

Neurogenetics and Epigenetics of Loneliness

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Abstract: Loneliness, an established risk factor for both, mental and physical morbidity, is a mounting public health concern. However, the neurobiological mechanisms underlying loneliness-related morbidity are not yet well defined. Here we examined the role of genes and associated DNA risk polymorphic variants that are implicated in loneliness via genetic and epigenetic mechanisms and may thus point to specific therapeutic targets. Searches were conducted on PubMed, Medline, and EMBASE databases using specific Medical Subject Headings terms such as loneliness and genes, neuro- and epigenetics, addiction, affective disorders, alcohol, anti-reward, anxiety, depression, dopamine, cancer, cardiovascular, cognitive, hypodopaminergia, medical, motivation, (neuro)psychopathology, social isolation, and reward deficiency. The narrative literature review yielded recursive collections of scientific and clinical evidence, which were subsequently condensed and summarized in the following key areas: (1) Genetic Antecedents: Exploration of multiple genes mediating reward, stress, immunity and other important vital functions; (2) Genes and Mental Health: Examination of genes linked to personality traits and mental illnesses providing insights into the intricate network of interaction converging on the experience of loneliness; (3) Epigenetic Effects: Inquiry into instances of loneliness and social isolation that are driven by epigenetic methylations associated with negative childhood experiences; and (4) Neural Correlates: Analysis of loneliness-related affective states and cognitions with a focus on hypodopaminergic reward deficiency arising in the context of early life stress, eg, maternal separation, underscoring the importance of parental support early in life. Identification of the individual contributions by various (epi)genetic factors presents opportunities for the creation of innovative preventive, diagnostic, and therapeutic approaches for individuals who cope with persistent feelings of loneliness. The clinical facets and therapeutic prospects associated with the current understanding of loneliness, are discussed emphasizing the relevance of genes and DNA risk polymorphic variants in the context of loneliness-related morbidity.

Keywords: addiction, affective, alcohol, anti-reward, anxiety, depression, dopamine, cancer, genes, cardiovascular, cognitive, medical, motivation, social isolation, reward deficiency

Oh, loneliness, how harsh your temper is

Your shining compasses of iron

Is what you link your freezing circle with

Not heeding useless promises or vows.

Bella Akhmadulina

As it was, we all acted alone, we were caught alone, and every one of us will have to die alone. But that doesn't mean that we are alone.

Hans Fallada

Introduction

Emotional and physical consequences of present or past collective traumatic events, like the COVID-19 pandemic, extend beyond those directly impacted by the virus to millions of individuals who experience prolonged loneliness¹ because of self- and/or government-imposed social isolation.² By and large, people undergoing such periods resort to constructive coping strategies, eg, structured daily routine, regular contacts with family and friends, physical exercise, and productive vocational engagements.³ However, a sizable population segment succumbs to anxious and depressive affective states,⁴ cognitive distortions,⁵ memory problems,⁶ an enhanced propensity for psychosis⁷ and suicide.⁸ Dependence on social attachments may be juxtaposed to addictive disorders.^{9,10} So, longing for meaningful social interactions may be akin to craving and hunger¹¹ and, if not satisfied, could lead to the worsening of behavioral and chemical addictions, overeating, obesity, and promiscuity.¹²⁻¹⁴ Hence, it appears that loneliness encompasses a comprehensive set of systemic changes that coincide with alterations in immunometabolism patterns¹⁵ and contribute to the development of cardiovascular, gluco-regulatory and oncological morbidity.¹⁶⁻¹⁹

Given such a profound impact on emotional and physical wellbeing,²⁰ it is reasonable to assume a neurobiological basis for loneliness.²¹ In fact, findings from neuroscience research substantiate the notion that loneliness should be considered as part of a broader spectrum involving reward deficiency and anti-reward.^{22,23} This spectrum encompasses personality traits and mental disorders characterized by a state of reduced dopamine activity in the reward circuitry, resulting in diminished motivation, inability to experience pleasure²³⁻²⁶ in conjunction with heightened stress that is not effectively alleviated by rewards.²⁷ The dopaminergic neurons in the dorsal raphe nucleus are implicated in the negative affects arising in the context of loneliness,^{28,29} along with the exhilaration experienced with the termination of solitude²⁸ and reestablishment of the normative reward and motivational function.³⁰ Thus, dopaminergic activity in the limbic-raphé-cortico-striatal circuits is associated with motivational longings, ie, drugs, food³¹ and loved ones.³²⁻³⁴

However, loneliness is not a unitary entity defined by straightforward behavioral and physiological mechanisms. Quite the reverse, it is a complex biopsychosocial phenomenon comprising genetic factors that play an important role in the vulnerability, course, and outcomes of various loneliness-associated conditions. The present review will elucidate loneliness' neuro- and epigenetic underpinnings. To that end, an English-language literature search on loneliness-related genes, and related topics was undertaken using PubMed, Medline, and EMBASE from launch until March 2023. The selected Medical Subject Headings encompassed addiction, affective, alcohol, anti-reward, anxiety, depression, dopamine, cancer, genes, cardiovascular, cognitive, medical, motivation, social isolation, and reward deficiency. Data on the neuroscience of addiction and the neurobiology/neurochemistry of social attachments were also drawn from comprehensive reviews of these topics.^{9,11,21,27,35-40} To expand the search, we also conducted manual searches within the reference lists of the selected papers and utilized PubMed's Similar Articles function to identify related articles. The resulting paper consists of ten sections, including this Introduction. The second section offers clinical and

epidemiological perspectives on loneliness. The subsequent six sections delve into the neuropharmacology of reward, as well as the neurogenetics and epigenetics associated with loneliness. The final ninth and tenth sections present limitations, therapeutic implications with summary and conclusions.

Loneliness: Epidemiological and Clinical Context

Loneliness is an intensifying public health problem in the US⁴¹ and throughout the world.^{42,43} While most of surveyed people across all ages consistently report alienation, the risk of loneliness seems to increase with age.⁴¹ According to systematic reviews,⁴⁴ 27.6% (95% CI: 22.6–33.0%) and 31.3% (95% CI: 21.0–42.7%) of 65–75- and over 75-year-old people surveyed, respectively, reported loneliness.⁴⁴ A study of adolescents,⁴⁵ uncovered persistent loneliness and paucity of meaningful friendships in 18.1% (95% CI: 16.4–20.0%) with girls, in comparison to boys, displaying greater propensity for feeling lonely (14.6% vs 9.2%), while boys were more concerned about not having close friends (8.7% vs 7.2%). These data may partially inform the Global School-based Student Health Surveys⁴⁶ implicating loneliness as a significant risk factor for suicidal behavior among adolescents; similar trends have been observed in adults.⁸ The ongoing recognition of loneliness' societal costs has naturally spurred the development of therapeutic interventions targeting social skills, social support, social contacts, and social cognition.²⁰ However, given the ongoing rise in loneliness prevalence,⁴⁷ there is a pressing need for fresh perspectives that can contribute to enhanced prevention, identification, and management strategies. Inquiry into genetic mechanisms may have heuristic value in terms of mapping pathophysiologic pathways driven by vulnerability genes underlying given traits as well as the environmental impacts reflected in the epigenetic alterations.

