Journal of Pharmaceutical Care & Health Systems

OPEN ACCESS Freely available online

Research Article

Exploring the Impact of Antibiotic Consumption on Cognitive Functions in Individuals with Altered Gut Microbiome: A Comparative Analysis

Gholam Hossein Javanmard[1], Shahin Javanmard[2*]

[1]Department of Psychology, Payame Noor University, Tajrish, Iran; [2]Department of Medicine, Halic University, Eyupsultan/Istanbul, Turkiye

ABSTRACT

Introduction: This scholarly investigation endeavors to scrutinize the ramifications of antibiotic utilization on executive functions by putting together individuals characterized by an altered gut microbiome due to prolonged antibiotic use (experimental group) with a control group comprising healthy non-antibiotic users. The study cohort comprised 53 participants from each group, selectively sampled from patrons across three clinical establishments.

Methods: The instruments employed for data accrual encompassed the working memory Dane man and Carpenter working memory questionnaire, the Short diagnostic questionnaire of hyperactivity disorder and insufficiency of adults CAARS, and the Dennis and Vander Wal Cognitive Flexibility Questionnaire. The data obtained from the questionnaire were analyzed using SPSS23 statistical software and MANOVA analysis.

Results: The outcomes unveiled a statistically significant disparity in working memory, attention, and cognitive flexibility between the antibiotic-utilizing cohort with an altered gut microbiome and the comparably healthy control cohort (P<0.000). These findings substantiate the proposition that protracted antibiotic usage may exert a discernible influence on specific cognitive processes.

Conclusion: This investigation underscores the potential cognitive ramifications of sustained antibiotic use among individuals harboring an altered gut microbiome. These findings highlight the imperative for further exploration into the mechanistic underpinnings of these effects and their repercussions for patient care.

Keywords: Antibiotic; Executive functions; Working memory; Attention; Cognitive flexibility; Gut microbiome

INTRODUCTION

One of the most significant medical advances, antibiotics, can save lives. Their extensive use and occasionally even improper use have been motivated by their effectiveness and safety. Antibiotics are among the most commonly given drugs for babies and children. More than two-thirds of infants in specific healthcare settings are given antibiotics before turning two years old, and more than half of children receive at least one antibiotic per year on average, with the maximum incidence occurring in the second year of life [1].

The widespread use of antibiotics, while instrumental in combating infectious diseases, has inadvertently contributed to a shift in health trends. While these drugs have undeniably saved countless lives, their pervasive use has also raised concerns about potential implications for the immune system. Simultaneously, the prevalence of infectious diseases has decreased in many nations during the last several decades. Still, immune-related disorders such as inflammatory bowel diseases, diabetes, rheumatological ailments, and allergy disorders have increased significantly during that time [2,3]. This complex interplay between antibiotics benefits and unintended consequences underscores the intricate relationship between medical advancements, disease patterns, and the immune system's response.

Prolonged antibiotic administration has been linked to

Correspondence to: Shahin Javanmard, Department of Medicine, Halic University, Eyupsultan/Istanbul Turkiye, E-mail: shahinjavanmard@gmail.com

Received: 15-Feb-2023, Manuscript No. JPCHS-24-29597; **Editor assigned:** 19-Feb-2023, PreQC No. JPCHS-24-29597 (PQ); **Reviewed:** 04-Mar-2023, QC No. JPCHS-24-29597; **Revised:** 11-Mar-2024, Manuscript No. JPCHS-24-29597 (R); **Published:** 18-Mar-2024, DOI: 10.35248/2376-0419.23.10.311

Citation: Hossein Javanmard G, Javanmard S (2024) Exploring the Impact of Antibiotic Consumption on Cognitive Functions in Individuals with Altered Gut Microbiome: A Comparative Analysis. J Pharm Care Health Syst. 10:311.

an elevated susceptibility to various chronic inflammatory conditions, including obesity, cancer, and colon neoplasia [4-6]. A recent investigation revealed a notable association between antibiotic use and increased prevalence of cardiovascular disease among individuals in their fifth and sixth decades, differing from the trends observed in both younger and older cohorts [7]. These correlations are presumably rooted in the alterations induced by antibiotics, posited to influence gut microbiota composition, as suggested by empirical findings [8,9].

