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Posted Date: 12 January 2024

doi: 10.20944/preprints202401.0996.v1

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Finding Inner Peace, Forging Inner Strength with GABA: The Intertwined Dance of Mental Relaxation and the Immune System

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Abstract: This article describes a novel topical composition constituted by gamma-amino butyric acid (GABA) and microbial chondroitin sulfate. This composition exhibits potential for non-invasive intervention in anxiety management, sleep quality enhancement, and promotion of brain-related functions like meditation and nonlocal consciousness. The core component comprises GABA, a key inhibitory neurotransmitter within the central nervous system, complexed with a suitable carrier molecule, microbial chondroitin sulfate. This complexation aims to enhance transdermal absorption and optimize delivery of GABA to target tissues. The proposed mechanism of action involves modulation of GABAergic signal transduction pathways. Application of the topical composition allows GABA penetration into the skin and potentially deeper tissues, where it interacts with GABA receptors. This interaction leads to mental calmness and relaxation as assessed by electroencephalography. The influence of GABAergic signaling on brain circuits demonstrated in this article, when associated with meditation and nonlocal consciousness, suggests potential for the composition to support these practices. The advantage of such an approach consists in avoiding the potential systemic side effects associated with oral or injectable administration of GABA, anxiolytics or hypnotics. Furthermore, the combination of GABA and microbial chondroitin sulfate may offer synergistic benefits, potentially enhancing the overall biological effects. In conclusion, this article presents a novel topical approach for managing anxiety, enhancing sleep quality, and potentially facilitating meditation and nonlocal consciousness through modulation of GABAergic signaling pathways. While further research is necessary, the potential for a non-invasive and potentially side-effect-free intervention in these areas is promising.

Keywords: brain; immune system; gamma-aminobutyric acid GABA; chondroitin sulfate; relaxation; stress

Introduction

In the modern world, chronic stress and relentless demands have become the norm. Yet, amidst the whirlwind of deadlines and anxieties, one vital aspect often takes a backseat: our mental well-being (Mariotti 2015). This article argues that fostering inner peace, far from being a luxury, is a crucial pillar of our immune system's resilience. This article unveils the intricate dance between mind and body, where serenity strengthens our defenses against disease.

Chronic Stress, the Inner Saboteur

Chronic stress acts as a malevolent puppeteer, pulling the strings of our nervous system and influencing a cascade of detrimental effects on the immune system. Stress triggers the release of cortisol, a hormone that suppresses the immune system's inflammatory response, hindering its ability to fight off pathogens. This chronic dampening leaves us vulnerable to infections and weakens our body's natural defenses. Stress disrupts the delicate communication between immune cells, hindering their ability to detect and neutralize threats. This miscommunication can lead to

 doi:10.20944/preprints202401.0996.v1

autoimmune reactions and an overall weakened immune response. Chronic stress disrupts the gut microbiome, creating an environment less hospitable for health-supporting microbes. This gut dysbiosis further impacts the immune system, as the gut plays a crucial role in immune cell development and activation (for a review on the biological effects of chronic stress, please see Yaribeygi *et al*. 2017).

Gamma-aminobutyric acid GABA: The Neurochemical Peacemaker

Enter GABA, the neurotransmitter renowned for its calming and stress-reducing properties. By promoting relaxation and reducing stress, GABA counteracts the detrimental effects of cortisol on the immune system. This allows for a more balanced and effective immune response, strengthening our defenses against various threats. GABA may also enhance communication between immune cells, facilitating their coordinated response to invading pathogens. This improved dialogue strengthens the immune system's overall effectiveness (for a review on the effects of GABA on the immune system, please see Jin *et al*. 2013).

However, despite its presence in food and produced naturally within the body, orally administered GABA faces formidable obstacles on its journey to influencing neuronal activity. These challenges can be broadly categorized into two key hurdles:

1. Limited Intestinal Absorption. The human digestive system efficiently breaks down and absorbs nutrients from ingested food. Unfortunately, GABA falls victim to this very process. Due to its amino acid structure, it is readily metabolized by intestinal enzymes before reaching the bloodstream, rendering it largely unavailable for central nervous system action and it is estimated that only a small percentage of orally ingested GABA crosses the intestinal barrier (Li *et al*. 2015).

2. The Blood-Brain Barrier. Even if GABA manages to escape the digestive gauntlet, it still faces the formidable obstacle of the blood-brain barrier (BBB) as it has been demonstrated since 1971 (Kuriyama and Sze 1971). This semipermeable membrane meticulously regulates what enters the brain, protecting it from harmful substances. Unfortunately, GABA, despite its naturally occurring role within the brain, is largely excluded by the BBB due to its polar structure and lack of efficient transport mechanisms. This further restricts the amount of orally administered GABA that can reach its target site of action - the neurons responsible for relaxation and stress regulation.

The limited bioavailability of oral GABA translates into several key limitations for its use in the context of mental relaxation and immune system modulation. Studies investigating the effects of oral GABA supplementation on anxiety and sleep have yielded mixed results, with some showing minimal to no improvements compared to placebo (Boonstra *et al*. 2015). This can be attributed to the low levels of GABA actually reaching the brain, rendering its calming effects negligible. In addition, attempting to overcome the absorption hurdles by increasing the dosage can be counterproductive. High doses of GABA can saturate the limited transport mechanisms at the BBB, further hindering its entry into the brain. Additionally, while GABA itself is generally safe, high doses of oral supplements may interact with certain medications, particularly sedatives and tranquilizers, potentially leading to dangerous side effects (for a review on safety and potential side effects of orally administered GABA, please see Oketch-Rabah *et al*. 2021).

