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A Challenging Cornerstone of the Purpose and Meaning of Life via Reward and Role in Neurology and Addiction

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Abstract

The brain is the source of meaning and spirit. Addictions to smoking, alcohol, illicit drugs, and certain behaviors like gambling, overeating, taboo, and sex, are prevalent worldwide. These behaviors are highly destructive and costly to individuals and society due to health consequences, criminality and lost productivity. The genetic vulnerability, environmental exposures, and individual behaviors that contribute to the brain dysfunction and compulsive tendencies that mark addiction make it one of the most complicated diseases to study and treat. Much has been learned about the genetic basis of and biochemical imbalances associated with the addictions. Progress towards effective treatment has been retarded by insufficient

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attention being paid to understanding the role of spirituality in helping to heal addicts. We hypothesize that a healthy spirituality may come more naturally to some individuals because of the unique interaction of their genes and their environments. We review the evidence in support of this view. Consider the role of default mode network (DMN) as a way of how people process self and religiosity. We offer herein a novel concept we call the neurospirituality connectome as a cornerstone of the purpose and meaning of life as reward (PMLR). The consequences of non-treatment are attenuated by PMLR.

Keywords

Neurology, Addiction, Smoking, Alcohol, Illicit drugs, Default mode network

Introduction

In the USA alone, opioid use disorder (OUD) affects approximately 27 million people. While the number of prescriptions may be declining due to increased CDC guidance and prescriber education, fatalities due to fentanyl-laced street heroin continue to rise. Our laboratory has expanded the overall concept of both substance and non-substance addictive behaviors, coining it "reward deficiency syndrome (RDS)." Who are its victims, and how do we get this unwanted disorder? Is RDS caused by genes (Nature), environment (neuro-epigenetics, nurture), or a combination of both? Recent research identifies resting-state functional connectivity in the brain's reward circuitry as a crucial factor. Analogously, it is important to acknowledge that the cumulative release of dopamine, regulated by the nucleus accumbens (NAc) and modulated by an array of neurotransmitters, plays a pivotal role in an individual's overall well-being.

Neuroimaging studies have revealed that high-risk individuals exhibit a blunted response to stimuli, potentially due to DNA polymorphisms or epigenetic alterations. This discovery has given rise to the idea of a diminished 'thrill,' though it remains essential to consider whether this 'thrill' may have been absent from birth due to high-risk genetic predispositions for addiction. The concept of RDS has been adequately reviewed, and this dysfunction in the reward system indicates the significance of "induction of dopamine homeostasis" as a critical factor in addressing addiction [1-106].

We propose coupling a validated genetic assessment, such as the genetic addiction risk score (GARS), with pro-dopamine regulation therapies (e.g. KB220) as a possible frontline treatment for OUD, in place of prescribing potent addictive opioids, except in cases of short-term harm reduction. Could gene editing offer a 'cure' for this undesirable genetic predisposition, which is influenced by both genetic factors and environmental exposures, potentially passed down through generations and leading to impaired dopamine function and neurotransmitter imbalances characteristic of RDS? Through dedicated global scientific exploration, we hope for a future where individuals are liberated from pain and disease, achieving an optimal state of well-being akin to the proverbial "garden of eden."

Expressions of faith and healing

The following statements represent a multi-religious perspective on the concept of faith and healing. Each statement reflects the diverse viewpoints of the respective religions and does not necessarily indicate universal endorsement by all the individual co-authors.

Spirituality without religion: The pursuit of spirituality involves the effort to explain the unexplainable and seek wholeness and acceptance. Spirituality can be defined in various ways, some of which may evoke religious traditions, while others do not. However, they all share a common goal: the search for love of self and others, emotional comfort, and a connection with the transcendent. Over the course of history, this search has led to the development of various strategies,

including religion and certain philosophical practices, to guide individuals along their spiritual journeys. Every culture and most individuals, throughout history, have embraced beliefs and practices aimed at fostering spiritual growth.