Numerous adoption and twin studies involving both children and adults have indicated^{48–51} that the perception of social isolation has a genetic basis while clinical research has uncovered a significant correlation between social isolation and loneliness,⁵² suggesting that these concepts share common elements (around 15% of variance) and are both linked to depression. When entered into a regression analysis together, loneliness had a stronger association with depression than did social isolation. Nevertheless, comparable degrees of genetic impact were noted for both social isolation (40%) and loneliness (38%), though depressive symptoms displayed a lesser genetic influence (29%). This indicates that the unexplained variability can be attributed to factors in the non-shared environment. The investigation unveiled noteworthy genetic correlations, with an *r*-value of 0.65 between isolation and loneliness, and an *r*-value of 0.63 between loneliness and depression implying a substantial genetic influence on the simultaneous occurrence of these characteristics. Thus, individuals who experience loneliness may be prone to depression due to shared genetic factors influencing both conditions.

Loneliness Construct

In ancient times, individuals deprived of social connections often faced a grim fate in terms of demise from violence and starvation. Such harsh reality laid the evolutionary foundation for the preponderance of extended families, tribes, states, nations, and religions across various cultures and locations. And so, the innate drive to seek social bonding and the subsequent rewards and stresses associated with its attainment and loss are deeply ingrained. It is worth noting that addictive drugs target the same neural mechanisms that are naturally designated to facilitate social attachments,⁹ leading to the proposition that social bonding can be seen as the “primary form of addiction”.^{9,53,54} In fact, the initial euphoria experienced upon forming a romantic attachment shares similarities with the euphoria induced by drug use. Similarly, phenomena such as tolerance, withdrawal, and craving, as well as giving up important activities, are observed in the context of broken romantic ties,^{54,55} along with psychological distress.⁵⁶ For example, in the War and Peace novel, the protagonist describes feeling “an electric shock” and experiencing “some fearful pain” that seemed to pierce her heart upon learning about the loss of her brother. The heroine of yet another masterpiece by the same author, Ana Karenina, resorts to the use of morphine to cope with her reactive depression following the rejection by a beloved person.

Even though several studies identified genetic associations between loneliness and genetic polymorphisms, these findings may not be specific enough since various psychological traits may have common neurobiological and neurochemical correlates and vice versa. Hence, a recent investigation⁵⁷ explored the overlap of genome-wide association studies (GWAS) within the major Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision

(DSM-5-TR) disorders (such as anorexia nervosa, anxiety disorders, attention deficit hyperactivity disorder, autism, bipolar disorder, major depressive disorder, and schizophrenia) across various brain morphometric indices, cognitive traits (educational attainment and general cognitive function), and personality features (agreeableness, aggressive behavior, conscientiousness, depressive symptoms, extraversion, loneliness, neuroticism, openness to experience, and subjective well-being). The researchers identified 48 genes containing distinct markers associated with multiple traits (gene-level pleiotropy), along with nine genes possessing different markers that independently correlated with specific traits (allelic heterogeneity). This warrants the question of whether the construct of loneliness per se can be considered a realistic endophenotype or is just a symptom of the reward deficiency anti-reward syndrome impacted by the environment (epigenetics).

Indeed, when it comes to elucidating the genetic mechanisms underlying loneliness, the initial challenge lies in determining a precise definition and operationalization for this widely discussed concept, which has been defined in numerous ways throughout the literature. Loneliness can be described as a distressing state that arises when the need for human connection is not sufficiently fulfilled or when an individual's social network does not align with the preferences, whether in terms of quantity or quality.¹⁵ Various perspectives, including philosophical, emotional, poetic, and social,^{58–60} contribute to the definition of loneliness. Here we propose a psychopathological entity entailing an allostatic deficit in the reward and motivation systems²⁶ resulting from perceived or actual alienation or social isolation⁶¹ and manifested in emotional numbing and pain, stress (ie, anti-reward), longing for social interactions, compensatory consumption of substances, or engagement in activities with high hedonic impact (eg, palatable food, gambling, or sexual promiscuity).^{11,24} While there are multiple valid approaches to operationalizing “loneliness”, the method described here offers several notable benefits. Firstly, it provides a clear definition based on pathophysiological criteria involving a combination of reward deficiency and anti-reward syndromes.^{11,27,39} Secondly, it is built upon a solid foundation of clinical research.^{21,22} Lastly, its connection to loss of social ties and reward-seeking behaviors that yield negative outcomes has been extensively supported by evidence.^{62–64}

Neuropharmacological Underpinnings of Reward

The fundamental Brain Reward Cascade (Figure 1) comprises a sequential circuit connecting the ventral tegmental area, nucleus accumbens, and ventral pallidum via the medial forebrain bundle.⁶⁵ A shared characteristic observed in addictive drugs is their propensity to be actively self-administered by laboratory animals. Addictive drugs also enhance the activity of the brain's dopaminergic reward circuitry, resulting in the sought-after “high” experienced by drug users.³⁵

Although originally assumed to only determine the hedonic set point as a key component of hedonostasis,²⁷ these circuits are now postulated to be functionally far more complex, also encoding attention, expectancy of outcomes, discrepancy between the actual and expected outcome (prediction error), contextual processing, incentive motivation, and even the specific construct of loneliness.^{11,24,27,66,67} It is now generally accepted that allostatic dysregulation within these circuits leads to combined reward deficiency and anti-reward syndromes (see below), including substance use disorders and other types of addiction.^{11,27,39} Drug self-administration is regulated by the nucleus accumbens' dopamine concentration, which is normatively kept within a physiologically defined hedonostatic range.²⁷ Chronic use of certain addictive drugs, such as opioids, leads to the development of tolerance to their euphoric effects. As a result, post-use dysphoria develops due to allostatic processes in the reward circuit's hedonic tone. Consequently, addicted individuals use drugs not to experience “high”, but merely to feel normal or “get straight”, depending on the extent of impairment.^{11,27,68} There are important genetic variations in vulnerability to drug addiction, yet environmental factors such as stress and social defeat also alter brain reward mechanisms to impart epigenetic vulnerability to addiction^{11,24,25,27,39,69–85} in the context of its biopsychosocial nature.⁸⁶

