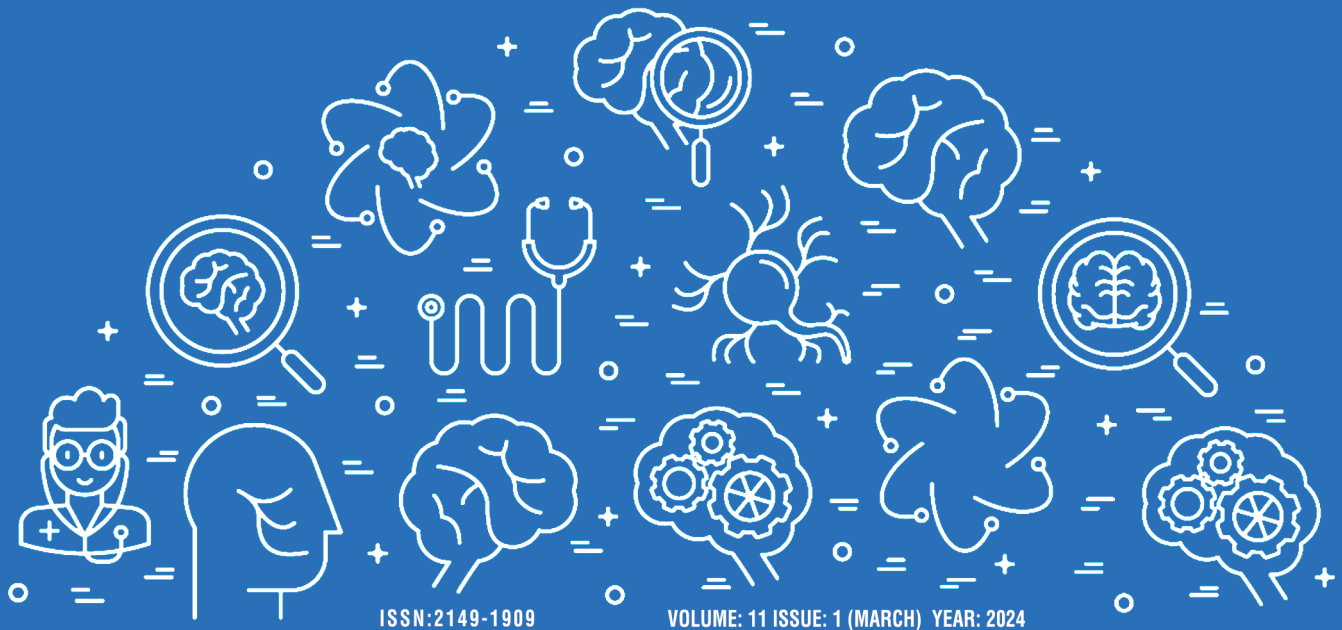

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JNBS (J. Neuro. Behav. Sci) is a comprehensive scientific journal in the field of behavioral sciences. It covers many disciplines and systems (eg neurophysiological, neuroscience systems) with behavioral (eg cognitive neuroscience) and clinical aspects of molecules (eg molecular neuroscience, biochemistry), and computational methods in health.

The journal covers all areas of neuroscience with an emphasis on psychiatry and psychology as long as the target is to describe the neural mechanisms underlying normal or pathological behavior. Pre-clinical and clinical studies are equally acceptable for publication. In this context; the articles and treatment results of computational modeling methods of psychiatric and neurological disorders are also covered by the journal.

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Submit manuscripts electronically (.doc format with including all figures inside) via the online submission system of our website (https://review.jow.medknow.com/jnbs).

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- In the publication, source numbers are indicated in parentheses or as superscripts at the end of the sentence - name - in which the source is used.
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According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1]
S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7-9,11]

The Reference Section:

• Journal Article:

Russell FD, Coppell AL, Davenport AP. In vitro enzymatic processing of radiolabelled big ET-1 in human kidney as a food ingredient. Biochem Pharmacol 1998;55(5):697-701. doi: 10.1016/s0006-2952(97)00515-7.

Gonen, M. Planning for subgroup analysis: a case study of treatmentmarker interaction in metastatic colorectal cancer. Controlled Clinical Trials 2003;24 : 355-363. doi: 10.1016/s0197-2456(03)00006-0.

• Authored Book:

Lodish H, Baltimore D, Berk A, Zipursky SL, Matsudaira P, Darnell J. Molecular cell biology. 3rd ed. New York: Scientific American; 1995.

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The Journal of Neurobehavioral Sciences

Volume 11 ¦ Issue 1 ¦ January-March 2024

Contents

Review Article

Hormonal Catalysts in the Addiction Cycle of Muscle Dysmorphia: A Neuroendocrine Perspective

Abstract

Muscle dysmorphia (MD) is a subtype of body dysmorphic disorder characterized by an obsessive belief that one's body is insufficiently muscular. This review provides a comprehensive examination of the addiction cycle in MD, particularly in the context of anabolic steroid and performance-enhancing drug (PED) use. Utilizing a systematic search across databases such as PubMed, PsycINFO, Scopus, and Web of Science, the review draws on peer-reviewed literature published in the past two decades to uncover the roles of hormonal and neural alterations in perpetuating this cycle. Inclusion and exclusion criteria were meticulously applied to ensure a robust analysis of relevant studies. The article details the interaction between exogenous hormonal supplementation from steroids and PEDs and brain receptors, which significantly disrupt neurotransmitter systems and affect mood, cognition, and stress responses. The synthesis of data reveals that hormonal imbalances due to substance abuse lead to profound changes in brain plasticity and function, instigating psychiatric disorders and complicating withdrawal and treatment. Therapeutic strategies are critically assessed, with emphasis on the success of cognitive-behavioral therapy, the role of pharmacological management, and the promise of emerging treatments targeting neuroendocrine disruptions. The review suggests an integrated, holistic treatment model that includes hormonal therapy and neurological considerations, underscoring the importance of personalized and sustained interventions. In conclusion, the intricate cycle of addiction in MD, fueled by the hormonal effects of steroids and PEDs on the brain, calls for an integrated approach to treatment. Future research should focus on the neuroendocrine impact of these substances to refine therapeutic strategies for MD.

Keywords: *Addiction cycle, anabolic steroids, muscle dysmorphia, neuroendocrine effects, performance-enhancing drugs*

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Introduction

Muscle dysmorphia (MD) represents a unique and often misunderstood domain within the spectrum of body dysmorphic disorders.[1] Characterized by an obsessive preoccupation with not being sufficiently muscular or lean, individuals with MD typically engage in behaviors aimed at increasing muscle mass and reducing body fat. This preoccupation often leads to the use of anabolic steroids and performance-enhancing drugs (PEDs), substances that have become increasingly associated with this condition. The use of these substances in the MD community is not merely a matter of physical enhancement but is intricately tied to psychological factors. The distorted self-perception inherent in MD drives individuals toward a perpetual cycle of substance use, where steroids and PEDs play a pivotal role. This cycle is not only a psychological phenomenon but also is deeply rooted in the physiological effects; these substances have on the human body, particularly regarding hormonal and neural changes.

Methods

Locating and selecting data

The data for this review were systematically sourced from an array of academic databases, including PubMed, PsycINFO, Scopus, Wiley, Google Scholar, and Web of Science. The search strategy was designed to encompass a comprehensive suite of keywords and MeSH terms relating to muscle dysmorphia, anabolic steroids, performance-enhancing drugs, addiction cycles, and hormonal effects on neuroendocrine function. Boolean

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operators ("AND," "OR") were utilized to refine the search and ensure a broad yet relevant collection of literature. Inclusion criteria were established *a priori*: articles must be peer reviewed, published within the past 20 years, and specifically discuss the hormonal and addiction aspects of MD. Exclusion criteria included non-English articles, case studies, and articles not focusing on the neuroendocrine implications of steroid and PED use.

Extracting data

On retrieval of articles, abstracts were screened for relevance, and full texts were obtained for those meeting the inclusion criteria. Data extraction focused on the hormonal mechanisms involved in MD, the neuroendocrine effects of anabolic steroids and PEDs, the psychological and physiological aspects of addiction cycles, and current therapeutic approaches. A standardized form was used to extract relevant data, including study design, sample size, outcomes, and conclusions related to the scope of this review.

Synthesizing data

The extracted data were then synthesized using a narrative approach, allowing for the integration of findings from diverse study designs and methodologies. This approach enabled the articulation of complex interactions between hormonal dysregulation and neurological changes within the context of MD and substance addiction. The synthesis involved a thematic analysis, where patterns and themes were identified and grouped to provide a comprehensive overview of the existing literature. Discrepancies and gaps in the research were also documented, highlighting areas for future investigation.

Ensuring quality and rigor

To ensure the quality and rigor of the review, the PRISMA guidelines were adhered to throughout the process. In addition, a bias assessment was conducted using the Cochrane Collaboration's tool to identify any potential bias within individual studies.[2] Articles were also cross-referenced to confirm the accuracy of extracted data and the validity of the authors' interpretations.

Results

Role of steroids and performance-enhancing drugs in muscle dysmorphia

Anabolic steroids and PEDs are known for their ability to rapidly increase muscle mass and improve athletic performance. However, their use extends beyond the enhancement of physical attributes. In the context of MD, these substances are used as a means to attain an unattainable ideal of physical perfection, often at the expense of mental and physical health.[3] The relationship between steroid/PED use and MD is complex. On the one hand, these substances provide a temporary solution to the distress caused by perceived inadequacies in muscularity. On the other hand, they exacerbate the condition by reinforcing the distorted self-image and perpetuating the cycle of abuse. This relationship is further complicated by the hormonal effects of these substances, which have a profound impact on brain function and structure, influencing mood, cognition, and behavior.

Hormonal catalysts in the cycle of addiction

The central focus of this review is to explore the hormonal catalysts that intensify the cycle of addiction in individuals with MD abusing steroids and PEDs. Unlike traditional forms of substance abuse, the addiction cycle in MD is significantly influenced by the direct hormonal effects of these substances.[4] Steroids and PEDs, through their interaction with specific brain receptors, lead to alterations in neurotransmitter systems, impacting critical brain functions related to mood, cognition, and stress responses.

Hormonal effects and neural mechanisms

Steroids and PEDs can significantly skew the body's hormonal homeostasis.[5] The influx of synthetic hormones mimics the effects of testosterone, which not only fuels the increase in muscle mass but also triggers a series of neurochemical events. The activation of androgen receptors in the brain alters the normal functioning of neurotransmitters, such as dopamine and serotonin, which are critical to mood regulation, motivation, and reward. This disruption can lead to mood disorders, aggression, and an altered stress response, all of which are common in individuals with MD. The psychological implications of these hormonal changes are multifaceted. On a behavioral level, the initial euphoria and increased performance can reinforce the continued use of these substances, despite potential adverse effects. However, the altered hormonal milieu also impacts cognition, potentially leading to impaired judgment, decision-making, and heightened risk-taking behaviors. These cognitive effects can perpetuate the cycle of abuse as individuals with MD may be less able to recognize the long-term consequences of their actions or to engage effectively in treatment strategies.

Physiologically, the persistent imbalance in hormone levels due to steroid and PED use can induce changes in brain plasticity. This refers to the brain's ability to change and adapt as a result of experience. However, in the case of substance abuse, these changes are often maladaptive. For example, chronic steroid use can lead to alterations in brain areas responsible for memory and emotional regulation, such as the hippocampus and amygdala. These changes not only have immediate effects on behavior but may also lay the groundwork for long-term psychiatric vulnerabilities.

Moreover, the endocrine system's disruption has secondary effects on other physiological systems. For instance, the hypothalamic–pituitary–adrenal axis, which is integral to stress response and is closely linked to the development of

depression and anxiety, can become dysregulated.[6] This dysregulation can exacerbate the psychological burden experienced by those with MD, potentially leading to a worsening of symptoms and a deepening of the dependency cycle.

