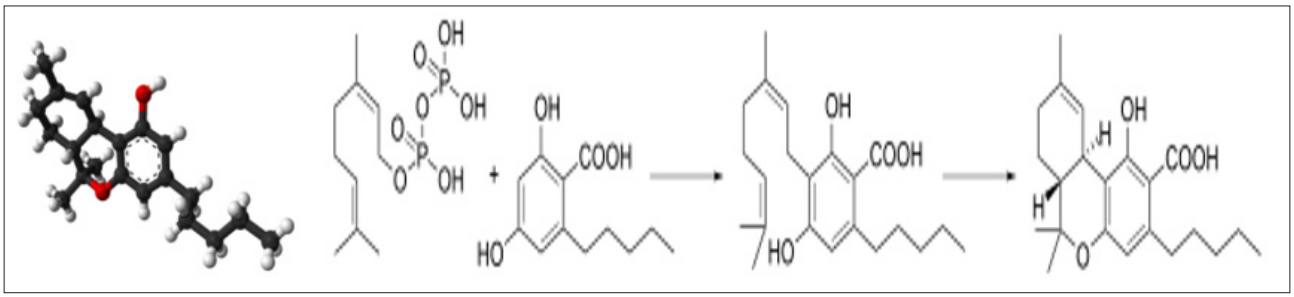
For many, the experience of persevering is part of what gives movement meaning and what makes the experience rewarding. This is the less heralded but perhaps most lasting side effect of the persistence high: You get to experience yourself as someone who digs in and keeps going when things get tough. Neuroscientists describe endocannabinoids as the "don't worry, be happy" chemical. Areas of the brain that regulate the stress response, including the amygdala and prefrontal cortex, are rich in receptors for endocannabinoids. When endocannabinoid molecules lock into these receptors, they reduce anxiety and induce a state of contentment. Endocannabinoids also increase dopamine in the brain's reward system, which further fuels feelings of optimism.

As it turns out, the chemistry of a runner's high also primes us to connect. In a 2017 review of how the endocannabinoid system works in the brain, scientists identified three things that reliably amp it up: cannabis intoxication, exercise and social connection. The three psychological states most strongly linked to low levels of endocannabinoids? Cannabis withdrawal, anxiety and loneliness. Endocannabinoids aren't just about not worrying and being happy; they are also about feeling close to others. Higher levels of them increase the pleasure you derive from being around other people. They also reduce the social anxiety that can get in the way of connecting. Giving rats an endocannabinoid blocker makes them less interested in socializing with other rats. In mice, it makes new mothers neglect their pups. The endocannabinoid system (ECS) is a biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors (CBRs), and cannabinoid receptor proteins that are expressed throughout the vertebrate central nervous system (including the brain) and peripheral nervous system [1, 2].



Effect of treadmill and wheel running

Memory - Mice treated with tetrahydrocannabinol (THC) show suppression of long-term potentiation in the hippocampus, a process that is essential for the formation and storage of long-term memory [3]. These results may concur with anecdotal evidence suggesting that smoking cannabis impairs short-term memory [4]. Consistent with this finding, mice without the CB1 receptor show enhanced memory and long-term potentiation indicating that the endocannabinoid system may play a pivotal role in the extinction of old memories. One study found that the high-dose treatment of rats with the synthetic cannabinoid HU-210 over several weeks resulted in stimulation of neural growth in the rats' hippocampus region, a part of the limbic system playing a part in the formation of declarative and spatial memories, but did not investigate the effects on short-term or long-term memory [5]. Taken together, these findings suggest that the effects of endocannabinoids on the various brain networks involved in learning and memory may vary.