The limitations of oral GABA supplementation necessitate a shift in perspective. To truly harness its potential for promoting mental well-being, alternative strategies that circumvent the absorption barriers and directly target the GABAergic system are needed.

Transdermal Delivery: Bypassing the Barriers, Achieving Serenity

Transdermal delivery systems offer a revolutionary alternative, circumventing the limitations of oral administration (Wong *et al*. 2023). Here, an original GABA transdermal delivery system compounded under the form of a cream is described. When applied directly to the skin, it allows GABA to enter the bloodstream avoiding the digestive tract's metabolic gauntlet. This bypass translates to several key advantages such as enhanced bioavailability: unlike oral preparations, where only a negligible percentage reaches the brain, transdermal delivery offers significantly higher bioavailability (Denda *et al*. 2002). In addition, precise placement of the cream on specific locations,

 doi:10.20944/preprints202401.0996.v1

like the inner wrist or behind the ear, further optimizes delivery by leveraging areas with thinner skin and increased blood flow. This targeted approach maximizes the amount of GABA reaching its intended neuronal targets. The transdermal delivery system also acts as a miniature reservoir, allowing for gradual and sustained release of GABA over an extended period, typically 24 h. This sustained delivery translates to longer-lasting calming effects, offering relief throughout the day or night. By bypassing the digestive system, transdermal delivery avoids the potential gastrointestinal discomfort associated with high oral doses. Additionally, the controlled release minimizes the risk of side effects typically associated with overdosing on oral GABA.

A key component of the original transdermal delivery system described in this article is constituted by microbial (*i.e.* non-animal-derived) chondroitin sulfate (CS).

Microbial CS: a Paradigm Shift in the Field of Glycosaminoglycans

Traditionally, CS extracted from animal cartilage has formed the mainstay of clinical applications. However, the inherent heterogeneity of this source, encompassing a spectrum of molecular weights and sulfation patterns, has raised concerns about inconsistent efficacy and therapeutic potential. Recent advancements in microbial fermentation have yielded a novel form of CS characterized by remarkable homogeneity and a precisely defined structure closely mirroring that found in human synovial fluid. Animal-derived CS exhibits considerable structural heterogeneity, comprising a complex mixture of high- and low-molecular-weight species with variable sulfation profiles. This inherent variability compromises its pharmacokinetic properties, hindering absorption and bioavailability. Furthermore, the presence of contaminants, including protein impurities and heavy metals, poses potential safety concerns. The United States Pharmacopoeia acknowledges these limitations, allowing an acceptable CS purity range of 90–105% and tolerating protein contamination up to 6%. This underscores the limitations of animal-derived CS as a therapeutic agent demanding further refinement. Microbial fermentation presents a transformative approach, enabling the production of a highly purified and homogeneous CS. This novel form shows a 99% purity level, a precisely defined low-molecular-weight structure, and a sulfation pattern mirroring that of human CS. These advantageous characteristics translate into significantly improved pharmacokinetic profiles, facilitating superior absorption and bioavailability. Moreover, the controlled production process eliminates the presence of contaminants, thereby enhancing safety and potentially minimizing adverse effects. Clinical studies comparing microbial CS with its animal-derived counterpart highlight the former's superior efficacy. Notably, one investigation demonstrated that microbial CS exhibited a two-fold greater plasma concentration and doubled charge density compared to bovine CS. This enhanced bioavailability translated into superior therapeutic outcomes, with microbial CS demonstrating significantly greater efficacy in reducing arthritic scores and inflammatory markers in an animal model compared to high-molecular-weight animal-derived CS (for a review on microbial CS and its advantages over animal-derived CS, please see Ruggiero and Pacini 2018) .

In the quest for efficient and targeted transdermal delivery systems, microbial CS emerges as a promising protagonist. This naturally occurring glycosaminoglycan, long touted for its joint-supporting properties, possesses unique physicochemical characteristics that make it an ideal candidate for ferrying biologically active molecules, like GABA, through the skin's intricate barrier. In the next paragraphs, the original CS-based GABA transdermal delivery is described, exploring its advantages, limitations, and potential applications.

The Skin's Gatekeeper and CS's Sneaking Tricks

The human skin, much like a medieval castle, guards its inner *sanctum* meticulously. Its multi-layered structure presents a formidable obstacle for most molecules, including many biologically active molecules. Transdermal delivery systems aim to overcome this barrier, delivering biologically active agents directly into the bloodstream through passive diffusion (for a review on the histological structure of the skin and the role of transdermal delivery systems, please see Pacini *et al*. 2007). Microbial CS, with its unique properties briefly described above, plays a crucial role in this endeavor.