The withdrawal from steroids and PEDs introduces a new set of challenges. The body's natural hormone production may be suppressed, leading to a state of hypogonadism, characterized by low or absent levels of testosterone. This hormonal deficit can have dire consequences for mental health, including the emergence of depressive symptoms, anxiety, and irritability. The neurological impact of withdrawal can be profound, with individuals experiencing a stark contrast from the heightened neural activity during substance use to a significant decline when ceasing use.

Hormonal impact on brain function

The hormonal impact on brain function is a complex and nuanced topic, particularly when discussing the effects of steroids and PEDs. These substances significantly alter the endocrine system, which is intricately linked to brain function.[7] The use of steroids and PEDs introduces exogenous hormones into the body, often in quantities that exceed physiological levels, leading to an imbalance that can profoundly affect mental health.

Endocrine disruption

The endocrine system's disruption through the use of steroids and PEDs has a domino effect on various bodily functions.[8] Testosterone and its derivatives, when introduced exogenously, can suppress the body's natural hormonal rhythm. This suppression can result in a range of mental health issues, including mood swings, irritability, and even long-term mood disorders. The hormonal imbalance can also lead to behavioral changes; for instance, increased aggression, commonly referred to as "roid rage," has been reported in steroid users. This is likely due to the heightened levels of androgens that affect the limbic system, a brain area crucial for emotion regulation.

Receptor interaction

Steroids and PEDs exert their effects by binding to androgen receptors in the brain, which are not only present in reproductive tissues but also widely distributed in various brain regions, including the hippocampus, amygdala, and prefrontal cortex.[9] The interaction with these receptors leads to changes in cellular functioning and gene expression, which can influence brain plasticity and long-term brain health.[10] The activation of androgen receptors modulates the synthesis and release of neurotransmitters and neurotrophic factors, which can affect neuronal growth and survival.

The consequences of these interactions are far-reaching. Neurotransmitters such as serotonin and dopamine, which are critical for mood regulation and the experience of pleasure, can be dysregulated by the hormonal fluctuations caused by steroids and PEDs. This dysregulation can alter an individual's stress response, potentially leading to heightened anxiety or diminished ability to cope with stress. In addition, cognitive functions such as memory, executive function, and decision-making can be impacted due to the changes in the neural circuits that govern these processes.

Neurotransmitter Alterations and Psychological Dependencies

Impact on neurotransmitter systems

Steroids and PEDs exert a profound influence on the brain's neurotransmitter systems, which play a critical role in regulating mood, behavior, and the reward circuitry.[11] Neurotransmitters such as dopamine and serotonin are particularly affected by these substances. Dopamine, often referred to as the "feel-good" neurotransmitter, is central to the reward pathway and is associated with feelings of pleasure, motivation, and concentration. The influx of synthetic hormones can cause a surge in dopamine levels, leading to a heightened sense of well-being and euphoria.[12] This artificially induced state can make the activities associated with steroid and PED use extremely reinforcing, laying the groundwork for psychological dependence. Conversely, serotonin, which is crucial for mood stabilization, impulse control, and overall emotional well-being, can become dysregulated through the use of these drugs. Such dysregulation can manifest as mood swings, depression, or anxiety when the substances are not present, reinforcing use as a form of self-medication. Over time, the individual's brain chemistry adapts to the presence of steroids and PEDs, establishing a new normal where the absence of these substances results in a significant deficit in neurotransmitter activity.[13] This adaptation can lead to withdrawal symptoms when the individual attempts to discontinue use, which may include depression, irritability, and a general lack of pleasure or motivation. The impact on these neurotransmitter systems extends beyond temporary mood alterations; it can cause long-lasting changes in the brain's neurochemistry and function. Chronic use can alter the sensitivity and density of neurotransmitter receptors, leading to a diminished response to natural rewards and a reduced ability to experience pleasure without the use of steroids or PEDs. This anhedonia-like state can perpetuate the cycle of abuse, as individuals may continue using these substances to chase the diminishing rewards they once provided. The modulation of neurotransmitter systems by steroids and PEDs thus represents a significant factor in the development and maintenance of substance dependence, highlighting the need for targeted interventions that address the neurochemical aspects of recovery.

Cycle of addiction

The cycle of addiction, particularly in the context of steroid and PED use, is intricately tied to the ebb and flow of

neurotransmitter levels within the brain. Steroids and PEDs, by amplifying the release and action of neurotransmitters such as dopamine and serotonin, can create a temporary sense of heightened confidence, well-being, and physical prowess.[14] This artificially induced state can be intensely rewarding, reinforcing the behavior of substance use and embedding it as a response to both internal and external cues. However, this elevated state is invariably followed by a stark withdrawal phase, characterized by an emotional downturn. Users may experience a marked decrease in mood, increased anxiety, and a pervasive sense of dissatisfaction when not using these substances, which starkly contrasts the earlier feelings of euphoria and invincibility. The adverse emotional states that accompany withdrawal can be distressing, driving individuals to resume substance use to alleviate their discomfort. This self-medication perpetuates the cycle of abuse, as each subsequent use reinforces the neural pathways associated with addiction. The brain's reward system, hijacked by the repeated chemical stimulation, becomes increasingly reliant on the presence of these substances to function optimally. The behavioral patterns become entrenched, and the psychological need for the drug's effects becomes as compelling as physiological dependence. Over time, the cycle of positive reinforcement (use of the drug leading to positive emotions) and negative reinforcement (use of the drug to avoid negative emotions) becomes deeply ingrained.

This cyclic pattern of addiction is further complicated by the potential for tolerance, where the individual requires progressively larger doses of the substance to achieve the same effect, increasing the risk of overdose and severe physiological damage.[15] The cycle of addiction is thus a complex interplay of enhanced neurotransmitter activity during use and the subsequent psychological and physical withdrawal symptoms. This vicious cycle is challenging to break, as the physical withdrawal symptoms are often accompanied by psychological cravings, leading to a high risk of relapse. Effective treatment must address both the physiological aspects of withdrawal and the psychological drive to use, incorporating strategies such as detoxification, counseling, and support groups to help individuals achieve and maintain sobriety.

Long-term brain changes

The chronic use of steroids and PEDs can lead to significant alterations in the brain's structure and functionality.[16] These modifications are not only deep seated but also multifaceted, influencing various aspects of neurological health and psychological well-being. Specifically, they may exacerbate the psychological symptoms associated with MD – a disorder characterized by a preoccupation with not being sufficiently muscular or lean. Individuals with MD often engage in compulsive behavior to improve their body images, such as excessive weightlifting and steroid abuse, despite potential negative health consequences. The brain changes from prolonged PED use can make these psychological symptoms more severe, entrenching the belief that one's body is inadequately muscular. Furthermore, these changes can complicate recovery efforts, making it challenging to reverse the dependency on these substances. Dependence on steroids and PEDs is not solely a matter of willpower; rather, it is entwined with substantial neurological adaptations that may sustain the cycle of abuse and complicate the path to sobriety.[17] Hence, understanding the neurological impact of these substances is crucial for developing effective treatment strategies for MD and associated substance dependency.

The Addiction Cycle

Physical health risks

The prolonged and unchecked use of steroids and PEDs carries with it a plethora of grave physical health risks, often leading to severe and sometimes irreversible consequences.[18] The spectrum of potential health issues spans from cardiovascular complications, manifesting as early-onset heart attacks and strokes, to hepatological conditions, such as liver tumors and jaundice. Renal failure is also a significant risk, alongside the potential for other organ damage due to the systemic effects of these substances.[19] These physical detriments do more than just impact the physiological state of the user; they intricately contribute to the complexity of the addiction cycle. By inducing physical dependence, the substances create a situation where the user's body may require them to avoid withdrawal symptoms, making cessation a challenge. In addition, the physical harm caused by steroids and PEDs can perpetuate psychological dependence, as individuals may continue using to maintain the enhanced physique that these drugs can facilitate, despite the detrimental health effects. The intertwining of physical health risks with psychological dependence creates a formidable barrier to breaking the cycle of addiction, as one must navigate not only the desire for the drug's effects but also the need to mitigate or manage the physical damage incurred. This complex interplay makes addressing steroid and PED addiction a multifaceted challenge requiring a holistic approach to treatment that encompasses both the physical and psychological domains of health.

Psychiatric and cognitive effects

The implications of steroid and PED use extend well beyond the confines of physical health, delving into the realm of psychiatric and cognitive effects. Individuals who engage in chronic use of these substances often find themselves grappling with an array of mental health challenges. These can include psychosis, a state of losing touch with reality, characterized by hallucinations or delusions; depression, marked by persistent sadness and loss of interest; anxiety, involving excessive worry and nervousness; and aggression, which can manifest as irritability and anger.[20-22] These psychiatric symptoms are not mere by-products of substance

misuse; rather, they actively contribute to the exacerbation of MD, intensifying the disorder's symptoms. MD, a condition characterized by a distorted body image and an obsessive desire to gain muscle mass, can be significantly aggravated by the mental health issues induced by steroids and PEDs. This interaction creates a perilous cycle where psychiatric problems can drive increased substance use as individuals attempt to self-medicate or cope with the stress of their altered mental state. Conversely, the use of steroids and PEDs can worsen psychiatric symptoms, further entrenching the individual in the cycle of addiction and mental health deterioration. The interplay between these factors underscores the need for a comprehensive approach to treatment that addresses both the psychiatric manifestations and the underlying substance use disorder, recognizing the complex bidirectional relationship between mental health and substance abuse in the context of MD.

Challenges in overcoming dependence and withdrawal

The journey to surmount the shackles of dependence on steroids and PEDs is fraught with numerous challenges, both psychological and physiological.[23] The psychological dependence that ensues from the alteration of neurotransmitter systems and hormonal balances is particularly insidious. It is characterized by a deeply ingrained belief in the necessity of these substances to maintain not only a certain physical appearance but also emotional stability. Individuals trapped in this cycle believe that the use of steroids and PEDs is integral to their self-worth and emotional well-being, making cessation an arduous endeavor. When attempts are made to discontinue the use of these substances, individuals often encounter withdrawal symptoms that can be both physically and psychologically taxing. These symptoms may include profound depression, anxiety, significant loss of muscle mass, and a host of other discomforts that can impinge on everyday functioning. The intensity of these symptoms can be overwhelming, frequently leading to relapse as the immediate cessation of substance use unveils the full brunt of withdrawal effects.[24] In the quest to mitigate these distressing symptoms, individuals may find themselves reverting to substance use, thus perpetuating the cycle of dependence.

This complex web of psychological dependence, coupled with the daunting withdrawal symptoms, underscores the need for a robust support system and a comprehensive treatment plan. Such a plan must address both the psychological facets of addiction and the physiological aftermath of withdrawal. Effective treatment is multifaceted, often requiring medical intervention, counseling, and long-term support to navigate the precarious path of recovery and to reduce the likelihood of relapse.

The self-perpetuating cycle of addiction

In the context of MD, the addiction cycle fuelled by the use of steroids and PEDs takes on a particularly pernicious form, largely due to the direct hormonal catalysts these substances provide.[25] The introduction of synthetic hormones into the body can cause a cascade of effects, altering everything from physical appearance to brain chemistry and emotional states. This hormonal upheaval can amplify the symptoms of MD, as the individual's perception of their body and compulsive behaviors to modify it become intertwined with the drug's effects. Hormonal imbalances induced by steroids and PEDs not only contribute to the maintenance of the addiction cycle but also intensify it. These imbalances can lead to erratic emotional regulation and cognitive function, further entrenching the user in a state of dependence. The challenge in breaking this cycle is multidimensional, requiring a keen understanding of the hormonal underpinnings at play. Effective interventions must be comprehensive, tackling not only the psychological aspects of MD, such as body image distortion and compulsive exercise but also addressing the physiological dependencies that arise from the drug-induced hormonal imbalances.

This necessitates a treatment strategy that is both holistic and nuanced, capable of managing the withdrawal symptoms while also supporting the individual's mental health. Medical treatments may need to be combined with psychotherapy to deal with the psychological reliance on the substances, while strategies to stabilize hormonal levels are also implemented. Understanding the complex interplay between the psychological and physiological elements of this addiction cycle is critical for developing effective treatment plans that can break the relentless grip of dependence.