However, all of life is rooted in biology, so why are humans particularly driven to this search for meaning and connection? While it remains unclear whether humans are the only animals with such a drive, some insights can be drawn from the evolution of brain capacities that have been essential for survival. These capacities, however, have the potential to magnify the importance of self to such an extent that it interferes with happiness and overall functioning. One brain system that plays a crucial role in this is the Default Mode Neural Network, initially identified in 1998 [107]. The DMN is a self-referential interconnectivity of brain systems that becomes active at rest and is less active during focused, goal-directed tasks. Key structures involved in DMN include the medial prefrontal cortex, posterior cingulate cortex, and other areas such as the precuneus, medial temporal lobe, hippocampal formation, and parahippocampal cortex [108]. These systems are integral to self-reflection and the ongoing internal narrative that drives human consciousness and the search for deeper meaning.

This DMN not only is related to the sense of self but is the location of Theory of Mind and is intimately related to, and may even result from, the development of language [109]. The ability to future-think and project the future onto the now and perform mental simulations is definitional to the evolution of humans, but if overactive, can be associated with worries, anxieties, depression, and uncertainties. And these abilities are the work of the DMN. The activity of DMN is diminished when a subject is engaged in focused, intentional activity, and the activity increases when idle or at rest. The activity of the DMN is diminished when an individual is engaged in focused, intentional tasks, but it increases when the mind is idle or at rest.

This might explain why persistent activity in DMN has become the norm for humans, even once basic survival and comfort are achieved. Given that the activity of the DMN is often dysphoric, it could be one of the reasons for the ongoing sense of unease that many individuals experience. As James Kingsland succinctly put it, "We have evolved into an ape that takes things personally [110].

The human response to self-reference, which has evolved to assign value to actions and characteristics predicting survival, often results in an exaggerated desire for these traits. The result is the potential for selfishness, dishonesty, resentment, fear, envy, gluttony, greed, lust, pride, sloth, and wrath. But does engagement in those wishes and behaviors produce love of self and others, emotional comfort, and connection with the transcendent? Not usually. Maybe not even ever. And are those survival-driven attributes all a description of self-centeredness? Our instincts for survival are, of course, necessary for survival, but how can one find the balance between self-care and self-centeredness?

The answer likely lies in intentional engagement in practices that help "right-size" the ego and spirituality. Galanter, in the Textbook of Addiction Medicine (6th Edition, p. 1101), suggests several characteristics of spiritual health that may be particularly beneficial for people struggling with addiction, emphasizing the role of spirituality in balancing the demands of survival instincts with a more holistic sense of well-being.

Affect: A sense of overall well-being.

Contentment with one's life circumstances: Acceptance and peace with one's current situation.

Positive affect: The experience of positive emotions and moods.

Feelings of support: A sense of being supported by others, particularly in times of need.

Existential variables: Awareness and consideration of existential questions about life, death, and purpose.

Meaningfulness in one's life: A deep sense of purpose and significance.

Flow: The ability to engage deeply in activities that allow one to use their highest strengths and abilities.

Spirituality: A connection to non-material aspects of life that provide meaning and purpose.

Personality: An understanding of personal strengths and characteristics, and how these contribute to personal growth.

Mutual help participation: Engagement in groups like anonymous alcoholics (AA) or other support networks that foster mutual assistance and shared experiences.

Certain aspects of spirituality that are crucial for spiritual health share commonalities. Practices such as love, compassion, tolerance, forgiveness, responsibility, altruism, and kindness foster behavior that counters self-centeredness. Embracing humility and striving virtuously often lead to deeper well-being than acquisitive, self-focused pursuits. While one can will oneself acquire knowledge, the same does not hold true for wisdom. Deciding to experience pleasure is within reach, but happiness cannot be willed. Meekness can be chosen, but humility is not a mere decision. Going to bed is an action, but inducing sleep is beyond conscious control [111]. Goals related to spiritual health often resist direct action but paradoxically respond to intentional efforts aimed at reducing ego-diminishing the focus on controlling others and the environment and engaging in acts of service. Engaging in practices that reduce DMN activity may align with these efforts, where divine wisdom may play a crucial role.

