ECRONICON OPEN ACCESS

EC NEUROLOGY
Review Article

Neurospirituality Connectome - Role in Neurology and Reward Deficiency Syndrome (RDS)

Kenneth Blum[1-10]*, Eric R Braverman[1], Milan Makale[11], Foojan Zeine[8,12], A Kenison Roy 111[13], Jag Khalsa[14], David E Smith[15], David Baron[2,16], Nicole Jafari[3,17], Debasis Bagchi[18], Catherine A Dennen[1,19], Abdalla Bowirrat[4], Albert Pinhasov[4], Panyotis K Thanos[1,4,20], Keerthy Sunder[2,10,21], Kevin T Murphy[9], Miles R Makale[22], Edward J Modestino[1,23], Kai-Uwe Lewandrowski[1,23,24-26], Alireza Sharafshah[1,23,27], Igor Elman[4,23,28], Aryeh Pollack[1], Chynna Levin[1], Rossano Kepler Alvim Fiorelli[29], Sergio Schmidt[30], Alex PL Lewandrowski[1], Shaurya Mahajan[1], Daniel Gastelu[1], Gianni Martire[1] and Rajendra D Badgaiyan[1,23,31]

[1]Division of Reward Deficiency Syndrome, The Kenneth Blum Behavioral and Neurogenetic Institute, Austin, TX, USA

[2]Division of Addiction Research and Education, Center for Sports, Exercise, and Global Health, Western University Health Sciences, Lebanon, OR, USA

[3]Division of Developmental Progression, Global Growth Institute, San Clemente, CA, USA

[4]Department of Molecular Biology and Adelson School of Medicine, Ariel University, Ariel, Israel

[5]Brain and Behavior Laboratory, Department of Psychology, Curry College, Milton, MA, USA

[6]Division of Personalized Pain Mechanisms, Center for Advanced Spine Care of Southern Arizona, Tucson AZ, USA

[7]Institute of Psychology, ELTE Eötvös Loránd University, Budapest, Hungary

[8]International Awareness Integration Institute, San Clemente, CA, USA

[9]Division of Personalized Neuromodulation, Peak Logic, Del Mar, CA, USA

[10]Division of Neurogenetics and Behavior, Sunder Foundation, Palm Springs, CA, USA

[11]Department of Radiation Medicine and Applied Sciences, UC San Diego, La Jolla, CA, USA

[12]Department of Health Science, California State University at long Beach, Long Beach, CA, USA

[13]Department of Psychiatry, Tulane University, School of Medicine, New Orleans, LA, USA

[14]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

[15]Department of Pharmacology, University of California San Francisco, School of Medicine, San Francisco, CA, USA

[16]Department of Psychiatry, Stanford University, School of Medicine, Palo Alto, CA, USA

[17]Department of Applied Clinical Psychology, The Chicago School of Professional Psychology, Los Angeles, CA, USA

[18]Department of Pharmaceutical Sciences, Southern University College of Pharmacy, Houston, TX, USA

[19]Department of Family Medicine, Jefferson Health Northeast, Philadelphia, PA, USA

[20]Behavioral Neuropharmacology and Neuroimaging Laboratory, Clinical Research Institute on Addictions, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA

[21]Department of Psychiatry, University of California, Riverside School of Medicine, Riverside, CA, USA

[22]Department of Psychology, University of California San Diego, La Jolla, CA, USA

[23]Brain and Behavior Laboratory, Department of Psychology, Curry College, Milton, MA, USA

[24]Department of Orthopaedics, Fundación Universitaria Sanitas Bogotá D.C., Colombia

[25]Department of Surgery, University of Arizonia, School of Medicine, Tucson, AZ, USA

[26]Department of Orthopaedics, Universidade Federal do Estado do Rio de Janeiro, Brazil

[27]Cellular and Molecular Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[28]Department of Psychiatry, Harvard University School of Medicine, Cambridge, MA., USA

[29]*Department of General and Specialized Surgery, Gaffrée e Guinle Universitary Hospital, Federal University of the State of Rio de Janeiro (UNIRIO), Brazil*

[30]*Post-Graduate Program in Neurology, Federal University of the State of Rio de Janeiro, Brazil*

[31]*Department of Psychiatry, Texas Tech University Health Sciences, School of Medicine, Midland, TX, USA*

***Corresponding Author:** Kenneth Blum, Division of Reward Deficiency Syndrome, The Kenneth Blum Behavioral and Neurogenetic Institute, Austin, TX, USA.

Received: December 20, 2024; **Published:** January 27, 2025

Abstract

Addictions are alarmingly prevalent worldwide, leading to severe health issues, disruptive relationships, diminished productivity, and increased criminal behavior, which collectively impose substantial and tragic costs on individuals, families, and society. Addiction arises from a complex interplay of factors, including genetic predispositions, environmental triggers, and individual behavioral patterns, rendering addiction research and treatment particularly challenging. Although considerable data on the neurophysiology of addiction exists and pharmacological interventions are available, patient compliance and motivation remain crucial factors that have been relatively overlooked. Spirituality may play a significant role in fostering healing behaviors and deserves more attention in addiction treatment. Due to the unique interaction between genetic and environmental factors, healthy spirituality may come more naturally to some individuals than others. This hypothesis is supported by the literature we review, which situates spirituality within the cognitive and emotional processes of self-identity and religiosity. Evidence suggests that recovery from substance use disorders is often more successful when individuals have well-defined life goals. The brain's Default Mode Network (DMN) may be instrumental in this context. We introduce the novel concept of the Neurospirituality Connectome, which we posit as central to the understanding of reward processing. This proposed synergy between the psycho-neural substrates of cognition, emotion, and spirituality could provide a self-sustaining impetus and framework, aiding patients in navigating the complex psychophysiological landscape of addiction recovery.

Keywords: *Neurospirituality Connectome; Purpose and Meaning of Life as Reward (PMLR); Genetic Addiction Risk Severity; Hypodopaminergia; Religiosity; Geneospirituality; Self-Help Groups*

Introduction

Neuro-spirituality connectome

Those viewing at addiction from the outside, see it as damaging, noting that addictions of various kinds are rampant in human societies worldwide and are associated with known genetic antecedents [1]. However, it is widely held that neurogenetic predispositions are not the only drivers of addiction, rather it is thought that addictions derive from what is termed "Purpose Meaning of Life as Reward (PMLR)" deficiencies. From the internal perspective of individuals possessing the neurogenetic phenotype underlying addiction (e.g. opioids), the condition is perceived as an internal conflict, marked by horrific suffering often exacerbated by public misunderstanding.

In the patients experience purposeful meaning of life as reward deficiencies are not the cause of addiction but rather a symptom.

In a 1996 article, Reward Deficiency Syndrome (RDS), implicated psycho-neural reward deficiency as a creative influence for manifesting substance use disorder and cyclic relapse [2]. Yet addicts bear the disrespect of those who believe they brought addiction

upon themselves and deserve what they get. Addiction is the only disease in which the patient is vilified and disrespected with judgements implying a deficiency of purpose, meaning, character and integrity.

Neural reward deficiency serves as a creative influence for manifesting substance use disorder and cyclical relapse. The treatment strategy based on RDS has developed over decades of intensive neuropharmacological research and incorporates two separate approaches that are not mutually exclusive requiring intensive investigation.

The type 1 approach involves psychopharmacologic interventions, that can currently be realized, offering temporary mitigation of addiction severity. However, this method is not a cure, and any given patient will require careful monitoring over his or her lifespan [3].

The type 2 pathway which has not been tested, would be based on specifically targeted genetic editing which could offer the possibility of a cure. For example, CRISPR is a gene editing tool for gene regulation, chromatin engineering, epigenetic editing, and imaging, and may eventually be a viable methodology in the context of addiction treatment [3]. However, development of transplice molecules and its processing is much better without directly affecting DNA.

It is clear that genetic approaches will take time, and that physiological, epigenetic, psychotherapeutic, and spiritual factors may interrelate to play a major role in addiction treatment. Hence, an effective approach is required now to address what is an urgent public health and societal need.

A key approach that can be pursued and that needs to be explored is Neurospirituality, a concept that is based on two components, (1) a spiritual, and (2) a behavioral neurogenetic electrochemical. For our purposes we apply the term *"spirit"* to represent our soulful aspects, and the term *"flesh"* to represent the molecular neurobiological aspects of reward. Our thesis relates to the somewhat mystical concept which states that while *spirit* and *flesh* are separate, it seems even more reasonable to consider the strong interaction of these two elements and as such the integration of these two human elements could help repair the epigenetic dysfunction which induces deleterious states such as addiction [4,5]. It is noteworthy that there are novel psychological approaches such as positive mindfulness, and Awareness Integration Therapy (AIT) that could induce some relief.

Sacred texts from all religious faiths inspire man's spirituality, mind-body interaction, encouraging positive thinking, which may evoke a more circular neurological healing process to restore reward homeostasis. Does the spiritual enter a reciprocal relationship with the flesh? Is this unique to human brain circuitry, rather than non-human primates [6]. Previously wellness practices, align mind and body in an integration of the flesh with spirit. The use of the wellness practices in addiction treatment has resulted in significant reductions of relapse and increases in wellbeing [7].

Early in the last century, societal perceptions often characterized substance abuse as moral deviance, but contemporary scientific understanding recognizes it as a complex interplay of genetic, neurobiological and environmental factors, leading to a more compassionate approach to support individuals facing these challenges.

The connection between religion/spirituality was first made by Durkheim (1912) who observed spirituality decreases substance abuse by preserving norms and social bonds. The importance of social norms and customs as constraints on substance abuse is validated by numerous studies over the past three decades addressing binge drinking in college undergraduates in the United States and Europe. In this, genomic era of medicine, addictions are recognized as endotypes of impairments in brain reward circuitry. When neurogenetic and neurobiological influences known as RDS, are untreated, substance use disorders behaviors result, perhaps appearing as deviance, to those who misunderstand the neurobiology driving self-medication.

Spirituality as a key measure in addiction recovery was examined by Schoenthaler and colleagues (2015) who investigated a population sample size of 2,947. These subjects were interviewed one year after treatment and asked about relapse [7]. The researchers hypothesized that subjects with low spirituality had elevated relapse rates for substance use, while subjects with high spirituality exhibited greater remission rates. Results varied according to substance. Expectedly individuals with assumed preexisting neurogenetic and neurobiological antecedents, self-medicated with different drugs, including alcohol, cocaine in all its forms, including crack, heroin and marijuana. Likert scale measurement of religious attendance frequency, intensity of religious belief, frequency of reading religious books, watching religious programing, meditation and prayers reported a 7 to 21% decrease in drug use, as compared to those labeled nonreligious. Higher rates of remissions were supported by Puffer., *et al*. who found that weekly attendance of religious services correlated with significantly higher rates of remission [8].

