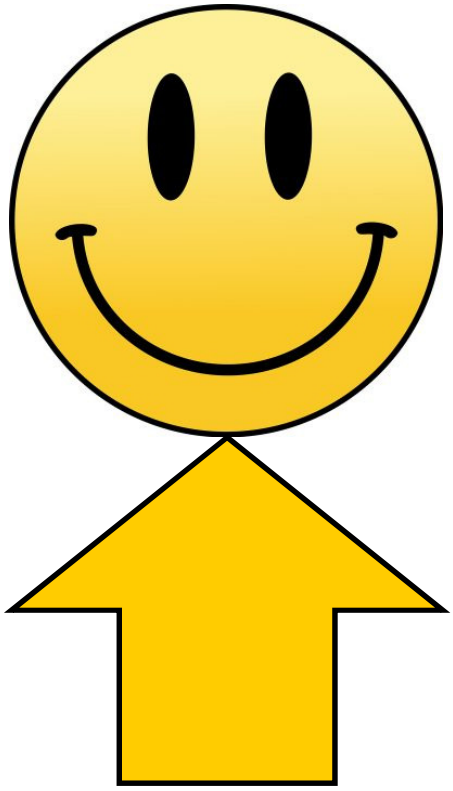

Happy Place™

Helping People Find Their Happy Place™

Executive Summary

HappyPlace™ is a revolutionary new system that can provide relief for millions of people suffering from depression symptoms. Serotonin is a neurotransmitter present in the human brain, a deficit of which has been correlated to experiencing depression symptoms. HappyPlace™ uses noninvasive Vagus nerve stimulation (nVNS) to increase the serotonin levels in a user's Central Nervous System (CNS) to help mitigate those symptoms. However, brain serotonin levels are only directly observable through examination of brain tissue, which is obviously contraindicated. However, Heart rate variability (HRV) (the physiological phenomenon of variation in the time interval between heartbeats) is known to be strongly associated with the operating state of the autonomic nervous system, the operation of which is correlated at least in part with brain serotonin levels. Consequently, we use HRV as a proxy to identify when the patient may benefit from additional serotonin through VNS – and to determine the nVNS dose to be applied - and then apply the nVNS. The user's actual HRV response is tracked and a user-specific nVNS treatment protocol is developed for the user.

Happy Place™ – Be Your Best Self

Your Serotonin Level and Feeling Good

Your human brain is an incredibly complex and wonderful machine. Although there are over 50 potential neurotransmitters that may play a part in its functioning, the four major neurotransmitters that regulate mood are Serotonin, Dopamine, GABA and Norepinephrine.

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that is a contributor to feelings of well-being and happiness, though its actual biological function is complex and multifaceted, modulating cognition, reward, learning, memory, and numerous physiological processes. Approximately 90% of the human body's total serotonin is produced in the "gut" or Gastrointestinal (GI) Tract. Serotonin assists in digestion, but serotonin is also transmitted to the serotonergic neurons of the Central Nervous System (CNS), where it aids in the regulation of mood, appetite, and sleep.[1]

It is generally believed that an imbalance in serotonin levels may influence mood in a way that leads to depression. Possible problems include low brain cell production of serotonin, a lack of receptor sites able to receive the serotonin that is made, inability of serotonin to reach the receptor sites, or a shortage in tryptophan, the chemical from which serotonin is made. If any of these biochemical glitches occur, researchers believe it can lead to depression, as well as obsessive-compulsive disorder, anxiety, panic, and even excess anger.

