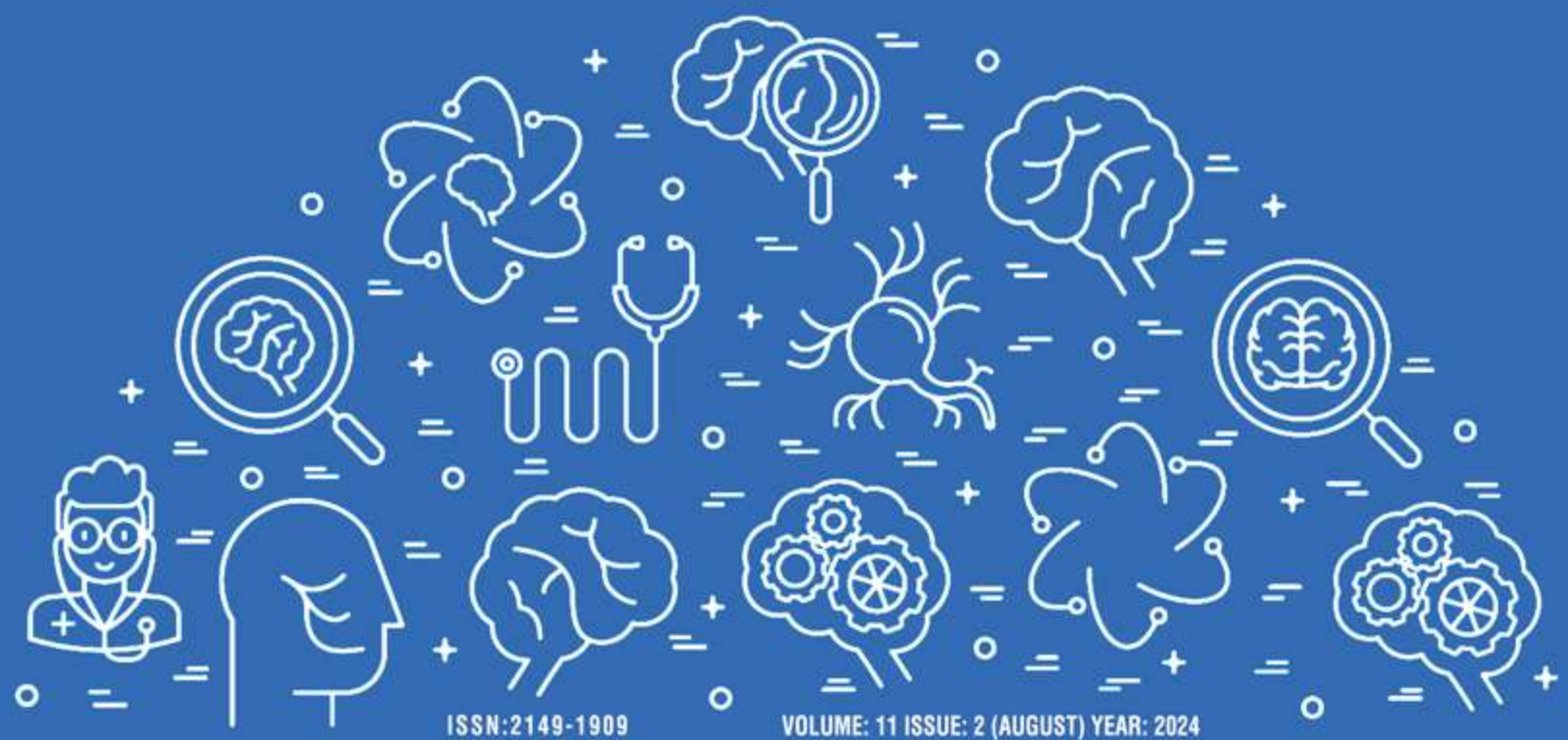

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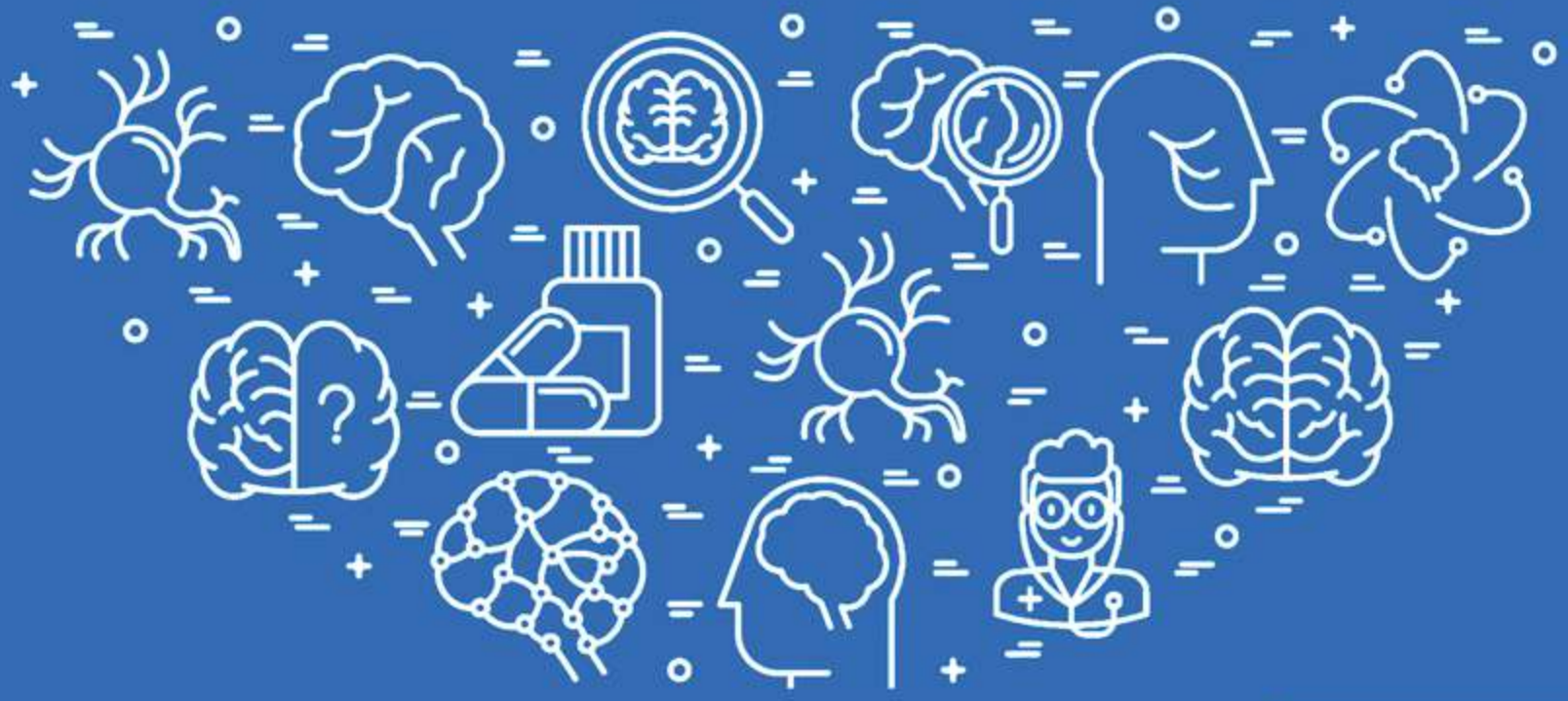
THE JOURNAL OF NEUROBEHAVIORAL SCIENCES

NEUROPSYCHIATRY STUDIES



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ABOUT THIS JOURNAL

Publication Policy
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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. Preclinical 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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- Neurophysiology
- System neuroscience
- Molecular neuroscience
- Computational Neuroscience
- Neuromodulation, Neurolinguistic, Neuromarketing
- Biochemistry
- Computational and simulation methods and interdisciplinary applications in medicine
- Artificial Intelligence (AI) and interdisciplinary applications in medicine
- Brain imaging
- In vivo monitoring of electrical and biochemical activities of the brain
- Molecular Biology
- Genetics
- Bioinformatics
- Psychiatric Nursing

INSTRUCTIONS FOR AUTHORS
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.

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Submit manuscripts electronically (.doc format with including all figures inside) via the online submission system of our website (https://dergipark.org.tr/en/pub/jnbs).

> Prof. Dr. Turker Tekin Erguzel, Ph.D Co-Editor, Journal of Neurobehavioral Sciences Department of Psychology Uskudar University Altunizade Mh., Universite Sk No: 14, İstanbul-Turkiye

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)

Cover Letters
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;

*The proposed category under which the manuscript was submitted;

*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;

*That APA style (Publication Manual, 6th edition) has been followed;

*The disclosure of any conflicts of interest with regard to the submitted work;

*A request for masked review, if desired, along with a statement ensuring that the manuscript was prepared in accordance with the guidelines above.

*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.

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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.

Select MathType or Equation Editor 3.0 in the drop-down menu.

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

Graphics files are welcome if supplied as Tiff, EPS, or PowerPoint files. Multipanel figures (i.e., figures with parts labeled a, b, c, d, etc.) should be assembled into one file.

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

PUBLICATION ETHICS AND PUBLICATION MALPRACTICE STATEMENT (ETHICAL GUIDELINES FOR PUBLICATION)

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.)

Reporting standards

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

Authors may be asked to provide the raw data in connection with a paper for editorial review, and should be prepared to provide public access to such data (consistent with the ALPSP-STM Statement on Data and Databases), if practicable, and should in any event be prepared to retain such data for a reasonable time after publication.

Originality and plagiarism

The authors should ensure that they have written entirely original works, and if the authors have used the work and/or words of others, that this has been appropriately cited or quoted.

Plagiarism takes many forms, from 'passing off' another's paper as the author's own paper, to copying or paraphrasing substantial parts of another's paper (without attribution), to claiming results from research conducted by others. Plagiarism in all its forms constitutes unethical publishing behavior and is unacceptable.

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Proper acknowledgment of the work of others must always be given. Authors should cite publications that have been influential in determining the nature of the reported work. Information obtained privately, as in conversation, correspondence, or discussion with third parties, must not be used or reported without explicit, written permission from the source. Information obtained in the course of confidential services, such as refereeing manuscripts or grant applications, must not be used without the explicit written permission of the author of the work involved in these services.

Authorship of the paper

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.

Examples of potential conflicts of interest which should be disclosed include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. Potential conflicts of interest should be disclosed at the earliest stage possible.

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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The editor of a peer-reviewed journal is responsible for deciding which of the articles submitted to the journal should be published, often working in conjunction with the relevant society (for societyowned or sponsored journals). The validation of the work in question and its importance to researchers and readers must always drive such decisions. The editor may be guided by the policies of the journal's editorial board and constrained by such legal requirements as shall then be in force regarding libel, copyright infringement and plagiarism. The editor may confer with other editors or reviewers (or society officers) in making this decision.

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Disclosure and conflicts of interest

Unpublished materials disclosed in a submitted manuscript must not be used in an editor's own research without the express written consent of the author.

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Editors should require all contributors to disclose relevant competing interests and publish corrections if competing interests are revealed after publication. If needed, other appropriate action should be taken, such as the publication of a retraction or expression of concern.

It should be ensured that the peer-review process for sponsored supplements is the same as that used for the main journal. Items in sponsored supplements should be accepted solely on the basis of academic merit and interest to readers and not be influenced by commercial considerations.

Non-peer reviewed sections of their journal should be clearly identified.

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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.

Duties of reviewers

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Contribution to editorial decisions

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.

Promptness

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.

Acknowledgement of sources

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: 11 | Issue 2 | April-August 2024

Contents

Repeated benzodiazepines ingestions affected behavioral and neurochemical profiles, with mild effect on histological integrities: modulatory efficacy of Nigella sativa oil

Abstract

Background: Benzodiazepines (BZDs) are a class of depressant drugs that have enjoyed widespread use in conventional clinical management of anxiety-related conditions such as panic disorders that require therapeutic central relaxation and sedation. Meanwhile, prolonged administration of benzodiazepines even at low doses has however been linked to variety of undesirable effects such as discontinuation relapse with the associated risk of abuse and dependency. **Aim:** This study investigated the behavioral, histological and biochemical outcomes of long-term low dose diazepam use and explored the potential role of nigella sativa oil (NSO) in the amelioration of the associated side effects. **Methods:** Adult Wistar rats (n=32) were randomized into four groups that received normal saline; diazepam; diazepam + NSO; or NSO only, respectively for 14 days. At the end of the period of the various exposures, the rats were taken through behavioral paradigms after which they were sacrificed for chemical and histological profiling. **Results:** diazepam-exposed rats exhibited stress-related manifestations with relatively poor performance in memory-related tasks. Repeated diazepam ingestion reduced brain antioxidant biomarkers while causing elevation of brain oxidative stress markers. On histological observation, mild degenerative changes were evident in the various brain regions of the diazepam-exposed rats. **Conclusion:** Interventional nigella sativa oil administration showed therapeutic potentials by mitigating and reversing the observed effects of diazepam, largely due to its antioxidant and anti-inflammatory effects as observed in the present study.

Keywords: Benzodiazepines, memory, behavior, oxidative stress, inflammation.

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Introduction

The pharmacologic benefits of benzodiazepines (BZDs) as psychoactive drugs in the clinical management of sleep disorders[1], epilepsy, and anxiety[3, 4] has contributed to their popularity. In the central nervous system, benzodiazepines work as positive allosteric modulators that bind to GABAA receptors, inducing conformational alterations that increase affinity for the GABA molecule, and enhancing GABA-induced neuronal hyperpolarization[2,5]. However, long-term use of BZDs presents concomitant major health risks such as addiction and dependence[1, 6], thereby increasing its potential for abuse and co-abuse with opioids and alcohol. BZD abuse has been associated with cognitive decline[7], hypothermia, respiratory suppression, coma, and death [4,8]. Typical of sedatives, they inhibit locomotor activity to varying levels leading to a higher incidence of falls and making the operation of machinery and vehicles potentially hazardous[8]. Benzodiazepines are frequently found in post-mortem blood samples of heroin users and in those related to overdose of other opioid substances where they appear co-administered to potentiate opioid effects[8]. Despite the level of awareness of the detrimental effects of BZD abuse, an estimated 3% of adults are still thought to have used BZDs for at least six months at some point in their lives[6], a significant portion of which may be without appropriate medical prescription. In rodents, BZD use has been associated with decreases in cerebral blood flow, decreases in caudate nucleus size, increases in lateral ventricular size[8], and decreases in dendritic spine density in pyramidal neurons. However, the mechanism by which BZDs exact these changes in the brain remains elusive[7]. The potential for benzodiazepine usage to cause certain detrimental effects is thus established, it, therefore, becomes imperative to discover and develop antidotes to counter these effects and save lives. Acting through GABA receptors, diazepam, like other BZDs, increases the levels of GABA in the brain through which it perpetuates its calming effect on the central nervous system. Therefore, prolonged diazepam use for longer than four weeks is not recommended. Following a strong caution by Penninx et al[7] against prolonged use of benzodiazepines as monotherapy in the management of anxiety and other related disorders with the subsequent recommendation that it be used only as a short-term adjunct, Nardi et al [8] claim that when carefully and judiciously prescribed, benzodiazepines are effective and well toler-

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Ethics committee approval: Ethics committee approval: Ethical review and approval for this study was granted by the Ethical Review Committee of the Faculty of Basic Medical Sciences on 21.04.2017, University of Ilorin, with reference number UIL/UERC/AN2074.

ated. In a similar effort, Dubovsky and Marshall [9] criticized data presented in the literature as involving conflict of interest. According to Silberman et al [10], there is an overestimation of the rate of abuse and dependence among patients without previous record of substance abuse while also concluding that dose escalation is not necessary for long-term therapeutic benefits. Hirschtritt et al [11] also opined that benzodiazepines are a safe and effective option for the management of anxiety disorders following necessary screening of patient for a history of substance abuse, active opioid medications, cognitive impairment and age above 65 years, all of which contribute to negative outcomes. Likewise, Prashant et al [12], in contradistinction to findings by Penninx et al[7], suggests the possibility of bias reporting in favor of the risks against the therapeutic benefits of benzodiazepines. Nigella sativa oil (NSO) has been shown to prevent or reverse indications of neurological damage induced by various neurotoxins such as agricultural organophosphates in healthy rodent brains[13, 14]. NSO contains thymoquinones, riboflavin, and alkaloids as some of its bioactive ingredients which confer neuroprotective properties amongst a host of other pharmacological functions[13, 14]. The specific mechanism of action of NSO has not been fully elucidated but is thought to be linked to its antioxidant and anti-inflammatory properties[13, 14]. This study aims to determine the specific determinable histological, biochemical, and behavioural changes of prolonged BZD (diazepam) use in rats and the potential for NSO to prevent or reverse them. Here, we show that prolonged oral ingestions of diazepam surprisingly affected neurocognitive phenotypes with its central mechanism of toxicity being oxidative stress and inflammation. Meanwhile, a post-exposure intervention with the oil of nigella sativa markedly restored the affected psycho-cognitive behaviors induced by diazepam, majorly by preserving the intrinsic antioxidant and anti-inflammatory defense architectures in the exposed brains.

Materials and methods

Ethics committee approval: Ethical review and approval for this study was granted by the Ethical Review Committee of the Faculty of Basic Medical Sciences on 21.04.2017, University of Ilorin, with reference number UIL/UERC/AN2074.

Study subjects

This study used adult male Wistar rats (N = 32) (100 g – 120 g) obtained from the murine breeding centre in Ogbomosho, Oyo State, Nigeria, and housed in the animal facility of the Faculty of Basic Medical Sciences, University of Ilorin in accordance with the university's Guide for the Care and Use of Laboratory Animals. There was an acclimatization period of seven days during which animals were allowed free access to food and water.

Experimental Design

Experimental animals were assigned randomly as follows; n = 8 animals each in four groups (I - IV) with each group treated as accordingly. Group I received 1 ml of normal saline /kg/day; Group II received diazepam at 2 mg/kg/day only; Group III received diazepam at 2 mg/kg/day with NSO at 1 ml/kg/day; and Group IV received NSO at 1 ml/kg/day only. Oral administration was done once in a day for fourteen consecutive days.

Assessment of behavior and memory

Morris water maze procedure

The Morris water maze (MWM) was used to assess the spatial, long-term (LTP) and short-term (STM) memories in a standardized black pool filled with 23 ˚C – 24 ˚C water with dimensions 60 cm depth X 136 cm diameter. The pool was divided into quadrants and had a submerged circular platform. Standard MWM protocols were followed[10] and trials were recorded by video system. Trial sessions were given on days 11, 12 and 13. On day 14, the LTM was assessed using the escape latency, duration in seconds to navigate to the hidden platform while the STM was recorded as the average escape latencies of two subsequent trials. After removal of the hidden platform, the percentage time spent in the platform quadrant constituted reference memory (RM).

Open field test procedure

All rats were placed in a standardized well-lit box whose floor was divided into 4 X 4 squares and observed for exploratory, locomotor and anxiety-related behaviors. Time spent in the centre before the commencement of motion (freezing time), the number of lines crossed within the testing period (line crossing frequency). Anxious rats are less mobile and will also tend to avoid the central squares.

Biochemical evaluations

Brain tissues harvested from each group were treated in 30% sucrose solution after which they were homogenized (100 Mm Tris-HCl [Ph 7.6]) in 0.1 M DDT) and centrifuged at 2500 revolutions per minute for 10 min, and the resuting supernatant was collected into labelled tubes for various assays.

Glutathione (GSH) Assay

Supernatant from homogenate of previously frozen brain samples was used for the assay following instructions from the reagent kit while the concentrations of reduced and oxidized glutathione in fixed quantity of the brain tissue were calculated and expressed as µmol of GSH/mg protein.

Quantification of Malondialdehyde (MDA)

Malondialdehyde as marker of lipid peroxidation shows the rate of degradation of polyunsaturated fatty acids that are typical of neuronal membranes. Through its reaction with thiobarbituric acid (TBA) in the form of thiobarbituric acid reactive substance (TBARS), the quantity of MDA is derived from the amount of TBARS due to their MDA-TBA (1:2) adduct product of their reaction. The concentration of TBARS was determined according to a method of Mihara and Uchiyama and was expressed as nmol/mg of protein.

Quantification of Superoxide dismutase activity (SOD)

Superoxide dismutase activity is increased in situations of exposure to oxidative stress in the cells which induces rapid synthesis of the enzyme. The antioxidant enzyme breaks down (dismutates) reactive oxygen species-derived superoxide radicals into hydrogen peroxide and molecular oxygen which is its mechanism of defense against cellular toxicity of superoxide radicals. This SOD activity assay is based on the rate of inhibi-

tion of nitroblue tetrazolium (NBT) in the biochemical reaction where SOD competes with NBT for the superoxide radical generated by the xanthine-xanthine oxidase.

Immunohistochemical evaluations

Tumor necrosis factor alpha (TNF-α) quantification assay

The principle of TNF- α assay is based on an immunoassay technique that uses TNF-α–specific (anti-TNF-α) antibody. The presence of TNF-α is then determined by its binding to the anti-TNF-α antibody which has been mobilized in a microplate. TNF-α is a marker of inflammation which assay is used to determine the presence or progression of inflammation and proliferation of tumor cells.

Interleukin-10 (IL-10) assay

IL-10 is an anti-inflammatory cytokine that is used as a marker for inflammatory and autoimmune pathologies due to its role in the prevention of these cellular events. Hippocampal tissue homogenate was centrifuged at 14,000 x g at 4˚C for 20 minutes and sandwich ELISA was performed (BioSource International, Camarillo, CA) with the limits of detection at 25 pg/ml, following manufacturer's instructions.

Nitric Oxide (NO) assay

The level of NO in the brain homogenate was measured with Griess reagent in the form of nitrite. The Griess protocol which was performed per manufacturer's instruction is a two-step reaction during which nitrite is reduced to nitrogen oxide which then reacts with a second reagent that ends in a stable product detectable at 540 nm absorbance.

Tissue processing and Histology

Alcohol dehydrated brain tissues were processed through xylene to provide tissue transparency and subsequently paraffin embedded. Serial sectioning of the whole brain at 5 µm was done followed by staining with Cresyl violet for Nissl substance.

Statistical Analysis

Behavioural and biochemical data was analysed using one-way analysis of variance (ANOVA) followed by a *post hoc* Bonferroni's multiple comparison test. Graphpad Prism software (version 5.0, La Jolla, CA) was used to obtain results expressed as mean ± standard error with $p < 0.05$ considered statistically significant.

Results

Diazepam led to poor cognitive and motor behaviors

Marked reduction in line crossing frequency in the open field assay was recorded in animals that were given BZD. Meanwhile, this trend was significantly reversed by treatment with NSO as higher line crossing frequencies was observed in the intervention group compared to the BZD exposed rats (Figure 1A). The freezing period of the BZD rats was increased beyond that observed in the control rats but co-administration with NSO marginally reduced it to levels comparable with the controls (Figure 1C).

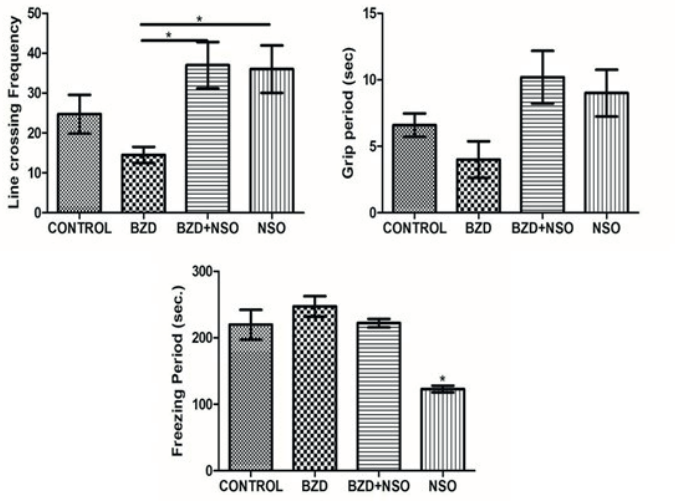

Figure 1: Motor and Anxiety-like behaviors in rats after exposure to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil. Single asterisk (*) indicates significant (p≤0.05) increase or decrease from the control and or other groups

Short- and long- term memory (STM and LTM) behavioural assay as quantified by escape latency in the MWM showed delayed escape latencies for the BZD exposed rats while NSO treatment in co-exposed and sole ingestion rats caused reduction in the latency to find the hidden platform, when compared with the BZD exposed rats (Figure 2A). Reference memory (RM) was quantified by the amount of time spent in the platform quadrant after the platform was removed. We observed that BZD exposure does not affect the time that the rats spent around the quadrant region compared to control. Nonetheless, reference memory was evidently improved by the ingestions of NSO, either in co-exposure or NSO only, as the rats in these groups had higher platform latency relative to the BZD and control (Figure 2C).

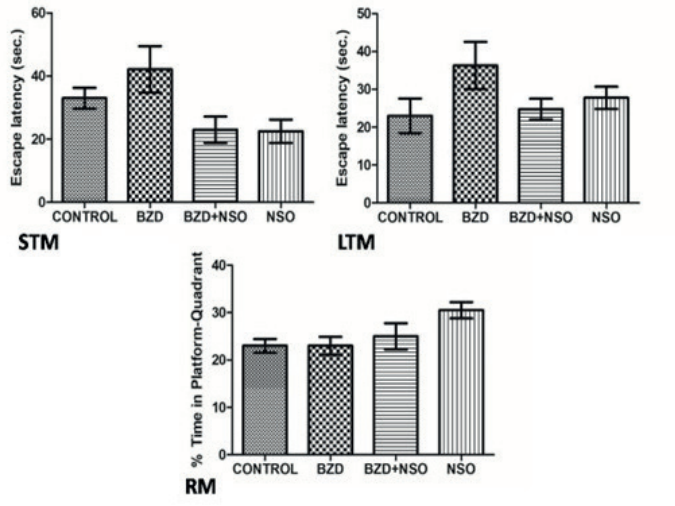

Figure 2: Memory indices in rats after exposure to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

Benzodiazepine uptake reduces glutathione redox activity

Exposures to BZD did not affect the brain concentrations of reduced glutathione (GSH) which is a trend observed across all the test and control rats. However, in contrast to what is observed in GSH, the brain concentrations of other glutathione isoforms (glutathione peroxidase, glutathione S-transferase, and glutathione reductase) were depleted following BZD exposure, although only GST was significant (Figure 3). Interventions with NSO shows a statistically significant potential for enhanced antioxidant ability by boosting the concentrations of GPX, GST and GR in the brains of the treated rats ($p<0.05$) (Figure 3).