Thankfully in the genomic era of precision medicine, patients possessing neurogenetic addiction background can get assistance for the brain impairment known as Reward Deficiency Syndrome. RDS predates the act of self-medication for relief through substances and the myriads of addiction subsets [9]. Figure 1 is useful to illustrate the concept of an array of anatomical loci that house important regions linked to neurotransmission, which regulate the net release of dopamine in the Nucleus Accumbens (NAc), in the mesolimbic region of the brain.

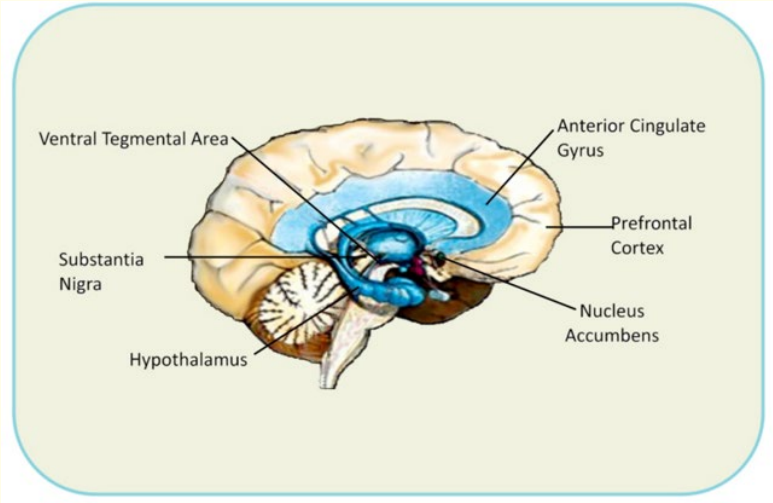


Figure 1: *Illustrates the anatomical connections involved in the brain reward cascade (BRC) and is obtained from the internet (internet image at https://search.yahoo.com/search?fr=mcafeeandtype=E210US739G0andp=brain+reward+circuitry+) accessed 2024.*

Carlsson, Greengard and Kandel's psycho-pharmacological research investigated network signaling which balances serotonin, endorphins, glutamate and dopamine for which they were awarded a Nobel Prize. Other early pioneers, Blum, Gold, Volkow, Nester etc. have a produced series of seminal works, which form the very foundation for understanding the context of dopamine as a driver, to various signaling functions and behaviors [10]. More so, they created language/terminology utilized by second-generation scientists, such as "brain reward cascade, dopamine depletion, biogenetics, reward deficiency syndrome and genomic medicine".

There is such a discrepancy of understanding between research and practice, regarding addiction and mental health disorder clusters. Traditional treatment protocol prescribed opioids, and easy access drive this epidemic of overdoses, and opioid use disorders (OUDs). Presently on the practitioner level, the clinical consensus is to treat OUD as if it were an opioid deficiency syndrome, with long-term to

life-long opioid substitution therapy (Medication Assisted Therapy - MAT). Opioid agonist administration is seen as necessary to replace missing opioids, treat OUD, and prevent overdoses, like insulin is used to treat diabetes. Treatment of OUD and addiction, in general, is similar to endocrinopathy conceptualization, in that opioid agonist MAT is held to be an essential central therapy. Ironically, the industry wants to treat drug abuse with drugs, in a trial and error fashion with could help, but may not, and far worse, could cause harm. Is this approach logical? Other than as harm reduction, is using opioids to treat OUD therapeutic or harmful in the long term? We now know many mechanistic underpinnings related to not only heroin seeking but also the induction of neuroplasticity associated with addiction and addictive behaviors, and how does MAT relate to these processes?

Pursuing addictive drugs is controlled by synaptic plasticity, in the nucleus accumbens core and entails plasticity in D1- and D2-medium spiny neurons (MSNs). Synaptic plasticity and drug seeking behavior, which is elicited by drug-paired cues, relies on plasticity, in the canonical pre- and post-synapse, and on cue-induced changes, in astrocytes and the extracellular matrix (ECM) adjacent to the synapse. But the coordination of differential plasticity between the D1and D2 cell types remains unclear.

The neurological details include explanation that drug cue-induced signaling in the ECM is regulated by catalytic activity of matrix metalloproteases-2 and 9 (MMP-2 and MMP-9). Chioma., *et al*. (2021) hypothesized that cell-type specific synaptic plasticity is linked to simultaneous cell-specific MMP-2 and MMP-9 activity. They found that heroin-paired cues (transiently) increased MMP-9 activity, around D1-MSM dendritic spines, as well as increasing synapse-proximal astro-glial processes. On the other hand, extinction training induced long-lasting increases in the activity of MMP-2 adjacent to D2-MSN synapses. Additionally, heroin-paired cues increased tissue inhibitor of MMP-1 and MMP-2, which caused transient inhibition of MMP-2 activity around D2-MSNs during cue-induced heroin seeking [11]. Although the details listed above are challenging for those who are not neuroscientists.

Animal studies lead to applications for humans, like the Genetic Addiction Risk Severity (GARS) test, which is essential for neurological analysis for informed genomic pharmaceutical intervention. This test provides evidence to help in understanding the underlying causes of Reward Deficiency and suggests potential methodologies for DNA guided precision regulation of dopamine levels.

Dopamine is a major neurotransmitter implicated in behavioral and substance addictions, yet still there remains controversy about how to modulate dopamine clinically to treat and prevent various types of addictive disorders. Traditional treatment modalities from the last century choose dopamine antagonist treated from back when they thought addiction was about pleasure. However, understanding the importance of Blum's concept Reward Deficiency Syndrome, and those research participants fortunate enough to know that mild dopamine agonist therapy has been helpful may be the wave of the future. Perhaps a better approach may be biphasic; a short-term blockade followed by long-term dopaminergic upregulation.

Enhancing brain reward functional connectivity volume, is the goal. Dopamine deficiency is the cause of highly stressful symptomology of addiction, such as anhedonia, craving, dysphoria, impulsivity, etc. By utilizing GARS, patient's gene variances are identified, and based upon neurological analysis of these issues, a precision genomic response can be implemented [12]. Precision Addiction Management (PAM) or Precision Behavioral Management (PBM) are therapies which assist the client in achieving dopamine homeostasis. Nutrient supplements are essential to helping heal the brain and reverse the impairment [13].

To complement GARS screening, understand neurological challenges, brain imaging tools are also helpful for research and practice. Dr. Daniel Amen utilizes spectroscopy (SPECT), an isotope based modality for brain imaging, allowing neuro-specific pharmaceuticals to locate and reveal regional cerebral blood flood (rCBF) [15]. Basically, this reveals oxygen availability, which is thought to equate to brain activity. Dr. Braverman utilizes Brain Electrical Activity Mapping for evaluation of electrophysiological anomalies [14]. In fact, not only are we seeing an increase in further development of neuroimaging techniques to help access for example addiction liability, but the coupling of these brain electro-magnetic diagnostic technologies has important relevance even to help target physiological deficits identified by

these imaging analyses. Thus, electromagnetic therapies, coupled with these imaging predictive risk tools, along with addiction genetic risk, are valuable resources help attenuate anxiety and depression, increasing meditation, and facilitating restorative rest.

Self-help and the neuro-spirituality connectome

Some psychologists believe that alcoholism and drug abuse are not diseases, not consequences of a brain disorder, as posited by the American Society of Addiction Medicine (ASAM) [16]. Some argue that substance abusers have the capacity to abstain and lessen their alcohol and drug intake. Last century's understanding and solution seemed to embrace the entering of the 12-Step Program and Fellowship. And notably there have been a few one chip wonders who were able to maintain sobriety. This raises the question of nature (genetic DNA antecedents to pre-addiction as a trait) or possibly the easier recovery for these individuals is associated with nurture (environmental epigenetic mechanisms as a state not trait condition). Some followed the Harm Reduction Model. Some found God. Some picked up white chip after white chip. Many died. One study of great interest, Blum., *et al*. attempted to delineate individual differences in recovery, and/or spirituality by defining the molecular neurobiological basis within the 12 Step Program [17].

Precision genomic addiction medicine, employing a molecular neurobiological approach to recovery can greatly enhance a patient's ability to settle into the community of the 12 steps fellowship, making it easier to sustain abstinence.

When a client achieves dopamine homeostasis, life is easier all the way around. They no longer have to fight the war within, and the shift to self-love and self-nurturance is the beginning of a beautiful life. Moreover, Blum., *et al*. previously cited the current literature to help explain the molecular neurobiological and genetic links, particularly as they correlate to the role of epigenetic changes that are likely in people who regularly attend Alcoholics Anonymous (AA) meetings [17]. It is widely acknowledged that spirituality helps in coping with substance abuse and managing cravings. For instance, in the former USSR, where alcoholism was widespread and atheism prevalent average lifespan dropped to 57 years, indicating the detrimental impact of substance abuse and lack of spiritual support on public health.

An oft confusing question asks "Does the 12 steps programs and fellowship" cause neuroplasticity and continued dopamine D2 receptor proliferation in spite of carrying hypodopaminergic type polymorphisms such as DRD2 A1 allele? Absence of the so-called "*psycho-social-spiritual trio*," may not result in the significant benefits afforded by adopting 12-step principles. Are we better off combining medical assisted treatment (MAT) that favors mixing dopamine agonist modalities (DAM) as possible histone-deacetylase activators with the 12 steps followed by a program that encompasses either one or the other? While there are several unanswered questions, we have reached a stage at which "science meets recovery," and thus can potentiate the challenging process of attaining joy in recovery.

From a spirituality view Step One clearly proclaims *Honesty*: *"We admitted that we were powerless over alcohol/addictions/and to find meaning/reward and that our lives had become unmanageable".* While Step Two proclaims *Hope: "Came to believe that a power greater (i.e., God) than ourselves could restore us to sanity".* While the concept of POWERLESSNESS [17] is open to frank discussion, the initial phase is accepting individual powerlessness in the face of overwhelming cravings, which indeed is backed by the actual mechanisms implicated in neurobiological circuits.

