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**The Journal of Neurobehavioral Sciences (JNBS) is a peer-reviewed open-access neuroscience journal without any publication fees.
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**JNBS accepts articles written in English language.

ABOUT THIS JOURNAL

Publication Policy

The Journal of Neurobehavioral Sciences (J Neuro Behav Sci) is a peer-reviewed open-access neuroscience journal without any publication fees. All editorial costs are sponsored by the Üsküdar University Publications and the Foundation of Human Values and Mental Health. Each issue of the Journal of Neurobehavioral Sciences is specially commissioned, and provides an overview of important areas of neuroscience from the molecular to the behavioral levels, delivering original articles, editorials, reviews and communications from leading researchers in that field. JNBS is published electronically and in the printed form 3 times a year by Uskudar University. The official language of JNBS is English. The average time from delivery to first decision is less than 30 days. Accepted articles are published online on average on 40 working days prior to printing, and articles are published in print at 3-6 months after acceptance. Please see our Guide for Authors for information on article submission. If you require any further information or help, please email us (jnbs@uskudar.edu.tr)

Aims & Scope

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.

JNBS emphasis on psychiatric and neurological disorders. However, studies on normal human behavior are also considered. Animal studies and technical notes must have a clear relevance and applicability to human diseases. Case Reports including current neurological therapies or diagnostic methods are generally covered by JNBS.

Besides; The scope of JNBS is not limited to the abovementioned cases, and publications produced from the interdisciplinary studies established in the following fields and with the behavioral sciences are included in the studies that can be published in JNBS.

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• Molecular neuroscience
• Computational Neuroscience
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• In vivo monitoring of electrical and biochemical activities of the brain
• Molecular Biology
• Genetics
• Bioinformatics
• Psychiatric Nursing

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Prior to submission, please carefully read and follow the submission guidelines entailed below. Manuscripts that do not conform to the submission guidelines may be returned without review.

Submission

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

Prof. Dr. Turker Tekin Erguzel, Ph.D Co-Editor, Journal of Neurobehavioral Sciences Department of Psychology

Uskudar University Altunizade Mh., Haluk Türksoy Sk No: 14, İstanbul-Turkey

General correspondence may be directed to the Editor's Office.

In addition to postal addresses and telephone numbers, please supply electronic mail addresses and fax numbers, if available, for potential use by the editorial and production offices.

Masked Reviews

Masked reviews are optional and must be specifically requested in the cover letter accompanying the submission. For masked reviews, the manuscript must include a separate title page with the authors' names and affiliations, and these ought not to appear anywhere else in the manuscript. Footnotes that identify the authors must be typed on a separate page. Make every effort to see that the manuscript itself contains no clues to authors' identities. If your manuscript was mask reviewed, please ensure that the final version for production includes a byline and full author note for typesetting.

Similarity Rate: The similarity of the submitted articles with the Ithenticate program is determined. The similarity rate should be below 20%.

Types of Articles: Brief Reports, commentaries, case reports and minireviews must not exceed 4000 words in overall length. This limit includes all aspects of the manuscript (title page, abstract, text, references, tables, author notes and footnotes, appendices, figure captions) except figures.

Brief Reports also may include a maximum of two figures.

For Brief Reports, the length limits are exact and must be strictly followed. Regular Articles typically should not exceed 6000 words in overall length (excluding figures).

Reviews are published within regular issues of the JNBS and typically should not exceed.

10000 words (excluding figures)

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All cover letters must contain the following: A statement that the material is original —if findings from the dataset have been

previously published or are in other submitted articles, please include the following information:

*Is the present study a new analysis of previously analyzed data? If yes, please describe differences in analytic approach.

*Are some of the data used in the present study being analyzed for the first time? If yes, please identify data (constructs) that were not included in previously published or submitted manuscripts.

*Are there published or submitted papers from this data set that address related questions? If yes, please provide the citations, and describe the degree of overlap and the unique contributions of your submitted manuscript.

*The full postal and email address of the corresponding author; *The complete telephone and fax numbers of the same;

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*A statement that the authors complied with APA ethical standards in the treatment of their participants and that the work was approved by the relevant Institutional

Review Board(s).

*Whether or not the manuscript has been or is posted on a web site;

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*Authors should also specify the overall word length of the manuscript (including all aspects of the manuscript, except figures) and indicate the number of tables, figures, and supplemental materials that are included.

Manuscript Preparation

Prepare manuscripts according to the Publication Manual of the American Psychological Association (6th edition).

Review APA's Checklist for Manuscript Submission before submitting your article. Double-space all copy. Other formatting instructions, as well as instructions on preparing tables, figures, references, metrics, and abstracts, appear in the Manual.

Below are additional instructions regarding the preparation of display equations and tables.

Display Equations

We strongly encourage you to use MathType (third-party software) or Equation

Editor 3.0 (built into pre-2007 versions of word) to construct your equations, rather than the equation support that is built into Word 2007 and Word 2010. Equations composed with the built-in Word 2007/Word 2010 equation support are converted to low-resolution graphics when they enter the production process and must be rekeyed by the typesetter, which may introduce errors.

To construct your equations with MathType or Equation Editor 3.0:

Go to the Text section of the Insert tab and select Object.

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If you have an equation that has already been produced using Microsoft Word 2007 or 2010 and you have access to the full version of MathType 6.5 or later, you can convert this equation to MathType by clicking on MathType Insert Equation. Copy the equation from Microsoft Word and paste it into the MathType box. Verify that your equation is correct, click File, and then click Update. Your equation has now been inserted into your Word file as a MathType Equation.

Use Equation Editor 3.0 or MathType only for equations or for formulas that cannot be produced as word text using the Times or Symbol font.

Tables

Use Word's Insert Table function when you create tables. Using spaces or tabs in your table will create problems when the table is typeset and may result in errors.

Abstract and Keywords

All manuscripts must include an English abstract containing a maximum of 250 words typed on a separate page. (It should contain headings such as Background, Aims and Objectives, Materials and Methods, Results, Conclusion etc.) After the abstract, please supply up to five keywords or brief phrases.

References:

Vancouver is a numbered referencing style used in JNBS.

Citations to someone else's work in the text, indicated by the use of a number. A sequentially numbered reference list at the end of the document providing full details of the corresponding in-text reference.

General rules of in-text citation:

- A number is allocated to a source in the order in which it is cited in the text. If the source is referred to again, the same number is used.
- Use Arabic numerals (1,2,3,4,5,6,7,8,9).
- Either square [ ] or curved brackets ( ) can be used as long as it is consistent.
- 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.
- If the sources with consecutive numbers are to be displayed at the same time, the first and last numbers are separated with "-"

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.

Millares M, editor. Applied drug information: strategies for information management. Vancouver: Applied Therapeutics, Inc.; 1998.

Figures

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The minimum line weight for line art is 0.5 point for optimal printing

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The publication of an article in the peer-reviewed journal JNBS is an essential building block in the development of a coherent and respected network of knowledge. It is a direct reflection of the quality of the work of the authors and the institutions that support them. Peer-reviewed articles support and embody the scientific method. It is therefore important to agree upon standards of expected ethical behaviour for all parties involved in the act of publishing: the author, the journal editor, the peer reviewer, the publisher and the society of society-owned or sponsored journals.

Uskudar University, as publisher of the journal, takes its duties of guardianship over all stages of publishing extremely seriously and we recognise our ethical and other responsibilities.

We are committed to ensuring that advertising, reprint or other commercial revenue has no impact or influence on editorial decisions. In addition, Editorial Board will assist in communications with other journals and/or publishers where this is useful to editors. Finally, we are working closely with other publishers and industry associations to set standards for best practices on ethical matters, errors and retractions - and are prepared to provide specialized legal review and counsel if necessary.

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(These guidelines are based on existing COPE's Best Practice Guidelines for Journal Editors.)

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Authors of reports of original research should present an accurate account of the work performed as well as an objective discussion of its significance. Underlying data should be represented accurately in the paper. A paper should contain sufficient detail and references to permit others to replicate the work. Fraudulent or knowingly inaccurate statements constitute unethical behavior and are unacceptable. Review and professional publication articles should also be accurate and objective, and editorial 'opinion' works should be clearly identified as such.

Authors are required to state in writing that they have complied with the Declaration of Helsinki Research Ethics in the treatment of their sample, human or animal, or to describe the details of treatment.

Data access and retention

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An author should not in general publish manuscripts describing essentially the same research in more than one journal or primary publication. Submitting the same manuscript to more than one journal concurrently constitutes unethical publishing behavior and is unacceptable.

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Authorship should be limited to those who have made a significant contribution to the conception, design, execution, or interpretation of the reported study. All those who have made significant contributions should be listed as co-authors. Where there are others who have participated in certain substantive aspects of the research project, they should be acknowledged or listed as contributors.

The corresponding author should ensure that all appropriate coauthors and no inappropriate coauthors are included on the paper, and that all co-authors have seen and approved the final version of the paper and have agreed to its submission for publication.

Hazards and human or animal subjects

If the work involves chemicals, procedures or equipment that have any unusual hazards inherent in their use, the author must clearly identify these in the manuscript. If the work involves the use of animal or human subjects, the author should ensure that the manuscript contains a statement that all procedures were performed in compliance with relevant laws and institutional guidelines and that the appropriate institutional committee(s) has approved them. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

Disclosure and conflicts of interest

All authors should disclose in their manuscript any financial or other substantive conflict of interest that might be construed to influence the results or interpretation of their manuscript. All sources of financial support for the project should be disclosed.

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Fundamental errors in published works

When an author discovers a significant error or inaccuracy in his/her own published work, it is the author's obligation to promptly notify the journal editor or publisher and cooperate with the editor to retract or correct the paper. If the editor or the publisher learns from a third party that a published work contains a significant error, it is the obligation of the author to promptly retract or correct the paper or provide evidence to the editor of the correctness of the original paper.

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An editor should take reasonably responsive measures when ethical complaints have been presented concerning a submitted manuscript or published paper, in conjunction with the publisher (or society). Such measures will generally include contacting the author of the manuscript or paper and giving due consideration of the respective complaint or claims made, but may also include further communications to the relevant institutions and research bodies, and if the complaint is upheld, the publication of a correction, retraction, expression of concern, or other note, as may be relevant. Every reported act of unethical publishing behavior must be looked into, even if it is discovered years after publication.

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Peer review assists the editor in making editorial decisions and through the editorial communications with the author may also assist the author in improving the paper. Peer review is an essential component of formal scholarly communication, and lies at the heart of the scientific method. JNBS shares the view of many that all scholars who wish to contribute to publications have an obligation to do a fair share of reviewing.

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Any selected referee who feels unqualified to review the research reported in a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

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Any manuscripts received for review must be treated as confidential documents. They must not be shown to or discussed with others except as authorized by the editor.

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Reviews should be conducted objectively. Personal criticism of the author is inappropriate. Referees should express their views clearly with supporting arguments.

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Reviewers should identify relevant published work that has not been cited by the authors. Any statement that an observation, derivation, or argument had been previously reported should be accompanied by the relevant citation. A reviewer should also call to the editor's attention any substantial similarity or overlap between the manuscript under consideration and any other published paper of which they have personal knowledge.

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The Journal of Neurobehavioral Sciences

Volume 10 ¦ Issue 3 ¦ September-December 2023

Contents

The Pervasiveness of Autism Spectrum Disorder and the Calibrated Interventions

Autism spectrum disorder (ASD) is an umbrella term comprising a group of neurological conditions marked by severe difficulties with social interaction and communication. According to the World Health Organization,[1] in 100 children worldwide suffer from ASD, and 1 in 500 Indian children receive an autistic diagnosis. With four men diagnosed for every female, boys are more likely than females to be impacted by autism. Compared to Down syndrome, which affects one in 800 newborns, autism occurs more often. Children may exhibit a spectrum of symptoms, varying in intensity, from recurring patterns of limited interests and unusual behaviors to challenges in transitioning between activities or events, as well as unexpected reactions to sensory cues in their surroundings. While a cure for autism is not currently evident, interventions play a crucial role in assisting children to effectively manage their symptoms. By tailoring treatment plans to individual needs, these interventions contribute to an improved quality of life.

Autism symptoms significantly affect a person's ability to communicate, comprehend relationships, and connect with others, which is why they are typically identified in their first 3 years of life. People with autism are often associated with strange or stereotypical activities and may have a higher or lower sensitivity to sensory stimulation. ASD is a neurological disorder that affects a person's lifetime cognitive development and cannot be healed. People with autism frequently appreciate routines, and when these patterns are disturbed, they may get frustrated or anxious. Individuals with ASD are resistant to change and insist on maintaining rigidity in daily schedules in different settings (school, home, work). According to epidemiological statistics supported by the Centres for Disease Control and Prevention,[2] autism being a multifaceted and diversified disorder, several people may be affected by distinct factors: genetic basis like Fragile X Syndrome or tuberculosis, prenatal difficulties, having a sibling with ASD, abnormalities in the brain and being born to elderly parents with advanced maternal age.

All autistic people experience some of the same challenges since autism is a spectrum disorder, but being autistic will have different effects on each individual. Some autistic people experience learning challenges, mental health problems, or other disorders, necessitating varying degrees of help. Understanding the underlying causes and creating efficient interventions that are provided through early diagnosis and holistic treatment plans to provide required levels of support for persons with ASD. Personalized treatments, therapies, and prescribed medications could potentially be recommended to meet the specific requirements of each individual with ASD. When tackling the complex issues related to autism and its comorbidities, a multidisciplinary approach comprising health-care providers, medical professionals, therapists, and educators can often be helpful.

