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Neurotransmitter Fluctuation in Childhood: Exploring Variations in the Levels of GABA, Glutamate, Dopamine and Noradrenaline in Individuals Under 18

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Abstract

Aims/Background: This study investigates neurotransmitter levels in a cohort of pediatric patients, aiming to provide valuable insights into the relationships between demographic factors, clinical diagnoses, and mean neurotransmitter levels across different age groups.

Methods (Materials/Patients and Methods): The research involved 135 participants, consisting of 54 males (40.0%) and 81 females (60.0%), with an average age of 12.57 years (SD = 4.43). The observed age ranged from 5 to 18 years. Urban residents constituted the majority, accounting for 60% of the total participants. The study categorized participants into three groups based on pediatrician diagnoses: Group I (control) included 37 patients (27.4%), Group II comprised 65 patients (48.1%) with psychoanxiety disorders, and Group III encompassed 33 individuals (24.4%) with mental disorders. Statistical analyses confirmed normal distributions within these groups.

Results: To assess neurotransmitter levels, paraclinical analyses were conducted, including serotonin, GABA, glutamate, cortisol, and DHEA, employing enzymatic, colorimetric, and spectrophotometric methods.

Conclusion: Preliminary findings highlight the intricate relationship between demographic variables, clinical diagnoses, and neurotransmitter levels, providing a foundation for further exploration of neurochemical dynamics in pediatric populations.

Keywords: Neurotransmitters; GABA; Glutamate; Dopamine; Noradrenaline

Introduction

Brief summary

This study develops into neurotransmitter levels among 135 pediatric patients, exploring the intricate interplay between demographics, clinical diagnoses, and neurochemical profiles. The cohort, spanning ages 5 to 18, exhibited normal distributions across three diagnostic groups. Preliminary findings underscore the originality of this research, shedding light on the nuanced connections between age, clinical conditions, and neurotransmitter concentrations. This exploration holds promise for advancing our understanding of pediatric neurochemistry, emphasizing the significance of tailored interventions for diverse age groups and diagnostic categories.

Introduction

The levels of neurotransmitters are influenced by age [1]. It has been observed that the main changes take place until the age of 6, after which the levels of neurotransmitters, such as serotonin, are within the same limits as in adults [2]. Recent studies show that neurotransmitter levels undergo significant changes by age 6, with subsequent maintenance within adult-like ranges [3]. Among these neurotransmitters, serotonin plays a crucial role, and its adaptation during these developmental years is important in understanding behavior and cognitive functioning in children under 18 years of age [4].

GABA, an inhibitory neurotransmitter, demonstrates significant variations with age [5]. By analyzing these changes, we can gain a deeper understanding of how the central nervous system of children under 18 adapts and regulates cognitive and emotional functions [6].

Studies indicate significant changes in glutamate levels with age [7]. By analyzing these fluctuations, we can gain important information about how this excitatory neurotransmitter contributes to the development and functioning of children's nervous systems [8].

Dopamine levels show a 28.1% decrease with age in children under 18 [9,10]. Further understanding of this process may provide critical insights into how this chemical influences aspects such as motivation and reward in young people [11].

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Both noradrenaline, with a decrease of 24.1%, and adrenaline, with a non-significant change of 0.1%, undergo distinct changes with age [12-14]. Analyzing these changes provides insight into the adaptation of the sympathetic nervous system to children's development [14].

The NADR/ADR ratio decreases by 14% as age increases in children under 18 years of age [15]. This analysis provides a more detailed understanding of the balance between these two neurotransmitters and how it changes as children grow and develop [16,17].

The objective of this study is to determine and understand the neurochemical changes associated with aging, focusing on fluctuations in the levels of GABA, glutamate, dopamine, noradrenaline, adrenaline, and the NADR/ADR ratio. The aim is to contribute to the development of preventive and therapeutic strategies in the management of cognitive health and emotions among the elderly population.