The concept of POWERFULNESS, which is used in rational and cognitive behavioral therapy is also backed by neurobiological circuits. There is a neurology for every emotion, feeling, thought, and action. A neurology of empowerment, spirituality, faith, hope, love. There is a theory which says we choose our thoughts. So, what will it be? Resentment or Gratitude. The new age of recovery wants to know when is genomic medicine going to be available to the average patient? When genomic medicine is taught to practitioners, patients may gain access to genetic screening, nutrient therapies, and genomic interventions, which will be helpful in assisting one to achieve dopamine homeostasis. In the genomic era of addiction medicine, the first step should be healing the impaired brain. This is the standard and in comparison, traditional treatment is no longer good enough.

The aggregate statistical data suggests that alcoholism reduces a person's life expectancy by 24 - 28 years [18]. The suicide rate is high in chronic alcoholics, and the risk of suicide increases the longer alcohol has been abused. About 3 - 15% of alcoholics commit suicide and over 50 percent of all suicides are associated with alcohol or other drug dependency [19]. Suicide is relatively frequent in adolescent alcohol abusers, with 25% of suicides in this age category tied to alcohol abuse [19,20]. The outcomes of a 60-year trajectory of alcoholic men showed that "return to controlled drinking infrequently continued for over a decade without relapse or evolution into abstinence" [21]. Accordingly, the notion of a "return-to-controlled drinking", as reported in some short-term studies, is often illusory". In contrast, others believe heartedly in the Harm Reduction Model.

Valliant noted the importance of eight positive emotions. Exploring the intricate dimensions of human experience unveils a tapestry of emotions and spirituality, encompassing elements such as a sense of the miraculous, love/attachment (embodied in love languages, notably touch), trust, faith, compassion, gratitude, forgiveness, joy, and hope. These constituents collectively form what we define as spirituality, a domain often overlooked in psychiatric discourse [22].

Valliant's insights into organizations like Alcoholics Anonymous (AA) yield nuanced propositions:

- AA's effectiveness lies in supporting a select few to abstain from drinking.
- For the majority, AA proves less productive and even may exacerbate alcohol addiction [22].
- The strength of AA lies in fostering unwavering belief rather than curbing problem drinking.
- Compatibility with AA is more tied to personality type than drinking patterns.
- Black-and-white thinkers find resonance in AA, while those favoring gray areas seek empirical evidence [22].

Despite Valliant's acknowledgment of the 12-step approach's potential in reducing relapse risk, contemporary research explores broader dimensions. Our laboratory, for instance, establishes an inverse relationship between spirituality and substance abuse [7]. Neurophysiological studies hint at the role of receptors like 5-HT-1A in spiritual experiences, although findings vary. Genetic factors, such as the short 5-HTTLPR, influence spiritual acceptance [24,25].

Mindfulness practices, exemplified by meditation, illuminate the link between spirituality and brain reward circuitry [26,27]. Expert meditators exhibit enhanced impulse control, suggesting potential modulation of dopamine release. This could contribute to better clinical outcomes and sustained resistance to relapse. Venturing into unconventional perspectives, we propose that the "Neuro-spirituality connectome" might unveil a visionary path, echoing the concept of mirror neurons. This neuronal adaptation for action understanding could signify a socio-cognitive role in evolutionary processes [28]. Controversially, we consider the interplay of the universal force (Big Bang) with spirituality, suggesting a parallel between the initial creation and the divine influence in subsequent scientific advancements. The theological premise that a higher power, encompassing genetics, science, math, and physics, guides humanity through challenging times aligns with the concept of "Positive Thinking". Even those skeptical or atheistic may turn to a higher power during distress, finding solace in the idea of an accepting and omnipotent entity.

This broader perspective sheds light on the relevance of approaches like Alcoholics Anonymous (AA), founded in 1935 [30]. AA's twelve-step program, which emphasizes spiritual and character development, is considered alongside criticisms, including a high dropout rate [32,33]. Integrating precision genetic testing and modalities inducing pro-dopamine regulation could enhance the acceptance of AA or similar doctrines [17,34]. A multimodal treatment approach, blending scientific rigor with spirituality, aims for improved outcomes. Examining Pastor Warren's doctrines further intertwines reward mechanisms, epigenetic repair, and the search for life's purpose. Warren's teachings, such as "The Flourishing Tree" and "The Absolute Creation of Everything," offer a contemporary view that bridges

science and spirituality [37]. Understanding life as a reward from God provides a framework for addressing addictive behaviors and achieving epigenetic repair.

Synthesizing scientific inquiry, spiritual exploration, and innovative approaches can pave the way for a more comprehensive understanding of addiction and recovery. The intertwining threads of neuroscience, genetics, spirituality, and therapeutic modalities offer a rich tapestry for addressing the complexities of human behavior and the pursuit of well-being. The uniqueness of human brain in the universe coupled with its ability to create a nonexperimental yet thoroughly profound and relevant discipline like higher mathematics, is exceedingly suggestive of a God-like dimension to humanity. Accordingly, Kenneth Blum's group has formulated some interesting concepts such as the interplay between the cosmos and evolutionary biology, alpha bonding in biological molecules, and environmentally induced epigenetic effects on DNA.

They also discover how physical forces can impact human memory, behavioral traits, and rates of addiction. Impulsiveness is used to epitomize how environmental changes can impact epigenetics and hereditary changes. Blum., *et al*. suggest the idea of the existence of a "mental universe," where brain functionality like consciousness is a continuum of physically altered pathways [38]. This may relate to humanity's link to God and the evolution of higher mathematics. The understanding that the universe and all of its principles remains a secret is echoed in the lack of a standardized "unified" physics theorem and mathematical equation that can elucidate universal dimensions (physical and mental), and as such, so is the complex nature of the functionality of the human brain. As such Blum's group provided a suggestion to remedy possible confusion, whereby they attempt showing the brain as a complex quantum-like organ and the effect of epigenetics on behavioral expression.

The behavioral and neurogenetic view: Connecting the dots

There is proof that through the 12-step program and fellowship, crosstalk between the prefrontal and cingulate cortex, the site of decision-making, and the NAcc, the site of craving behavior, is developed. Over half a century of scientific research on the mesolimbic system has provided insight into the neurogenetic mechanisms driving the addictive brain. The aforementioned brain structures comprise the reward center, where chemical messengers, including dopamine (DA), serotonin, enkephalins, and γ-aminobutyric acid (GABA), work together, to provide a net release of DA in the NAcc. Genes regulate various aspects of neurotransmitters function, including synthesis, vesicular storage, metabolism and catabolism as well specific receptors expression, binding and activity [39-41]. One of the signaling pathways deeply regulated by different polymorphic variations in these genes responsible for the neuronal events termed "The Brain Reward Cascade" ultimately involving DA release (See figures 1-4) [42]. A breakdown of this Cascade will lead to the dysregulation and dysfunction of DA homeostasis. Dopamine has been recognized as the "PLEASURE AND ANTI-STRESS MOLECULE".

Any decline in DA function can lead to a deficiency in reward that causes substance seeking behavior [43]. However, those with substance use disorders know - self-medicating is about relieving pain, not achieving pleasure. From their perspective of an addict, pleasure has been off the table for quite a while. These individuals need to feel comfortable in their own skins, needing a desperate reprieve from the neurobiology precedents which is the war within, full of anxiety, craving, stress, not feelings comfortable in their own skin, an insatiability knowing that something is terribly wrong, mood swings, dysphoria and most of all, self-hatred. However, despite the enormity of the challenge, despite the ugliness of public opinion, some do achieve a meaningful, purposeful life. Some addicts are doctors, some are even scientists. Some may be spiritualists. Some even die sober.

After an extensive span of hundreds of thousands, potentially millions, of years, in stark contrast to a purported 6,000 years, *Homo sapiens* continues its evolutionary journey. Driven by biological imperatives essential for species survival, humans navigate a complex array of necessities such as drinking, eating, reproducing, and seeking pleasurable experiences linked to well-being and reproduction. While the brain of a chimp, based on cognitive tests, can perform well as a young human child, the human brain size has quadrupled over 4

million years including structures across our reward system, and vastly outstrips the chimpanzee in terms of intellectual capabilities and cognitive-emotional subtly and complexity [44]. The rapid pace of human evolution is evident in recent traits, including straight black hair, blue eyes, and lactose tolerance, suggesting a form of guided evolution under the influence of a higher power, often interpreted as the hand of God by those conditioned by religion. A contrary perspective would disagree, seeing religion as mental illness and noting that other species seem to be at peace with source quite naturally, without making up stories which are factual in face of critical thinking. Everyone has the right to choose a god of their own understanding, but the choice to believe in religion, in a god, is a personal truth. Science is concerned with empirical truth, one that be replicated, measured, adapted through application.

The transition from hunting and gathering to agrarian societies marked a pivotal shift, allowing for new advantageous mutations driven by enhanced reproductive opportunities. The unfolding human genome and subsequent generations are anticipated to be compilations of past genetic information, influenced by the dynamic processes of epigenetics. The ability to construct elaborate structures such as churches, skyscrapers, and cities underscores the profound distinction between *Homo sapiens* and our closest relative, *Homo ergaster*. Notably, the human brain, surpassing that of a chimpanzee in terms of intellectual capabilities and cognitive-emotional subtlety, has quadrupled in size over 4 million years, with considerable expansion and superbly nuanced functions in structures associated with our reward system [44]. So how is it that human beings seem to have lost their way, created deities but lost their balance, with source. Creating religion, god in their own image, but killing the mother earth which gives them life?

Dysregulation of the intricate mechanisms governing reward responses to natural processes manifests in various impulsive, compulsive, and addictive behaviors influenced by genetic polymorphic antecedents. This raises the question: Is dysregulation also a symptom of religious experiences? There is a growing movement in psychology to classify belief in religion as a form of mental illness. Which neurochemicals are involved in this process? While we have a robust understanding of the brain centers involved in dopamine depletion-related mental health disorders, including addiction, the role of the right temporal lobe, which has been associated with spirituality and religious experiences, remains less clear. How does the human brain manifest genetic variations within mesolimbic activity? Polymorphisms of key genes encoding the serotonergic 2A receptor (5-HT2AR), serotonergic transporter (SERT), DA D2 receptor (DRD2), DA D4 receptor (DRD4), DA transporter (DAT1), catechol-O-methyltransferase (COMT), and monoamine oxidase (MAO) enzymes contribute to predispositions for excessive cravings and atypical reward-driven behaviors (See figure 2).

The concept of Reward Deficiency Syndrome (RDS) emerged in 1996, describing behaviors associated with a common genetic variant involving DRD2 polymorphisms as potential predictors of impulsive, compulsive, and addictive behaviors (See table 1).