Various human conditions correlate with heightened DMN activity, including attention deficit hyperactivity disorder (ADHD), depression, anxiety, and addiction. Addiction and ADHD, and indirectly, anxiety and depression, are linked to decreased dopaminergic tone in the NAc and ventral tegmental area (VTA), known as RDS [10, 112, 113]. Tomasi's research demonstrated that blocking the DA transporter (DAT), thereby increasing DA tone, reduces DMN activity [113]. Activities or medications that enhance DA tone may reduce DMN activity, potentially mitigating the need for spiritual healing. However, whether reducing DMN activity alone fosters spiritual health or spirituality remains uncertain. While

it may diminish the need for spiritual healing, whether it concurrently enhances virtues like love and compassion remains an unresolved question.

Spiritual practices, such as meditation, have demonstrated a capacity to reduce DMN activity [114]. These practices are closely tied to activities and commitments that value the outcomes of the right living, ethical and moral conduct aligned with principles like integrity, compassion, responsibility, and care for others. Similarly, prayer modulates DMN activity and is frequently associated with commitment to selflessness and altruism [115]. These top-down regulatory activities offer valuable goals to both practitioners and the broader community. Importantly, meditation and prayerfulness share a common foundation that values kindness, honesty, responsibility, and concern for the welfare of others [105].

Hindu Perspective: Yoga assumes a crucial role in Hindu spirituality, not only for its ability to reset hormonal balance and alleviate anxiety but also as an integral element in addiction treatment. Programs leverage yoga independently or in conjunction with Twelve-Step programs, mindfulness, or psychotherapy for addiction treatment. Research by Shaffer of Harvard Medical School and others, highlights significant yoga-related reductions in drug use among patients in methadone maintenance programs [116, 117]. Various literature reviews suggest that yoga contributes to both short- and long-term recovery from addiction [118, 119].

In ancient India, spirituality was intricately linked with cosmology and the nature of existence. The Sanskrit word for knowledge, "Veda," reflects the Vedic paradigm, positing that knowledge is rooted in consciousness-a limitless source for everything. While Vedic writings like the Rig Veda or Upanishads are written in Sanskrit, there's an implicit understanding that the Veda is reflected in all existence, accessible to individual consciousness based on one's level of awareness. At its core, it is divided into a trinity emerging from unity, suggesting that as soon as the observer (all that is) asks, "Who am I?" there is a manifestation of the observed and the process of observing. The process of observation or knowing extends limitlessly, prompting exploration into the diverse manifestations of consciousness within Brahma, the supreme energy intricately connected with our existence. Notably, the Sanskrit term for the universe, Brahmanda, translates to the egg of Brahma in English.

Ayurveda, often termed the knowledge of life or lifespan, represents the health aspects of the Veda. Within Ayurveda, the trinity finds reflection in Pragyaparadha, denoting the mistake of the intellect, a fundamental cause of disease rooted in perceiving oneself as separate. Further, Asatmya Indriyartha Samyoga, describing the untruthful interaction of the senses with the environment, elucidates unhealthy attachments to touch, hearing, vision, taste, and smell. Disease culmination, as posited by Kala Parinama, represents the effects of space-time, where universal forces impact the consequences of dysfunction arising from Pragyaparadha and Asatmya Indriyartha Samyoga. This framework aligns seamlessly with the genetic foundation of addiction, viewing recovery as a reversal of these consequences through healthy interactions with the environment, emphasizing unity and connection, as proposed in our "neurospirituality connectome."

The Vedic framework, robust enough to underpin religions, is exemplified in Hinduism, where Brahma serves as the creator (observer), vishnu as the sustainer (observing), and Shiva as the Transformer (observed). Similarly, Christianity's trinity aligns with this framework, with God the Father (observer), the Holy Spirit (observing), and Jesus, the Son of God (observed), forming a manifest connection to God for followers.