Role in Hippocampal Neurogenesis

In the adult brain, the endocannabinoid system facilitates the neurogenesis of hippocampal granule cells [6. 7]. In the subgranular zone of the dentate gyrus, multipotent neural progenitors (NP) give rise to daughter cells that, over the course of several weeks, mature into granule cells whose axons project to and synapse onto dendrites on the CA3 region [8]. NPs in the hippocampus have been shown to possess fatty acid amide hydrolase (FAAH) and express CB1 and utilize 2-AG. Intriguingly, CB1 activation by endogenous or exogenous cannabinoids promote NP proliferation and differentiation; this activation is absent in CB1 knockouts and abolished in the presence of antagonist [9].

Induction of Synaptic Depression

Endocannabinoids are known to influence synaptic plasticity, and are in particular thought to mediate long-term depression (LTD, which refers to neuronal firing, not psychological depression). Short-term depression (STD) has also been described (see the next paragraph). First reported in the striatum, this system is known to function in several other brain structures such as the nucleus accumbens, amygdala, hippocampus, cerebral cortex, cerebellum, ventral tegmental area (VTA), brain stem, and superior colliculus [10, 11]. Typically, these retrograde transmitters are released by the postsynaptic neuron and induce synaptic depression by activating the presynaptic CB1 receptors [12].

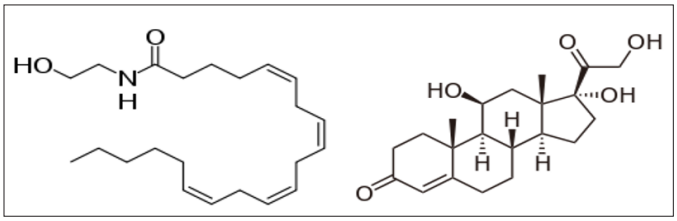
It has further been suggested that different endocannabinoids, i.e. 2-AG and anandamide, might mediate different forms of synaptic depression through different mechanisms. The study conducted with the bed nucleus of the stria terminalis found that the endurance of the depressant effects was mediated by two different signaling pathways based on the type of receptor activated. 2-AG was found to act on presynaptic CB1 receptors to mediate retrograde STD following activation of L-type calcium channeles, while anandamide was synthesized after mGluR5 activation and triggered autocrine signalling onto postsynapic TRPV1 receptors that induced LTD. These findings provide the brain a direct mechanism to selectively inhibit neuronal excitability over variable time scales. By selectively internalizing different receptors, the brain may limit the production of specific endocannabinoids to favor a time scale in accordance with its needs.

Appetite

Evidence for the role of the endocannabinoid system in food-seeking behavior comes from a variety of cannabinoid studies. Emerging data suggests that THC acts via CB1 receptors in the hypothalamic nuclei to directly increase appetite.[58] It is thought that hypothalamic neurons tonically produce endocannabinoids that work to tightly regulate hunger. The amount of endocannabinoids produced is inversely correlated with the amount of leptin in the blood [13]. For example, mice without leptin not only become massively obese but express abnormally high levels of hypothalamic endocannabinoids as a compensatory mechanism. Similarly, when these mice were treated with an endocannabinoid inverse agonists, such as rimonabant, food intake was reduced. When the CB1 receptor is knocked out in mice, these animals tend to be leaner and less hungry than wild-type mice. A related study examined the effect of THC on the hedonic (pleasure) value of food and found enhanced dopamine release in the nucleus accumbens and increased pleasure-related behavior after administration of a sucrose solution [14]. A related study found that endocannabinoids affect taste perception in taste cells In taste cells, endocannabinoids were shown to selectively enhance the strength of neural signaling for sweet tastes, whereas leptin decreased the strength of this same response [15]. While there is need for more research, these results suggest that cannabinoid activity in the hypothalamus and nucleus accumbens is related to appetitive, food-seeking behavior [13].

Energy Balance and Metabolism

The endocannabinoid system has been shown to have a homeostatic role by controlling several metabolic functions, such as energy storage and nutrient transport. It acts on peripheral tissues such as adipocytes, hepatocytes, the gastrointestinal tract, the skeletal muscles and the endocrine pancreas. It has also been implied in modulating insulin sensitivity. Through all of this, the endocannabinoid system may play a role in clinical conditions, such as obesity, diabetes, and atherosclerosis, which may also give it a cardiovascular role [16].