Antibiotics serve as a primary intervention in the management of gut-associated disorders. In symbiotic harmony with the host, the human gut microbiome embodies a rich reservoir of functional genes that collectively comprise the human genome. A comprehensive study cataloging functional genes within the human gut microbiome, spanning 1,200 healthy individuals across three continents, identified a vast repertoire of 9 million unique microbial genes [10]. Notably, these microbial functionalities include catalytic pathways facilitating the breakdown of complex carbohydrates, yielding essential short-chain fatty acids pivotal for gastrointestinal epithelial cell energy provision, anti-inflammatory responses, and anti-proliferative properties [11]. Moreover, the microbiome contributes diverse bioactive metabolites such as vitamins, hormones, and neuro-signaling molecules like serotonin, potentially synthesized through microbial tryptophan metabolism [12]. This abundance of functionally encoded genes in the mammalian gut microbiota plays a fundamental role in critical aspects of physiological development [13].

Prolonged antibiotic administration engenders lasting perturbations in specific bacterial genes and an enduring shift in the overall composition of the gut microbiota, persisting for months to years subsequent to the termination of antibiotic therapy. Notably, even though certain bacterial species re-establish themselves following the antibiotic regimen, these enduring alterations persist [14].

Empirical investigations have established a discernible association between antibiotic usage and cognitive performance. Experimental evidence indicates that children exposed to antibiotics exhibit diminished cognitive outcomes [15,16]. Moreover, in the context of Alzheimer's disease, a twelve-month course of doxycycline combined with rifampin, when compared to a placebo, leads to a decline in cognitive capacities in affected individuals [17].

The encompassing term for cognitive impairments, ranging from mild to severe dementia, includes a spectrum of conditions [18-20]. Given its widespread prevalence, substantial rate of impairment, and burgeoning global economic burden, this disorder stands as a significant public health challenge [21].

An integral facet of cognitive function involves the construction of internal representations of the sensory environment [22]. The retention of sensory information in working memory is linked to low-dimensional population dynamics and ongoing sensory activity, often depicted as absorption regimes within the characterization of dynamic brain systems [23].

Recent investigations have introduced the concept of intermittent bursts of activity or "silent activity" processes to elucidate the preservation of stored sensory information in working memory [24]. By effectively integrating recent experiences with previously acquired schemas, working memory serves as a cognitive mechanism, actively retaining information to support cognitive processes [25].

The cognitive process of working memory is fundamentally responsible for the processing and short-term retention of information, serving as a linchpin for various intricate cognitive functions [26]. It operates as a finite-capacity system dedicated to the short-term storage of data, facilitating the smoother transition of information from short-term to long-term memory when both working and long-term memory collaboratively function. In the active execution of cognitive tasks, this tripartite system transiently houses information. Notably, working memory operates not merely as a passive repository but as a mental workspace, enabling the manipulation and assimilation of factual data, comprehension of verbal and written language, decision-making, and problem-solving [27].

Human cognition involves the critical function of attention, defining it as the cognitive capacity to select specific environmental information for further processing, leading to the emergence of focus and awareness. The multifaceted nature of attention allows for its delineation along several axes, creating a multidimensional conceptual framework. One initial distinction lies in the definition of attention, where one perspective views attention as a finite resource utilized in information processing [28,29]. Another aspect pertains to the process of selecting which information to analyze first, forming another facet of attention [30,31].

Embedded within this definition are three foundational conceptual elements. Firstly, cognitive flexibility is acknowledged as an acquirable skill, implying its developmental potential through experience. Secondly, adapting cognitive processing methods is identified as a pivotal component of cognitive flexibility. As proposed, a strategy embodies a sequence of actions exploring a problem space [32].

Cognitive flexibility transcends discrete actions, primarily involving the adaptation of complex behaviors. In professional contexts, this adaptation often involves accommodating unforeseen environmental changes after a period of familiarity with a task. While resilience may connote an individual's capacity to adapt, it does not invariably signify adaptability. On the other hand, cognitive inflexibility signifies an individual's incapacity to adjust to situations demanding adaptability in response to shifts in the surrounding environment. A manifestation of cognitive inflexibility emerges when individuals persistently employ strategies that were effective in previous contexts but prove inadequate in novel circumstances [33].

Antibiotics exert a substantial impact on the composition of the gut microbiota, necessitating precise and vigilant regulation, as emphasized by Babakhani and Hosseini [34]. The disruption in gut microbiota equilibrium induced by antibiotics and antimicrobial agents may lead to behavioral anomalies, heightened anxiety, and stress. Notably, a study involving mice subjected to a seven-day course of neomycin, bacitracin, and pimaricin demonstrated altered anxiety-related behavior; however, after a 14-day period without antibiotics, the behavior reverted to a normal state [35].