Clinical Implications and Treatment Strategies

This section focuses on the clinical implications of the addiction cycle in MD, particularly concerning the abuse of steroids and PEDs, and discusses potential treatment strategies that address both the psychological and physiological aspects of this condition.

Current therapeutic approaches for muscle dysmorphia and substance abuse

The treatment of MD and concurrent substance abuse, particularly the abuse of steroids and PEDs, incorporates a multifaceted therapeutic approach to address the complex interplay between psychological issues and physiological dependencies.

Psychological interventions

At the forefront of psychological treatments is cognitive behavioral therapy (CBT), a form of intervention that is particularly effective in tackling the underlying body image issues and the distorted perceptions that characterize MD.[26] CBT works by helping individuals recognize and challenge their harmful thought patterns and behavior, gradually learning to replace them with healthier ones. This approach

is beneficial in managing the compulsions associated with steroid and PED use, such as the obsessive pursuit of a more muscular physique. Other psychological counseling methods, such as psychoeducation, group therapy, and motivational interviewing, also play a significant role in supporting the individual's journey toward recovery.

Pharmacological treatments

Alongside psychological therapies, pharmacological interventions may be necessary, especially when steroid and PED use has induced significant hormonal imbalances and psychiatric complications. Medications may be prescribed to stabilize mood, manage depression, and alleviate anxiety symptoms that have been exacerbated by substance abuse.[27] These medications can range from antidepressants to mood stabilizers and antipsychotics, depending on the individual's specific symptoms and needs. The careful management of these medications is crucial, as it is essential to avoid substituting one dependency for another while ensuring that the psychological interventions have the best chance of success.

Overall, the current therapeutic strategies for MD and substance abuse highlight the importance of an integrated treatment plan that considers both the mental health aspects and the physiological effects of steroid and PED abuse. The goal is to provide a comprehensive support system that enables individuals to regain control over their lives, free from the constraints of addiction and the distortions of MD.

Addressing hormonal and neural aspects in treatment

Treatment approaches for steroid and PED abuse, especially when intertwined with MD, must incorporate strategies that directly address the hormonal and neural changes incurred by substance use.

Hormonal therapy

Hormonal imbalances are a central consequence of chronic steroid and PED use, and correcting these imbalances is essential for recovery. Hormonal therapy can be an integral part of treatment, including hormone replacement therapies or other medical interventions to restore the body's natural hormonal balance.[28] This aspect of treatment is particularly crucial because it targets the physiological dependencies that perpetuate the addiction cycle, helping to reduce cravings and withdrawal symptoms that can trigger relapse.

Neurological considerations

Steroids and PEDs have profound effects on brain function, altering neurotransmitter systems that can lead to changes in mood, behavior, and cognitive processes. Treatment, therefore, may require a focus on neurological health to rebalance neurotransmitter levels and address any long-term cognitive or neurological impairments. This could involve the use of medications that support neurotransmitter function or cognitive rehabilitation techniques that help individuals recover from any cognitive deficits. Moreover, strategies such as neurofeedback, which can train the brain to function more effectively, or mindfulness-based interventions, which can improve neurological health and emotional regulation, may also be beneficial.

In summary, a comprehensive treatment plan for individuals struggling with steroid and PED addiction and MD should involve both hormonal and neurological interventions. The aim is to provide a holistic approach that addresses the wide-ranging effects of these substances, facilitating a return to both physical and mental health and ultimately breaking the cycle of addiction.

Emerging therapies and holistic approaches

The landscape of treatment for MD and steroid/PED addiction is continually evolving, with emerging therapies reflecting the latest research into the neuroendocrine effects of these substances.

Research-based interventions

As our understanding of the impacts of steroids and PEDs on the brain advances, new treatment modalities are on the horizon. These could encompass cutting-edge pharmacological agents designed to specifically target the neuroendocrine disruptions caused by these substances.[29] Similarly, therapeutic techniques that emerge from ongoing research might offer tailored approaches to rebalance the hormonal and neural systems affected by MD and substance abuse. Such interventions could range from neuromodulation techniques, which aim to recalibrate brain activity, to new classes of medications that more precisely rectify hormonal imbalances.

Integrative treatment models

Given the complex nature of MD and steroid/PED addiction, a holistic and integrative treatment model is recognized as the most beneficial approach.[30] This model advocates for the combination of various therapeutic elements: psychological counseling to address mental health components, medical treatment for hormonal and physical issues, nutritional guidance to restore and maintain physical health, and physical rehabilitation to recover from the physiological damages wrought by substance abuse. By encompassing all aspects of health, this integrative model aims to provide comprehensive care that addresses every facet of the individual's well-being. The effectiveness of such a holistic approach lies in its ability to treat the person as a whole, recognizing that the psychological, physical, and hormonal elements are deeply interconnected and must be treated concurrently for the best chance of recovery.

Challenges and considerations in treatment

The management of MD and steroid/PED addiction presents unique challenges and necessitates careful consideration of several critical factors in treatment planning.

Tailoring treatment to individual needs

The personal nature of MD and the varied responses to steroid and PED use demand that treatment plans are highly customized. Individuals come with their own set of experiences, psychological profiles, and physiological responses to substances. A one-size-fits-all approach is not feasible for such complex conditions. Treatment must be adaptive, considering personal history, the severity of the dependency, and the specific psychological and physiological effects experienced by the individual. This personalized approach may involve a combination of different therapeutic interventions, which could range from various forms of counseling and behavioral therapy to specific medical treatments targeting the individual's unique hormonal imbalances.

Long-term management

MD and steroid/PED addiction typically require sustained and often long-term treatment strategies. The chronic nature of these conditions, coupled with the high potential for relapse, underscores the necessity for continuous support and intervention. Long-term management might include ongoing counseling, support groups, and potentially maintenance pharmacotherapy, all aimed at sustaining recovery and preventing relapse. Regular monitoring of psychological and physical health is also crucial to identify and address any signs of relapse early. In addition, since lifestyle factors such as exercise routines, diet, and social influences can significantly impact recovery, these areas should also be included in the long-term management plan. The ultimate goal is to support the individual in maintaining a healthy lifestyle and psychological well-being over time, acknowledging that recovery is a continual process rather than a single event.

Discussion

The interplay between hormonal effects and neurological function in the context of MD and the abuse of steroids and PEDs is a critical nexus for understanding addiction. This complex cycle of addiction, intensified by direct hormonal modulation of brain function, represents a significant departure from classical addiction paradigms, which have traditionally emphasized the psychological and behavioral aspects of substance dependence. Steroids and PEDs, by their pharmacological nature, are designed to enhance physical performance and appearance, primarily through their anabolic effects. However, their impact extends far beyond the musculoskeletal system, reaching into the very fabric of neural function. The acute hormonal shifts induced by these substances lead to marked changes in neurotransmitter systems, particularly those associated with reward and stress, such as the dopaminergic and serotonergic pathways. The resulting neurochemical imbalance manifests as alterations in mood and cognition, which can range from increased aggression to impaired judgment. The abuse of steroids and PEDs in individuals with MD is often motivated by an intense, pathological drive to achieve and maintain an idealized muscular physique. This drive, while partially rooted in psychological factors such as body image disturbances and perfectionism, is compounded by the reinforcing hormonal effects of the substances themselves. The enhanced dopaminergic activity associated with steroid and PED use may not only create a sense of well-being and heightened energy but can also lead to compulsive drug-seeking behavior, further entrenching the addiction cycle. As these individuals continue to use these substances, their brain chemistry adapts, potentially leading to tolerance and the need for higher doses to achieve the desired effect. Such adaptations can result in a chronic state of neuroendocrine dysregulation, which may be difficult to reverse. Moreover, the alteration in hormonal levels can have deleterious effects on the brain's plasticity, potentially leading to long-term cognitive deficits and increased vulnerability to psychiatric disorders. The withdrawal phase presents its challenges. The cessation of steroid and PED use can precipitate a significant drop in endogenous hormone levels, leading to a state of hypoandrogenism. This hormonal imbalance can have profound neurological implications, including the onset of depressive symptoms, anxiety, and cognitive fog. Such symptoms not only pose a challenge for the individual's mental health but also increase the likelihood of relapse into substance use as a means of alleviating the discomfort associated with withdrawal. The chronic use of steroids and PEDs has been associated with irreversible damage to both the body and the brain. On a structural level, there is evidence to suggest that long-term use can lead to changes in brain morphology, particularly in areas involved in memory, emotion, and executive function. These alterations may contribute to the psychiatric comorbidities often observed in long-term steroid users, such as mood disorders and cognitive impairments. The cycle of addiction in MD is thus a product of an intricate interaction between the endocrine system and neural mechanisms. The hormonal effects on neurotransmission and brain structure create a biological underpinning for the psychological and behavioral manifestations of the disorder. Addressing this cycle requires a nuanced approach that considers both the physical and psychological dimensions of addiction. Therapeutic strategies need to be as multifaceted as the disorder itself, combining pharmacological interventions to restore hormonal and neurochemical balance with psychotherapeutic treatments aimed at addressing the underlying psychological issues. CBT, motivational interviewing, and mindfulness-based interventions can be effective in modifying the cognitive and behavioral patterns associated with MD. Support groups and family therapy may also play a role in providing psychosocial support, challenging societal norms surrounding muscularity, and fostering a more positive body image. In terms of research,

there is a pressing need for comprehensive studies that investigate the long-term neurological and psychiatric outcomes of steroid and PED abuse. Longitudinal research is particularly crucial for understanding the chronic effects of these substances on brain structure and function, which could inform the development of more effective treatment protocols and preventative strategies. Such research should also explore the potential reversibility of the neurological damage associated with steroid and PED use, providing hope for recovery and rehabilitation.

Conclusion

The cycle of addiction in MD reflects a complex interplay between hormonal influences and neurological changes. This cycle is perpetuated by the direct effects of steroids and PEDs on the brain, which complicate the psychological aspects of addiction and pose significant challenges for treatment. An integrated approach, encompassing both medical and psychological interventions, is essential for effectively addressing this unique form of addiction. Future research efforts must aim to unravel the long-term effects of hormonal agents on neurological function, which will be instrumental in advancing our understanding and treatment of MD.

Patient informed consent

There is no need for patient informed consent

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Original Article

How Entropy Explains the Emergence of Consciousness: The Entropic Theory

Abstract

Aim: Emergentism as an ontology of consciousness leaves unanswered the question as to its mechanism. I aim to solve the body–mind problem by explaining how conscious organisms emerged on an evolutionary basis at various times in accordance with an accepted scientific principle through a mechanism that cannot be understood, in principle. **Proposal:** The reason for this cloak of secrecy is found in a seeming contradiction in the behavior of information with respect to the first two laws of thermodynamics. Information, the microstate of particles within an isolated system's macrostate, can, like first-law energy, be neither created nor destroyed, yet the information in the system, like second-law entropy, will inevitably increase. To explain information increasing without being created, Laplace's demon is invoked, able to predict where each particle is destined. This doesn't work for emerging events like consciousness, which are unpredictable. This can be understood in terms of the derivation of entropy, and the emergence of classical physics, from the Relativistic Transactional Interpretation of Quantum Mechanics. I propose that the increased entropy in a time-irreversible, unpredictable (emergent) isolated system requires the simultaneous deletion of information concerning the steps, or calculations, involved. **Conclusion:** Thus, the steps leading to consciousness are immediately destroyed and must remain a mystery. Implications include that entropy, not panpsychism, is the universal principle generative of consciousness, that our being conscious proves that we are not predetermined, and that consciousness requires assuming an "entropy debt" that can only be repaid by living organisms, prohibiting the emergence of conscious machines.

Keywords: *Consciousness, emergence, entropy, evolution*

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The Ontology of Consciousness

Introduction

The purpose of this paper is to solve the problem of emergentism within consciousness. There are two views as to how tissues inside the vaults of our craniums can create the wonders of this experience. Panpsychism holds that all the component subatomic particles of those tissues participate in a form of consciousness, and have done so since their origin at the beginning of the universe. Its proponents have acknowledged the theoretical "binding problem:" how the minute consciousnesses of so many components can be melded into the singular conscious entities of living organisms. In addition, I'll show that they face a sterner problem posed by an inability to repay the debt owed by consciousness to entropy. The alternative to panpsychism is emergentism, which holds that consciousness arises exclusively within nervous systems of living animals (and possibly within homologous structures in plants, maybe even smaller organisms). Proponents of this theory are challenged to explain by what magic consciousness can emerge from nonconscious components within living tissues.