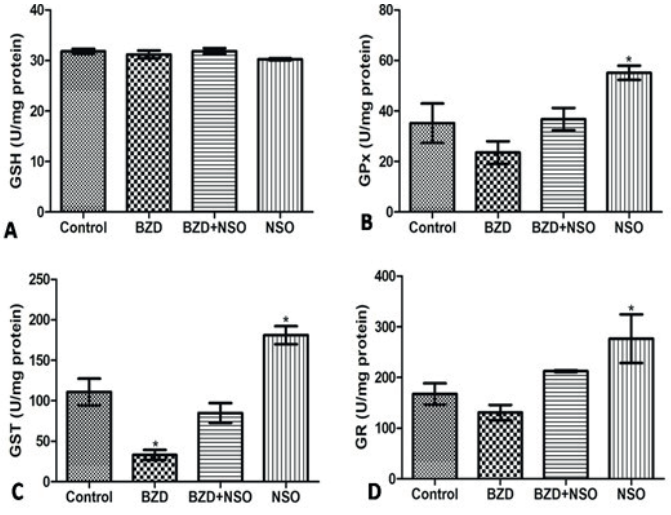

Figure 3: Glutathione redox activities in rats exposed to diazepam and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil. Single asterisk (*) indicates significant (p≤0.05) increase or reduction from control and or other groups.

Benzodiazepines elevate levels of oxidant and pro-inflammatory markers

Significant reduction in total antioxidant capacity was evident in BZD treated rats but which was elevated NSO exposed rats, albeit to non-statistically significant levels. This is supported by observations of elevated levels of ROS, MDA and SOD accompanied by reduced levels of catalase in BZD treated rats (Figure 4). The levels of ROS were rather indistinguishable in the BZD+NSO and NSO groups (Figure 4B), however additional parameter comparison between the two groups showed lower levels of MDA and SOD (Figures 4C and 4D) and higher levels of catalase in the NSO group (Figure 4E). NSO clearly improved the total antioxidant capacity and marginally lowered ROS and MDA relative to the BZD group. The levels of some pro- and anti-neuroinflammatory markers, cytokines and chemokines released by activated macrophages and astrocytes, were investigated. Elevated concentrations of TNF-α in the BZD treated group ($p < 0.05$) were consistent with increased likelihood of ongoing inflammatory processes. Nitric oxide (NO) levels were maintained at near control rat levels as contrasted with the drastically lowered levels observed in the rats exposed to NSO in both the NSO and BZD+NSO groups providing credence to the NO reduction effect of NSO. Interleukin-10 (IL-10) levels were however lowered in the BZD group and markedly elevated ($p\leq0.05$) in the NSO group, indicative of greater anti-inflammatory potential in the latter group (Figure 5).

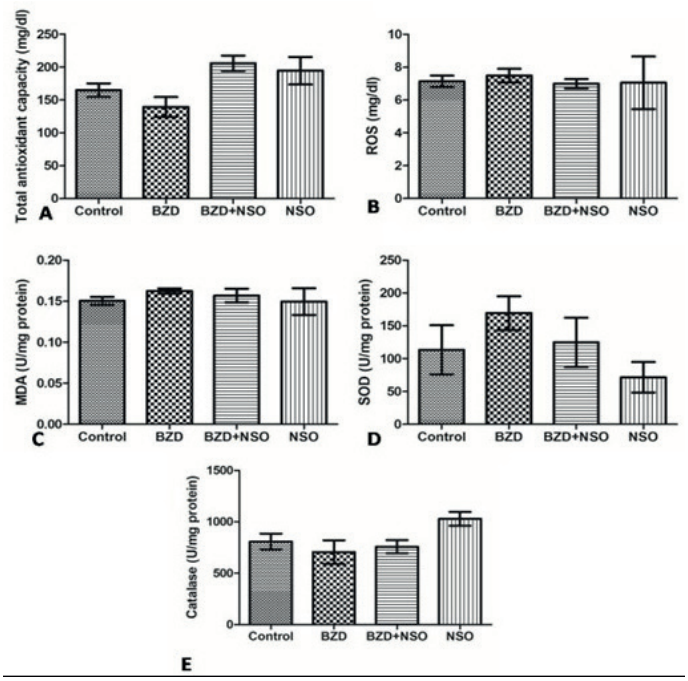

Figure 4: Antioxidant, oxidative and lipid peroxidation markers in rats exposed to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

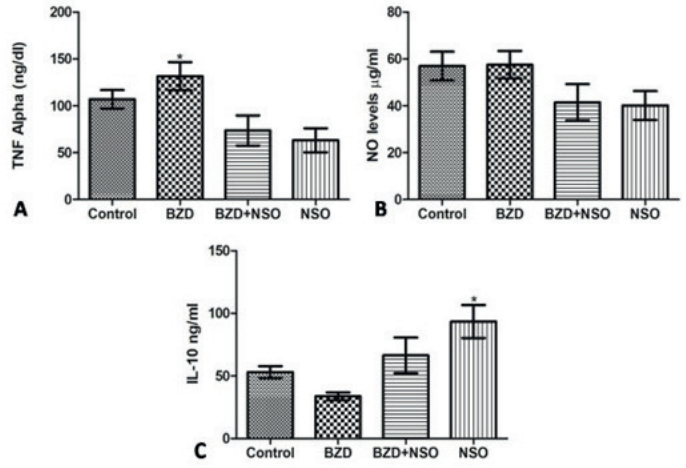

Figure 5: Pro and anti-inflammatory markers in rats exposed to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil. Single asterisk (*) indicates significant (p≤0.05) increase from the control and or other groups.

Benzodiazepine uptake diminished neurotransmitter levels to varying extents

The levels of the inhibitory neurotransmitter, gamma aminobutyric acid (GABA), the receptor of which is acted upon by BZDs, were depleted in the BZD exposed group (Figure 6A) but markedly elevated above normal levels in the NSO group. Similarly, acetylcholine (ACh) levels though depressed in BZD exposed animals were significantly increased in the BZD+NSO and NSO groups (Figure 6B). Co-administration of BZD and NSO had a more profound recoil effect on the ACh levels than on GABA. The levels of catecholamines and monoamines were reduced in the BZD groups but consistently elevated in the NSO only groups (Figure 7). Concentrations of serotonin

and dopamine in the BZD+NSO group were higher than in the control rats whereas lower levels of noradrenaline were recorded (p>0.05).

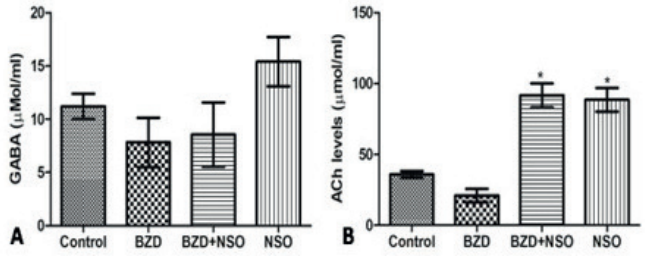

Figure 6: GABA and ACh levels in rats after exposure to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil. Single asterisk (*) indicates significant (p≤0.05) increase from the control and or other groups.

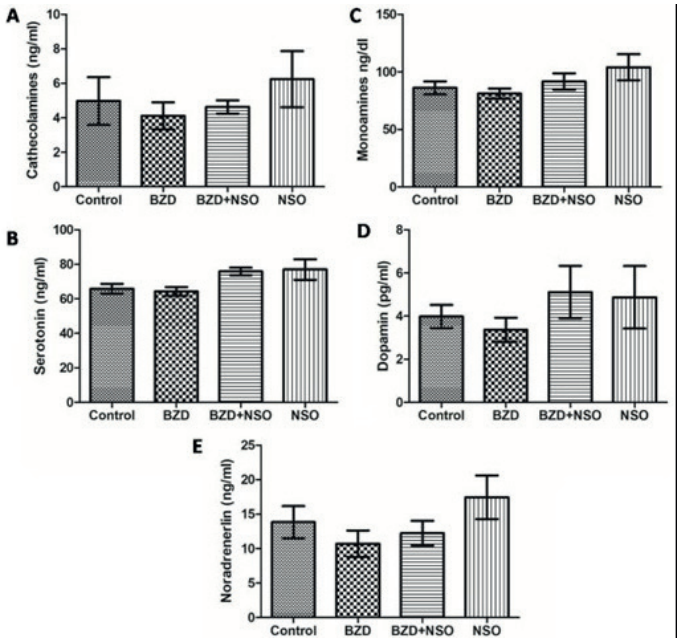

Figure 7: Catecholaminergic neuromodulators in rats following exposure to benzodiazepine and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

Benzodiazepine administration increases neuronal metabolism and apoptosis

Caspase 3 and GLUT 4 levels were relatively elevated in the BZD administered group which contrasted with those observed in the NSO group that demonstrated lower levels than those observed in the controls (Figure 8). The co-administration of NSO with BZD lowered caspase 3 levels to a much larger extent than observed with GLUT 4.

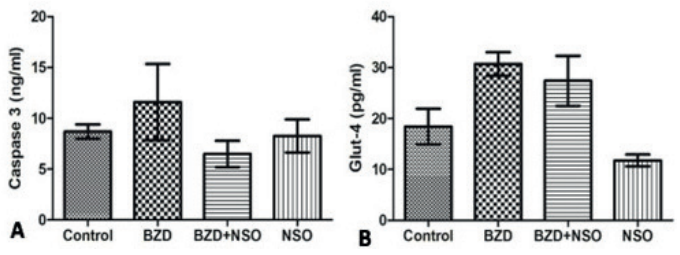

Figure 8: Caspase 3 and Glut-4 levels in rats exposed to benzodiazepine and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

Histoarchitecture of various brain regions

Degenerative changes, although mild, were evident in all parts of rat brains exposed to BZD (Figures 9 - 11). Cells in the motor cortex and putamen appear lighter stained and larger with apparent intracellular vacuoles after treatment with BZD, compared to the controls (Figure 9). The stain intensity in the brain regions show a qualitative increase after the ingestion of NSO. Purkinje cells were fewer and more dispersed in the cerebella of BZD rats but were clearly more numerous and closely packed in the control rats but more loosely packed in the BZD+NSO rats. Individual cell boundaries of the hippocampal regions were less distinct in the BZD group as well as fewer cells in the hilar region than any of the other groups.

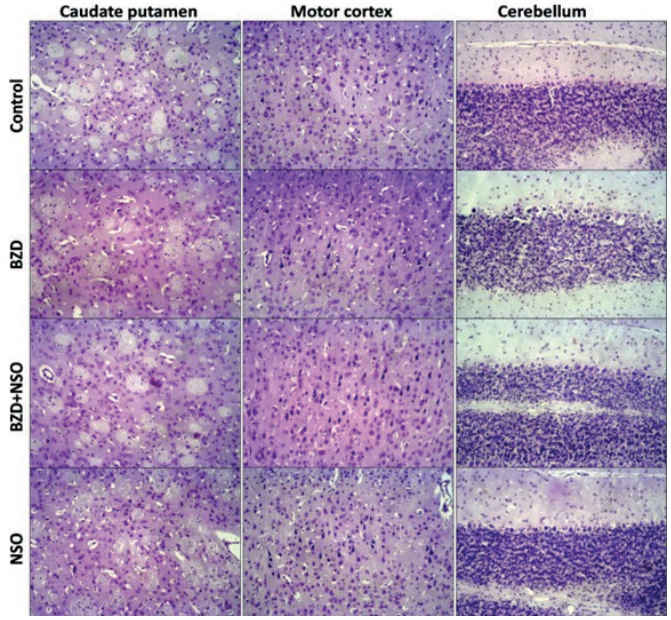

Figure 9: Representative photomicrographs of the caudate putamen, primary motor cortex and cerebellum of rats exposed to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

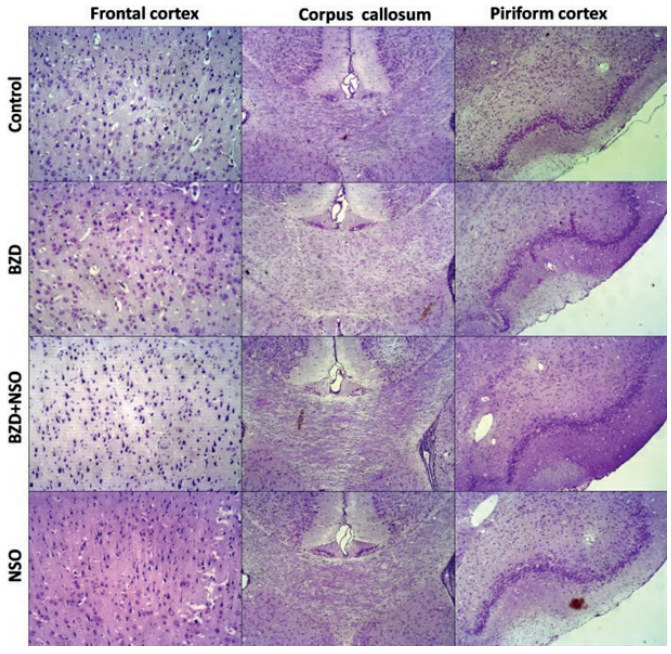

Figure 10: Representative photomicrographs of the frontal cortices, corpus callosum and the piriform cortices of rats exposed to benzodiazepines and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

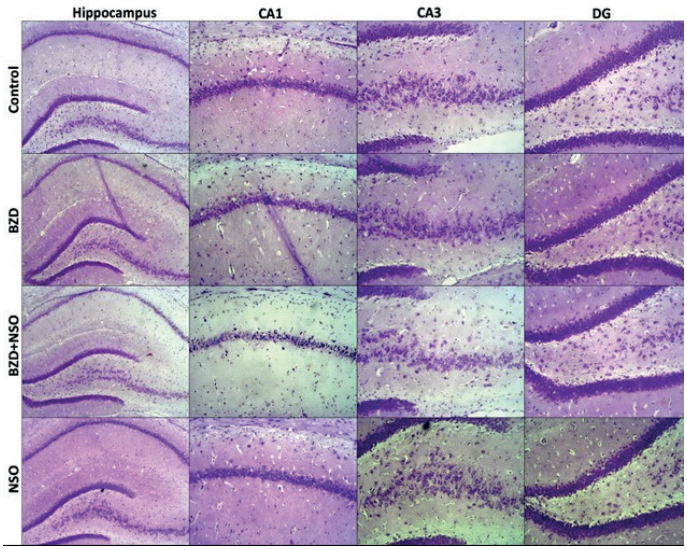

Figure 11: Representative photomicrographs of the hippocampus of rats exposed to benzodiazepine and Nigella sativa oil. Control: Normal Saline, BZD: Benzodiazepine, BZD+NSO: Benzodiazepine + Nigella Sativa Oil and NSO: Nigella Sativa Oil.

Discussion

As highlighted by Griffin and colleagues[2] in their review on the beneficial pharmacological effects and clinical uses of BZDs in various pathological and postoperative states, the effects of BZDs are not always detrimental and undesired with some benzodiazepine derivatives exhibiting anti-inflammatory properties[17]. However, this study shows that prolonged intake of benzodiazepines even at a relatively low dosage may affect psycho-cognitive behaviors and related functions, and these effects may be associated to the marked reduction in antioxidant capacities, which was accompanied by non-proportional elevation of oxidative stress and neuro-inflammatory biomarkers coupled with imbalance in neurotransmitters concentrations in the brains of the exposed rats. Oxidation related stress and neuro-inflammation are associated with myriad of neurologic sequelae and are positively identified where neurotoxicity is suspected [18, 19, 20,15]. This study also showed that co-administration of NSO potentially alleviates or reverses the neurotoxic events generated by the long-term use of BZD.

The Morris water maze was used as a standardized assay of hippocampal-dependent learning memory in rodents, whereas, the open field test was used to assess motor activity and anxiety-like behaviors. The major observed behavioral changes in this study were the registration of significantly lowered memory indices quantified as short time, long time, and reference memory, as well as the drastic reduction in normal locomotor activity in the rats chronically subjected to BZD ingestion. These changes were like those observed in other experiments from our lab, where we exposed rats to low dosages of potentially neurotoxic chemicals [15,16], or those in which the antioxidant capacity of rodents was experimentally reduced [21, 19, 22]. These neurological, cognitive and motor findings were worrisome considering the ubiquity of BZD prescription and the further unregulated abuse of the same by people that have developed dependence and addiction.

The direct effects of BZD use could account for some of these observations, as BZD activity characterised by binding to the BZ1 is associated with anterograde amnesia and possibly poor performance where memory tests are concerned [2]. Central inflammatory responses also lead to "sickness behavior" characterised in part by reduced locomotor and social activities. Paradoxically, BZD in short-term use is useful as an anxiolytic in the management of anxiety and social avoidance post social distress in rodents [3]. Here, rats exposed BZD were observed with fear or anxiolytic-like behaviors and reduced exploratory/locomotor abilities, as evidenced in the prolonged freezing periods and low line crossing frequencies in the open field test. These effects on motor and anxiety-like behaviors may in part be associated the recruitment of circulating peripheral monocytes into the CNS following chronic inflammation as reported above. Further credence to impaired behaviors of BZD-exposure is the reduced antioxidant activity, increased oxidative stress markers, increased inflammatory markers, altered neurotransmitters release and brain histoarchitecture in the exposed rats.

Repeated oral ingestions of BZDs reduces the brain's capacity for antioxidant activity as demonstrated by a reduction in GPx, GST and GR concentrations coupled with reduced total antioxidant capacity and catalase activity. Previous studies have confirmed the tendency for lowered antioxidant capacity to lead to inflammatory response and oxidative stress before the body's response mechanisms have had an adequate chance to engage compensatory changes [23]. Upregulation of genes associated with glutathione metabolism has been observed in the short-term post glutathione depletion event although it was not linked to an increase in GSH levels[23]. An actual compensatory elevation of GSH was previously reported 48 hours post depletion showing evidence of robust anti-inflammatory compensatory mechanisms in the brain[19, 24], however this was most probably due to their use of a once off depletion event rather than multiple repeated insults used in our study. GSH levels in our study remained rather low, yet it is a crucial element in the preservation and recovery of neurons faced by oxidative stress[25, 26, 27]. Furthermore, marginal increases in the levels of ROS and MDA in the BZD exposed rats provided further credence to the concept of suppressed antioxidant activity.

Surprisingly, a key antioxidant enzyme, SOD recorded elevated activity in BZD exposed rat's brain, probably as the body's compensatory mechanism in enhancing the depleted antioxidant activity from other chemical systems. This result may be buttressed with the finding obtained in Sprague-dawley rats 24 – 48 hours post single event depletion of GSH [19]. However, in our case this compensation could not re-establish balance as it may have led to the production of H_2O_2 while the downstream enzymes, GPx and catalase, for its neutralisation remained suppressed in activity. Zhang et al., 2018 [22] also observed reduced catalase activity in stressed rats although in their case, it was also coupled with lowered SOD activity. The lowered GPx and GST observed in this study thus rendered the BZD rats vulnerable to chronic oxidative stress and accompanying pathological changes. Synaptic dysfunction and depletion of neural connections associated with lowered antioxidant capacity are known to impair learning memory[19], as was observed in the behavioral manifestation of impaired memory and reduced locomotor activity of rats exposed to BZD in this study.

We have shown that prolonged use of benzodiazepines leads to sustained neurological insult that depresses the brain's protection against exaggerated neuroinflammation and oxidative stress.

This study also observed sustained high levels of pro-inflammatory markers. Elevation in inflammatory cytokines/chemokines has been widely associated with cognitive dysfunction, and as an integral event in the genesis of neurotoxicity, neurodegenerative diseases, and psychosis. TNF-α, a potent proinflammatory cytokine often used as an indicator of inflammation [28] was markedly elevated in BZD exposed rats. TNF-α binds to TNF receptor 1, initiating a cascade of chemical processes, part of which is cell death through the death domain in the tail end of this receptor. Nitric oxide which ordinarily is a vasodilator and anti-inflammatory molecule, is pro-inflammatory when produced in excess amounts. The production of such cytokines and secondary messengers by activated microglia and astrocytes function to initiate protective mechanisms for CNS tissue under normal physiological conditions but lead to undesirable chemical, pathological and physical changes when prolonged. Interleukin 10 (IL-10) being an anti-inflammatory cytokine plays a crucial, and often essential role in the prevention and remediation of inflammation and pathologies of autoimmunity post inflammatory insult [29]. The right amounts of IL-10 have to be present to exert delicate control moderating the extent neuroinflammation [30,31,32]. The suppressed levels of IL-10 coupled with depressed anti-inflammatory markers in the BZD exposed brains of this study provided a plausible cause for the relatively unchecked inflammatory response and resultant neurodegeneration.

Continuous use of BZD led to a reduction in the brain levels of GABA, an inhibitory neurotransmitter and neuromodulator that has a calming effect on the brain overall and has also been linked to improved memory and relief of mental stress[33,2,3,4]. A decrease in GABA levels is associated with the display of anxiety- and stress-like behaviors exemplified by fear to explore new surroundings, avoiding the central squares, keeping to the walls and generalised reduced locomotor activity. The concentrations of dopamine, serotonin and monoamines were reduced in all BZD rats, albeit not to statistically significant levels. The "biogenic amine hypothesis of depression" links low amine levels to depression and anxiety, and forms the basis of amine elevation in antidepressant management. Noradrenaline deficiency too is linked to certain forms of cognitive and memory impairments that involve projections from the locus coeruleus[35,36]. Lowered amines would thus disrupt the rats' ability to learn and recall resulting in poor memory-linked behavioural performances. Previous studies have demonstrated that anxious and neuroinflamed rats demonstrate suppressed exploratory behaviour [35, 15, 16], corresponding to lower line-crossing frequencies observed in the current study. Our study showed lowered levels of acetycholine in the BZD exposed rats, which was subsequently restored following interventional ingestions of NSO. Acetycholine (Ach) has been identified as essential in the learning memory processes being related to the cognitive deficits of dementias such as Alzheimer's disease (AD), with an increase in ACh levels has been shown to reverse some of the observed deficits [22].

Caspase 3 is a recognised marker that mediates programmed neuronal death (apoptosis) during embryological brain development and delays neuronal death following neurological insult such as during ischemic injury or traumatic brain injury [37; 38]. The levels of caspase 3 in the brains of BZD exposed rats were reasonably higher than those of controls. This depicts events during neuronal cell death in rats exposed to extended duration treatment with BZD. GLUT-1 is one of the transporters of glucose in capillaries supplying brain cells and thereby satisfying the energy demand of neurons in brain[39]. Depletion of this transporter results in the death of neurons due to starvation. In this study result, BZD significantly reduced the level of GLUT-1 in exposed rats, thereby leading to cell death. High TNF-α level as observed in the inflammatory result, is also associated with excitotoxicity, which is one of the potential mechanisms that can contribute to neuronal cell death.

The reduction in the levels of inflammation in rodent models after induction of brain injury is often associated with better functional recovery outcomes. The functional and behavioral outcomes investigated in this study were STM, LTM and RM in the MWM, and locomotor activity as determined by the open field test. It is evident that co-administration with NSO sub-served this role as rats in the BDZ+NSO group outperformed the BZD group in both the STM and LTM tasks. It can be concluded that administration of NSO which as an anti-oxidant and anti-inflammatory agent to the injured brain prevented development of psychological and behavioral phenotypes associated with CNS insult. The rats treated with NSO alone further excelled at the memory, locomotion and anxiety tasks compared to the control animals, and demonstrated lower oxidative stress and pro-inflammatory marker levels, further confirming the efficiency of NSO as an anti-oxidant and anti-inflammatory agent. This result corresponds with that of other studies showing the potency of NSO against oxidative stress and neuroinflammation-driven impaired memory and motor dysfunction[40; 16, 41, 42]. NSO also improved the levels of apoptosis markers; Caspase 3 and GLUT-1, thereby preserving the histoarchitecture of the brains treated with it. Various studies have reported the improvement of memory and locomotion with increased neurotransmitters activities[43,44,45]. NSO increased GABA, ACh, Catecholamine, Monoamine, Serotonin, and Dopamine neurotransmitters, when administered together with/without BZD, modulating the depleting effect of BZD on neurotransmitters levels, and generally improving their activity in exposed rats.

Conclusion

In conclusion, prolonged ingestion of low dose benzodiazepines leads to oxidative stress, neuro-inflammation with altered neurotransmitters levels and degenerative changes in the brain as evidenced by the reduction of antioxidant and anti-inflammatory biomarkers. These elevation of inflammatory markers of oxidative stress, and brain neurotransmitter level imbalance as well as various region-specific cyto-architectural alterations were observed across the brain. This leads to various manifestations of behavioral impairment, including impaired memory, impaired locomotion, and anxiety. Finally, interventional NSO demonstrated therapeutic potentials against BZD dependency-linked neurotoxicity affecting behavioural and psycho-cognitive abilities by offering improvements in the areas studied.

Patient informed consent: There is no need for patient informed consent.

Ethics committee approval: Ethics committee approval: Ethical review and approval for this study was granted by the Ethical Review Committee of the Faculty of Basic Medical Sciences on 21.04.2017, University of Ilorin, with reference number UIL/UERC/AN2074.

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Author contribution subject and rate:

Imam Aminu (20%): 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.

Kudirat Funmi Lambe-Oladeji (10%): Concept and design of the study, experimental studies, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

Abdulwasiu Taiwo Lawal (10%): Concept and design of the study, experimental studies, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

Oluwadamilola Eunice Ajibola (10%): Concept and design of the study, experimental studies, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

Samson Chengetanai (10%): Concept and design of the study, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

Musa Iyiola Ajibola (10%): Concept and design of the study, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

Ibrahim Abdulmumin (10%): Concept and design of the study, literature search, collection of data and analysis, analysis and interpretation of data, manuscript editing and review and final approval of the version to be published.

Moyosore Salihu Ajao (20%): 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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Thymoquinone Ingestions Reversed Inflammation Driven Glia activation and Impaired Cognitive associated Behaviour in Cypermethrin Exposed Rats

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Abstract

Background: Pyrethroids pose health risks to humans. Therefore, it is imperative to assess the preventive benefits of thymoquinone against neurotoxicity induced by cypermethrin- in the hippocampal dentate gyrus. **Methods:** Forty male adult Wistar rats with an average weight of 180-200g were randomly allocated to five (5) groups, and each comprising eight rats (n=8 per group). The groups were designated as follows, through oral administrations for 14 days: 0.5ml phosphate- buffered saline (PBS) was given to group one; Group two received 20mg/kg of cypermethrin (CYM); Group three received 10 mg/kg of thymoquinone (THQ); Group four received 20 mg/kg of cypermethrin followed by 10mg/kg of thymoquinone (CYM-10mgTHQ); and Group five received 20 mg/kg and 5mg/kg cypermethrin and thymoquinone respectively (CYM-5 mgTHQ). Behavioral, histological, immunohistochemical, and biochemical analyses were conducted post-treatment. **Results:** Cypermethrin administration caused the rise in pro-inflammatory cytokine TNF-α, Nuclear Factor-kappa B (NF-κB) and increased expression of astrocytes, microglia, and pro-apoptotic protein Bax. Additionally, cypermethrin reduced levels of anti-inflammatory cytokine IL-10 and acetylcholinesterase (AChE) activity. Cytoarchitectural disruption of dentate gyrus were observed. Cognitive deficits were evident. Thymoquinone treatment attenuated TNF-α and NF-κB elevation, reduced astrocyte, microglial, and Bax expression, and increased IL-10 and AChE. **Conclusion:** Thymoquinone demonstrated anti-inflammatory and anti-apoptotic effects against cypermethrin-induced neurotoxicity, improving cognitive function in rats.