Several classes of antidepressants, such as the SSRIs (Selective serotonin reuptake inhibitors) and the SNRIs (Serotonin–norepinephrine reuptake inhibitors) treat depression by helping to regulate and maintain serotonin levels by reducing the body's ability to reabsorb serotonin. One theory about how depression develops centers on the regeneration of brain cells -- a process that some believe is mediated by serotonin, and ongoing throughout our lives. According to some scientists, depression may occur when there is a suppression of new brain cells and that stress is the most important precipitator of depression. They believe that the common antidepressant medications known as SSRIs, which are designed to boost serotonin

[1] https://en.wikipedia.org/wiki/Serotonin

levels, help kick off the production of new brain cells, which in turn allows the depression to lift.[2]

Unfortunately, although it is widely believed that a serotonin deficiency plays a role in depression, there is no way to measure serotonin levels in the living brain – because such measurement could only be achieved by directly sampling the brain tissue of the patient. Therefore, there have not been any studies proving that brain levels of serotonin or any other neurotransmitter are in short supply in the brain when depression or any mental illness develops. Blood levels of serotonin are measurable -- and have been shown to be lower in people who suffer from depression - but researchers don't know if blood levels reflect the brain's actual level of serotonin. Also, researchers don't know whether the dip in serotonin causes the depression, or the depression causes serotonin levels to drop. Also, serotonin is not the only neuro transmitter implicated in depression – and the relative impacts of the various neurotransmitters is not well characterized. However, the majority of scientist accept that there is a correlation between depression and serotonin levels in the brain.

However, psychological stress has been shown to a chronic inflammatory condition that adversely impacts brain chemistry. Chronic stress can indirectly result in damage to neurons that produce serotonin or the other parts of the brain that are involved and the serotoninic pathways that make the system work less effectively. In other words, stress causes inflammation, which is bad news for your brain because it negatively impacts your serotonin levels. However, the exact pathway is unclear and may be variable from person to person.

[2] https://www.webmd.com/depression/features/serotonin#1
https://www.medicalnewstoday.com/articles/232248.php#deficiency-symptoms
https://www.healthline.com/health/serotonin-deficiency#symptoms
https://www.wellandgood.com/good-advice/how-to-increase-serotonin/
https://www.integrativepsychiatry.net/seritonin-and-seritonin-deficiency.html

Heart Rate Variability (HRV) and Stress

Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. It is measured by the variation in the beat-to-beat interval.[3] In a nutshell, the interaction of the sympathetic and the parasympathetic nervous system (PSNS), which respond to stress, influences the variation of heart rate from one beat to the next. For example, in a non-stressed person, heart rate may vary due to factors such as breathing. Conversely, it has been determined that a person experiencing stress has a lower HRV than a relaxed person. That is, for stressed people, their heart beats more uniformly – too uniformly!

Several studies have investigated using HRV as a marker for clinical depression:
https://www.sciencedirect.com/science/article/pii/S0010482519302586
https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00735/full
https://academic.oup.com/ijnp/article/16/9/1937/795717

Other investigators recommend monitoring your HRV level so that you can be aware of when your stress level is high – and thus seek to reduce it, presumably though ceasing activities that are stressing you.
https://www.health.harvard.edu/blog/heart-rate-variability-new-way-track-well-2017112212789

Measuring HRV

HRV may be measured in a variety of fashions, but new systems for measuring HRV have become especially convenient. One such system is the EliteHRV by Coresense[4]. The Elite HRV is a fingertip-based sensor that transmits the user's HRV information to an app on their smartphone. The app provides analysis and trending of the user's HRV so that the user can know if their HRV is better or worse than their typical score – of the scores of others physiologically similar to the user – so that the user can know if they are in a stressed state.

[3] https://en.wikipedia.org/wiki/Heart_rate_variability
[4] https://elitehrv.com/corsense

The Role Of The Vagus Nerve

The Vagus Nerve[5] is the longest nerve of the autonomic nervous system. The impact of the vagus nerve on our internal organs is astounding because it comprises between 80% and 90% of afferent nerves mostly conveying sensory information about the state of the body's organs to the central nervous system. Due to the vagus nerve's interaction with substantially all human organ function, investigators are looking into a huge number of clinical and therapeutic applications involving the vagus nerve for a host of human medical conditions.[6]

One of the myriad areas of research that investigators are pursuing is Vagus nerve stimulation[7] (VNS) for treatment of clinical depression. In this regard, a therapy using a neurostimulator implanted in the chest is a treatment used since 1997 to control seizures in epilepsy patients and has been approved for treating drug-resistant cases of clinical depression. One such product is LivaNova which provides an implantable (invasive) VNS stimulation device[8], for treatment of clinical depression. It has been observed that the LivaNova increases bloodstream serotonin levels and is believed to increase serotonin levels in the brain. It is believed that the increase in serotonin levels is one of the primary treatment pathways that the LivaNova uses to treat depression.