Consciousness can be loosely defined as what it is like to be oneself, including introspection, subjective sense perceptions (qualia), integrated sense perceptions, subjective awareness, self-awareness, emotions, feelings, wakefulness, thoughtfulness, memory, awareness of memory, inquisitiveness, communicativeness, purposefulness, a drive toward problem-solving, and, as I will maintain, causative agency.

In particular, Yunus Çengel described a hierarchy of causative agencies, with

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consciousness as a purposive agency, endowed with a directed causality.[1] This is opposed to the laws of physics, which are nonpurposive causative agencies, and simple emergent properties, which are noncausative. Emergent theories of consciousness are interesting because they can allow consciousness to interact with and control a material brain.

Karl Popper and John Eccles noted that monist theories of consciousness, such as radical materialism/behaviorism, and the dualisms of panpsychism, epiphenomenalism, parallelism, and identity theory deny that, or cannot explain how, consciousness can causally affect the material brain.[2] For example, they cannot account for the mental effort that can be needed for the mind to direct the brain to retrieve a specific memory, and then evaluate the accuracy of the brain's performance. Popper held that mental processes evolved under the pressure of natural selection, based on the need for purposeful behaviors to ensure survival and reproductive success. (Eccles noted that if consciousness hadn't made a difference, it wouldn't have evolved.) This is the starting point linking my proposed ontogeny of emergentism with a causally directive consciousness.

Why consciousness is necessary

Consciousness is a property of a neurological analytic facility that, to survive, must blend all our experienced perceptions with the signals of internal homeostasis. It must match these with expectations, apprehend the nature of problems, rank their urgency, and solve them based on an analysis that has to have a representation of the self in the world. For this, the brain creates a metaphorical surround-sound movie screen that Daniel Dennett called the "Cartesian theater."[3] This must transpire without the benefit of a "little man," or homunculus, to view the scene from within, since the homunculus, in turn, would need a homunculus, regressing infinitely. As Antonio Damasio put it: "The sense of the self in the act of knowing emerges within the movie. Self awareness is actually part of the movie, thus it creates the "seen" and the "seer," the "thought" and the "thinker," with no separate spectator for the movie-in-the-brain."[4] Our conscious experience is the homunculus. It is rapidly supplied with pertinent information about our internal and external milieux in a format that's readily understood, including the ability to feel changes in our bodies that are provoked in our minds by its directing our own actions. So, in effect, we are left with the question, not "Why do we have consciousness?", but "What possible alternative way of experiencing the world could there be?"

But why did the need for conscious experience evolve? Imagine a world in which we had no more consciousness than a machine, but more intelligence than a rock. In this world, we could computationally reason that it was time to seek food or shelter, and that we must earn money in order to pay for these, but we could not reason or imagine, in the absence of the sensations of pleasure, love, reward, or enjoyment, that it is time to seek romance, or to perform an act that will lead to the birth of children, or to care for them afterward. Consciousness, therefore, is more than a result of Darwinian selection for self-preservation. It is also the result of sexual selection for the sights, smells, and sounds of beauty and the emotional package leading to reproduction. The environment of mating rituals and the efforts required to make ourselves (and then our children) fit, educated and attractive, is the primary driver of much conscious programming.

Consciousness is a very neat trick, but how does the brain pull it off? To answer this, it is necessary to understand the universal drive toward diversity and disorder.

The Interaction between Consciousness and Entropy

Thermodynamic entropy: Microstates within macrostates

Living organisms are islands of reduced thermodynamic entropy within their environments, far from thermal equilibrium. Consciousness further reduces this entropy multifocally around the world, as is seen by an examination of the structures conscious minds have built. Compared to the thermodynamic entropy of the brain's sensory inputs, the thermodynamic entropy of the output of consciousness is lower, i.e. it is more organized, which is what makes the brain interesting.

Thermodynamic entropy, as described by the second law of thermodynamics, is the tendency for disorder in a closed system of particles, i.e. gas molecules, always to increase. In the 19th century, Ludwig Boltzmann linked this concept mathematically to the distribution of molecules in space, thereby determining the foundational equation of statistical mechanics: S (the entropy) = k. Log W, where W is the number of real microstates corresponding to a gas's macrostate. The entropy of a macroscopic state is proportional to the number of configurations of microscopic states of a system where all microscopic states are equiprobable.[5] Later, it was realized that there was an analogy between the distribution of molecules in a gas and the amount of information in a message.

Thermodynamic entropy and information

According to John Wheeler, information is fundamental to the physics of the universe.[6] He suggested the emergence of the physical from enough information, saying "more is different" and "The rich complexity of the whole does not in any way preclude an extremely simple element such as a bit of information from being what the universe is made of."[7] David Chalmers built on this in his analysis of consciousness, writing "If so, then information is a natural candidate to also play a role in a fundamental theory of consciousness. We are led to a conception of the world on

which information is truly fundamental, and on which it has two basic aspects, corresponding to the physical and the phenomenological features of the world."[8] There is a connection between information and entropy, microstates and macrostates, which needs exploration to understand consciousness.

The amount of information in a message is, in most contexts, proportional to its length in characters or digits. Likewise, Entropy, per Boltzmann's equation, is the number of digits of probability in a system, and represents the possible combinations of activity that we're ignorant of. The more certain an event is, the less surprising it will be and the less information it will contain, and therefore, a gain in information (by which, I don't imply known information, which has zero entropy) is an increase in uncertainty or entropy. An increasing entropy implies an increasing uncertainty, or number of possible outcomes, being associated with an increased number of microstates within a macrostate. (Microstates are subunits of a system, or macrostate, which can be imperceptibly rearranged within it.) If we are about to toss a coin, or roll a die, there isn't yet any information about the outcome, and zero entropy. Having tossed the coin, with two equally likely outcomes, the information gained, or surprise upon learning the result will be less than the information gained, or surprise on learning the result, of the die roll, with six possible outcomes. An increase in the number of possible outcomes in "information space" is equivalent to an increase in disorder in the world. The information space can refer to the possible arrangements of sand grains on a beach, or atoms in a jar, impossible to apprehend. Entropy is the amount of "missing information" needed to determine what specific microstate your system (or information space) is in. While the thermodynamic entropy of a physical system is measured in physical units (Joules of energy divided by the absolute temperature), the informational entropy is measured in abstract mathematical units - bits, short for "binary digits."

In fact, once we learn the result of the coin toss, or the roll of the die, the information, its uncertainty and its entropy, drops to zero. Information here is defined as the opposite of knowledge. The loss of entropy associated with gaining knowledge is compensated for by the increase in entropy associated with our brain's activity, especially that associated with maintaining consciousness, as well as the activities it directs. Additionally, the more we learn, the more we realize what we still don't know, increasing our uncertainty. Or, according to a quote generally attributed to John Wheeler, "We live on an island surrounded by a sea of ignorance. As our knowledge grows, so does the shore of our ignorance."[9] One could reasonably describe the brain as an instrument for expanding entropy through the conversion of information into knowledge.

The entropic brain theory and Shannon entropy

To avoid possible confusion, I'll mention here that the Entropic Theory of the Emergence of Consciousness is not related to, and contradicts aspects of, the Entropic Brain Hypothesis of Carhart-Harris *et al*.[10] The latter considers the human brain to have a higher entropy, or disorder, than the brains of other animals, i.e. a greater repertoire of potential mental states, which expanded greatly relatively recently in our evolutionary history. This occurs with an increased entropy suppression during normal consciousness, relative to the degree of suppression characteristic of archaic humans and also of infants. This hypothesis is couched in terms of thermodynamic entropy, but also described in terms of Shannon entropy. Shannon entropy is a measure of the amount of information, or surprise, contained in a variable, or unit of storage/transmission that can take different values following some process, such as in a message. It is eponymic for Claude Shannon, who realized that the equation for representing this concept resembled the Boltzmann equation for thermodynamic entropy, except with a minus sign in front.[11] The minus sign in this context means that information is the opposite of entropy.[12] It means that a message with zero surprise has no Shannon entropy, whereas a room with almost zero thermodynamic entropy would have all the air molecules concentrated in one corner: a very surprising state of affairs indeed! The Entropic Brain Hypothesis is also consistent with Karl Friston's "Free-Energy Principle" theory of consciousness, which asserts that conscious organisms seek to minimize their Free Energy.[13] For clarity's sake, I'll continue the discussion in terms of thermodynamic entropy.

The Entropic Brain Hypothesis posits that the entropy reduction manifest by consciousness is associated with highly organized activity in the Default Mode Network of the brain, as described by Raichle *et al*., and with related neural connections.[14] Carhart-Harris considers this to be secondary consciousness. Under conditions such as sleep, general anesthesia, seizures, and depression, entropy is further suppressed, focused inwards, and unable to access a healthy diversity of thoughtful states. On the other hand, infant consciousness, dreaming, magic thinking, near-death experiences, and psychedelic drug trips increase entropy, allowing access to mental states no longer tethered to reality. These "hyperconscious" states, which Carhart-Harris considers to be primary consciousness, can approach "self-organized criticality," the transition point from order to disorder, where so-called "power-law scaling" can result in avalanches of neural cascades. This is clinically manifest in the "dissolution of the self" reportedly experienced during psychedelic drug use.

The Entropic Theory of the Emergence of Consciousness, while in agreement with the idea of entropy reduction during normal consciousness, disagrees with Entropic Brain Theory on significant points. In particular, the idea that sedation, anesthesia, depression, etc., represent further decreases in entropy beyond the reduction associated with normal consciousness is a good description in terms of Shannon entropy, because in these states, one is less

apt to produce surprising behavior. However, in terms of thermodynamic entropy, in these states, one is much less likely to do anything constructive that decreases the entropy of the immediate outside world. Because of this, subconscious states are equivalent to an increase in thermodynamic entropy relative to normal consciousness. I'd argue that during evolution, organisms of relatively low, poorly organized levels of consciousness, having high thermodynamic, but low and subcritical Shannon entropy, developed higher levels of more organized consciousness. This reduced their thermodynamic entropy (but increased their Shannon entropy to a point little below criticality). It seems intuitively sensible that the state of consciousness would arise from a state of unconsciousness rather than from a state of hyperconsciousness: otherwise, one is left to wonder how the hyperconscious state first appeared. I submit that consciousness emerged from unconsciousness, and the uncertainty associated with this, the seeming impossibility of our being able to understand it, guarantees that thermodynamic entropy will, perhaps counterintuitively, favor this process of emergence.

The Paradox of Emergence without Creation

The emergence and destruction of information in a determined universe

By now, it should be clear that the term "information" has meanings at different levels which could be confused, especially with regard to the (imperfect) analogy between information and entropy. For instance, the first law of thermodynamics states that in an isolated system, energy can be neither created nor destroyed; it is believed that the same applies to information, with two caveats. What's known as the "Black Hole paradox" suggests that information may be destroyed by a black hole that subsequently radiates away; this paradox may have been solved at the time of writing,[15] but doesn't concern this discussion. Confusion is added by the second law of thermodynamics, which states that the amount of entropy in an isolated (closed) system cannot decrease – it tends inevitably to increase until the system achieves equilibrium. This is a property which seems to "emerge" from quantum physics, in which all interactions are perfectly reversible. According to Ruth Kastner's Relativistic Transactional Interpretation of Quantum Mechanics, a "direct action theory" of objective reduction, this occurs with the loss of any "phase coherence" in quantum states, with the resultant "throwing out of information" to create "blurring" at the classical level.[16] In particular, it emerges when we are dealing with large numbers of particles in a statistical fashion. Also, while information is conserved, entropy is not. Therefore, if the amount of information is proportional to the entropy, then this means that the amount of information, too, must increase until the universe reaches the equilibrium of heat death far off in the future. Sean Carroll explained that the information which is conserved is that of the microstate, made up of the positions and momenta of particles, unknown to us, and not the information in the system's macrostate, of which we might or might not have knowledge.[17] The embedded, classical, or macroscopic information, of which we can seek knowledge, is not conserved, and can be copied or deleted perfectly. Therefore, a book, full of classical-level information, can be destroyed in a fire, which will increase the entropy of the macrostate, as well as (one might think) that of the scattered atoms in the microstate. However, the radiation and the atoms in the smoke and the ash could theoretically be traced back to their original positions in the book, so this conserves information at the level of the microstate (it is not destroyed), even as we know this, being equivalent to the reassembly of a broken egg, would decrease the entropy of the scattered particles and will never happen. The law of conservation of information seems to assume that the second law of thermodynamics does not apply at the microstate level. Likewise, the question of what happens to all the information in our brains, if not our minds, at death is analogous to what happens to the information in the incinerated book. Someone who knew all the trajectories of all the particles after classical information is destroyed could reconstruct all the information laid out in neural pathways.