Keywords: Pyrethroids, Astrocytes, Microglia, Dentate gyrus, NF-κB.

Introduction

Microglia play a major role in the protection and repair of neurons. However, over-activation of microglia in response to neuronal insult can lead to neuroinflammation, contributing to the progression of neurodegenerative disorders [1, 2, 3]. Prolonged microglial activation results in chronic neuro-inflammation, causing neuronal loss and ultimately neurodegeneration[4] partly due to the rise in pro-inflammatory cytokines and reactive oxygen species (ROS) [5,6].

In recent years, the widespread use of inorganic insecticides, such as pyrethroids, has raised concerns due to their adverse effects on neurological health [7,8,9]. Cypermethrin, a type II pyrethroid, is known for its neurotoxic effects, primarily through the prolonged opening of voltage-gated sodium channels (VGSC) [10] most insecticides commercially developed act on the sodium channel and the GABA system. Pyrethroids slow the kinetics of both activation and inactivation gates of sodium channels resulting in prolonged openings of individual channels. This causes membrane depolarization, repetitive discharges and synaptic disturbances leading to hyperexcitatory symptoms of poisoning in animals. Only a very small fraction (~1%, and its ability to move across the blood-brain barrier exacerbates its neurotoxicity [11] . Cypermethrin exposure has been linked with the rise of pro-inflammatory cytokines, TNF-α, IL-1, and apoptotic changes characterized by reduced Bcl2 levels and increased Bax expression [12].

Nigella sativa, has a long history of medicinal use and contains thymoquinone (THQ) as its primary active component [13,14]. THQ has demonstrated various medicinal properties, including anti-inflammatory and antioxidant effects, making it a promising candidate for neuroprotection [15,16]. THQ has been shown to mitigate oxidative and inflammatory damage in brain tissue by down-regulating pro-inflammatory cytokines, inhibiting lipid peroxidation, and preventing apoptosis [17]. Moreover, THQ exhibits neuroprotective effects by maintaining mitochondrial membrane potential, preventing dopaminergic neuron degeneration, and reducing excitotoxicity[18,19].

Given the potential neuroprotective properties of THQ, this study aims to evaluate its effectiveness in mitigating neuroinflammation and associated cognitive deficits induced by cypermethrin exposure.

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Materials and Methods

This study was approved by the University of Ilorin ethical review committee. Approval date 10th June 2021. Approval no UERC/ASN/2021/2137. Identification Code UERC/BMS/182

Experimental Design

This study employed 40 adult male Wistar rats weighing between 180grams and 200 grams. The thymoquinone used in study was acquired from the MedChemExpress (MCE) in the United States of America (Catalog No: HY-d0803), while Ibukun Oluwa Agrochemical Distop based in Ilorin Nigeria sold the 10% cypermethrin (EC) with a reference number ACEC20L068, and accompanied by a NAFDAC Number: A5-0108. The animals were housed in cages within the animal house of the faculty of basic medical sciences, University of Ilorin. These animals were maintained under normal day-night cycles, a standard chow diet was provided, and had access to water freely.

The animals were allocated randomly into five groups, each comprising eight rats (n=8 per group). The groups were designated as follows through oral administrations for 14 days: 0.5ml phosphate- buffered saline (PBS) was given to group one; Group two received 20mg/kg of cypermethrin (CYM); Group three received 10 mg/kg of thymoquinone (THQ); Group four received 20 mg/kg of cypermethrin followed by 10mg/kg of thymoquinone (CYM-10mgTHQ); and Group five received 20mg/kg and 5mg/kg cypermethrin and thymoquinone respectively (CYM-5mgTHQ). Following the treatment regimen, behavioral assessments, histological examinations, immunohistochemistry analyses, and biochemical evaluations were conducted. On the 14th of the experiment, the animals were exposed to behavioural studies using Y-maze paradigms and open field test.

Behavioral Assessments

The working memory index (i.e. Assessment of Spatial Memory) of experimental Wistar rats was evaluated using the Y-maze paradigm adapted from[20], while motor-related behavior was assessed using the open field test maze (OFT) [21].

Tissue Harvesting

Following the transcardial perfusion of these animals, the entire brain was removed and subsequently post-fixed overnight in 4% paraformaldehyde. The hippocampal CA regions were then carefully removed and these tissues were placed in a 30% sucrose solution for equilibration. 2 µm thick sections were obtained from the paraffin-embedded tissue blocks and they were later mounted onto glass slides.

Tissue Staining and Immunostaining Techniques

Hematoxylin and eosin staining techniques was utilized to visualize the entire cellular architectural organization of the hippocampus. Immunohistochemistry was employed to identify astrogliosis, characterized by increased expression of glial fibrillary acidic protein (GFAP). Also, it was used to detect activated microglia using ionized calcium-binding adapter molecule 1 (Iba1). The presence of neuronal cell death was assessed through the detection of Bax expression. The avidin-biotin complex procedure was employed for the immunostaining, with all antibody markers diluted at a ratio of 1:100. The tissue samples were then processed, sectioned to a thickness of two microns using a rotary microtome, and subjected for 40 minutes to heat treatment at 90°C, to enhance tissue adherence. Quantification of immunopositive cells was performed using the cell counter tool in ImageJ software.

Biochemical Evaluation

The hippocampal tissue was extracted from rats in each experimental group and homogenized in a 0.25M sucrose solution using a mortar and pestle. The obtained homogenate underwent centrifugation at 5000 revolutions per minute for ten minutes. Subsequently, the resulting supernatant was gathered and preserved at -4°C. Following this, an analysis of inflammatory markers including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-10 (IL-10), Nuclear Factor-kappa B (NF-**κB**), and Acetylcholinesterase (AChE) was conducted. However, the assays for Tumor Necrosis Factor-alpha, Interleukin-10, and Nuclear Factor-kappa B utilized the sandwich enzyme-linked immunosorbent assay (ELISA) principle, as outlined by Hornbeck [22]. While A modified Ellman method was employed to determine AChE activity (23). The data obtained were analyzed using GraphPad Prism 8.0, where a four-parameter logistic curve (4PL-curve) was generated and used to extrapolate the values of the samples.

Statistical Analysis

Analysis of the data was conducted with GraphPad Prism version 8.0. To depict the data, the mean and standard error of the mean (M ± SEM) were used. For comparison of mean differences among multiple groups, analysis of variance (ANOVA) was applied. Subsequently, the Tukey post hoc test was employed to ascertain significance at a threshold of $p < 0.05$.

RESULTS

Thymoquinone Improved Cognitive functions following Cypermethrin Toxicity

The CYM group exhibited a significant decrease in percentage alternation (28.40 ± 1.27) compared to the PBS and THQ groups (Fig. A1). Conversely, spontaneous alternation significantly increased in both CYM-LTHQ and CYM-HTHQ groups compared to the CYM group (Fig. 1A). While ambulation in CYM-exposed animals was lower compared to PBS and other experimental groups, this reduction did not reach statistical significance (Fig. 1B). Rearing frequency was higher significantly in the PBS group when compared to CYM. Additionally, there was an increase in rearing frequency in the intervention groups CYM-LTHQ and CYM-HTHQ compared to CYM-exposed animals (Fig. 1C).

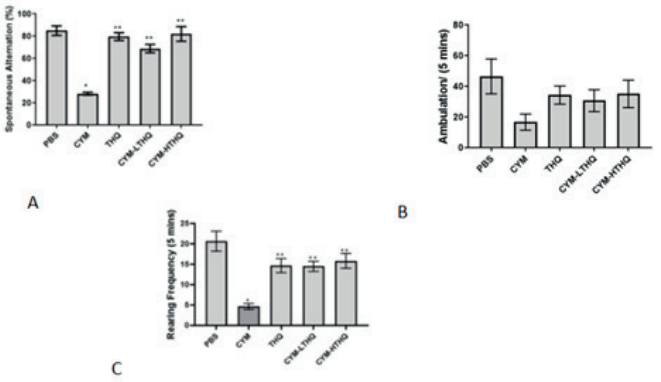

Figure 1: (A): Spontaneous alternation, (B): Ambulation and (C): Rearing frequency.

PBS= Phosphate buffer saline; CYM = Cypermethrin; THQ = thymoquinone; CYM-LTHQ = Cypermethrin before 5 mg of thymoquinone and CYM-HTHQ= Cypermethrin before 10 mg of thymoquinone. Single asterisk (*) indicates significant (p < 0.05) compared to PBS, Double asterisk (**) indicates significant (p < 0.05) compared to CYM.

Thymoquininone Modulates Inflammatory Responses in Cypermethrin Neurotoxicity

The concentration of TNF-α was higher in the CYM group (12.00 ± 0.86) compared to the other groups: PBS, THQ, CYM-LTHQ, and CYM-HTHQ; however, the difference in these groups were not significant. Subsequently, there was significant reduction in IL-10 levels of CYM group (4.93 ± 0.27) compared to PBS (13.60 ± 2.05), and THQ groups (11.90 ± 1.44). The experimental groups; the CYM-LTHQ and CYM-HTHQ had increased IL-10 levels than in the CYM group, nevertheless, the difference in these groups were not significant. CYM exposure increased Nf-kB concentration significantly to the PBS control and the other experimental groups, except for the CYM-LTHQ group, which was not significant (Table 1).

The AChE activity was significantly lower in CYM group (1886 ± 9.70) as compared to PBS group (2087 ± 32.50), but not significant when compared with the THQ group (2209 ± 81.90). However, there was a significant rise in AChE activities of CYM-LTHQ and CYM-HTHQ groups as compared to the CYM group (Table 1).

Histological and Immunohistochemistry

Observable distortion in the cellular arrangement of the dentate gyrus and loss of cell shapes were noted in the CYM-treated animals. Additionally, numerous necrotic-like pyknotic cells were seen as well as loss of cells in the granular layer of the CYM-exposed rats (Fig. 2A). THQ post-treatments restored the integrity of the dentate gyrus and reduced the level of observable pyknotic cells. High expression of GFAP was observed in the CYM-treated rats, indicating astrocyte activation in this group of animals (Fig. 2B). Similarly, there was an increase in microglial expression in the dentate gyrus, as evidenced by high Iba-1 expression in the CYM-exposed group of animals (Fig. 2C). Bax-positive cell expression was also high as a result of CYM exposure (Fig. 2D). Post-treatment with THQ was observed to lower the expression of GFAP, Iba-1, and Bax-positive cells (Fig. 2D), thereby reducing the activation of astrocytes, microglia, and apoptotic cell death.

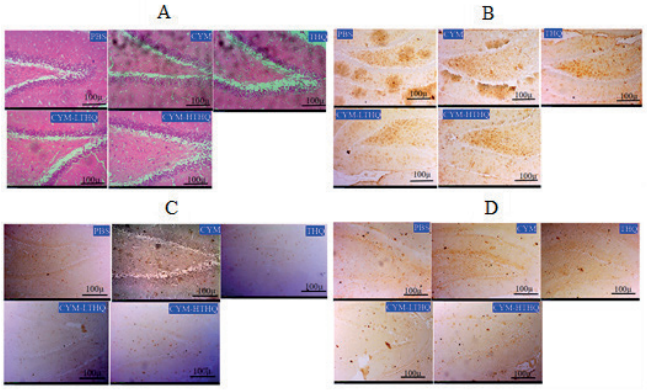

Figure 2: Photomicrograph of dentate gyrus; A- H&E, B- Anti-GFAP, C- Anti-Iba-1, D- Anti-Bax.

PBS- (Phosphate buffered saline); CYM- (Cypermethrin); THQ- (Thymoquinone); CYM-LTHQ- (Cypermethrin before 5 mg/kg of thymoquinone); CYM-HTHQ- (Cypermethrin before 10 mg/kg of thymoquinone). Scale bar 100μ

DISCUSSION

Inflammation is a common response to disruptions in tissue homeostasis caused by various stimuli such as pathogens, tissue injury, or contaminants, involving the activation of innate and adaptive immunity [24,25]. Cognitive impairment is a prevalent manifestation of neurodegenerative diseases like Alzheimer's and Parkinson's diseases, highlighting the urgent need for therapeutic drugs to counteract the neurodegenerative processes associated with cognitive deficits. Mitochondrial dysfunction,

Table1: Effects of Thymoquinone on Cypermethrin-induced inflammatory responses and Acetylcholinesterase activity in adult male Wistar rats

Groups N=6	TNF-α (pg/mL)	IL-10 (pg/mL)	NF-kB (ng/mL)	AChEs (unit/L)
PBS	6.82±1.40	13.60±2.05	1.40±0.12	2087±32.50
CYM	12.00±0.86	4.93±0.27*	2.20±0.11*	1889±9.70*
THQ	9.64±2.89	11.90±1.44**	1.04±0.17**	2209±81.90
CYM-LTHQ	8.31±1.00	7.68±1.56	1.90±0.20	2393±89.40
CYM-HTHQ	7.33±0.89	7.16±1.56	1.51±0.16**	2626±43.30**

CYM-(Cypermethrin); THQ-(Thymoquinone); CYM-LTHQ-(Cypermethrin before 5mg/kgb.w of thymoquinone); CYM-HTHQ-(Cypermethrin before 10mg/kgbw of thymoquinone).a,b,c showing significant difference from PBS, CYM and THQ respectively at p<0.05.

neuroinflammation, oxidative stress, autophagic-lysosomal cascade alterations, and excitotoxicity, are all known to play critical roles in the process of neurodegenerative diseases. Acetylcholine (ACh) is a crucial neurotransmitter that regulates learning and memory; its inhibition can lead to learning and memory deficits as well as impairments in motor functions [21,26,27].

In this study, exposure to cypermethrin markedly reduced AChE activity, a typical effect of insecticides, and likely attributable to the potent neurotoxic effects of cypermethrin. Pyrethroids like organophosphates and other pesticides act as AChE-specific inhibitors due to their binding affinity for the enzyme's ester site, leading to its inactivation [28,29]. However, although AChE inhibitors are crucial in managing memory deficits, CYM-induced inhibition of AChE did not enhance learning and memory in the experimental rats, likely due to the induction of inflammation and neuronal damage by CYM, established causes of cognitive impairment. AChE inhibition caused by CYM and other insecticides is a long-term effect. An increase in AChE activity would likely reduce the concentration of acetylcholine neurotransmitter, which is detrimental to learning and memory [27]. However, it might lead to reduced motor and anxiety-related behaviors such as muscular paralysis, convulsions, bronchial constriction, and death by asphyxiation [27]. Induction of inflammation and loss of dentate gyrus neuronal integrity are important factors contributing to the spatial memory loss observed in this study. Thymoquinone intervention modulated neuroinflammation, which caused the reduction in ROS generation and improved dentate gyrus cytoarchitecture, thereby enhancing memory and motor functions. These findings align with those of Kassab & El-Hennamy, [30], who reported increases in AChE and ATPase activities in various brain regions of rats following exposure to arsenic.

Anti-inflammatory therapy has proven beneficial against many diseases of microglial activation, ROS generation and inflammation origins [31,32]. In this study, thymoquinone modulated inflammatory-mediated cognitive deficits by deactivating NF-κB. NF-κB is a regulatory protein whose nuclear translocation, following phosphorylation of its inhibitory agent IkB, induces the proliferation of pro-inflammatory cytokines; IL-1, TNF-α, COX-2, iNOS, and vascular adhesion molecules. Prolonged TNF-α release due to persistent NF-κB activation leads to compensatory increases in cellular ROS generation. Excessive ROS generation leads to decreased expression and activity of antioxidant enzymes. Exposure of experimental rats to cypermethrin caused increased levels of the NF-κB transcription factor due to phosphorylation of the IkB inhibitory factor, eventually leading to the stimulation of transcription and release of tumor necrosis factor-alpha, as observed in this study. However, the anti-inflammatory cytokine level was low due to cypermethrin exposure, explaining its potential as a neurotoxicant that induces toxicity, including inflammation. Previous research by Singh *et al*., [33] and Tiwari *et al*., [34] found that cypermethrin exposure caused the increase of prominent pro-inflammatory protein IL-1 in the striatum of adult rats, as well as increased levels of TNF-α in the substantia nigra and striatum, respectively. The findings revealed that administration of thymoquinone at two separate doses of 5 mg/kg and 10 mg/kg respectively; body weights reduce the concentration of transcription factor NF-κB, indicating an inhibitory action of thymoquinone on NF-κB. This suggests that thymoquinone exerted its anti-inflammatory role on cypermethrin-induced neurotoxicity by deactivating NF-κB, leading to a decrease in TNF-α levels and subsequent increase in IL-10 levels.

The anti-inflammatory effects of thymoquinone observed can also be attributed to its ability to inhibit the phosphorylation of IKB, as phosphorylation of IKB enables the activation of NF-κB, allowing its translocation into the nucleus where it initiates the downstream transcription of inflammatory proteins [35,36]. Also, Wang *et al*., [37] reported the anti-inflammatory role of thymoquinone, where they found that thymoquinone inhibited IL-1β, TNF-α, NO, and PGE2 production, as well as suppressing NF-κB.

Environmental toxins and heavy metals have been shown to cause mild to severe damage in neuronal cyto-architectures, such as pyknotic nuclei and neuronal cell shape deformation. In this study, cypermethrin caused disorganization of the granular layer in the dentate gyrus, with pyknotic cells, vacuolated cells, and a loss of granule cell spherical shape. The evident pyknosis, resulting from DNA fragmentation and chromatin condensation causing nuclear disintegration and vacuolization, indicates that dentate gyrus and hippocampal neurons undergo degeneration from CYM neurotoxicity. This loss of morphological integrity in the granule cells due to cypermethrin exposure may be attributed to its lipophilic nature, enabling CYM, like other pyrethroids, to cross the blood-brain barrier, where it alters sodium channels in the nerve membrane Sallam *et al*., [38] . Because the dentate gyrus is crucial in hippocampal formation, a disruption in its morphological integrity undoubtedly contributes to the development and progression of memory loss, changes in perception, and training, and a reduction in recollection capacity [39]. This strengthens the observed loss of cognitive function due to cypermethrin despite a reduce AChE activity. Latuszynska *et al*., [40] and Cao *et al*., [41], reported focal pyknosis in the cortex cerebri and concentrations of neurocytes in the cytoplasm of the stratum granulosum, hypothalamus, and cerebral cortex following exposure of rats to a mixture of CYM and chlorpyrifos, were in line with this study. Additionally, Ahmad *et al*., [42] reported graded degeneration of pyramidal neurons in the cerebral cortex and Purkinje cell degeneration in the cerebellar cortex of rabbits due to CYM administration.

Thymoquinone preserved the histoarchitecture and function of the dentate gyrus against the neurodegenerative effects of CYM. It also reduced the extent of vacuolated cells and chromatin condensation, thereby contributing to improved neuronal connections of the hippocampal formation. Since lesions in the dentate granule cells result in memory loss, restoring the lesions is crucial for restoring memory impairment. Nigella sativa oil has been reported to improve the histoarchitecture of the brain by reducing neuronal cell degeneration in various brain regions following dichlorvos exposure [26]. In the study by Imam *et al*., (43), Nigella sativa oil, the parent compound of thymoquinone, preserved cerebellar Purkinje cells after aluminum chloride administration. The findings of this study are supported by those of Adana *et al*., [44], who reported that thymoquinone preserved hepatic cytoarchitecture in rats following cyclophosphamide administration.

Astrocyte and microglial activation following CYM exposure were observed in the dentate gyrus. Astrocyte activation induces microglial cells to start secreting various immune response factors, such as pro-inflammatory cytokines, chemokines, cy-

totoxic factors, and mitochondrial fragmentation, causing a corresponding increase in astrocyte activation [45.46.47]. The increase in the NF-κB and TNF-α levels seen in this study may be due to gliosis caused by CYM administration, as microglial activation increases the production of inflammatory cytokines, the stimulation astrocytes indicates increased ROS generation. Thymoquinone modulated the regular functions of astrocytes and microglia by reducing their hyperactivity, decreasing NF-κB levels, and corresponding TNF-α levels, likely attributable to THQ's potent anti-inflammatory and antioxidant effects. Since increased microglial activation leads to increased inflammatory cytokines and ROS generation [48], a reduction in microglial activation due to THQ, can also be linked to a decrease in the TNF-alpha levels, and the increase in IL-10 levels.

The effects of cypermethrin induced an increase in the proliferation of the pro-apoptotic protein Bax, as well as a marked increase in Bax immunopositive cells. Cypermethrin induces apoptosis in the rat brain through the generation of ROS and cytotoxins, mitochondrial damage, the cytochrome c release, and caspases 3 and 9 activation; these are important in extrinsic and intrinsic process of apoptosis. Pandey *et al*.,[49] showed that cypermethrin administration caused increased expression of P53 and decreased Bcl-2 levels by inducing miR-200 and apoptosis in neuronal cells. Raszewski *et al*., [50] reported that cypermethrin and chlorpyrifos can induce apoptosis in human's neuroblastoma cell line SH-SY5Y. Stressing that, they induce apoptosis by increasing the activation.caspase-3. Singh *et al*., [33] and Agrawal *et al*., [51] reported that cypermethrin caused mitochondrial damage and can lead to increased levels of the following enzymes which include; cytochrome c, activation of caspase-3, as well as the increased expression of Bax and COX-2, and P53 protein.

The increased Bax expression levels following exposure to cypermethrin in this study could be due to damage to mitochondria and a subsequent increase in free radical generation, as cypermethrin has been shown to disrupt mitochondrial integrity and increase ROS generation. Similar to the observation of this study, Pandey *et al*.,[48] demonstrated that cypermethrin treatment raised P53 expression and lowered Bcl-2 levels in neural cells by inducing miR-200 and death. Raszewski *et al*., [49] discovered that cypermethrin and chlorpyrifos increase caspase-3 activation, triggering apoptosis. Singh *et al*., [33] found that cypermethrin caused mitochondrial damage, resulting in higher levels of cytochrome c, activating caspase-3, elevating COX-2 protein. Thymoquinone reduced Bax immunopositive cell expression, inhibiting its apoptotic action, suppressing its oligomerization, and inhibiting mitochondrial release of apoptogenic chemicals. Also, the antiapoptotic activity of thymoquinone may directly block cytochrome c production and hence inhibit the adaptor molecule APAF-1 and activation of caspase-9. Thymoquinone also acts as an anti-proliferative agent and regulates apoptosis in cancer progression by decreasing Bcl-2 expression, increasing Bax/BAD levels, and inducing tumor and cancer cell apoptosis and autophagy. Thymoquinone suppresses the growth of malignancies in various organs, such as the prostate and breast. An earlier study found that thymoquinone ingestion decreased the expression of both Bcl-2 and p53 genes, however, there was an observable increment in the expression of the Bax/BAD gene in MCF-7 cells; but in non-cancer HEK293 cells, there was an increase expression of Bcl-2 and p53 genes and decrease in the proliferation of Bax/BAD genes. Thymoquinone has been proven to protect the cortex of rats against acrylamide-induced neurotoxicity via MAP kinase signaling pathways.

CONCLUSION

In conclusion, this study underscores the detrimental actions of cypermethrin exposure on cognitive function and neuronal integrity in experimental rats. Cypermethrin induced significant alterations in AChE activity, inflammatory cytokine levels, dentate gyrus morphology, and apoptotic protein expression, which have all contributed to the cognitive deficits and neuronal damage.

However, thymoquinone (THQ) demonstrated promising neuroprotective effects against cypermethrin-induced toxicity. THQ treatment mitigated the reduction in AChE activity, attenuated inflammatory responses by modulating NF-κB signaling and cytokine levels, preserved dentate gyrus histoarchitecture and inhibited apoptotic pathways. These findings suggest that THQ holds therapeutic potential in mitigating the neurodegenerative effects associated with pesticide exposure.

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Abubakar Lekan Imam: 20%: Study conception and design

Akeem Ayodeji Okesina: 15%: Critical revision and writing of the manuscript

Fatimo Ajoke Sulamon: 10%: study analysis and interpretation

Aminu Imam: 15%: Study analysis and interpretation

Ruqayyah Yetunde Ibiyeye: 10%: Data collection

Misturah Yetunde Adana: 10% critical review of the manuscript

Omoola Olasheu Oluwatosin: 10%: Referencing

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Review Article

The Impact of Early Childhood Adversity on Neurodevelopment: A Comprehensive Review

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Abstract

Early childhood is a vital period for brain development, characterized by rapid growth and high plasticity. Adverse experiences during this time, such as abuse, neglect, violence, and poverty, can significantly affect neurodevelopment and have lasting impacts on mental health and behavior. This review explores the influence of early adversity on brain development, emphasizing key mecha-nisms and outcomes. Research indicates that early adversity causes alterations in brain regions like the prefrontal cortex, amygdala, hippocampus, and corpus callosum, impairing cognitive functions such as learning, memory, and executive functioning. Chronic stress disrupts the hypothalamic-pituitary-adrenal (HPA) axis, resulting in elevated cortisol levels that hinder emotional regulation and heighten the risk of mental health disorders such as depression and anxiety. Epigenetic changes show how adversity can modify gene expression, affecting brain development without altering the DNA sequence. The repercussions of early adversity include cognitive deficits, emotional and beha-vioral problems, and social development challenges. However, resilience factors, including indivi-dual traits and supportive environments, can mitigate these negative impacts. Robust study designs, such as longitudinal and multidisciplinary approaches, are crucial for understanding the long-term effects of early adversity. Ethical considerations and precise measurement are vital for protecting vulnerable populations. Policy implications suggest that findings should inform child welfare, edu-cation, and mental health policies, focusing on early identification and intervention. Practitioners should adopt trauma-informed approaches, implement early intervention programs, and support parents and caregivers. Addressing early childhood adversity is crucial for promoting healthy neu-rodevelopment and well-being. Comprehensive interventions can reduce adverse effects, support healthy development, and contribute to a resilient society.

Keywords: Early Childhood Adversity, Neurodevelopment, Brain Development, Abuse, Neglect.

Introduction

The early years of childhood are crucial for brain development, characterized by rapid growth and high plasticity.[1] During these formative years, the brain undergoes significant changes in structure and function, laying the foundation for cognitive, emotional, and social functioning throughout the lifespan. [2] Adverse experiences during early Early childhood experiences, such as abuse, neglect, and exposure to violence, and living in poverty, can profoundly impact neurodevelopment and have long-lasting consequences for mental health and behavior. [3] The impact of early adversity on brain development is a critical area of research, [4] as understanding these effects can inform the development of interventions and policies aimed at mitigating the negative outcomes associated with such experiences.