ASD traits include difficulties with social engagement and communication, such as avoiding eye contact, refusing to participate in interactive play, making no facial motions or expressions, refusing to recognize when people are wounded, and displaying very little interest in talks. During childhood, children with autism may not develop as well as their neurotypical peers in the areas of interpersonal relationships, social skills, cognitive abilities, and processing of sensory input. Dysfunctional behaviors may also begin to emerge as hyper/hypoactivity, attention and sleep deficits, poor facial expressions and insensitivity to pain, self-harming behaviors (e.g. hand-biting, head-bashing), and self-stimulatory conduct (e.g. repetitive, nongoal-directed actions like rocking, hand flapping).

Most people's actions and learning are governed by the brain processing and hierarchical development of their fundamental senses. Sensory integration and development are often erratic in children with ASD. Due to issues with touch, children with autism face delays in their social development. These youngsters resist "touch" on various areas of their bodies, struggle with it, and parents eventually stop allowing it. Delays in early self-regulation and lack of typical reactions to touch are directly and linearly associated, according to research from the Qigong Sensory Training Institute.[3] Because the early self-regulation milestones, which build the framework for the rest of development, are missed by the autistic kid, the 1st-year self-regulation milestones are generally behind schedule in autistic children.

A multidisciplinary team consisting of a pediatrician, psychiatrist or psychologist, occupational therapist, special educators, and speech pathologist may conduct a thorough evaluation and provide an accurate diagnosis of ASD by the time a child is 2–3 years old. Teams supported by the government work in hospitals and with private practitioners to examine and diagnose kids with ASD. Children with diagnoses should receive a variety of psychosocial therapies and educational interventions that are relevant to the growing needs and preferences of the people. After diagnosis, the child's carers (parent, siblings) should be given pertinent information about treatment, therapy

Ethics committee approval: There is no need for ethics committee approval.

services, prompt access to early intervention, behavioral support in a variety of settings (home, shop, and school), and participation in treatment decisions by understanding the child's ASD symptoms. Individuals with autism can benefit from a variety of therapies, including speech, occupational, and behavioral therapy, as they can help them manage their behaviors, enhance their quality of life, and develop abilities to communicate and interact with others.

To properly manage the disease, it is also crucial to include family carers in peer support groups for people with autism and other community services. Regularly doing parent education sessions is a good way to influence your kids' social and communication abilities for the better. These sessions may be conducted one-on-one or in a group setting, and providing them with education manuals would also be beneficial for helping them control the issue behavior effectively. It would be advantageous to employ reinforcement theory while teaching about parent management tactics, social skills training, and child behavior management approaches.

For the various forms of assistance that people with ASD need for their health, rehabilitation, and care, treatment plans for the condition are complicated and necessitate collaboration with several experts. Interventions that are inclusive, accessible, and help people with ASD live better lives by lowering symptoms and behavior that interfere with everyday functioning. To ensure that treatment goals and progress are in line with the particular difficulties faced by people with ASD, communication between stakeholders and carers is essential. The Centre for Disease Control and Prevention[4] divides the various approaches used in the comprehensive treatment plans for ASD into "Complementary/traditional" to promote health, education, employment, and social care. These approaches include behavioral, developmental, educational, sociorelational, psychological, and alternative treatments.

At special or inclusive schools, learning experiences for students with ASD can be changed, and Individualized Education Plans are created to maximize student engagement by giving them opportunities to practice social skills, increase communication motivation, develop their physical skills, and boost their self-confidence. Jameson (Jewel Autism Centre, 2023)[5] explains in her article that by promoting social engagement and reciprocity, responsiveness, flexibility, and overall standard of training at both school and home, children with ASD receive extensive assistance from an interdisciplinary team in schools that consists of the student, special education teachers, social service providers, occupational therapy professionals, physical therapists, applied behavior analysis therapists or behavior clinicians, speech therapists, and the parent. Each individual with autism is different to respond interventions, and there exists no universal approach to treating the condition. Play can be combined with social, instructive, therapeutic, behavioral, and medical strategies to improve functional learning, expressive communication, self-help abilities, joint attention, adaptability, social interaction, and controls of disruptive or maladaptive behaviors.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

There is no need for ethics committee approval.

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Conflict of interest

There is no conflict of interest to declare.

Author contribution area and rate (%)

- 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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Review Article

The Neurological and Psychological Effects of Breastfeeding on Women

Abstract

Breastfeeding is the key element of infant feeding and has played a vital role in promoting infant health throughout history. It provides all the necessary nutrients for infants to grow and develop. The World Health Organization (WHO) recommends initiating breastfeeding right after birth and continuing with exclusive breastfeeding for the first 6 months, followed by complementary feeding up to 24 months of age. The WHO has also set targets to increase exclusive breastfeeding rates by 2025. As scientific research has advanced, the benefits of breastfeeding for infant health have become increasingly apparent, not only for metabolic diseases but also for cognitive health. As a result, researchers have started examining whether breastfeeding has any neurological or psychological effects on lactating mothers. In this review, we examined current research on the neurological and psychological effects of breastfeeding on women.

Keywords: *Breastfeeding, maternal health, neuroscience*

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Introduction

Breastfeeding has become an essential issue for infant nutrition over the years. The importance of breastfeeding for both mother and child has been known since prehistoric times.[1] According to archaeological research, it is shown that mothers in prehistoric times breastfed their children until the 6th month after birth. Breastfeeding was considered sacred in ancient Egypt and Greece. Although it was neglected during the Renaissance, the importance of breastfeeding emerged with the development of medicine.[1]

The World Health Organization (WHO) recommends that breastfeeding should be started 1 h after birth and continued for the first 6 months.[2] Exclusive breastfeeding refers to feeding the infant only breast milk.[3] After the first 6 months, the WHO recommends breastfeeding and complementary feeding until 24 months of age.[2] The United Nations International Children's Emergency Fund released data on breastfeeding worldwide in 2021. While 47% of newborns started breastfeeding early, 67% were fed only with breast milk in the first 2 days after birth.[4] By 2025, the WHO aims to increase the rate of exclusive breastfeeding to at least 50% in the first 6 months.[5]

Breast milk provides nutrients such as protein, vitamins, and minerals that ensure growth and development for babies. In addition, breast milk protects newborns against infections and reduces infant mortality.[6] Studies show that breastfed newborns have a low risk of obesity and diabetes in childhood and adulthood.[6,7] In addition, high intelligence and high cognitive performance may be associated with breastfeeding.[6,8] Breastfeeding is not only beneficial for children. Breastfeeding women have a lower risk of certain metabolic diseases, cardiovascular diseases, breast, and ovarian cancers.[6,9-13]

After all these studies and developments in neuroscience and psychology, scientists questioned the neurologic and psychological effects of breastfeeding on women. Most of the studies are focused on neurologic disease and breastfeeding, depression and anxiety, cognitive performance, hormonal changes, and their effects on women. In this review, we examine current studies about these effects.

Breastfeeding and Cognitive Functions

Some scientists have found that breastfeeding can affect cognitive

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performance in women, while others have found contrary evidence. For example, Fox *et al*.[14] investigated the connection between cognitive functions and breastfeeding in 50-year-old and older women. The research assessed delayed recall, learning, executive functioning, and processing speed. After taking a reproductive history, a depression variable was included in the research. In the results, women who breastfed had better scores in every domain than those who did not breastfeed. Furthermore, in the nondepressed group, women had better scores in all four domains. In the depressed group, only executive functioning and processing speed scores were high. There was no significant difference between the duration of breastfeeding (1–12 months or >12 months). These results indicate that breastfeeding may protect the brain's cognitive health.[14]

In a study conducted with 5487 postmenopausal women in China showed that breastfeeding was helpful for cognitive health. While longer or shorter than 12 months of breastfeeding was linked with a higher risk for cognitive impairment, there was no significant difference.[15] Some studies search for connections between reproductive health history, cognitive impairment, and breastfeeding as one of the variables in the research.[16-19] In a study that was held in Japan, it was found that there was no connection between breastfeeding and cognitive impairment.[16] Another study that was conducted with 1364 Swedish women's health history data supported this result.[17] However, Harville *et al*.[18] and Yoo *et al*.[19] provide evidence for the relationship between less breastfeeding and better cognitive health. According to Yoo *et al*.,[19] breastfeeding for <6 months was associated with a lower risk of dementia. If the duration of breastfeeding had been longer than 6 months, the risk for dementia increased. On the contrary, Harville *et al*.[18] indicate that breastfeeding for more than 12 weeks is beneficial for women.

The reasons for the relationship between breastfeeding and cognitive health are still controversial. One of the possible reasons is estrogen and its effects on the neurological system. Estrogen hormone may have a role in the amyloid-β and Tau protein regulation, which are involved in the pathogenesis of Alzheimer's disease (AD).[20,21] After the studies revealed that estrogen could be protective against AD, scientists searched for the reproductive history and duration of estrogen exposure and their impact on dementia and AD. The above-mentioned articles also discuss the effects of estrogen on cognitive health.[15-19] However, the results are contradictory. Three of the studies revealed that estrogen had no impact on cognitive health, or its impact was unclear.[15,17,18] On the other hand, according to another two studies, short estrogen exposure throughout life was linked with worse cognitive function in women.[16,19] Another study that supports these results was conducted with 8222 Singaporean Chinese women.[22] Shimizu *et al*.[16] indicate that longer estrogen exposure is related to less cognitive impairment. Nulliparity is generally separated from the never-breastfed group in studies.[14,16,18] Yoo *et al*.[19] and Harville *et al*.[18] found that nulliparity and cognitive impairment were correlated. These results point out that the mechanism and effect of estrogen on cognitive health remain unknown.

Other than the estrogen hypothesis, cardiovascular, and metabolic diseases such as hypertension and diabetes may have a role in the development of dementia and AD.[23-25] Harville *et al*.[18] show that gestational diabetes correlates with cognitive impairment while hypertension does not.

Breastfeeding and Stroke

As adequate scientific evidence exists that breastfeeding affects the risk of cardiovascular diseases,[9,10,26-30] some studies show breastfeeding reduces stroke risk in women.[31,32] In a study, 80,191 women between 50 and 79 years old were investigated and it demonstrated that women who breastfed had less stroke risk than those who did not. The duration of breastfeeding was negatively correlated with stroke risk. The authors highlighted that this association was stronger for non-Hispanic Black women.[31] Another cohort study from China supports the finding that breastfeeding reduces the risk of stroke in women who breastfeed. In addition, authors indicate that breastfeeding affects subtypes of stroke differently and the underlying mechanisms of every type can cause this difference.[32] However, a recent study by Jeong *et al*.[33] revealed that breastfeeding enhanced the risk for myocardial infarction, but not stroke in premenopausal women.

Breastfeeding and Multiple Sclerosis

The relationship between multiple sclerosis (MS) and breastfeeding is another research area for scientists. Some of the studies line up with the benefits of breastfeeding, while some of them do not support it. In a systematic review and meta-analysis of Krysko *et al*.,[34] 24 studies were investigated. The study reveals that breastfeeding is beneficial for women with MS. Especially, women who breastfed exclusively for at least 2 months have fewer relapses than those who breastfed nonexclusively or did not breastfeed. In a study conducted with 466 women, breastfeeding exclusively was related to a reduced risk of relapses in the first 6 months postpartum.[35] The researchers indicated that using disease-modifying treatment (DMT) did not impact the relapse rate in the 1st year postpartum. Furthermore, there was no connection between disease severity and breastfeeding preference.[35]

A study from Turkey supports the benefits of breastfeeding. One hundred and two pregnancies from women who have relapsing-remitting MS were examined. Women who breastfed for <3 months or who never breastfed had more relapses in the postpartum period. Moreover, using DMT

during pregnancy and problems with the fetus were not associated.[36] In a study by Hradilek *et al*.[37] which 1533 pregnancies were investigated, breastfeeding for <3 months was related to having a higher risk for relapses. In another study that compared pregnant women with nonpregnant women, Expanded Disability Status Scale (EDSS) scores were lower between 4 and 6 months postpartum in the pregnant and lactating groups.[38] In a study by Ostrem *et al*.,[39] 74 women with an EDSS score higher than three were evaluated for DMT use, magnetic resonance imaging, and breastfeeding. Breastfeeding for at least 3 months reduced the risk of postpartum relapses. However, it is important to emphasize that breastfeeding here defines both exclusive and nonexclusive breastfeeding.[39] Lorefice *et al*.[40] found that breastfeeding for more than 6 months was connected to lower white matter volume in the postpartum period. On the contrary, Zuluaga *et al*.[41] investigated the effects of menarche, pregnancy, and breastfeeding on MS. The risk of clinically definite MS, McDonald 2010, and the EDSS 3.0 and 6.0 were evaluated for participants. The results revealed that breastfeeding did not affect the risk of MS or clinically isolated syndrome.

It is noteworthy that in some of the studies, it was found that women with higher disease activity tend to breastfeed less than women with lower disease activity and these women are more likely to receive DMTs after labor.[34,36,38,40] Effects of DMTs during pregnancy are still unknown and more information is needed. According to Capone *et al*.,[42] the choice between using DMT or breastfeeding a baby should be specific to every case so that the pros and cons can be discussed. Furthermore, in some studies, breastfeeding is approached as exclusive breastfeeding[35,38,40] and in others just as "breastfeeding."[36,39,41] Hence, it is controversial how any breastfeeding or exclusive breastfeeding influences the results.