Having inherited genetic polymorphisms, that the religious may perceive as potentially endowed by the creator, (but more pragmatically inherited from parents), may result in diminished serotonergic and/or dopaminergic receptor densities. Or accelerated rates of synaptic dopamine (DA) catabolism, especially in individuals with a high catabolic genotype of the COMT gene, leading to reduce DA availability. Why is it that some are born with problematic blueprints which will cause suffering for themselves and others? Why is it that those with substance use disorders will also have to carry the brunt of public lack of understanding? So many who suffer neurological imbalances will also suffer hate, bullying, violence and loathing.

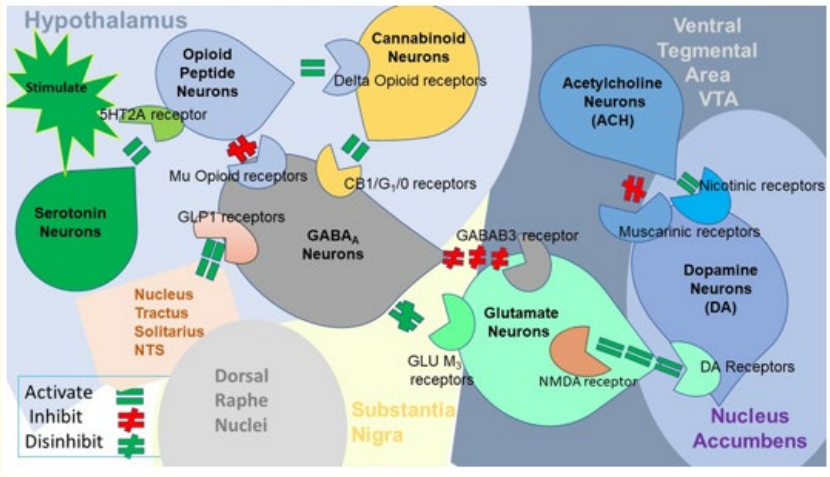


Figure 2: *The mesolimbic Brain Reward Cascade (BRC). This cartoon illustrates the interaction of some well-known BRC neurotransmitter pathways. Environmental stimulation initiates the release of serotonin in the hypothalamus, which in turn, via 5 HT-2 A receptors (for example) activates (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons. Then, in the Substantia Nigra (SN), the opioid peptides bind to two distinct opioid receptors with different properties. One is through the mu-opioid receptor that inhibits (red hash sign) GABAA neurons (possibly via an opioid peptide like enkephalins). The second stimulates endocannabinoid synthesis (for example, the Anandamide and 2-arachidonoylglycerol (2-AG)) (green equal sign) through beta-endorphin-linked delta receptors, which inhibit GABAA neurons. When released, cannabinoids, primarily the 2-AG, can disinhibit (green hash sign) GABAA neurons indirectly by G1/0 coupled to CB1 receptor activation. The Glutamate neurons in the Dorsal Raphe Nuclei (DRN) disinhibit GABA-ergic neurons in the Substantia Nigra indirectly through GLU M3 receptor activation (green hash sign). When disinhibited, GABA-ergic neurons will powerfully inhibit (red hash signs) VTA glutaminergic drive via GABAB 3 receptors. At the Nucleus Accumbens (NAc), Acetylcholine (ACH) neurons activate (red hash sign) muscarinic and stimulate Nicotinic (green hash) receptors. GABAA neurons, when stimulated, will, in turn, powerfully (red hash signs) inhibit VTA glutaminergic drive. Glutamate neurons in the VTA will project to dopamine neurons through NMDA receptors (green equal sign) to preferentially release dopamine at the NAc leading to a euphoria, or "wanting" response. The figure also shows that the GLP1 from the Nucleus Tractus Solitarius (NTS) stimulates GABAA in the Substantia Nigra. The result is that when dopamine release is low (endorphin deficiency), unhappiness is felt while general (healthy) happiness depends on the dopamine homeostatic tonic set point (Blum ©.2020 reference 113 modified with permission).*

Addictive Behaviors		**Impulsive Behaviors**		**Obsessive Compulsive Behaviors**	**Personality Disorders**
Substance Related	**Non Substance Related**	**Spectrum Disorders**	**Disruptive Impulsive**		
Alcohol	Thrill seeking (novelty)	Attention-deficit Hyperactivity	Anti-social	Body Dysmorphic	Paranoid
Cannabis	Sexual Sadism	Tourette and Tic Syndrome	Conduct	Hoarding	Schizoid
Opioids	Sexual Masochism	Autism	Intermittent Explosive	Trichotillomania (hair pulling)	Borderline

Sedatives/Hypnotics	Hypersexual		Oppositional Defiant	Excoriation (skin picking)	Schizotypal
Stimulants	Gambling		Exhibitionistic	Non-suicidal Self-Injury	Histrionic
Tobacco	Internet Gaming				Narcissistic
Glucose					Avoidant
Food					Dependent

Table 1: *Reward deficiency syndrome (from Blum., et al. modified copyright with permission-reference 46).*

The association between drug use and the release of DA in the mesocorticolimbic system or the brain's reward pathway is illustrated in figure 3 [50]. Without sufficient DA function, individuals may be inclined to self-medicate with substances or behaviors that stimulate DA release, including alcohol, nicotine, psychostimulants, opiates, glucose, sex, gambling, and excessive internet gaming [51].

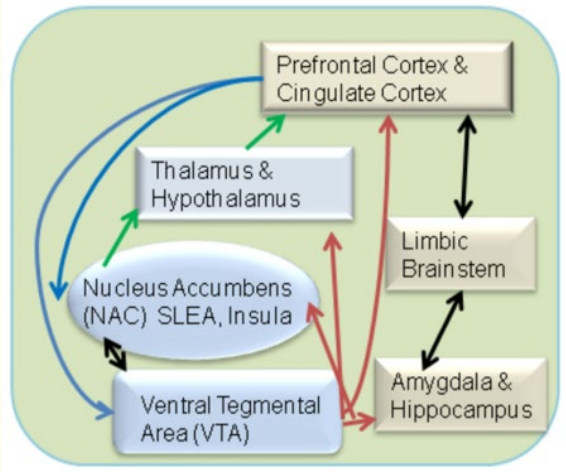


Figure 3: *Brain Reward sites (internet image at https://search.yahoo.com/search?fr=mcafeeandtype=E210US739G0andp=brain+reward+circuitry+) accessed 2024.*

Activation of the dopaminergic system produces feelings of reward and pleasure, a process influenced by epigenetic factors [52,53]. However, hypodopaminergic functioning can trigger drug-seeking and other RDS behaviors, overlaying the potential for addiction [54,55]. Gene polymorphisms can induce hypodopaminergic functioning through mechanisms such as diminished DA receptor density, blunted response to DA, or increased DA catabolism in the reward pathway [56]. The cessation of chronic drug use can also lead to a hypodopaminergic state, prompting drug-seeking behaviors in an attempt to address withdrawal-induced states [57].

It seems that both religion and narcotics are drugs which influence neurology - religion can impact neural processes related to emotion, cognition, and social behavior, while narcotics directly affects neurotransmitter systems in the brain, such as dopamine, leading to profound alterations in mood and behavior.

While one may ask the question arises: Can God's design show the way forward? Another may wonder "If this religious nonsense will ever stop causing problems for others? The narrative suggests a lack of love, a lack of spirituality, or a disrespect for other human beings. Could all of this negativity really come down to DA D2 receptors, DNA, amino acids, sugar molecules? [58].

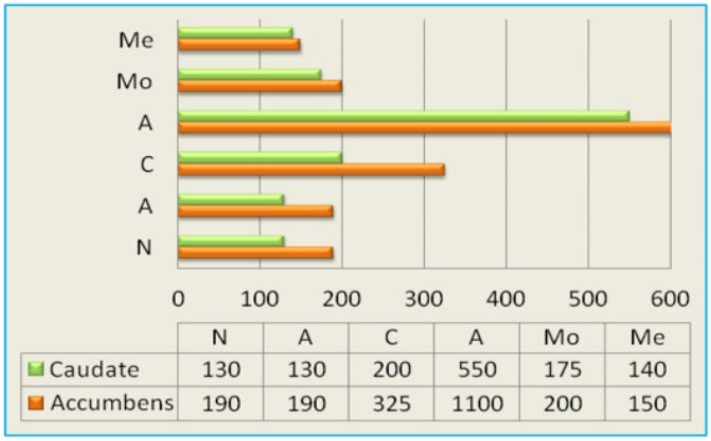
In vitro studies show that continuous stimulation of the DA receptor system with a known D2 agonist, even in low doses, leads to significant negative feedback mechanisms, inducing the expression of mRNA and resulting in the proliferation of D2 receptors. Gene therapy, such as DNA-directed overexpression of DRD2 receptors, has demonstrated a substantial decrease in both alcohol and cocaine craving behavior in animals [60-62]. But this is one neurotransmitter, one out of a hundred.

The old narrative from the last century is that human brains can be hijacked by powerful substances created by humans. The narrative from this century is that underlying neurobiological influences are shared commonalities in mental health disorders. Yes, scientists in the know realize addiction is an endotype, a symptom. When the practitioner and layperson world remain out of touch, and out of date with cutting edge science, they can harm those who are already suffering beyond merit. It is the conscientiousness of the recovering world that if doctors cannot step up, they at least step down.

The hypothesis presented here suggests that the powerful effects of drugs, music, food, and sex on human motivation followed by a rewarding event may be partially attributed to DA function in the ventral striatum [73]. This indeed is not spiritual it is physiological.

This narrative explores the human need for three essential motivated behaviors: hunger, thirst, and sex, positing that these behaviors have molecular-genetic antecedents. Impairments in these antecedents can result in abnormal behaviors. Scientific evidence supports the hypothesis that sexual activity, akin to drugs, food, and music, activates the brain's mesolimbic reward circuitry. Dopaminergic genes and their polymorphisms are proposed to influence both hedonic (pleasure) and anhedonic behavioral outcomes. The anticipation is that future genetic studies of sex addiction will unveil polymorphic associations, leading to the identification of sexual typologies based on clinical evaluations.