Addiction, exemplified by combined reward deficiency and anti-reward syndrome, is marked by a dysfunctional brain reward circuitry. This dysfunction involves reduced dopaminergic activity and abnormalities in noradrenergic, serotonergic, opioidergic, endocannabinoid, GABAergic, and glutamatergic neurotransmission.³⁹ The anti-reward component is manifested by outpouring of stress-related hormones³⁸ within the extended amygdala structures involved in stress, anxiety, and fear⁸⁷ and through the habenula, which further inhibits dopamine activity thus aggravating reward deficiency.^{88–91} From a neuroanatomical perspective, the progression from occasional recreational substance use to

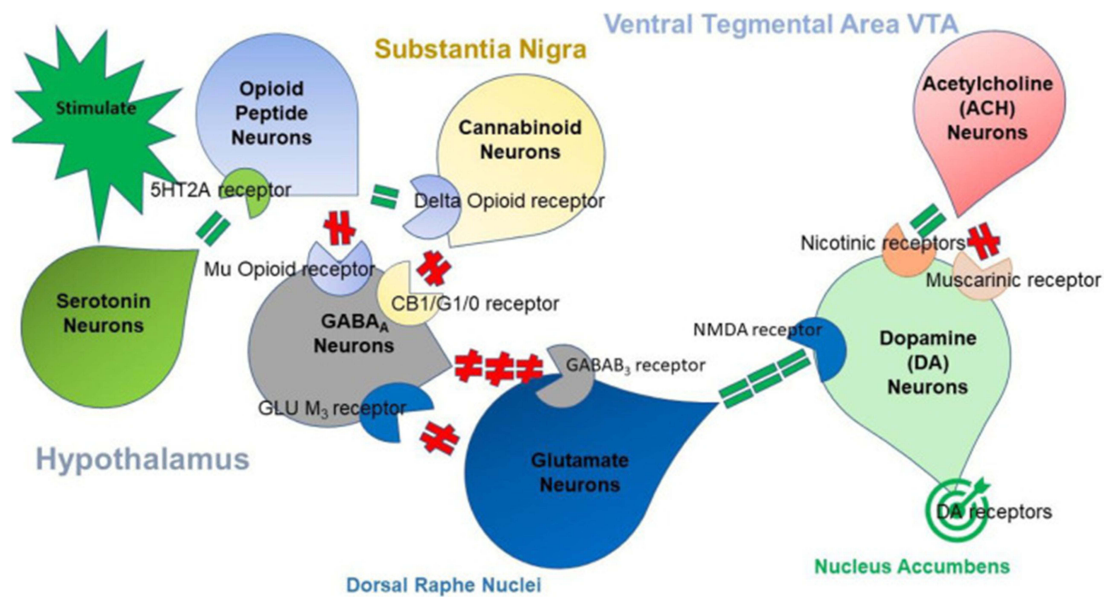


Figure 1 Displays the interplay of multiple neurotransmitter pathways involved in the Brain Reward Cascade (BRC). The process commences with an environmental stimulus triggering the release of serotonin in the hypothalamus, which, in turn, activates the release of opioid peptides from opioid peptide neurons, mediated by 5HT_{2a} receptors (indicated by a green equal sign). Subsequently, the opioid peptides have two distinct effects through different opioid receptors. One effect involves inhibition (indicated by a red hash sign) via the mu-opioid receptor, which projects to GABA_A neurons in the Substantia Nigra. The other effect involves stimulation (indicated by a green equal sign) of cannabinoid neurons, facilitated by delta receptors linked to Beta-Endorphin. The activated cannabinoid neurons inhibit GABA_A neurons in the Substantia Nigra. Additionally, cannabinoids, particularly 2-archidonilyglycerol, can indirectly disinhibit (indicated by a red hash sign) GABA_A neurons by activating G1/0 coupled to CB1 receptors in the Substantia Nigra. In the Dorsal Raphe Nuclei (DRN), glutamate neurons indirectly disinhibit GABA_A neurons in the Substantia Nigra through the activation of GLU M₃ receptors (indicated by a red hash sign). When GABA_A neurons are activated, they strongly inhibit (indicated by red hash signs) the glutamergic drive from the Ventral Tegmental Area (VTA) through GABAB₃ neurons. Stimulation of acetylcholine (ACh) neurons in the Nucleus Accumbens activates both muscarinic (indicated by a red hash sign) and nicotinic (indicated by a green hash sign) receptors. Finally, glutamate neurons in the VTA project to dopamine neurons via NMDA receptors (indicated by a green equal sign), leading to the predominant release of dopamine at the Nucleus Accumbens, depicted as a bullseye, representing a euphoric or motivational (“wanting”) response. The result is that low dopamine release leads to feelings of unhappiness, while maintaining a balanced dopamine homeostatic tonic set point is crucial for overall well-being and happiness.

Notes: Reprinted from Blum K, McLaughlin T, Bowirrat A, Modestino EJ, Baron D, Gomez LL, Ceccanti M, Braverman ER, Thanos PK, Cadet JL, Elman I, Badgaiyan RD, Jalali R, Green R, Simpatico TA, Gupta A, Gold MS. Reward Deficiency Syndrome (RDS) Surprisingly Is Evolutionary and Found Everywhere: Is It “Blowin’ in the Wind”? *J Pers Med.* 2022 Feb 21;12(2):321. Creative Commons.²⁵

impulsive and eventually uncontrollable consumption is implicated in a neuroanatomical shift from the ventral striatum (nucleus accumbens) to the dorsal striatum, which underlies compulsive drug-seeking behavior and craving.^{92,93}

Craving is commonly elicited by exposure to addictive drugs, stress, and environmental cues associated with drug-taking behavior,³⁵ activating the shared circuitry involving frontostriatal glutamatergic pathways,³⁶ the nucleus accumbens and related dopaminergic circuitry,^{94–96} as well as the basolateral nucleus of the amygdala, the hippocampus, the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the noradrenergic nuclei in the brain stem, which are associated with norepinephrine and corticotropin-releasing factor (CRF) release during stress-induced activation of anti-reward pathways.^{97–100} Loneliness may be relevant to all these triggers. When repeatedly paired with drugs, withdrawal-related stress, and environmental cues, loneliness can become a conditioned stimulus that independently triggers various forms of craving. Therefore, loneliness is included in the HALT acronym, which represents the major relapse risks: being hungry, angry, lonely, and tired.¹⁰¹