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Microbial CS's highly negatively charged sulfate groups hold onto water molecules, creating a hydrated environment within the skin. This hydrophilic nature facilitates the diffusion of water-soluble molecules, like GABA, through the skin's predominantly aqueous layers. The linear, flexible structure of microbial CS allows it to interact with the skin's proteins and lipids, forming temporary "channels" or pores. These transient openings provide a pathway for hydrophilic molecules like GABA, to piggyback on microbial CS and traverse the barrier. CS is a naturally occurring component of human cartilage and connective tissues. This inherent biocompatibility, highlighted in microbial CS, minimizes risks of skin irritation or allergic reactions, making it a safe and well-tolerated delivery vehicle.

Entangled in the Membrane: Exploring the Molecular Interactions of GABA and CS

CS, a glycosaminoglycan traditionally associated with joint health, seems an unlike partner for GABA, a neurotransmitter. While their functions seem far apart, the realm of molecular interactions promises a fascinating interaction between these two molecules, thus paving the way for novel transdermal delivery strategies. Here, the possible intermolecular dialogues between GABA and CS are described; their impact on skin penetration, and the intriguing avenues they open for future research are explored.

Microbial CS, with its negatively charged sulfate groups, attracts GABA, a zwitterionic molecule with both positive and negative charges, through electrostatic interactions. This initial attraction acts as a bridge, drawing GABA towards the skin's surface and facilitating its interaction with the epidermal layers. Microbial CS's inherent hydrophilicity creates a water-rich environment within the skin. This "hydration highway" provides a congenial path for GABA, a water-soluble molecule, to navigate the predominantly aqueous layers of the epidermis. Microbial CS, acting like a water-holding sponge, could create temporary water channels that allow GABA to hitch a ride and penetrate deeper into the skin. Beyond the aqueous layers lies the *stratum corneum*, a lipid-rich barrier. Here, microbial CS's interactions become more intricate. Its flexible structure and polar groups could potentially interact with the phospholipids of the *stratum corneum*, creating transient pores or disrupting their tight packing. This temporary "dance floor disruption" could allow GABA, with its own amphiphilic nature, to slip through the lipid maze and gain access to the deeper dermal layers. While passive diffusion is the primary model for transdermal delivery, the possibility of more active interactions between GABA and microbial CS cannot be ignored. GABA receptors are present on various skin cell types. It can be hypothesized that microbial CS, through its interactions with specific cell surface proteins, may trigger signaling pathways that facilitate GABA uptake or modulate its activity within the skin.

Materials and Methods

Validating transdermal delivery of GABA by electroencephalography (EEG): The Citizen Science Approach

The citizen science paradigm represents a transformative force in the landscape of scientific inquiry. By embracing the public as co-creators of knowledge, this approach holds immense potential to revolutionize research methodologies, foster scientific literacy, and address grand challenges facing our planet. As we move forward, embracing the transformative power of citizen science promises to unlock a future where scientific discovery is not just an elitist pursuit, but a collaborative endeavor enriching both the research process and the lives of those involved. In such a context, the availability of low-cost, portable EEG recording systems represents a valuable tool for the study of the mind and, as far as this article is concerned, the study of GABA effects on brain function.

Advancements in neuro-technology provide tools like Muse (RRID:SCR_014418), a portable EEG recording system that represents a paradigm shift in EEG accessibility. This is a portable scalp EEG system that can be used to measure brain activity. It is battery powered and has four active electrodes located at 10-20 coordinates TP9, AF7, AF8, and TP10. It includes an accelerometer and works with desktop and mobile EEG acquisition and visualization software. Unlike the cumbersome, lab-bound systems of the past, Muse boasts a sleek, user-friendly design, empowering individuals to

record their own brainwaves from the comfort of their homes. The four dry electrodes integrate into a headband, capturing the fluctuations in voltage generated by neuronal activity. These bioelectrical signals, amplified and digitized by Muse, are then translated into data accessible through a dedicated app, offering a real-time glimpse into the brain's inner workings. Recent peer-reviewed articles demonstrated the validity of data obtained by Muse in the context of neurosciences (Krigolson *et al*. 2017; LaRocco *et al*. 2020; Krigolson *et al*. 2021; Moontaha *et al*. 2023).

This sophisticated hardware synergistically interacts with innovative algorithmic processing within the accompanying Muse app. Unlike conventional approaches focused on individual frequency bands, Muse delves into the intricate interplay of brainwaves thanks to algorithms that analyze higher-order combinations of primary, secondary, and tertiary characteristics within raw EEG data. This innovative approach enables Muse to differentiate states like calmness, focus, and neutrality. In addition to brain waves, the Muse headband, thanks to the presence of a photoplethysmography (PPG) sensor measures heart rate. The sensor emits a near-infrared light that shines through the skin and into the underlying tissue. Some of the light is absorbed by the hemoglobin in blood, while the rest is reflected back to the sensor. As the heart beats, the amount of blood in the tissue changes, affecting the amount of light that is absorbed. The PPG sensor detects these changes in light absorption. The Muse app analyzes the changes in light absorption to compute the heart rate. Finally, an accelerometer measures body movement. In short, thanks to the technology of Muse, it is possible to quantitatively assess mental and body relaxation. Using its proprietary algorithm, the device provides measure of heart rate and percent of time spent in mind relaxation during a neurofeedback training session; the Muse app offers a variety of different neurofeedback sessions.