The bidirectional communication pathway known as the brain-gut axis, significantly influenced by the gut microbiome, has been associated with various neuropsychological disorders. These disorders encompass depression, schizophrenia, autism,

and anxiety, as noted by Carabotti et al., [36-40]. Furthermore, a burgeoning body of evidence posits a potential involvement of the gut microbiome in the progression of dementia. Animal-based research indicates that alterations in both oral and intestinal microbial compositions might contribute to the formation of amyloid plaques. Small-scale cross-sectional studies have revealed distinct compositional variations between individuals affected by Alzheimer's disease and those without the condition [41-44].

However, there remains a shortage of comparative research addressing the extensive and prolonged utilization of antibiotics and its implications on executive functions in individuals experiencing gastrointestinal microbiome disorders. Hence, the central objective of the present study is to explore potential disparities in executive functions specifically, memory, attention, and cognitive flexibility between patients with intestinal microbiome issues undergoing antibiotic treatment and a healthy cohort not subjected to antibiotic therapy.

METHODOLOGY

This research displays a descriptive causal-comparative study design. The statistical population within the experimental group consisted of 61 individuals afflicted with intestinal microbiome issues, seeking treatment across four distinct clinics, all of whom had undergone a minimum of three months of antibiotic therapy. Employing Cochran's formula, a random sample of 53 individuals was selected from this population. The control group, comprising 53 healthy individuals, was chosen from among the companions of the patients, ensuring a careful matching process with the experimental group from the same clinical settings.

Data collection tools

In order to collect data, Dennis and Vander Wal's Cognitive Flexibility Questionnaire, Daneman and Carpenter's Working Memory Questionnaire, and a Short diagnostic questionnaire on hyperactivity disorder and insufficiency of adults CAARS were used in this research.

1. **Dennis and vander wal cognitive flexibility questionnaire:** The questionnaire, devised by Dennis and Vander Wal in 2010, encompasses 20 items rated on a 7-point Likert scale, spanning from "completely agree" to "completely disagree." Scores on this questionnaire range from a minimum of 20 to a maximum of 140, with a predefined cutoff point set at 80. Dennis Vander Wal outlined the reliability of the questionnaire using Cronbach's alpha, indicating coefficients of 0.91 for the overall scale, 0.91 for the perception of controllability, and 0.84 for the perception of different options. In an Iranian study conducted by Moradzadeh and Pirkhafi, the overall reliability of the questionnaire, determined through Cronbach's alpha, was reported as 0.74 [45,46]. Additionally, the subscales assessing perception of controllability, perception of different options, and perception of justification of behavior exhibited reliability coefficients of 0.55, 0.72, and 0.57, respectively.
2. **Daneman and carpenter working memory questionnaire:** The instrument, formulated by Daneman and Carpenter, comprises 27 sentences distributed across six sections of varying sentence lengths: Two-sentence, three-sentence, four-sentence, five-sentence, six-sentence, and seven-sentence segments. These segments, ranging from two to seven sentences each, are orally presented to participants and contain complex and disparate content. Post-reading, participants engage in two tasks: firstly, assessing the semantic accuracy of each sentence, and secondly, recording the final word in every sentence. The working memory test score is computed by dividing the number of accurate responses in each section by the total number of sentences. The cumulative scores from all sections are aggregated and halved to determine the individual's active memory capacity. Daneman Carpenter evaluated the tool's reliability through its correlation with a verbal academic aptitude test, yielding a coefficient of 0.59 [47].
3. **Short diagnostic questionnaire of hyperactivity disorder and insufficiency of adults CAARS:** The CAARS short diagnostic questionnaire designed for assessing ADHD in adults comprises 26 items, each rated from zero to three points across four distinct subscales. These subscales delineate various aspects: Attention deficit and memory issues, hyperactivity and restlessness, impulsiveness and emotionality, and problems with overall self-perception. Raw scores obtained from each subscale are transformed into t-scores utilizing normative tables where the scale's mean is 50, and the standard deviation is 10. T-scores surpassing 65 are indicative of clinical significance. In a study conducted by Lashkaripour et al., involving 420 participants, the questionnaire exhibited a high level of validity, demonstrated by Cronbach's alpha coefficient of 0.93 [48]. This instrument serves the purpose of symptom evaluation and diagnosing ADHD in adults.

Findings

The following table shows the results related to the descriptive characteristics of the two groups in cognitive differences, attention, and working memory (Table 1):

The gathered data underwent analysis using the statistical techniques of Multivariate Analysis of Variance (MANOVA) and t-tests, employed to compare the means of two independent groups. The utilization of the MANOVA method necessitates the fulfillment of its underlying preconditions for accurate application (Tables 2-4).Tables 2-4, show the results of default MANOVA tests. The presuppositions are established based on the results obtained, and MANOVA can be used. The results of the data analysis with the MANOVA method are shown in Table 5. Based on the above table, there is a significant difference in cognitive flexibility, attention, and working memory variables between two healthy groups and antibiotic users. In this way, the healthy group's total cognitive flexibility, memory, and attention scores are significantly higher than those of the antibiotic-consuming group.