While the HALT acronym encompasses common stressors, loneliness is also strongly connected to traumatic events and subsequent post-traumatic stress disorder (PTSD).¹⁰² To explore the developmental links between victimization and loneliness, data were extracted from the Environmental Risk (E-Risk) Longitudinal Twin Study, which involves a birth cohort of 2232 children born in England and Wales.¹⁰³ The findings revealed a unique association between childhood bullying victimization and loneliness, independent of concurrent psychopathology, social isolation, and genetic risk. Moreover, childhood bullying victimization predicted loneliness in young adulthood, even after the bullying had ceased. Analyses within twin pairs suggested that genetic factors played a role in explaining this longitudinal association. During adolescence, various forms of victimization were correlated with loneliness, maltreatment, social neglect, and cyber

victimization remaining significant even after controlling for genetic influences.¹⁰³ These results indicate that vulnerability to loneliness among victimized young individuals may be influenced by genetic factors.

Neurogenetics of Loneliness

Multiple research studies indicate that there is an overlap between genes associated with slight variations in loneliness and genes involved in deviant behaviors, including those related to substance use.¹⁰⁴ Understanding why some lonely individuals become addicted following exposure to addictive drugs and/or behaviors while others do not remains a major challenge in devising science-driven interventions in addiction medicine and mental health.⁹⁰ Imaging studies generally align with preclinical discoveries, suggesting that brain circuits modulated by dopamine and implicated in reward, memory, executive function, and motivation may explain certain aspects of the individual differences observed in the shared tendencies for addiction and loneliness.^{105–107} Genetic polymorphism in the dopamine and opioid systems seems to be an important mediator.¹⁰⁸ Furthermore, in both drug addiction and obesity, the enhanced salience of the respective reinforcer (drugs or food) is modulated by genetic factors^{90,109} or personality features,¹¹⁰ underscoring the importance of multidimensional approaches in understanding and treating addictive disorders in the context of loneliness.^{111,112}

GWAS studies and candidate gene analysis have supported loneliness' heritable nature, pointing to genes associated with dopamine, serotonin, and oxytocin systems.^{113–117} For example, the dopamine D2 receptor candidate gene (*DRD2*) has been confirmed through GWAS as being linked to schizophrenia and has been found to be associated with major depressive disorder.^{118–120} Our group has uncovered significant links between schizoid-avoidant behavior and the *DRD2* Taq A1 allele, as well as with the dopamine transporter gene (*DAT1*).¹²¹ Furthermore, shared genetic risk factors and specific polymorphisms within the *ANKKI/DRD2* gene have been associated with both schizoid and avoidant personality disorders.^{121,122} Notably, schizoid personality disorder, which involves social avoidance and ambivalence toward social contact, has been subdivided into avoidant personality disorder and schizoid-avoidant behavior, corresponding to the concept of loneliness as described in DSM-5 TR.¹²³ Individuals with schizoid-avoidant personalities or traits have a heightened susceptibility to addictions, with the heritability of perceived isolation estimated at around 50%.¹²⁴ Additionally, a study has linked polymorphism of the oxytocin receptor gene (*OXTR*) to the development of loneliness.¹²⁵

GWAS split-half validation analyses have shown that individuals with autism spectrum disorders, bipolar disorder, major depression, and schizophrenia tend to have lower sociability scores.¹¹⁸ The sociability score was found to be significantly heritable, composed of 18 independent loci and 56 gene-wide significant genes, including *ARNTL*, *DRD2*, and *ELAVL2*. Importantly, the sociability score demonstrated negative genetic correlations with autism spectrum disorders, depression, schizophrenia, loneliness, and social anxiety.¹¹⁸ The strongest association in the single-nucleotide polymorphism (SNP)-based GWAS was observed on chromosome 11p15, encompassing the *ARNTL* gene, which is a circadian clock gene.¹²⁶ Another GWAS reported 19 independent genetic associations in 16 loci, while our research group identified 58 genome-wide significant genes associated with loneliness across subjects from five Western countries.¹²⁷ The genetic association signals were enriched in genes expressed in specific brain regions, particularly cortical and cerebellar regions, and the genetic risk for loneliness was associated with various health-related traits. Some of the top candidate regions and genes included *TCF4*, *PHF2*, *AC091969.1*, *ERBB4*, *RP11-6M13.1*, *BPTF*, *EPB4112*, *STAU1*, *TAOK3*, *RP11-259G18.1*, *CELF1*, and *RERE*.¹⁰⁹

According to the five annual waves longitudinal study utilizing the Latent Growth Curve Modeling, the *5-HTTLPR* genotype is associated with the development of loneliness.¹¹⁷ Specifically, individuals carrying the short allele exhibited steady levels of loneliness over time, whereas those with the long-long allele genotype reported diminishing loneliness. Interactions were observed between maternal support and the *5-HTTLPR* genotype, indicating that adolescents perceiving low levels of maternal support and carrying a short allele were at a heightened risk of developing loneliness. Additionally, recent studies have demonstrated a significant association between a rs1044396 variation in the *CHRNA4* gene (encoding the neuronal nicotinic acetylcholine receptor alpha-4 subunit) with loneliness and depression.¹²⁸ Notably, the same *CHRNA4* gene variation affects acetylcholine regulation of dopamine release in the nucleus accumbens (Figure 1). Further investigations have identified two key regions, *1p22.2-BARHL2* and *3p21.31-CAMKV*, associated

not only with social isolation but also with pleiotropy across various complex traits. For instance, there is an association between the polygenic score for loneliness in the oxytocin signaling pathway (154 genes) and apolipoprotein A1, a major protein component of HDL.^{61,129} Another study¹³⁰ revealed that the GG genotype for the *OXT*R gene is linked to the development of loneliness in adolescence, and this association is moderated by both sex and genotype for a dopamine-related gene (*DRD2* A1 allele). Moreover, adults who experience loneliness also excessively express pro-inflammatory genes that are responsive to mindfulness-based stress reduction programs.¹³⁰