Encouraging both academic and clinical scientists to engage in neuroimaging studies of natural dopaminergic agonistic agents, such as KB220Z™, is emphasized by a number of investigators. The aim is to systematically target specific gene polymorphisms and normalize hyper- or hypo-sexual responses [74,75]. Insights from drug-microinjection studies, particularly those involving opioids in brain reward regions like the ventral medial striatum, highlight their role in enhancing the liking of sweet-taste rewards. The addiction cycle is noted to sometimes commence with substances like sugar, carbohydrates, salt, fat, and sex. Hedonic hotspots within brain structures, identified through *Fos* plume mapping, contribute to the amplification of liking for specific rewards [76]. Excessive hedonic liking is implicated in conditions like RDS and may lead to compulsive consumption. Figure 4 presents a succinct schematic introduction to mesolimbic reward circuitry, offering a framework for understanding the potential interplay of neurogenetics and neurotransmission, particularly involving DA, in the development of well-being. The application of this understanding is proposed in the context of the 12-step doctrine, suggesting a molecular neurobiology model for recovery within a spiritual context, as previously discussed in earlier publications [17].



	N	A	C	A	Mo	Me
Caudate	130	130	200	550	175	140
Accumbens	190	190	325	1100	200	150

Figure 4: *Percent of dopamine release in the caudate and accumbens as measured by microdialysis. Di Chiara G, Imperato [51] A -modified-Abbreviations: Me (Methadone); Mo (Morphine); A (Amphetamine); C (Cocaine); E (Ethanol); N (Nicotine) (modified with permission Blum., et al. [115]).*

Geno-spirituality: A snapshot

In our exploration of how spirituality might be linked to the human genome, it's crucial to clarify the term "spirituality". In this context, spirituality is not synonymous with religion or supernaturalism. Religion is viewed as a system of beliefs about specific realities, while supernaturalism is the philosophical assumption that there are causal realities beyond the perceptible through empirical methods of inquiry. Instead, spirituality, as conceptualized here, is recognized as a system of meta-meaning associated with an individual's ultimate concerns. It refers to the importance of objects or events beyond superficial or mundane relationships, always describing 'something-more' in terms of how an individual understands their personal purpose and value in the world.

Spirituality encompasses all beliefs, thoughts, attitudes, experiences, and behaviors associated with or about realities outside the self. Self-transcendence, prevalent in most spiritual rituals, represents a way of seeing oneself in the world that extends into a way of being in the world. Spirituality can be positive or negative, healthy or unhealthy. In the words of Jerome Dollard, "Spirituality is a lot like health. We all have health; we may have good health or poor health, but it is something we cannot avoid having. The same is true of spirituality: every human being is a spiritual being. The issue is not whether we 'have spirituality' but whether the spirituality we have is a negative one that results in isolation and self-destruction or one that is more positive and life-giving [77].

With this understanding of spirituality, the narrative suggests that some individuals may be genetically susceptible to 'spiritual health'. The call for research into the genetics of spirituality is motivated by phenomenological proof suggesting an association between spirituality and addiction. The hypothesis proposes that healthy spirituality may come more naturally to some individuals due to their distinctive gene-environmental interactions. This connection between genes and spirituality is referred to as *geneospirituality*.

Acknowledging the association of addiction, spirituality, and the brain, the narrative observes that addicts seek positive experiences by using substances to impact the brain. The inquiry into geneospirituality raises questions about how addictive substances work against spirituality and vice versa. To answer this question, it is crucial to establish that the brain mediates all conscious and unconscious experiences, including spiritual ones. Wesley J. Wildman, in his book "Religious and Spiritual Experiences," describes this as the neural mediation hypothesis [78]. He emphasizes that the mind does nothing we can detect that is not exhaustively mediated by and expressed

in the brain. Although this is still a point of debate, Wildman points out that this thesis is well-supported, and skeptics would bear the burden of proof to explain otherwise.

Research findings, such as those by Nilsson and his colleagues highlight genetic associations with spirituality [79]. The short 5-HTTLPR genotype and short AP-2beta genotype are linked to self-transcendence and spiritual acceptance, with substantial interactive effects noted between these genotypes. The association of addiction, spirituality, and the brain is instinctively acknowledged by observing that addicts seek positive experiences by using substances to impact the brain. This leads to the exploration of neurochemistry and genetics connected to these effects and their relevance to spirituality.

Nilsson and coworkers [79] observed that self-transcendence and spiritual acceptance were negatively associated with the short 5-HTTLPR genotype and positively associated with the short AP-2beta genotype, among boys. Interactive effects were noticed between 5-HTTLPR and AP-2beta genotypes in both boys and girls concerning measures of self-transcendence and spiritual belief. The existence of the short 5-HTTLPR, combined with homozygosity for the long AP-2beta genotype, was associated with lower scores on self-transcendence and spiritual acceptance.

The exploration of geneospirituality emphasizes the intricate interplay between genetics, neurochemistry, and spirituality. Genetic predispositions are considered influential in shaping an individual's spiritual health, with implications for addiction and overall well-being..

Subjects with homozygosity for the long AP-2beta genotype scored substantially lower on self-transcendence and spiritual acceptance [80]. In this respect, Comings and associates have found gene polymorphic associations with spirituality [80]. Hamer, in his popular book "The God Gene," indicated that the selection for dopaminergic spirituality genes was driven by their ability to produce an innate sense of "feel-good" optimism [81]. Therefore, this would have discerning value in the sense that optimism relates to the will to continue living and procreating, in spite of the fact that death is unavoidable [82]. Moreover, studies have revealed that optimism seems to endorse better health and faster recovery from disease, features that would have positive selective value [83]. Newberg suggested a distinct kind of relationship of spirituality with a feel-good sensation. They proposed that the neurological machinery of spiritual transcendence might have evolved from neural circuitry (limbic system) that grew for mating and sexual experience [84].

This view aligns with outcomes on dopaminergic genes and DA function in relation to their roles in improving pleasure and diminishing stress [84]. Comings., *et al*. and others, also found the role of a specific gene in spirituality [80]. The gene was the DA D4 receptor gene (DRD4) gene, which was observed to play a role in novelty seeking, one of the personality traits in Cloninger's Temperament and Character Inventory, and has been correlated with compromised DA signaling in an *in vitro* study [85,86]. Comings., *et al*. did recognize the genetic importance of self-transcendence, but the association of this gene and novelty seeking related to dopaminergic circuits did not arise in a sample of substance abusers [87,88]. Specifically, there was a borderline association with a self-forgetful sub-score but a strong correlation with spiritual acceptance. Additional gene which encodes to vesicular transporter (VMAT2), was also described to be associated with spirituality [80]. The fact that two dissimilar genes, DRD4 and VMAT2, have been found to be associated with spirituality, and the fact that DA is a feel-good neurochemical, could help explain why spirituality plays an influential role in the human condition and why the majority of people derive great comfort and happiness from a belief in a God [89].

It is of additional importance that in the Comings., *et al*. studies, those individuals who scored high on self-transcendence were less prone to abuse alcohol or drugs [80,90]. Consequently, this might be because individuals whose reward pathways, and perhaps other interacting pathways (serotonergic) were activated by spirituality, and thus would have less need to artificially activate their reward circuitry with foreign substances like ethanol and cocaine. This is certainly the central pillar of AA's twelve steps [17].

Moreover, Borg., *et al*. at the Karolinska Institute in Sweden reported that the binding of ethanol was lowest in those with the maximum scores for self-transcendence, suggesting, "Such individuals had higher levels of brain serotonin" [24]. They demonstrated that the serotonin1A receptor gene was significantly related to scores on the self-transcendence scale and with the substance of spiritual acceptance. It is notable that the lysergic moiety in LSD structurally resembles 5-HT and has modifying effects through psychedelic spiritual experiences. Moreover, Wilson was very interested in utilizing LSD to mitigate alcoholism [17]. Lastly, many diverse plants around the world contain a range of psychedelic drugs (serotonergic, opioid, and catecholaminergic), which are able to powerfully enhance one's spirituality and/or spiritual awareness. Comings and colleagues, and others, further pointed out that these entheogens (good-producing substances) played a deep and vital role in enabling humans' early belief in a god or gods and in the development of religion [80,91]. Bachner-Melman formulated the fascinating notion that serotonergic neurotransmission in some human studies appeared to facilitate human religious and spiritual experiences [92]. We thus hypothesize that the association between AVPR1a and SLC6A4 reflects the social communication, courtship, and spiritual facets of the dancing phenotype instead of other aspects of this complex phenotype, such as sensorimotor integration.

It is important that generalized healing is reliant on expressions of genes and its resultant activity-dependent neurogenesis, and stem cell healing is anticipated as the molecular-genomic-cellular basis of rehabilitative medicine, physical, and occupational therapy along with many alternative and complementary approaches to mind-body healing. According to Rossi, the therapeutic replaying of enriching life experiences that evoke the novelty of a neurogenesis effect during creative instants of art, music, drama, dance, humor, literature, poetry, and spirituality, along with cultural rituals of life changes (birth, puberty, marriage, illness, healing, and death) can adjust consciousness, personal relationships, and healing in a manner that has much in common with the Psychogenomic basics of naturalistic and complementary medicine [93]. The complete history of alternative and complementary methods to healing aligns with this new neuroscience world view about the role of psychological arousal and captivation in modulating gene expression, neurogenesis, and healing via the psychosocial and cultural rites of human societies.

In terms of church attending and genes, Kendler and Myers noted that as individuals mature, they progressively shape their own social environment in large part by means of their genetically influenced temperament [94]. When individuals are younger and living at home, recurrent church attendance imitates a range of familial and social-environmental influences that decrease levels of substance use. In adulthood, by contrast, high levels of church attendance mainly index genetically affected temperamental factors that are protective against substance use.

In a paper by Boomsma., *et al*. data on personality, anxiety, depression, and several aspects of religion were gathered in 1974 Dutch families comprised of adolescent and young adult twins and their parents [95]. The main point of this type of research was that upbringing moderates the influence of genetic factors on sensation seeking in male twins. Furthermore, Koopmans., *et al*. analyzed the role of religious upbringing as a mediator of both shared environmental and genetic effects on the peril of alcohol use initiation in a large population-based sample of Dutch adolescent and young adult twins (1967 twin pairs) [96]. They hypothesized that "the comparative magnitude of the genetic influences on the risk of alcohol usage initiation would be greater for those adolescents and young adults who were raised in a less religious environment compared to those adolescents and young adults who were raised in a more religious environment". In principle, they found more heritability for females without a religious upbringing compared to females with a religious upbringing: particularly, genetic influences accounted for 40% of the variation in alcohol usage initiation in nonreligious females, compared to 0% in religiously raised females. There may be powerful epigenetic influences at work in these contexts.