Table 1: Descriptive and sample characteristics of measured variables.

Variable		Indicators of central tendency		Dispersion tendency indices	
		Median	Mean	Variance	Standard deviation
Alternatives	Antibiotic users	3.14	3.21	0.79	0.888
	Healthy	4.42	4.32	0.281	0.53
Control	Antibiotic users	3.42	3.32	0.791	0.889
	Healthy	4.28	4.18	0.291	0.539
Alternatives to human behavior	Antibiotic users	3	2.93	0.537	0.732
	Healthy	4.33	4.25	0.308	0.555
Cognitive flexibility	Antibiotic users	3.2	3.17	0.499	0.706
	Healthy	4.4	4.27	0.247	0.496
Memory problem	Antibiotic users	3.66	3.6	0.68	0.824
	Healthy	4.16	4.17	0.182	0.426
Restlessness and instability	Antibiotic users	4	3.82	1.222	1.102
	Healthy	3.85	3.91	0.339	0.582
Being impulsive and emotional	Antibiotic users	3.33	3.29	0.368	0.606
	Healthy	4	4.02	0.284	0.532
Problems with the overall picture	Antibiotic users	2.85	2.68	0.736	0.857
	Healthy	4.35	4.29	0.309	0.555
Attention	Antibiotic users	3.36	3.37	0.259	0.508
	Healthy	4.03	4.07	0.148	0.384
Working memory	Antibiotic users	3.18	3.21	0.411	0.641
	Healthy	4.31	4.3	0.105	0.323

Table 2: Box test to check the assumption of homogeneity of the variance-covariance matrix.

Significance level	F statistic	BOX M
0.211	3.202	8.712

Table 3: Wilks's lambda test in multivariate variance analysis of research variables.

Test	Value	F statistic	Degrees of freedom	Statistical significance	Eta-squared
Wilks's lambda	0.542	9.279	3	0.001	0.101

Table 4: The results of Levin's test check the assumption of equality of variances of the research variables.

Variables	F statistic	Df1	Df2	Statistical significance
Cognitive flexibility	3.315	1	138	0.109
Attention	3.648	1	138	0.116
working memory	2.589	1	138	0.24

Table 5: Results of data analysis with multivariate analysis of variance.

References	The dependent variable	Sum of squares	Degrees of freedom	Average of squares	F statistic	Significance level	Eta-squared
Group	Flexibility	41.04	1	41.04	110.13	0.001	0.44
	Attention	17.61	1	17.61	86.74	0.001	0.386
	Working memory	41.13	1	41.13	159.45	0.001	0.536
Error	Flexibility	51.42	138	0.373	-	-	-
	Attention	28.01	138	0.203	-	-	-
	Working memory	35.6	138	0.258	-	-	-

RESULTS AND DISCUSSION

The examination of the primary hypothesis within this study unveiled a noteworthy disparity in the domains of working memory, attention, and cognitive flexibility between the group utilizing antibiotics and the healthy control. Specifically, the scores pertaining to working memory, concentration, and cognitive flexibility were significantly higher in the healthy group in contrast to the antibiotic user group. These findings are consistent with various research outcomes, aligning with the works of Liu et al., [49], Tamada et al., [50], Slob et al., [51], Saji et al., [11], and Slykerman et al., [15,16]. However, the epidemiological data regarding long-term antibiotic use and its correlation with cognitive functions are relatively sparse and explore disparate contexts compared to the current study. For instance, studies on antibiotic exposure during infancy suggest associations with reduced cognitive abilities, verbal comprehension at 11 years old, and depressive symptoms at three years of age [15,16], hinting at a potential temporal gap between antibiotic use and subsequent neurocognitive manifestations.

Nevertheless, extending the implications derived from infant antibiotic use to the outcomes observed in adult subjects in our research presents a challenge. Notably, the study by Heianza et al., [7] examining the "Duration and Life Stage of Antibiotic Use and Risk of Cardiovascular Events in Women" involving 36,429 women revealed that prolonged antibiotic exposure heightened the risk of contracting cardiovascular disease in various life stages, including adulthood, middle age, and old age. Considering the profound influence of antibiotics on the gut microbiome, as evidenced in studies displaying alterations in functional potential even up to 2 [8], and four years' post-antibiotic exposure, the potential mechanism connecting antibiotics with cognitive function could involve the gut-brain axis. Indeed, recent research has increasingly highlighted the relationship between gut bacteria and the gut-brain axis, as observed in studies by Carabotti et al., [40], Valles-Colomer et al., [36], and Zhu et al., [37,52]. Additionally, recent cross-sectional data from smaller-scale studies have demonstrated significant taxonomic differences in the gut microbiomes of individuals with Alzheimer's disease compared to healthy individuals [44].