Breastfeeding and Mood Disorders

There is much research that investigates the relationship between mood disorders and breastfeeding. The prevalence of postpartum depression was found at 17.22% worldwide.[43] According to some research, breastfeeding affects disorders such as postpartum depression and anxiety. In addition, breastfeeding and maternal bonding may be connected. In a study conducted in Portugal, women were examined from pregnancy to the 3rd month of postpartum. Women who exclusively breastfeed in the first 3 months of postpartum had fewer depression symptoms in the 3rd and 6th months of postpartum. Furthermore, women who had depression symptoms at the beginning of pregnancy breastfed less.[44]

A recent meta-analysis reveals that women who breastfeed have a lower risk of postpartum depression. Moreover, according to this meta-analysis, exclusive breastfeeding and nonexclusive breastfeeding do not show the same effect.[45] In a study from Bangladesh, the risk for postpartum depression rises for women who do not breastfeed.[46] Research from Croatia supports this finding. The researchers found that mothers who did not breastfeed were more depressed.[47] In another study conducted with 511 mothers in Turkey, the connection between breastfeeding and postpartum depression was examined with the Edinburgh Postpartum Depression Scale (EPDS) and the Breastfeeding Self-Efficacy Scale (BSES). The results show that mothers who breastfed more had lower scores on the EPDS and higher scores on the BSES. Furthermore, the study indicates that results could be bidirectional. Mothers with depression breastfeed their babies less.[48] There is research that supports this finding. For instance, in a study by Wallenborn *et al*.,[49] women with depression before pregnancy breastfed their babies less. However, according to Woldeyohannes *et al*.[50] postpartum depression has no impact on exclusive breastfeeding.

Moreover, early weaning from breastfeeding is more common in depressed or anxious mothers.[51-55] A study demonstrates depressed mothers have problems with the initiation of breastfeeding.[56] However, according to van der Zee-van den Berg *et al*.,[57] not initiating breastfeeding reduces the risk of depression. Furthermore, researchers indicate that if you are still breastfeeding after 3 weeks of postpartum, the risk of depression decreases.

A recent study by Park and Choi[58] reveals that breastfeeding might be advantageous later in life. 1372 women in the postmenopausal period were examined and it was found that an increase in the number of breastfed babies and breastfeeding time reduces the risk of depression. Some research shows breastfeeding can impact maternal bonding between mother and child positively.[59-61] In response to this, there are studies claiming that other factors, besides breastfeeding, might affect maternal bonding, or that there is no connection with feeding style.[62-64]

Taken together, the results of postpartum depression or anxiety and breastfeeding are still controversial. Some studies highlight that the education and age of the mother, social support, and problems with breastfeeding can affect mood or anxiety disorders in mothers.[46,48,49,65] Furthermore, hormones such as oxytocin and prolactin are thought to have a role in mood and attachment. For instance, Matsunaga *et al*.[66] found that oxytocin was related to positive emotions in mothers. Furthermore, oxytocin was found to relate to stress reduction and a better mood.[67] However, Whitley *et al*.[68] demonstrated oxytocin levels did not differ between depressed or anxious women and the control group. In a study conducted with breastfeeding mothers and bottle-feeding mothers, breastfeeding mothers were more sensitive to their babies. In addition, mothers with high levels of prolactin hormone were to be more sensitive. However, there was no significant difference in prolactin levels between breastfeeding mothers and bottle-feeding mothers.[69]

Conclusion and Recommendations

It is shown that breastfeeding has a potential effect against some metabolic disorders in mothers. The causes of many diseases and human behaviors are revealed with the increase in studies to understand the brain and nervous system together with neuroscience, which is a developing field in recent years. Thus, neuroscience has included studies on the causes and consequences of maternal and breastfeeding behaviors and revealed that breastfeeding has not only metabolic but also neurological and psychological effects on mothers.

Considering the studies, the effects of breastfeeding on cognitive performance in old age are controversial. Based on the research, there may be a relationship between AD and hormones, which was also emphasized in previous studies. Therefore, studies are being done on the cognitive performance of the estrogen hormone in women and the development of dementia. Breastfeeding is also included in these studies as a period of hormonal change. While some studies have indicated that breastfeeding may protect the mother against dementia and AD in later life, others have not found any link. Further research is needed to elucidate these effects.

Researchers are working to ensure that pregnant and lactating women with an MS diagnosis can get through these periods in the most comfortable way and without disability for both themselves and their babies. For this reason, we focused on breastfeeding, which is thought to be a natural preventive method in addition to drug treatments. Considering the results of the research, it can be said that breastfeeding for the first 6 months may be protective for women who have less frequent attacks before delivery. Therefore, women can be encouraged to breastfeed their babies. For women with more progressive diseases, the necessity of drug therapy combined with breastfeeding should be questioned for the optimum health of the mother and baby.

The effects of breastfeeding on postpartum anxiety have been revealed by research. For this reason, mothers should be encouraged to breastfeed by both their relatives and health professionals. In this way, the mother can establish a positive bond with her baby. Mothers who cannot breastfeed for various reasons should not feel guilty for not being able to breastfeed.

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There is no need for patient informed consent.

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There is no conflict of interest to declare.

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- Tuğba Yılmaz Esencan (40%): Contributed with manuscript organization and editing.

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Original Article

Neuromorphological and Biochemical Effects of Co-exposure to Bisphenol A and Cadmium in Insulin-resistant Rats

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Abstract

Background: Cadmium (Cd) and bisphenol A (BPA) are known industrial additives and environmental toxicants that have been extensively reported for their various deleterious effects on biological systems, particularly endocrine disruption and neurotoxicity. In high-fat diet-induced insulin-resistant model rats, we studied the neurotoxicity and oxidative stress effects of co-exposure to Cd and BPA. **Aims:** This study aims to look at prefrontal microarchitecture and antioxidant profiles in insulin-resistant rats. **Materials and Methods:** Twenty-five adult Wistar rats were randomly assigned into five groups (A– E; $n = 5$). With A receiving normal saline; B: 40 mg/kg. bw $CdCl_2$ + high-fat diet (HFD) + Suc; C: 40 mg/kg. bw BPA + HFD + Suc; D: 40 mg/kg. bw BPA + 40 mg/kg. bw $CdCl_2$ + HFD + Suc; and E: HFD + Suc orally for 56 days. Finally, brains were excised from each group and the medial prefrontal cortex was dissected from both hemispheres with right hemisphere samples processed for hematoxylin and eosin histology and left hemisphere samples homogenized for biochemical evaluation of oxidative stress markers. One-way analysis of variance and Tukey's *post hoc* test were used for data analysis with $P < 0.05$ considered statistically significant. **Results:** From our findings, prefrontal glutathione levels were significantly lower ($P < 0.05$) in the insulin-resistant rats (Cd + BPA + HFD + Suc: 120.9 ± 21.89, HFD + Suc: 93.27 ± 17.29) compared with control rats (244.0 ± 11.57), while prefrontal glutathione reductase activity was significantly elevated (Cd + BPA + HFD + Suc: 41.02 ± 5.5, HFD + Suc: 41.09 ± 1.68, $P < 0.05$) compared to the control rats (20.17 ± 3.27). Prefrontal neurons showed nuclear condensation, cytoplasmic vacuolations, and clumping of cells. **Conclusion:** Morphological and biochemical evidence from the present study suggests that environmental and metabolic factors do combine to induce profound adverse effects on prefrontal microanatomy and antioxidant system.

Keywords: *Bisphenol A, cadmium, insulin resistance, oxidative stress, prefrontal cortex*

Introduction

An extensive body of research has identified bisphenol A (BPA) as a well-known endocrine-disrupting chemical.[1] Environmental pollutant to which humans and living organisms get exposed in varying concentrations and durations can reach toxic levels and has been confirmed to lead to oxidative stress due to the build-up of reactive oxygen species, increased lipid peroxidation, and alteration of DNA structure through nucleotide base modifications that disrupts DNA synthesis and repair pathways.[2-5] Exposure and contamination with BPA has been reported to be through leaching from various consumer goods and wearable products that find their way into the bloodstreams and membranes through nasal, oral, and dermal routes and has been detected in hazardous levels in urines of individuals in a wide range of population studies.[1,6]

Another candidate of interest due to its occurrence in the environment, industrial production and usage in manufacturing, and other commercial purposes is cadmium which is a member of a class of naturally occurring elements known as heavy metals.[7] Heavy metals have been described as metallic elements having higher densities relative to water which thus confers their toxicities that can be induced following exposure even to low concentrations.[8] The commercialization of cadmium which increases its concentrations

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in the environment further increases its potential for human exposure.[9] The public health concern to heavy metals generally, is with respect to biological systems that include plants and animals, is due to their reported disruption of cellular components and morphology as well as critical biochemical and metabolic processes through the alteration of normal enzyme-mediated pathways and cellular processes.[10] Thereby, leading to tissue damage, uncontrolled cell division, and increasing the potential for tumourigenesis, unprogrammed cell death (apoptosis) affecting normal tissue development.[11] Likewise, cerebellar ataxia induced by environmental toxins that include heavy metals have been reported to be owed to the perturbation to cerebellar cortical and Purkinje neurons.[12] Meanwhile, affluent and busy lifestyles have continued to exhibit far-reaching impacts on our day-to-day quality of life. Moreover, this is because it has led to an increasing palate for fast foods (also known as western diets [WDs]) which are essentially high fat based and the prolonged consumption of which has been widely associated with insulin resistance (IR) and accompanying diabetes leading to precocious cognitive and memory impairments which are functions of the hippocampus and parts of the prefrontal cortex (PFC).[13] Arnold *et al*. reported that, in addition to inducing brain IR in both cerebral cortical tissue and hippocampus, high-fat diets (HFDs) produced impairment in spatial working memory due to observed decreased T-maze alternation.[14] Although there are other underlying genetic and epigenetic permutations such as gene polymorphism that increase the risk of Alzheimer's disease (AD), however, prolonged HFD consumption has been established as a major influence in the pathophysiology. A study by Del Olmo and Ruiz-Gayo highlighted the relationship between hippocampal learning/memory deficits and nutritional/endocrine inputs derived from HFDs on juvenile hippocampal morphology and neurotransmission.[15] Since the earliest description of HFD, extensive studies have established it as a promoter of hyperglycemia and whole-body IR and thus accepted as a valid rodent model for simulating the metabolic syndrome and its associated IR and compromised functions of the pancreatic beta cells.[16] Diets high in fats and calories are known as HFDs or WDs and as the rate of their consumption continues to rise globally, especially in the more industrialized nations, it has become a major source of public health concern due to its attending obesity which is associated with a myriad of metabolic diseases that includes type II diabetes, cardiovascular diseases, stroke, gastrointestinal and respiratory diseases as well as several kinds of cancers.[17,18] Meanwhile, Akinola *et al*. linked poorly treated diabetes mellitus with neural complications and varying degrees of neurobehavioral manifestations.[19] Moreover, the mechanism of such neural complication could not be far from the fact that fatty acids being components of phospholipids cell membranes and thus their involvement in the interaction between proteins and lipid and their influences on membrane properties, cellular processes, and susceptibility to cell death as a result of the length of their carbon atom chains.[20] In other words, diet-induced obesity (and IR) has been linked with cognitive deficits and neurodegenerative diseases such as AD through mechanistic processes that involve the exacerbation of brain inflammation and acceleration of brain aging.[17]

Insulin-dependent diabetes mellitus, also known as type I diabetes, and insulin-independent diabetes mellitus (type 2 diabetes) are metabolic diseases that manifest in chronic hyperglycemia in the body. Type I diabetes is a condition that is characterized by low or complete lack of pancreatic insulin production, while type 2, on the other hand, is propagated by insulin production which is insufficient enough to effectively keep up with the glucose metabolic demands of the body. An imbalance in this systemic glucose–insulin dynamics precipitates abnormal glucose metabolism secondary to the development of IR. This is due to problems with the transport of glucose into the cells and its normal metabolism which, therefore, keeps glucose levels in the bloodstream elevated, which is characteristic of both types I and II diabetes. The resulting metabolic complications, such as neuropathy, renal failure, retinopathy, cardiovascular diseases, and peripheral vascular diseases, make it of significant concern.[21,22]

We, therefore, aimed to study the effects of simultaneous oral exposure to BPA and Cd on prefrontal cortical function and oxidative stress in a model of insulin-resistant rats.

Materials and Methods

Ethics committee approval was granted for this study the Postgraduate Ethical Review Committee of the University of Ilorin on 12.09.2019 with the number (UERC/ASN/2019/1854).

All experimental protocols and animal handling were in accordance with the guidelines of the University Ethical Review Committee and the Institutional Animal Care and Use Committee.

Chemicals and high-fat diet

Cadmium chloride (Kermel Chemical Reagent Co., Ltd., Tianjin, China) was obtained from Labtrade (Nig) Co, and BPA (Loba Chemie Pvt Ltd, India) was procured from Mich-Mikedenson Nig. Ltd. Other chemicals used are of analytical grade. High-fat feed was compounded at Ogo-Oluwa Livestock and Aqua Feeds Enterprises, Ilorin.