This explains how information in the book escapes destruction, but how is information not created as the book's entropy is increased, and its atoms scattered? Anyone who knew the trajectories of all the relevant particles before the book was burnt would know the information concerning each particle that was about to change as the printed paper burned. Since they would be able to predict what would happen next, the information of this system is thus changed without being "created," and doesn't actually increase. Again, the conservation of information requires sacrificing the second law of thermodynamics at the level of the microstate. It simply denies that the scattering of all that particulate information is chaotic, or able to increase entropy. This needs to be rethought.

Consider the process of my writing this paper, and thus increasing the amount of information in the world, about a new theory. The creation of information by Laplace's Demon would mean a rearrangement of known information without any unpredictable ideas being able to emerge. Since he could predict the trajectories of all the atoms in my brain as they directed my fingers on the keyboard, he would explain the increased information in this paper as being a process of reshuffling the ideas of other people. But this would not produce a surprising, emergent, unpredictable creative idea.

The key feature of this paper, an unpredictable solution to the problem of emergence, is an emergent result of brain evolution as an organ of problem-solving. Its biological drive to ensure the survival and success of its owner was

facilitated by the emergence of consciousness, so that the nature of the problems and the implementation of their solutions could be understood. Creative new ideas are thus a feature of an evolved computational process resulting in the emergent unpredictability of consciousness in our brains.

The first and second laws can be reconciled by asserting that information in a single system can be increased by a process of rearrangement, without being created. However, this comes with a serious problem. It requires that the future course of the atoms and particles be predetermined by knowledge of the system at present, and denies the existence of spontaneous creativity, or of emergent phenomena: those which are, by definition, unpredictable, even given a complete understanding of their underlying constituents. If the universe is not deterministic, then the paradox of the conservation of information and its increase with increasing entropy has not been solved at all.

The emergence of information in an undetermined universe

A nondeterministic theory suggests that information is related to but not equivalent to entropy. What is conserved is some combination of them, with one increasing as the other decreases. For instance, as information is converted into knowledge, the information decreases in amount, and, locally, so does entropy, but, overall, as knowledge increases, like the shore of Wheeler's island, entropy does also. A deterministic knowledge of the future is no longer required. Given the quantum necessity of chaotic indeterminism in the universe, for instance, as described by Ilya Prigogine,[18] I believe this is key to resolving the paradox.

Yunus Çengal has suggested that "the notion of conservation of information should be limited to the physical universe governed by the laws and forces of physics, and it should be referred to as *physical information*…to clearly distinguish it from other forms of information or knowledge."[19] There are limits to the reach of the theory of the Conservation of Information, such as occurs when it encounters an unpredictable, irreversible transaction such as the leap into consciousness. This leap is a computational process, which decreases our personal entropy, but must balance this with an increase in entropy. It turns out that the act of performing calculations causes this increase in entropy.

Computation, entropy, and the deletion of information in emergence

Computation requires a temporary storage of information, upon which the mind (or calculator) acts in order to perform the calculation. It cannot be stored indefinitely, and must be erased in order to proceed to the next calculation. Rolf Landauer proposed that any logically irreversible computation, i.e. erasing a bit of information, requires work, expels heat, and increases entropy; information is physical.[20] Ruth Kastner and Andreas Schlatter have resolved earlier controversies concerning this by asserting that it applies not to epistemic information loss (our ignorance of the microstate) during resets, but to ontological uncertainty about the quantum nature of the microstate itself.[21]

It is clear there is a great decrease in entropy resulting from the creation of conscious knowledge, which is mirrored in the organization we have imposed on the world around us. Considering the activity of each brain cell involved with the generation of consciousness as an informational transaction, the decrease in our personal entropy must be at least balanced by the simultaneous increase in entropy associated with the possible microstates involved with consciousness. Physically, these computations must involve, at a minimum, interacting electrons and their exchange of photons which occur during exothermic chemical reactions. The aromatic amino acid tryptophan, ubiquitous in microtubules, cell membranes, and other important biological and neural mega-networks, strongly absorbs ultraviolet photons and fluoresces in response.[22] The entropy of the mysterious computations that engender consciousness and the uncertainty surrounding them being significantly high, the likelihood of our ever understanding these transactions becomes correspondingly small. I propose that emergent systems, such as the emergence of classical from quantum physics, the emergence of life from chemistry, and the emergence of consciousness, involve the irretrievable destruction of microscopic information and that the uncertainty about them is the result of entropy.

Kastner has discussed how entropy itself may arise together with classical physics from a loss of quantum-level information when photons, emitted by excited electrons, are absorbed by other electrons.[16] This collapse of the photon's wave function, she wrote: "can be understood as leading to a generalized form of spontaneous symmetry breaking," a natural emergent phenomenon. Entropy thus arises from the spontaneous breaking of the symmetry of the unitary time evolution of the quantum state according to Schrödinger's wave function equation, which otherwise would result in the possible outcomes of particle interactions always being deterministic. The relevant context for the Relativistic Transactional Theory of Quantum Mechanics is that the nonunitary evolution is nondeterministic, even though the probabilities involved sum to a unitary 100%. This occurs with the destruction of any "computation" involved in the symmetry breaking, in the form of the loss of phase coherence in quantum states which, as we've seen, "throws out the information" to create the emergent, but "blurred," classical level. The more the microscopic information about a process is erased, the less we can predict about that process macroscopically, and uncertainty increases. An emergent increase in macroscopic (conscious) information in this setting is simply not predictable. I propose that to avoid the "creation" of information during emergence,

confounding the putative first law, the increase in entropy "requires," or occurs with, the simultaneous destruction of the computational pathways involved in the emergence. This, then, destroys an equivalent amount of information. Only in this way can the first and second laws be reconciled during the phenomenon of emergence. The destruction of the information at the level of microstates required by entropy means that information is related to but not equivalent to entropy, and that only some combination of the two is being conserved. (As a corollary to this, I think we can say that physical determinism is incompatible with the emergent phenomenon of consciousness, and that therefore, since we are conscious, we are not predetermined.)

Quantum effects and negative entropy

David Layzer and Robert O. Doyle have shown that the creation and embodiment of information occurs with a local decrease in entropy, or a pocket of negative entropy.[23] Entropy greater than the information increase must be radiated away as heat or as pure information. In quantum mechanics, information is governed by a conservation law, which prohibits the exchange of heat for negative entropy. Doyle notes that quantum mechanics combines a deterministic wave aspect with an indeterministic particle aspect. An electron can end up randomly in any one of the physically possible states of a measuring apparatus plus the electron, with the probabilities of each state given by the wave function. This "collapse of the wave function," reducing multiple probabilities into one actuality, drops local entropy of the measuring device commensurate with the increased information and there is a discharge of heat to carry away the positive entropy. This irreversibly creates information at a purposive level (the deliberate measurement) and negative entropy newly embodied in the apparatus. Adequate but imperfect determination occurs, said Doyle, through averaging huge numbers of quantum interactions over large objects.

I propose the following solution for the enigma of how quantum information may increase while still being conserved.

A proposed new thermodynamic principle solves the paradox of emergence

This reconciliation between the first and second laws required by the quantum conservation of information can be stated as a new principle within thermodynamics: the increase in entropy in a time-irreversible, unpredictable (emergent) isolated system requires the simultaneous permanent deletion of information concerning the steps, or computations, involved. The local increase in negative entropy is balanced by positive entropy radiated as heat.

It says, in effect, that to increase information without creating it, the process of creating the information must be deleted simultaneously with creating it.

The Emergence of Consciousness: A Tale of Two Demons

Emergence and convergence exchange information for negative entropy

This new law seems to me to be necessary to explain emergent phenomena. At the quantum level, information is binary bits related to the microstates of particles. This is believed to be conserved in a manner analogous to energy. It cannot be created because it represents the arrangement of energy in the universe, and since that cannot be created, there is a limit on its possible arrangements. Its destruction would be equivalent to the destruction of the "missing" information needed to determine what microstate your system is in. This would be equivalent to the destruction of entropy, and is, therefore, at least in nonemergent systems, impossible. But at the classical level, information can be in the form of ideas, and can be copied or deleted perfectly – it can be scrambled without being lost, and Laplace's Demon keeps track of it all. The emergence of the classical level, like the emergence of consciousness, requires the creation of an emergent level of new, unpredictable information. To increase the level of order in the world gained by our becoming conscious, entropy must simultaneously increase through the loss of certainty associated with the unpredictable process. This occurs through the destruction of a portion of the information space that could become known to us, specifically, that portion involved in the process of emergence. When the "Entropy Demon" responsible for this opens the gate between our subconscious and our consciousness, the information that is erased is that describing the pathway of how consciousness emerges. This might most economically happen immediately after all the qualia associated with the perception, say, a face, a voice, and an emotion, have been assembled together by transcortical communications such as axonal connections, brain waves, or electromagnetic waves. However, the Orchestrated Objective Reduction Theory of Roger Penrose and Stuart Hameroff, places these calculations at the level of microtubules within neurons.[24] One level up, nerve cell membranes have unique ion channel proteins and G-protein coupled receptors of different masses and energy levels. Mostyn Jones described how their electrical activity generates nerve impulses and fields in different sensory detector cells.[25] These, together with limbic hormone receptors, in a noncomputational manner, could be responsible for qualia and the differences between them.[26] Oscillating electromagnetic fields can cause oscillations in brain circuits, which, in turn, help guide cognition. In "The Computational Brain," Clem *et al*. give a brief overview of how research is expected to elucidate the circuits responsible for emotional valences, cognitive decision-making, and memory.[27] So, these are all ways that our subconscious brain cells and their circuits can prepare communications to send past the Entropy Demon. A recent study by Panda *et al*. as part of the Human Brain

Project suggests that this may require two neural circuits.[28] The posterior cortical regions and Default Mode Network hubs are needed to convey information while thalamic, frontal, and temporal-parietal regions, responsible for various cognitive processes, must be correctly integrated to broadcast information, with appropriate glucose consumption, or else consciousness is lost or disturbed. According to my proposal, in all these activities, to the extent that they help generate consciousness, something is going on that must be considered irreversible computations in the context of the Entropy Demon. Furthermore, whatever is going on that allows our subconscious to become conscious must be accompanied by a complementary irreversible, unpredictable process that converts our thoughts back again into subconscious instructions to move muscles, for neurons to follow. Call it a process of "convergence." During convergence as thus defined, information is deleted and the entropy of the subconscious is temporarily reduced during the performance of the corresponding activity.