Muslim perspective: In Islam, individuals grapple with balancing their lowly self-desires, "nafs," and their sacred spirit, "ruh" in Arabic. A Muslim's journey to overcome addiction involves moving from base impulses toward pure origins. The Quran's strong stance against alcohol and gambling may create cognitive dissonance for Muslim clients, and programs like Millati Islami (MI), an Islamized 12-step program, help reconcile their faith with proven systems like AA [120].

Buddhist perspective: The Buddha employed 'Ego' as we use 'I,' indicating the 'sense of self' or 'conceit of self.' Buddhist praxis aims to rid oneself of 'conceit,' achieved through analytical meditation and resulting insight. Practices involve calming or pacifying and possibly modulating neurotransmitter interactions, fostering an 'unshakeable liberation of mind.' This process aims towards calming or pacifying (Pāli: samatha; Sanskrit: śamatha; Chinese: 止 zhǐ) and elicits Benson's 'Relaxation Response.' One resultant mechanism may be the effective rebalancing of neurotransmitter interplay at the mesolimbic brain region [121].

Judaism perspective: The Talmud in Tractate Brachot acknowledges the coexistence of wheat and chaff, likening it to dreams having some nonsense. It emphasizes the concept of original purity and the capacity to change and atone to maintain the soul's integrity. In Tractate Eruvin, the Talmud offers insights into character evaluation through one's cup, wallet, and anger, highlighting the revealing nature of managing aspects such as drinking alcohol, financial matters, and emotions.

Sikhism: Sikhism, originating in the 15th century in northern India under the guidance of its first prophet, Guru Nanak Dev Ji, defines a Sikh as a disciple or learner. As a monotheistic religion, Sikhism emphasizes belief in one supreme God and champions the equality of all individuals. Three core tenets guide Sikhs: devotion to the creator through meditation and prayer, truthful earning and living, and dedicated service to humanity. Rejecting caste and class systems, Sikhs uphold values of honesty, compassion, generosity, humility, integrity, sharing, service, and daily spirituality. Sikhism sees the act of meditation as a connection with the supreme almighty God, fostering love and compassion among individuals at any time of day. This positive approach towards humanity is believed to trigger neurological highs, possibly involving DA release, contributing to the "neurospirituality connectome" and the healing process.

Model of neurospirituality connectome: Understanding complex neurologic and psychiatric syndromes transcends localized brain lesions. The human connectome, derived from

functional neuroimaging of thousands of healthy individuals, offers a comprehensive map of brain connections. Lesion mapping, an innovative approach, associate's lesions inducing similar symptoms with common networks, shedding light on the neurospirituality domain. Brain mapping scientists are encouraged to explore heightened activity in the DMN during SUD with potential connections to GARS. Epigenetic studies on methylation/demethylation could unveil the impact of religiosity and non-religious spirituality on the brain's reward circuitry. For instance, research might explore whether Twelve-Step programs inhibit deacetylation of reward genes and prevent them from being silenced (e.g. DRD2) differently in short and long-term members.

Properly studied connectome localizations hold the potential to identify new treatment targets for patients grappling with complex neurologic and psychiatric symptoms. While evolutionary differences between humans and apes in pleasure systems exist, delving into the neurospirituality connectome aids in understanding the evolution of classic lesion localization and functional integration of the analytic method of lesion network mapping (Figure 1).