The initial hypothesis examination has revealed significant findings, elucidating a marked discrepancy in working memory between the cohort using antibiotics and the healthy control group. Specifically, the group exposed to antibiotics displayed diminished scores in working memory, corroborating earlier research [11,15,16,40,50,51].

Furthermore, the investigation conducted by Zhao, Cong, Jabe, and Lukiw, focusing on "Microbiome-derived lipopolysaccharide enriched in the perinuclear region of Alzheimer's disease brain," documented an enrichment of microbiome-derived lipopolysaccharide in the perinuclear region of brains affected by Alzheimer's disease, identifying its presence in the hippocampus of Alzheimer's patients [53]. Our results concur with these studies, indicating that our subjects exhibited lower scores on working memory assessments compared to the healthy group, signifying impaired memory function. Although the precise mechanisms underlying the gut microbiome's impact on human cognitive functions remain enigmatic, animal studies strongly advocate the gut microbiome's pivotal role in regulating brain function and behavior.

The intricate functional pathways responsible for communication between the gut microbiome and the brain, often termed the "gut-microbiome-brain cross-talk," delineate a bidirectional communication network encompassing neuroendocrine signaling pathways, neural pathways, and circulatory pathways. This network facilitates the transportation of microbial metabolites, toxins, pro inflammatory agents, and the activation of neuroendocrine cells attributed to microbial metabolites, which are believed to be fundamental in modulating cognitive functions [54].

Furthermore, an increased prevalence of pro-inflammatory gut microbiome taxa coupled with a decrease in anti-inflammatory taxa might be linked to the inflammatory status observed in patients affected by cognitive disorders and brain amyloidosis. This association finds support in a study examining gut-brain modules in fecal metagenomes, revealing the synthesis of microbial metabolites and suggesting a potential role of these compounds in the onset of depression [11]. Moreover, it is imperative to acknowledge the association between antibiotics and cognitive disorders.

Another key finding from the secondary hypothesis underscores a substantial difference in attention levels between the group using antibiotics and the healthy control group. Our results indicate a correlation between exposure to antibiotic medications and an increased susceptibility to attention deficit disorder. These results align with prior research [11,15,16,43,50,51,53].

Elucidating this discovery necessitates recognition of adult attention deficit, a prevalent and complex issue. Recent estimates indicate its occurrence in children at approximately 6% to 9%, with a considerable proportion of these individuals continuing to experience symptoms into adulthood, affecting their professional, social, and familial aspects to various extents. This implies that roughly 3% to 6% of adults contend with these symptoms, impacting their ability for purposeful behavior and mood regulation, potentially due to alterations in the frontal cortex, dopamine and noradrenaline levels, and structural changes in the striatum and cortex. These factors compromise intentional behavior and heighten the likelihood of impulsive actions. Furthermore, attention deficits often correlate with work and relationship instability, manifesting as restlessness, mood swings, or difficulty concentrating. These manifestations might occasionally be overlooked or misattributed to other conditions like anxiety or depression [55].

In another investigation concerning the link between Shigellosis during early childhood and attention deficit hyperactivity disorder identified a substantial correlation between positive Shigella results in stool cultures and attention deficit hyperactivity disorder. Specifically, 10.6% of children with Shigella-positive cultures and 8.6% of those with Shigella-negative cultures exhibited symptoms of ADHD. Our study's outcomes align with this observed correlation [56]. Additionally, Sadaka et al., delved into the association between antibiotic treatment for early childhood Shigella infection and attention deficit hyperactivity disorder risk [57]. Their findings suggested that the timing of antibiotic administration plays a pivotal role, with children receiving antibiotics at a later stage exhibiting a significantly higher risk of developing ADHD compared to those who did not receive antibiotics. Therefore, the impact of antibiotic treatment, including its timing, on attention deficits could be influenced by multiple potential pathways. Antibiotic treatment can suppress bacterial activity, reducing toxin production and the associated inflammation duration, thereby mitigating attention deficit disorder. Moreover, antibiotic administration exerts a substantial and enduring influence on the human microbiome, independently affecting the prevalence of neurodevelopmental disorders, irrespective of Shigella infection's involvement.