Animals and experimental design

Twenty-five adult male Wistar rats (*Rattus norvegicus*) (95–120 g) (Ogo-Oluwa Livestock and Feed Mills, Ilorin) were used for this study. The animals were kept in cages at the animal holding facility of the university with a 12-h light/dark cycle under standard room temperature/humidity with liberal access to rat pellets (Ogo-Oluwa Livestock and Feed Mills, Ilorin) and distilled water.

Treatment plan

The rats were randomly assigned into five groups of five animals each as follows: Group A (control: free access to distilled water), Group B (daily oral $CdCl_2$ at 40 mg/kg) + HFD + Suc.), Group C (daily oral BPA at 40 mg/kg) + HFD + Suc, Group D (daily oral $CdCl_2$ at 40 mg/kg + BPA at 40 mg/kg + HFD + Suc), and Group E (daily oral HFD + Suc daily). The administration lasted for 56 consecutive days.

Evaluation of brain and body weight

Body weights of rats were recorded on arrival at the animal house and every week of the 8-week (56 days) duration of the study. Weekly weights were taken to study the changes in weights across the groups through the study duration. Body weight changes were calculated as follows:

Change in body weight (%) = (Body weight at day 56– Body weight at day 0)/Body weight at day 56 × 100%

Prefrontal oxidative stress

On the last day of exposure, animals fasted overnight, final body weights were taken, tails were pricked to collect arterial blood, and fasting blood glucose was estimated by the glucose oxidase method using Accu chek (Roche, Belgium) and animals were anesthetized with intraperitoneal injection of ketamine (20 mg/kg). Blood samples from the left ventricle of the heart were collected through cardiac puncture into appropriate plain bottles and left to clot at room temperature (23°C) for 30 min. Blood samples were subsequently centrifuged at 3000 × g for 15 min. The serum was frozen at −20°C pending hormonal and glucose analysis. The animals were decapitated and brain tissues were harvested and separated into the right and left hemispheres. Hemispheres were dissected on cold plate to excise the PFC. Right hemisphere tissues for histological protocol were immediately fixed in 4% paraformaldehyde (Central Research Laboratories, Tanke, Ilorin). The left hemispheres were used for enzymatic analysis and preserved in 0.25 M sucrose solution at 4 ºC and were homogenized using Omni Prep Homogenizer (Omni International, GA, USA). The subsequent homogenates were centrifuged at 1957 × g for 10 min using a hematocrit centrifuge to obtain supernatants and pellets. Finally, the supernatants were aspirated into fresh tubes and both were stored at −20°C until further processing.[22] Protocol for hematoxylin and eosin (H and E) was carried out for histological studies.

Assay for fasting serum insulin and glucose

Serum glucose was assayed using the glucose oxidase method diagnostic enzyme kit (Span Diagnostic Chemicals, India), and insulin levels were assayed using the AccuBind enzyme-linked immunosorbent assay Microwells Insulin Test System (Monobind Inc. CA, USA) per manufacturer's instruction.

Estimation of insulin resistance

IR was estimated using the homeostasis model assessment of IR (HOMA-IR) method as previously reported[23] as follows:

(Fasting serum insulin [μU/L] × fasting serum glucose [mg/dL]/405)

Prefrontal photomicrography

The harvested brain tissues were fixed with 10% phosphate-buffered formaldehyde and subjected to the routine method for paraffin wax embedding to produce the required paraffin wax-embedded tissue blocks. To obtain the tissue blocks for staining, the fixed tissues were taken through the routine tissue processing protocol for H and E. Photomicrographs were taken with an Axiocam ERc 5s camera attached to a Carl Zeiss AX10 microscope and analyzed using the ZEN Core 3.5 software.

Data analysis

To analyze body weight and prefrontal oxidative stress parameters, GraphPad Prism software version 9 (GraphPad Software, Inc., San Diego, CA, USA) was used. One-way analysis of variance was used to compare differences in means, followed by Tukey's multiple comparison tests where necessary. All data are presented as mean ± scanning electron microscopy with a significance value set at $P < 0.05$.

Results

Body weight

The result from this study [Table 1] shows weight increase and percentage change in body weight was significantly higher in the HFD + Suc (116.0 ± 1.8, 29.96 ± 1.13) and BPA + HFD + Suc (109.4 ± 1.6, 26.12 ± 1.12) groups. Meanwhile, Cd seems to prevent much weight gain as the groups exposed to the chemical recorded the lowest mean weight and percentage increase in weight, Cd + BPA + HFD + Suc (80.2 ± 0.7, 3.18 ± 0.83) and Cd + HFD + Suc (82.2 ± 1.9, 22.22 ± 2.11), respectively.

Fasting blood glucose

HFD + Suc exposed group recorded the highest significant ($P < 0.05$) fasting blood glucose as well as the highest significant increase throughout the period of administration among all the groups. The fasting blood glucose level of the negative control (Ngtv Ctrl) group remained relatively stable throughout the duration of the study [Figure 1].

Fasting serum insulin

Cd + HFD + Suc recorded the highest fasting serum insulin levels. There was a significant increase ($P < 0.05$) in the levels of serum insulin in both Groups B and C relative to Group A (Ngtv Ctrl). There was, however, no significant difference in the levels of serum insulin in Groups D and E relative to the Ngtv Ctrl Group (A) at the end of 56 days of exposure [Figure 2].

Fasting serum glucose

There were significant differences ($P < 0.05$) in fasting serum glucose levels of Group D (Cd + BPA + HFD + Suc) and E (HFD + Suc) relative to the Ngtv Ctrl group. Group D (47.4 ± 0.6) and E (51.5 ± 1.2) both have higher fasting serum glucose levels than group control group (37.3 ± 0.6). However, there was no significant difference in fasting serum glucose levels between the control group and other insulin-resistant groups [Figure 3].

Insulin resistance

All the rat groups (B, C, D, and E) exposed to the agents HFD and Suc recorded significantly higher ($P < 0.05$) HOMA-IR scores compared to the Ngtv Ctrl group [Figure 4].

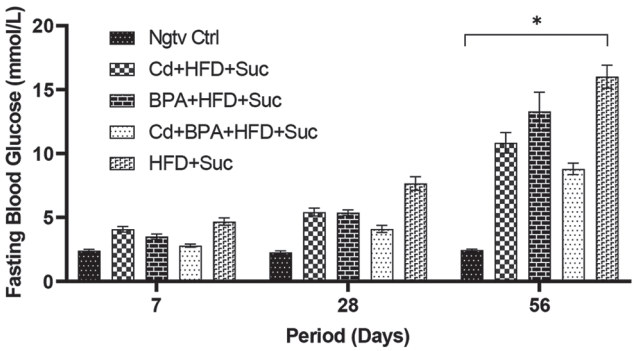

Figure 1: Fasting blood glucose levels across the groups following exposure for 7 days, 28 days, and 56 days. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

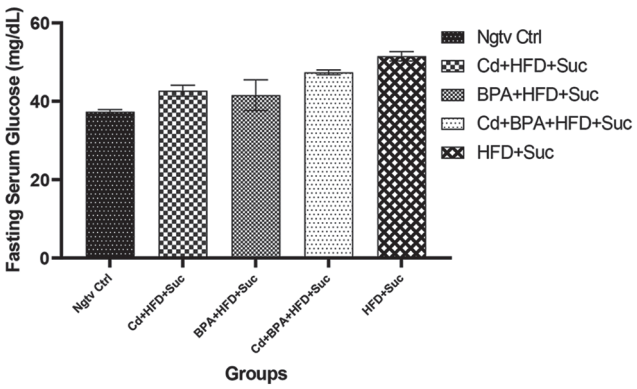

Figure 3: Fasting serum glucose levels across the groups following exposure for 56 days. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

Prefrontal superoxide dismutase

There were significant differences ($P < 0.05$) in the mean levels of prefrontal superoxide dismutase (SOD) across the groups. The group exposed to BPA + HFD + Suc (298.1 ± 45.8) had the highest prefrontal SOD levels relative to every other group with the group exposed to HFD + Suc (196.3 ± 41.1) recording the lowest SOD level [Figure 5].

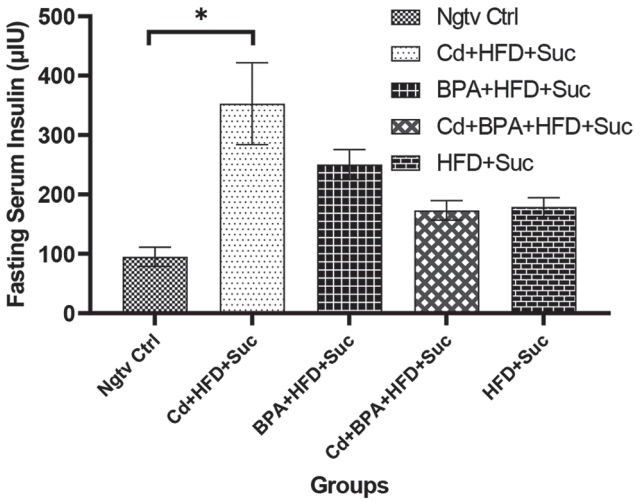

Figure 2: Fasting serum insulin levels across the groups following exposure for 56 days. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

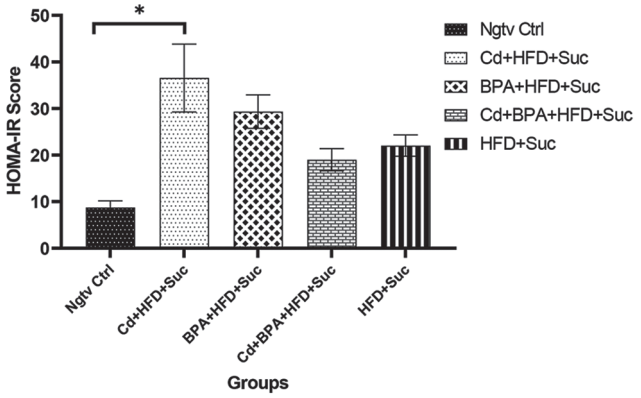

Figure 4: HOMA IR score across all groups following 56 days of exposure. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

Table 1: Comparison of weight (g) and percentage change in weight across groups (%)

Groups	Initial weight (g)	Final weight (g)	Weight difference (%)
Ngtv Ctrl	73.4±1.8	98.4±2.4	25.14±3.17
Cd + HFD + Suc	63.3±1.4	82.2±1.9	22.22±2.11
BPA + HFD + Suc	80.8±1.3	109.4±1.6*	26.12±1.12
Cd + BPA + HFD + Suc	78.2±1.3	80.2±0.7	3.18±0.83
HFD + Suc	81.8±1.6	116.0±1.8*	29.96±1.13

Values are expressed as mean±SEM with the level of significance shown as *($P<0.05$). SEM: Standard error of mean, Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

Prefrontal glutathione levels

The result in Figure 6 shows glutathione level was significantly higher ($P < 0.05$) in the control group (244.0 ± 11.57) compared to every other group exposed to the various toxicants. The exposed groups recorded lower glutathione levels suggesting that they are undergoing various degrees of oxidative stress.

Prefrontal glutathione reductase

Figure 7 shows glutathione reductase (GR) activity was higher in the HFD + Suc exposed group, followed by the group administered Cd + BPA + HFD + Suc. The GR activity level was lowest in the Ngtv Ctrl group. The higher GR activity in the exposed groups suggests an increased antioxidant response to the oxidative stress from the toxicants.

Histomorphology of the prefrontal cortex

All groups exposed to metabolic and environmental toxicants showed various forms and degrees of perturbations from the normal histoarchitecture of the PFC. These perturbations range from apparent nuclear condensation of granule cells of layer II, which is one of the early signs of apoptosis, clumping together of neurons, loss of granule cell density in some groups as well as necrotic blood vessels [Figure 8a].

External granular layer shows evenly stained and well-differentiated nuclei in the Ngtv Ctrl group. Cd + BPA + HFD + Suc treated group presents with aggregations of larger and deeply pigmented granule cells. There, however, appears to be fewer granule cells across the external granular in the BPA + HFD + Suc exposed group. Furthermore, sections from the treatment groups, especially the Cd + BPA + HFD + Suc and HFD + Suc groups, present with apparent histoarchitectural alterations that can be described as isolated aggregations of darkly stained nuclei present across the layers which is consistent with cellular pyknosis [Figure 8b].