Here, it is important to highlight that this is not an investigation on human subjects. The healthy subject mentioned in this study is the Author himself who performed the Muse neurofeedback training sessions and applied the GABA/CS cream voluntarily, in accordance with the principles of citizen science, that is with the goal of contributing to the advancement of science in this particular context. The informed consent to publish the results is implicit in the fact that the Author is the subject of this study. In addition, since these observations do not produce generalizable knowledge, nor are they part of an investigation of an FDA-regulated product, Institutional Review Board review is not required for this activity.

As far as self-experimentation is concerned, the history of science is rife with examples of researchers who pushed the boundaries of knowledge by experimenting on themselves. Here are a few fascinating examples:

1. Luigi Galvani (1737-1798): The Italian physiologist, best known for his work on electricity and muscle contraction, famously experimented on himself to understand the effects of electricity on the human body. He applied electrical currents to his own tongue and muscles, observing the resulting twitches and spasms.
2. Werner Forssmann (1908-1970): The German physician revolutionized cardiology by performing the first human cardiac catheterization in 1929. In the absence of volunteers, Forssmann inserted a catheter into his own vein, threading it all the way up to his heart chamber. He then walked to the X-ray department and confirmed the catheter's position under fluoroscopy. Though initially ridiculed, his daring self-experiment paved the way for modern cardiac diagnostics and procedures.
3. Albert Hofmann (1906-2008): The Swiss chemist inadvertently discovered the psychedelic properties of LSD in 1943 by accidentally ingesting a small amount in his lab. Despite initial fear and paranoia, Hofmann embarked on a series of self-experiments with LSD, documenting his detailed introspective experiences and contributing significantly to our understanding of its effects on the human mind.
4. Barry Marshall (b. 1951): The Australian physician revolutionized our understanding of peptic ulcers by proving they were caused by the bacterium Helicobacter pylori, not stress or spicy food. In a controversial move, Marshall intentionally swallowed a culture of H. pylori to demonstrate its ability to induce ulcers. His self-experimentation, followed by rigorous clinical

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trials, led to a paradigm shift in ulcer treatment and earned him a Nobel Prize in Physiology or Medicine in 2005.

Beyond these famous examples, countless other researchers across diverse fields have engaged in self-experimentation. From physiologists testing muscle fatigue to nutritionists exploring dietary needs, their contributions, while often overshadowed, have fueled scientific progress and expanded our understanding of the human body and mind.

Results

The following figures show the effects on mental relaxation following application of the GABA/CS transdermal delivery system described in the previous paragraphs. The transdermal delivery system compounded under the form of a cream, was applied by the Author onto the skin behind the left ear (Figure 1).

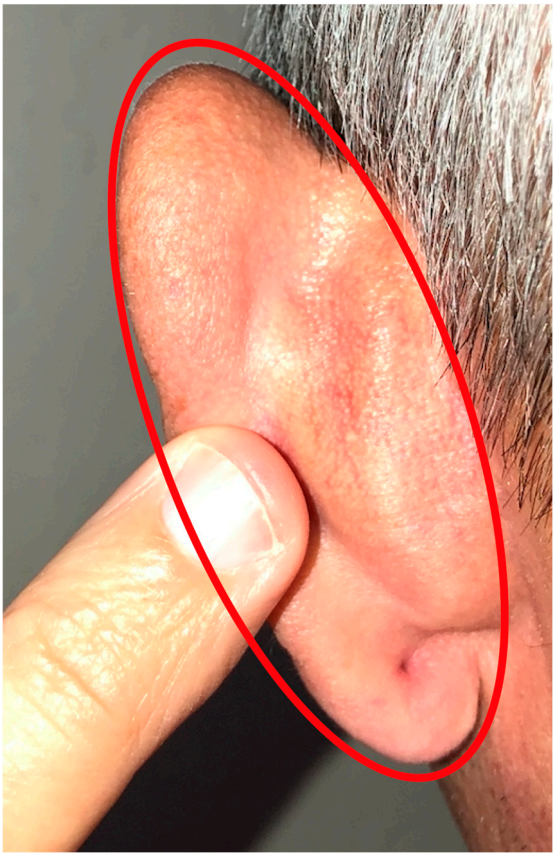

Figure 1. Area of application of the cream. This area of the skin is one of the thinnest in the human body and is highly vascularized. It is an area commonly used in auriculotherapy (Corrêa et al. 2020). The cream was gently rubbed for about 30 sec.

Before application of the cream, the Author performed a 5 min unguided neurofeedback training session denominated "Heart Session Healing Drum" following the instruction of the Muse EEG system (Figure 2, left panel). Thirty min after application, the Author performed another identical session (Figure 2, right panel). Both sessions were performed in a dimly illuminated, quiet room, far from potential distractions. During both sessions, the Author maintained the Seiza position, a traditional position for meditation that involves kneeling on the floor with the tops of the feet flat on the ground and the gluteal region resting on the heels. The results of the sessions were recorded on the Author's smartphone, and exported directly as screen shots, with no modification. As illustrated in Figure 2, following the application of the cream, the overall percentage of time spent in calm state increased from 41% to 66%. In detail, the calm state increased from 125 to 199 sec (60% increase), whereas the neutral state decreased from 173 to 100 sec. The heart rate did not change significantly.

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Figure 2. Results of a 5 min unguided neurofeedback training session "Heart Session Healing Drum" following the instruction of the Muse EEG system. Left panel: before application of the cream. Right panel: after application of the cream.