The study aims to identify correlations between specific neurotransmitter changes and the aging process, providing the basis for further research and interventions to effectively address these changes. The ultimate goal is to develop methods and strategies to improve the quality of life as age advances, including through pharmacological or non-pharmacological interventions, to counteract the negative impact of neurochemical changes on cognitive and emotional functions.

Materials and Methods

This study aimed to examine individuals receiving treatment at a private nutrition practice in Oradea, Romania, from 2020 to 2022, following the principles outlined in the Declaration of Helsinki by the World Medical Association. The chosen participants, aged 5 to 18 years, presented gastrointestinal issues including non-infectious diarrhea and constipation, along with other disorders such as flatulence, satiety, gas, belching, and abdominal pain.

Out of the initial 1145 patients assessed, 135 were selected to take part in the study, undergoing monthly consultations in adherence to the established guidelines. Exclusion criteria encompassed individuals below 5 years or above 18 years of age, those undergoing drug treatments that might influence neurotransmitter concentrations (such as SSRIs, SNRIs), and those who declined to participate. The primary aim of the study was to investigate the relationship between oxidative stress and clinical and paraclinical factors, while also discerning variations among the different groups examined.

To maintain sample uniformity, individuals aged 18 and above, those who declined to participate, and individuals with chronic illnesses that could impact the outcomes were excluded. The sample size was determined using a formula tailored for such research, indicating a minimum of 85 cases to achieve a 95% probability level.

Every patient experienced gastrointestinal disorders and adhered to dietary suggestions emphasizing regulated caloric consumption and scheduled meal timings. Additionally, both study groups were provided with an individualized probiotic intervention designed to target their particular gastrointestinal concerns. The recommended probiotics exhibited variations in proportions and combinations, featuring *Bifidobacteria, Lactobacilli*, and *Saccharomyces ssp*., and formulations were devoid of gluten, dairy, yeast, or eggs. The dosage of probiotics was adjusted based on age and weight, and for individuals with constipation, inulin supplementation was introduced.

These individuals, experiencing an imbalance, underwent naturopathic treatment involving Melissa extract, rhodiola, magnesium, and vitamin B6. Importantly, they did not receive SSRI or SNRI treatment, allowing for the assessment of the efficacy of probiotic therapy and dietary interventions.

2.1. Clinical evaluation

Clinical evaluation took place in a medical setting, emphasizing general symptoms like headaches, fatigue, mood fluctuations, hyperactivity, aggression, sleep disturbances, and difficulty concentrating. The patient's medical background encompassed the identification of personal medical history, medication usage, smoking, alcohol consumption, or any use of prohibited substances.

2.2. Paraclinical evaluation

Paraclinical assessments were conducted to reinforce the diagnosis. Analysis of neurotransmitter levels, encompassing serotonin, GABA, glutamate, cortisol, and DHEA, took place at the commencement and

conclusion of the study period. These assessments utilized enzymatic, colorimetric, and spectrophotometric methods in the assay laboratory. Furthermore, specific urine and saliva tests were employed to evaluate the presence of stress hormones in the body, utilizing CTL and Ortholabor GmbH, based in 26160 Bad Zwischenahn, Germany.

2.3. Statistical analyses

Statistical analyses involved the examination of alterations in biomarkers over time. Comprehensive numerical and graphical summaries of individual case profiles, featuring changes from reference values, were presented. Biomarker distributions displayed no substantial deviation from normality. To model changes over time, a linear mixed model with random effects and unstructured correlation for repeated measures was employed. Testing time was initially incorporated as a categorical variable for comparing mean changes, and later as a continuous variable to analyze trends in biomarker over time. Pearson correlations were utilized to evaluate the relationships between biomarkers. SPSS software (IBM, Chicago, IL, USA, version 20) was employed for the analyses, with the significance level set at $p < 0.05$. Statistical tests encompassed two-variable ANOVA and a three-variable Bonferroni post-hoc test. The residuals of the fitted model were scrutinized to assess its appropriateness for each biomarker at every time point.