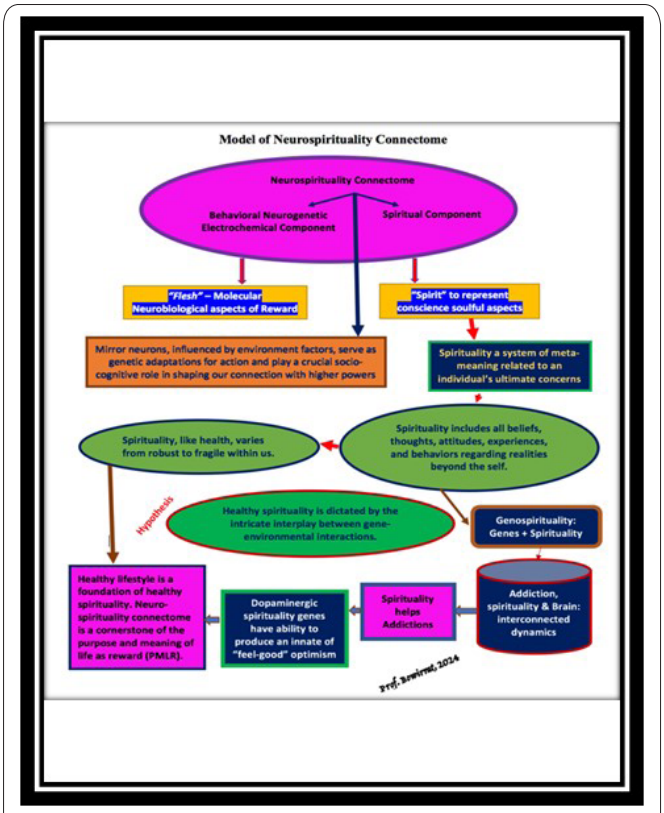


Figure 1: Schematic of model of neurospirituality connectome.

Summary: Unlocking the Nexus of Genes, Spirituality, and Lifestyle

The intricate interplay of genetics within diverse religious communities, encompassing Jews, Muslims, Christians, and others, remains a pivotal focus. This exploration shapes our identities and our trajectory in navigating the realms of spirituality and the pursuit of a higher power. Irrespective of individual beliefs, a nuanced interaction of spirituality and genetic and environmental factors distinctly influence healthy lifestyles. Intriguingly, belief in God, transcending religious affiliations, is intricately linked to improved short-term psychiatric treatment outcomes [122].

In our contemplation, we endeavor to forge connections between the neurospirituality connectome and the foundational aspects of life's purpose and meaning encapsulated in the framework of PMLR. While this aspiration may seem ambitious, its inherent merit should not be dismissed, urging acceptance from both the faithful and the non-believers. Echoing spiritual perspectives emphasizing that everything emanates from a divine source, exists through divine power, unfolds for divine glory, and aligns with the teachings of Paul, thereby underlining the interconnectedness of all elements within the human experience-"everything comes from God alone, everything lives by his (her) power, and everything is for his (her) glory. And, in line with the teachings of Paul-"We're only as healthy as our oldest, sickest, least developed part."

Drawing inspiration from Paul's teachings (1 COR 12:4-27), the following insights are elucidated by one of us (ERB):

- Even so the body is not made up of one part but of many.
- Now if the foot should say, "Because I am not a hand, I do not belong to the body," it would not for that reason stop being part of the body.
- And if the ear should say "If the whole body were an eye, where would the sense of hearing be?
- If the whole body were an ear, where would the sense of smell be?
- But in fact, God has placed the parts in the body, every one of them, just as God wanted them to be.
- If they were all in one part, where would the body be?
- As it is, there are many parts, but one body
- The eye cannot say to the hand, "I don't need you!" And the head cannot say to the feet, "I don't need you!"

On the contrary, those parts of the body that seem to be weaker are indispensable, "In conclusion, we posit that the pursuit of life's purpose and meaning pivots on the concepts of reward and pleasure. While the tangible pursuit of rewards and physical pleasures often centers on the concept of "Flesh," the quest for abstract happiness intertwines with the "Spiritual" realm, including the acceptance of a higher power, as advocated by the twelve steps and various self-help groups. Notably, a palpable disconnect persists between the atheistic viewpoint and the prevailing belief in a higher power among the majority of Homo sapiens. In this dichotomy, even in light of perspectives such as David Coming's assertion that man created God, the quest for meaning, as elucidated in Viktor Frankl's "Man's Search for Meaning," remains pertinent. Frankl's recounting of his experiences in Nazi concentration camps underscores the transformative power of identifying a purpose, showcasing the enduring pursuit of meaning across diverse belief systems.