These results indicate that application of the original GABA/CS transdermal delivery system described in the previous paragraphs is associated with a significant increase of mental calmness, a phenomenon that is consistent with the known effects of GABA.

The results described in Figure 2 appear to be independent from the type of neurofeedback training session among those proposed by the Muse app. For example, the following day, approximately 24 h after the observation described in Figure 2, the Author performed other two 5 min unguided sessions, this time with a program denominated "Mind Session Desert" observing superimposable results in terms of increase of calmness following application of the cream (Figure 3).

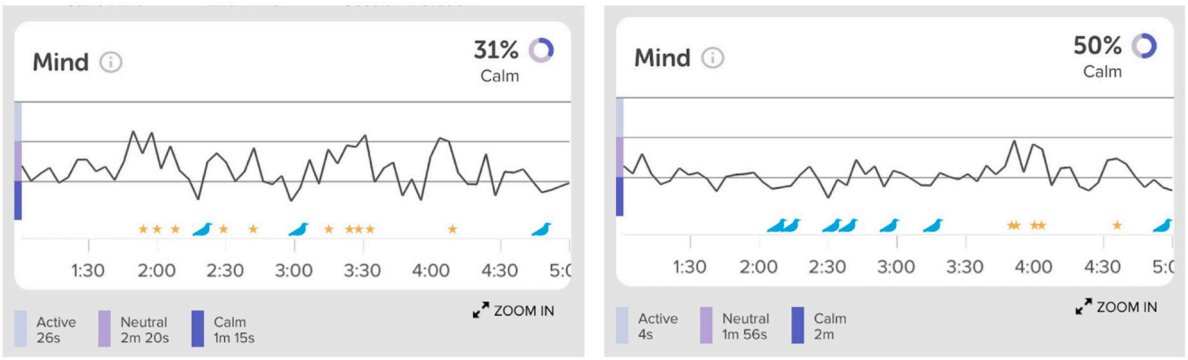

Figure 3. Results of a 5 min unguided neurofeedback training session "Mind Session Desert" following the instruction of the Muse EEG system. Left panel: before application of the cream. Right panel: after application of the cream.

The time spent in calm state increased from 75 to 120 sec (60% increase) regardless of the fact that the percentage of time spent in calm state during both sessions was lower than that recorded the previous day. In other words, the increase in calmness seems to be independent from the starting conditions.

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Consistent with these results, stillness, as measured by the accelerometer, increased from 43 to 85% of time during another 5 min unguided neurofeedback training session denominated "Heart Session Healing Drum" (Figure 4). More specifically, the relaxed state increased from 126 to 255 sec.

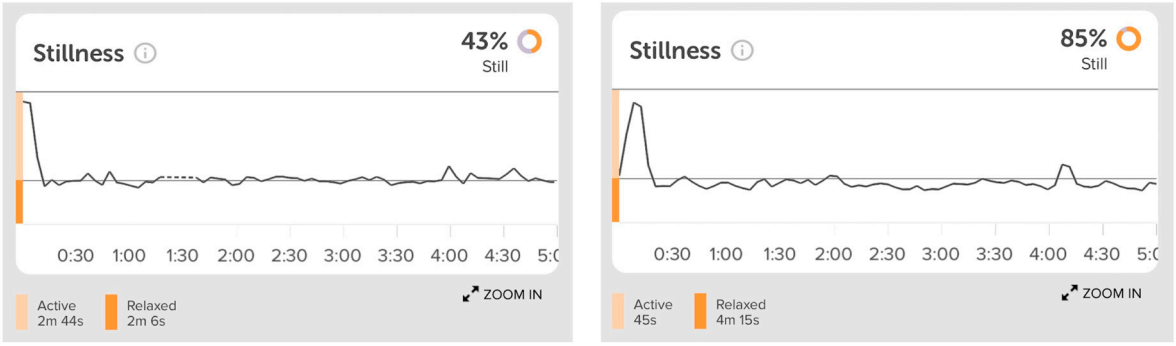

Figure 4. Stillness: results of a 5 min unguided neurofeedback training session "Heart Session Healing Drum " following the instruction of the Muse EEG system. Left panel: before application of the cream. Right panel: after application of the cream.

Discussion

Finding Stillness in the Storm: The Crucial Role of Mental Relaxation in the Modern World

The whirring of technology, the constant barrage of information, and the never-ending demands of a globalized world - these are the hallmarks of modern life. We are wired to be "on," hyper-connected, and perpetually productive. Yet, amidst this relentless march, a vital need goes neglected: the need for mental relaxation. This article shows a simple, efficient, and safe method to cultivate the ability to quiet the mind; this is not a luxury but a necessity in the modern world, critical for our physical, psychological, and even societal well-being.

The detrimental effects of a perpetually stressed mind are well-documented. Chronic stress weakens the immune system, increases cardiovascular risk, and fuels mental health issues like anxiety and depression. The "always-on" mentality also hinders cognitive function, impairing focus, creativity, and decision-making. In essence, living in a constant state of mental arousal becomes self-defeating, robbing us of the very resources we need to navigate the complexities of modern life.