Shared environmental influences accounted for 54% of the variance for nonreligious females and 88% of the variance in religious females. Comparable but non-significant effects were seen for males. Most captivatingly, current evidence from the work of Haber., *et al*. underlines the role of religious/spirituality (RS) as a specific risk factor for alcohol dependence (AD), especially at the initiation phase

[97]. Though, after drinking has started, it is genetic influences that maintain AD not RS as much. This work does support the initial involvement of spirituality in families with a history of alcoholism.

Being aware of the role of specific neurotransmitter gene polymorphisms, epigenetics, and acceptance or non-acceptance of a higher power (spirituality beliefs as defined herein), and the role of RDS on the beginning of drug and alcohol usage (likely relapse as well), our laboratory has embarked on an outcome study using two independent samples - the NIDA funded Drug Addiction Treatment Outcome Study (DATOS) and alumni data derived from a holistic treatment center in North Miami Beach, Florida. Excitingly, we noticed a significant inverse relationship between stronger spirituality beliefs and lower relapse rates in both independent samples [7].

One definition of spirituality suggested by the consensus of a conference held at the Royal College of Psychiatrists on March 4, 2011, on spirituality as a construct in Psychiatry, espoused 'Improving the quality of spiritual care as a dimension of palliative care': 'the aspect of humanity that mentions to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to Nature, and to the significant or sacred' [98]. While there is some evidence for the increasing disbelief of "GOD Conscience" decreasing, there is indeed evidence for health benefits related to spirituality. In 1999, Koenig., *et al*. examined the survival rate of around 4000 people aged 65 and above during a 6-year period. His team reported that those who went to Church once or more per week were likely to live around 10 years more compared to those who did not [99]. While not necessarily related to GOD or even spirituality, is the observation that in these subject's reward circuits are activated when empathy is felt; the empathic person receives a strong internal reward [100].

Moreover, meditation is a key process and is described as a spiritual practice accepted for its positive effects on both the behavior and mental state of the meditator. The question for neuroimaging is whether there are particular brain changes that come with meditation or whether the experienced advantages of the meditator are simply 'imagination'. There have now been a number of papers studying various methods of meditation and the distinct aspects of the technique. Nevertheless, in 2010 a review paper was published on 'The neural substrates of mindfulness: an fMRI investigation' by Ives-Deliperi., *et al*. [101]. They demonstrated that there was a network of areas all close to the brain midline, which responded during the meditation with a substantial signal decrease. The key areas were the anterior insula, the left ventral and anterior cingulate cortex, the right medial pre-frontal cortex, and the bilateral precuneus. The anterior insula is an area that plays an important role in the experience of emotion by processing convergent information to generate an emotionally relevant context for sensory experience.

The left ventral and anterior cingulate cortex, with its posterior dorsal regions, has been demonstrated to be associated with executive, evaluative, and cognitive functions respectively, and the ventral area plays a central role in emotion. The right medial prefrontal cortex is associated with processing and evaluating self-referential stimuli and judgment of emotional stimulation. The precuneus is an additional region that is prominent in self-referential thought or first-person perspective and, more commonly, processing and integrating self-referential stimuli. A paper by Ives-Deliperi., *et al*. [101] suggests that possibly the default node network of central areas is involved in meditation, and importantly these downregulate many areas engaged with self-referential thought or integration. This has meaning in terms of the practice of Buddhism whereby self-actualization and ego must be attenuated via dampening of amygdala related activity in the brain [102].

Kjaer., *et al*. performed the first *in vivo* demonstration of a correlation between endogenous neurotransmitter release and conscious experience [103]. Using 11C-raclopride PET, they showed increased endogenous dopamine release in the ventral striatum during Yoga Nidra meditation. For the duration of meditation, 11C-raclopride binding in ventral striatum decreased by 7.9%. This relates to a 65% increase in endogenous DA release. The decreased raclopride binding correlated significantly with a consequent increase in EEG theta activity, a distinctive feature of meditation. All participants reported a reduced desire for action during meditation, together with heightened sensory imagery.

There are even questions related to brain size linked to years of meditation practice. For example, does meditation cause an increase in the size of the brain in specific areas? Additionally, does the number of years meditating affect brain size? A recent study by Brita., *et al*. in 2008 examined these questions [104]. They used mindfulness meditation practitioners, 20 meditators and 20 controls, and measured voxel-based morphometry. They noticed that meditation affected three distinctive regions: the left inferior temporal gyrus, the right anterior insular and the right hippocampus. They reported that the temporal lobe has been implicated in religious activity and mystical experiences; that all these areas were largely temporal and therefore could relate to the feelings of mystic experience in the meditation sittings that had led to brain growth in these areas. Besides, there was a relationship between the growth of distinct brain areas and the length of meditation practice. They observed one specific area in the medial orbital frontal cortex, which related to the total hours of meditation training. They contended that the orbital frontal cortex played a vital role in emotion regulation by downregulating the amygdala activity. They also indicated that the medial orbital frontal cortex is directly implicated in extinction retention after fear conditioning. The authors further proposed that the increase in size in this area may describe the better capability of meditators to alter their emotional responses. Saver and Rabin agreed with the possibility of temporal structures being involved [105].

In addition, Aftanas and Golocheikine [106] looked at the electrical changes of the brain by means of the EEG during Sahaja Yoga meditation. They observed that at the time of the presence of the experience of bliss, high power in the theta band was seen frontally, and this was also found in states with diminished appearance of thoughts. There is thus a close correlation between the meditators' experience of bliss and thoughtlessness and the EEG picture. These discoveries support the idea of a role for the left frontal region in intense emotion and in states of attention. In 2010, another study by Urgesi., *et al*. [107] examined the release phenomena associated with transcendence that happened in the brain after it had been damaged. They noticed that there was a high correlation between transcendence scores and the left inferior parietal lobule along with the right angular gyrus. They indicated that their findings hint at the role of left and right parietal systems becoming activated in the experience of self-transcendence. They also add, remarkably, that changes in religious attitudes and behaviors in neurological and mental disorders may occur if these structures are damaged.

Beauregard and Paquette [108] imaged brain activity of 15 Carmelite nuns while they were undergoing the feelings they had while remembering the memory of intense meditation. The meditation, they said, resulted in a sense of having touched the fundamental ground of reality, experience of timelessness and space lessness, feelings of positive affect, peace, joy and unconditional love and ultimately a sense of union with humankind and the universe. The main aim of this functional magnetic resonance imaging (fMRI) study was to find the neural correlates of a mystical experience. The brain activity of Carmelite nuns was recorded while they were subjectively in a state of union with God. This state was related to significant loci of activation in the right medial orbitofrontal cortex, right middle temporal cortex, right inferior and superior parietal lobules, right caudate, left medial prefrontal cortex, left anterior cingulate cortex, left inferior parietal lobule, left insula, left caudate, and left brainstem. Other loci of stimulation were seen in the extra-striate visual cortex. These findings imply that mystical experiences are mediated by several brain regions and systems.

Finally, religion and spirituality (R/S) have been prominent aspects of most human cultures through the ages; however, scientific inquiry into this phenomenon has been limited. Others have conducted a systematic literature review of research on the neurobiological correlates of R/S, which resulted in 25 reports studying primarily R/S with electroencephalography, structural neuroimaging (MRI), and functional neuroimaging (fMRI, PET) [109]. These studies evaluated a wide range of religions (e.g. Christianity, Buddhism, Islam) and R/S states and behaviors (e.g. resting state, prayer, judgments) and employed a wide range of methodologies, some of which (e.g. no control group, varying measures of religiosity, small sample sizes) raise concerns about the validity of the results. However, despite these limitations, the findings of these studies collectively suggest that the experience of R/S has specific neurobiological correlates and that these correlations are distinct from non-R/S counterparts.

In considering the idea of universal challenges to society, it is important to point out how society, in spite of the thousands of neurophysiological, genetic and epigenetic articles, seems to unfortunately embrace stigma to all forms of reward deficiency and subsequent addiction -like seeking behaviors. So, we must think out of the box and seek answers to very perplexing questions and provide non-scientific jargon to more carefully respond to age old retort.

Where in medicine, where in the name of love or spirituality, is it appropriate to blame the one suffering? To kick them when they are down. Why is love less common than loathing. When does religion lose its soul? When did those of us who have been terribly hurt start hurting ourselves? Why did we choose to lie to ourselves, and to believe the lie? The addict might ask "When did we stop loving ourselves and begin hating ourselves? The religious might benefit from asking "Do I need a bigger god?" Indeed, is it necessary to believe in a higher power, especially if the human brain is known to heal itself. For some, believing is indeed comforting and may have a very positive influence on one's wellbeing as previously reviewed by others [110-112].

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, functional imaging, and integrating the analytic method of lesion network mapping (Refer to figure 5).

Figure 5

Conclusion

The findings implicate several brain regions potentially associated with R/S development and behavior, including the medial frontal cortex, orbitofrontal cortex, precuneus, posterior cingulate cortex, default mode network, and caudate. This research may suggest future clinical applications and interventions related to R/S and various conditions, including mood, anxiety, psychotic, pain, and vertiginous disorders. Certainly, further studies with more rigorous research designs are warranted to elucidate the neurobiological mechanisms involving both genetics and epigenetics of R/S and their potential clinical applications. Finally, it is to be noted that the brain is a biological computer, acknowledged for its complexity, fragility, and vulnerability, but more dynamic in terms of its ability to react to environmental cues such as epigenetic expression for multiple generations without effecting one's DNA directly. This uncanny ability to induce "neuroplasticity" has been denoted in many experiments in both animal models of reward deficiency and clinical trials in humans. In fact, this self -repair is one factor that enables psychological tools like AIT, mindfulness and CBT, trauma therapy and even potential psychedelic assisted therapy (PAT) to have unique benefits in treating RDS.

Conflict of Interest

Dr. Blum is the inventor of GARS and KB220 and has received many global patents thereof. He has licensed KB220 to Victory Nutrition International (VNI). There are no more conflicts to re-port.

Author Contribution

KB and ERB wrote the initial draft. AP, MTM, FZ, edited the entire manuscript. AB provided graphics. All other authors provided many comments and writings and approved of the final manuscript.

Acknowledgements

We the authors appreciate the expert edits of Margaret A. Madigan.

Funding Support

Dr. Blum along with Marjorie Gondre-Lewis (Howard University) funded by R01 NS073884/NS/NINDS NIH HHS/United States. Dr. Badgaiyan is funded by I01 CX000479/CX/CSRD VA/United States/VA/VA/United States and Dr. Thanos is funded by DA046794/National Institutes of Health (US); Q0942016/New York Research Foundation, R01 DA046794/DA/NIDA NIH HHS/United States, HD070888/ National Institutes of Health (US).