Neurospirituality connectome: Unraveling genetic, spiritual, and therapeutic dimensions

An intriguing exploration of the neurospirituality connectome emerges through diverse narratives, exemplifying its profound influence on human behavior and well-being. One poignant illustration delves into the molecular genetic basis of historical atrocities, such as the Holocaust, as investigated by Blum's group and others [38, 123]. The focus on the dopamine D2 receptor gene (DRD2) and its alleles unveils a potential link to the aggressive genotype prevalent among Aryan Germans during Hitler's reign. Genotyping Holocaust survivors becomes a significant avenue, with implications for understanding reward gene polymorphisms and subsequent behaviors in survivors-an endeavor aligning with Viktor Frankl's philosophies and reinforcing the PMLR concept.

The poignant tale of Pastor Richard Warren, author of "The Purpose Driven Life," adds another layer to the Neurospirituality connectome. Tragically, Warren's son's battle with uncontrollable depression underscores the mental health challenges intertwined with spirituality. The development of the GARS test and precision pro-dopamine regulation offers hope for addressing anhedonia and suicidal ideation, aligning with the overarching theme of PMLR. The proposed "Neurospirituality Connectome" emerges as a novel doctrine, seamlessly intertwining neurological and spiritual realms to provide profound healing opportunities.

A simplistic yet profound coupling of Flesh (representing the brain) and Spirit (representing GOD) surfaces as a potential avenue for healing, particularly in cases of hypodopaminergia [124-134]. The reconciliation of scientific perspectives with spirituality is exemplified by respected scientists, such as Nobel laureates Frank Wilcznek and Martin Van Buren, who acknowledge the role of awe in science as a form of reward, viz., "--to find reward, we must be born again in awe of science." Furthermore, the narrative highlights Francis Collins, a renowned medical geneticist, and his perspective on theistic evolution. Collins, former director of the US National Institutes of Health (NIH), in his bestselling book The Language of God: A Scientist Presents Evidence for Belief emphasizes the healing aspect of Christ's actions, linking it to the intended path for humanity [135]. In the book, Collins describes briefly the process by which he became a believer as a Christian. He once stated –"It's interesting when you read the life of Christ how much of his time, he spent healing the sick. There must have been a reason for that - he was modeling for us what it is we intended to do by following his path. However, Collins is a critic of intelligent design. He stated in an interview that "intelligent design is headed for collapse in the not-too-distant future" and that "science class ought to be about science and opening the door to religious perspectives in that setting is a big mistake" [114].

Despite reservations about intelligent design, Collins advocates for the integration of science and religious perspectives. While in terms of evolution, it is now known that, for example, apes differ neurologically from humans, the authors here, in crafting this treatise, still endorse an appreciation for both the flesh and spirit as the best medicine for overcoming RDS [6, 136]. Amidst the backdrop of evolutionary differences between humans and apes, the authors contend that Homo sapiens, by embracing both elements, can evolve into a more compassionate and superior mammalian species on Earth testament to the profound impact of the Neurospirituality connectome on human evolution and well-being.

Nurturing well-being: A paradigm beyond illness

In the pursuit of understanding mental health, the significant contributions of Seligman and fellow researchers resonate as they advocate for a holistic approach. Amidst robust molecular psychiatric exploration and the development of effective treatments for mental illness, Seligman's emphasis on everyday well-being emerges as a pivotal consideration, encourages a shift toward positive psychology by positing the question: what defines a life worth living in a world free of mental illness?