So, how does one achieve this elusive state of mental relaxation? The answer lies not in escapism, but in intentional engagement with practices that cultivate inner stillness. These practices are diverse and deeply personal, ranging from meditation and mindfulness exercises to nature walks, creative pursuits, and spending time with loved ones. What matters most is the conscious effort to disengage from the constant mental chatter and allow the mind to enter a state of calm awareness. The transdermal GABA/CS delivery system described in this article was designed precisely for achieving the elusive state of mental relaxation and stillness.

The benefits of regular mental relaxation as that described following application of the GABA/CS cream are profound. On a personal level, it promotes resilience, enhances cognitive function, and fosters emotional well-being. Calmer minds are more apt to cope with stress effectively, find creative solutions to problems, and cultivate positive relationships. This ripple effect extends beyond the individual, impacting society as a whole. Workplaces with cultures that prioritize employee well-being and mindfulness demonstrably experience higher productivity and lower turnover. Communities that foster spaces for shared relaxation and reflection exhibit increased social cohesion and decreased rates of crime and violence.

The argument for prioritizing mental relaxation extends beyond mere anecdotal evidence. Research in neuroscience confirms the potent impact of relaxation practices on the brain. Meditation, for example, has been shown to increase activity in the prefrontal cortex, an area associated with self-

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control, focus, and emotional regulation. Additionally, relaxation practices can modulate the stress hormone cortisol, promoting physical and mental health.

Despite the compelling evidence, cultivating mental relaxation in the face of modernity's demands is a challenge and this is the reason why the GABA/CS cream described in this study was developed. We are conditioned to equate busyness with productivity, and stillness often feels like a luxury we cannot afford. Yet, prioritizing this seemingly " unproductive" time is an investment in our overall well-being, ultimately enhancing our capacity to engage with the world in a more effective and meaningful way.

The modern world, with its unrelenting pace and pressures, demands not just our productivity but also our presence. Embracing mental relaxation is not a retreat from life's challenges but a necessary counterpoint, a cultivation of the inner stillness that allows us to face those challenges with greater resilience, creativity, and compassion. By integrating practices of relaxation as well as the use of tools such as the cream described in this article into our daily lives, we not only invest in our own well-being but also contribute to a society that values human flourishing over relentless pursuit.

The potential benefits of transdermal GABA delivery, as evidenced by the results presented above, extend beyond individual well-being. In a world plagued by stress-related illnesses and diminished productivity, this technology holds promise for broader societal and economic gains. By effectively mitigating stress and anxiety, the transdermal GABA/CS delivery system could translate to a reduction in stress-related disorders like depression and anxiety, leading to improved overall population health and reduced healthcare costs. A calmer and more focused workforce leads to increased productivity and innovation, potentially boosting economic growth and competitiveness. Finally, transdermal GABA presents a safe and effective option for individuals across different age groups, from adolescents struggling with exam anxiety to older adults experiencing age-related sleep disturbances.

The Potential Role of transdermal GABA in Nonlocal Consciousness

The burgeoning field of nonlocal consciousness, encompassing phenomena exceeding the conventional limitations of space and time, has garnered increasing scientific interest; the transdermal GABA/CS delivery system here described is posed to give a significant contribute to this field of research. Within this arena, the state of dreaming, characterized by rapid eye movement (REM) sleep, emerges as a key window into these elusive experiences and it is well known that GABA plays a key role in REM sleep (Kim *et al*. 2019). Recent research has unveiled tantalizing connections between dream content, electro-cortical activity, and potentially, neurotransmitter signaling – specifically, the involvement of GABA, in facilitating nonlocal consciousness during dreaming.

A meta-analytic study examined 40 dream-ESP studies (comprising 52 datasets) conducted by 51 researchers between 1966 and 2016. Rigorous design and execution criteria ensured the inclusion of only the most robust investigations. Employing sophisticated statistical analyses, the study yielded a remarkable conclusion: dream content could be used to accurately identify target materials significantly more often than mere chance would dictate (Schwartz 2018). This finding provides compelling evidence for nonlocal consciousness during dreaming, where information seemingly transcends the physical constraints of space and time.

Further bolstering this notion, distinct alterations in electro-cortical activity have been observed during nonlocal experiences. Notably, a study by Delorme *et al*. (2013) documented statistically significant anomalous communications, defying conventional explanation, during specific experimental conditions. These anomalous communications were, furthermore, found to coincide with peculiar changes in electro-cortical activity, particularly the increased presence of theta waves.

Intriguingly, the neurotransmitter GABA has been intricately linked to the generation of theta waves. A study by Kopp *et al*. (2004) demonstrated a direct modulation of theta activity by GABA(A) receptor signaling. This finding, when considered alongside the link between theta waves and anomalous communications during nonlocal experiences (Delorme *et al*. 2013), suggests a potential role of GABA in facilitating nonlocal consciousness.

 doi:10.20944/preprints202401.0996.v1

While further research is crucial to fully elucidate the intricate relationships between GABA, theta waves, and nonlocal consciousness, these initial findings offer a fascinating glimpse into the mechanisms underlying this enigmatic phenomenon. Future investigations aimed at understanding the precise role of GABAergic signaling in dream-associated nonlocal experiences represent a promising avenue for advancing our comprehension of this captivating domain.