Discussion

Industrialization has contributed to the increased exposure of humans to heavy metals such as cadmium, aluminum, lead, arsenic, and others.[24] Through primarily oxidative stress and mitochondrial dysfunction, these metals induce various levels of toxicities with manifestations ranging from motor to cognitive impairments.[25-27]

Results from this study indicate that exposure to HFD and sucrose drink precipitates IR in animals which leads to consequently higher serum insulin and serum glucose levels in the exposed groups compared to the control. Patience Ojo *et al*. (2022) reported increased glucose and diminished insulin sensitivity in a study of high fructose (sugar) diet exposure.[28] The metabolic imbalance that results from insulin insensitivity (IR) is exhibited by the observed significant

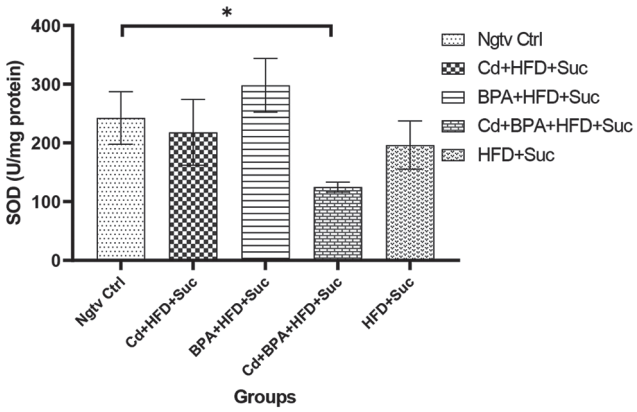

Figure 5: SOD readings of all groups at the end of the 56 days of simultaneous exposure to metabolic and environmental toxicants. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

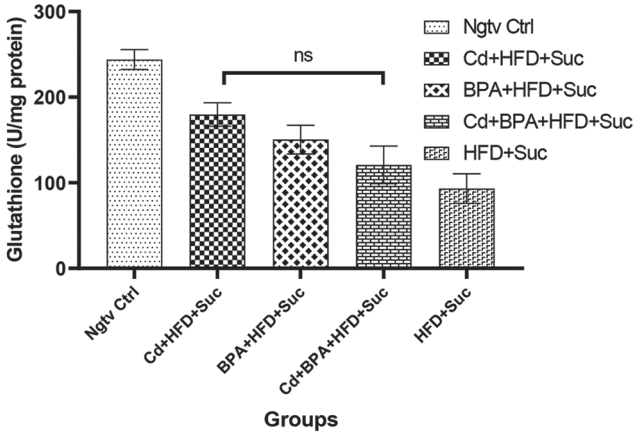

Figure 6: Glutathione levels across the groups at the end of the period of administration of Cadmium, bisphenol A, high fat, and sucrose diet. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

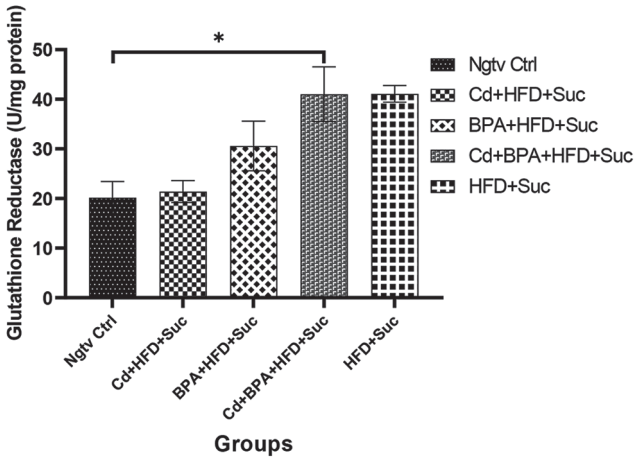

Figure 7: Glutathione reductase levels across the rat groups at the end of administration. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

increase and higher percentage gain in body weight in the insulin-resistant groups. Moreover, this finding is consistent

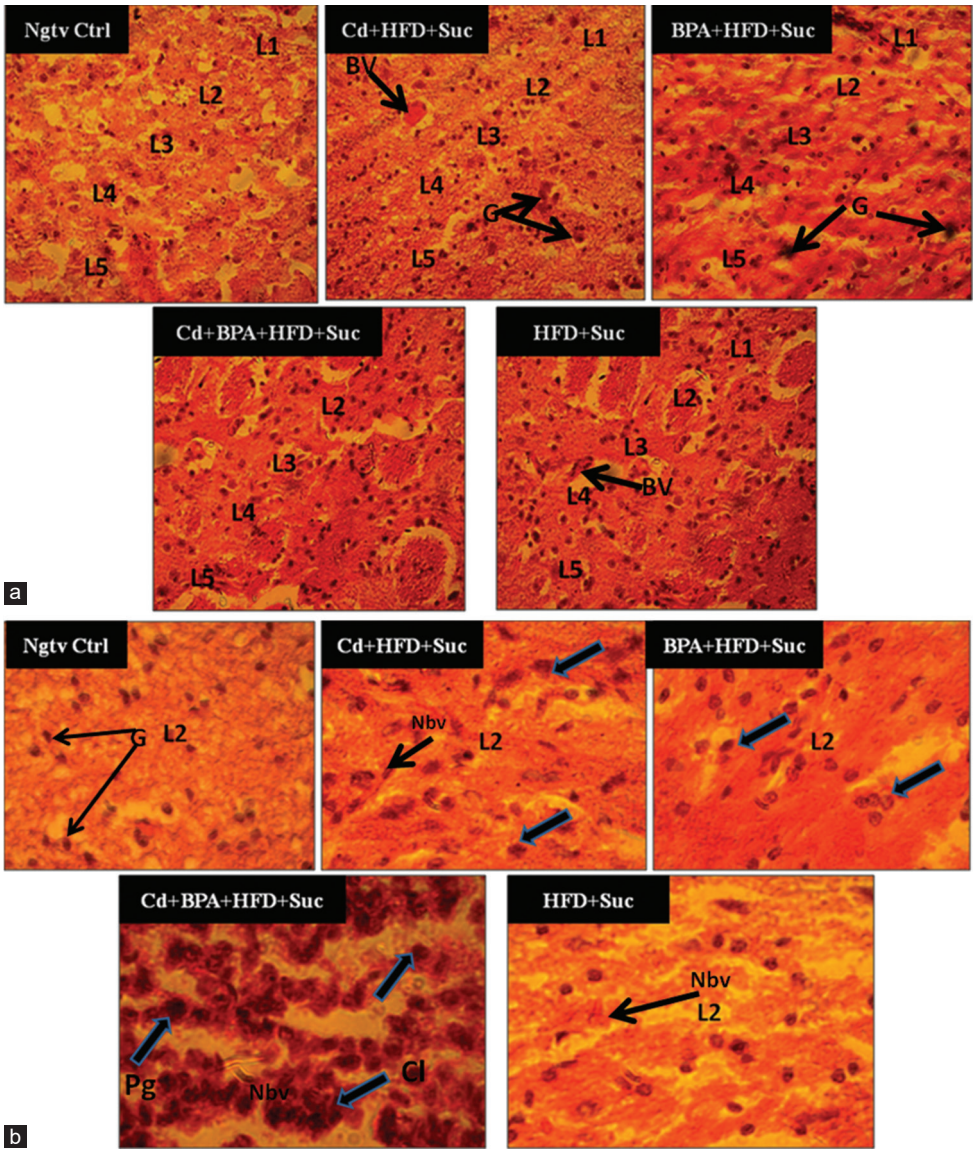

Figure 8: (a) Representative light micrograph of the prefrontal cortex of all groups exposed for 56 days. Stain: H and E, ×100. (b) Representative light micrograph of the prefrontal cortex of all groups exposed for 56 days. Stain: H and E, ×400. L1: Layer 1, L2: Layer 2, L3: Layer 3, L4: Layer 4, L5: Layer 5, BV: Blood vessel, G: Granule cell, V: vacuolation, Nbv: Necrotic blood vessel, Cl: Clumping, Tg: Tangling, Pg: Deeply pigmented cells. Ngtv Ctrl: Negative control, Cd: Cadmium, HFD: High-fat diet, BPA: Bisphenol A, Suc: Sucrose

with reports from studies conducted by Mohammed *et al*. and Akbari *et al*.[13,29] Likewise, exposure to the heavy metal, cadmium, and the endocrine-disrupting chemical, BPA resulted in notable oxidative stress on the treated animals. For instance, GR activity was significantly elevated in BPA-exposed groups bar the positive control. The expression of the antioxidant and SOD was also most highly elevated in the group exposed to BPA. Kobayashi *et al*. also reported on oxidative effects of BPA in a study where it contributed to a significant reduction in free radical scavenging capacity in plasma after 2- and 4-week exposure to BPA as well as significantly increased levels of SOD1 after 8 weeks of BPA treatment and alteration of ROS-induced signaling pathways in the brain.[30] Serum glucose and serum insulin were the insulin–glucose homeostasis markers analyzed and the reported result suggests that combined exposure to HFD and sucrose results in high serum glucose and insulin levels. Moreover, this observation is further buttressed by the reported higher score for assessment of IR (HOMA-IR) in the HFD and sucrose-treated groups. On histopathological examination, neuronal loss, nuclear condensation, and cytoplasmic vacuolations of granule cells characterized the PFC. Imam *et al*. also reported global cerebellar neurodegenerative changes characterized by numerous perineural spaces and reductions in neural density indicative of cellular shrinkage following aluminum chloride exposure.[25]

Conclusion

Reports from this work lends further credence to previous studies on the oxidative stress-inducing effects of heavy

metals and neuroendocrine-disrupting effects of HFD, sucrose (high sugar) drink, and endocrine-disrupting chemical, BPA. Overall, we demonstrated that isolated or co-exposure to cadmium chloride and BPA in high fat and sucrose diet-induced insulin-resistant rats precipitated prefrontal cortical lesions that could progress to neurodegenerative changes with the associated perturbation of cognitive and affective functions.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

Ethics committee approval was granted for this study the Postgraduate Ethical Review Committee of the University of Ilorin on 12.09.2019 with the number (UERC/ASN/2019/1854).

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No funding was received.

Conflict of Interest

There is no conflict of interest to declare.

Author Contributions subject and rate

- Abdulwasiu Taiwo Lawal (35%): Concept and design of the study, definition of intellectual content, experimental studies, literature search, collection of data, analysis and interpretation of data, manuscript preparation, editing and submission of manuscript.
- Ahmed O Sharafadeen (30%): Concept and design of the study, experimental studies, literature search, collection of data and analysis.
- Oluwole Busayo Akinola (35%): Concept and design of the study, provision of laboratory, definition of intellectual content, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

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Review Article

Neuroesthetics and its Excitatory Sensitization of the Cerebral Cortex

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Abstract

The human mind receives, perceives, and processes visual and auditory input daily from the everyday world of art and culture as an esthetic neural experience involving several regions of the cerebrum. It is important to comprehend how this process of neuroesthetics works and how it affects each individual's emotions and behavior. This article will incorporate various clinical scanning techniques and methods to examine the anatomical cerebral structures where the effects of external neuroesthetic stimuli can be correlated with its resultant neural cognitive response. The effects of neuroesthetic stimuli on the clinical improvement in patients experiencing depression, cognitive decline, and other forms of behavioral manifestations will be reviewed. The results of these studies (including international examples, along with various comparative analyses) demonstrate the beneficial effects of art on the pleasure centers of the brain and its consequent positive effects on patients' behavior and emotions, thus exemplifying the short- and long-term importance of incorporation of neuroesthetics in not only the clinical setting but also in our global society.

Keywords: *Cerebral cortex, cognitive neuroscience, functional magnetic resonance imaging, neuroesthetics*

Neuroesthetics, What Happens in Your Brain When You See/Experience Art?

Neuroaesthetic is a subfield of cognitive neuroscience concerned with the neural basis of esthetics, particularly in the field of visual arts. The term neuroesthetics appeared in the last decade of the 20th century. Esthetic encounters are widespread in our daily lives, and delving into their biological underpinnings can help us better understand human behavior in key areas such as mate selection, consumer behavior, communication, and art. Neuroscientific studies in this area have used imaging and neurophysiological techniques such as functional magnetic resonance imaging (fMRI), electroencephalography, and magnetoencephalography.

"An aesthetic experience is one that allows the beholder to 'to perceive-feel-sense' an artwork (from the Greek aisth-ese-aisthanomai), which in turn implies the activation of sensorimotor, emotional and cognitive mechanisms."[2]

Esthetic experiences can be found in a variety of settings (e.g., museums, galleries, and churches). Esthetic experience was viewed as a rewarding process by some psychological viewpoints, and a link between esthetic experience and pleasure was proposed.[3] Esthetic experiences include the feelings, judgments, and behaviors that these items inspire as well as the methods used in their creation and interpretation. Researchers are interested in how the brain initiates esthetic experiences and how our understanding of brain mechanisms contributes to our comprehension of these experiences. This area combines cognitive and emotional neuroscience with empirical esthetics. A descriptive or experimental approach to neuroesthetics is possible to form. Observations are used in descriptive neuroaesthetics which helps brain facts to be connected aesthetic impressions. The claims are qualitative in persona. Experimental studies for neuroaesthetics generates quantitative and statistically validated data. The technique puts hypotheses to the test, predicts outcomes, and welcomes feedback. It is either a replication or a falsification.[2]

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These sensory systems are activated by esthetic interactions in that as we view a work of art, it produces a subjective impression of movement and reactively activates the visual motion regions. Portraits stimulate the fusiform gyrus's face area, whereas landscape paintings activate the parahippocampal gyrus's place area. Astonishingly, in addition to classifying visual elements, these sensory areas may also be involved in evaluating them. Beautiful faces stimulate the fusiform face (and adjacent) areas (the FFA), located in the inferior temporal cortex (IT) within the fusiform gyrus (Brodmann area 37). The pleasure people get from gazing at beautiful images activates our reward circuitry automatically. Attractive faces stimulate the FFA and ventral striatum areas, even when people are not thinking about how gorgeous they are. Beautiful visual images generate reactions in the orbito- and medial-frontal cortex, ventral striatum, anterior cingulate, and insula, whereas music and architectural spaces evoke responses in the medial orbitofrontal cortex and adjacent cingulate cortex.[1] Some studies demonstrate that the beauty of art imagery boosts brain activity in visual areas, much as it does with faces.