Anandamide **glucocorticoids**

Stress Response

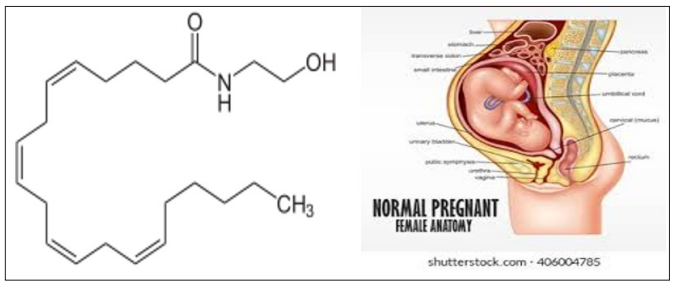
While the secretion of glucocorticoids in response to stressful stimuli is an adaptive response necessary for an organism to respond appropriately to a stressor, persistent secretion may be harmful. The endocannabinoid system has been implicated in the habituation of the hypothalamic-pituitary-adrenal axis (HPA axis) to repeated exposure to restraint stress. Studies have demonstrated differential synthesis of anandamide and 2-AG during tonic stress. A decrease of anandamide was found along the axis that contributed to basal hypersecretion of corticosterone; in contrast, an increase of 2-AG was found in the amygdala after repeated stress, which was negatively correlated to magnitude of the corticosterone response. All effects were abolished by the CB1 antagonist AM251, supporting the conclusion that these effects were cannabinoid-receptor dependent [17]. These findings show that anandamide and 2-AG divergently regulate the HPA axis response to stress: while habituation of the stress-induced HPA axis via 2-AG prevents excessive secretion of glucocorticoids to non-threatening stimuli, the increase of basal corticosterone secretion resulting from decreased anandamide allows for a facilitated response of the HPA axis to novel stimuli.

Exploration, Social Behavior and Anxiety

These contrasting effects reveal the importance of the endocannabinoid system in regulating anxiety-dependent behavior. Results suggest that glutamatergic cannabinoid receptors are not only responsible for mediating aggression, but produce an anxiolytic-like function by inhibiting excessive arousal: excessive excitation produces anxiety that limited the mice from exploring both animate and inanimate objects. In contrast, GABAergic neurons appear to control an anxiogenic-like function by limiting inhibitory transmitter release. Taken together, these two sets of neurons appear to help regulate the organism's overall sense of arousal during novel situations [18].

Immune System

In laboratory experiments, activation of cannabinoid receptors had an effect on the activation of GTPases in macrophages, neutrophils, and bone marrow cells. These receptors have also been implicated in the migration of B cells into the marginal zone and the regulation of IgM levels [19].



Anandamide, an endogenous ligand of CB_1 and CB_2

Female Reproduction: Pregnancy

The developing embryo expresses cannabinoid receptors early in development that are responsive to anandamide secreted in the uterus. This signaling is important in regulating the timing of embryonic implantation and uterine receptivity. In mice, it has been shown that anandamide modulates the probability of implantation to the uterine wall. For example, in humans, the likelihood of miscarriage increases if uterine anandamide levels are too high or low [20]. These results suggest that intake of exogenous cannabinoids (e.g. cannabis) can decrease the likelihood for pregnancy for women with high anandamide levels, and alternatively, it can increase the likelihood for pregnancy in women whose anandamide levels were too low [21, 22].

Autonomic Nervous System

Peripheral expression of cannabinoid receptors led researchers to investigate the role of cannabinoids in the autonomic nervous system. Research found that the CB1 receptor is expressed presynaptically by motor neurons that innervate visceral organs. Cannabinoid-mediated inhibition of electric potentials results in a reduction in noradrenaline release from sympathetic nervous system nerves. Other studies have found similar effects in endocannabinoid regulation of intestinal motility, including the innervation of smooth muscles associated with the digestive, urinary, and reproductive systems.