Limitations and Conclusive Remarks. Moving Beyond Dichotomies: Rethinking the Narrative in Evidence-Based Medicine

This article has a significant limitation that deserves consideration since the data presented in the Results section were observed on a single subject, the Author. Although this is a limitation, the value of the observations remains since they may be considered N-of-1 trials *as per* the definition by Nunn (2011); it has been argued that N-of-1 trials in the field of medical sciences are at the top evidence hierarchy because *they in fact represent the highest standards of establishing the benefits and harms of therapy in an individual* (Montori and Guyatt 2008). In addition, N-of-1 trials provide an unique opportunity *So a story of one person can trump the systematically reviewed stories of many experiments* (Nunn 2011).

It is generally believed that the gold standard of evidence in medicine consists in the randomized controlled trial (RCT), often positioned on a pedestal, while anecdotes languish at the bottom of the evidence hierarchy, deemed inconsequential or even irrelevant. This dichotomous view, where quantitative analysis reigns supreme and qualitative narratives are ostracized, has bled into other domains, leading to "evidence-based education" and "evidence-based government." The essay by Nunn (2011) challenges these artificial divisions, questioning the rigid separation of numbers from narratives, and science from the humanities. It specifically focuses on reclaiming the value of stories in medical evidence.

First, we must recognize the inherent narrative nature of all scientific evidence. Published reports are, at their core, stories of conducted experiments. Systematic reviews distill narratives of individual studies into broader narratives. Similarly, reviews of systematic reviews weave their own narratives from the tapestry of existing narratives. Yet, despite this interwoven web of stories, anecdotes are often ostracized, categorized as mere "soft" evidence.

However, it is crucial to acknowledge the diversity within narratives themselves. Some, like case studies, are grounded in direct observation and offer rich understanding of individual experiences. Others, like theoretical frameworks, weave stories based on existing evidence and logic to explain observed phenomena. Each narrative, regardless of its scale or structure, adds a thread to the tapestry of knowledge, offering valuable insights into what works in medicine.

Furthermore, dismissing narratives for their lack of statistical rigor fails to recognize the limitations of RCTs themselves. Blind spots exist in any methodology, and RCTs are not immune. They often struggle to capture the complicated reality of lived experience, the nuances of individual patient responses, and the complexities of real-world clinical settings. Narrative accounts, conversely, can fill these gaps, offering deeper context and a more holistic understanding of how interventions impact patients beyond mere statistical significance.

Therefore, to truly advance medical knowledge, we must move beyond rigid hierarchies of evidence and embrace the multifaceted nature of scientific inquiry. This requires acknowledging the value of diverse forms of evidence, including the N-of-1 trial here described, narratives, alongside quantitative data. By harnessing the power of both numbers and stories, we can weave a richer, more nuanced tapestry of medical knowledge, ultimately leading to better care for patients.

The promise of a pill for peace may remain largely unfulfilled with oral GABA. However, transdermal delivery technology offers a paradigm shift, paving the way for a future where harnessing the calming power of GABA is not a pipedream but a tangible reality. With its superior bioavailability, targeted delivery, and sustained release, transdermal GABA presents a potent tool for combating the modern epidemic of mental stress and promoting well-being across society. As research continues to refine this technology and address regulatory hurdles, transdermal GABA

stands poised to revolutionize the landscape of mental health interventions, offering a beacon of hope in a world desperately seeking inner peace.

Author Contributions: The author contributed solely to the work.

Funding: The author did not receive any funding for this study.

Consent to participate: Implicit in the authorship.

Ethical approval: Not applicable.

Acknowledgements: The author wishes to thank Dr. Christine Schaffner for encouragement in pursuing this line of research as well as for inspiring discussion.

Conflicts of Interest: The formula described in this study inspired the manufacture of a product that is commercially available. However, the author does not receive any benefit from the sales of this product.

References

Boonstra E, de Kleijn R, Colzato LS, Alkemade A, Forstmann BU, Nieuwenhuis S. Neurotransmitters as food supplements: the effects of GABA on brain and behavior. Front Psychol. 2015 Oct 6;6:1520. doi: 10.3389/fpsyg.2015.01520. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594160/

Corrêa HP, Moura CC, Azevedo C, Bernardes MFVG, Mata LRFPD, Chianca TCM. Effects of auriculotherapy on stress, anxiety and depression in adults and older adults: a systematic review. Rev Esc Enferm USP. 2020 Oct 26;54:e03626. Portuguese, English. doi: 10.1590/S1980-220X2019006703626. https://pubmed.ncbi.nlm.nih.gov/33111737/

Delorme A, Beischel J, Michel L, Boccuzzi M, Radin D, Mills PJ. Electrocortical activity associated with subjective communication with the deceased. Front Psychol. 2013 Nov 20;4:834. doi: 10.3389/fpsyg.2013.00834. https://pubmed.ncbi.nlm.nih.gov/24312063/

Denda M, Inoue K, Inomata S, Denda S. gamma-Aminobutyric acid (A) receptor agonists accelerate cutaneous barrier recovery and prevent epidermal hyperplasia induced by barrier disruption. J Invest Dermatol. 2002 Nov;119(5):1041-7. doi: 10.1046/j.1523-1747.2002.19504.x.
https://pubmed.ncbi.nlm.nih.gov/12445190/

Jin Z, Mendu SK, Birnir B. GABA is an effective immunomodulatory molecule. Amino Acids. 2013 Jul;45(1):87-94. doi: 10.1007/s00726-011-1193-7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680704/