Entropy debt: Implications for consciousness artificial intelligence and the reality of our existence

There is a startling implication for general artificial intelligence. Since we can never learn for ourselves the computations that lead to consciousness, we'll never be able to program them into a computer. Furthermore, a computer will never need to be conscious to perform its computations. The computer selects from its database to create an emergent answer, but unlike the emergence of consciousness, this is a noncausal emergence. Although the steps involved aren't retained, they don't need to be destroyed. The actual causation of the emergence of the answer lies in the algorithm, which originated with a conscious person. The reduction in entropy necessary to become conscious does not come for free, and conscious organisms must continually repay their entropy debt. A computer will not be able to do this unless being conscious enables it to perform computations that it couldn't otherwise perform, or need to perform. Even then, it would still need to be able to print them out or otherwise act on them somehow, reintroducing Descartes' mind–"body" problem. I believe that the process of becoming conscious must be evolutionary, perhaps associated with, if not fully originating from, the massive increase in complexity brought about when asexually reproducing organisms began to reproduce sexually. With this development arose a need for a primitive understanding of why and how to perform reproduction successfully, without which consciousness would have remained superfluous. It follows that ethicists need not worry about fair treatment of conscious computers until two computers should fall in love, and are prepared to die in order to defend their baby. At the moment, the development of "kinematic self-replication in reconfigurable organisms," or "xenobots," may open a pathway leading to self-motivated, programmable robots, but kinematic self-replication doesn't involve genetic reproduction, and the replicants are therefore not "babies."[29] What type of "intelligence," or consciousness they might be capable of remains to be seen. They show no evidence of emotions whatsoever. Furthermore, if consciousness can't be programmed into a computer, we cannot be simulations in some future computer algorithm, contrary to ideas proposed by Bostrom[30] and Chalmers.[31] This ensures that our reality is really "real," and should be especially reassuring to those who lie awake at night, fearful that they may exist as a Boltzmann's brain that could disintegrate before morning. This is impossible because there is no way to permit the requisite reduction in thermodynamic entropy, especially in a condition of thermodynamic equilibrium, and no way to repay the consequent entropy debt, necessary for such a structure to become conscious.

Can this New Thermodynamic Principle be Falsified?

In principle, the Entropic Theory of the Emergence of Consciousness should be falsifiable, in keeping with Popperian conjectures and refutations, but probably not with current technology. One would have to be able to calculate the amount of heat emitted by the known activities of all the components of a network of neurons that are active during consciousness, both during consciousness and during states of unconsciousness. Then, one would need to be able to measure the actual heat emitted by those same neurons, say, during wakefulness and during deep sleep. My theory predicts that there would be a close match between the two results during deep sleep, but that during conscious activity, the measured amount of heat production would exceed the amount predicted. Furthermore, the possibility that the entropy debt may be repaid through the violation of a conserved quantity, not heat, cannot be excluded, as suggested by Vaccaro and Barnett.[32] Popper would have probably considered a proposal such as mine to be a "metaphysical research programme," which can be evaluated by its logical consistency, explanatory power, problem-solving capacity, and successfulness empirically.[33] In this regard, it is worth remembering that the only theory to compete with emergentism in consciousness is the nonemergent "theory" of panpsychism. Panpsychism regards consciousness as a trait which has been possessed by all physical particles since the beginning of the universe, with no explanation as to how or why. It has the same explanatory power as the phrase "God wills it." There is no conceivable test to falsify panpsychism at all! My proposal posits consciousness, and emergent phenomena in general, to be the result of an accepted scientific principle, entropy, that has existed since the beginning of the universe, and yet can account for the emergence of discrete, causally conscious living entities on an evolutionary basis at appropriate time points distant from the beginning of the universe. Unlike panpsychism, entropy requires ongoing

increases in complexity, and it is paid for. Also, it explains why consciousness must emerge, bind into functional units and evolve. It provides the best complement, in my opinion, to the various nonpanpsychist theories of mind, such as Global Neuronal Workspace Theory, Higher Order Theory, Conscious Electromagnetic Information Field Theory, and Orchestrated Objective Reduction, as they try to explain the cerebral cellular goings on, or neural correlates of consciousness.

Conclusion

The emergence and convergence of consciousness are hidden deep within the computational workings of the brain by the inescapable tyranny of thermodynamic entropy and its irreversible tendency toward increasing diversity and disorder. As Colin McGinn noted, the problem is "cognitively closed" to us, but not because it's too difficult for our limited minds.[34] Instead, it is impossible to understand, in principle. However, we can say that the situation is inconsistent with simple monism, but is an emergent dualism, specifically, a causally interactive dualism that is, at a hidden level, monist. There's no need for the explanatory gap to be bridged by panpsychism. We must return to the question: "What possible alternative way of experiencing the world could there be?" as being the best answer to the body–mind question. I doubt it will ever be possible to characterize consciousness more descriptively than that. Indeed, I must conclude that the body–mind problem will never be solved until entropy can be defied, sometime after all the world's broken eggs have reassembled, and all the world's toothpaste has squeezed back into the tubes.

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Original Article

Anticonvulsant Effects and Histopathological Changes in the Hippocampus of Pentylenetetrazole (PTZ)-induced Epileptic Mice Model following Mentat Treatment

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Abstract

Background: Epilepsy is a neurological illness that disturbs the central nervous system and is characterized by regular convulsions. Over 70 million people worldwide are thought to have epilepsy, with the prevalence rate estimated to be around 1%. **Aims:** The objective of this study was to assess antiepileptic activities and histological changes after Mentat administration in the hippocampus of pentylenetetrazole (PTZ)-induced seizure mice. **Materials and Methods:** Twenty Swiss albino mice (18–28 g) were divided into four groups (n = 5) and were given the following intraperitoneally, 2 ml/kg distilled water and 50 mg/kg PTZ to Groups 1 and 2 animals, respectively. Groups 3 and 4 animals were given 200 mg/kg and 400 mg/kg of Mentat, respectively, 1 h before the administration of PTZ and were observed for 300 s. After the experiment, all surviving animals in the various groups were humanely sacrificed and the brains were harvested and preserved in 10% buffered formalin. The brain tissues were processed using routine histological procedures and stained with hematoxylin and eosin. **Results:** Results of this revealed that Mentat was able to delay the onset time of seizure and offered quantal protection to the animals. Mentat also showed a dose-dependent ameliorative effect against histological changes following PTZ administration in mice. **Conclusion:** Mentat attenuates PTZ-induced seizure in mice.

Keywords: *Herbal supplement, histopathology, Mentat, neurological disorder, seizure*

Introduction

Epilepsy is a neurological condition characterized by persistent seizures. The aberrant electrical activity in the brain that causes seizures can cause a variety of symptoms, including loss of consciousness, convulsions, and sensory problems. Estimates of the prevalence of epilepsy range from 5 to 10 cases per 1000 people worldwide.[1] It is estimated that 50 million people worldwide suffer from epilepsy, making it one of the most prevalent neurological conditions worldwide.[2] Studies on the prevalence of epilepsy in Nigeria have produced numbers between 3.1 and 37/1000, resulting in one of the greatest differences in the prevalence of epilepsy globally.[3]

The temporal lobe is one of the areas of the brain that is frequently impacted by epilepsy. This is due to the temporal lobe's role in memory and sensory input processing, as well as the fact that it frequently serves as the origin of seizures in persons with epilepsy.[4] A key structure of the temporal lobe, the hippocampus, is frequently linked to the pathophysiology of temporal lobe epilepsy (TLE).[5] The hippocampus is essential for the creation and consolidation of memories as well as spatial navigation.[6] The hippocampus frequently experiences pathological alterations in TLE, such as cell loss and gliosis, which can lead to hippocampal sclerosis (HS).[7] Up to 80% of TLE patients have HS, making it a frequent neuropathological finding in those with the condition.[8] The hippocampus has been identified in human research as a crucial focus for the beginning and progression of seizures in TLE.[7]

Pentylenetetrazole (PTZ)-induced convulsions in rodents are a widely used

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experimental paradigm for researching epilepsy.[9] Because PTZ-induced seizures can resemble some features of human epileptic seizures, including the activation of neural networks and the production of epileptiform activity, they are frequently utilized in epilepsy research.[10] PTZ is commonly administered intraperitoneally or subcutaneously in animal models, with the dosage and route of administration depending on the species and strain of the animal used.[11] PTZ-induced seizures are used by researchers to investigate the onset, progression, and termination of seizures as well as the impact of possible antiepileptic medicines.[11]

Mentat is an herbal remedy made from a variety of plant extracts that are frequently used in conventional Ayurvedic medicine to treat neurological conditions, including epilepsy. According to reports, the medication contains antiepileptic and neuroprotective properties that have been attributed to its phytochemical ingredients.[12,13] Mentat has been shown in numerous studies to enhance cognitive performance and lessen the intensity and frequency of seizures brought on by PTZ.[14,15] Thus, this study aims at assessing the antiepileptic activities and histological changes in PTZ-induced epileptic mice.

Materials and Methods

Ethical committee approval

The Faculty of Basic Medical Sciences Committee on Animal Use and Care, University of Calabar, approved the use of experimental animals for this research project by the institution's established policies and procedures.

Breeding of animals

In the Animal House of the Department of Human Anatomy, Faculty of Basic Medical Sciences, University of Calabar, Calabar, Nigeria, 20 adult Swiss albino mice of either sex, weighing between 18 and 28 g, were raised. The mice were housed in well-ventilated plastic cages with iron nettings. They were fed with typical animal feed and given access to free water while being housed in a sanitary environment and at regular room temperature.

Drugs and chemicals

Mentat and PTZ were purchased from the Pharmacology Department of the University of Calabar in Calabar and were of analytical quality. For the experiment, ketamine (50 mg/mL ketamine hydrochloride injection USP) was utilized as the anesthetic. It was procured from Swiss Parenterals Pvt. Ltd., Gujarat, India.

Drug preparation

Nine hundred and fifty-one milligrams of Mentat was dissolved in 10 mL of injection water. This served as the stock solution from which working solutions were taken. Twenty grams of PTZ was also dissolved in 10 mL of injection water and was given to the animals at a dose of 50 mg/kg body weight by taking quantities from the stock that were equal to the dose for each mouse.

Experimental design and treatment of animals

Twenty animals were randomly assigned into four groups (n = 5): Groups 1, 2, 3, and 4. The mice in group 1 served as the general control group (n = 5) and were given 2 mL/kg of distilled water. The mice in group 2 served as the epileptic control group (n = 5). Animals in this group, each received a dose of 50 mg/kg body weight of PTZ dissolved in injection water. The mice in the experimental groups (3 and 4) were given Mentat at varying doses. Group 3 received 200 mg/kg body weight of Mentat, and Group 4 animals, each received 400 mg/kg body weight of Mentat. Both Mentat and PTZ were given to the animals intraperitoneally. Mentat was given to the animals 1 h before the administration of PTZ and the animals were observed for 300 s (5 min).

Animal sacrifice and histology

At the end of the experiment, the mice that survived were anesthetized with chloroform and humanely sacrificed. The brains of the animals were removed and quickly fixed in fixative (10% buffered formalin) for 48 h to prevent putrefaction and autolysis and stained with hematoxylin and eosin.

Data analysis

All results were calculated using a one-way analysis of variance to test statistical differences between the test groups and the epileptic control group. Data were expressed as mean ± standard error of the mean. The final results arrived at were considered significant at $P \leq 0.05$.

Results

Antiepileptic activity

The results of the antiepileptic effects of Mentat and PTZ are presented in Table 1.

Histological observations

Histological studies were conducted on the section of the hippocampus CA1 in Group 1, which was administered with 2 mL/kg of distilled water. The results of the study showed that the nerve fibers appeared normal, and there were scattered small neurons observed in the molecular cell layer. In the pyramidal cell layer, large pyramidal-shaped neurons with a coarse chromatin pattern and prominent nuclei were present. Additionally, in the polymorphic cell layer, there were scattered neuronal cell bodies observed, some of which had fusiform shapes, while others had triangular or ovoid cell bodies, but their numbers were relatively low [Figure 1].