The relationship between the brain-derived neurotrophic factor (*BDNF*) gene polymorphism and loneliness vary in accordance with gender. The presence of the Met allele in girls and the Val Val allele in boys is linked to distinct alterations in dopamine release from the nucleus accumbens, thereby influencing loneliness experience.¹¹³ Latent Growth Curve Modeling has demonstrated interactions between parental support and *DRD2* genotype, indicating that adolescents with the A2A2 allele (normal) who perceive limited support from their parents exhibit the highest baseline levels of loneliness. Moreover, adolescent carriers of the *DRD2* A1 allele corresponding to reduced *DRD2* receptors' expression, are insensitive to the rewarding effect of parental support, potentially due to hypofunctional reward circuitry. The Methylene tetrahydrofolate reductase (*MTHFR*) C677T is another relevant polymorphism, which is linked to loneliness and reward deficiency, independent of age, education, cognitive function, and mood.^{131,132} Stress plays an important role in addiction^{98,133,134} and is also a part of loneliness experience. In older adults, the impact of stress inherent in rare contact with children and low levels of social support on loneliness is influenced by two SNPs, namely rs1876831 and rs242938, located within the corticotropin-releasing hormone receptor 1 (*CRHR1*) gene.¹³⁵ Those homozygous for the C allele of rs1876831, in comparison to the carriers CT/TT allele are lonelier in the context of infrequent encounters with the children and their consequently diminished support. See [Figure 2](#) for summary.

Human Social Networks and Genetics

In humans, heritable personality traits have been associated with dominance,¹³⁶ and superior status interacts with various neurotransmitter systems, including dopamine D2/D3 receptor binding. Higher binding of these receptors is linked to higher social status,¹³⁷⁻¹³⁹ suggesting the presence of biological mechanisms that process information related to social rank and hierarchies.¹⁴⁰ Brain responses to perceiving superiority or inferiority appear to be distinct, both when encountering an individual of a specific status and when faced with outcomes that can impact one's position in the hierarchy.¹⁴⁰ The perception of a superior individual triggers the engagement of perceptual-attentional, saliency, and cognitive systems, particularly the dorsolateral prefrontal cortex. Additionally, the hierarchical social consequences of performance are neurally separate and hold comparable significance to monetary rewards, providing a neural foundation for the strong motivational value of status. This research highlights the significance of hierarchical status in social networks, linking status to the reward circuitry, a crucial site for emotions and well-being.^{11,27}

To some extent, an individual's happiness is influenced by the people they are connected to within their social network.¹⁴¹ Clusters of happy and unhappy individuals can be observed within the network, and the influence of happiness can extend up to three degrees of separation, reaching the friends of one's friends' friends. Individuals who are surrounded by happy people and those who hold central positions in the network are likely to be happy themselves. Having a nearby happy friend, a happy spouse, a happy sibling, or just a happy next-door neighbor increases the proband's happiness probability by 25% (95% CI: 1% to 57%), 8% (CI: 0.2% to 16%), 14% (CI: 1% to 28%), and 34% (CI: 7% to 70%), respectively. The National Longitudinal Study of Adolescent Health and the Framingham Heart Study revealed the presence of the *DRD2* A1 allele's positive correlation (homophily) and *CYP2A6* (SNP rs1801272) allele's negative correlation (heterophily) in the context of friendship networks.¹⁴² These unique findings indicate that genetic homophily and heterophily occur at the allelic level, suggesting that association tests should consider the genes of friends and evolutionary theories should account for the fact that humans may be metagenomic in relation to those around them. This supports the notion that like-minded individuals tend to associate with each other¹⁴³ and even indicates a potential impact on political affiliation¹⁴⁴ ([Figure 3](#)). Relevant to the topic of happiness genes and social networks, our original study associated the *DRD2* A1 allele with severe alcoholism.¹⁴⁵ Furthermore, the *DRD2* A1 allele has been linked to various behaviors related to reward deficiency syndrome.¹⁴⁶ There are genetic data beyond SNPs, such as copy number variation studies and genome sequencing studies focused on rare variants (SNVs), which are also relevant.¹⁴⁷