Results

3.1 Demographic Profile

Out of the 135 participants in the study, 54 were males, comprising 40.0%, and 81 were females, making up 60.0% of the total. The average age of the participants was 12.57 years old, with a standard deviation of 4.43. The observed age ranged from a minimum of 5 years to a maximum of 18 years. The majority of patients, 60% of the total, originated from urban areas. Statistical analysis confirmed normal distributions in the research groups, as evidenced by the skewness and kurtosis test, with values falling within the range of -3.00 to +3.00. According to the pediatrician's diagnosis, participants were categorized into three groups: Group I (control) included 37 patients (27.4%), Group II comprised 65 patients (48.1%) with psychoanxiety disorders, and Group III encompassed 33 individuals (24.4%) with mental disorders **(Table 1).**

Parameters	Age category						p
	6-10 years		11-14 years		15-18 years		
	Mean	SD	Mean	SD	Mean	SD	
GABA	13.32	5.73	14.29	1.51	7.34	1.34	0.001**
Glutamate	26.44	5.84	27.64	5.89	16.80	5.18	0.001**
Dopamine	557.40	68.72	619.57	100.35	273.81	123.25	0.001**
Noradrenalin	50.11	18.95	48.39	14.87	32.92	14.47	0.001**
Adrenalin	7.30	4.77	4.89	4.58	7.41	1.87	0.018**
NADR/ADR	9.25	4.96	14.81	5.77	4.33	1.33	0.001**

Table 1: Description of mean neurotransmitter levels by age groups.
SD=standard deviation, NADR/ADR=noradrenalin/adrenalin ratio, p=statistically significance

After processing the data with the Post-Hoc Bonferroni test, presented in **Figure 1**, the following observations were made:

In the case of dopamine, statistically significant differences were recorded ($p < 0.05$) in both the 6-10 years and 11-14 years groups ($p = 0.045$), the 6-10 years and 15-18 years groups ($p = 0.001$), as well as the 11-14 years and 15-18 years groups ($p = 0.001$).

For noradrenaline, significant differences were observed between the 11-14 years and 15-18 years groups ($p = 0.001$), the 6-10 years and 15-18 years groups ($p = 0.001$), and between the 6-10 years and 11-14 years groups, where significant differences were not observed ($p > 0.05$).

Adrenaline exhibited significant differences between the 6-10 years and 11-14 years groups ($p = 0.033$), as well as the 11-14 years and 15-18 years groups ($p = 0.021$). Insignificant differences were recorded for the 6-10 years and 15-18 years groups ($p = 1.000$).

GABA showed significant differences between the 6-10 years and 15-18 years groups (p = 0.001), and between the 11-14 years and 15-18 years groups (p = 0.001). Insignificant differences were found for the 6-10 years and 11-14 years groups (p = 1.000).

NADR/ADR exhibited statistically significant differences (p < 0.05) in both the 6-10 years and 11-14 years groups (p = 0.045), the 6-10 years and 15-18 years groups (p = 0.001), and the 11-14 years and 15-18 years groups (p = 0.001).

Glutamate was significantly different between the 6-10 years and 15-18 years groups (p = 0.001), and between the 11-14 years and 15-18 years groups (p = 0.001). Insignificant differences were recorded for the 6-10 years and 11-14 years groups (p = 1.000).