Esthetic pleasure may be the result of interactions between brain structures that support the perception of particular images (e.g., parahippocampus for sceneries and neurotransmitter distribution in the cerebral cortex). When we observe images of actions, it has been observed that certain regions of the motor cortex in the brain are activated. This suggests that there is a connection between visual perception of actions and the motor system. There is a network of neurons called mirror neurons, which are part of the extended mirror neuron system, that play a role in this process. Mirror neurons were found in monkeys and birds and are known to respond to both action execution and perception. Interestingly, humans also possess a similar system of mirror neurons. Humans have a similar system.

Furthermore, the activation of reward networks and the default mode network during the creation and perception of art is another topic of investigation for neuroesthetic researchers. Dopamine, serotonin, and oxytocin are the "feel-good" neurochemicals produced by the reward system and are responsible for pleasure and happy feelings. When we engage in esthetic experiences or create and behold the arts, we activate the brain's pleasure centers and can observe that these areas become illuminated upon imaging.[3]

Several studies have found that art museums can be beneficial as therapeutic settings. These advantages include improved memory, reduced stress, and increased social inclusion. People with enduring mental health problems, such as dementia, and the socially isolated have all been studied. Furthermore, both traditional and modern galleries increased positive social effect and cognitive well-being in a research study of patients with dementia and their caretakers.[4] Furthermore, an emotional state is important in the improvement of our body and brain. Exempli gratia, "Joy or sorrow can emerge only after the brain registers physical changes in the body," says Antonio Damasio, a well-known neuroscientist who conducts research on the brain networks underlying emotion, decision-making, memory, language, and consciousness at the Brain and Creativity Institute of the University of Southern California. According to Damasio in an interview with Scientific American Mind, the brain continually receives information from the body and registers what is happening within each of us. After the impulses have been processed, brain maps are assembled in structures known as somatosensory centers. It is evident from reading the maps that sentiments and emotional shifts have been noted.[3]

Art is a challenging experience. It is the outcome of multiple cognitive and emotional processes interacting with one another. Neuropsychology and neuroimaging studies have shown the enormous network of brain areas on which it is built. This network has three functional components:

i. The prefrontal, parietal, and temporal cortical regions support evaluating judgment, attentional processing, and memory retrieval
ii. The reward circuit, which encompasses the cortical and subcortical areas as well as some of its regulators, is involved in the formation of pleasurable experiences and emotions, as well as the appraisal and anticipation of reward
iii. Modulating activity in low-, mid-, and high-level cortical sensory areas enhances perceptual processing of certain characteristics, relations, places, or objects.[5]

Art expression has been proven to be a powerful instrument for well-being. Advanced fMRI investigations are revealing the structure of the brain. Neuroplasticity influences the brain's evolution, structure, and capacity to repair or re-route circuits. Both hemispheres of the brain are activated and stimulated by art, with the motor cortex being stimulated even when there is no movement involved. This is a significant step forward in the treatment of neurological conditions such as stroke and traumatic brain injury. Researchers analyzed post-retirement effects on people using fMRI and half of them showed "art intervention" for 10 weeks. Those who received the visual art intervention demonstrated improved functional connectivity in the frontal and parietal cerebral cortices. This was linked to a higher level of psychological/stress resilience. In the control group, no such effects were seen. The research was noteworthy since it was the "first to show the neural of visual art output on psychological resilience in adulthood."[6]

Another fMRI research based on the neuroesthetics of Noh masks (a Japanese theatrical mask) postulated that the amygdala would respond when a negative emotion, such as grief, was represented by a theatrical mask. Masks are utilized by actors in traditional Japanese Noh drama to reflect several of the characters' mental states. A fMRI

research in which participants' brains were examined while watching Noh masks with beautifully mournful features was presented. Viewing sad masks stimulated the right amygdala, according to the results of an area of interest study. We hypothesize that such tiny sorrowful masks might stimulate the amygdala, presumably because they are similar to emotions such as fear and disgust.[7]

In addition,[8] they aimed to identify the neural correlates of both the visual esthetic experience (VAE) general aspect and those that were more intimately connected to the content of the artworks. Forty-seven fMRI tests from 14 published publications were subjected to a general activation likelihood estimation (ALE) meta-analysis. In addition, they conducted four separate ALE analyses to identify the neural substrates of reactions to specific categories of artworks, namely portraits, representation of real-world visual scenes, abstract paintings, and body sculptures. The general ALE revealed that the VAE relies on a bilateral network of areas, and the individual ALE analyses revealed that maximal activation for the categories of the artworks differed depending on their content. Many content-dependent sections of the ventral visual stream, as well as a few other brain locations, are involved in VAE. Art-related neural responses, as a result, activate widely distributed networks in both hemispheres, including content-dependent ventral visual stream brain areas. Esthetic emotions involve sensory, perceptual, and cognitive processes, according to the findings.

How could we comprehend the human brain's unique and wonderful talents to produce and enjoy art in biological terms? In the last decade, neuroscience has made significant progress in terms of establishing experimental methodologies and theoretical frameworks for understanding emergent features arising from vast neural networks' activity. The 37 articles that make up this special Frontiers Research Topic combine theoretical and experimental research, connecting cutting-edge understanding of the brain with the phenomena of art.[9] It includes contributions from eminent authorities on vision, audition, somatosensation, movement, and film, and it covers a wide range of issues.

The purpose of art is perception. It may be assumed that artists, whether intentionally or unintentionally, find proof of the brain bases of esthetic perception. Because art serves as a visual representation of reality, it drives artists to explore new methods to enhance the representation, usually using perceptual shortcuts that our brains cannot discern apart from reality. Visual information is processed in the primary visual cortex, which is the first section of the brain to process it. Neurons in this region of the brain detect lines and corners. After detecting lines and corners in the visual field, information is then sent to the brain's ventral and dorsal visual processing centers via two independent, yet related, routes. The ventral stream, sometimes recognized unofficially as the "what" pathway of perception, is responsible for processing information on shape, color, and object recognition in general. From the main visual cortex to the IT lobe, this neuronal route runs. The dorsal stream (unofficially recognized as the "where" pathway of perception) projects to the posterior parietal cortex and is important for spatial information.

Manipulation of the reward center has also been demonstrated to boost esthetic appreciation. A 2014 research investigated whether esthetic perception may be enhanced by utilization of transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex (lDLPFC), which is projected from the ventral tegmental area. They were effective in establishing a connection between lDLPFC activity and appreciation of esthetic beauty. Affinity for artistic images was higher in those who got tDCS to the lDLPFC than in those who did not. Although the lDLPFC has been connected to esthetic pleasure in the past, this study is the first to demonstrate a causal connection. Studies using fMRI have revealed a strong correlation between reward circuit activation and looking at artistic imagery. These studies demonstrate that reward processing is essential for enjoying visual art.[10]

In conclusion, the research suggests that emotions are at the heart of the esthetic experience. The associated emotional reaction appears to be the ultimate reward, whether it is seeking out the best works of art or simply enjoying the view. The neural activity of areas involved in both positive and negative emotional processing, such as the nucleus accumbens, the prefrontal cortex, and the amygdala, among others, transcends artistic mediums. By increasing the number of art forms studied through neuroscience, the functions that these regions exhibit may become even more solidified. Esthetic experiences have been shown to alter cognitive and emotional states as well as improve physical and psychological well-being. Perhaps, the future of neuroesthetics will reveal more about the origins and evolution of art than our neurological reactions to it.

Patient informed consent

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Review Article

Impact of Nutrition on Depression: A Review of Some Dietary Components with Antidepressant Effects and Their Mechanism of Action

Abstract

Recent years have seen a surge in psychiatric diseases, which has resulted in considerable disease distress and considerably decreased living conditions. Many considerable synthetic medications have been used to treat these illnesses throughout the years, but they have been found to have limited effects and substantial recurrence risks in many individuals. Mental illnesses such as depression and anxiety are persistently on the rise around the world, posing serious challenges to the affected person's and their family members' personal lives. There is mounting evidence that suggests the gut–brain axis (GBA) contributes to the genesis and development of psychiatric diseases. This review focuses on contemporary dietary therapies such as Mediterranean diets and dietary supplements and emphasizes nutrition's critical role in psychiatric care through the GBA. Several research have indicated that dietary quality affects mental health because it controls metabolic processes, has anti-inflammatory and antiapoptotic characteristics, and promotes neurogenesis and synaptogenesis. This study demonstrates many dietary components, their relationships to depression, and how they work. The use of dietary recommendations to support mental health appears to be a novel, affordable, useful, nonpharmacological intervention for people with mental problems.

Keywords: *Dietary supplements, gastrointestinal connection, lifestyle, mental health, mental illnesses*

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Introduction

With more diet-related or nutrient-oriented supplement treatment being put in place and the availability of a wealth of preclinical and epidemiological data, nutritional psychiatry has recently undergone a rapid evolution. Much work has been done recently to establish a strong connection between nutritional quality and mental health. This emerging paradigm entails using nutrient-based supplements or proper clinical inspection to modify or improve prescribed diets to prevent or treat mental health issues.[1] It is intriguing to see that the expense of numerous noncommunicable diseases, including mental illnesses, is expected to total US$47 trillion by the year 2020.[2] Because of this, there has to be a change in clinical practice and policy in the area of mental health that emphasizes the importance of nutrition.[3]

Nutritional psychiatry, the discipline of employing diets and nutrient-based dietary supplements as a treatment option for mental health issues, has developed into a viable option for clinical intervention for patients with depression and anxiety.[4] Given how frequently these illnesses occur and how they are becoming an issue for public health, it is highly likely that the prevalence of depressive illnesses will be on the rise, in the coming years. They are prevalent across all cultural contexts and pose a significant challenge to the families of those who are affected, leading to extreme suffering, impairment, and increased mortality, especially if left untreated.[5] In future, depression is anticipated to overtake cardiac diseases as the primary source of disease burden, surpassing depression as the current primary reason for disability in the world.[6] Depression is a prevalent psychological state characterized by reduced mood, loss of enjoyment or interest, decreased vitality, self-blame or sense of inferiority, disrupted eating or sleeping, and trouble focusing. These issues might intensify over time or repeat,

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which significantly impairs one's capacity to handle daily responsibilities.[7] Around the world, depression impacts over 264 million individuals across all age groups,[8] whereas Nigeria has a prevalence rate of 3.9% or 7 million people.[9] The prevalence of depression is considerable, and it may have a significant effect on one's life. Medical care and counseling can help ease symptoms in many cases, but lifestyle changes, including eating a healthy diet, can also improve one's well-being.[10]

Causes of Depression

Even though ongoing research in neurophysiology and neuropsychiatry has helped us grasp the pathophysiology of depression, the specific mechanism (s) through which it arises is still unknown. This is because depression is a diverse condition with a complicated phenomenon and a wide range of possible etiologies. Although the underlying neurobiology of depression has not yet been fully elucidated, aberrations at the molecular and cellular levels are thought to combine with hereditary and environmental variables to cause depression.[11] The development of depressive mood diseases is influenced by several factors, including environmental, psychological, and genetic factors.[12] Typically, genetics account for a sizable portion of the risk of depressed mood illnesses.[13]

Pathophysiology of Depression

The hypothalamic–pituitary–adrenal (HPA) axis dysfunction, the biogenic amine hypothesis, and genetic and environmental variables are all part of the way depression affects the body's normal functioning. Other conceivable factors comprise neurogenesis, elevated amounts of corticotrophin-releasing factor (CRF), anomalies of second messenger systems, enhanced synthesis of inflammatory cytokines (immunologic factors),[11] and alterations in the mechanisms for oxidative and nitrosative stress. No single theory fully accounts for all the indications and manifestations of depression, and it is probable that depression entails various interconnected pathological mechanisms that present as a combination of indications and manifestations that define depression. This makes it difficult to understand the pathophysiologic mechanisms by which depression occurs.[11]

Nutritional Psychiatry

A growing area known as nutritional psychiatry establishes diet and mental health relationships.[14] It is a rapidly expanding field that focuses on using diet and supplements to deliver necessary nutrients as part of an integrated or alternative approach to treating mental well-being conditions.[15] The foods we eat can affect our physical well-being, and diseases and dietary modifications may have an impact on the progression of many chronic diseases.[16] An article in the journal *Nutrients* claims that individuals who consume more fruits and vegetables are happier and more confident in their abilities.[17]

Nutritional Psychiatry and Depression

It is possible that changes to our food do not directly impact our mood or depression symptoms.[18] However, possibly a connection exists connection between diet and emotional state, which is encouraging information for the estimated over 264 million individuals globally who suffer from depression.[19] The development, intensity, and course of depression can all be significantly influenced by nutrition. Many readily observable dietary habits present before depression also exist during the depression, including things such as reduced appetite, missing meals, and a predominance of sweet food cravings.[18]

According to studies, those who adopt an improved eating pattern, such as a Mediterranean-style diet, appear to have the ability to protect against the onset of depression with time, whereas individuals who consume more fast food, sweets, and sugary beverages are at a higher risk of getting depression.[20] Lack of key nutrients, such as omega-3 fatty acids, B Vitamins, Vitamin D, magnesium, and zinc, is linked to an increased danger of depression.[21] Diets high in B vitamins, particularly folate, pyridoxine (B-6), and methylcobalamin (B-12), may be particularly useful in treating depression. They are cofactors for enzymes that make it easier for neurotransmitters that control mood, such as norepinephrine, serotonin, and dopamine, to be made. There are various processes by which nutrients improve mood. Some minerals, including omega-3 fatty acids, magnesium, and zinc may boost enhanced brain-derived neuro factor (BDNF) production, which improves neuroplasticity and increases the brain's resilience to stress, lowering the risk of depression. It is a commonly accepted fact that omega-3 fatty acids and a few B vitamins play significant anti-inflammatory and neuroprotective roles; this could potentially have an impact on the antidepressant effects of these nutrients. According to research, the microbiome, which comprises bacteria found in the large and small intestines, may influence inflammatory chemicals and neurotransmitters involved in mood regulation as well as general physical and mental health.[22] Furthermore, according to Senra,[23] there is proof that certain dietary habits and minerals have a preventative influence on the development of depression. A reduction in oxidative stress, a drop in inflammatory indicators, a rise in the endothelial role, and alterations to serotonin synthesis and function are a few of the processes underlying this association.