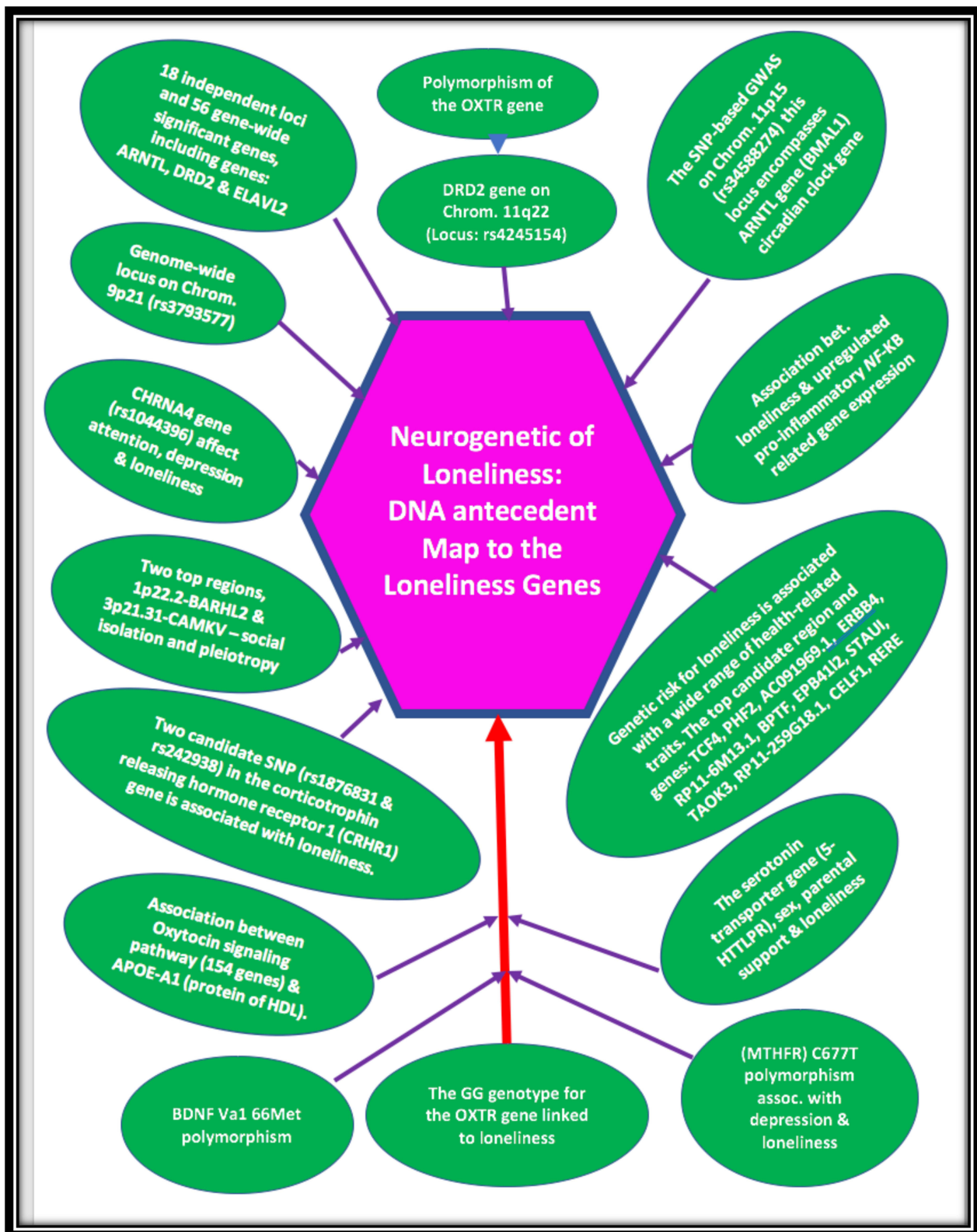


Figure 2 A schematic showing a proposed DNA antecedent map to the loneliness construct.

Clusters of individuals who engage in drinking or abstaining behavior were found within the network, and these clusters extended up to three degrees of separation.¹⁴⁸ These clusters were not solely a result of selective social ties among drinkers but also indicated interpersonal influence. Changes in alcohol consumption of a person's social network (eg, relatives and friends),

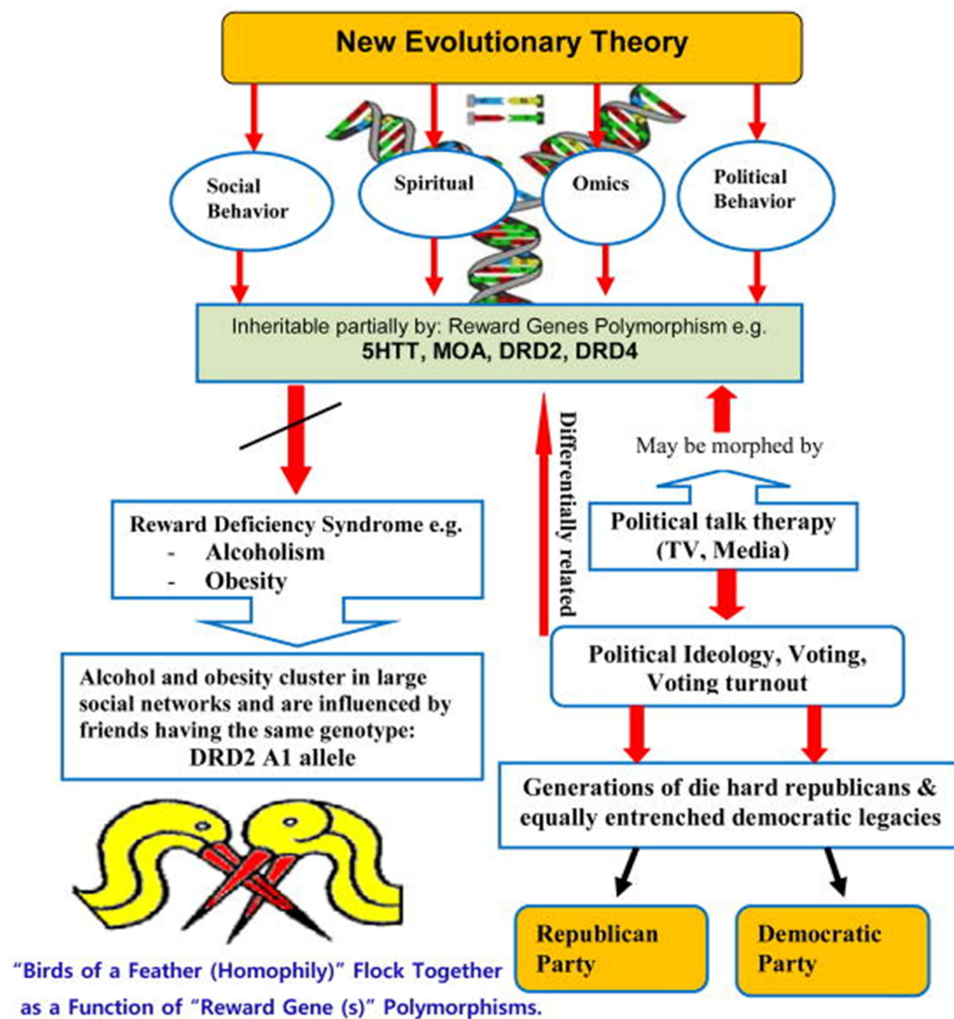


Figure 3 Genes and Human Networks.

Notes: Reprinted from Blum K, Oscar-Berman M, Bowirrat A, Giordano J, Madigan M, Braverman ER, Barh D, Hauser M, Borsten J, Simpatico T. Neuropsychiatric Genetics of Happiness, Friendships, and Politics: Hypothesizing Homophily ("Birds of a Feather Flock Together") as a Function of Reward Gene Polymorphisms. *J Genet Syndr Gene Ther.* 2012;3(112):1000112. Creative Commons.

not immediate neighbors and coworkers, had a statistically significant impact on that person's subsequent intake of alcohol. Similarly, clusters of obese individuals were present in the network and also extended up to three degrees of separation.¹⁴¹ These clusters did not solely arise from selective social ties among obese individuals. The likelihood of an individual becoming obese increased by 57% (95% CI, 6 to 123), 40% (95% CI, 21 to 60) or 37% (95% CI, 7 to 73) if a friend, sibling or spouse gained a substantial amount within a certain time period. The same effects were not observed among neighbors in the immediate geographic location. Interestingly, in comparison to the opposite sex, same sex individuals had a relatively stronger influence on each other. These findings align with our own data in a five-generational genotyping for the *DRD2* A1 allele, using reward deficiency syndrome as a generalized phenotype, showed that every member of the family carrying the *DRD2* A1 allele married a person who also carried the same gene.^{100,149}