Disclaimer

It is to be noted that opinions related to spirituality may not reflect the opinion or endorsement of all the co-authors.

Bibliography

1. Blum K., *et al*. "Allelic association of human dopamine D2 receptor gene in alcoholism". *Journal of the American Medical Association* 263.15 (1990): 2055-2060.

2. Blum K., *et al*. "The D2 dopamine receptor gene as a determinant of reward deficiency syndrome". *Journal of the Royal Society of Medicine* 89.7 (1996): 396-400.

3. Zipperly ME., *et al*. "Regulation of dopamine-dependent transcription and cocaine action by Gadd45b". *Neuropsychopharmacology* 46.4 (2021): 709-720.

4. Blum K., *et al*. "Buprenorphine response as a function of neurogenetic polymorphic antecedents: can dopamine genes affect clinical outcomes in reward deficiency syndrome (RDS)?" *Journal of Addiction Research and Therapy* 5 (2014): 1000185.

5. Birnie MT., *et al*. "Plasticity of the reward circuitry after early-life adversity: mechanisms and significance". *Biological Psychiatry* 87.10 (2020): 875-884.

6. Blum K., *et al*. "Our evolved unique pleasure circuit makes humans different from apes: Reconsideration of data derived from animal studies". *Journal of Systems and Integrative Neuroscience* 4.1 (2018): 10.

7. Schoenthaler SJ., *et al*. "NIDA-drug addiction treatment outcome study (DATOS) relapse as a function of spirituality/religiosity". *Journal of Reward Deficiency Syndrome* 1.1 (2015): 36-45.

8. Puffer ES., *et al*. "Changes in religious coping and relapse to drug use among opioid-dependent patients following inpatient detoxification". *Journal of Religion and Health* 51.4 (2012): 1226-1238.

9. Bowirrat A and Oscar-Berman M. "Relationship between dopaminergic neurotransmission, alcoholism, and Reward Deficiency syndrome". *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 132B.1 (2005): 29-37.

10. Gold MS., *et al*. "Neurological correlates of brain reward circuitry linked to opioid use disorder (OUD): Do homo sapiens acquire or have a reward deficiency syndrome?" *Journal of the Neurological Sciences* 418 (2020): 117137.

11. Vivian C Chioma., *et al*. "Heroin seeking and extinction from seeking activate matrix metalloproteinases at synapses on distinct subpopulations of accumbens cells". *Biological Psychiatry* 89.10 (2021): 947-958.

12. Blum K., *et al*. "Genetic addiction risk score (GARS): molecular neurogenetic evidence for predisposition to reward deficiency syndrome (RDS)". *Molecular Neurobiology* 50.3 (2014): 765-796.

13. Blum K., *et al*. "Promoting precision addiction management (PAM) to combat the global opioid crisis". *Biomedical Journal of Scientific and Technical Research* 2.2 (2018): 1-4.

14. Braverman ER and Blum K. "Substance use disorder exacerbates brain electrophysiological abnormalities in a psychiatrically ill population". *Clinical Electroencephalography* 27.4 (1996): 5-27.

15. Amen DG., *et al*. "The clinical utility of brain SPECT imaging in process addictions". *Journal of Psychoactive Drugs* 44.1 (2012): 18-26.

16. Smith DE. "The process addictions and the new ASAM definition of addiction". *Journal of Psychoactive Drugs* 44.1 (2012): 1-4.

17. Blum K., *et al*. "The molecular neurobiology of twelve steps program and fellowship: Connecting the dots for recovery". *Reward Deficiency Syndrome* 1.1 (2015): 46-64.

18. Westman J., *et al*. "Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden". *Acta Psychiatrica Scandinavica* 131.4 (2015): 297-306.

19. O'Connor RC., *et al*. "A thematic analysis of suicide notes". *Crisis* 20.3 (1999): 106-114.

20. Zygo M., *et al*. "Prevalence and selected risk factors of suicidal ideation, suicidal tendencies and suicide attempts in young people aged 13-19 years". *Annals of Agricultural and Environmental Medicine* 26.2 (2019): 329-336.

21. Vaillant GE. "Alcoholics Anonymous: cult or cure?" *Australian and New Zealand Journal of Psychiatry* 39.6 (2005): 431-436.

22. Vaillant GE. "Psychiatry, religion, positive emotions and spirituality". *Asian Journal of Psychiatry* 6.6 (2013): 590-594.

23. Karlsson H., *et al*. "No association between serotonin 5-HT 1A receptors and spirituality among patients with major depressive disorders or healthy volunteers". *Molecular Psychiatry* 16.3 (2011): 282-285.

24. Borg J., *et al*. "The serotonin system and spiritual experiences". *American Journal of Psychiatry* 160.11 (2003): 1965-1969.

25. Nilsson KW., *et al*. "Genes encoding for AP-2beta, and the Serotonin Transporter are associated with the Personality Character Spiritual Acceptance". *Neuroscience Letters* 411.3 (2007): 233-237.

26. Brefczynski-Lewis JA., *et al*. "Neural correlates attentional expertise in long-term meditation practitioners". *Proceedings of the National Academy of Sciences of the United States of America* 104.27 (2007): 11483-11488.

27. Liu Y., *et al*. "The mesolimbic dopamine activity signatures of relapse to alcohol-seeking". *Journal of Neuroscience* 40.33 (2020): 6409-6427.

28. Cook R., *et al*. "Mirror neurons: from origin to function". *Behavioral and Brain Sciences* 37.2 (2014): 177-192.

29. Wong PTP. "Existential positive psychology and integrative meaning therapy". *International Review of Psychiatry* 32.7-8 (2020): 565-578.

30. Chappel JN and DuPont RL. "Twelve-step and mutual-help programs for addictive disorders". *Psychiatric Clinics of North America* 22.2 (1999): 425-446.

31. Blum K. "Alcohol and the addictive brain". New York, USA: The Free Press (1991).

32. Timko C., *et al*. "Newcomers to Al-Anon family groups: Who stays and who drops out?" *Addictive Behaviors* 39.6 (2014): 1042-1049.

33. Galanter M. "The value of experimental support for the acceptance of alcoholics anonymous by clinicians". *Journal of Addiction Medicine* 14.5 (2020): 360-361.

34. Timko C and DeBenedetti A. "A randomized controlled trial of intensive referral to 12-step self-help groups: one-year outcomes". *Drug and Alcohol Dependence* 90.2-3 (2007): 270-279.

35. Kalivas PW and Brady K. "Getting to the core of addiction: hatching the addiction egg". *Nature Medicine* 18.4 (2012): 502-503.

36. Blum K., *et al*. "Hatching the behavioral addiction egg: Reward Deficiency Solution System (RDSS)™ as a function of dopaminergic neurogenetics and brain functional connectivity linking all addictions under a common rubric". *Journal of Behavioral Addictions* 3.3 (2014): 149-156.

37. Botkin J. "Ethical issues and practical problems in preimplantation genetic diagnosis". *Journal of Law, Medicine and Ethics* 26.1 (1998): 17-28.

38. Blum K., *et al*. "Hypothesizing molecular genetics of the holocaust: Were dopaminergic page 5 of 5 genes involved or brain wash?" *SOJ Psychology* 3.2 (2016): 1-5.

39. Hodge CW., *et al*. "Dopamine receptors in the medial prefrontal cortex influence ethanol and sucrose-reinforced responding". *Alcohol, Clinical and Experimental Research* 20.9 (1996): 1631-1638.

40. Hodge CW., *et al*. "Norepinephrine and serotonin receptors in the paraventricular nucleus interactively modulate ethanol consumption". *Alcohol, Clinical and Experimental Research* 20.9 (1996): 1669-1674.

41. Hodge CW and Cox AA. "The discriminative stimulus effects of ethanol are mediated by NMDA and GABA(A) receptors in specific limbic brain regions". *Psychopharmacology (Berl)* 139.1-2 (1998): 95-107.

42. Blum K and Kozlowski GP. "Ethanol and neuromodulator interactions: A cascade model of reward". In: Ollat H, Parvez H, editors. Alcohol and Behavior. Utrecht and Netherlands: Prog Alcohol Res VSP (1990): 131-149.

43. Blum K., *et al*. "Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors". *Journal of Psychoactive Drugs* 32.i-iv (2000): 1-112.

44. Hawks J. "Still evolving (after all these years)". *Scientific American* 311.3 (2014): 86-91.

45. Blum K., *et al*. "Dopamine D2 receptor gene variants: association and linkage studies in impulsive-addictive-compulsive behaviour". *Pharmacogenetics* 5.3 (1995): 121-141.

46. Blum K., *et al*. "The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem". *Functional Neurology* 10.1 (1995): 37-44.

47. Grandy DK., *et al*. "The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP". *American Journal of Human Genetics* 45.5 (1989): 778-785.

48. Fried L., *et al*. "Hypodopaminergia and "Precision Behavioral Management" (PBM): It is a Generational Family Affair". *Current Pharmaceutical Biotechnology* 21.6 (2020): 528-541.

49. Smith GP and Schneider LH. "Relationships between mesolimbic dopamine function and eating behavior". *Annals of the New York Academy of Sciences* 537 (1988): 254-261.

50. Di Chiara G and Imperato A. "Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats". *Proceedings of the National Academy of Sciences of the United States of America* 85.14 (1988): 5274-5278.

51. Comings DE., *et al*. "The DRD4 gene and the spiritual transcendence scale of the character temperament index". *Psychiatric Genetics* 10.4 (2000): 185-189.

52. Rutter JL and Volkow ND. "Re-defininG AddiC(CH3)Tion: genomics and epigenomics on substance use disorders". *Molecular Genetics and Genomic Medicine* 2.4 (2014): 273-279.

53. Eisenberg DT., *et al*. "Season of birth and dopamine receptor gene associations with impulsivity, sensation seeking and reproductive behaviors". *PLoS One* 2.11 (2007): e1216.

54. Tomasi D., *et al*. "Overlapping patterns of brain activation to food and cocaine cues in cocaine abusers: association to striatal D2/D3 receptors". *Human Brain Mapping* 36.1 (2015): 120-136.

55. Dackis CA and Gold MS. "New concepts in cocaine addiction: the dopamine depletion hypothesis". *Neuroscience and Biobehavioral Reviews* 9.3 (1985): 469-477.