Early childhood adversity comprises various forms of negative experiences that can disrupt normal development. [5] Abuse and neglect, for example, can deprive children of the necessary stimulation and security needed for healthy brain development. [6] Exposure to chronic stress, whether due to familial instability, socioeconomic disadvantage, or traumatic events, can alter the brain's stress response systems, leading to modifications in brain architecture and activity. [7] These adverse experiences can trigger a cascade of neurobiological changes that affect cognitive, emotional, and social development. [8] Recent advancements in neuroimaging and molecular biology have provided a deeper understanding of how early adversity affects brain development. [9] Studies indicate that early adversity can cause changes in brain regions responsible for emotion regulation, executive functioning, and social behavior, such as the prefrontal cortex, amygdala, and hippocampus. [10] Additionally, chronic stress exposure can disrupt the HPA axis, leading to long-lasting alterations in stress hormone levels that affect brain development. [11] Modifications in epigenetics, which affect gene expression without changing the DNA sequence, have also been identified as a crucial mechanism linking early adversity to long-term neurodevelopmental outcomes. [12]

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The consequences of early childhood adversity are far-reaching, affecting various domains of development. [13] Cognitively, children who experience early adversity may exhibit deficits in learning, memory, and executive functions. [14] They face a heightened emotional risk for mental health issues such as depression, anxiety, and post-traumatic stress disorder (PTSD). [15] Behaviorally, these children may exhibit increased aggression, impulsivity, and difficulties in social interactions. [16] The cumulative effect of these developmental disruptions can lead to significant impairments in academic achievement, interpersonal relationships, and overall quality of life. [17]

Nonetheless, not all children who encounter early adversity experience adverse outcomes. [18] Resilience, the capacity to adapt successfully in the face of challenges, is vital in shaping developmental trajectories. [19] Factors such as individual temperament and intelligence, as well as environmental elements like nurturing relationships and stable living conditions, can mitigate the negative effects of early adversity. [20] Programs and interventions that build resilience and offer supportive environments have shown effectiveness in lessening the impact of early adversity on neurodevelopment. [21]

This review aims to present a comprehensive overview of current literature on the impact of early childhood adversity on neurodevelopment. It will explore the definitions and prevalence of early adversity, delve into the neurobiological mechanisms underlying its effects, and discuss the cognitive, emotional, and social outcomes associated with such experiences. Furthermore, the review will emphasize resilience factors and protective interventions that can mitigate the negative effects of early adversity. By synthesizing existing research, this article seeks to inform future studies and guide practitioners and policymakers in addressing the needs of children exposed to early adversity.

Definitions

Early childhood adversity encompasses a range of negative experiences that can disrupt normal development and have lasting impacts on neurodevelopment and behavior. [22] Below are detailed definitions of various forms of early adversity:

Abuse

Abuse refers to intentional acts that cause harm or potential harm to a child. It includes three primary categories: physical abuse, emotional abuse, and sexual abuse.

Physical Abuse

Physical abuse involves inflicting physical injury on a child through actions such as hitting, shaking, burning, or otherwise causing physical harm. These acts can result in visible injuries like bruises, burns, fractures, or internal damage. Physical abuse can also have long-term effects on a child's physical and mental health, leading to chronic pain, disabilities, and psychological disorders. The repeated nature of physical abuse often exacerbates its impact, leading to a cycle of fear and trauma. [23]

Emotional Abuse

Emotional abuse, also known as psychological actions that harm a child's self-esteem or emotional health are forms of abuse. This form of abuse can be more challenging to recognize as it does not leave visible marks but can be equally damaging. Emotional abuse includes constant criticism, threats, rejection, isolation, and manipulation. It can lead to severe consequences, including Low self-worth, anxiety, depression, and struggles with forming healthy relationships. Emotional abuse undermines a child's sense of security and belonging, often leading to long-term emotional and psychological issues. [24]

Sexual Abuse

Sexual abuse involves engaging a child in sexual activities, whether by direct contact or exploitation. This can include inappropriate touching, forced participation in sexual acts, or exposure to sexual content. Sexual abuse can cause profound physical and psychological trauma, including injuries, sexually transmitted infections, and long-lasting emotional distress. Victims of sexual abuse often suffer from guilt, shame, and fear, which can persist into adulthood and affect their mental health, relationships, and overall well-being. Sexual abuse is a gross violation of a child's trust and safety, with devastating and enduring effects. [25]

Understanding these definitions is crucial for identifying and addressing the various forms of abuse that children may endure. Each type of abuse requires specific interventions and support to help children recover and thrive despite their adverse experiences.

Neglect

Neglect is the failure to provide for a child's basic needs, which are essential for their physical, emotional, and cognitive development. [26] Neglect can be as damaging as abuse and often co-occurs with other forms of maltreatment. It includes various types, each with specific implications for a child's well-being:

Physical Neglect

Physical neglect encompasses the failure to meet a child's essential physical needs, such as providing adequate food, shelter, and clothing. Children subjected to physical neglect may suffer from malnutrition, poor hygiene, and inadequate living conditions. These children often face health issues due to improper nutrition and living in unsafe or unsanitary environments. Physical neglect can result in developmental delays and chronic health problems, hindering the child's ability to thrive both physically and academically. [27]

Emotional Neglect

Emotional neglect refers to the failure to provide the essential emotional support, love, and nurturing required for a child's healthy psychological development. This type of neglect is particularly insidious as it does not leave visible scars but deeply impacts a child's emotional and mental health. Children who experience emotional neglect may feel unloved, unwanted, and isolated. They may develop low self-esteem, depression, and anxiety, and struggle to form secure attachments and trusting relationships. Emotional neglect can impair a child's ability to regulate emotions and cope with stress, leading to long-term psychological issues. [28]

Educational Neglect

Educational neglect occurs when a caregiver fails to ensure that a child receives an education. This can involve not enrolling a child in school, allowing frequent absences, or failing to address special educational needs. Educational neglect can have severe

consequences for a child's intellectual and social development. Children who are educationally neglected are often at a disadvantage academically, which can limit their future opportunities and perpetuate cycles of poverty and disadvantage. They may struggle with basic literacy and numeracy skills and are at a higher risk of dropping out of school and experiencing social exclusion. [29]

Medical Neglect

The failure to offer necessary medical treatment constitutes medical neglect, which can include not seeking treatment for illnesses and injuries, failing to provide prescribed medications, or neglecting to attend regular health check-ups. Medical neglect can lead to untreated health conditions, chronic pain, and in severe cases, life-threatening situations. Children who do not receive appropriate medical care may suffer from preventable diseases, prolonged illnesses, and poor overall health. This neglect can impact their physical development and quality of life, as well as their ability to participate fully in educational and social activities.

By understanding the different forms of neglect and their prevalence, researchers, practitioners, and policymakers can better identify and address the needs of neglected children. Effective interventions and support systems are essential to mitigate the adverse effects of neglect and promote the healthy development and well-being of affected children. [30]

Witnessing Domestic Violence

Witnessing domestic violence involves children observing violent or abusive behavior between caregivers or within the household. This adversity can significantly impact a child's emotional and cognitive development, often leading to long-term psychological trauma. The following outlines the effects and implications of such exposure:

Emotional Impact

Children who witness domestic violence are often exposed to chronic stress and fear. These children may experience a constant sense of anxiety and insecurity, as their home environment, which should be a place of safety and stability, becomes unpredictable and frightening. [31] This persistent state of stress can lead to mental health conditions including depression, anxiety, and PTSD. Feelings of helplessness and powerlessness are common, as children may feel incapable of protecting themselves or their non-abusive parent. Additionally, they might internalize the violence, believing it is somehow their fault, which can lead to intense feelings of guilt and shame. [32]

Cognitive Impact

The cognitive development of children exposed to domestic violence can also be significantly affected. Chronic exposure to violence can impair the brain's development, particularly in areas responsible for learning, memory, and executive functioning. These children might have difficulty concentrating, experience delays in language development, and struggle with academic performance. [33] The constant activation of the stress response system can alter brain structures, such as the hippocampus and prefrontal cortex, which are crucial for cognitive processes. As a result, children may exhibit problems with attention, problem-solving, and impulse control.

Behavioral Impact

Witnessing domestic violence can lead to a range of behavioral issues. Children may exhibit aggressive behavior, mimicking the violence they observe, or they may become withdrawn and avoidant, attempting to escape their traumatic environment. Some children might develop conduct disorders, showing a pattern of disruptive and violent behavior. [34] Others may become overly compliant and exhibit heightened sensitivity to conflict, constantly trying to avoid any situation that might lead to violence. These behavioral issues can affect their interactions with peers and adults, leading to difficulties in forming healthy relationships.

Social Impact

The social development of children exposed to domestic violence can also be compromised. These children might struggle with trust and attachment issues, finding it difficult to form secure relationships with others. They may isolate themselves socially or have trouble maintaining friendships due to their emotional and behavioral difficulties. [35] Furthermore, witnessing violence can normalize aggressive behavior, increasing the risk that they might become perpetrators or victims of violence in their own relationships as they grow older. The social stigma associated with domestic violence can also lead to feelings of isolation and shame, further hindering their social development.

Long-term Consequences

The long-term effects of exposure to domestic violence are significant. Children who are raised in violent homes are more likely to continue the cycle of violence in their adult lives, either as victims or perpetrators. They may experience persistent mental health issues such as depression, anxiety, and PTSD, which can hinder their ability to function in various areas of life. Their educational and occupational outcomes may also suffer due to the cognitive and emotional challenges they encounter. Early intervention and supportive services are essential to mitigating these long-term effects and fostering resilience. [36]

Understanding the impact of exposure to domestic violence on children is essential for developing effective interventions and support systems. By providing a safe and supportive environment, fostering healthy relationships, and offering therapeutic interventions, it is possible to help these children overcome the adverse effects of their experiences and promote their emotional and cognitive well-being.

Poverty

Poverty is a pervasive form of early childhood adversity that affects millions of children worldwide. It encompasses more than just a lack of financial resources, extending to inadequate access to essential services and basic needs such as nutrition, healthcare, education, and safe living conditions. [37] The impact of poverty on a child's development is profound, influencing their physical health, cognitive abilities, emotional well-being, and social relationships.

Global Prevalence

According to UNICEF, nearly 356 million children globally live in extreme poverty, [38] defined as living on less than $1.90 a day. These children face severe deprivation, which can hinder their

overall development and limit their future opportunities. In low- and middle-income countries, the prevalence of child poverty is particularly high, exacerbating the challenges these children face in achieving healthy development.

Poverty in High-Income Countries

Child poverty is not limited to low-income countries; it is also a significant issue in high-income countries. [39] In these regions, child poverty rates vary substantially, often influenced by economic policies, social safety nets, and regional disparities. For example, in the United States, the Census Bureau reports that approximately 11 million children live in poverty, representing about 16% of the child population. In European countries, child poverty rates can range from below 10% in some nations to over 30% in others, highlighting the uneven distribution of resources and support.

Impact on Physical Health

Children living in poverty are more susceptible to various health problems due to poor nutrition, restricted access to healthcare, and unsafe living environments. [40] Malnutrition is prevalent, resulting in stunted growth, weakened immune systems, and higher vulnerability to diseases. Overcrowded housing and exposure to environmental toxins can lead to chronic health issues such as asthma, lead poisoning, and infectious diseases. The limited availability of healthcare services further worsens these conditions, as children in poverty are less likely to receive preventive care and timely medical treatment.

Impact on Cognitive Development

Poverty can severely impact cognitive development, hindering a child's ability to learn and achieve academic success. Children in poverty often lack access to educational materials and enriching experiences that foster cognitive growth. The stress of living in poverty can disrupt brain development, especially in areas related to memory, attention, and executive functions. [41] Research indicates that children from low-income families usually start school with lower readiness levels, including poorer language skills, general knowledge, and early math abilities, which can continue to affect their educational progress.

Impact on Emotional and Social Development

The chronic stress of living in poverty can also negatively impact a child's emotional and social development. Children in poverty are more prone to feelings of shame, low self-esteem, and helplessness. They often exhibit higher levels of anxiety and depression and are at a greater risk for behavioral problems. [42] The instability often accompanying poverty, such as frequent relocations, changes in caregivers, and exposure to violence, can disrupt a child's sense of security and attachment, making it difficult to form healthy relationships. Social isolation and the stigma of poverty can further intensify these emotional challenges.

Long-Term Consequences

The long-term consequences of growing up in poverty can be far-reaching. As adults, individuals who experienced poverty as children are more likely to have lower educational attainment, reduced earning potential, and poorer health outcomes. [43] They may also face a higher risk of involvement in the criminal justice system and perpetuate the cycle of poverty with their own children. Addressing child poverty through comprehensive policies and targeted interventions is crucial for breaking this cycle and promoting the well-being and potential of affected children.

Addressing Child Poverty

Efforts to address child poverty must be multifaceted, involving economic support, access to quality education and healthcare, and the provision of safe and stable living environments. Social safety nets, such as food assistance programs, housing subsidies, and healthcare access, play a critical role in mitigating the effects of poverty. Additionally, early childhood education programs and community support services can provide the necessary resources and support to help children in poverty reach their full potential. [44]

Understanding the prevalence and impact of poverty on children's development is essential for developing effective interventions and policies. By addressing the root causes of poverty and providing targeted support, it is possible to improve the outcomes and opportunities for millions of children worldwide.

Parental Mental Illness or Substance Abuse

Children growing up in households where a parent has a mental health disorder or substance use disorder face unique challenges that can significantly impact their development and well-being. [45] The presence of parental mental illness or substance abuse can create an unstable and unpredictable environment, leading to various forms of stress and adversity for the child.

Prevalence

About 1 in 5 children in the United States live with a parent who has a mental health condition, which can range from depression and anxiety to more severe disorders such as bipolar disorder and schizophrenia. [46] Additionally, the Substance Abuse and Mental Health Services Administration (SAMHSA) reports that around 1 in 8 children live with at least one parent who has a substance use disorder, including the abuse of alcohol, illegal drugs, or prescription medications.

Impact on Emotional and Psychological Development

The emotional and psychological development of children living with a parent who has a mental health disorder or substance use disorder can be profoundly affected. [47] These children often experience high levels of stress and anxiety, stemming from the unpredictability and instability in their home environment. Parental mental illness or substance abuse can result in inconsistent parenting, emotional unavailability, and impaired caregiving. Children may feel neglected or unloved, leading to low self-esteem, depression, and difficulty forming healthy attachments.

Living with a parent who struggles with mental health issues or substance abuse can also expose children to secondary traumatic experiences, such as witnessing parental conflict, domestic violence, or even overdose incidents. These experiences can contribute to the development of post-traumatic stress disorder (PTSD) and other anxiety-related disorders. The chronic stress associated with such environments can interfere with brain development, particularly in areas related to emotion regulation and stress response.

Impact on Cognitive Development and Academic Achievement

Children of parents with mental health disorders or substance use disorders often face significant challenges in their cognitive development and academic achievement. The chaotic and unstable home environment can hinder their ability to focus, learn, and succeed academically. These children may have higher rates of absenteeism and lower academic performance due to the lack of support and encouragement from their caregivers. Additionally, they may struggle with cognitive functions such as memory, attention, and executive functioning, which are critical for academic success. [48]

The stress and trauma associated with living in such environments can also impair brain development, particularly in areas responsible for cognitive processes. This can result in difficulties with problem-solving, planning, and organizing tasks. Furthermore, children may lack access to stimulating educational materials and enriching experiences that promote cognitive growth, further exacerbating the academic challenges they face.

Impact on Social Development and Relationships

The social development of children living with a parent who has a mental health disorder or substance use disorder can also be adversely affected. These children may experience social isolation and stigma, as they may feel embarrassed or ashamed of their family situation. They may have difficulty forming and maintaining friendships, as their social interactions are often disrupted by the chaos and instability at home. The lack of positive role models and supportive relationships can hinder their ability to develop healthy social skills and trust in others. [49]

Children may also exhibit behavioral problems, such as aggression, defiance, or withdrawal, as coping mechanisms for dealing with their stressful environment. These behaviors can further alienate them from their peers and lead to disciplinary issues at school. The absence of stable and nurturing relationships can impact their ability to form secure attachments and develop healthy interpersonal relationships later in life.

Long-Term Consequences

The long-term consequences of growing up with a parent who has a mental health disorder or substance use disorder can be significant. As adults, these individuals may be at higher risk for developing their own mental health disorders or substance use issues, perpetuating the cycle of adversity. [50] They may also face challenges in their educational and occupational achievements, as well as in forming and maintaining stable relationships. The intergenerational transmission of trauma and adversity underscores the importance of early intervention and support for these children.

Addressing the Needs of Affected Children

Addressing the needs of children living with a parent who has a mental health disorder or substance use disorder requires a comprehensive and multifaceted approach. Providing access to mental health services for parents is crucial in creating a more stable and supportive home environment. Additionally, offering targeted support for children, such as counseling, support groups, and educational assistance, can help mitigate the impact of their adverse experiences. [51]

Early intervention programs that focus on building resilience and coping skills can empower children to navigate their challenging circumstances more effectively. Community-based support systems, including schools, healthcare providers, and social services, play a critical role in identifying and supporting these children. By fostering a network of care and support, it is possible to improve the outcomes and well-being of children affected by parental mental illness or substance abuse. [52]

Understanding the prevalence and impact of parental mental illness and substance abuse on children is essential for developing effective interventions and policies. By addressing the root causes and providing targeted support, it is possible to break the cycle of adversity and promote the healthy development and future success of affected children.

Natural Disasters and War

Natural disasters and war represent severe forms of early childhood adversity that can have devastating effects on children's development and well-being. [53] The United Nations estimates that over 420 million children live in conflict-affected areas, and millions more are affected by natural disasters each year. These experiences can profoundly impact children's physical, emotional, cognitive, and social development.

Impact of Natural Disasters

Natural disasters, such as earthquakes, hurricanes, floods, and wildfires, can cause immediate and long-term disruptions in a child's life. [54] The impact of these disasters varies based on their severity, duration, and the child's proximity to the event. Common effects include:

Physical Health and Safety: Natural disasters can lead to injuries, loss of life, and damage to homes and infrastructure. [55] Children may suffer from physical injuries or health issues resulting from poor living conditions in temporary shelters. Lack of access to clean water, food, and healthcare can exacerbate these health problems, leading to malnutrition and increased susceptibility to diseases.

Emotional and Psychological Impact: Experiencing a natural disaster can be highly traumatic for children, leading to feelings of fear, anxiety, and helplessness. [56] The sudden loss of loved ones, homes, and familiar surroundings can result in severe emotional distress. Children may develop post-traumatic stress disorder (PTSD), depression, and anxiety disorders. The ongoing stress and uncertainty can disrupt their sense of security and stability, affecting their overall emotional well-being.

Cognitive and Educational Impact: Natural disasters can disrupt education by damaging schools and displacing families. [57] Children may miss significant amounts of school, leading to delays in learning and academic achievement. The stress and trauma associated with the disaster can also affect cognitive functions such as memory, attention, and problem-solving abilities, further hindering their educational progress.

Social Impact: Displacement due to natural disasters often results in the loss of community networks and social support systems. [58] Children may be separated from friends, extended family, and familiar environments, leading to social isolation. The lack of stable social connections can impact their ability to develop healthy relationships and social skills.

Impact of War and Armed Conflict

War and armed conflict represent extreme forms of adversity, exposing children to violence, displacement, and severe disruptions to their lives. The impact of living in conflict-affected areas includes:

Exposure to Violence: Children in war zones are often exposed to violence, including bombings, shootings, and other acts of aggression. [59] Witnessing or experiencing such violence can lead to severe psychological trauma, including PTSD, anxiety, and depression. The constant threat to their safety can result in chronic stress and hypervigilance.

Displacement and Loss: Conflict often forces families to flee their homes, leading to displacement and loss of belongings. [60] Refugee and internally displaced children face harsh living conditions in camps or temporary shelters, lacking access to basic necessities such as food, clean water, and healthcare. The loss of home and community disrupts their sense of stability and security.

Disruption of Education: Conflict can severely disrupt education, with schools being damaged, closed, or repurposed for military use. [61] Children may miss years of schooling, which affects their cognitive development and future opportunities. In conflict zones, education systems may be inadequate or non-existent, further exacerbating the educational disadvantages faced by these children.

Health and Nutrition: Children living in conflict-affected areas are at higher risk of malnutrition and health problems due to food shortages, lack of healthcare, and poor living conditions. [62] The stress and trauma of living in a war zone can weaken their immune systems, making them more susceptible to illnesses.

Social and Emotional Development: The loss of social networks and community support systems can impact children's social and emotional development. [63] Children in conflict zones may struggle with forming and maintaining relationships, and the pervasive atmosphere of fear and mistrust can hinder their ability to develop social skills. The long-term emotional impact of growing up in a war zone can affect their ability to lead healthy, productive lives in the future.

Long-Term Consequences

The long-term consequences of experiencing natural disasters or war during childhood can be profound and far-reaching. [64] These experiences can affect a child's development across multiple domains, leading to enduring physical, emotional, cognitive, and social challenges. As adults, individuals who experienced such adversity as children may face ongoing mental health issues, difficulties in educational and occupational achievements, and challenges in forming and maintaining stable relationships.

Addressing the Needs of Affected Children

Addressing the needs of children affected by natural disasters and war requires a comprehensive and coordinated approach. [65] Humanitarian aid organizations play a crucial role in providing immediate relief, including food, shelter, healthcare, and psychological support. Long-term interventions should focus on rebuilding education systems, providing mental health services, and supporting family and community resilience.

Psychosocial support programs are essential to help children cope with trauma and rebuild their sense of security and stability. [66] These programs should be culturally sensitive and tailored to the specific needs of the affected children. Education initiatives, such as temporary learning spaces and accelerated learning programs, can help mitigate the disruption to children's education and support their cognitive development.

International cooperation and policy efforts are also critical in addressing the root causes of conflict and promoting peace and stability. By prioritizing the well-being of children in humanitarian responses and development programs, it is possible to improve the outcomes and future prospects of children affected by natural disasters and war.

Understanding the prevalence and impact of natural disasters and war on children is essential for developing effective interventions and policies. [67] By addressing the immediate and long-term needs of these children, it is possible to promote their resilience, recovery, and healthy development.

Brain Development Overview

The brain undergoes significant development from infancy through early childhood, characterized by rapid growth and high plasticity. Understanding the key stages of brain development helps elucidate how early adversity can affect neurodevelopmental trajectories.

Infancy (0-2 years)

During infancy, the brain experiences a tremendous growth spurt, forming approximately one million new neural connections every second. [68] This period is characterized by several key developmental milestones that lay the foundation for future cognitive, emotional, and social functioning. One of the most significant processes during this time is synaptogenesis, the rapid formation of synapses, or connections between neurons, [69] which facilitates communication within the brain. This process is most intense in the first few years of life, allowing for the rapid development of neural networks that underpin learning, memory, and overall brain function.

Concurrently, myelination occurs, which is the development of the myelin sheath. This fatty layer insulates axons, the long projections of neurons, and speeds up neural transmission, [70] enhancing the efficiency and speed of communication between different parts of the brain. Myelination begins in the prenatal period and continues well into adulthood, [71] but it is particularly rapid during infancy. This rapid myelination supports the quick development of motor skills and cognitive functions that are essential for interacting with the environment.

Sensory and motor development also progresses significantly during infancy. [72] The brain areas responsible for sensory and motor functions mature early, enabling infants to gain control over their movements and start processing sensory information from their surroundings. This development allows infants to explore and interact with their environment, [73] which is crucial for cognitive and physical growth. For example, as infants develop their motor skills, they begin to reach for and manipulate objects, which helps them understand cause and effect and enhances their problem-solving abilities.

Additionally, the foundations of emotional regulation and at-

tachment are established during infancy. Infants form bonds with their primary caregivers, which are crucial for their emotional and social development. [74] These early relationships influence the child's ability to manage emotions and form secure attachments. A secure attachment provides a sense of safety and security, allowing the child to explore their environment and develop independence. It also plays a vital role in the development of social skills, empathy, and the ability to form healthy relationships later in life. Emotional regulation, the ability to manage and respond to emotional experiences appropriately, [75] begins to develop as infants learn to rely on their caregivers for comfort and support.

Overall, the first two years of life are a period of remarkable brain growth and development, with critical processes such as synaptogenesis, myelination, sensory and motor development, and the formation of attachment and emotional regulation laying the groundwork for future cognitive, emotional, and social functioning. Early experiences during this period can have lasting effects, highlighting the importance of providing a nurturing and stimulating environment to support optimal brain development.

Early Childhood (3-6 years)

In early childhood, the brain continues to develop at a rapid pace, with significant advancements in cognitive, emotional, and social functions. One of the key processes during this period is synaptic pruning, where the brain begins to eliminate excess synapses that are not frequently used. This process makes neural networks more efficient by strengthening the essential connections that are used regularly. By refining these neural pathways, the brain becomes more adept at processing information and performing complex tasks. [76]

Language development is particularly notable during early childhood, as this period includes critical windows for language acquisition. Children experience rapid growth in their vocabulary, grammar, and communication skills. They begin to understand and use language more effectively, which is crucial for expressing thoughts, needs, and emotions. The ability to communicate fluently supports not only cognitive development but also social interactions and learning.

Another significant development in early childhood is the maturation of executive functions, which are primarily associated with the prefrontal cortex. This area of the brain is responsible for planning, decision-making, and impulse control. As these executive functions develop, children become better at self-regulation and adaptive behavior. They learn to set goals, make plans, and control their impulses, which are essential skills for navigating their environment and interacting with others.

Social and emotional skills also undergo substantial development during early childhood. Children learn to navigate social interactions, develop empathy, and build relationships with their peers. They begin to understand social norms and expectations, which helps them function effectively in group settings. Emotional regulation continues to mature, influenced by experiences and interactions with caregivers and peers. Children learn to manage their emotions, cope with challenges, and respond appropriately to different social situations.

Overall, early childhood is a period of remarkable brain development, characterized by synaptic pruning, language acquisition, maturation of executive functions, and the development of social and emotional skills. These advancements lay the foundation for future learning and behavior, highlighting the importance of providing a supportive and stimulating environment during these formative years.

Critical Periods

Critical periods in brain development are specific times when the brain is particularly sensitive to environmental influences. Exposure to positive experiences during these windows can promote optimal development, while exposure to adversity can have detrimental effects. Understanding these critical periods is essential for recognizing the impact of early adversity on neurodevelopment.