Epigenetics and Loneliness

Much has been learned on how physical, chemical, and social environments affect human health, predisposing certain subpopulations to adverse health outcomes, especially the socio-environmentally disadvantaged. Translational data on gene and adverse environment, termed aberrant epigenomic modulation, translates into impaired gene expression via messenger ribonucleic acid dysregulation, reflecting abnormal protein synthesis and hence dysfunctional cellular

differentiation and maturation. The epigenetic influence on gene expression observed in most literature includes the physical, chemical, physicochemical, and, recently, social environment.¹⁵⁰

Loneliness is a multifaceted concept influenced by various genetic and environmental factors.¹⁵¹ Studies focusing on candidate genes and gene expression have identified genes associated with neurotransmitters¹¹⁵ and the immune system,^{152,153} which are likely to be related to loneliness. These findings align with the evolutionary theory of loneliness (ETL),¹⁰⁴ which suggests that loneliness is an inherited adaptation that signals a threat to social connections and motivates individuals to reconnect with others. The exploration of the genetic basis of loneliness has been greatly influenced by the fundamental principles of the ETL, prompting researchers to delve deeper into the genetic roots of this emotion. The ensuing research on gene-environment interactions have discovered that social-environmental factors, like low social support, can significantly affect feelings of loneliness, especially in individuals who have sensitive variants of certain candidate genes.¹⁰⁴

Loneliness or social isolation elevate the risk of stress-related major depressive disorder and PTSD that are linked via shared neuroinflammatory etiology.^{152,153} In a mice model of PTSD/suicide-like behavior four weeks of social isolation cause a reduction in peroxisome proliferator-activated receptor (PPAR) ligand-activated nuclear receptor and transcription factor that in addition to enhancing neurosteroid biosynthesis and exerting anti-inflammatory effect improves anxiety and depressive symptomatology.¹⁵⁴ Such reduction is accompanied by enhanced methylation of cytosines in CpG-rich regions of the PPAR- α gene, evident in impaired neurosteroid biosynthesis and in histone deacetylases (HDAC)1 and methyl-cytosine binding protein (MeCP)2 increases along with decreased expression of ten-eleven translocator (TET)2, favoring a state of hypermethylation. These changes correlated with elevated activation of toll-like receptor 4 (TLR-4) and pro-inflammatory markers, such as TNF- α , in the hippocampus, mediated by NF- κ B signaling (known to be implicated in loneliness). The induction of social isolation stress targeted epigenetic modifications associated with PPAR- α downregulation, suggesting a potential therapeutic approach to counteract the detrimental effects of loneliness.¹⁵⁴

A mice study explored how social isolation affects the epigenome. The researchers observed global DNA methylation changes with an increase in DNA methyltransferase activity. They also found di- and trimethylation of global histone H3 lysine 4 (H3K4), alongside heightened activities of histone methyltransferases, histone acetyltransferases, and histone deacetylases resulting in an overall increase of histone H3 lysine 9 (H3K9) acetylation.¹⁵⁵ Furthermore, this study also revealed gene-specific impacts caused by social isolation. Genes such as Hdac1, Hdac3, and the serotonin transporter Slc6a4 displayed abnormal DNA methylation patterns, with decreased methylation in the CpG islands. This led to the downregulation of the Slc6a4 gene and a general increase in DNA methylation.¹⁵⁵ These findings provide valuable insights into how social isolation can influence the epigenetic mechanisms underlying specific behavioral effects in mice. A recent human study likewise revealed significant association between loneliness and methylation in stress related *BDNF* and the glucocorticoid receptor gene.¹⁵⁶

Early life stress (ELS) triggers complex neurochemical processes that influence interconnected neurophysiopathology, including behaviors associated with addiction and a sense of loneliness.^{157,158} Rats exposed to maternal separation stress (MS), a model of ELS, displayed a threefold increase in ethanol consumption over a three-week period, along with a significant reduction in dopaminergic ventral tegmental area neurons positive for tyrosine hydroxylase.¹⁵⁸ These rats exhibited depressive-like symptoms and anhedonia, which are clinically associated with the construct of loneliness.¹⁵⁹ Furthermore, MS rats displayed twofold higher immobility time in the forced swim test and reduced sucrose drinking compared to control rats. The motivation to seek social contact can be influenced by both positive and negative emotional states, as social interaction can be rewarding while social isolation can be aversive.²⁸

Therapeutic Considerations

Genes inherited at birth from parents determine a hardwired portion of the perception and responsivity to loneliness as well as the potential to develop loneliness-induced neuropsychiatric and/or medical morbidity. Studies in monozygotic twins albeit showed high correlation yet only about 35% of the variance in loneliness may be attributable to the genetic substrate^{160,161} c.f. 90% heritability for height,¹⁶² 50% heritability for body mass index¹⁶³ and 50% heritability for

happiness.¹⁶⁴ Hence symptoms and sequelae of loneliness may be targeted in accordance with individualized formulations, based on genetic risk assessment battery akin to the one designed by us for the assessment of the propensity for addiction¹⁶⁵ in conjunction with clinical assessments, functional neuroimaging, psychotherapy, and psychopharmacology.

It is reasonable to expect that variability in the magnitude of (epi)genetic, psychological, social, and environmental contributors to overall symptomatology could define the nature and type of appropriate intervention alleviating symptoms of loneliness and improving general processing of information by the brain. To that end, reward abnormalities can be addressed by the Positive Psychology methods¹⁶⁶ including the Positive Affect Treatment¹⁶⁷ and the Positive Affect Stimulation and Sustainment techniques.¹⁶⁸

Diminished dopaminergic neurotransmission in the mesolimbic pathway underlying reward deficiency,^{24,165} presents opportunities for therapeutic interventions including antidepressants and cognitive enhancers like bupropion,¹⁶⁹ solriamfetol,¹⁷⁰ or modafinil.¹⁷¹ Additional methods for restoring dopaminergic hedonostasis^{27,39} include anticonvulsants, atypical antipsychotics,^{11,89,172} nootropics,¹⁷³ and N-methyl-D-aspartate glutamate receptors' antagonists.¹⁷⁴ A dietary supplement, acetyl-L-carnitine¹⁷⁵ with neurotrophic, neuroprotective, and antidepressant properties likewise presents heuristic value in managing reward deficiency.¹⁷⁶

Adrenergic agents as $\alpha 2$ adrenoceptor agonists or $\alpha 1$ adrenoceptor antagonists (eg, clonidine, guanfacine, or prazosin) is a rational therapeutic approach to anti-reward symptomatology. Such agents are already used successfully for other conditions that are frequently associated with feelings of loneliness^{102,177} eg, substance use disorders^{178,179} and PTSD.¹⁸⁰ Despite the complexities surrounding reward deficiency and anti-reward mechanisms, exploring these therapeutic options provides hope for better understanding and potentially alleviating loneliness and its related effects.