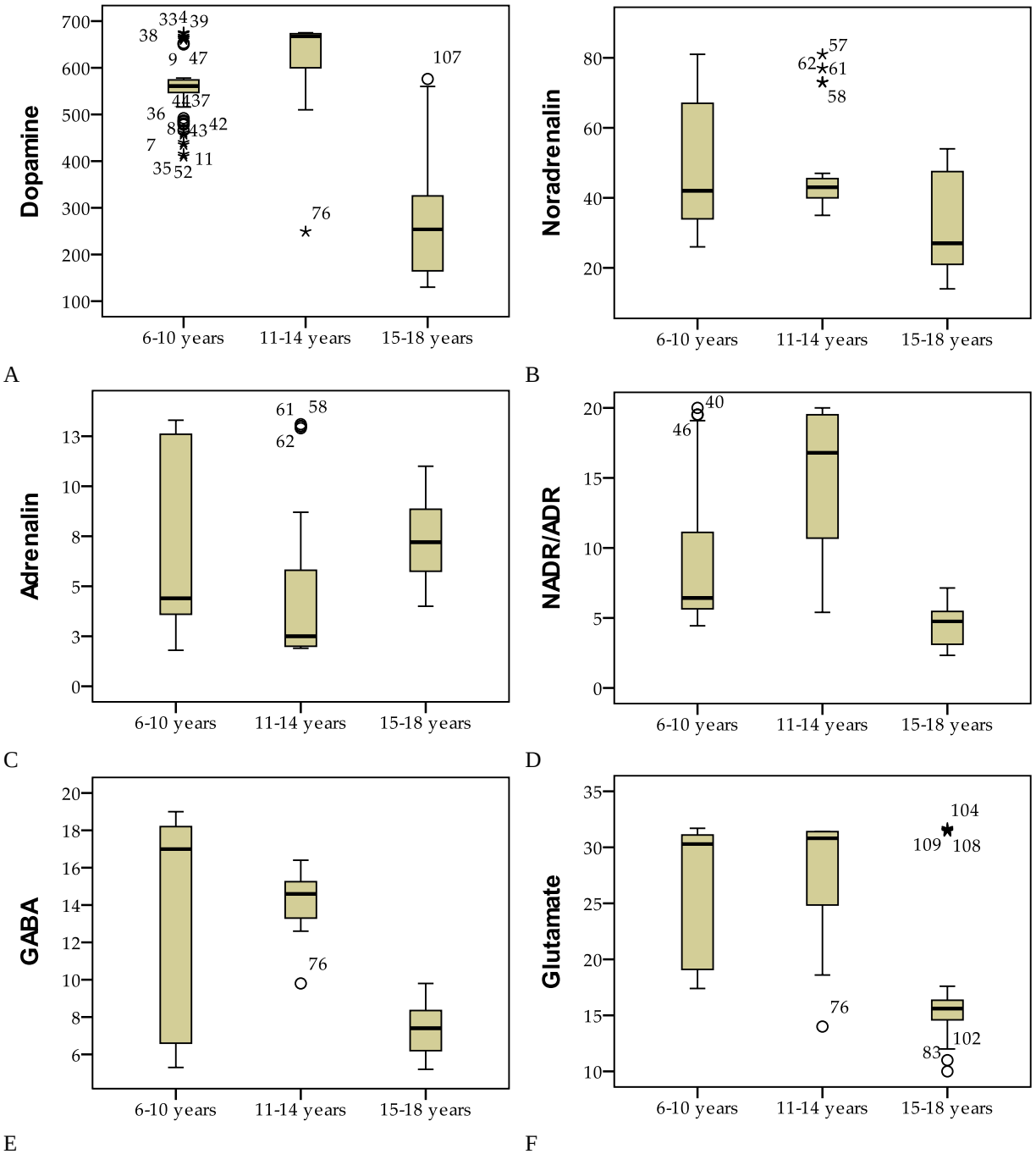
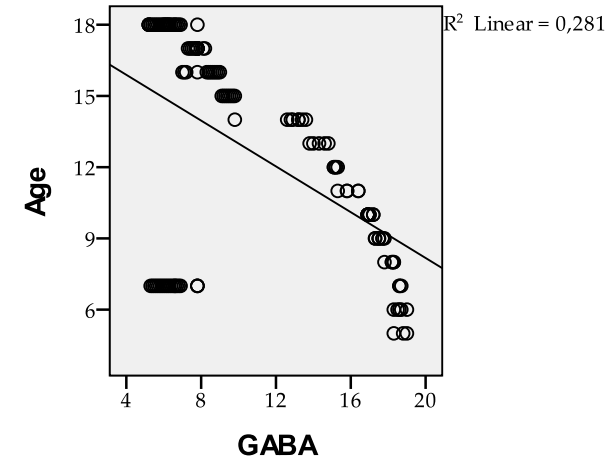