Analgesia

At the spinal cord, cannabinoids suppress noxious-stimulus-evoked responses of neurons in the dorsal horn, possibly by modulating descending noradrenaline input from the brainstem. As many of these fibers are primarily GABAergic, cannabinoid stimulation in the spinal column results in disinhibition that should increase noradrenaline release and attenuation of noxious-stimuli-processing in the periphery and dorsal root ganglion. The endocannabinoid most researched in pain is palmitoylethanolamide. Palmitoylethanolamide is a fatty amine related to anandamide, but saturated and although initially it was thought that palmitoylethanolamide would bind to the CB1 and the CB2 receptor, later it was found that the most important receptors are the PPAR-alpha receptor, the TRPV receptor and the GPR55 receptor. Palmitoylethanolamide has been evaluated for its analgesic actions in a great variety of pain indications and found to be safe and effective. Modulation of the endocannabinoid system by metabolism to N-arachidinoyl-phenolamine (AM404), an endogenous cannabinoid neurotransmitter, has been discovered to be one mechanism for analgesia by acetaminophen (paracetamol). Endocannabinoids are involved in placebo induced analgesia responses [23-25].

Thermoregulation

Anandamide and N-arachidonoyl dopamine (NADA) have been shown to act on temperature-sensing TRPV1 channels, which are involved in thermoregulation [25]. TRPV1 is activated by the exogenous ligand capsaicin, the active component of chili peppers, which is structurally similar to endocannabinoids. NADA activates the TRPV1 channel with an EC50 of approximately of 50 nM. The high potency makes it the putative endogenous TRPV1 agonist [26]. Anandamide has also been found to activate TRPV1 on sensory neuron terminals, and subsequently cause vasodilation. TRPV1 may also be activated by methanandamide and arachidonyl-2'-chloroethylamide (ACEA).

Sleep

Increased endocannabinoid signaling within the central nervous system promotes sleep-inducing effects. Intercerebroventricular administration of anandamide in rats has been shown to decrease wakefulness and increase slow-wave sleep and REM sleep [27]. Administration of anandamide into the basal forebrain of rats has also been shown to increase levels of adenosine, which plays a role in promoting sleep and suppressing arousal [28]. REM sleep deprivation in rats has been demonstrated to increase CB1 receptor expression in the central nervous system.[28] Furthermore, anandamide levels possess a circadian rhythm in the rat, with levels being higher in the light phase of the day, which is when rats are usually asleep or less active, since they are nocturnal [29].

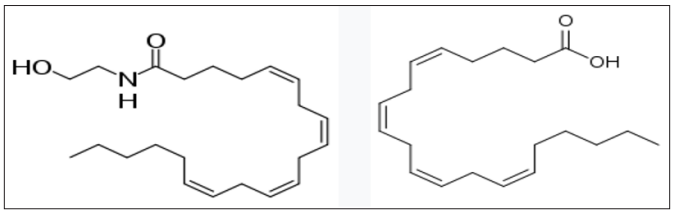
Physical Exercise

Anandamide is an endogenous cannabinoid neurotransmitter that

binds to cannabinoid receptors [30]. The ECS is also involved in mediating some of the physiological and cognitive effects of voluntary physical exercise in humans and other animals, such as contributing to exercise-induced euphoria as well as modulating locomotor activity and motivational salience for rewards. In humans, the plasma concentration of certain endocannabinoids (i.e., anandamide) have been found to rise during physical activity; since endocannabinoids can effectively penetrate the blood–brain barrier, it has been suggested that anandamide, along with other euphoriant neurochemicals, contributes to the development of exercise-induced euphoria in humans, a state colloquially referred to as a runner's high [31].