Limitations

Limitations that should be considered in interpreting our data refer to causality, scope, generalizability, the nature of the review and ongoing research. Establishing causality is challenging given the predominance of observational studies, and the cross-sectional design limiting the ability to firmly conclude whether loneliness directly causes neurobiological alterations or the other way around. Further research with prospective cohorts and comprehensive measures of loneliness is warranted to better understand the complex interplay between gene, loneliness, and neurobiological mechanisms. Also, the cited studies were conducted in specific populations and may not capture the full range of genetic and epigenetic factors influencing loneliness in different cultural, social, or age groups pointing to limited external validity.

Being a narrative review, the emphasis was placed on integrating key concepts and insights derived from existing knowledge and expertise rather than rigorous adherence to stringent selection criteria and quality assessment for the sources typical of systematic reviews. Systemic reviews may be vulnerable to publication bias as studies with significant findings are more likely to be published, while those with non-significant or negative results might be omitted, potentially skewing the overall picture. Given that discussed topics are subjects of ongoing research including the heritability of loneliness and the findings in this paper are not exhaustive, combining both narrative and systematic reviews that are representing the depth of experts' insight with the breadth of extant evidence is an important prerequisite for fostering new discoveries and evolving insights that may reveal additional dimensions or nuances that are not covered here.

Concluding Remarks

Key findings of this exploration of loneliness, a well-documented risk factor for both mental and physical morbidity, can be abridged within the domains of genetic antecedents, genes and mental health, epigenetic influences, and neural correlates. Regarding genetic antecedents, multiple genes appear to be involved in the interrelated processes of reward, stress, immunity, and loneliness as they are modulated by environmental factors. From the mental health perspective, genetic associations with personality traits and underlying neuropsychopathology provide insights into the intricate network of interactions converging on the experience of loneliness, enriching our understanding of its multifaceted nature. Epigenetically, loneliness and social isolation are significantly impacted by DNA methylations arising in the context of negative childhood experiences, underscoring the pervasive effects of early life adversity on loneliness-related outcomes. On the neural level being critical for the survival, loneliness system is embedded within the overlapping reward and stress circuitry responsible for continued existence of individuals and species via pursuit of food, water, sex,

and social affiliations^{9,11,89} while loneliness-related affective states and cognitions may be driven by hypodopaminergic reward deficiency,^{23–25} particularly in the context of early life stress, such as maternal separation.

About 55 years after its release, the “All You Need Is Love” hit by the Beatles remains an anthem for peace-loving people throughout the world. This is part due to its epitomizing the universal human longing for connectedness and acceptance or in the words of a Poet (Robert Burns, 1794) “I could range the world around, For the sake o’ Somebody”. Even though various neuro(epi)genetic mechanisms have been put forward to explain yearning for social attachments, they do not seem to fully explain its complexity. Once it became evident that genes associated with reward deficiency and anti-reward neuroadaptations are involved in loneliness, a subsequent question arises: Are some individuals, even in the absence of actual loneliness, predisposed to serious health problems due to a neuropathological vulnerability inherent in their genetic makeup, specifically in terms of social anhedonia?¹⁸¹ This concept is supported by neuroimaging studies that implicate a reward deficiency state characterized by depressed dopaminergic activity in the striatum, which corresponds to feeling “several drinks behind” the rest of the world.¹⁸² This state is a risk factor for the development of substance use disorders,¹⁸³ with consequently reduced social engagement leading to loneliness.¹⁸⁴

And so, people afflicted with social anhedonia are vulnerable to experiencing loneliness due hereditary and/or acquired neuropsychopathological alterations inherent in their genome. These alterations may be worsened by addictive substances consumption accompanied by excessive stress exposure. No consensus has yet been established on optimal therapeutic stratagems for social anhedonia and other conditions within the combined reward deficiency and anti-reward spectrum perhaps because further research is warranted on the specific pathways that lead to social anhedonia or loneliness sequelae, or whether a target psychotherapeutic or psychopharmacologic approach might be suitable to address the underlying cause. In this review we identified a potential system involved in reward and stress, which may be aimed at in clinical trials and in mechanistic research.

If the findings of clinical studies confirm our insights, they could have significant implications for the prophylactic measures against loneliness. Identifying neurogenetic vulnerability factors for loneliness may enable primary prevention in terms of screening and genetic counseling for individuals at risk that can help making informed decisions about emotional well-being and reproductive choices. High loneliness vulnerability due to genetically determined impairments in reward and stress function could prompt guidance to avoid loneliness, manage stress, and steer clear of addictive behaviors. To that end, healthcare providers may offer targeted interventions such as social support programs, cognitive-behavioral therapies at an early age as well as customized interventions in the form of behavioral and pharmacological treatments addressing the specific genetic and epigenetic factors contributing to feelings of loneliness. Detection of the epigenetic factors related to negative childhood experiences and their impact on loneliness can guide the development of therapeutic strategies aimed at addressing early life trauma and its long-term consequences on social and emotional well-being. Furthermore, patients could be targeted for early interventions, even in the presence of mild loneliness-related issues, as a secondary preventive approach. Governments and healthcare organizations can use this knowledge on a broader scale to design and implement public health initiatives to combat loneliness and its associated health risks, particularly in vulnerable populations. Such innovative preventive, diagnostic, and therapeutic approaches hold promise in addressing the growing public health concern of loneliness and its associated mental and physical morbidity.

In view of the high prevalence of loneliness among psychiatric and medical patients, we anticipate that understanding the role of genes and associated DNA risk polymorphic variants impacted by the environment through epigenetic mechanisms (eg, methylation/acetylation on histones) will provide substantial relief to the at risk- and the afflicted population. Early genetic assessment of the loneliness construct, when available coupled with structured psychometric assessments following required research, could offer valuable insights for generations to come and help provide for better psychological and medical management tailored to unique needs and biopsychosocial characteristics of each individual. This journey is far from complete, and the current stage is but a steppingstone in a broader quest to fully grasp the complex nature of the loneliness construct and its profound implications for health and disease.

Disclosure

Dr Milan Makale reports personal fees from PeakLogic Inc, outside the submitted work; In addition, Dr Milan Makale has a patent “Miniaturized rTMS system” pending. Dr Kenneth Blum reports royalties from and discloses many pending

USA and foreign patents on GARS and KB220 variants licensed to Synaptamine. The authors report no other conflicts of interest in this work.

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