The Relationship between the Gut and the Brain

The relay pathway that links the gut and the brain is known as the "gut–brain axis (GBA)." This arrangement is for exchanging information between the digestive system and the brain. The digestive system-brain has a two-way transmission channel that involves central and enteric neural systems that unite the brain's expressive and intellectual regions to peripheral digestive activities.[24]

Numerous associations exist between the digestive and the brain, anatomically and enzymatically;

Neurological System and the Vagus Nerve

The central nervous system and the brain of an individual have around 100 billion neuronal cells, which are cells that provide the body with behavioral instructions.[25] Around 500 million neuronal cells in the digestive system relay with the brain through nervous system nerves.[26] The vagus nerve, the most significant nerve that relieson the digestive tract and the brain, carries impulses both ways.[27]

Neurotransmitters

The brain and the digestive tract are likewise related by neurotransmitters, which control feeling and emotion. Serotonin, for instance, is a neurotransmitter that aids to regulate the body clock and is connected to positive feelings.[28] It is crucial to understand that countless of these neurotransmitters are created by the billions of microbes that live in our digestive tract and other cells there. In the case of the brain neurotransmitter serotonin, the digestive tract produces 90% of it.[29] In addition, gut microbes create the neurotransmitter gamma-aminobutyric acid (GABA), which aids in reducing nervousness and panic.[30]

Elements with Antidepressant Effects

Selenium

Selenium is a vital nutrient that is found in most natural foods and is sometimes obtainable as a dietary additive. Selenium performs significant roles in the metabolism of thyroid hormone, oxidative stress, DNA synthesis, and reproduction.[31] Selenium exists in organic (selenomethionine and selenocysteine) and inorganic (selenate and selenite) forms.[32] About 28%–46% of selenium is deposited in the skeletal muscle, which makes up the total selenium content.[33] Brazil nuts, organ meats, and shellfish are rich sources of selenium.[31] Diets such as dairy products, meats with muscle, grains, and cereals also contain selenium.[34] Lean pork, mushrooms, beef, turkey, chicken, eggs, yogurt, beans, spinach, milk, cashews, and bananas are selenium are other foods that contain selenium.[35]

The link between selenium and depression

Eating more selenium might enhance emotion and lessen anxiety, which may lead to a lower prevalence of depression.[10] Selenium has a protective effect against free radicals by sustaining greater enzyme activity. This is because it is associated with the glutathione peroxidase enzyme.[36] Selenium prevents the liver's glutathione peroxidase from decreasing with low selenium intake because the brain has to capacity to store selenium.[37] Low selenium intake may implicate certain brain functions, including memory or feeling,[38,39] suggesting that low levels of selenium may be detrimental to depression. Selenium has a role in the onset time of depression by enhancing endothelial function, lowering oxidative stress and inflammatory indicators, and altering the synthesis of serotonin and its activity.[23] Selenium also modulates thyroid metabolism and the activities of selenoproteins on the serotonergic, dopaminergic, and noradrenergic systems disturb a person's propensity to experience depression.[40]

Mechanism of action of selenium

Selenium increases mood by sustaining the health of the metabolic, oxidative, and central nervous systems. Interference of selenium with the modulation of metabolism can predispose an individual to depression. Iodothyronine deiodinases (DIOs), which contain selenium, are necessary for the proper synthesis and metabolism of thyroid hormones. The correlation linking selenium amounts and depression may lead to an imbalance of oxidative and inflammatory pathways. Studies have shown that selenium proteins protect against lipoperoxidation and oxidative cell injury (thioredoxin reductases, glutathione peroxidases, and selenoprotein). Decreased levels of C-reactive protein (CRP), growth differentiation factor-5, and interleukin-6 (IL-6) have been associated with lower amounts of selenium.[41,42] The pathophysiology of depression is marked by more and oxidative stress inflammation.[42]

Selenium modulates the actions of several neurotransmitter systems, suggesting its antidepressant properties. It also significantly modulates the serotonergic, dopaminergic, and noradrenergic systems.[43] This contributes to the physiopathology of mental illnesses such as depression.[44] Neurochemical evidence shows that m-CF3-PhSe2 disturbs the serotonergic system by specifically hindering an enzyme, monoamine oxidase A, associated with 5-HT breakdown ensuing in 5-HT raising its entire availability in the synaptic cleft.[45] Furthermore, selenium control dopaminergic neurons' defense against oxidative stress through selenoprotein, thereby offering neuroprotection against neurodegeneration.[46]

Vitamin D

Vitamin D is a fat-soluble secosteroid that has biological effects that boost the absorption of calcium, phosphate, and magnesium.[47] Vitamin D3 (cholecalciferol) and Vitamin D2 (ergocalciferol) are the two vital classes of this vitamin in humans.[48] On exposure to the sun, lower layers of the skin epidermis produce cholecalciferol, which is a natural source of this vitamin.[49] Ergocalciferol and cholecalciferol can be obtained from supplements or as part of a healthy diet.[50] Fatty fish such as tuna, mackerel, and salmon, as well as fortified foods such as orange juice, soybeans, cereals, liver, cheese, beef, milk, and egg yolks, are examples of foods that naturally contain Vitamin D.[51] A slight genetic objective occurs for Vitamin D that is generated by the skin or taken through diet. First, protein is hydroxylated in the liver before occurring in the kidneys.[52] Cholecalciferol is converted into calcifediol, whereas ergocalciferol is changed into 25-hydroxyergocalciferol in the liver.[53]

25(OH)D levels in the serum of an individual determines the person's vitamin D level.[54]

The link between Vitamin D and depression

Vitamin D, an important neurosteroid hormone, can be a significant component in lessening depression. In Vitamin D lacking patients, Vitamin D additives can efficiently cure depression, as stated by many studies.[55] Generation and advancement of depression have been hypothesized to be accompanied by a shortage of vitamin D among other factors. Shortage of Vitamin D may lead to advanced-age depression.[56,57] A high level of Vitamin D in the serum can reduce the danger of having depression and other neurological conditions.[58,59] According to Mohammad Zahedi *et al*.,[60] consuming foods high in Vitamin D can aid in lowering the indications of depression because of the Vitamin D receptors present in the cingulate cortex and the hippocampus. Neuroplasticity, neuroimmunomodulation, the control of neurotrophic factors, brain growth, and neuroprotection are some of the neurological actions that can be impacted by Vitamin D. Studies suggest that consuming Vitamin D additives can mitigate both depression and lessen an individual's threat of having it.[61] The huge number of Vitamin D receptors in the human brain are responsible to regulate several neurotransmission pathways, such as those for serotonin, noradrenaline, glutamine, and dopamine.[62]

Mechanism of action

Regulation of the expression of the elements of the Ca2 + signaling toolkit, one of Vitamin D's most significant functions, helps to sustain and reduce latent Ca2 + levels in the cytosol. According to stability theory, the maintenance of Ca2 + and redox balance is maintained by Vitamin D.[63] Vitamin D has been revealed to decrease brain Ca2 + levels, which may help relieve depression.[64] Lack of Vitamin D results in increased amounts of Ca2 + and reactive oxygen species (ROS) in brain cells,[63] which may give an understanding association between depression and this disease.

Tyrosine hydroxylase and tryptophan hydroxylase, the rate-limiting enzymes in the production of serotonin and dopamine respectively, are also associated with Vitamin D, which elucidates the connection between a Vitamin D deficit and depression.[65] Since Vitamin D regulates serotonin production, depression and Vitamin D deficit are connected.[66] Vitamin D suppresses the expression of the tryptophan hydroxylase action and stimulates the growth of the serotonin-producing gene tryptophan hydroxylase 2. Serotonin is formed by tryptophan hydroxylases 1 and 2, respectively. As a result, Vitamin D capacity to retain fixed levels of serotonin may aid in the prevention of depression.[67]

Omega-3 fatty acids

Omega-3 fatty acids, which are polyunsaturated fatty acids, are also known by various names, such as omega-3 oils and omega-3 oils, omega-3 fatty acids, and n-3 fatty acids.[68] The chemical structure of omega-3 fatty acids has three atoms distant from the final methyl group.[69] They are broadly found in nature, and they play a significant function in animal lipid metabolism. Besides, omega-3-fatty acids also show a significant role in human food and composition.[70] Omega-3 fatty acids occur in three forms: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and linolenic acid (ALA). The first is seen in plant oils, whereas the other two are seen in marine oils. Walnut, hemp oil flaxseed oil, edible seeds, algal oil, sacha inchi oil, and clary sage seed oil are common sources of ALA oil-containing plants, whereas sources of animal omega-3 fatty acids, EPA, and DHA are squid oils, fish, krill oil, fish oils, and eggs from hens.[69]

The link between omega-3 fatty acids and depression

Growing body of studies reveals that mega-3 polyunsaturated fatty acids, also called omega-3 PUFAs, can be used to manage depression.[71] The combination of DHA[72] and EPA[73] can help alleviate the symptoms of depression. They can also play a significant role in sustaining the fluidity of the membrane and its structure. In addition, they have anti-inflammatory property.[74]

Mechanism of action in depression

The possible association between omega-3 consumption and dopaminergic and serotoninergic transmission, including release, metabolism, absorption, and receptor function, has been theorized to have a promising impact on depressive status. DHA and EPA are known to remarkably affect the organization of several cell types' fluidity due to their extensive unsaturation.[75] Membrane-bound enzymes, such as omega-3 PUFA and Na/K-dependent ATPase, likewise regulate signal transduction by improving protein kinase C[76] and G-protein-mediated signal transmission.[77] Dopaminergic and serotonergic neurotransmission could be enhanced by omega-3 PUFA consumption that regulates membrane changes, which are usually malfunctioned in depressed patients. Hypothetically, the current receptor and neurotransmitter concepts of depression are connected to fatty acids by variations in dopamine receptor and serotonin (5-HT) amount and function brought on by variations in PUFA.[78] Violent suicide attempts during depression have been related to lesser levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite that characterizes serotonin turnover, in the cerebrospinal fluid (CSF).[79] Healthy individuals with higher plasma DHA concentrations have increased serotonergic neurotransmission (higher CSF 5-HIAA), according to several studies.[80] Contrarily, a lack of omega-3 leads to a rise in frontal cortex serotonin receptor (5HT2) density, likely as a result of the body's response to a reduced serotonergic activity.[81] Several evidence from research show reduced amounts of the prefrontal cortex dopamine turnover and up to 6-fold greater of nucleus accumbens amounts of dopamine from animal model studies.[82]

Proinflammatory cytokines that are influenced by eicosanoid release and linked to depression, such as IL-1, IL-2, and

IL-6, tumor necrosis factor-42, can be significantly reduced by EPA and DHA consumption. Furthermore, through their precursor arachidonic acid, DHA and EPA can both lessen inflammation. Arachidonic acid levels are reduced in both the cells and plasma as EPA and DHA interact with arachidonic acid to produce membrane-based phospholipids.[83]

Due to the overactivity of the HPA axis, which is largely caused by over secretion of CRH, depression has been connected to an increased amount of cortisol in the blood. EPA may bring to normal the dysfunction of the HPA axis linked to depression by causing a reduction of how corticotrophin-releasing factor is expressed and the secretion of corticosterone.[84] Studies have shown that omega-3 PUFA reduces P-glycoprotein activity from a molecular perspective,[85] which are transport proteins in charge of the increased blood–brain barrier cortisol trafficking in depressed individuals.[86] The HPA axis's feedback control would be restored to normal once cortisol disseminated into the brain returns to normal.[87]

Antioxidants

Antioxidants are constituents that avert oxidation, a chemical process that can result in free radicals and cascade actions that could cause injury to the cells of an organism.[88] Carrots asparagus, broccoli, apricots, maize, green peppers, beets, cantaloupe, mangoes, pink grapefruit, nectarines, peaches, kale, spinach, sweet potatoes, tangerines, tomatoes, and watermelon all contain Vitamin A. Kale, cantaloupe, mango, Brussels sprouts, cauliflower, snow peas, honeydew, kiwi, nectarine, papaya, sweet potato, grapefruit, tomatoes, orange, strawberries, berries, broccoli, and red, green, or yellow peppers are foods that contain high amounts of Vitamin C. Foods high in Vitamin E include broccoli (boiled), pumpkin, mustard, chard, papaya, mangoes, turnip greens, nuts, avocado, and red peppers.[89]

The link between antioxidants and depression

The inverse relationship between (dietary total antioxidant capacity) DTAC and anxiety and depression can be elucidated by the antioxidative and anti-inflammatory properties of antioxidant-rich diets. It is been established that inflammation and weakened antioxidant defense are strongly correlated with sad mood.[90] Free radicals are the byproducts of normal human functions that can accumulate in the body and are removed by antioxidants. Oxidative stress can occur if the body is unable to remove enough free radicals. Numerous health issues, such as anxiety and depression, may follow.[10]