Kim S, Jo K, Hong KB, Han SH, Suh HJ. GABA and l-theanine mixture decreases sleep latency and improves NREM sleep. Pharm Biol. 2019 Dec;57(1):65-73. doi: 10.1080/13880209.2018.
https://pubmed.ncbi.nlm.nih.gov/30707852/

Kopp C, Rudolph U, Löw K, Tobler I. Modulation of rhythmic brain activity by diazepam: GABA(A) receptor subtype and state specificity. Proc Natl Acad Sci U S A. 2004 Mar 9;101(10):3674-9. doi: 10.1073/pnas.0306975101. https://pubmed.ncbi.nlm.nih.gov/14990800/

Krigolson OE, Hammerstrom MR, Abimbola W, Trska R, Wright BW, Hecker KG, Binsted G. Using Muse: Rapid Mobile Assessment of Brain Performance. Front Neurosci. 2021 Jan 28;15:634147. doi: 10.3389/fnins.2021.634147. https://pubmed.ncbi.nlm.nih.gov/33584194/

Krigolson OE, Williams CC, Norton A, Hassall CD, Colino FL. Choosing MUSE: Validation of a Low-Cost, Portable EEG System for ERP Research. Front Neurosci. 2017 Mar 10;11:109. doi: 10.3389/fnins.2017.00109. https://pubmed.ncbi.nlm.nih.gov/28344546/

Kuriyama K, Sze PY. Blood-brain barrier to H3-gamma-aminobutyric acid in normal and amino oxyacetic acid-treated animals. Neuropharmacology. 1971 Jan;10(1):103-8. doi: 10.1016/0028-3908(71)90013-x https://pubmed.ncbi.nlm.nih.gov/5569303/

LaRocco J, Le MD, Paeng DG. A Systemic Review of Available Low-Cost EEG Headsets Used for Drowsiness Detection. Front Neuroinform. 2020 Oct 15;14:553352. doi: 10.3389/fninf.2020.553352. https://pubmed.ncbi.nlm.nih.gov/33178004/

Li J, Zhang Z, Liu X, Wang Y, Mao F, Mao J, Lu X, Jiang D, Wan Y, Lv JY, Cao G, Zhang J, Zhao N, Atkinson M, Greiner DL, Prud'homme GJ, Jiao Z, Li Y, Wang Q. Study of GABA in Healthy Volunteers: Pharmacokinetics and Pharmacodynamics. Front Pharmacol. 2015 Nov 10;6:260. doi: 10.3389/fphar.2015.00260.
https://pubmed.ncbi.nlm.nih.gov/26617516/

Mariotti A. The effects of chronic stress on health: new insights into the molecular mechanisms of brain-body communication. Future Sci OA. 2015 Nov 1;1(3):FSO23. doi: 10.4155/fso.15.21. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5137920/

Montori VM, Guyatt GH. Progress in evidence-based medicine. JAMA. 2008 Oct 15;300(15):1814-6. doi: 10.1001/jama.300.15.1814. https://pubmed.ncbi.nlm.nih.gov/18854545/

Moontaha S, Schumann FEF, Arnrich B. Online Learning for Wearable EEG-Based Emotion Classification. Sensors (Basel). 2023 Feb 21;23(5):2387. doi: 10.3390/s23052387.
https://pubmed.ncbi.nlm.nih.gov/36904590/

Nunn R. Mere anecdote: evidence and stories in medicine. J Eval Clin Pract. 2011 Oct;17(5):920-6. doi: 10.1111/j.1365-2753.2011.01727.x. https://pubmed.ncbi.nlm.nih.gov/21815971/

Oketch-Rabah HA, Madden EF, Roe AL, Betz JM. United States Pharmacopeia (USP) Safety Review of Gamma-Aminobutyric Acid (GABA). Nutrients. 2021 Aug 10;13(8):2742. doi: 10.3390/nu13082742. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8399837/

Pacini S, Gulisano M, Punzi T, Ruggiero M. Transdermal delivery of Clostridium botulinum toxin type A by pulsed current iontophoresis. J Am Acad Dermatol. 2007 Dec;57(6):1097-9. doi: 10.1016/j.jaad.2007.08.037. https://pubmed.ncbi.nlm.nih.gov/18021859/

Ruggiero M, Pacini S. Rationale for the design of a novel tool for immunotherapy based on an emulsion of glycosaminoglycan. Integr Cancer Sci Therap, 5(4): 2-5 2018 doi: 10.15761/ICST.1000285.
https://www.oatext.com/pdf/ICST-5-285.pdf

Schwartz SA. Non-Local Consciousness and the Anthropology of Dreams. Explore (NY). 2018 Mar-Apr;14(2):107-110. doi: 10.1016/j.explore.2017.12.005. https://pubmed.ncbi.nlm.nih.gov/29426694/

Wong WF, Ang KP, Sethi G, Looi CY. Recent Advancement of Medical Patch for Transdermal Drug Delivery. Medicina (Kaunas). 2023 Apr 17;59(4):778. doi: 10.3390/medicina59040778.
https://pubmed.ncbi.nlm.nih.gov/37109736/

Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A. The impact of stress on body function: A review. EXCLI J. 2017 Jul 21;16:1057-1072. doi: 10.17179/excli2017-480. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5579396/