Implantation of the VNS device is usually done as an out-patient procedure. The procedure goes as follows: an incision is made in the upper left chest and the generator is implanted into a little "pouch" on the left chest under the collarbone. A second incision is made in the neck, so that the surgeon can access the vagus nerve. The surgeon then wraps the leads around the left branch of the vagus nerve, and connects the electrodes to the generator. Once successfully implanted, the generator sends electric impulses to the vagus nerve at regular intervals. The left vagus nerve is stimulated rather than the right because the right plays a role in cardiac function such that stimulating it could have negative cardiac effects. Importantly, the "dose" administered by the device then needs to be set, which is done via a magnetic wand; the parameters adjusted include current, frequency, pulse width, and duty cycle.

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[5] https://en.wikipedia.org/wiki/Vagus_nerve
[6] https://spectrum.ieee.org/biomedical/devices/the-vagus-nerve-a-back-door-for-brain-hacking?utm_source=techalert&utm_medium=email&utm_campaign=techalert-01-23-20&mkt_tok=eyJpIjoiWmpZNU1qVTFZVGt3TlRrNSIsInQiOiJldjdDNlFBTXVHdDdqbkQ5dDh0U0Q5cjdTRWpmNFFpMXYwbHBKNGFYd3RxaUZcL2N1SE9vV1FUSEhyYkU2TU94UUFVWlwvV3phYVYxc2FZZDRLUHZQeUdqMnFGZ1wvRFJWVVBZc0NMalpYMFpRcG11dEg0WkVGZlIyMkRUR0k1aUt4YyJ9
[7] https://en.wikipedia.org/wiki/Vagus_nerve_stimulation
[8] https://www.livanova.com/en-US/Home/Products-Therapies/Neuromodulation/Patients.aspx

However, in conventional VNS, dose determination is patient-specific and determined by a doctor specifically for a patient based on the patient's unique physiology and disease state. There is also no way to physiologically measure the impact of the VNS on brain serotonin levels, so dosage is generally determined based on verbal feedback from the patient with regard to their emotional state.

Non-Invasive Vagus Nerve Stimulation

ElectroCore has developed a product[9] to administer vagus nerve stimulation non-invasively (nVNS) by delivering a proprietary signal through the skin to either the right or the left branches of the vagus nerve in the neck. To date, ElectroCore has focused on the treatment of migraines through nVNS.[10] They have developed a small, portable, hand-held device called gammaCore[11] to allow migraine patients to administer self-treatment. The gammaCore self-treatment is[12]:

> As soon as a migraine starts
> Give yourself a treatment consisting of 2 two-minute gammaCore (nVNS) stimulations.
> - Apply the conductive gel before each stimulation. After 2 minutes, gammaCore will beep twice and automatically turn off.
> - The device should remain off for 10 seconds after each stimulation
> - Stimulations can be administered on the same side of the neck, or you can switch sides, if preferred
> - If pain remains 20 minutes after the start of treatment 1, apply 2 more stimulations
> - Two more stimulations may be applied if pain remains 2 hours after the start of treatment 1

[9] https://www.electrocore.com/nVNS/
[10] https://www.electrocore.com/future-developments/therapeutic_areas/
[11] https://www.gammacore.com/about/
[12] https://www.gammacore.com/for-migraine/migraine-dosing/

Importantly, the signal amplitude of the gammaCore is set by the user[13], not a doctor (see video) and typically ranges in intensity level between 15-25. Further, the video notes that even for an individual user, their effective intensity level may not be the same for every stimulation event. The GammaCore device is rechargeable and is charged by the user when they replace it in its case. The number of treatments that the GammaCore device provide is limited as prescribed by a doctor.