Section of the hippocampus CA1 of the group that received 50 mg/kg body weight of PTZ revealed intact molecular, pyramidal, and polymorphic cell layers of the hippocampus with sparsely populated pyramidal shape neurons in the

Table 1: Antiepileptic activities of Mentat on pentylenetetrazole-induced mice

Groups (*n*=5)	Treatments	Dose (mg/kg)	Mean onset of convulsion (s)	Quantal protection	Protection (%)	Mortality (%)
1	Distilled water	2	0.00±0.00	5/5	100	0
2	PTZ	50	120±24.49*	0/5	0	100
3	Mentat I + PTZ	200+50	180±37.95*	4/5	80	20
4	Mentat II + PTZ	400+50	120.00±26.83*	3/5	60	40

*P<0.05 when the PTZ-induced group was compared to the control group. n=5; mean±SEM, one-way ANOVA, Tukey *post hoc* test.
SEM: Standard error of the mean, PTZ: Pentylenetetrazole, ANOVA: Analysis of variance

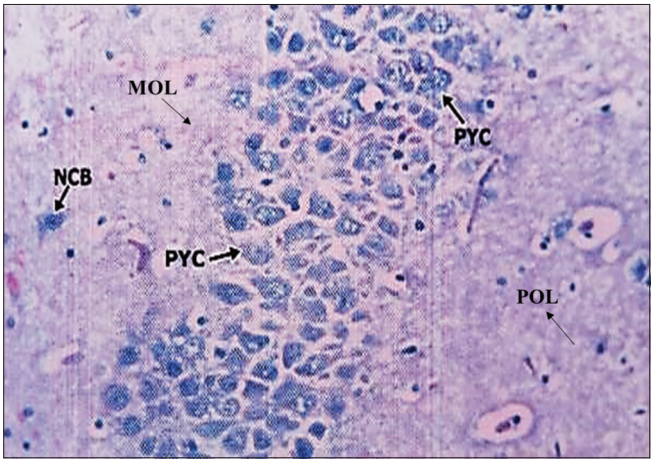

Figure 1: Photomicrograph of the hippocampus (CA1) of group 1 (normal control) showing the normal histological architecture of the CA1 and neuronal cells. Molecular layer (MOL); Pyramidal layer (PYL); Pyramidal cell (PYC); Polymorphic layer (POL); Neuronal cell body (NCB). H & E (Mag. X 400)

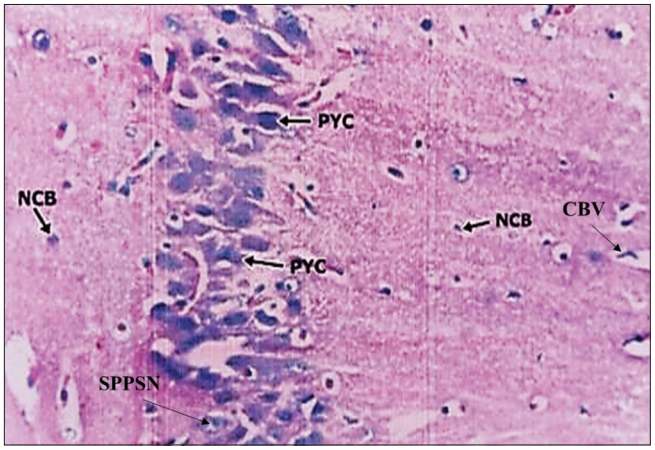

Figure 2: Photomicrograph of the hippocampus (CA1) of group 2 (epileptic control) administered with 50 mg/kg PTZ showing intact molecular, pyramidal, and polymorphic cell layers of the hippocampus with sparsely populated pyramidal shape neurons (SPPSN) in the pyramidal cell layer and congested blood vessels (CBV) in the polymorphic cell layer. Pyramidal cell (PYC); Neuronal cell body (NCB). H & E (Mag. X 400)

pyramidal cell layer and congested blood vessels in the polymorphic cell layer [Figure 2].

The hippocampal CA1 section of Group 3 treated with 200 mg/kg body weight of Mentat and 50 mg/kg body weight of PTZ revealed the three cortical layers of the hippocampus with densely packed pyramidal cells with poor nuclei outline and some cells displaying chromatolysis in the pyramidal cell layer and congested blood vessels in the polymorphic cell layer [Figure 3].

Section of the hippocampus CA1 of group 4 treated with 400 mg/kg body weight of Mentat and 50 mg/kg body weight of PTZ revealed the three cortical layers of the hippocampus with densely packed medium to large pyramidal-shaped neurons with deeply stained nuclei having a clumped chromatin pattern and inconspicuous nucleoli in the pyramidal cell layer [Figure 4].

Discussion

Epilepsy continues to be a serious public health concern, impacting people of all ages, genders, and races, despite advancements in medical research and treatment choices. It can have a significant effect on a person's life, including social stigma, diminished cognitive and physical functioning, and an elevated risk of harm or death.[16]

It is generally known that the hippocampus is susceptible to seizures. The hippocampus is a crucial brain area for memory formation, spatial navigation, and learning.[17] In addition, it is one of the most typical places for seizure onset in patients with TLE, the most prevalent type of epilepsy in adults.[17]

PTZ has been used experimentally to research seizure events and find drugs that could reduce seizure susceptibility.[18] One of these medications is called Mentat, which is an herbal combination of many Ayurvedic herbs.[19] It is well-known that Mentat improves memory and learning. In addition, it is utilized to treat neurological conditions such as epilepsy and seizures.

In this study, Mentat offered a dose-dependent protection against the convulsion effect. The low dose of Mentat showed more antiepileptic effects than the high dose group. The seizure was delayed more in the low-dose treated group than in the high-dose treatment group. The low-dose treatment group also showed less mortality rate compared to the high-dose group. The fact that seizures took longer to start after Mentat treatment in this research is proof of the drug's effectiveness. This indicates that the medication is successful in lessening the frequency and intensity of seizures, which may result in a longer period of seizure-free time.[20] It is complicated and not entirely known how antiepileptic medications delay the onset of seizures. However, it is thought that these medications work by controlling the activation of ion channels and neurotransmitters in the brain.[20]

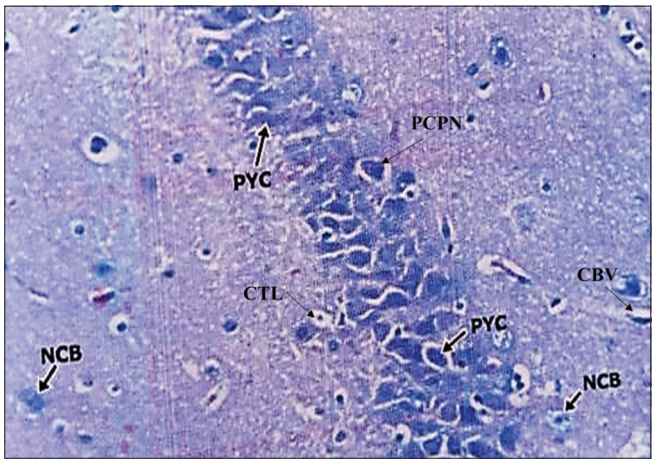

Figure 3: Group 3 (200 mg/kg Mentat + 50 mg/kg PTZ) showing densely packed pyramidal cells with poor nuclei outline (PCPN) and some cells displaying chromatolysis (CTL) in the pyramidal cell layer and congested blood vessels (CBV) in the polymorphic cell layer. Pyramidal cell (PYC); Neuronal cell body (NCB). H & E (Mag. X 400)

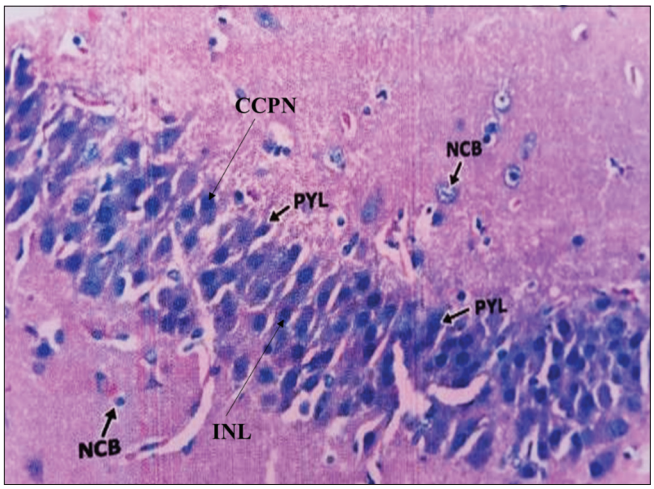

Figure 4: Group 4 (400 mg/kg Mentat + 50 mg/kg PTZ) of the hippocampus CA1 showing neurons with deeply stained nuclei having a clumped chromatin pattern (CCPN) and inconspicuous nucleoli (INL)in the pyramidal cell layer. Pyramidal layer (PYL); Neuronal cell body (NCB). H & E (Mag. X 400)

There is limited scientific research on the mechanism by which Mentat exerts its antiepileptic effects. However, some research points to its active ingredients as having the potential to control the brain's neurotransmitter levels, thereby decreasing the likelihood of seizure initiation. According to a study that appeared in the *Journal of Ethnopharmacology*, the main component of Mentat, *Bacopa monnieri*, can raise the brain's levels of gamma-aminobutyric acid (GABA). It has been suggested that the inhibitory neurotransmitter GABA has a role in the pathophysiology of epilepsy and helps regulate neuronal activity. *B. monnieri* may lessen neuronal excitability and delay the onset of seizures by raising GABA levels.[21] Another study examined the impact of *Convolvulus pluricaulis*, another component of Mentat, on seizure activity in animal models of epilepsy. According to the research, *Convolvulus pluricaulis* extract has anticonvulsant properties and could delay the beginning of seizures indicating that the extract may work by modifying the amounts of neurotransmitters in the brain, such as GABA and glutamate.[13] Overall, Mentat's antiepileptic actions are probably a result of the combination of its active components, which may work in concert to modify neurotransmitter levels and lessen neuronal excitability.

Analogous to this study is the study by Kulkarni and George,[22] on the effect of Ashwagandha or BR - 16 (Mentat) on reserpine (RES)-induced catalepsy. They noticed a higher catalepsy score (40.9 3.0) in the low dose of Mentat (50 mg/kg body weight) compared to the high dose (28.48 3.9 mg/kg body weight) of the same medication. Furthermore, Choudhary *et al*.[23] found that the antiepileptic potential of Mentat in Wistar rats was greater at lower doses than at higher levels. Subsequent investigations have revealed that higher doses of Mentat exhibit significantly greater antiepileptic activity compared to lower doses.[24-26]

Histological study revealed normal histology and neuronal cells in the hippocampus of the control group with distinct layers of molecular, pyramidal, and polymorphic layers, while group 2 administered with only PTZ showed histopathological conditions such as congested blood vessels and sparsely populated neurons. Groups 3 and 4 were treated with Mentat and showed a dose-dependent improvement in the cytoarchitecture of the hippocampus. PTZ can, according to studies, lead to neuronal apoptosis and necrosis in the hippocampus, especially in the dentate gyrus (DG) area.[27,28] There are several causes for this cell death, such as oxidative stress, excitotoxicity, and inflammation.[29,30] Altering synaptic structure and function is another histological effect of PTZ on the hippocampus. PTZ has been demonstrated to have an impact on dendritic spine density and architecture in the hippocampus, particularly in the CA1 and CA3 areas.[31,32] These alterations could play a role in the emergence and maintenance of epileptic activity in the hippocampal region. In addition, PTZ can affect the hippocampus' neurogenesis. PTZ can lessen the amount of newly formed neurons in the DG region, according to studies, which may be a factor in the cognitive impairments connected to epilepsy.[33,34]

Mentat may help treat a variety of neurological conditions, including epilepsy, as it has been demonstrated to have a neuroprotective impact on the brain. Numerous researchers have looked into how Mentat affects the hippocampus, a part of the brain that is important for memory and learning and frequently impaired in epilepsy. In a study conducted by Mohan *et al*.,[35] examining the effect of Mentat on seizure-induced hippocampal mutilation in rats found that treatment with Mentat remarkably reduced the amount of hippocampal damage caused by seizures. Another study conducted by Al-Otaibi *et al*.[36] investigating the effect of Mentat on oxidative stress and inflammation in the hippocampus of rats with seizures revealed that treatment

with Mentat remarkably reduced oxidative stress and inflammation in the hippocampus, indicating that Mentat may have a protective effect on this brain region. Goyal *et al*.,[37] in their study on the effect of Mentat on cognitive function and hippocampal neurogenesis in rats with seizures, revealed that treatment with Mentat significantly boosted hippocampus neurogenesis and improved cognitive performance in the rats, indicating that Mentat may benefit brain plasticity.