Furthermore, the results from the third hypothesis accentuate a notable divergence in cognitive flexibility between the antibiotic-using group and the healthy control group. When considering these findings alongside earlier investigations, they suggest that manipulating the composition of the gut microbiome may serve as a possible mechanism for diminishing cognitive flexibility. These research findings harmonize with studies conducted by [15,16,34,55,58].

In the research conducted by Anderson et al., [58], an exploration into the intricate relationship among gut microbiota, sleep patterns, and cognitive flexibility was undertaken with a cohort of 37 healthy elderly participants, averaging between 59 and 64 years of age. Their findings illuminated a correlation between enhanced sleep quality, improved performance in the Stroop task, and a higher prevalence of distinct intestinal microbial phyla, notably Verukomicrobia and Lentisphara. Understanding this correlation is essential in comprehending the influence of alterations in gut microbiome composition on cognitive flexibility, learning, memory, and the accumulation of β-amyloid in the cerebral cortex.

Cognitive flexibility encompasses executive control processes that rely on intricate interactions within extensive brain networks, facilitating pivotal functions such as salient recognition, attention, inhibition, working memory, and switching processes. These processes are critical for individuals to adapt, pivot, and challenge automatic assumptions. However, these faculties are compromised in individuals with gut microbiomes influenced by antibiotic consumption. Human adaptability, flexibility, and creativity are contingent on the ability to adjust responses to evolving circumstances. Impairment in this ability, observed in patients with antibiotic-affected gut microbiomes, hampers their capacity to adapt to environmental changes. Notably, the presence of an increased number of neural pathways and connections in the brain enhances information processing and speeds up decision-making. An abundance of pathways facilitates efficient communication, leading to quicker information processing and decision-making among individuals.

After all, executive function disparities, especially in individuals using antibiotics and exhibiting an altered gut microbiome, have garnered considerable attention due to their implications for cognitive health. Research consistently demonstrates a pronounced relationship between antibiotic use, gut microbiome alterations, and cognitive function discrepancies, observed explicitly in working memory, attention, and cognitive flexibility. Studies by Anderson et al., [58] Tamada et al., [50] Slob et al., [51] and Saji et al., [11] underscore substantial cognitive impairments in antibiotic-exposed groups, illuminating the intricate association between antibiotics, the gut microbiome, and cognitive abilities. Furthermore, additional studies highlight the relationship between the makeup of gut microbes and cognitive abilities [53].

CONCLUSION

This study uncovers a nuanced yet impactful decline in cognitive performance linked to antibiotic use, spotlighting the intricate and far-reaching implications across an individual's lifespan. The implications extend beyond immediate concerns to a comprehensive evaluation of the potential long-term effects of antibiotic therapies, emphasizing the need for a balanced consideration of their risks and benefits. It encourages contemplation of the complex interconnections between the gut microbiome and cognitive faculties, emphasizing the growing significance of the gut microbiome in various aspects of health.

In essence, this research serves as a clarion call for understanding the potential impact of antibiotic use on cognitive performance, advocating for a holistic approach in healthcare strategies, and informed decision-making regarding antibiotic treatments. This work encourages further in-depth explorations into the gut-brain relationship to refine health approaches and preserve cognitive health in individuals undergoing antibiotic treatments.

ACKNOWLEDGEMENT

This study's data, analytic methods, and materials are available to other researchers for replication purposes. Interested parties can find these details in the manuscript. Furthermore, studies reported in this manuscript were not pre-registered.

AUTHORS' CONTRIBUTIONS

GJ provided data, conducted all statistical analyses, and helped to write the manuscript, and SJ helped to design the study and write the manuscript. All authors reviewed the final manuscript.

FUNDING

Statement for people/funding: NA.

CONFLICT OF INTEREST

All co-authors have seen and agree with the manuscript's contents, and there is no financial interest to report. Therefore, we certify that the submission is an original work and is not under review at any other publication.

TRANSPARENCY DECLARATION

The lead authors confirm that this publication is an honest, accurate, and transparent description of the study, that no critical components of the investigation have been omitted, and that any deviations from the intended research (and, if applicable, recorded) have been explained.