56. Blum K., *et al*. "Suppression of ethanol withdrawal by dopamine". *Experientia* 32.4 (1976): 493-495.

57. Hietala J., *et al*. "Striatal D2 dopamine receptor binding characteristics *in vivo* in patients with alcohol dependence". *Psychopharmacology (Berl)* 116.3 (1994): 285-290.

58. Melis M., *et al*. "The dopamine hypothesis of drug addiction: hypodopaminergic state". *International Review of Neurobiology* 63 (2005): 101-154.

59. Rothman RB., *et al*. "Dual dopamine/serotonin releasers as potential medications for stimulant and alcohol addictions". *AAPS Journal* 9.1 (2007): E1-E10.

60. Boundy VA., *et al*. "Agonists and antagonists differentially regulate the high affinity state of the D2L receptor in human embryonic kidney 293 cells". *Molecular Pharmacology* 48.5 (1995): 956-964.

61. Thanos PK., *et al*. "Overexpression of dopamine D2 receptors reduces alcohol self-administration". *Journal of Neurochemistry* 78.5 (2001): 1094-1103.

62. Thanos PK., *et al*. "DRD2 gene transfer into the nucleus accumbens core of the alcohol preferring and nonpreferring rats attenuates alcohol drinking". *Alcohol, Clinical and Experimental Research* 28.5 (2004): 720-728.

63. Thanos PK., *et al*. "Dopamine D2R DNA transfer in dopamine D2 receptor-deficient mice: effects on ethanol drinking". *Life Sciences* 77.2 (2005): 130-139.

64. Thanos PK., *et al*. "D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats". *Synapse* 62.7 (2008): 481-486.

65. Siciliano CA., *et al*. "Increased presynaptic regulation of dopamine neurotransmission in the nucleus accumbens core following chronic ethanol self-administration in female macaques". *Psychopharmacology (Berl)* 233.8 (2016): 1435-1443.

66. Blum K., *et al*. "Association of polymorphisms of dopamine D2 receptor (DRD2), and dopamine transporter (DAT1) genes with schizoid/avoidant behaviors (SAB)". *Molecular Psychiatry* 2.3 (1997): 239-246.

67. Robbins TW and Everitt BJ. "Neurobehavioral mechanisms of reward and motivation". *Current Opinion in Neurobiology* 6.2 (1996): 228-236.

68. Wightman RM and Robinson DL. "Transient changes in mesolimbic dopamine and their association with 'reward'". *Journal of Neurochemistry* 82.4 (2002): 721-735.

69. Epping-Jordan MP., *et al*. "Dramatic decreases in brain reward function during nicotine withdrawal". *Nature* 393.6680 (1998): 76-79.

70. Cooper ML., *et al*. "Drinking to regulate positive and negative emotions: a motivational model of alcohol use". *Journal of Personality and Social Psychology* 69.5 (1995): 990-1005.

71. Yamada M., *et al*. "Superiority illusion arises from resting-state brain networks modulated by dopamine". *Proceedings of the National Academy of Sciences of the United States of America* 110.11 (2013): 4363-4367.

72. Heinz A., *et al*. "Neurobiological correlates of the disposition and maintenance of alcoholism". *Pharmacopsychiatry* 36.3 (2003): S255-S258.

73. Blum K., *et al*. "Overcoming qEEG abnormalities and reward gene deficits during protracted abstinence in male psychostimulant and polydrug abusers utilizing putative dopamine D2 agonist therapy: Part 2". *Postgraduate Medicine* 122.6 (2010): 214-226.

74. Blum K., *et al*. "Activation instead of blocking mesolimbic dopaminergic reward circuitry is a preferred modality in the long term treatment of reward deficiency syndrome (RDS): a commentary". *Theoretical Biology and Medical Modelling* 5 (2008): 24.

75. Koob GF. "Neurobiological substrates for the dark side of compulsivity in addiction". *Neuropharmacology* 56.1 (2009): 18-31.

76. Peciña S., *et al*. "Hedonic hot spots in the brain". *Neuroscientist* 12.6 (2006): 500-511.

77. Medlock MM., *et al*. "Religious coping in patients with severe substance use disorders receiving acute inpatient detoxification". *American Journal on Addictions* 26.7 (2017): 744-750.

78. Wildman Wesley J. "Religious and Spiritual Experiences". Cambridge University Press NY (2011).

79. Nilsson KW., *et al*. "Genes encoding for AP-2beta and the serotonin transporter are associated with personality character spiritual acceptance". *Neuroscience Letters* 411.3 (2007): 233-237.

80. Comings DE., *et al*. "The DRD4 gene and the spiritual transcendence scale of the character temperament index". *Psychiatric Genetics* 10.4 (2000): 185-189.

81. Hamer D. "The God Gene". Doubleday New York (2004).

82. Comings DE. "Did man create god? is your spiritual brain at peace with your thinking brain?" Hope Press California. Durate (2008).

83. Newberg A. "The brain and the biology of belief: An interview with Andrew Newberg, MD. Interview by Nancy Nachman-Hunt". *Advances in Mind-Body Medicine* 24.1 (2009): 32-36.

84. Archer T., *et al*. "Neurogenetics and epigenetics in impulsive behaviour: impact on reward circuitry". *Journal of Genetic Syndromes and Gene Therapy* 3.3 (2012): 1000115.

85. Cloninger CR., *et al*. "A psychobiological model of temperament and character". *Archives of General Psychiatry* 50.12 (1993): 975-990.

86. Asghari V., *et al*. "Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants". *Journal of Neurochemistry* 65.3 (1995): 1157-1165.

87. Cohen MX., *et al*. "Connectivity-based segregation of the human striatum predicts personality characteristics". *Nature Neuroscience* 12.1 (2009): 32-34.

88. Cohen HL., *et al*. "Religion and spirituality as defined by older adults". *Journal of Gerontological Social Work* 51.3-4 (2008): 284-299.

89. Comings DE., *et al*. "A multivariate analysis of 59 candidate genes in personality traits: the temperament and character inventory". *Clinical Genetics* 58.5 (2000): 375-385.

90. Borg J., *et al*. "The serotonin system and spiritual experiences". *American Journal of Psychiatry* 160.11 (2003): 1965-1969.

91. Bartlett VL and Johnson RL. "God and genes in the caring professions: clinician and clergy perceptions of religion and genetics". *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 151C.1 (2009): 41-51.

92. Bachner-Melman R., *et al*. "AVPR1a and SLC6A4 gene polymorphisms are associated with creative dance performance". *PLOS Genetics* 1.3 (2005): e42.

93. Rossi E. "The bioinformatics of psychosocial genomics in alternative and complementary medicine". *Forsch Komplementarmed Klass Naturheilkd* 10 (2003): 143-150.

94. Kendler KS and Myers J. "A developmental twin study of church attendance and alcohol and nicotine consumption: a model for analyzing the changing impact of genes and environment". *American Journal of Psychiatry* 166.10 (2009): 1150-1155.

95. Boomsma DI., *et al*. "A religious upbringing reduces the influence of genetic factors on disinhibition: evidence for interaction between genotype and environment on personality". *Twin Research* 2.2 (1999): 115-125.

96. Koopmans JR., *et al*. "The influence of religion on alcohol use initiation: evidence for genotype X environment interaction". *Behavior Genetics* 29.6 (1999): 445-453.

97. Peter Fenwick. The Neuroscience of Spirituality.

98. Koenig HG., *et al*. "Does religious attendance prolong survival? A six-year follow-up study of 3,968 older adults". *Journal of Gerontology, Medical Sciences* 54.7 (1999): M370-M377.

99. Grit Hein and Tania Singer (Zurich). "I feel how you feel but not always: the empathic brain and its modulation". *Current Opinion in Neurobiology* 18.2 (2008): 153-158.

100. Ives-Deliperi V., *et al*. "The neural substrates of mindfulness: An fMRI investigation". *Social Neuroscience* 6.3 (2011): 231-242.

101. Kirkby LA., *et al*. "An amygdala-hippocampus subnetwork that encodes variation in human mood". *Cell* 175.6 (2018): 1688-1700.e14.

102. Kjaer TW., *et al*. "Increased dopamine tone during meditation-induced change of consciousness". *Brain Research. Cognitive Brain Research* 13.2 (2002): 255-259.

103. Britta K Hölzel., *et al*. "Investigation of mindfulness meditation practitioners with voxel-based morphometry". *Social Cognitive and Affective Neuroscience* 3.1 (2008): 55-61.

104. Saver JL and Rabin J. "The neural substrates of religious experience". *Journal of Neuropsychiatry and Clinical Neurosciences* 9.3 (1997): 498-510.

105. Aftanas LI and Golocheikine SA. "Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation". *Neuroscience Letter* 310.1 (2001): 57-60.

106. Urgesi C., *et al*. "The spiritual brain: selective cortical lesions modulate human self-transcendence". *Neuron* 65.3 (2010): 309-319.

107. Beauregard M and Paquette V. "Neural correlates of a mystical experience in Carmelite nuns". *Neuroscience Letter* 405.3 (2006): 186-190.

108. Rim JI., *et al*. "Current understanding of religion, spirituality, and their neurobiological correlates". *Harvard Review of Psychiatry* 27.5 (2019): 303-316.

109. Haber JR., *et al*. "Religion/spirituality, risk, and the development of alcohol dependence in female twins". *Psychology of Addictive Behaviors* 27.3 (2013): 562-572.

110. Weber SR and Pargament KI. "The role of religion and spirituality in mental health". *Current Opinion in Psychiatry* 27.5 (2014): 358-363.

111. Park SY., *et al*. "Digital methods for the spiritual and mental health of generation Z: Scoping review". *Interactive Journal of Medical Research* 13 (2024): e48929.

112. Pinto CT., *et al*. "Spiritual intelligence: a scoping review on the gateway to mental health". *Global Health Action* 17.1 (2024): 2362310.

113. Gold MS., *et al*. "Spiritual Neurological correlates of brain reward circuitry linked to opioid use disorder (OUD): Do homo sapiens acquire or have a reward deficiency syndrome?" *Journal of the Neurological Sciences* 418 (2020): 117137.

114. Blum K., *et al*. "The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem". *Functional Neurology* 10.1 (1995): 37-44.

115. Chen TJ., *et al*. "Gene narcotic attenuation program attenuates substance use disorder, a clinical subtype of reward deficiency syndrome". *Advances in Therapy* 24.2 (2007): 402-414.

Volume 17 Issue 2 February 2025