Early Infancy (0-2 years)

During early infancy, the development of sensory and motor systems is highly plastic, meaning the brain is especially responsive to environmental inputs and experiences. Adequate sensory stimulation and motor experiences are crucial for proper development. Infants learn about the world through their senses and movements, and these experiences help to shape the neural pathways that support sensory processing and motor skills. [77] For example, visual and auditory stimuli, as well as opportunities for grasping, crawling, and exploring, contribute to the maturation of these systems. However, adverse experiences such as neglect or sensory deprivation can lead to deficits in sensory and motor development. Without adequate stimulation, the brain may not develop the necessary connections to process sensory information and coordinate motor actions effectively, potentially leading to long-term impairments.

Attachment formation is another critical aspect of early infancy. The formation of secure attachments with primary caregivers is vital during the first two years of life. Secure attachment provides a sense of safety and security, which is essential for healthy emotional and social development. Through consistent and responsive caregiving, infants learn to trust their caregivers and develop the ability to regulate their emotions. This secure base allows them to explore their environment confidently and engage in social interactions. Disruptions in attachment, due to caregiver inconsistency, neglect, or maltreatment, can impair emotional regulation and social functioning. Children who do not form secure attachments may struggle with trust, experience anxiety, and have difficulties forming healthy relationships later in life.

The stress response system, particularly the HPA axis, is also particularly sensitive during infancy. [78] The HPA axis plays a crucial role in regulating the body's response to stress. During early infancy, chronic exposure to stress or trauma can dysregulate the HPA axis, leading to heightened stress sensitivity and long-term health consequences. Infants exposed to high levels of stress may exhibit increased levels of cortisol, the primary stress hormone, which can affect brain development and functioning. Dysregulation of the HPA axis can lead to difficulties in managing stress, increased risk for anxiety and depression, and other health problems later in life.

Overall, early infancy is a period of critical importance for the development of sensory and motor systems, the formation of secure attachments, and the regulation of stress responses. Ad-

equate stimulation, consistent caregiving, and a stable environment are essential to support healthy development during these formative years. Understanding the significance of these processes highlights the importance of early intervention and support for infants who experience adverse conditions, to promote their well-being and optimal development.

Early Childhood (3-6 years)

Early childhood, spanning ages 3 to 6, is a critical period for various aspects of development, including language acquisition, emotional regulation, and executive functions. During this time, the brain continues to exhibit remarkable plasticity, making it especially receptive to environmental influences and experiences.

Language acquisition is particularly significant during early childhood. This period is marked by rapid advancements in vocabulary, grammar, and overall communication skills. Adequate exposure to language through social interactions with caregivers, peers, and educators is essential for developing these skills. Children learn to understand and use language effectively, which is crucial for expressing thoughts, needs, and emotions. [79] Neglect or a lack of linguistic stimulation can result in language delays, making it challenging for children to achieve later academic success. These delays can have long-term consequences, affecting literacy, academic performance, and social interactions.

Emotional regulation also develops significantly during early childhood. The ability to manage and respond to emotional experiences appropriately is shaped by positive interactions with caregivers and peers. Children learn to identify, understand, and manage their emotions through these relationships. They develop skills such as empathy, self-soothing, and impulse control. However, adverse experiences, such as exposure to domestic violence or emotional neglect, can hinder the development of emotional regulation skills. Children exposed to such adversity may struggle with emotional and behavioral problems, including anxiety, aggression, and difficulty forming healthy relationships.

The prefrontal cortex, which is responsible for executive functions such as planning, decision-making, and impulse control, undergoes significant maturation during early childhood. Experiences that promote problem-solving, planning, and self-control are crucial for the development of these cognitive skills. Activities that challenge children's thinking, encourage exploration, and require them to follow rules and make decisions support the maturation of executive functions. However, adversity, such as chronic stress or instability, can impair the development of these critical skills. Children exposed to high levels of stress may find it difficult to focus, control impulses, and solve problems effectively, which can impact their academic performance and social interactions.

Overall, early childhood is a period of profound growth and development in language acquisition, emotional regulation, and executive functions. Ensuring that children have access to a nurturing and stimulating environment during these formative years is essential for their overall development. Understanding the critical nature of this period highlights the importance of early intervention and support for children exposed to adverse conditions, promoting their well-being and long-term success.

Recognizing these critical periods highlights the importance of early intervention and support for children exposed to adversity. Providing a nurturing and stimulating environment during these sensitive windows can help mitigate the negative effects of adverse experiences and promote healthy neurodevelopment. Understanding the timing and nature of these critical periods is essential for developing effective strategies to support children at risk and optimize their developmental outcomes.

Mechanisms Linking Early Adversity to Neurodevelopment

Early adversity can significantly impact neurodevelopment through various mechanisms, including changes in brain structure and function, alterations in stress response systems, and epigenetic modifications. [80] Understanding these mechanisms is crucial for comprehending how adverse experiences in childhood can lead to long-term cognitive, emotional, and behavioral outcomes.

Neurobiological Mechanisms

Early adversity can lead to profound changes in brain structure and function. Neuroimaging studies have shown that children who experience maltreatment, neglect, or other forms of adversity often exhibit alterations in brain volume, connectivity, and function. Key areas affected include the prefrontal cortex, the amygdala, the hippocampus, and the corpus callosum. [81]

The prefrontal cortex, which is involved in executive functions such as planning, decision-making, and impulse control, is particularly vulnerable to the effects of early adversity. This region of the brain is crucial for higher-order cognitive processes and self-regulation. Studies have shown that children who experience significant adversity often have reduced volume in the prefrontal cortex, which can impair their ability to plan, make decisions, and control impulses. Additionally, altered connectivity within this region has been associated with difficulties in self-regulation, leading to increased risk for behavioral problems such as aggression, impulsivity, and difficulty in maintaining attention and focus.

The amygdala, which plays a central role in processing emotions and detecting threats, often shows increased volume and hyperactivity in children exposed to adversity. This hyperactivity can lead to heightened emotional reactivity and increased anxiety. The amygdala is essential for the emotional response to threats and stress, and when it becomes overactive due to chronic stress or trauma, it can result in a state of constant hyperarousal. This condition makes children more prone to anxiety disorders, fearfulness, and difficulties in emotional regulation. They may react excessively to perceived threats, even in safe environments, which can further impair their social interactions and overall emotional well-being.

The hippocampus, essential for memory formation and stress regulation, may exhibit reduced volume in response to chronic stress and trauma. The hippocampus is crucial for learning and memory consolidation, and its reduced volume can impair cognitive functions such as learning, memory, and spatial navigation. Chronic exposure to high levels of stress hormones like cortisol can damage hippocampal neurons, leading to difficulties in forming new memories and recalling information. This impairment can hinder academic performance and make it

challenging for children to cope with new learning experiences. Furthermore, the hippocampus plays a role in regulating the HPA axis and stress responses, so its damage can contribute to difficulties in managing stress, perpetuating a cycle of chronic stress and impaired cognitive function.

The corpus callosum, which facilitates communication between the brain's hemispheres, can also be affected by early adversity. Adverse experiences can lead to reduced integrity of this structure, impacting the coordination of cognitive and emotional processes. The corpus callosum is essential for integrating information between the left and right hemispheres of the brain, allowing for coherent cognitive and emotional functioning. Damage to this structure can result in deficits in tasks that require the integration of verbal and spatial information, such as reading and problem-solving. It can also affect emotional processing, leading to difficulties in understanding and expressing emotions appropriately. Children with compromised corpus callosum integrity may struggle with complex cognitive tasks and exhibit inconsistent or inappropriate emotional responses.

Overall, the neurobiological mechanisms linking early adversity to changes in brain structure and function underscore the critical importance of early intervention and support. By understanding how specific brain regions are affected, targeted therapeutic and supportive strategies can be developed to mitigate these impacts and promote healthy brain development. Early interventions that provide stable, nurturing environments and address the specific needs of children exposed to adversity can help improve their cognitive, emotional, and behavioral outcomes, ultimately enhancing their resilience and well-being.

Stress Response Systems

The HPA axis is a central component of the body's stress response system, and early adversity, particularly chronic stress, can dysregulate this system, leading to long-term alterations in neurodevelopment. The HPA axis controls the release of cortisol, a hormone that helps manage stress, and dysregulation of this system due to early adversity can result in several significant impacts on a child's development.

One major effect of HPA axis dysregulation is elevated cortisol levels. Chronic stress can lead to persistently high levels of cortisol, which can be neurotoxic and cause damage to critical brain regions such as the hippocampus and prefrontal cortex. The hippocampus, involved in memory formation and stress regulation, and the prefrontal cortex, responsible for executive functions like decision-making and impulse control, are particularly vulnerable to the damaging effects of prolonged high cortisol levels. This can result in impairments in cognitive functions, such as difficulties with learning, memory, and problem-solving. Additionally, high cortisol levels are associated with increased vulnerability to mental health disorders, including anxiety and depression, due to their impact on brain regions that regulate mood and emotions.

Altered stress responsivity is another consequence of HPA axis dysregulation. Children exposed to early adversity may develop either an exaggerated or blunted stress response. An exaggerated stress response means that the child reacts excessively to stressors, even those that are relatively minor or non-threatening. This heightened reactivity can manifest as increased anxiety, hypervigilance, and difficulty calming down after a stressful event. On the other hand, a blunted stress response indicates that the child does not react adequately to stress, which can be equally problematic. This blunted responsivity can lead to a lack of appropriate emotional reactions and difficulties in recognizing and responding to danger, potentially putting the child at risk in situations that require a rapid stress response. Both altered stress responses can interfere with a child's ability to cope with everyday challenges and regulate their emotions effectively. [82]

Dysregulation of the HPA axis can also impact other neuroendocrine functions, influencing growth, immune function, and metabolic processes. For example, chronic stress and elevated cortisol levels can suppress the immune system, making children more susceptible to infections and illnesses. This suppression can lead to frequent health issues that further disrupt a child's development and well-being. Additionally, chronic stress can affect growth hormone production, potentially leading to growth delays and other developmental concerns. Metabolic processes can also be altered, increasing the risk of conditions such as obesity and metabolic syndrome, which have their own long-term health consequences.

The combined effects of these neuroendocrine disruptions highlight the critical role of the HPA axis in linking early adversity to long-term health outcomes. The impact of chronic stress on this system underscores the importance of providing supportive environments and interventions for children who have experienced significant adversity. Early interventions that reduce stress and promote healthy coping mechanisms can help mitigate the negative effects of HPA axis dysregulation. For example, therapeutic approaches that focus on building resilience, such as trauma-informed care and mindfulness practices, can help children develop better stress management skills and improve their overall emotional and physical health. Addressing the root causes of chronic stress, such as ensuring stable and nurturing caregiving environments, can also play a vital role in supporting the healthy development of children exposed to early adversity.

Epigenetics

Epigenetic mechanisms provide a crucial link between environmental experiences and gene expression, and early adversity can lead to epigenetic changes that profoundly influence brain development and function without altering the underlying DNA sequence. These changes include DNA methylation, histone modification, and the impact of non-coding RNAs, all of which play significant roles in how genes are expressed in response to environmental factors.

DNA methylation involves the addition of methyl groups to DNA molecules, typically acting to suppress gene expression. Early adversity, such as exposure to chronic stress or trauma, can increase the methylation of specific genes, which can alter their normal function. For instance, increased methylation of the glucocorticoid receptor gene has been observed in individuals who experienced early adversity. The glucocorticoid receptor is critical for regulating the body's response to stress, and its reduced expression can impair the ability to manage stress effectively. This epigenetic change can lead to heightened stress sensitivity and an increased risk for mental health disorders such as anxiety and depression. [83]

Histone modification is another epigenetic mechanism affected by early adversity. Histones are proteins around which DNA is

wound, and their modification can influence the accessibility of genes for transcription. Adverse experiences can lead to changes in histone acetylation or methylation, altering how tightly or loosely DNA is coiled around histones. These modifications can either enhance or suppress gene expression, impacting genes involved in neural plasticity, stress regulation, and emotional regulation. For example, changes in histone modification may affect genes that regulate synaptic connectivity and neural growth, leading to altered brain structure and function. These changes can contribute to difficulties in learning, memory, and emotional regulation, highlighting the long-term impact of early adversity on cognitive and emotional development.

Non-coding RNAs, which do not encode proteins but play roles in regulating gene expression, are also influenced by early adversity. These molecules, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), can affect the expression of genes critical for brain development and function. Adverse experiences can alter the levels and activity of non-coding RNAs, impacting the regulation of genes involved in neural plasticity, synaptic function, and stress responses. For example, specific miRNAs may be upregulated or downregulated in response to stress, leading to changes in the expression of target genes that influence neuronal growth and connectivity. These alterations can have lasting effects on brain development, potentially contributing to cognitive deficits and increased susceptibility to mental health disorders.

The epigenetic changes induced by early adversity are dynamic and can be influenced by subsequent experiences and interventions. This plasticity offers potential pathways for mitigating the impact of early adversity. Positive experiences and supportive interventions can reverse some of the adverse epigenetic modifications, promoting resilience and recovery. For instance, enriched environments, nurturing caregiving, and therapeutic interventions can lead to beneficial epigenetic changes that enhance neural plasticity and cognitive function. Understanding the epigenetic mechanisms linking early adversity to neurodevelopment underscores the importance of providing supportive environments and targeted interventions for affected children.

Addressing these epigenetic changes through early intervention and support can help improve developmental outcomes and reduce the long-term impact of early adversity. Interventions that focus on creating stable, nurturing environments and promoting positive experiences can counteract the negative effects of adverse experiences on gene expression and brain development. By targeting the underlying epigenetic mechanisms, it is possible to enhance resilience and promote healthy development in children who have experienced early adversity.

Neurodevelopmental Outcomes of Early Adversity

Early adversity has profound and multifaceted effects on neurodevelopment, influencing cognitive, emotional, behavioral, and social outcomes. Understanding these outcomes is crucial for developing effective interventions and support systems to mitigate the long-term impacts on children exposed to adverse experiences. [84]

Cognitive Outcomes

Early adversity can significantly impair cognitive development, affecting learning, memory, and executive functions. Children who experience maltreatment, neglect, or chronic stress often exhibit deficits in these areas. For instance, adversity can hinder the development of the hippocampus, a brain region critical for memory formation and retrieval. This impairment can lead to difficulties in learning new information and recalling previously learned material, which negatively impacts academic performance and overall cognitive abilities. Moreover, the prefrontal cortex, which is responsible for executive functions such as planning, decision-making, and impulse control, can also be adversely affected. Children exposed to early adversity may struggle with tasks that require these executive functions, leading to challenges in organizing their thoughts, controlling impulses, and making informed decisions. These cognitive deficits can persist into adolescence and adulthood, affecting educational and occupational outcomes and overall life success.

Emotional and Behavioral Outcomes

The effects of early adversity on emotional regulation and mental health are profound. Children who experience significant adversity often struggle with emotional regulation, which is the ability to manage and respond to emotional experiences appropriately. This can manifest as heightened emotional reactivity, difficulty calming down, and challenges in coping with stress. Consequently, these children are at an increased risk for mental health disorders such as depression and anxiety. The chronic stress associated with adverse experiences can lead to persistent feelings of sadness, hopelessness, and worry, which can impair daily functioning and quality of life. Behavioral issues are also common among children exposed to early adversity. These children may exhibit increased aggression, defiance, and conduct disorders. The inability to regulate emotions and cope with stress effectively can result in disruptive behaviors both at home and in school. Such behavioral problems can lead to disciplinary issues, social isolation, and further exacerbate emotional difficulties, creating a cycle of maladaptive behavior and emotional distress. [85]

Social Outcomes

Early adversity can profoundly impact social development and relationships. Children who experience adverse conditions often face challenges in forming and maintaining healthy relationships. Attachment theory suggests that secure attachments formed in early childhood are critical for social development. However, children exposed to neglect, abuse, or instability may struggle to develop secure attachments, leading to difficulties in trusting others and forming close relationships. These children may exhibit social withdrawal, reluctance to engage with peers, and difficulties in understanding social cues and norms. The lack of positive social interactions can hinder the development of social skills, such as empathy, cooperation, and effective communication. As a result, these children may experience social isolation, bullying, and difficulties in building supportive peer networks. The impact on social development can persist into adolescence and adulthood, affecting the ability to establish and maintain intimate relationships, friendships, and professional connections.

Understanding the neurodevelopmental outcomes of early adversity highlights the critical need for early intervention and support. By addressing the cognitive, emotional, behavioral, and social challenges faced by children exposed to adverse ex-

periences, it is possible to mitigate the long-term impacts and promote resilience. Interventions that provide stable, nurturing environments, promote positive relationships, and offer therapeutic support can help improve outcomes for these children. Early identification and targeted support are essential for fostering healthy development and ensuring that children have the opportunity to reach their full potential despite the challenges of early adversity. [86]

Resilience and Protective Factors

Understanding resilience and the protective factors that can buffer children from the adverse effects of early adversity is crucial for developing effective support systems and interventions. These factors can be broadly categorized into individual traits, environmental factors, and specific interventions that collectively promote positive neurodevelopmental outcomes. [87]

Individual Factors

Certain individual traits can enhance a child's resilience in the face of adversity. Temperament plays a significant role; children with a positive, easy-going temperament tend to cope better with stress and are more likely to form positive relationships with caregivers and peers. High intelligence is another protective factor, as it often correlates with better problem-solving skills and adaptive coping mechanisms. Additionally, children with strong self-regulation skills, including the ability to manage emotions and behaviors, are better equipped to navigate stressful situations. These traits can help children remain resilient even when exposed to significant challenges, reducing the negative impact of early adversity on their development.

Environmental Factors

Supportive relationships and stable environments are critical in mitigating the effects of early adversity. The presence of at least one stable, caring, and supportive adult in a child's life can significantly enhance resilience. This relationship can provide emotional security, model positive coping strategies, and offer practical support during difficult times. Stable environments, including consistent routines and safe living conditions, also play a vital role in promoting resilience. Schools and communities that offer supportive and nurturing environments can further bolster a child's ability to cope with adversity. These environments can provide opportunities for positive social interactions, learning, and personal growth, helping children develop the skills and confidence needed to overcome challenges.

Interventions

Effective interventions and programs can support neurodevelopment in children exposed to early adversity. Trauma-informed care is a comprehensive approach that recognizes the impact of trauma on development and incorporates strategies to promote healing and resilience. This approach can be applied in various settings, including schools, healthcare, and social services, to create supportive environments that address the needs of children with traumatic experiences. Parenting programs that teach caregivers positive parenting techniques and stress management can also be beneficial. These programs can help caregivers provide the stable, nurturing environment essential for healthy development. Additionally, therapeutic interventions such as cognitive-behavioral therapy (CBT) can help children process and cope with their experiences, improving emotional regulation and reducing the risk of mental health disorders. Community-based programs that offer social support, recreational activities, and academic assistance can also play a significant role in fostering resilience. By providing children with opportunities to build positive relationships, develop skills, and achieve successes, these programs can counteract the negative effects of early adversity.

Understanding the factors that contribute to resilience and implementing effective interventions can help children exposed to early adversity achieve better neurodevelopmental outcomes. By focusing on individual traits, supportive environments, and targeted interventions, it is possible to promote resilience and support the healthy development of children who have faced significant challenges.

Methodological Considerations in Research

Research on the impact of early adversity on neurodevelopment employs various study designs, each with strengths and limitations. Longitudinal studies follow individuals over time, offering insights into long-term effects and developmental trajectories but requiring significant resources and facing participant attrition. Cross-sectional studies compare different individuals at a single point, useful for identifying correlations but limited in establishing causality. Experimental studies, including randomized controlled trials (RCTs), test intervention effectiveness and control for confounding variables, though ethical constraints limit their feasibility with vulnerable populations.

Challenges in this research include ethical considerations, measurement issues, and participant variability. Ethical concerns necessitate protecting vulnerable participants from harm, ensuring informed consent, and maintaining confidentiality. Measurement issues involve accurately capturing diverse adverse experiences and neurodevelopmental outcomes, requiring sophisticated tools such as neuroimaging and cognitive assessments. Participant variability, due to differences in genetics, resilience, and environmental contexts, complicates generalization, demanding large, diverse samples and careful study design.

Future research should integrate multidisciplinary approaches from neuroscience, psychology, genetics, and social sciences to understand the complex interplay between biological, psychological, and environmental factors. More longitudinal and interventional studies are needed to track long-term effects and evaluate intervention effectiveness. Advanced measurement techniques, such as neuroimaging and biomarker analysis, can enhance accuracy and reliability, identifying specific neural pathways and mechanisms affected by early adversity. Additionally, exploring protective factors and resilience mechanisms can inform interventions that promote healthy development in at-risk children. Considering cultural and contextual factors is crucial for generalizing findings and tailoring interventions to specific settings. [88]

Implications for Policy and Practice

Research on early adversity and neurodevelopment should inform child welfare, education, and mental health policies. Prioritizing early identification and intervention can mitigate adverse effects. Child welfare policies should ensure timely support for affected children, including funding for stable environments and

trauma-informed care training for caregivers. Educational policies should integrate social-emotional learning (SEL) curricula and provide resources for trauma-responsive school environments, including mental health services. Mental health policies must expand access to evidence-based therapies, increase funding, and support community-based programs addressing poverty and housing instability. [89]

Practitioners working with children who have experienced early adversity can adopt several strategies. Creating safe, supportive environments, building trust, and being sensitive to trauma signs are essential aspects of trauma-informed care. Early intervention programs, such as parent-child interaction therapy (PCIT), can strengthen attachment and support emotional regulation. Incorporating SEL into schools helps children manage emotions and build relationships. Providing access to therapies that address trauma, like cognitive-behavioral therapy (CBT) and trauma-focused CBT (TF-CBT), is crucial.

Supporting parents through education and resources can help caregivers create supportive environments. A collaborative approach among educators, social workers, and healthcare providers ensures comprehensive support. Additionally, practitioners can advocate for policies and practices that support affected children by participating in policy discussions and raising awareness. [90]

Implementing these strategies and informing policies with research findings can create environments that support healthy development and resilience in children exposed to early adversity.

Conclusion

The review has explored the profound impacts of early childhood adversity on neurodevelopment, revealing how adverse experiences can fundamentally alter brain structure, function, and overall developmental trajectories. Neurobiological changes, including alterations in the prefrontal cortex, amygdala, hippocampus, and corpus callosum, demonstrate how early adversity can impair cognitive functions such as learning, memory, and executive functioning. These structural and functional changes underlie the observed deficits in cognitive development and highlight the critical periods during which the brain is most vulnerable to adverse experiences.

In examining the stress response systems, we found that dysregulation of the HPA axis due to chronic stress leads to elevated cortisol levels, impacting emotional regulation and increasing the risk of mental health disorders like depression and anxiety. The role of epigenetics further elucidates how early adversity can induce changes in gene expression, affecting brain development and function without altering the DNA sequence. These epigenetic changes can persist throughout life, influencing susceptibility to various neurodevelopmental and mental health issues.

The review also highlighted the diverse outcomes of early adversity, including cognitive deficits, emotional and behavioral problems, and social development challenges. Children exposed to early adversity often face significant hurdles in learning and memory, emotional regulation, and social interactions, leading to long-term implications for their academic and personal lives. The importance of resilience and protective factors was emphasized, noting that individual traits such as temperament and intelligence, along with supportive relationships and stable environments, can buffer against the negative impacts of early adversity.

Methodological considerations underscored the necessity of employing robust study designs, such as longitudinal and multidisciplinary approaches, to capture the long-term effects and complex interplay of factors influencing neurodevelopment. Ethical considerations and measurement challenges were also discussed, emphasizing the need for accurate and reliable assessment tools and the importance of protecting vulnerable populations in research.

Policy implications derived from these findings advocate for early identification and intervention strategies in child welfare, education, and mental health services. Policies should focus on creating trauma-informed care systems, integrating social-emotional learning (SEL) in schools, and expanding access to mental health services. Practitioners are encouraged to adopt trauma-informed approaches, provide early intervention programs, and support parents and caregivers through education and resources.

In conclusion, addressing early childhood adversity is paramount for promoting healthy neurodevelopment and overall well-being. The findings from this review underscore the critical need for comprehensive, multidisciplinary approaches that incorporate individual, familial, and systemic interventions. By fostering stable and nurturing environments, enhancing resilience through targeted interventions, and informing policies with robust research, we can mitigate the detrimental effects of early adversity and support the healthy development of affected children. This collective effort not only improves individual outcomes but also contributes to the creation of a more resilient and healthier society.

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Review Article

Hormonal Underpinnings of Emotional Regulation: Bridging Endocrinology and Psychology

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Abstract

This review explores the intricate relationship between hormonal fluctuations and emotional regulation, emphasizing the critical role of hormones in mood, stress responses, and psychological well-being. By examining key hormones involved in emotional regulation—such as those from the Hypothalamic-Pituitary-Adrenal (HPA) axis, gonadal hormones (estrogen and testosterone), thyroid hormones, oxytocin, and metabolic hormones like insulin, leptin, and ghrelin—we uncover how these biochemical messengers impact emotional states and contribute to mood disorders. The paper discusses methodological challenges and future research directions, highlighting the necessity for interdisciplinary approaches to deepen our understanding of hormonal influences on emotional regulation.

The review underscores the importance of considering hormonal mechanisms in developing targeted treatments for mood disorders, advocating for a holistic perspective that bridges endocrinology and psychology. By integrating current research findings with clinical implications, our objective is to enhance the biological foundation of emotional regulation, paving the way for innovative therapeutic strategies and improved mental health care. This comprehensive overview aims not only to consolidate existing knowledge but also to identify gaps in research, encouraging further exploration into the hormonal underpinnings of emotional states. Through this endeavor, we aspire to contribute to a broader understanding of emotional regulation, offering new perspectives on treating mood disorders and enhancing overall emotional well-being.

Keywords: Hormonal Regulation, Emotional Regulation, Mood Disorders, HPA Axis.

Introduction

Emotional regulation encompasses the myriad strategies individuals deploy to manage and modify their emotional experiences and expressions [1]. This regulatory process is essential for social adaptation[2] psychological well-being [3], and overall mental health [4]. It involves a complex interplay between awareness [5], understanding [6], acceptance [7], and the modulation of emotional responses [8] to meet situational demands and personal goals. While the cognitive and behavioral aspects of emotional regulation have been extensively explored, emerging research underscores a critical yet often overlooked dimension: the biological and hormonal foundations of emotional states and their regulation.

Hormones, as the biochemical messengers of the body [9], play a central role in regulating not only physical processes but also emotional and psychological states [10]. These substances, produced and secreted by various glands within the endocrine system [11], travel through the bloodstream to target organs, exerting their effects on mood, energy levels, and stress responses [12]. The influence of hormones on emotions can be profound, with fluctuations or imbalances in hormonal levels being linked to significant changes in emotional regulation, mood disorders, and overall mental health [13].

The interaction between hormones and emotional regulation is complex and bidirectional [14]. On one hand, emotional states can influence hormonal secretion [15]; for instance, stress triggers the release of cortisol, a hormone that prepares the body to respond to perceived threats. On the other hand, hormones can modulate the intensity and quality of emotional experiences [16]; for example, variations in estrogen and progesterone levels across the menstrual cycle are associated with changes in mood and emotional sensitivity in many women.