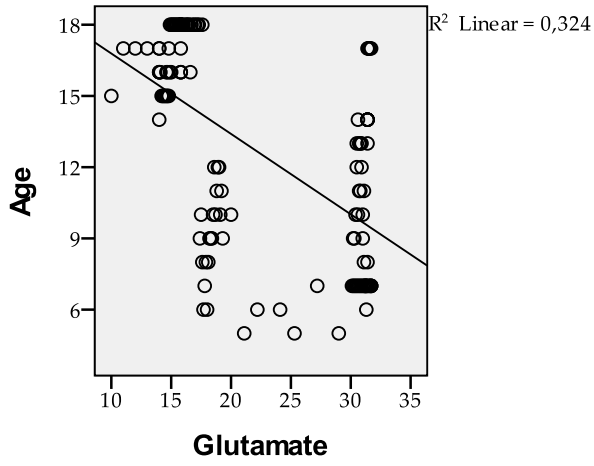
Figure 1: Boxplot graphical presentation of dopamine (A), noradrenalin (B), adrenalin (C), NADR/ADR (D), GABA (E), Glutamate (F) levels across three age categories.

The impact of age on neurotransmitter concentrations has been investigated. Notably, in adulthood, a 52% difference in higher neurotransmitter secretion has been observed between genders, favoring men. However, for individuals under the age of 18, specialized studies have yielded ambiguous results. Nevertheless, age appears to exert an influence on neurotransmitter levels.

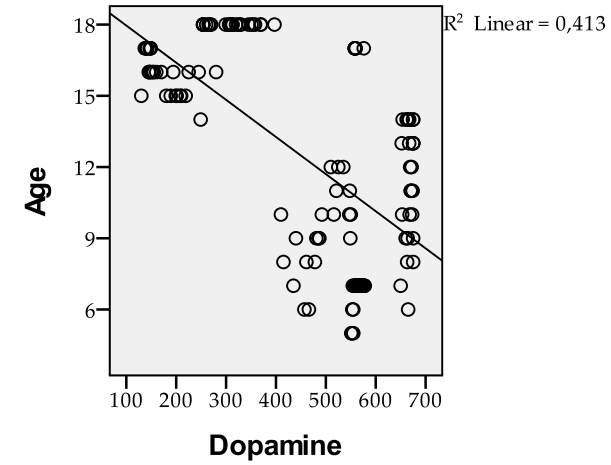
In this study, we explored the correlation between neurotransmitter levels and age, revealing a consistent trend of decreasing neurotransmitter levels with advancing age, as illustrated in **Figure 2**. In the absence of definitive benchmarks, the following observations can be made:
- GABA levels decrease by 28.1% with increasing age (R2=0.218).
- Glutamate levels decrease by 32.4% with increasing age (R2=0.324).
- Dopamine levels decrease by 28.1% with age (R2=0.281).
- Noradrenaline levels show a decrease of 24.1% with advancing age (R2=0.241).
- Adrenaline levels decrease insignificantly by 0.1% as age advances (R2=0.001).
- The NADR/ADR ratio decreases by 14% as age increases (R2=0.140).