Cannabinoids in Plants

The endocannabinoid system is by molecular phylogenetic distribution of apparently ancient lipids in the plant kingdom, indicative of biosynthetic plasticity and potential physiological roles of endocannabinoid-like lipids in plants and detection of arachidonic acid (AA) indicates chemotaxonomic connections between monophyletic groups with common ancestor dates to around 500 million years ago (Silurian; Devonian) [32]. The phylogenetic distribution of these lipids may be a consequence of interactions/adaptations to the surrounding conditions such as chemical plant-pollinator interactions, communication and defense mechanisms.

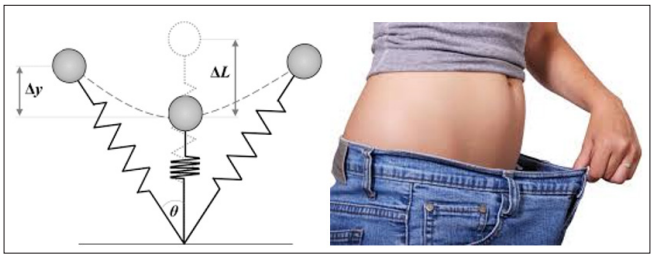


Chemical ethanolamide anandamide **Arachidonic acid(AA)**

The two novel EC-like molecules derived from the eicosatetraenoic acid juniperonic acid, an omega-3 structural isomer of AA, namely juniperoyl ethanolamide and 2-juniperoyl glycerol (1/2-AG) in gymnosperms, lycophytes and few monilophytes, show AA is an evolutionarily conserved signalling molecule that acts in plants in response to stress similar to that in animal systems [33]. A runner's high does the opposite: It helps us bond. Many people have told me they use running as an opportunity to connect with friends or loved ones. I've heard from people who rely on a daily workout to be more caring parents or partners. As one runner notes, "My family will sometimes send me out running, as they know that I will come back a much better person." One study found that on days when people exercise, they report more positive interactions with friends and family. When spouses exercise together, both partners report more closeness later that day, including feeling loved and supported. When I came across the research linking endocannabinoids with social connection, I thought about something anthropologist Herman Pontzer had told me about how early humans adapted to a changing landscape and how running is not the only factor that helped them survive. "If you had to pick one behavior that marks the beginning of hunting and gathering, that is the game changer," he said. "It's sharing".

Hunting and gathering is a division of labor. Some members of the group go out hunting, while others forage for plants. "You bring those together at the end of the day, and you share and everyone has enough to eat," Pontzer said. Groups who were better at sharing were more likely to survive, and natural selection started favoring not just traits that enhance physical endurance, like longer leg bones, but also traits that encourage within-group cooperation. By priming you to connect, the runner's high should also make sharing the spoils with your tribe more rewarding. An experiment at the Sapienza University of Rome suggests that physical activity can have this effect. Participants played an economic game that required contributing money to a communal pool. The more they contributed, the more all parties would benefit. Participants who exercised for 30 minutes before playing the game shared more than when they played the game without exercising first.

Your brain becomes more sensitive to any pleasure that activates the endocannabinoid system; it can take in more joy. This includes the runner's high but it also includes social pleasures, like sharing, cooperating, playing and bonding. In this way, regular exercise may lower your threshold for feeling connected to others — allowing for more spontaneous feelings of closeness, companionship and belonging, whether with family, friends or strangers. At first glance, the runner's high seems an unlikely antidote to social isolation. Yet the neurobiological reward that kept our ancestors from starving may now save us from a more pressing modern need: loneliness.



Sweet Effect of Running

Spring-like leg behavior is a general feature of mammalian bouncing gaits, such as running and hopping. Although increases in step frequency at a given running speed are known to increase the stiffness of the leg spring (kleg) in non-amputees, little is known about stiffness regulation in unilateral transfemoral amputees. Thus Consequently, the unilateral transfemoral amputees attained the desired step frequency in the unaffected limb, but were unable to match the three highest step frequencies using their affected limbs. These results suggest that the stiffness regulation strategy during running differs between the affected and unaffected limbs [34].

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