Conclusion

The results of this study imply that Mentat has a protective effect against seizure-induced mice and may be employed in the control and treatment of seizures and other neurological diseases.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The Faculty of Basic Medical Sciences Committee on Animal Use and Care, University of Calabar, approved the use of experimental animals for this research project by the institution's established policies and procedures.

Financial support and sponsorship

No funding was received.

Conflict of interest

There is no conflict of interest to declare.

Author Contributions subject and rate

- Ekpo Ubong Udeme (60%): Design the research, data collection, and analyses
- Igiri Anozeng Oyono (40%): Supervision and research organization.

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Case Report

Klüver–Bucy Syndrome Secondary to A Dominant Middle Cerebral Artery Ischemic Stroke: A Case Report and Review of The Literature

Abstract

Klüver–Bucy syndrome (KBS) is a neuropsychiatric disorder secondary to temporal lobe damage. This can be associated with various causes. This syndrome is rarely caused by stroke. We describe the case of a KBS, admitted to the neurology department of the military hospital of Agadir, in September 2022 secondary to ischemic stroke in middle cerebral artery territory. The patient presented most of the clinical features of KBS. These neurobehavioral manifestations improved after the start of treatment.

Keywords: *Case report, ischemic stroke, Klüver–Bucy syndrome*

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Introduction

Klüver–Bucy syndrome (KBS) is a neuropsychiatric disorder that can be associated with various neurological pathologies. A young 22-year-old patient suffering from herpes simplex meningoencephalitis with bilateral destruction of both temporal lobes was the first described case of KSB syndrome.[1] The main symptoms of KBS described[2] are mouthing tendency, visual agnosia, behavioral changes such as lack of emotional reaction, apathy, hypersexuality, and hyperamorphosis, but also changes in eating habits. Causes of Koch syndrome include herpes simplex encephalitis, Alzheimer's disease, head trauma, toxoplasmosis, and tuberculous meningitis.[3,4] We present the unusual case of a patient with KBS syndrome due to a stroke in the left middle cerebral artery territory.

Case Report

A 58-year-old man, suffering from diabetes mellitus, presented to the emergency room of the Agadir Military Hospital on September 12, 2022, with right-sided weakness, paralysis right facial, and speech disorders. His symptoms had started 3 days earlier. Brain magnetic resonance imaging (MRI) showed ischemic stroke of the left middle cerebral artery [Figure 1]. Additional examinations looking for the etiology of stroke were normal. Markers of vasculitis and autoimmune diseases as well as serologies were unremarkable. Transthoracic and transesophageal echocardiography, carotid, and spinal Doppler ultrasound revealed no abnormalities.

In the 1st weeks after his stroke, the patient had difficulty recognizing family members, got lost when away from home, and had difficulty remembering the names of objects and people. Over the next few months, the patient gradually developed hypersexuality and hyperorality that came to the fore. Other symptoms subsequently appeared including hypermetamorphosis, hyperphagia, and other behavioral changes. The patient was hospitalized in the psychiatric department. Therefore, he started taking 10 mg escitalopram once daily in combination with 1 g levetiracetam twice daily. After a few days, his condition improved significantly and he was able to return home.

Discussion

This is the first reported case of KBS in Morocco following a unilateral ischemic stroke of the dominant temporal lobe.[5] Changes in sexual behavior and hyperorality were the major clinical manifestations in the case of our patient and subsequently, the symptoms appeared allowing us to retain the diagnosis.[6]

The eating and sexual disorders that our patient initially presented may mimic a behavioral variant of frontotemporal

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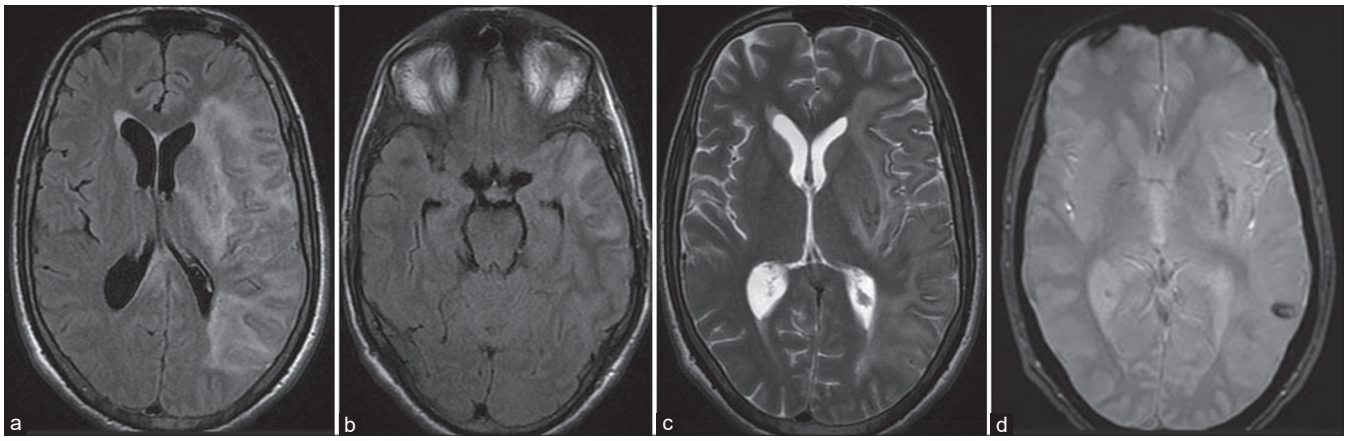

Figure 1: (a and b) Axial section of the brain (fluid-attenuated inversion recovery) shows extensive and total ischemic stroke in the territory of the left middle cerebral artery affecting the left temporal region. (c) Lesion described on T2-weighted magnetic resonance imaging. (d) Gradient echo shows hemorrhagic transformation

lobar degeneration, likely due to connections between the amygdala and orbitofrontal gyri. However, the limbic network can be destroyed by peritamygdalar lesions which lead to a disconnection syndrome. The amygdala would play a fundamental role in the pathophysiology of this syndrome.

Brain MRI should be considered first intention in patients presenting with cerebral insults. It should be noted that the scan can be perfectly normal without modifications in the temporal lobes with the presence of symptoms of KBS syndrome.

The effect of treatment varies from patient to patient. Some cases improved significantly when treated with antiepileptic medications, such as carbamazepine or serotonin reuptake inhibitors.[4,7] Other patients will have neuropsychological sequelae and others may develop Korsakoff syndrome.[8] The prognosis of this syndrome is variable.

Conclusion

The pathophysiology of KBS syndrome is not yet clearly elucidated. Additional studies are necessary to better understand it and propose potentially effective treatments. Treatment with antiepileptics or antipsychotics should be initiated upon confirmation of the diagnosis while evaluating it regularly.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

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Conflict of interest

There is no conflict of interest to declare.

Author Contributions subject and rate

- Mohamed Amine Mnaili (60%): contributed to the content, references, and written manuscript of the case report.
- Ahmed Bourazza (40%): contributed to expert revisions, details, and references of the manuscript.

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Socioemotional Reciprocity Difficulties in Children Living with Autism Spectrum Disorder

Dear Editor,

Children living with autism spectrum disorder (ClwASD) face challenges in social interactions and communication across different settings (classroom, playground, and home) due to socioemotional challenges. The *Diagnostic and Statistical Manual of Mental Disorders* – 5th Edition mentions deficits in conversations involving expressive and receptive language for these children due to abnormal social approaches such as sharing of reduced interests, affect, pace of communication, social skill deficits, and emotions.[1]

Lack of facial expressions and poor eye contact make it nonverbally hard for ClwASD to participate in communication in social situations. The ability to integrate body language and gestures with communication is essentially challenging for most of these children. Misinterpretation of social cues and language hinders comprehension of jokes, humors, and metaphors; ClwASD face challenges in responding to peers and adults by understanding their emotions and feelings. Many etiologies are identified for causing ASD, and the spectrum also encompasses a wide range of intellectual functioning abilities beyond the neurophysiological changes in the brain.

Play Perplexes through Socioemotional Complexities

Limited play is observed in ASD due to neurobiological changes in the brain that affect their imagination and creativity. Engaging in pretend or parallel play is puzzling for ClwASD as they have challenges in responding to social cues. Peers and adults interact to engage and socially provide cues for ClwASD in play; overwhelms the ClwASD to experience social anxiety due to discomfort in the settings, and socially, they tend to withdraw themselves.

Play can be used as a form of communication to treat challenging and injurious behavior in these children. Forms of self-expression can be taught using play, and response interruption/redirection is helpful in prompting among these children to reduce their maladaptive behavior during play activities. Fostering play skills can enhance social skills, teamwork, problem-solving, and choice-making in ClwASD – mentions the *World Journal of Clinical Pediatrics*.[2] Play is a comprehensive approach to teaching skills across various domains for ClwASD and play increases the developmental trajectory of milestones attained by neurotypical peers of the same age.

Sensory Challenges in Socioemotional Behavior

Regulating sensory sensitivities in environments around with adaptive responses is difficult for ClwASD. Hyper- and hyposensory behavior is related to the settings around leading to difficulties in emotional regulation and rigidity in ClwASD. Processing sensory stimuli is challenging as neural networks in the brain have difficulties in integrating signals, leading to sensory dysfunctions in most ClwASD. Specific visuals, sounds, textures, or smells elicit atypical behavioral responses and variations in 96% of ClwASD – mentions Pediatric Research.[3] Proximal development of senses in ASD phenotype is limited and makes it hard to understand facial gestures (visual), language deficits (auditory), or avoid hugs and touch (tactile). Resisting changes in schedules or routines is often associated with sensory behavioral differences in individuals with ClwASD. Additionally, new environments or interacting with unfamiliar people can exacerbate difficulties in multi-sensory integration for them.

Sensory behaviors can be regulated by understanding the under-responsiveness and over-responsiveness of sensory processing. Supportive sensory modification of the ambience (home, school, and playground) by eliminating overstimulating/understimulating objects enables ClwASD to participate successfully in their daily activities. Preparation of persons with ASD for changes in routine/schedule transitions can easily channelize their differences in sensory behavior. Occupational therapy is very efficient in facilitating sensory dysfunction; teaching the essential skills needed for coping with sensory processing difficulties is assessed and treated by an occupational therapist.

Rigidity in Patterns and Repetitive Behaviors

Emotional regulation is challenging due to the fixation of interests and routines in ClwASD. Socioemotional behaviors exhibit as deficits in social interactions when neurodivergent kids show more attachment to inanimate objects/items than people present around them. Preference for specific routes/routines/schedules leads to emotional distress when unexpected changes happen in daily life. Engaging in repetitive behaviors such as hand-flapping, body-rocking, and facial expressions for ClwASD when around peers/adults is to relieve their social anxiety and the sensory sensitivities they face.

To regulate social skills in ClwASD during various situations, many evidence-based treatment methods are

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suggested to the stakeholders. Scripting, behavior therapy, social stories, structured play groups, technology-aided instruction, functional communication training, peer-mediated interventions, and incidental teaching are some of the effective treatments for training social skills with objective outcomes.

Severity Patterns for Socioemotional Deficits

Difficulties in socioemotional reciprocity are diverse and range from mild to severe among ClwASD, which impacts their ability to navigate social situations around them in their daily lives. Interventions planned for ClwASD should be customized and tailored to support individualistic needs. Skill deficits are heterogeneous in ClwASD and the levels of support can vary widely. Significant development milestones and navigating social situations can be effective as interventions are provided at an early age after diagnosis.

Support should be accommodated with the levels of behaviors that interfere with the functioning of the individuals in their day-to-day lives. The use of empirical outcome-based treatments can reduce the levels of support and increase independence in persons with autism. The spectrum comprises unique phenotypes that require a display of empathy and understanding from society. Acceptance and awareness of autism can help individuals around to support differences in the abilities of ClwASD.

Patient informed consent

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- Jemima Wilson (50%): Contributed to writing a manuscript draft and literature search.
- Srikanth Pallerla (50%): Contributed to writing a manuscript draft and review of the manuscript.

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