This dual influence underscores the need for a comprehensive understanding of the hormonal mechanisms underlying emotional regulation [17]. Several key hormones have been identified as major players in this process, including:

- **Cortisol:** Often referred to as the "stress hormone," cortisol plays a critical role in the body's stress response and has been linked to emotional regulation and mood disorders [18].
- **Estrogen and Testosterone:** These sex hormones are known to influence mood and emotional states, with imbalances being associated with depression and mood

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swings [19].

- **Thyroid Hormones:** Thyroxine (T4) and Triiodothyronine (T3) regulate metabolism and energy levels, and their dysregulation can lead to mood disorders such as depression [20].
- **Oxytocin:** Dubbed the "love hormone," oxytocin is involved in social bonding, trust, and the modulation of social behaviors and emotional responses [21].

Understanding how these and other hormones influence emotional regulation offers a more holistic view of mental health, bridging the gap between biological sciences and psychology. By exploring the hormonal catalysts of emotional regulation, we aim to provide insights into the underlying biological mechanisms that shape our emotional experiences and offer new perspectives on treating mood disorders and improving emotional well-being [22].

The Role of Hormones in Emotional Regulation

Hormones, the biochemical messengers of the body, serve as critical components of the endocrine system, a network of glands that coordinates and regulates a myriad of physiological processes. These substances are secreted directly into the bloodstream and transported to various organs and tissues, where they exert their effects [23]. Beyond their well-known roles in growth, metabolism, reproduction, and homeostasis, hormones are instrumental in the complex domain of emotional regulation [14]. They act at the intersection of physiology and psychology, embodying the connection between the body's internal state and its external expressions of mood and emotion [24].

The endocrine system's interaction with the brain, particularly through the hypothalamus and pituitary gland, underscores the sophisticated level of coordination required to regulate emotional states [25].

The hypothalamus, often considered the endocrine system's master regulator, plays a pivotal role in maintaining homeostasis. It responds to a variety of signals from the brain and body, adjusting hormone production and secretion in response. The pituitary gland, under the influence of the hypothalamus, secretes hormones that regulate other glands in the endocrine system, further influencing emotional regulation [26].

This hormonal influence on emotions is mediated through various pathways and mechanisms:

1. **Neurotransmitter Modulation:** Many hormones interact with neurotransmitters, the chemical messengers of the nervous system, influencing mood, stress responses, and emotional resilience. For instance, cortisol affects neurotransmitter levels such as serotonin and dopamine, which are directly linked to mood and pleasure, respectively [27].
2. **Brain Structure and Function:** Hormones can impact the structure and function of brain regions involved in emotional processing. Estrogen, for example, has neuroprotective effects and influences the activity of the amygdala and prefrontal cortex, areas critical for emotional response and regulation [28].
3. **Stress Response:** HPA axis, a key player in the stress response, demonstrates the direct impact of hormones on emotional regulation. Activation of the HPA axis leads to the release of cortisol, preparing the body for a "fight or flight" response and influencing emotional states [29].
4. **Social and Bonding Hormones:** Oxytocin and vasopressin are hormones that play crucial roles in social bonding, trust, and empathy, directly affecting social behavior and emotional experiences in group settings [30].

Understanding the role of hormones in emotional regulation not only requires a grasp of these biochemical mechanisms but also an appreciation of the individual variability in hormonal responses. Factors such as genetic predispositions, environmental influences, and lifestyle choices can affect hormone levels and their impact on emotional regulation, contributing to the complexity of this dynamic interplay.

Melatonin

Reflecting on the hormonal catalysts of emotional regulation, it becomes evident that understanding, while extensive, remains poised for deeper exploration. Emerging research, particularly on the role of melatonin in synchronizing circadian rhythms and its implications for mood and anxiety disorders, exemplifies the dynamic nature of this field [31]. Such studies not only broaden the perspective on hormonal influences beyond the traditional realms but also illuminate potential pathways for innovative therapeutic interventions. The exploration of melatonin's impact on emotional regulation underscores the necessity for interdisciplinary research approaches that encompass the full spectrum of hormonal activity. As advancements continue, incorporating a broader array of hormonal interactions will be crucial in developing a more comprehensive understanding of their role in emotional well-being and mental health [32].

By exploring the multifaceted roles that hormones play in regulating emotions, we gain insights into the biological underpinnings of psychological states and behaviors. This knowledge is instrumental in developing more nuanced approaches to mental health care, emphasizing the importance of considering hormonal balance in therapeutic interventions for mood disorders and emotional dysregulation [33].

Objective of the Review

The overarching objective of this review is to synthesize and critically evaluate current research on the hormonal mechanisms underlying emotional regulation. In the intricate interplay between the endocrine system and psychological states, hormones emerge as pivotal regulators of mood, stress responses, and overall emotional well-being. Despite the significant advances in our understanding of this relationship, there remain gaps in my knowledge regarding the precise mechanisms through which hormones influence emotional regulation and how these processes contribute to mental health disorders.

To address this, the review seeks to accomplish the following specific aims:

1. **Comprehensive Synthesis:** Provide a comprehensive overview of the current state of research on the hormonal regulation of emotions, summarizing key findings from empirical studies, clinical trials, and meta-analyses. This includes examining the role of major hormones such as cortisol, estrogen, testosterone, thyroid hormones, and oxytocin

in emotional regulation.

2. **Mechanistic Insights:** Delve into the biological and neurochemical pathways through which hormones exert their influence on emotional regulation, highlighting the complex interactions between the endocrine system and the brain.
3. **Psychological and Behavioral Correlations:** Explore the psychological and behavioral implications of hormonal effects on emotional regulation, including the impact on mood disorders, stress-related conditions, and overall mental health.
4. **Identify Research Gaps:** Identify gaps in the current literature where further investigation is needed. This involves pinpointing areas where our understanding of hormonal influences on emotional regulation is limited, contradictory, or evolving.
5. **Future Directions:** Offer recommendations for future research, suggesting potential studies that could address the identified gaps and contribute to a more nuanced understanding of how hormonal regulation intersects with psychological health. This includes advocating for interdisciplinary research approaches that integrate endocrinology, neuroscience, and psychology.
6. **Clinical Implications:** Discuss the potential clinical implications of understanding hormonal mechanisms in emotional regulation. This includes considering how insights into hormonal influences on emotions could inform therapeutic strategies, improve diagnosis and treatment of mood disorders, and lead to the development of personalized medicine approaches.

By achieving these aims, this review intends to bridge the gap between endocrinology and psychology, providing a holistic perspective on the hormonal catalysts of emotional regulation. We aspire to contribute to a deeper understanding of the biological underpinnings of emotional states, offering a foundation for future research and clinical practices aimed at enhancing emotional well-being and mental health.

Hormonal Systems Involved in Emotional Regulation

Cortisol and Emotional Regulation: Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis represents a major part of the body's neuroendocrine system responsible for regulating stress responses, metabolism, immune function, and emotions. Activation of this axis is a prime example of the body's effort to maintain homeostasis in the face of stress [34]. The process begins in the hypothalamus, which releases corticotropin-releasing hormone (CRH) in response to a stress signal. CRH then stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn prompts the adrenal glands to produce cortisol. Once released into the bloodstream, cortisol prepares the body to handle stress by increasing glucose availability, enhancing the brain's use of glucose, and suppressing nonessential functions in a fight-or-flight response [35].

Cortisol's Role in Stress Response

Cortisol plays a pivotal role in the body's response to stress, serving both to mobilize resources necessary to deal with stressors and to restore equilibrium afterward. It affects various bodily functions to increase alertness, energy levels, and the ability to respond to environmental demands [36]. However, cortisol's influence extends beyond the physical, impacting emotional and psychological states as well. It modulates areas of the brain involved in emotional regulation, such as the amygdala and prefrontal cortex, affecting mood, motivation, and fear [37].

Impact on Emotional Regulation

While cortisol is essential for survival, its dysregulation can lead to emotional and psychological disturbances. Chronic activation of the HPA axis and prolonged exposure to high levels of cortisol have been linked to a range of mental health issues, including anxiety, depression, and post-traumatic stress disorder (PTSD) [38]. Such conditions often arise from or result in impaired emotional regulation, where individuals struggle to manage and respond to their emotional experiences effectively [39].

Excessive cortisol can impair the function of the hippocampus, a brain region vital for memory and emotional regulation, leading to difficulties in forming and retrieving memories and in managing emotional responses [40]. This can exacerbate the symptoms of stress-related disorders, creating a feedback loop that further hinders emotional regulation [41].

Furthermore, variations in cortisol levels throughout the day, known as the diurnal rhythm, are associated with mood fluctuations. Disruptions in this rhythm, such as those seen in shift workers or individuals with irregular sleep patterns, can negatively affect emotional well-being [42].

Therapeutic Implications

Understanding the role of the HPA axis and cortisol in emotional regulation opens pathways for therapeutic interventions. Treatments that target HPA axis dysregulation, such as pharmacological agents that modulate cortisol levels or psychological interventions that reduce perceived stress, hold promise for improving emotional regulation and mental health [43].

Additionally, lifestyle interventions, including stress management techniques, regular physical activity, and sleep hygiene, can help normalize HPA axis function and enhance emotional well-being [44].

Gonadal Hormones: Estrogen and Testosterone in Emotional Regulation

Gonadal hormones, estrogen, and testosterone, produced by the ovaries and testes respectively, play critical roles beyond their reproductive functions. They are pivotal in modulating mood, aggression, and emotional well-being, demonstrating the intricate relationship between hormonal levels and psychological states [45].

Estrogen and Mood

Estrogen is often termed a "mood enhancer" due to its positive effects on brain function and mood. It interacts with serotonin and other neurotransmitters involved in mood regulation, enhancing their availability and the sensitivity of their receptors [46]. Estrogen's neuroprotective properties also support cognitive functions, including memory and attention, which can indirectly

influence emotional regulation and mood stability [47].

Fluctuations in estrogen levels, such as those occurring during the menstrual cycle, pregnancy, or menopause, can significantly affect emotional well-being [48]. For example, periods of rapid estrogen decline are associated with mood swings, irritability, and increased susceptibility to depression and anxiety. This underscores the hormone's complex role in modulating mood and highlights the potential for hormonal interventions in treating mood disorders, particularly those that manifest or worsen in relation to menstrual cycle phases or menopausal transition [13].

Testosterone and Aggression

Testosterone is often associated with aggression, risk-taking behaviors, and dominance. While it is simplistic to draw a direct line between testosterone levels and aggressive behavior, research suggests a correlation, particularly in males. High testosterone levels have been linked to increased irritability, impulsivity, and aggression, potentially exacerbating conflict in social interactions and impacting emotional well-being [49].

However, the relationship between testosterone and aggression is nuanced and influenced by environmental and social factors. For instance, social challenges or threats can elevate testosterone levels, suggesting that its role in aggression may also be a response to external stimuli rather than a direct cause [50].

Testosterone and Mood

Apart from its links to aggression, testosterone plays a vital role in mood regulation for both men and women. Low levels of testosterone (a condition known as hypogonadism) are associated with depression, fatigue, and a decreased sense of well-being [51].

Testosterone replacement therapy has been shown to improve mood and energy levels in men with hypogonadism, indicating the hormone's importance in maintaining emotional equilibrium [52].

Age-related changes

Furthermore, the critical examination of gonadal hormones in emotional regulation invites attention to age-related hormonal changes and their profound impacts on mood and well-being. Particularly noteworthy is the concept of andropause, akin to menopause in women, where men experience a gradual decline in testosterone levels, potentially affecting emotional stability, mood, and cognitive functions [53]. This parallel underscores a broader spectrum of hormonal influences across different stages of life, highlighting the intricate balance between estrogen and testosterone and their pivotal roles in maintaining emotional regulation [54]. The exploration of andropause, alongside menopause, accentuates the need for a gender-inclusive understanding of hormonal transitions and their psychological implications. It beckons further research into these age-related hormonal shifts, aiming to unravel their complex relationship with mood disorders and emotional well-being, thereby fostering a more holistic approach to mental health across the lifespan [55].

Therapeutic Implications

Understanding the effects of estrogen and testosterone on emotional regulation offers valuable insights for developing gender-sensitive approaches to treating mood disorders and emotional dysregulation. Hormonal therapies, such as estrogen replacement therapy during menopause or testosterone replacement therapy for hypogonadal men, may provide effective strategies for improving mood and emotional well-being when carefully managed [56].

Thyroid Hormones and Emotional Regulation

The thyroid gland plays a vital role in maintaining the body's metabolic rate, energy production, and overall homeostasis. The hormones it secretes, T4 and T3, influence nearly every organ system, including the brain, where they impact neurotransmitter activity, neurogenesis, and the overall health of neural tissue. Given this extensive reach, it's perhaps unsurprising that thyroid hormone imbalances can profoundly affect mental health [57].

Hyperthyroidism and Mood Disorders

Hyperthyroidism, characterized by elevated levels of thyroid hormones, can lead to symptoms that mimic anxiety and other mood disorders. Individuals with hyperthyroidism often experience increased nervousness, restlessness, irritability, and mood swings. The physiological state induced by excess thyroid hormones can mimic a chronic stress response, leading to an enhanced sense of vigilance or agitation, which can exacerbate or mimic the symptoms of anxiety disorders [58].

Additionally, hyperthyroidism can cause difficulty sleeping, rapid heart rate, and other physical symptoms that further contribute to emotional distress and dysregulation. The overlap of these symptoms with anxiety and mood disorders makes accurate diagnosis and treatment crucial [59].

Hypothyroidism and Depression

Conversely, hypothyroidism, or insufficient thyroid hormone production, is often associated with depression. Symptoms of hypothyroidism, such as fatigue, lethargy, weight gain, and decreased concentration, closely parallel those of depressive disorders, leading to challenges in distinguishing between the two conditions. The reduced metabolic rate and energy production in hypothyroidism can contribute to a lowered mood, diminished motivation, and overall decreased sense of well-being [60].

Studies have shown that individuals with hypothyroidism have a higher prevalence of depression than the general population. Furthermore, even subclinical hypothyroidism, where hormone levels are borderline low, has been linked to increased risk of depression and cognitive dysfunction [61].

Interactions between thyroid disorders and autoimmune diseases

The intersection of thyroid disorders and autoimmune diseases represents a complex layer in understanding hormonal influences on emotional regulation. Notably, autoimmune thyroiditis, such as Hashimoto's disease, exemplifies this complexity by being intricately linked with an increased prevalence of mood disorders [62]. The autoimmune attack on thyroid tissue not only disrupts hormonal balance but also introduces an inflammatory response that may further exacerbate emotional dysregulation [63]. This association underscores the challenges faced in diagnosing and treating mood disorders within the context of concurrent autoimmune conditions. The bidirectional nature of thyroid function and immune system activity invites a more

nuanced approach to treatment, necessitating considerations beyond standard hormonal replacement therapies. It highlights the importance of an integrated care model that addresses the autoimmune component as a critical factor in restoring emotional equilibrium and overall mental health [64].

Therapeutic Implications

The bidirectional relationship between thyroid function and emotional well-being underscores the importance of screening for thyroid dysfunction in patients presenting with mood disorders. Proper diagnosis and treatment of thyroid conditions can lead to significant improvements in mood and cognitive function. For example, thyroid hormone replacement therapy in hypothyroidism often alleviates depressive symptoms, while treatments that normalize thyroid hormone levels in hyperthyroidism can reduce anxiety and agitation [65].

Understanding the role of thyroid hormones in emotional regulation and mood disorders highlights the necessity of a holistic approach to mental health, considering the potential contributions of endocrine factors to psychological conditions. It also points to the importance of interdisciplinary collaboration in the diagnosis and treatment of mood disorders, ensuring that patients receive comprehensive care that addresses both the psychological and physiological aspects of their condition [66].

Oxytocin: Bonding, Trust, and Emotional Regulation

Facilitation of Social Bonds

Oxytocin is integral to forming social bonds, including maternal behaviors, pair bonding, and group cohesion. Its release during childbirth and breastfeeding helps establish the initial mother-infant bond, a critical aspect of human development [67]. Beyond maternal behaviors, oxytocin facilitates social bonding by enhancing the rewarding aspects of social interactions and reducing social anxieties, promoting feelings of contentment and security in relationships [68].

Enhancement of Trust

Oxytocin's role in trust is one of its most fascinating aspects. Studies have shown that oxytocin increases individuals' trust in others in social and economic exchanges, even in the absence of personal familiarity or when the risk of betrayal is high [69]. This effect suggests that oxytocin acts on the brain's reward and fear systems, lowering defenses and inhibiting the fear responses associated with social betrayal, thus facilitating cooperative behaviors and trust [70].

Regulation of Emotional Responses

Oxytocin also plays a significant role in regulating emotional responses, particularly in the context of social interactions. It can diminish the stress response, reducing levels of cortisol and mitigating the fight-or-flight reaction in socially threatening situations. By doing so, oxytocin promotes calmness and reduces anxiety, enhancing individuals' ability to navigate social complexities and maintain emotional balance [67].

Furthermore, oxytocin has been implicated in enhancing empathy and the ability to read emotional cues in others, crucial components of effective social communication and emotional regulation. By facilitating a better understanding of others' emotional states, oxytocin strengthens social connections and promotes prosocial behavior [71].

Genetic factors influencing oxytocin receptor function

Incorporating the nuanced role of genetic factors into the discourse on oxytocin and its impact on emotional regulation unveils a fascinating layer of complexity. Variations in the OXTR gene, which encodes the oxytocin receptor, have been implicated in modulating individual differences in social behavior, emotional regulation, and susceptibility to mood disorders [72]. Studies suggest that certain polymorphisms within the OXTR gene may influence the efficacy of oxytocin receptor signaling, potentially affecting an individual's capacity for social bonding, empathy, and processing of social cues [73]. These genetic variations could explain the wide range of responses to social stressors and predispositions to conditions such as anxiety or depression. Recognizing the influence of OXTR gene polymorphisms not only enriches our understanding of the biological underpinnings of emotional and social regulation but also opens the door to personalized medical approaches. Tailoring interventions that consider an individual's genetic makeup, particularly in the context of oxytocin signaling, may enhance therapeutic outcomes for mood disorders and improve strategies for enhancing social functioning and emotional well-being. This genetic perspective underscores the importance of integrating genomics with neuroendocrinology to pave the way for precision medicine in psychiatry and behavioral health [74].

Therapeutic Implications

Given its profound effects on social behavior and emotional regulation, oxytocin has been investigated as a potential therapeutic agent for a range of conditions characterized by social deficits and emotional dysregulation, such as autism spectrum disorders, social anxiety, and certain forms of depression [75]. While the therapeutic application of oxytocin is still under investigation, preliminary studies suggest that oxytocin administration can enhance social cognition, improve emotional recognition, and reduce social anxiety in some individuals [76].

However, the complexity of oxytocin's effects and its varied influence depending on individual and contextual factors necessitate further research to understand its potential as a therapeutic tool fully. The promise of oxytocin lies not only in its capacity to enhance social bonding and trust but also in its potential to illuminate the neurochemical pathways that underlie these fundamental human experiences [77].

Other Hormones: Linking Metabolic States to Emotional Regulation

Insulin and Mood Regulation

Insulin, a hormone produced by the pancreas, plays a critical role in glucose metabolism, allowing cells to absorb glucose from the blood for energy. Beyond its metabolic functions, insulin has been implicated in brain function and mood regulation [78]. Insulin receptors are widely distributed in the brain, particularly in regions involved in mood and cognition, such as

the hippocampus and prefrontal cortex. Dysregulation of insulin signaling in the brain can lead to cognitive impairments and has been associated with mood disorders [79].

Studies have suggested a link between insulin resistance—a condition in which cells become less responsive to insulin—and depression. Insulin resistance can disrupt the balance of neurotransmitters and impair neuronal growth and survival, potentially contributing to depressive symptoms. Moreover, the physiological stress of managing chronic conditions like diabetes, which involves insulin management, can also affect emotional well-being, underscoring the complex relationship between insulin regulation and mood [80].

Leptin, Satiety, and Emotional Well-being

Leptin is a hormone produced by adipose (fat) tissue that signals satiety to the brain, helping to regulate energy balance and body weight. Interestingly, leptin receptors are found in brain areas involved in emotion and reward processing, suggesting that leptin may influence mood and emotional responses. Low levels of leptin have been associated with increased appetite and reduced motivation, which can contribute to the development of obesity [81]

Emerging research indicates that leptin may play a role in modulating mood and cognitive functions, with leptin resistance (a condition often seen in obesity) being linked to depressive-like behaviors in animal models. Furthermore, leptin has been investigated for its potential antidepressant properties, with some studies suggesting that leptin administration can produce antidepressant-like effects in certain contexts [82].

Ghrelin, Hunger, and Mood

Ghrelin, often referred to as the "hunger hormone," is produced in the stomach and signals the brain to stimulate appetite. Like leptin, ghrelin's influence extends beyond metabolic regulation to affect mood and emotional states [83]. High levels of ghrelin have been associated with stress-induced eating and may enhance the rewarding aspects of food, linking hunger directly with emotional states [84].

Interestingly, ghrelin has been shown to have anxiolytic and antidepressant effects in animal models, suggesting that it plays a complex role in emotional regulation [85]**.** The hormone appears to promote stress resilience and may have protective effects against stress-induced depression. This relationship between ghrelin and mood underscores the potential therapeutic implications of understanding and modulating ghrelin levels in treating mood disorders and emotional dysregulation [86].

Role of Vitamin D

Exploring the role of vitamin D in emotional regulation adds a compelling dimension to the hormonal influences on mood and mental health. Vitamin D, often referred to as the "sunshine vitamin," exerts hormone-like actions, with its receptors widely distributed throughout the brain, indicating its potential impact on neurological and emotional processes. Emerging evidence has drawn a correlation between vitamin D deficiency and an increased risk of mood disorders, including depression and anxiety, as well as cognitive impairments. The neuroprotective properties of vitamin D, along with its influence on neurotransmitter synthesis and brain plasticity, suggest a significant role in maintaining emotional balance and cognitive function.[87]

Consequently, the potential for vitamin D supplementation as an adjunctive treatment in mood disorders represents an area ripe for further investigation. Research exploring optimal vitamin D levels for emotional regulation and the efficacy of supplementation in improving mood disorder symptoms could provide valuable insights into non-traditional approaches to mental health treatment. This burgeoning field underscores the necessity of broadening our perspective on the hormonal underpinnings of emotional well-being, integrating nutritional and hormonal therapies into holistic psychiatric care [88].

Mood Disorders: Hormonal Imbalances and Their Impact

Depression and Hormonal Imbalances

Depression is a multifaceted mood disorder characterized by persistent feelings of sadness, loss of interest, and a range of emotional and physical symptoms. Research has identified several hormonal systems implicated in depression, highlighting the role of cortisol, thyroid hormones, and sex hormones in its pathophysiology [89].

- **Cortisol:** Elevated cortisol levels, indicative of HPA axis dysregulation, have been frequently observed in individuals with depression. The chronic stress response associated with increased cortisol can exacerbate depressive symptoms, impairing emotional regulation and contributing to the neurobiological changes seen in depression [90].
- **Thyroid Hormones:** Both hyperthyroidism and hypothyroidism have been linked to depressive symptoms. Thyroid hormone imbalances can affect neurotransmitter levels and brain function, influencing mood and cognitive processes central to depression [91].
- **Sex Hormones:** Fluctuations in estrogen and testosterone levels have also been associated with depression. For example, postpartum depression has been linked to rapid hormonal changes after childbirth, and testosterone deficiency in men can contribute to depressive symptoms [92].

Bipolar Disorder and Hormonal Fluctuations

Bipolar disorder, characterized by mood swings between manic/hypomanic episodes and depressive episodes, has also been associated with hormonal imbalances [93]. Research suggests that the HPA axis may be overactive during manic phases and underactive during depressive phases, indicating a complex relationship between cortisol levels and bipolar symptomatology. Additionally, thyroid dysfunction has been observed at a higher rate in individuals with bipolar disorder, with some studies suggesting that thyroid hormone supplementation may stabilize mood in certain cases [94].

Anxiety Disorders and Hormonal Dysregulation

Anxiety disorders, encompassing conditions like generalized anxiety disorder, panic disorder, and social anxiety disorder, have been linked to dysregulation in several hormonal systems. The HPA axis is particularly relevant, as heightened and prolonged cortisol release in response to stress can increase susceptibility to anxiety disorders [95]. Furthermore, sex hormones like

estrogen and progesterone have been implicated in anxiety, with fluctuations during the menstrual cycle, pregnancy, and menopause potentially affecting anxiety levels [96].

In the exploration of hormonal influences on mood disorders, the literature presents a landscape marked by both concordance and contention. Notably, while a substantial body of research underscores the link between cortisol levels and depression, findings are not universally consistent. Some studies report elevated cortisol levels in depressed individuals, suggesting a hyperactive HPA axis, whereas others document normal or even reduced cortisol levels, particularly in cases of chronic depression. This discrepancy may stem from factors such as the stage of depression, individual variability in stress response, and the presence of comorbid conditions, which can obscure the relationship between cortisol and mood [97].

Furthermore, the role of gonadal hormones in mood disorders, particularly depression, illustrates the field's complexity. While the decline in estrogen levels during menopause is often correlated with an increased risk of depression, the preventive and therapeutic efficacy of estrogen replacement therapy (ERT) remains a subject of debate [98]. Some clinical trials suggest that ERT can mitigate depressive symptoms in perimenopausal women, yet other studies caution against potential risks and the lack of long-term benefits, highlighting the need for personalized treatment approaches [99].

These examples of conflicting findings in the literature on mood disorders underscore the challenges inherent in delineating the hormonal underpinnings of emotional regulation. They reflect the multifactorial nature of mood disorders, where hormonal dysregulation interacts with genetic, environmental, and psychosocial factors in complex ways. This complexity necessitates a cautious interpretation of research findings and a critical consideration of individual differences in hormonal sensitivity and response mechanisms. [100]

Research Gaps and Future Directions

While significant advances have been made in understanding the hormonal underpinnings of mood disorders, several research gaps remain. The precise mechanisms by which hormonal imbalances contribute to mood disorders, the role of individual variability, and the effects of hormonal interventions on these conditions are areas requiring further investigation. Future research should also explore the interplay between hormonal systems and other biological, psychological, and environmental factors in the development and treatment of mood disorders.

Stress-Related Disorders: The Role of HPA Axis Dysregulation

Post-Traumatic Stress Disorder (PTSD)

PTSD is a condition characterized by persistent mental and emotional stress following the experience or witnessing of a traumatic event. Individuals with PTSD often exhibit a hyperactive or hypoactive stress response, indicating dysregulation of the HPA axis [101]. Research has shown that cortisol levels in PTSD patients may be lower than average, contrary to what might be expected in chronic stress conditions. This paradoxical response suggests a complex alteration in the feedback mechanisms regulating the HPA axis, possibly as an adaptive response to prolonged exposure to stress hormones [102].