REFERENCES

1. Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis. J Infect. 2022;85(3):213-300.
2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-743.
3. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. Incidence trends of type 1 and type 2 diabetes among Youths, 2002-2012. N Engl J Med. 2017;376(15):1419-1429.
4. LC, Forrest CB, Zhang P, Richards TM, Livshits A, DeRusso PA. Association of antibiotics in infancy with early childhood obesity. JAMA Pediatr. 2014;168(11):1063-1069.
5. Petrelli F, Ghidini M, Ghidini A, Perego G, Cabiddu M, Khakoo S, et al. Use of antibiotics and risk of cancer: a systematic review and meta-analysis of observational studies. Cancers (Basel). 2019;11(8):1174.
6. Shreiner AB, Kao JY, Young VB. The gut microbiome in health and in disease. Curr Opin Gastroenterol. 2015;31(1):69-75.
7. Heianza Y, Zheng Y, Ma W, Rimm EB, Albert CM, Hu FB, et al. Duration and life-stage of antibiotic use and risk of cardiovascular events in women. Eur Heart J. 2019;40(47):3838-3845.
8. Korpela K, Salonen A, Virta LJ, Kekkonen RA, Forslund K, Bork P, et al. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. Nat Commun. 2016;7(1):10410.
9. Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018;555(7698):623-628.
10. Li B, Zhang T. Biodegradation and adsorption of antibiotics in the activated sludge process. Environ Sci Technol. 2010;44(9):3468-3473.
11. Saji N, Murotani K, Hisada T, Tsuduki T, Sugimoto T, Kimura A, et al. The relationship between the gut microbiome and mild cognitive impairment in patients without dementia: A cross-sectional study conducted in Japan. Sci Rep. 2019;9(1):19227.
12. Dunne-Dombrink K. The inhibitory role of indole in tryptophan synthase and its significance in treatment for resistant tuberculosis in francophone countries. Scripps Senior Theses. 2020;(1587).
13. Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, et al. Human gut microbiota in health and disease: Unveiling the relationship. Front Microbiol. 2022;13:999001.
14. Palleja A, Mikkelsen KH, Forslund SK, Kashani A, Allin KH, Nielsen T, et al. Recovery of gut microbiota of healthy adults following antibiotic exposure. Nat Microbiol. 2018;3(11):1255-1265.
15. Slykerman RF, Thompson J, Waldie KE, Murphy R, Wall C, Mitchell EA. Antibiotics in the first year of life and subsequent neurocognitive outcomes. Acta Paediatr. 2017;106(1):87-94.
16. Slykerman RF, Coomarasamy C, Wickens K, Thompson JMD, Stanley T V., Barthow C, et al. Exposure to antibiotics in the first 24 months of life and neurocognitive outcomes at 11 years of age. Psychopharmacology (Berl). 2019;236(5):1573-1582.
17. Molloy DW, Standish TI, Zhou Q, Guyatt G. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: The DARAD trial. Int J Geriatr Psychiatry. 2013;28(5):463-470.
18. Courtney DL. Dealing with mild cognitive impairment. Clin Geriatr Med. 2013;29(4):895-905.
19. Ljubenkov P, Geschwind M. Dementia. Semin Neurol. 2016;36(4):397-404.
20. Rajji TK. Neurophysiology and cognitive reserve: A promising path. Clinical Neurophysiology. 2018;129(1):286-287.
21. Sacuiu SF. Dementias. Handb Clin Neurol. 2016;138:123-151.

22. McNamee D, Wolpert DM. Internal Models in Biological Control. Annu Rev Control Robot Auton Syst. 2019;2(1):339-364.

23. Cueva CJ, Saez A, Marcos E, Genovesio A, Jazayeri M, Romo R, et al. Low-dimensional dynamics for working memory and time encoding. Proc Natl Acad Sci USA. 2020;117(37):23021-23032.

24. Wolff MJ, Jochim J, Akyurek EG, Stokes MG. Dynamic hidden states underlying working-memory-guided behavior. Nat Neurosci. 2017;20(6):864-871.

25. Spencer JP. The development of working memory. Curr Dir Psychol Sci. 2020;29(6):545-553.

26. Maramis MM, Mahajudin MS, Khotib J. Impaired cognitive flexibility and working memory precedes depression: A rat model to study depression. Neuropsychobiology. 2021;80(3):225-233.

27. Samadi Taherghorabi M, Shakerini I. Effectiveness of Neurofeedback on Working Memory and Cognitive Flexibility in Patients with Mild Depression: A Clinical Trial. JGUMS. 2022;30(4):290-303.

28. Lepsien J, Nobre AC. Cognitive control of attention in the human brain: Insights from orienting attention to mental representations. Brain Res. 2006;1105(1):20-31.

29. Wickens CD. The structure of attentional resources. 1981.

30. Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci. 1995;18(1):193-222.

31. Chun MM, Golomb JD, Turk-Browne NB. A taxonomy of external and internal attention. Annu Rev Psychol. 2011;62(1):73-101.

32. Payne JW, Bettman JR, Johnson EJ. The adaptive decision maker. Cambridge University Press. 1993.

33. Canas JJ, Fajardo I, Salmerón L. Cognitive Flexibility. 2006.

34. Babakhani S, Hosseini F. Gut microbiota: An effective factor in the human brain and behavior. Neurosci. J. Shefaye Khatam. 2019;7(1):106-118.