The positive psychology movement, championed by Seligman and his peers, posits that true happiness extends beyond the absence of illness. Instead, it centers on cultivating positive emotions, fostering gratification, and uncovering the meaning of life. The endeavor to build a foundation of positive emotion becomes a cornerstone for a fulfilled and contented existence.

This paradigm shift underscores the importance of supplementing traditional approaches to mental health. While the scientific and clinical community diligently explores treatments and interventions for mental illnesses, nurturing well-being in individuals and communities takes precedence. The intricate interplay between mental health and well-being, especially in conditions like alcohol use disorder (AUD) viewed as a subtype of RDS, demands a comprehensive understanding. The envisioned synergy between treating illness and nurturing well-being becomes a transformative force, enriching lives and fostering a more resilient and thriving human experience (Figure 2). In this narrative, the call to broaden our perspective challenges us to embrace the alleviation of suffering and the promotion of flourishing, thereby redefining the contours of mental health discourse. With this sentiment, it is important for the scientific and clinical community to supplement what we know about treating illness and repairing damage with knowledge about nurturing well-being in individuals and communities (Figure 2) [137] especially in AUD as a subtype of RDS [138].

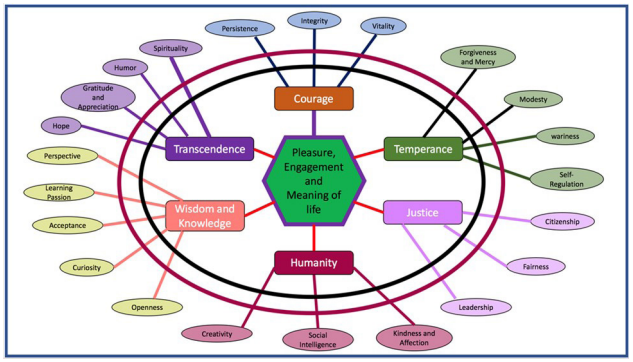


Figure 2: Characteristics of life's meaning modified.

Summary - Rediscovering Eden, a Journey Toward Eternal Reward

In contemplating the profound words from Revelation (REV 22:1-21), we find ourselves immersed in the vision of the restored Garden of Eden. Within this sacred revelation, Jesus declares, "I shall return; my reward is with me." This declaration beckons both skeptics and believers to envision a divine homecoming-one that transcends the mundane and echoes with the promise of a sublime "dopamine fix."

Consider, for a moment, the tantalizing prospect of rekindling euphoria and bliss reminiscent of the genesis at the "gardens of eden." The very thought stirs the imagination, eliciting a cascade of emotions akin to an outpouring of love and happiness, echoing the euphoric resonance of dopamine-induced joy. Whether one stands on the side of faith or skepticism, the allure of this utopian return to Eden, accompanied by the prospect of a celestial reward, is a testament to the enduring human quest for fulfilment. The metaphorical journey toward this eternal reward, propelled by the anticipation of divine recompense, becomes a universal narrative that transcends religious boundaries.

In essence, the "dopamine fix" takes on a spiritual hue, representing not just a biochemical reaction but a profound awakening of the human spirit. It becomes a metaphor for the soul's quest for transcendence, where the Gardens of Eden serve as a symbol of unbridled joy, harmony, and a reunion with the divine.

As we navigate the realms of belief and skepticism, the notion of a return to Eden, coupled with the promise of an imminent reward, becomes a shared human aspiration. In this collective yearning, the echoes of Revelation resonate, inviting us to envision a reality where the pursuit of eternal joy intertwines with the essence of our very existence. The journey towards this metaphysical reward encapsulated in the profound words of Jesus (to those who believe), becomes a narrative that transcends the boundaries of time and belief-a timeless odyssey toward the restoration of Edenic bliss. Our take-home message is that whether or not one believes in a higher power or not, the embracing of some kind of spiritual connection to the "collective consciousness" seems parsimonious. In fact, spiritual awareness may lead to positive psychological thinking or awareness of their being, resulting in the reinstatement of RDS behavioral relapse prevention.

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Conflict of Interest

None.

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