Furthermore, the sensitivity of glucocorticoid receptors within the HPA axis may be increased in individuals with PTSD, leading to an enhanced feedback inhibition of cortisol production. This altered feedback sensitivity can contribute to the symptoms of PTSD, including heightened reactivity to stress, flashbacks, and difficulty in extinguishing fear-related memories [103].

Other Stress-Related Disorders

Beyond PTSD, dysregulation of the HPA axis has been implicated in various stress-related disorders, including generalized anxiety disorder (GAD), acute stress disorder, and adjustment disorders. In these conditions, chronic activation of the HPA axis can lead to persistently elevated cortisol levels, which, over time, may contribute to a range of physiological and psychological effects. For example, chronic stress and elevated cortisol levels can impair cognitive functions, such as memory and attention, exacerbate mood disturbances, and increase vulnerability to anxiety and depressive disorders [104].

HPA Axis and Resilience to Stress

It's important to note that the relationship between HPA axis functioning and stress-related disorders is not solely one of pathology. Variability in HPA axis reactivity among individuals can influence resilience to stress and susceptibility to stress-related disorders [105]. Factors such as genetic predisposition, early life experiences, and environmental exposures can affect HPA axis regulation, potentially moderating the impact of traumatic events or chronic stress on psychological health [106].

Therapeutic Implications

Understanding the role of HPA axis dysregulation in stress-related disorders offers potential avenues for treatment. Interventions aimed at normalizing HPA axis function, such as psychotherapy, pharmacotherapy, and stress management techniques, can be effective in reducing symptoms and improving outcomes in individuals with PTSD and other stress-related conditions. Additionally, research into HPA axis modulation presents opportunities for developing novel therapeutic strategies targeting the biological underpinnings of stress resilience and vulnerability [107].

Impact of Life Stages on Emotional Regulation

Puberty

Puberty marks a period of rapid physical and psychological development, driven by surges in sex hormones including estrogen in females and testosterone in males. These hormonal changes can significantly impact emotional regulation during adolescence, contributing to mood swings, increased emotional sensitivity, and heightened vulnerability to stress [108]. The neurodevelopmental changes occurring during puberty, influenced by these hormonal fluctuations, can also affect risk-taking behavior and social dynamics, further complicating emotional regulation during this critical period [109].

Menstruation

The menstrual cycle involves cyclical changes in hormone levels, notably fluctuations in estrogen and progesterone, which can affect emotional well-being. Many women experience pre-

menstrual syndrome (PMS), characterized by mood swings, irritability, and increased emotional sensitivity, in the days leading up to menstruation [110]. For some, these symptoms escalate to premenstrual dysphoric disorder (PMDD), a more severe condition that significantly impairs emotional regulation and quality of life. Understanding the hormonal basis of these conditions is crucial for developing effective treatments and support mechanisms [111].

Pregnancy

Pregnancy is associated with substantial hormonal shifts, primarily increases in estrogen and progesterone, which support fetal development but can also influence maternal mood and emotional regulation. While many women experience heightened emotions and mood swings, some may develop antenatal depression or anxiety, underscoring the need for attention to emotional well-being during pregnancy [112]. Postpartum, the rapid hormonal withdrawal, particularly of estrogen and progesterone, can contribute to the development of postpartum depression in susceptible individuals [113].

Menopause

Menopause, the cessation of menstruation, involves significant hormonal changes, most notably a decrease in estrogen levels. These changes can lead to a range of physical and psychological symptoms, including hot flashes, sleep disturbances, and mood swings [114]. The transition through perimenopause to menopause can be particularly challenging for emotional regulation, with an increased risk of developing depression or anxiety disorders during this time. Perimenopausal women may experience physical and psychological changes that can affect their psychological well-being. To successfully adapt to these changes, particular coping emotional regulation strategies are necessary. A better *emotion regulation* was found to predict lower levels of psychological disorders such as depression and anxiety during the menopausal transition [115].

Therapeutic Implications and Support

Recognizing the impact of life stages and associated hormonal changes on emotional regulation is crucial for providing appropriate support and interventions. This may include hormonal therapies, such as contraceptive pills to manage PMS/PMDD symptoms [116] or hormone replacement therapy (HRT) during menopause, as well as psychological support and lifestyle interventions to enhance emotional well-being. Tailoring support and treatment to the individual's needs and life stage can significantly improve quality of life and emotional regulation [117].

Methodological Considerations

Research Challenges in Studying Hormonal Influences on Emotional Regulation

Complex Interactions

One of the foremost challenges in this research area is the complexity of hormonal interactions within the human body. Hormones operate within an intricate system of feedback loops and networks that influence a wide range of bodily functions, including mood and emotional regulation. The endocrine system's interconnected nature means that a change in one hormone can cascade through the system, affecting others in unpredictable ways. This complexity makes isolating the specific effects of individual hormones on emotional regulation a formidable task.

Moreover, hormones interact not just with each other but also with neurotransmitters and other biological systems, further complicating their study. For instance, cortisol, the stress hormone, interacts with neurotransmitters such as serotonin and dopamine, which are directly linked to mood and emotion. The dual roles of many hormones, affecting both physical and psychological states, add another layer of complexity to their study [118].

Individual Variability

Another significant challenge is the high degree of individual variability in hormonal responses and their psychological impacts. Factors such as age, sex, genetic background, lifestyle, and even the time of day can influence hormone levels and their effects on mood and behavior. For example, the menstrual cycle can dramatically affect hormonal balance in women, influencing mood and emotional regulation [119]. Similarly, stress levels, diet, and exercise can modulate hormonal responses differently across individuals [120,121].

This variability poses challenges for researchers attempting to draw broad conclusions from study findings. It necessitates large sample sizes and careful consideration of participant characteristics to ensure that results are not unduly influenced by individual differences [122]. [

Subjective Measures of Emotion

Emotions are subjective experiences, often assessed through self-report measures in research. While self-report instruments can provide valuable insights into an individual's emotional state and regulatory strategies, they are also subject to biases and inaccuracies. Participants may struggle to accurately recall or articulate their emotional experiences, leading to potential discrepancies in data collection.

Furthermore, the subjective nature of emotional experience complicates the task of establishing clear, objective criteria for emotional regulation and its dysregulation. This has led researchers to explore alternative, more objective measures of emotional regulation, such as physiological indicators (e.g., heart rate variability) and neuroimaging techniques, to complement self-reported data [123].

Measurement Techniques in Studying Hormonal Influences on Emotional Regulation

Blood, Saliva, and Urine Testing

The quantification of hormone levels often relies on biological samples such as blood, saliva, and urine. Each of these sampling methods has its own set of advantages and challenges:

- **Blood Testing:** Considered the gold standard for hormone measurement, blood testing provides accurate and comprehensive hormone profiles. However, it is relatively invasive and requires professional handling, making it less ideal for frequent sampling or studies with large sample sizes [124].

- **Saliva Testing:** Saliva testing offers a non-invasive alternative for measuring certain hormones, including cortisol and testosterone. It is particularly useful for studies requiring multiple daily measurements or those focusing on the stress response. Nevertheless, salivary hormone levels can be influenced by various factors such as food intake and oral health, potentially affecting accuracy [125].
- **Urine Testing:** Urine testing allows for the assessment of hormone metabolites over extended periods, providing a cumulative measure of hormonal output. This method can be useful for evaluating overall hormonal balance but lacks the specificity and temporal resolution needed for studying acute hormonal responses to emotional stimuli [126,127].

Functional Neuroimaging

Functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have become invaluable in studying the brain's role in emotional regulation and the effects of hormones on brain activity. These methods enable researchers to observe changes in brain regions associated with emotional processing and regulation in response to hormonal fluctuations or manipulations. While powerful, these techniques require substantial resources and expertise and are subject to limitations related to interpretation and the artificial nature of experimental conditions [128].

Psychophysiological Measures

Psychophysiological measures, including heart rate variability (HRV), skin conductance response (SCR), and electroencephalography (EEG), offer objective insights into the body's emotional responses. These measures can provide indirect evidence of hormonal effects on emotional regulation by capturing the physiological correlates of emotional arousal and regulation processes. However, they require careful interpretation as they can be influenced by a variety of non-emotional factors [129].

Ecological Momentary Assessment (EMA)

EMA involves the real-time assessment of emotions and behaviors in participants' natural environments, often using digital diaries or smartphone apps. This approach can capture the dynamic interplay between hormonal fluctuations and emotional regulation in everyday life, offering high ecological validity. The challenge lies in ensuring compliance and managing the extensive data generated [130].

Future Directions

Gaps in Research

Identifying gaps in the current research landscape on the hormonal influences on emotional regulation is essential for guiding future investigations. This endeavor reveals areas that are understudied or present conflicting findings, offering opportunities for new discoveries and advancements. Here are several notable gaps that we have identified, which require further exploration.

Long-term Effects of Hormone Therapy

One significant area that necessitates more research is the long-term effects of hormone therapy on emotional regulation. While hormone therapy is commonly prescribed for conditions like menopause, hypogonadism, and gender transition, the enduring impacts of these treatments on mood, emotional resilience, and psychological well-being remain poorly understood. Studies that track individuals over extended periods post-therapy could provide valuable insights into these effects, informing clinical practices and patient guidance [131].

Hormonal Interactions with the Microbiome

The interaction between hormonal systems and the gut microbiome presents an intriguing yet underexplored area. Emerging research suggests a bidirectional relationship between gut bacteria and hormones, which could significantly impact emotional regulation. Delving into how hormonal fluctuations influence the microbiome and vice versa could unveil novel mechanisms of emotional regulation and potential therapeutic targets [132].

Impact of Environmental Disruptors on Hormonal Balance

The influence of environmental disruptors, such as chemicals that mimic or interfere with the action of hormones, on emotional regulation is another area requiring more attention. These substances, found in plastics, pesticides, and personal care products, could have profound implications for hormonal health and, consequently, emotional and psychological well-being. Non-chemical factors, such as artificial light, radiation, temperature, and stress exposure, have not been thoroughly studied, despite their potential to significantly impact the endocrine system through the modification of hormone function. Understanding the extent of these impacts is crucial for public health measures and regulatory policies [133].

Hormonal Influences Across Diverse Populations

Much of the existing research on hormonal influences on emotional regulation has focused on relatively homogenous populations. There is a need for more studies that examine these dynamics across diverse populations, including different ethnicities, ages, and socioeconomic statuses [134]. Such research could uncover important variations in how hormonal changes affect emotional regulation, leading to more inclusive and effective treatment approaches.

Technological Innovations in Hormone Measurement

Another gap lies in the need for technological innovations that enable more accurate, non-invasive, and real-time monitoring of hormone levels. Current methods, while effective, often require invasive procedures or do not provide immediate results. Advances in wearable technology or biosensors could revolutionize the way hormones are studied, allowing for more dynamic assessments of their impact on emotional regulation in real-life settings [135].

Genetic and Epigenetic Factors in Hormonal Emotional Regulation

Finally, the role of genetic and epigenetic factors in determining individual sensitivity to hormonal fluctuations and their impact on emotional regulation is an area ripe for exploration [123]. Understanding the genetic underpinnings and how life experiences alter gene expression related to hormonal responses could lead to personalized treatment strategies and preventive measures for

mood disorders and emotional dysregulation [136].

Potential Therapeutic Approaches

Understanding the hormonal basis of emotional regulation opens promising avenues for developing new and more effective treatments for mood disorders. By delineating how hormonal imbalances contribute to conditions such as depression, anxiety, and bipolar disorder, researchers and clinicians can tailor therapeutic approaches that directly address these underlying biological mechanisms. Here are several potential therapeutic approaches that could emerge from a deeper understanding of the hormonal influences on emotional regulation:

Hormone Replacement Therapy (HRT)

For mood disorders linked to hormonal deficiencies or imbalances, such as those experienced during menopause or thyroid dysfunction, hormone replacement therapy could offer relief. By restoring hormonal balance, HRT has the potential to alleviate mood disorder symptoms. However, its application must be carefully considered, taking into account the individual's health profile and the risks associated with long-term hormone supplementation [137].

Selective Hormone Modulator Treatments

Developing treatments that selectively modulate hormone receptors could provide targeted relief from mood disorders without the broader effects of hormone replacement. For instance, selective estrogen receptor modulators (SERMs) have been explored for their potential to relieve symptoms of depression and anxiety in postmenopausal women, offering a more nuanced approach to hormone therapy [138].

Pharmacological Agents Influencing Hormonal Pathways

Pharmacological agents that influence hormonal pathways, such as those affecting the HPA axis or the synthesis and metabolism of sex hormones, could offer new ways to treat mood disorders. Medications that modulate cortisol levels or the sensitivity of cortisol receptors, for example, could be beneficial for stress-related mood disorders and those with a significant stress component, like PTSD [139].

Lifestyle Interventions and Behavioral Therapies

A hormonal understanding of emotional regulation can also inform non-pharmacological treatments. Lifestyle interventions that naturally balance hormone levels, such as diet, exercise, and stress management techniques, could serve as preventive measures or adjunctive therapies for mood disorders. Additionally, behavioral therapies that effectively reduce stress and improve emotional regulation might indirectly influence hormonal balance, contributing to mood stabilization [140,141].

Personalized Medicine Approaches

Insights into the hormonal underpinnings of mood disorders could lead to personalized medicine approaches, where treatments are tailored to the individual's specific hormonal profile and genetic predispositions. This could involve genetic testing to identify vulnerabilities to hormonal imbalances and customizing treatment plans that address these unique factors, potentially increasing treatment efficacy and reducing side effects.

The prospect of personalized medicine in the realm of emotional regulation and mood disorders represents a frontier of immense potential, guided by the nuanced understanding of hormonal influences. Tailoring treatments to individual genetic profiles, hormonal states, and environmental contexts holds the promise of revolutionizing mental health care. For instance, genetic variations affecting hormone receptor sensitivity or neurotransmitter function could inform customized treatment strategies, optimizing the efficacy of hormone-based therapies, psychotropic medications, and even lifestyle interventions. This approach necessitates a comprehensive integration of genomic data, endocrine assessments, and psychosocial evaluations, paving the way for treatments that are not only more effective but also minimize adverse effects. The move towards personalized medicine, rooted in the hormonal basis of emotional regulation, underscores the importance of interdisciplinary research, combining insights from endocrinology, genetics, and psychology to address the complexities of mood disorders [142].

Combination Therapies

Finally, understanding the multifaceted role of hormones in mood disorders suggests that combination therapies that address both hormonal and non-hormonal aspects of these conditions could be most effective. This might involve combining hormone therapy with antidepressants, psychotherapy, and lifestyle changes to tackle mood disorders from multiple angles.

Conclusion

This review has traversed the intricate landscape of hormonal influences on emotional regulation, shedding light on the complex interplay between various hormonal systems and their impact on mood, stress responses, and overall psychological well-being. Through an exploration from the foundational roles of the HPA axis and gonadal hormones to the nuanced effects of thyroid hormones, oxytocin, and metabolic hormones, the significant interconnectedness of endocrine and emotional systems has been underscored.

The challenges and methodological considerations delineated within this text reveal the intricate variables researchers face in elucidating the hormonal mechanisms underpinning emotional regulation. Despite these obstacles, the identification of potential therapeutic avenues offers promising directions for developing more effective, personalized treatments for mood disorders, rooted deeply in an understanding of hormonal regulation.

Highlighting gaps in current research, such as the long-term effects of hormone therapy on emotional regulation and the interplay between hormonal systems and the gut microbiome, sets a clear roadmap for future investigations. These domains promise to unlock further insights into how hormonal imbalances contribute to emotional dysregulation and mood disorders, paving the way for innovative treatments and interventions.

This examination into the hormonal catalysts of emotional regulation is not merely academic; it holds key implications for enhancing mental health care, offering new perspectives on treating mood disorders, and improving emotional well-being. As

the field continues to unravel the complex relationships between hormones and emotions, it moves closer to holistic, integrated approaches to mental health that recognize the inseparable ties between physical and psychological health.

Moreover, the dialogue surrounding hormonal therapy, particularly in addressing mood disorders, invites a nuanced consideration of its long-term implications on emotional regulation and overall health. The potential of hormonal therapy to offer relief for conditions characterized by hormonal imbalance underscores the necessity of rigorous, longitudinal research to fully comprehend its benefits and risks. Such investigations are pivotal in establishing safe, effective protocols that consider the complexities of hormonal interactions and their systemic effects.

The global implications of advancing our understanding of hormonal influences on emotional regulation extend far beyond the realms of academic interest, holding promise for transformative public health outcomes. As mental health disorders continue to pose significant challenges worldwide, elucidating the hormonal underpinnings of emotional dysregulation offers a pathway to more effective, holistic treatment approaches. Enhanced hormonal insights can inform public health strategies aimed at early detection, prevention, and intervention, potentially reducing the burden of mood disorders on individuals, families, and healthcare systems globally. Integrating hormonal health into mental health care and public health initiatives could foster a more resilient, emotionally well-regulated population, highlighting the broader societal and health-related benefits of this research.

This review's exploration emphasizes the indispensable need for a multidisciplinary approach in advancing our understanding and treatment of mood disorders influenced by hormonal regulation. Collaborations across endocrinology, psychology, neurology, and genetics promise to illuminate the intricate mechanisms at play, paving the way for innovative therapeutic strategies. By embracing a holistic perspective that integrates diverse scientific insights, the field can move towards personalized, comprehensive care strategies that address the multifaceted nature of mood disorders.

While comprehensive, this review represents a snapshot of a dynamic, evolving field. It invites further exploration, interdisciplinary collaboration, and innovative thinking to fully leverage this knowledge for improving mental health outcomes. The future of research in hormonal influences on emotional regulation is rich with possibilities, challenging the scientific community to expand understanding and to envision a future where emotional well-being is accessible to all, guided by the intricate dance of hormones that orchestrates our emotional lives.

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Review Article

Intractable Epilepsia in Pediatric Populations: Surgical Approaches, Results, and Therapy, A Comprehensive Systematic Review of the Literature in Hemispherectomy

Abstract

A hemispherectomy is a surgical procedure in which the basal ganglia are retained but the entire cerebral hemisphere is removed. This technique was used by Dandy in 1928 to remove a glioma. McKenzie, a Canadian doctor, performed the first hemispherectomy on an epileptic patient in 1938. A comprehensive review of the scientific literature was carried out using the recommended guidelines. Using PRISMA (Preferred Reporting Items for Systematic Reviews) guidelines, this study carefully evaluated the scholarly literature on surgical outcomes and treatment regimens. We followed the EXCEL criteria, Rayyan (Intelligent Systematic Review), and R software. Academic publications were found in databases such as ScienceDirect and PubMed/MEDLINE Studies published in English up until January 2024. Our study of epileptic patients with intractable epilepsy involved a total of 1157 patients, of whom 708 underwent hemispherectomy. Table 1-2-3, and Figure 2,3,4, 5show the patients' demographic breakdown: 195 patients, or 27.54%, had cortical dysplasia, seizures, or Rasmussen encephalitis; 305 patients, or 43.08%, had seizures; 87 patients, or 12.29%, had strokes or Weber syndrome; 449 patients, or 72.8% of the patients, out of 325 patients, had the Engel type 1 classification; and 232 patients, or 51.67% of the patients, had Engel type 2. The results of this pediatric systematic review led us to the conclusion that, once an infant's nonexistent seizure count is reached, either through conservative or immunoregulatory therapy or brain stimulation, hemispherectomy is the most stable course of action. Intractable epilepsy is essentially treatable.

Keywords: Intractable epilepsia, hemispherectomy, disconnections, syndromes, outcomes and treatments.

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Introduction

A hemispherectomy is a surgical procedure in which the basal ganglia are retained but the entire cerebral hemisphere is removed. This technique was used by Dandy in 1928 to remove a glioma. McKenzie, a Canadian doctor, performed the first hemispherectomy on an epileptic patient in 1938. Patients who underwent surgery experienced hemiplegia and intractable epilepsy. Twelve infants with intractable epilepsy and infantile hemiplegia underwent hemispherectomy. [1]. Hemispherectomies are among the most significant surgical procedures used to treat pediatric epilepsy. 16–21%. As a result, to administer this treatment, a vertical parasagittal route is employed in addition to the lateral aspect through the Sylvian fissure. Additionally, this method prevents postoperative seizures in up to 90% of instances. As a result, these hemisphere abnormalities may cause or provoke difficult-to-cure epilepsy in a child at a young age. in addition to CSF alterations being the main 1–15% issues. [2].

The most recent classification of epilepsy and seizures was released in 2017 by the International League Against Epilepsy. This group of seizures includes epileptic, hyperkinetic spasms such as automatism, focal motor, myoclonic, tonic or tonic-clonic, clonic, and atonic seizures. These are categorized as just generalized seizures that progress into focal onset seizures. Myoclonic-atonic or generalized epileptic; focal, non-motor; behavioral or emotional; absence with myoclonic genesis in the eyelids; and myolonic-tonic or clonic spasms. [3]. More and more epileptic patients are being connected to a location that may be successfully removed surgically, but is untreatable due to tumors, hippocampal atrophy, or underlying focal cortical dysplasia, thanks to the use of modern imaging techniques like magnetic resonance imaging. Accordingly, generalized epilepsy may also be successfully surgically removed, in the same way as the so-called infeasible spasms brought on by underlying focal cortical dysplasia can be treated surgically based on initial findings. Sturge-Weber and megalencephalic syndromes are categorized as catastrophic seizure diseases requiring prompt hemispherectomy. and one was the preoperative assessment, which identified the various regions of epileptic anomalies by utilizing data from electroencephalograms, positron emission tomography, magnetic resonance imaging, and photon alone type emission tomography. Further evidence suggests that epilepsy is also frequently seen in patients with

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

Marfan type 1, in patients with brain tumors associated with mesial temporal sclerosis that may be associated with or coexist with focal cortical dysplasia, in patients with a variety of epilepsy-related syndromes, and in situations where the epilepsy site is affected [4]. Sometimes they will show signs of drug resistance. Patients with concomitant medial temporal lobe cortical dysplasia, Marfan type 1, and mesial temporal sclerosis may be treated with medial temporal lobectomy [5].

This study intends to determine the effectiveness of the technique in connection to the location, frequency, and responsiveness to the intervention in order to better understand how hemispherectomy has improved the treatment of intractable epilepsy in pediatric patients.

Materials and methods

A comprehensive review of the scientific literature was carried out using the recommended guidelines. Using PRISMA (Preferred Reporting Items for Systematic Reviews) guidelines, this study carefully evaluated the scholarly literature on surgical outcomes and treatment regimens. We followed the EXCEL criteria, Rayyan (Intelligent Systematic Review), and R software. Academic publications were found in databases such as ScienceDirect and PubMed/MEDLINE by using the search phrases "Hemispherectomy OR Intractable Epilepsy" AND "resection by location", "resection by Lobectomy", "focal dysplasia resection", and "associated syndromes". Ethics approval: Not need, or not applicable. Studies published in English up until January 2024.

The PICO framework (population, intervention, comparison, and outcome) was used to the pediatric population with this type of disorder, which ranges in age from 0.3M to 17 years.

Shown Figure 1.

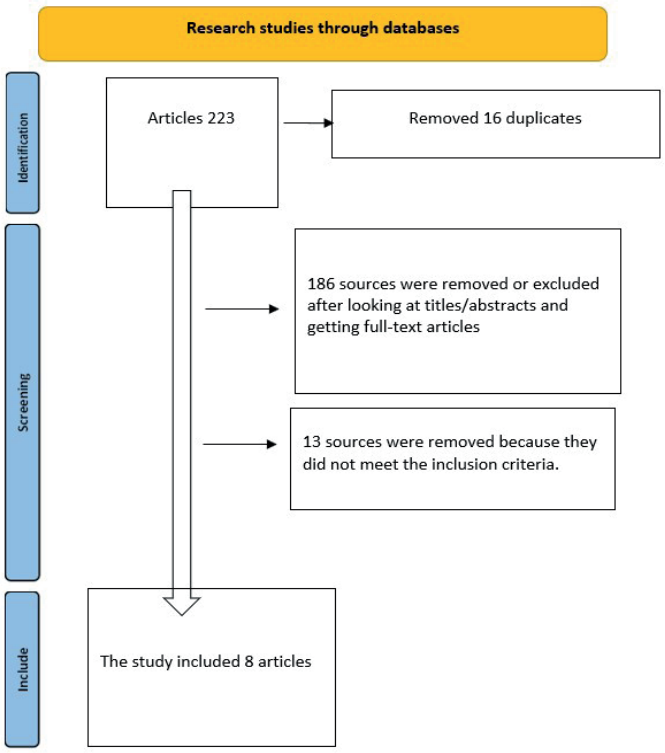

Figure 1: PRISMA Flowchart Hemispherectomy in Pediatric Patients with Intractable Epilepsia Study.

Search Strategy and Mesh Terms

The search strategy incorporated a comprehensive set of Mesh terms related to Hemispherectomy in an Intractable Epilepsia. ("Epilepsies, Partial/classification"[Mesh] OR "Epilepsies, Partial/complications"[Mesh] OR "Epilepsies, Partial/congenital"[Mesh] OR "Epilepsies, Partial/diagnosis"[Mesh] OR "Epilepsies, Partial/diagnostic imaging"[Mesh] OR "Epilepsies, Partial/drug therapy"[Mesh] OR "Epilepsies, Partial/epidemiology"[Mesh] OR "Epilepsies, Partial/etiology"[Mesh] OR "Epilepsies, Partial/genetics"[Mesh] OR "Epilepsies, Partial/history"[Mesh] OR "Epilepsies, Partial/pathology"[Mesh] OR "Epilepsies, Partial/prevention and control"[Mesh] OR "Epilepsies, Partial/psychology"[Mesh] OR "Epilepsies, Partial/radiotherapy"[Mesh] OR "Epilepsies, Partial/rehabilitation"[Mesh] OR "Epilepsies, Partial/surgery"[Mesh] OR "Epilepsies, Partial/therapy"[Mesh])

(Total Hemispherectomy AND Hemispherectomy, Total OR Partial Hemispherectomy AND Hemispherectomy, Partial OR Functional Hemispherectomy AND Hemispherectomy, Functional) AND ("Hemispherectomy/instrumentation"[Mesh] OR "Hemispherectomy/methods"[Mesh] OR "Hemispherectomy/rehabilitation"[Mesh] OR "Hemispherectomy/standards"[Mesh])

Selection Criteria and Search Strategy

The publications were found through a systematic search technique that focused on English-language journals published between January 2023 and January 2024. Strict standards were used in the selection procedure to ensure that articles about various forms of total hemisphere amputation were of high quality and applicable. surgical intervention is the last resort for localized seizure disorders associated with intractable epilepsy, or partly in epilepsy linked to syndromes displaying this type of illness.