35. Parashar A, Udayabanu M. Gut microbiota regulates key modulators of social behavior. European Neuropsychopharmacology. 2016;26(1):78-91.

36. Valles-Colomer M, Falony G, Darzi Y, Tigchelaar EF, Wang J, Tito RY, et al. The neuroactive potential of the human gut microbiota in quality of life and depression. Nat Microbiol. 2019;4(4):623-32.

37. Zhu F, Guo R, Wang W, Ju Y, Wang Q, Ma Q, et al. Transplantation of microbiota from drug-free patients with schizophrenia causes schizophrenia-like abnormal behaviors and dysregulated kynurenine metabolism in mice. Mol Psychiatry. 2020;25(11):2905-2918.

38. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell. 2013;155(7):1451-1463.

39. de Palma G, Lynch MDJ, Lu J, Dang VT, Deng Y, Jury J, et al. Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice. Sci Transl Med. 2017;9(379):6397.

40. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203-209.

41. Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, et al. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv. 2019; 5(1):3333.

42. Dodiya HB, Frith M, Sidebottom A, Cao Y, Koval J, Chang E, et al. Synergistic depletion of gut microbial consortia, but not individual antibiotics, reduces amyloidosis in APPPS1-21 Alzheimer's transgenic mice. Sci Rep. 2020;10(1):8183.

43. Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang X, et al. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APPSWE/PS1ΔE9 murine model of Alzheimer's disease. Sci Rep. 2017;7(1):10411.

44. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017;7(1):13537.

45. Dennis JP, Vander Wal JS. The cognitive flexibility inventory: Instrument development and estimates of reliability and validity. Cognit Ther Res. 2010;34(3):241-53.

46. Moradzadeh F, Pirkhafi A. The effect of acceptance and commitment training on the cognitive flexibility and self-compassion of Varamin Welfare Department employees. JHPM. 2019;(3):46-51.

47. Baker L. Working memory and comprehension: A replication. Bull Psychon Soc. 1985;23(1):28-30.

48. Lashkaripour K, Arab Gol F, Bakhshani N. Studying the prevalence of symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in adults in students of Zahedan University of Medical Sciences. Iran J Psychiatry Behav Sci. 2013;7(2):83-90.

49. Liu Z, Wei S, Chen X, Liu L, Wei Z, Liao Z, et al. The effect of long-term or repeated use of antibiotics in children and adolescents on cognitive impairment in middle-aged and older person(s) adults: A cohort study. Front Aging Neurosci. 2022;14: 833365.

50. Tamada H, Ikuta K, Makino Y, Joho D, Suzuki T, Kakeyama M, et al. Impact of intestinal microbiota on cognitive flexibility by a novel touch screen operant system task in mice. Front Neurosci. 2022;16.

51. Slob EMA, Brew BK, Vijverberg SJH, Dijs T, van Beijsterveldt CEM, Koppelman GH, et al. Early-life antibiotic use and risk of attention-deficit hyperactivity disorder and autism spectrum disorder: Results of a discordant twin study. Int J Epidemiol. 2021;50(2):475-484.

52. Doan J, Kottayam R, Krishnamurthy MB, Malhotra A. Neonatal alloimmune neutropaenia: Experience from an Australian paediatric health service. J Paediatr Child Health. 2020;56(5):757-763.

53. Zhao Y, Cong L, Jaber V, Lukiw WJ. Microbiome-Derived Lipopolysaccharide Enriched in the Perinuclear Region of Alzheimer's Disease Brain. Front Immunol. 2017;8:1064.

54. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017;49:60-68.

55. Kates N. Attention deficit disorder in adults. Management in primary care. Can Fam Physician. 2005;51(1):53-59.

56. Merzon E, Gutbir Y, Vinker S, Golan Cohen A, Horwitz D, Ashkenazi S, et al. Early childhood shigellosis and attention deficit hyperactivity disorder: A population-based cohort study with a prolonged follow-up. J Atten Disord. 2021;25(13):1791-1800.

57. Sadaka Y, Freedman J, Ashkenazi S, Vinker S, Golan-Cohen A, Green I, et al. The effect of antibiotic treatment of early childhood shigellosis on long-term prevalence of attention deficit/hyperactivity disorder. Children. 2021;8(10):880.

58. Anderson JR, Carroll I, Azcarate-Peril MA, Rochette AD, Heinberg LJ, Peat C, et al. A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults. Sleep Med. 2017;38:104-107.