[13] https://www.gammacore.com/about/using-gammacore/

Finding Your Happy Place™

We have developed a self-treatment protocol for the alleviation of depression symptoms wherein the Vagus nerve is stimulated to produce serotonin. The additional serotonin is present in the brain and thus not directly measurable *in situ*. However, HRV is strongly associated with the operating state of the autonomic nervous system, the operation of which is correlated at least in part with brain serotonin levels. Consequently, we use HRV as a proxy to identify when the brain's serotonin level may be less than optimal and thus identify when the production of additional serotonin through VNS may be desired. Although we are not able to measure actual brain serotonin levels, changes in the blood serotonin levels have been observed after VNS. However, we find that HRV provides a clearer and more easily measurable insight into the current state of the autonomic nervous system – so instead of attempting to determine how much actual serotonin the user has emitted or the brain's actual current serotonin level, we just observe the HRV and use VNS to cause more serotonin to be emitted until the HRV improves.

Our HappyPlace™ protocol includes three main parts - the app, the EliteHRV, and a modified gammaCore that we call HappyPlace™.

The first step is the establishment of a baseline HRV for the user. Consequently, the user is asked to take an HRV reading every hour when awake for 1-3 days. For each reading, the user is directed to correlate their user-perceived psychological states for depression and anxiety using a dropdown menu on our app.

The user also enters physiological data such as height, weight and gender. The physiological data is used to approximate neck thickness at the VNS region in order to determine an initial intensity level for the user.

After collecting three days of HRV data, the user has the option to enter a self-treatment mode. During the self-treatment mode, the user takes a HRV reading and the app compares the current HRV reading to the historical data to determine if the user might benefit from VNS – and if so, at what intensity level. If HappyPlace™ determines that VNS is desirable, a self-treatment

plan is determined and the user is directed to position the modified gammaCore at the VNS region.

The gammaCore has been modified to include a Bluetooth receiver that syncs with the app on the user's smartphone and is thus controllable by the smartphone. Thus, HappyPlace™ can control the modified gammaCore to administer the treatment program that it determined would be most efficacious – and the user only needs to position the gammaCore at the VNS region and hold it there.

For example, HappyPlace™ might recognize that a user's HRV, while on average a 70, has presently declined to 60. Based on the user's physiological data, HappyPlace™ may determine that an initial intensity of 20 is desirable. HappyPlace™ would then provide VNS for two minutes and monitor's the user's HRV over the next 20 minutes. Readings may either be taken continuously or HappyPlace™ may direct the user to take a reading every five minutes. Based on the increase in HRV, HappyPlace™ may then direct the user to perform additional stimulation, from a minimum of 1 minute up to a maximum of 5 minutes at one time, in intervals of 10 seconds. For example, if the user's HRV responded to the two-minute stimulation by rising to 65, then HappyPlace™ would direct another two-minute stimulation to hopefully raise HRV to at least 70.

Once the user's HRV rises to the average (70 in this case), the user is advised that their HRV is now at the average. The user may undergo additional stimulation, but only of one minute in length every 20 minutes (in order to prevent abuse and not overstress the body's serotonin production) up to a total maximum of 120 minutes in a 24-hour period.

In addition to time, as mentioned above, the user's physiological input is used to determine an initial intensity level, but the actual intensity level may be adjusted by the user.

Adaptive User Treatments

Once HappyPlace™ has accumulated data representing 50 treatments, HappyPlace™ can determine an improved, user-specific treatment protocol based on previous results. HappyPlace™ gets smarter with every treatment because it monitors the dose provided as well as the actual impact on HRV, including starting HRV, ending HRV, treatment time, number of treatments, and change in HRV. HappyPlace™ performs advanced statistical modeling to optimize the user's self-treatment – and can even adapt to changes in user response over time.