Comprehensive Search Strategy Keywords

In addition to the Mesh terms, keywords including "Intractable Epilepsy "Syndromes," "Hemiparesis," "Seizures," "Partial or total hemispherectomy and Pediatric epilepsy," and "treatments" were included in the search strategy.

Inclusion Criteria

Age range for children: 0.3 m to 17 yrs

Functional results, technique, care, and results of vertical interhemispheric hemispherectomy following a pediatric hemispherectomy

The purpose of hemispherectomy in Rasmussen encephalitis

Treatment for hemimegaloencephaly using hemisphere epilepsy surgery

Forecast or estimate the functional outcomes and seizure activity after a juvenile hemispherectomy.

Exclusion Criteria

Non-pediatric patients can range in age and have extremely severe epilepsy that is uncontrollably worse. For Patients with epilepsy, who hemispherectomy is not appropriate. Patients who are diagnosed with epilepsy but whose sei-

zures are proven to be tumor-related by magnetic resonance imaging are not eligible for hemispherectomy. papers that do not meet the requirements for intractable epilepsy and were not treated.

Data Extraction

Standardized approaches were employed to collect data from qualifying research, with a focus on each study's methodology, demographics, and characteristics of the intervention. This search approach took into account a number of factors, including the patient's age, the intervention's modalities, and the functional outcomes following the surgical period, in order to thoroughly locate the pertinent literature on hemispherectomy in young patients with uncontrollable epilepsy.

Results

Our study of epileptic patients with intractable epilepsy involved a total of 1157 patients, of whom 708 underwent hemispherectomy. Table 1 and Figure 2,3,4 show the patients' demographic breakdown: 195 patients, or 27.54%, had cortical dysplasia, seizures, or Rasmussen encephalitis; 305 patients, or 43.08%, had seizures; 87 patients, or 12.29%, had strokes or Weber syndrome; 449 patients, or 72.8% of the patients, out of 325 patients, had the Engel type 1 classification; and 232 patients, or 51.67% of the patients, had Engel type 2. These patients are summarized in Table 2 and Figure 5 and Table 3. In total, 1157 patients were present, and a total of 1161 people participated in 29 trials, and 1102 of them experienced seizures; the overall absence rate was 73.4%. Of the total, 16 papers (or 55%) offered relevant information about these seizures that occurred after hemispherectomy. Furthermore, although there was no significant difference (p=0.7) between this symptom and this type of procedure, nearby seizures showed 85% of acquired etiologies and another form of progressive development between 30%, 41%, and 29% consecutively. The two categories of acquired and progressive etiologies were found to be greater than the developmental etiologies, as evidenced by p=0.001. On the other hand, 20 investigations found issues. in addition to a CSF diversion of up to 14% in cases of hydrocephalus. Participants had a 30-day mortality limit of 2.2% and who had no variance in the types of hemispherectomies (p=0.8). [7].

Based on studies conducted at the Johns Hopkins Medical Institution between 1968 and 1996. A group of young kids with epilepsy underwent 27 surgeries: 7 patients had Sturge-Weber syndrome, 24 surgeries were for cortical dysplasia, 67% were for hemimegaloencephaly, and 89% of the surgeries were for Rasmussen syndrome. Despite the fact that 67% of the participants of the vascular group did not experience seizures as a result of their subpar performance, an additional item was included that included the frequency of seizures in addition to motor and intellectual dysfunction. As a result, it showed that children had better results both before and after surgery. [8].

Remarkably, a review conducted between 1979 and 2020 using 19 publications revealed that newborns who had hemispherectomy, or hemispherectomy with a range of 7% to 76%, did not have seizures one year after surgery. Seizures become independent in 40–70% of non-hemispheric type operations. Research from hemispherectomy procedures demonstrates that they help babies who have them from having seizures.[11].

Techniques for functional surgery in the posterior quadrant

This technique, similar to peri-insular hemispherectomy, makes the opercular cortices and the central peri-Roland area visible. The entire epithelium is intended to be punctured by the excision. A leptogenic lesion can be easily identified upon close inspection, and the core region, which includes the motor and sensory cortex, should be avoided. We also used somatosensory or motor evoked potentials to do a magnetic resonance imaging examination of the intraoperative anatomical surface based on arteries and veins in order to achieve resection and guarantee surgical safety. Similar to a periinsular hemispherectomy, the functional posterior quadrantectomy involves removing the mesial temporal region through the infra-insular window. The mesial temporal excision enabled by the infra-insular window in the superior temporal gyrus includes the uncus, amygdala, and hippocampus areas. A step before surgery is the disconnection of the temporal and parietal neocortex or the occipital lobes. The so-called infra-insular window extends posteriorly down the temporal horn to the trigone of the lateral ventricle, taking into account the preservation of the Labbe vein and the branches of the middle cerebral artery. the cortical incision at a higher level and the suprasylvian cortex, which is situated behind the primary sensory core, respectively, through the temporal cingulate. Complete eradication using subpial aspiration of the tainted area, a decision made at the cloister level. The third stage is entry. The trans-parietal disconnection is located in the superior diagonal cortical incision, directly behind the postcentral gyrus. The excision was carried out along the falx and its disconnection, up to the pia mater, till the sagittal position. A posterior callosotomy, or the removal of the corpus callosum inferiorly and at the superior level, would be the last operation. The parietal and occipital temporal lobes remain anatomically positioned after the procedure; however, they are completely severed from both the contralateral hemisphere and the ipsilateral frontal section of the lobe.[12].

The hippocampal and amygdala are removed during a temporal lobectomy known as a functional hemispherectomy. The body of the lateral ventricle is first made visible through a central excision. Subsequently, the anterior basal frontal area and the pericallosal cerebral artery separate the corpus callosum from the ventricle. At last, the corpus callosum is severed from the ventricle by performing the subpial disconnection. Lastly, the anterior basal frontal region and the subpial level of the cingulum gyrus divide the corpus callosum from the ventricle. [13].

Anterior temporal lobectomy

Compared to adult patients, we have a different understanding of the pathology of the pediatric temporal lobe. Although the underlying cause of refractory seizures is more likely to be neoplastic lesions or congenital problems like cortical dysplasia, the pathological basis of mesial temporal sclerosis is a less common finding in adults than in children. This results in changes to the degrees and frequency of approaches of the temporal lobe. For adults with refractory epilepsy, Anterior temporal lobectomy (LBTA) is the most prevalent resection method, with a lower percentage of procedures performed in the infantile form. It is noteworthy that these techniques are derived from the seminal

work of Spencer et al. from the middle of 1984. Consequently, we observed certain differences, including the degree of hippocampal resection and the extension of the temporal neocortical excision, which usually happens less than 4 and less than 6 cm from the front temporal lobe, respectively, on the dominant side. The modifications to the procedure will be based on the results of the electrophysiological test and the preoperative photographs. The surgery has a comparatively low 0-5% fatality rate, according to LBTA, while the review's morbidity ranged from 0-9.3. Common problems include the visual field, infection, and so-called neuropsychological alterations, namely the decline in verbal memory that results from removal of the dominant hemisphere. The contralateral hemisphere is attributed to the cognitive alterations in children, and the LBTA results are positive. Though verbal memory may deteriorate, children may experience better neuropsychological alterations than adults. [14].

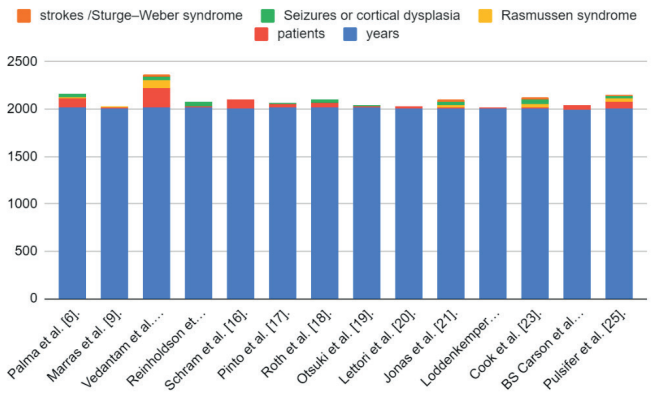

Figure 2. Research on hemispherectomy-treated intractable epilepsy and the most common disorders associated with it in children.

Table 1: Intractable Epilepsia in the Pediatric Population: Hemispherectomy as the Optional Treatment

Authors	years	Type of study	patients	Procedure / Anatomical and Functional	Rasmussen syndrome	Seizures or cortical dysplasia	strokes / Sturge–Weber syndrome	Follow up	P=value
Palma et al. [6].	2019	Retrospective	92	Hemispherectomy	10	38	71 sei-zure-free	two lost from follow-up, 73.3%	0.43
Marras et al.[9].	2010	Retrospective	13	Hemispherectomy and functional hemispherectomy	6	3	2	2–7 years	N/A
Vedantam et al. [10].	2018	Retrospective	208	Hemispherectomy	83	33	20	62.5%	0.01
Reinholdson et al. [15].	2015	Prospective observational study	12	Hemispherectomy	N/A	47	1	2 years	N/A
Schram et al. [16].	2012	Retrospective N/A	96	Hemispherectomy	N/A	N/A	N/A	1 year	N/A
Pinto et al. [17].	2014	retrospective observational study	36	Hemispherectomy	N/A	22	N/A	1 year	0.001
Roth et al. [18].	2021	Multicenter study	48	Hemispherectomy	N/A	28	N/A	51 months	.0001
Otsuki et al. [19].	2013	N/A	18	Hemispherectomy	N/A	13	N/A	N/A	N/A
Lettori et al. [20].	2008	prospective	19	Hemispherectomy	6	N/A	3	1 year	N/A
Jonas et al. [21].	2004	Comparative Study	15	Hemispherectomy	21	39	27	2 years	N/A
Loddenkemper et al. [22].	2007	Case reports	14	Hemispherectomy	N/A	N/A	N/A	6 months	N/A
Cook et al. [23].	2004	Comparative study	14	Hemispherectomy	32	55	27	0.5-2 years	N/A
BS Carson et al. [24].	1996	Review	52	Hemispherectomy	N/A	N/A	N/A	N/A	N/A
Pulsifer et al. [25].	2004	Crossectional	71	Hemispherectomy	37	27	7	2.4 to 37.5 years.	0.05

Procedures for Surgery

Benjamin Carson et al. First, a frontal lobectomy was performed, and then a temporal lobectomy involving the removal of the occipital lobe was performed. The coagulopathy was the main focus, not how long the surgery took. With a frontal lobectomy, there was no need to interfere with the anterior circulation because the majority of hemisphere bleeding happens in the midline. In order to preserve the ventricular system, the anterior cerebral artery branches were coagulated, and decortication was also performed. This left the thalamus and basal ganglia intact, along with a thin layer of white matter covering the ependymal surface. The identical trigonal area was exposed to CSF fluid leakage following a complete temporal lobectomy of the brain. gel foam and surgical mesh obstructed. It is necessary to build a ventricular surface because the cortical veins are bleeding more frequently. because they apparently enlarge as they drain into the sagittal sinus. In order to prevent hemimegaloencephaly in children, a parasagittal cortical canal connecting the anterior falx to the posterior extension of the occipital lobe is required. By blocking the cortical veins, this canal significantly reduces bleeding. Once cortical tissue is removed at the parasagittal level, the remaining portions of the cerebral venous system that enter the sagittal sinus need to clot and divide. After hemostasis is achieved, clean the region thoroughly, apply Gelfoam, and refrain from performing surgery on young children as this could cause cardiovascular instability.[24]

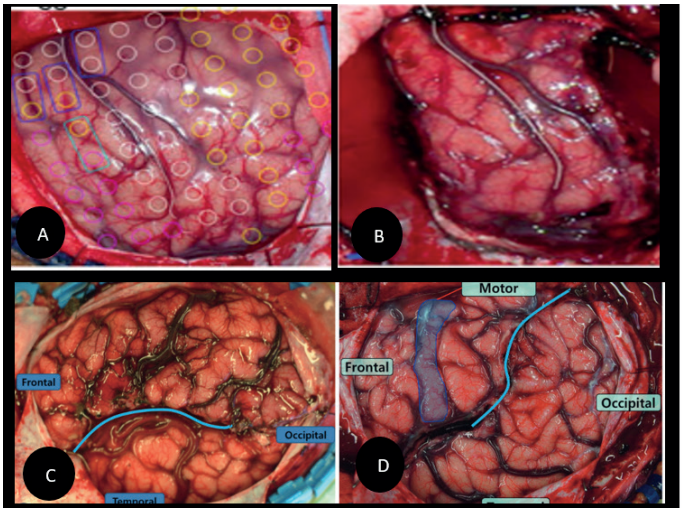

Figure 3.a: Complete and subtotal hemispherectomy; blue regions show jerks caused by stimulation; red and yellow spots show the locations of seizure initiation. b, hemispherectomy subtotal c, Frontal lobectomy after posterior quadrantectomy, seen from an operating perspective. c, the posterior quadrantectomy's final cortical incision margin, indicated in several anatomical areas.

Rasmussen encephalitis

RE is a rare condition that is thought to exist in a smaller population undergoing hemispherectomy; of the 32–39 documented cases of hemispherectomy, it accounts for a significant percentage of patients undergoing surgery, ranging from 1% to 42%. The primary inflammatory process associated with RE is Rasmussen syndrome has been reported to develop after a head injury or infection, and progressive unilateral hemisphere dysfunction is known to happen frequently along with inflammatory and histological imaging abnormalities. RdE affects children, but it is not normal for them; hence, there may be unilateral focal onset seizures that worsen. Autoantibodies against the glutamate receptor type 3 (GluR3) N-methyl-D-aspartate receptor (NMDA) linked to RdE and other severe forms of epilepsy are related to it. drifting, similar to classic partial epilepsy where hemiparesis is the final symptom caused by a progressive decrease of unilateral hemisphere function. Language function is also affected if the dominant hemisphere is damaged. An MRI shows areas of inflammation along with a consistent reduction. There have been several, but unevenly successful, attempts at immunomodulatory therapy to stop the illness, including plasma exchange, calcineurin inhibitors, high doses of corticosteroids, and intravenous immunoglobulin + immunoglobulin. Hemispherectomy is still the standard of care, however. [26].

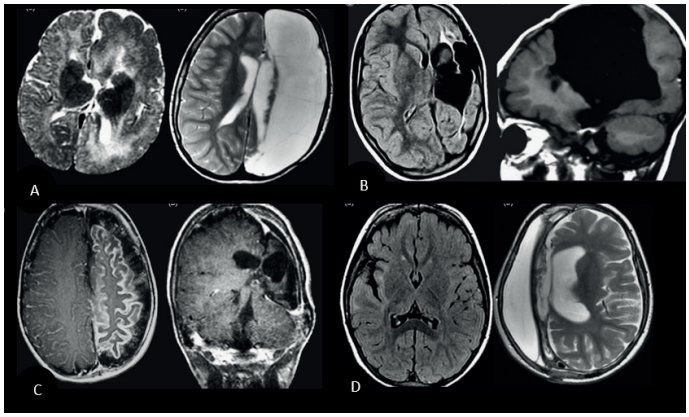

Figure 4. a) Hemimegaloencephaly. Axial T2w MRI shows extensive growth of the left hemisphere with enlargement of the white matter throughout the hemisphere, b) left porencephalic frontotemporal cyst affecting the basal ganglia and thalamus of the left ventricle with the dilated and exvacuo sylvian fissure, c) MRI of Sturge-Weber disease, axial T1w with gadolinium with cortical gyri in atrophic cerebral hemisphere. d) Rasmussen encephalitis. Preoperative axial FLAIR images, the subcortical white matter signal areas of the right insula are intensified, temporal and frontal lobes with parenchymal gliosis, with slight hemiatrophy of the right hemisphere.

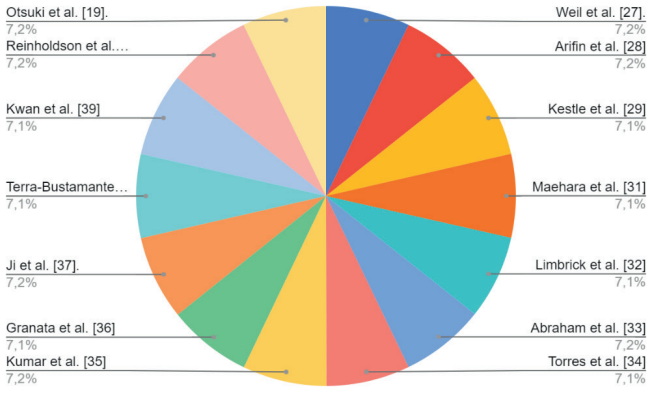

Figure 5 samples of people who had hemispherectomy treatments that went well according on the Engel type 1 and type 2 classifications.

Table 2 According to Engel's classification, studies concentrated on peri-insular hemispherectomy, which was followed by death and neurological changes such hemiparesis.

Author	year	Kind of study	Patients	Procedure	Engel 1	Engel 2	Follow up	Mortality	Neurological alterations	P=value
Weil et al. [27]	2014	Observational Study	69	Peri-insular Hemispherectomy	59	N/A	2	N/A	N/A	0.009
Arifin et al. [28]	2019	retrospective observational study	19	Peri-insular Hemispherectomy	12	13	6	N/A	Hemipare-sis 5	N/A
Kestle et al. [29]	1999	retrospective	16	Peri-insular	8	9	3	N/A	Hemiparesis	N/A
Villemure [30]		Clinical Trial	43	Peri-insular	34	N/A	9	1	N/A	N/A
Maehara et al. [31]	1998	Retrospective/ N/A	14	Peri-insular	6	12	4	N/A	Hemiparesis	N/A
Limbrick et al. [32]	2008	retrospective	35	Peri-insular	N/A	28	2	N/A	N/A	N/A
Abraham et al. [33]	2016	Retrospective	45	Peri-insular	41	43	4	N/A	N/A	N/A
Torres et al. [34]	2007	Clinical article	13	Peri-insular	10	12	3	N/A	Hemiparesis	N/A
Kumar et al. [35]	2013	Retrospective	14	Peri-insular	11	12	3	1	N/A	N/A
Granata et al. [36]	2009	Retrospective	11	Peri-insular	6	8	7	N/A	N/A	0.002
Ji et al. [37].	2017	retrospective	83	Peri-insular	69	70	2	N/A	N/A	0.019
Terra-Busta-mante et al. [38]	2005	retrospective	16	Peri-insular	62	N/A	N/A	N/A	N/A	N/A
Kwan et al. [39]	2007	Comparative Study	41	Peri-insular	N/A	N/A	72	N/A	Hemiparesis	.001
Reinholdson et al. [15].	2015	Prospective observational study	12	Hemispherectomy	1	6	2 years		14 Motor and speed impairment	N/A
Otsuki et al. [19].	2013		18	Hemispherectomy	6	19	11	N/A	N/A	N/A

Invasive monitoring

Patients with temporal lobe epilepsy should have craniotomy and dural opening procedures under long-term invasive surveillance. The polarity of phase inversion in the somatosensory evoked recordings after the median nerve is electrically stimulated should also be determined in order to identify the central sulcus. This is because direct cortical stimulation validates the precentral motor convolution. 64 Ad-Tech Medical Device Co. The frontal and temporal lobe surfaces are covered by electrode surface subdural grids, which are positioned according to the speech regions determined by FMRI, the seizure semiological data, and EEG recordings in the interictal and ictal scalp, or interictal peak sources... Ipsilateral subdural strips covered the temporal lobes anterio,r temporal tip and inferior surface. Five days of monitoring is recommended to detect the occurrence of interictal epileptiform discharges and ictal seizures in patients. This is accomplished by utilizing frameless stereotaxic navigation to place electrodes at depth in order to collect ictal data from the anterior parts of the temporal lobe, which may be supplied via subdural grids, specifically in the anterior and posterior hippocampus. Consequently, the motor, sensory, and language capacities were mapped in one or two sections as well as the third and fourth days after the grid was implanted. employing intraoperative electrocorticography in specific circumstances to carry out neocortical excision; sufficient data had already been obtained from the functional cortex and the so-called regions of epileptogenic; and the data from intrusive monitoring was used to make the decision to remove the hippocampal region.[40].

Table 3. Investigations based on the kind of hemispherectomy, the pathophysiology, and the intervention

Authors	anatomic hemispherectomy	functional hemispherectomy	peri-insular hemispherectomy	hemimegaloen-cephaly	ventriculoperito-neal shunt	P=value
Pinto et al.[17]	19	4	5		15	0.001
Roth et al. [18]	N/A	N/A	N/A	17	N/A	0001
Otsuki et al. [19]	N/A	N/A	N/A	16	N/A	N/A
Lettori et al.[20]	19	5	N/A	11	N/A	N/A
Jonas et al.[21]	N/A	N/A	N/A	16	N/A	N/A
Weil et al. [27]	3	67	N/A	11	N/A	0.009
Arifin et al.[28]	N/A	N/A	23	1	N/A	N/A

A study employed a database of eighty-nine children who had surgery for temporal lobe epilepsy. Out of this group, 77 had anterior temporal lobectomies, and the other group had preoperative resections modified to address an epileptogenic region or lesion. Thirteen underwent lesionectomy plus hippocampectomy, twenty underwent amylohippocampectomy with a P=0.023 with 77%, and thirty-three underwent satisfactory results in 74% of cases. and 14 patients who underwent lateral temporal lesionectomy, which ended their seizures, and whose logistics revealed the factors of an amygdalohippocampectomy with a P=0.021 and surgery on their left side with a P=0.017 as significant samples of a poor control of convulsions. The acceptable control exhibited just a modest reduction in verbal memory following the left procedures, and was independent of the histological diagnosis, even though the neuropsychological impairment was evident following the right temporal resections. Both contralateral functioning and attention improved after surgery.[41].

Discussion

Based on the etiologies, the demographic data displayed in the study photographs varied from prior studies that demonstrated hemispherectomy as a treatment, indicating a substantial decrease in seizures in 90% of cases of hemispheric disconnections in children. more than successful in treating uncontrollably occurring seizures. Records indicated that 73% of the 186 patients who had hemispherectomy for disconnection recovered from their seizures. 78 individuals revealed that 85% of the 92 juvenile epileptic patients in the research who underwent disconnection were seizure-free at follow-up. [42]. Observing malformations of cortical development in 25-72% of children in the magnetic resonance imaging, the contralateral type anomalies in the altered hemispheres shown in the preoperative magnetic resonance imaging with an extensive insular or subcortical heterotopic gray matter recognized as poor predictive factors of seizures. [43]. According to reports, somatic constitutional mutations of genes like AKT1, AKT3, DEPDC5, MTOR, NPRL2/3, PIK3CA, PIK3R2, and TSC1/2 are related to a continuous phenotype of malformations of cortical development, such as cortical dysplasia type II UP TO MEGALENCEPHALY OR DYSPLASTIC MEGALENCEPHALY. MTOR is a key regulator of cell growth, proliferation, and survival, autophagy, transcription, and protein synthesis in mammals. In 79% of type II patients, the brain mosaic rate was less than 5%, indicating a mutation. Up to 50% of the remaining individuals have dysplastic tissue mutations, with mosaic rates ranging from 6.5% to 18.6%. Of these, 50% carry constitutional alterations, with 41% of type II individuals unable to identify the source of these mutations. [44]. The incidence increased from 1.2 per 100,000 and other admissions in 2000 to 2.2 per 100,000 between 2009 for a p=0.05, according to the literature, in a study of 552 admissions admitted to hospitals for hemispherectomy procedures. The average age was 6.7 years with a range of 0-20. revealed a notable rise in the overall cost, from $42,807 in 2003 to $57,443 in 2009 (adjusted in 2009 currency; p=0.015). demonstrating no in-hospital mortality or postoperative complications in 5 patients, or 0.9%. nonetheless, revealed a rise in the use of ventricular shunts during hemispherectomy hospital stays, with a p-value of 0.056 for an increase in ventricular shunt usage from 6.7% to 16.5%. There was a higher rate of blood transfunctions (OR 3.7, p = 0.01) but a reduced incidence of mortality (OR of 0.08, p = 0.04).[45]. A structural lesion in intractable epilepsy will require surgery to be postponed in order to avoid the significant blood loss that is linked with intraoperative morbidity or fatality in infants receiving immunomodulatory treatment. If hemispherectomy is used in children, the literature states that the recovery period for hemimegaloencephaly is seven weeks. It is uncommon to do a functional hemispherectomy on newborns weighing less than 12 months. In inflammatory epilepsy, Rasmussen's encephalitis with a paradigmatic immune system resulted in a 50% reduction in seizures when steroid pulse therapy was used in 81% of cases, as opposed to 42% in tacrolimus cases or 42% in steroid therapy cases. blood-stream immunoglobulin. demonstrating that young patients can release up to 71% after hemispherectomy, compared to 8% and 5% with tacrolimus respectively. This was not observed when receiving intravenous immunoglobulin treatment.[46].

Limitations

According to this study, the outcome of left-sided amygdalohippocampectomy patients was not satisfactory in terms of seizures (P = 0.017). It was also highlighted how verbal memory impairment might develop after temporary resections for left surgeries that cause cognitive or neuropsychological damage, and how functional hemispherectomy in newborns under 12 months of age is uncommon. neglecting to mention that there is a 2.2 fatality rate from hydrocephalus diversion in 14% of pediatric patients, and that evaluations of language or reading behavior are scarce? Furthermore, it was not possible to ascertain in the

adolescent population the length of time for both the preoperative initial rehabilitation and the postoperative follow-up after hemispherectomy.

Conclusion

The results of this pediatric systematic review led us to the conclusion that, once an infant's nonexistent seizure count is reached, either through conservative or immunoregulatory therapy or brain stimulation, hemispherectomy is the most stable course of action. Intractable epilepsy is essentially treatable. technique that has demonstrated a 90% success rate in stopping seizures with infrequently repeating interventions.

An MRI shows areas of inflammation and progressive atrophy. To treat the disorder, immunomodulatory therapy has included calcineurin inhibitors, intravenous immunoglobulin plus high doses of corticosteroids, and/or plasma exchange, with varied degrees of success. Patients with epilepsy who undergo hemispherectomy have a good chance of recuperating normally from the procedure since children's recovery and adaption are significantly better than adults. Hemispherectomy also causes a kind of cognitive harm.

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Author contribution subject and rate:

Daniel Antonio Encarnacion-Santos (50%): Design the research, data collection and analyses and wrote the whole manuscript.

Gennady Chmutin (20%): Organized the research and supervised the article write-up.

Ismail Bozkurt (10%): Contributed with comments on research design and slides interpretation.

Jack Wellington (5%): Contributed with analysis of the manuscript.

Aysi Gordon Gullanyi (5%): Contributed to conceptualization of the manuscript

Bipin Chaurasia (10%): Contributed to vizualisation of the manuscript.

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