Mechanism of action

Antioxidants are known to be able to eliminate reactive nitrogen species (RNS) and ROS in the body by clearing free radicals and inhibiting the oxidative stress pathway. This further guards against injury to neurons triggered by nitrosative or oxidative stress causes in the brain, expectantly leading to the remission of anxiety or depression symptoms.[91] Flavonoid exerts their depressive action similarly to traditional antidepressants by making current neuropharmacology more readily available.[92]

B Vitamins

B vitamins, often known as the Vitamin B complex, are a collection of water-soluble vitamins that are critical for cell metabolism. These vitamins, which are chemically diverse, often coexist in some meals. Dietary additives that contain all eight of these vitamins are called Vitamin B complexes.[93]

They are vital to the preservation of health and well-being. B vitamins, which are the basis of a healthy body, unswervingly affect brain function, turkey, energy levels, and cell metabolism.[94] Salmon, fortified cereals, liver, eggs, oysters, clams, leafy greens, cattle, beans, milk, chicken, yogurt, pork, mussels, trout, and sunflower seeds are all good sources of B vitamins.[95]

The link between antioxidants and depression

Chemicals that impact mood and other neurological processes, produced by the brain are assisted by Vitamin B-12 and other B vitamins. Vitamin B-12 deficiency, along with other B vitamins such as Vitamin B-6 and folate, could be linked to depression.[96]

Mechanism of action

Vitamin B-12 has an impact on the levels of other neurotransmitters and serotonin in the brain. An individual mood is controlled by serotonin, and depression is associated with low serotonin levels.[97]

Zinc

Zinc is a significant mineral that is added to some meals, inertly found in others, and sold as a dietary additive. Zinc involves several processes in cellular metabolism. The catalytic activity of nearly 100 enzymes is dependent on it,[98] and it has a role in DNA synthesis and cell division,[99] immunological function, protein synthesis,[99] and wound healing.[100] Meat, whole grains, shellfish, eggs, legumes, seeds, nuts, dairy, vegetables, and fruits are foods that naturally contain zinc.[101]

The link between zinc and depression

Numerous receptors or transporters, including those for monoamines, are modulated on the postsynaptic side by zinc released from the presynaptic vesicles.[102] Individuals with depression have reportedly been linked to reduced serum amounts of zinc. Zinc amount drops in depressed patients.[103] Numerous studies show lower serum zinc amounts in depressed people in relation to healthy subjects, and a meta-analysis shows depressive symptoms at serum zinc amounts of 1.8 um or below.[104]

Mechanism of action

Zinc regulates the pathways of neurogenesis, neurotransmitter, and endocrine. Zinc ions serve as neurotransmitters in the cortex and the hippocampus and control synaptic

transmission,[105] altering voltage- and ligand-gated ion channels.[106] Zinc has an impact on serotonergic receptors producing antidepressant-like characteristics, which are seen in both preclinical and clinical investigations[102] and also linked to the endocrine pathway of depression is zinc insufficiency. The antioxidant and anti-inflammatory qualities of zinc augmentation may also contribute to the depressive properties of zinc. Previous research has shown that humans' CRP levels are reduced by zinc supplementation.[107] Zinc has preventive properties against lipid peroxidation.[108] Current research confirms the link between serious depression and lipid peroxidation,[109] indicating that zinc's antioxidant actions contribute to its observed antidepressant benefits. Finally, zinc's role as an antagonist of the glutamatergic N-methyl-d-aspartate (NMDA) receptor and its participation in the l-arginine-nitric oxide pathway as a nitric oxide synthase inhibitor may be related to its putative antidepressant qualities. Since glutamate homeostasis and neurotransmission are impaired in depressed individuals, the therapeutic targeting of NMDA has been applied in depression treatment during clinical and preclinical trials.[110]

Magnesium

More than 300 enzyme processes in the body of humans contain magnesium, making it a crucial component. One of its many functions is controlling blood pressure, helping to maintain healthy muscle and neuron function, and enhancing the immune system.[111] Avocados, nuts (almond, cashew, and Brazil nuts), legumes, seeds (pumpkin, flax, and chia), bananas, whole grains, fatty fish, and leafy greens are foods high in magnesium.[112]

The link between magnesium and depression

Depression development has also been connected to low levels of magnesium. Magnesium contributes to the control of NMDA glutamate receptor activity in the brain. Glutamate is an excitatory neurotransmitter that is important for normal function in the brain. Cells may become overstimulated if it is used excessively, though. Anxiety and depression are also associated with high levels of glutamate. Magnesium inhibits glutamate's effects on NMDA receptors. Cell injury and overexcitation may result from this. Magnesium may therefore be helpful in the treatment and prevention of depression.[113]

Mechanism of action

Magnesium modulates response to stress and is one of the potential mechanisms for magnesium's antidepressant effects. Magnesium can inhibit the overactivation of the HPA axis by modulating adrenocorticotropic sensitivity to ACTH and lowering the secretion of adrenocorticotrophic hormone (ACTH). Dysregulated HPA activity and high levels of cortisol are significantly observed in depressed patients, and irregular regulation of the HPA axis in adults has been strongly associated with depression and stress.[114]

Magnesium's function in the gut microbiota (GM) has recently attracted attention since changes in GM have been associated with mood disorders.[115] In addition, fluctuations in the inflammatory and oxidative response, indicated by an increase in cytokines and indicators of cellular stress, have been connected to modifications caused by magnesium in the microbiota.[116] By contributing to serotonergic and dopaminergic neurotransmitters and increasing BDNF expression, magnesium may also have antidepressant effects[117] and regulation of the sleep-wake cycle through augmentation of the production of melatonin.[118]

Proteins

It is a vital component of every diet and a component of every body cell. It aids the body's cellular and tissue repair and growth. One of the three macronutrients the body needs in larger amounts is protein. Twenty amino acid long chains make up its structure[119] (Brazier, 2020). Soy products, legumes, seeds, eggs, seafood, legumes (beans and peas), nuts, lean meats and poultry, and dairy products are all natural sources of protein (milk, cheese, and yogurt).[119]

The link between protein and depression

A protein diet helps build important neurotransmitters that fight depression and anxiety because it contains amino acids. Protein-rich foods can aid with energy levels, giving you the drive to move around and feel better. Amino acids, which are the building blocks of protein, play a significant function in the creation of neurotransmitters. The brain uses chemicals known as neurotransmitters to converse with each other. As an illustration, when someone eats protein-containing food, the body digests the protein and produces dopamine from the amino acid L-tyrosine. Several illnesses, including depression, are linked to reduced dopamine levels. Tryptophan, an amino acid included in dairy products, poultry, nuts, and fish, acts as a precursor to serotonin. The consumption of foods that contain high levels of L-tryptophan can enhance mood and boost the efficacy of antidepressants such as selective serotonin reuptake inhibitors.[120]

Mechanism of action

Tryptophan, an important amino acid that the brain uses to make serotonin, is known to be present in proteins. Reduced levels of the neurotransmitter serotonin are known to cause depression and are linked with depression in the brain. Foods high in protein help the brain produce more serotonin.[10]

Probiotics

Probiotics are living bacteria that, by supporting a healthy digestive system, may be able to prevent and treat several diseases. They are also frequently referred to as beneficial, healthy, or friendly bacteria. Beverages, foods, and dietary supplements can all include probiotics.[121] Certain products

made from maize, cassava, yam, millet, soybeans, and locust beans can also serve as sources of probiotics.[122]

The link between probiotics and depression

Studies have revealed a close relationship between the gastrointestinal system, and the brain, also known as the GBA. It connects the gastrointestinal tract to the central nervous system, which contains the spinal cord and brain. By creating and expressing neurotransmitters that might influence feeling, hunger, or sleep patterns and by lowering inflammation in the body, which can contribute to depression, microorganisms in the gut, particularly probiotics, play a critical function in the GBA.[123]

Mechanism of action

It has been established that the GM can synthesize neurotransmitters such as GABA, glutamate, serotonin, dopamine, norepinephrine, histamine, and acetylcholine.[124] In addition, it protects against depression through its anti-inflammatory function.[125] It has been demonstrated that probiotics have anti-inflammatory capabilities by either unswervingly reducing the plasma concentration of proinflammatory cytokines or by inhibiting the pathway of kynurenine and reinstating gut permeability, both of which have been connected to depression etiopathology. It has been demonstrated that administering probiotics can increase and restore the amounts of the neurotransmitters of interest, including 5-HT, GABA, dopamine, and norepinephrine, which have been linked to the development of depression.[126] Through the decrease of cortisol level, a stress biomarker in human patients, and cortisone level in animal models of depression, the role of probiotics in the improvement of the hyperactive HPA-axis linked to depression has been demonstrated[127] and a change in the HPA-axis-related neurotransmitter circuitry.[128]

Conclusion

For patients with depression and anxiety, nutritional psychiatry is becoming a viable option for treatment management. Healthy eating habits such as the Mediterranean diet or avoiding items that cause inflammation seem to offer some protection against depression. Nutritional psychiatry fills this gap by giving patients helpful, actionable instructions, and it has the possibility to be a potent tool for doctors and other health-care professionals. The GBA, a channel for information between the brain and the gut, is important in psychiatric disease and aids in our understanding of the relationship between disease and nutrition.

Patient informed consent

There is no need for patient informed consent.

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Author contribution subject and rate

- Ekpo Ubong Udeme (40%): developed the idea, drafted the outline, drafted the manuscript, and edited the manuscript
- Uduak Emmanuel Umana (30%): edited, revised, and organized the manuscript
- Abubakar Adamu Sadeeq (30%): edited, revised, and organized the manuscript.

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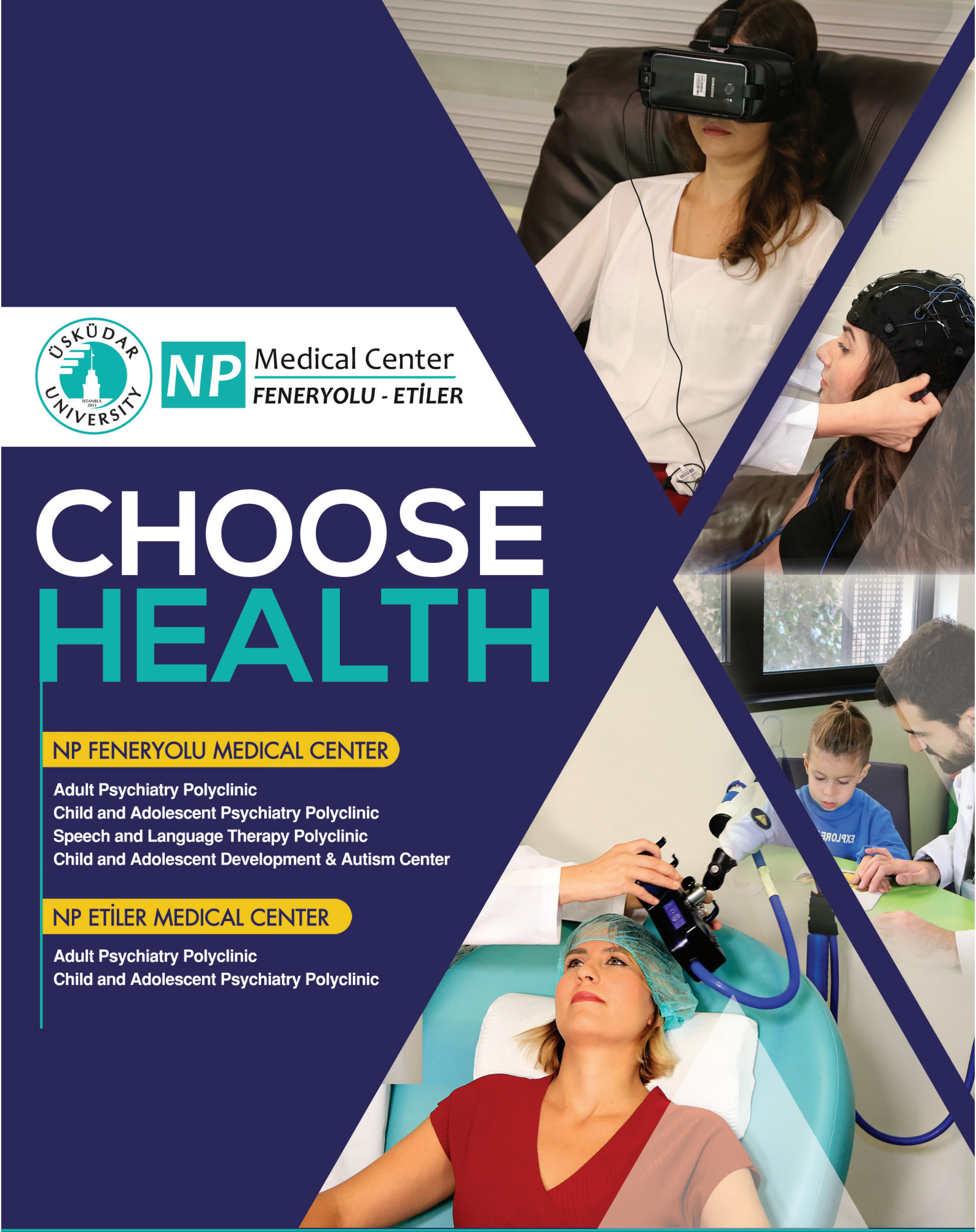

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