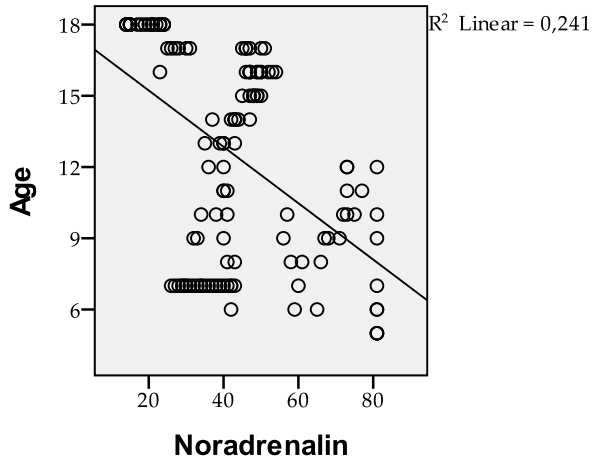
A



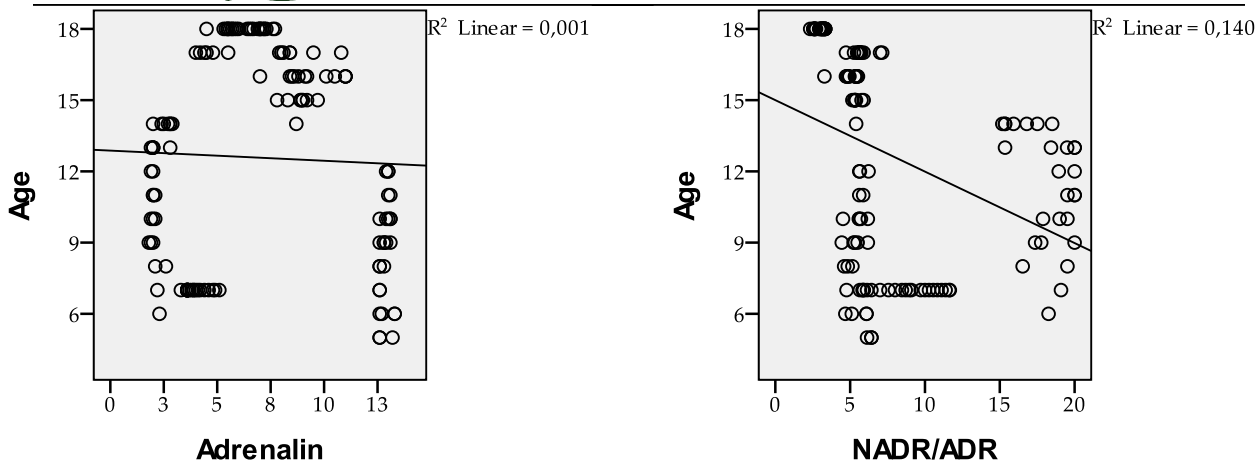
B



C



D



E F

Figure 2: Graphic presentation illustrating the impact of age on neurotransmitter concentrations, including GABA (A), glutamate (B), dopamine (C), noradrenaline (D), adrenaline (E), and NADR/ADR (F).

Discussion

Desensitization of glucocorticoid receptors is prevalent in individuals with major depression. In such cases, the negative feedback regulatory mechanism fails to function, resulting in the sustained hypersecretion of cortisol. Clinical evidence supporting this phenomenon is derived from the lack of suppression of plasma cortisol following the administration of dexamethasone, a synthetic corticosteroid [18-20]. In addition to the hyperactivity of the HPA (hypothalamic-pituitary-adrenal) axis, individuals with depression also exhibit heightened activity in the sympathoadrenal system [21,22]. The hypersecretion of noradrenaline has been documented in individuals with unipolar depression, evidenced by elevated plasma concentrations of noradrenaline and its metabolites, as well as increased levels in patients' urine. Treatment with tricyclic antidepressants has been shown to decrease plasma concentrations and urinary excretion of noradrenaline and its metabolites [23,24]. In this study, these mechanisms were observed through an interdependent relationship of neurotransmitters, highlighting their imbalances and interconnected mechanisms.