Building on the example above, if HappyPlace™ recognizes that the user's HRV, while on average a 70, has presently declined to 60 – and that previously, when a 10-point improvement in HRV was desired, it required a total of 4 minutes of dosing (previously presented in 2, 2-minute intervals) to restore the desired HRV, then HappyPlace™ will just direct the initial stimulation to take place for 4 minutes. The HRV will then be measured post-treatment and additional stimulation provided if needed.

VNS-Non-Responsive Users

We have determined that not all users receiving VNS will actually experience an improvement in HRV – although the overwhelming majority do experience an improvement. In this case, during the initial self-treatment of 2 minutes followed by the 20 minute "rest period", the user will be advised that the current treatment did not improve HRV, so a full 5-minute treatment is being attempted. If there is still no improvement to HRV, then the user is directed to adjust the intensity setting to the highest level they can experience without pain and another full 5-minute session is attempted. If there is still not change in HRV, then the user is directed to try again in 24 hours – when another high-intensity, 5-minute does is administered. If the user still does not experience an improvement in HRV, then they are so advised and we will accept their return of our product and provide them with a refund.

Upcoming HappyPlace™ Improvements

Compensation For Non-Linear HRV Response With Stimulation Time

Serotonin production is a physiological effect and for many patients physiological effects do not respond linearly to stimulation. Alternatively, physiological effects may respond approximately linearly during a first time period, but then experience a decline in response with additional stimulation time. Consequently, in order to lower the patient's total treatment time, the patient's actual HRV response is characterized for specific treatment times and a treatment protocol may be selected by the user to minimize total treatment time. (Note that the baseline protocol differs from this because it seeks to minimize total number of treatments – and it also projects a linear response with stimulation time.

As discussed above, the initial base treatment time is 2 minutes. In the non-linear system, the system records 10 of the 2-minute treatments and determines the average HRV improvement. Thus, the HRV improvement at the 2-minute interval is considered to be characterized. Additional 2-minute treatments will be included in an ongoing running average.

However, when the HappyPlace™ determines that more than 2 minutes of stimulation are needed (for example 4 minutes might be projected based on the linear modality above), then HappyPlace™ increases the treatment time to only 2:30 in order to characterize the HRV response at 2:30. In this way, HappyPlace™ characterizes actual user HRV responses from 1 minute to 5 minutes in 30-second intervals. In this fashion, HappyPlace™ can determine that a user typically achieves a 5 point HRV improvement with 2 minutes of stimulation. However, contrary to the linear model which would suggest a 10 point improvement in HRV for 4 minutes of stimulation, the patient only experiences an 8 point improvement HRV with 4 minutes. Thus, when a 10 point improvement is desired, a treatment protocol that lessens the total treatment time would suggest 2 minutes, followed by a break, and followed by another two minutes (4 minutes total treatment time)– instead of 4 minutes, followed by a break, and then followed by an additional 1 minute (5 minutes total treatment time.)

Continuous HRV Monitoring (Measuring and Treatment)

The Oura[14] is a new finger-based sensor that can allow for continuous HRV measurement over a 24-hour period. Patients can wear the Oura even while sleeping. If patients are wearing the HRV monitor continuously, it provides two advantages: first, we can develop a better baseline for their average HRV by averaging in the time when the patient is asleep. Second, we can allow the user to establish a warning threshold for HRV so that once the HRV drops below the threshold, the user can immediately be notified so that they can perform VNS stimulation.

[14] https://ouraring.com

Other Patents

The CEO passed on your recommendation to search the PTO's website, so I did. I made a list of the patents below. The CEO says that all of these patents look pretty close to what we came up with. However, the CEO says that you are the best patent attorney around and that you will be able to find a way to get us our patent without infringing on these other patents.

Patents:

US 20150208986 A1

US 20180125419 A1

US 20190038646 A1

US 20190313934 A1