DHEA, a steroid hormone that increases during adolescence, has previously been associated with anxiety, although the direction of this effect has been mixed [25-27]. Differential exposure to sex steroid hormones during adolescence activates neural circuits organized before birth, leading to cognitive and behavioral changes [28]. While some studies report anxiolytic effects of DHEA, this study found a link between low levels of DHEA and headache and aggression, and excess levels associated with a higher incidence of fatigue and impaired concentration.

Depression and anxiety are complex, multifactorial conditions influenced by factors such as diet, stress, medications, genetics, and the microbiome [29]. Evidence suggests that certain gut bacteria, including *Lactobacillus, Bifidobacterium, Bacillus, Escherichia*, and *Saccharomyces*, can influence neurotransmitter production, including GABA, acetylcholine, norepinephrine, dopamine, and serotonin [30,31]. Changes in gut microbiota have been reported in people with depression [32]. Imbalances in the neurotransmitter GABA can be associated with anxiety, depression, and other conditions, and gut microbiota play a role in its production [33]. Serotonin, another crucial neurotransmitter, is linked to the regulation of sleep, appetite, mood, and other physiological functions and can be influenced by stress [34]. Chronic stress can impact the gut microbiome, leading to changes in bacteria composition, but certain probiotic strains, such as *Lactobacillus* and *Bifidobacterium*, can help maintain normal cortisol levels in stressful situations [29,35]. Moreover, given the low probability of adverse events associated with psychobiotics and their demonstrated safety for long-term use, it can be reasonably inferred that achieving a significant effect, comparable to drug treatment, could present a substantial advantage in pediatric patients. This is particularly pertinent when considering the scenario where not just one neurotransmitter but several are found to be imbalanced.

While acknowledging the valuable insights gained from this study, it is essential to address certain limitations. Firstly, the homogeneity in the patient population, all of whom had gastrointestinal problems, raises the concern that these issues might have influenced neurotransmitter levels, potentially limiting the generalizability of the

findings. Secondly, the reliance on ambiguous studies as a benchmark, lacking identical reference values, introduces a challenge in precisely interpreting and comparing the results.

However, a notable strength of this study lies in its comprehensive evaluation of neurotransmitter levels across different age categories, establishing correlations that contribute significantly to our understanding of the intricate relationship between age and neurotransmitter dynamics. The elucidation of these associations enhances the applicability of the findings and underscores the importance of considering age-related variations in neurotransmitter profiles.

Conclusions

GABA levels exhibit a significant decrease of 28.1% with increasing age.
Glutamate levels decrease notably by 32.4% as age advances.
Dopamine levels experience a decline of 28.1% with age progression.
Noradrenaline levels show a notable decrease of 24.1% with advancing age.
Adrenaline levels demonstrate a marginal drop of 0.1% as age advances, which is not statistically significant.
The NADR/ADR ratio experiences a marked decrease of 14% as age increases.
These findings underscore the dynamic nature of neurotransmitter concentrations across different age groups, providing valuable insights into the age-related variations in the neurochemical landscape. Understanding these trends contributes to a more comprehensive appreciation of the physiological changes associated with aging and may inform targeted interventions for age-related neurochemical imbalances.

Author Contributions

Conceptualization, T.C.G.; methodology, T.C.G.; software, T.C.G.; validation, S.V.; formal analysis, R.F.; investigation, L.M.; resources, T.C.G.; data cura-tion, T.C.G.; writing—original draft preparation, T.C.G. and S.V.; writing—review and editing, T.C.G.; visualization, T.C.G.; supervision, T.C.G.; project administration, S.V.; funding acquisition, R.F. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declara-tion of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Oradea (protocol code: CEFMF/1; date of approval: 31 January 2023).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement

All the data processed in this article are part of the research for a doctoral thesis, being archived in the aesthetic medical office, where the interventions were performed.

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Conflicts of Interest

The authors declare no conflict of interest.

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