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Prenatal Ultrasound–Detected Structural Anomalies Associated with Autism Spectrum Disorder: A Narrative Review Page 24

Exploring Visual Representations of Safety in Virtual Relaxation Content: A Correlational Study
Page 14

Transition from Illness Anxiety Disorder to Delusional Disorder: A Case Series
Page 36

Proprioception and Cognitive Polarization in Autism: The Bipolar Tensile Model
Page 49

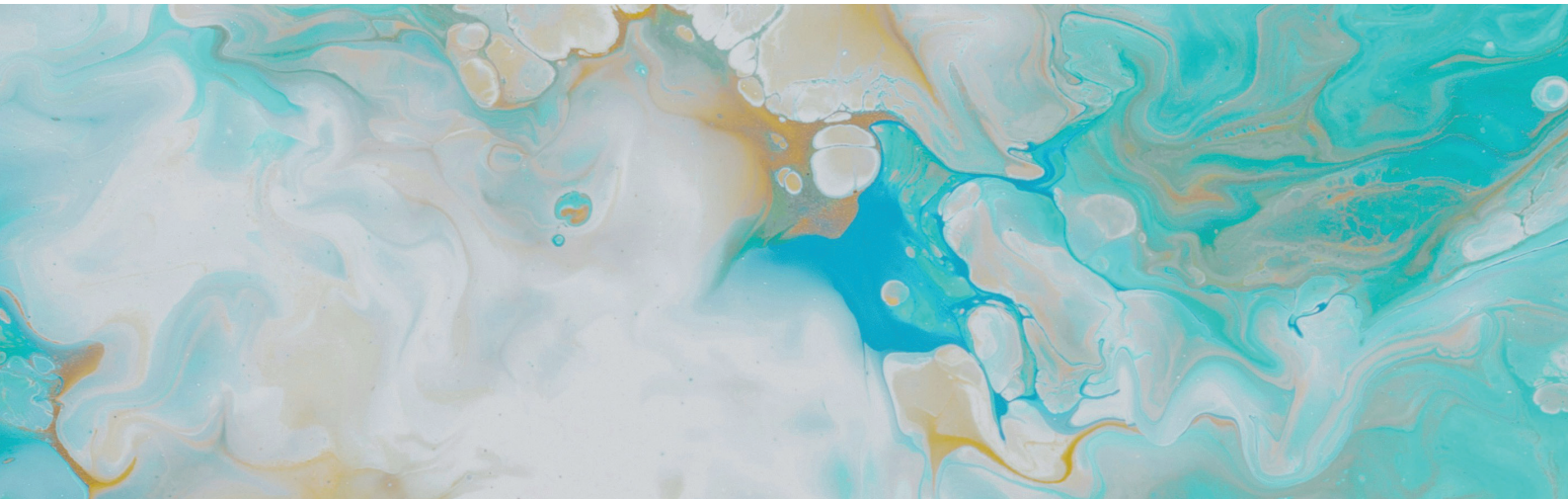

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Table of contents

RESEARCH

Mental Health and Quality of Life in Chronic and Recurrent vs First-Episode Dermatophytosis: A Cross-Sectional Study 5

Soumya Agarwal, Abdul Qadir Jilani, Sonal Singh, Akanksha Sharma, Anurag Pathak, Vikram Singh, Priyansh Jaiswal

Exploring Visual Representations of Safety in Virtual Relaxation Content: A Correlational Study 14

Tatyana Buzina, Anastasia Kotelnikova, Yury Zinchenko, Natalia Nikitina

REVIEW

Prenatal Ultrasound–Detected Structural Anomalies Associated with Autism Spectrum Disorder: A Narrative Review 24

Nazyar Khamenehei, Lyudmila Tokarskaya

CASE REPORT

Transition from Illness Anxiety Disorder to Delusional Disorder: A Case Series 36

Debanjan Bhattacharjee, Amrita Chowdhury

Hypothyroidism-Induced Psychotic Disorder with Prolonged Antipsychotic Treatment: A Case Report 42

José Eduardo López-Villa, Damaris Priscila Martín-Escoto

DISCUSSION

Proprioception and Cognitive Polarization in Autism: The Bipolar Tensile Model 49

Marco Sanna

LETTER TO THE EDITOR

Secondary Psychotic Syndromes Should Be Excluded before Assuming Idiopathic Digital "Folie à Trois" 60

João Gama-Marques

Response to the Letter to the Editor Titled «Secondary Psychotic Syndromes Should Be Excluded before Assuming Idiopathic Digital "Folie à Trois"» 62

Debanjan Banerjee

Mental Health and Quality of Life in Chronic and Recurrent vs First-Episode Dermatophytosis: A Cross-Sectional Study

Психическое здоровье и качество жизни при хронической и рецидивирующей дерматофитии в сравнении с впервые выявленным эпизодом: поперечное исследование

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Original research

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ABSTRACT

BACKGROUND: Chronic and recurrent dermatophytosis (CRD) might affect mental health morbidity as well as the quality of life of patients, although it has not been conclusively proven.

AIM: To study the quality of life and mental health burden in patients with CRD as compared to those presenting with first-episode superficial dermatophytic infection (SDI).

METHODS: The study included patients aged over 18 years with CRD or with first-episode SDI. Quality of life was assessed using the Dermatology Life Quality Index (DLQI), mental health morbidity — using the 12-item General Health Questionnaire (GHQ12) and the Hospital Anxiety and Depression Scale (HADS) defined as the HADS-A (anxiety) and the HADS-D (depression).

RESULTS: A total of 166 patients were examined: 104 with CRD and 62 with first-episode SDI. CRD patients had significantly poorer quality of life, especially in the "extremely large score category" as compared with SDI. The DLQI domains of "symptoms and feelings" and "daily activities" were the worst affected (in all cases $p<0.05$). In multivariate logistic regression analysis, body surface area involvement and HADS-A emerged as significant predictors of CRD.

CONCLUSION: CRD patients had greater deterioration in mental health (HADS-A) as compared to patients with first-episode superficial dermatophytosis.

АННОТАЦИЯ

ВВЕДЕНИЕ: Несмотря на отсутствие исчерпывающих доказательств, существует предположение, что хронические и рецидивирующие дерматофитии (ХРД) ассоциированы с повышенным риском психических расстройств и снижением качества жизни.

ЦЕЛЬ: Проанализировать качество жизни и бремя психических расстройств у пациентов с ХРД в сравнении с пациентами, у которых впервые выявлена поверхностная дерматофития (ПД).

МЕТОДЫ: В исследование были включены пациенты старше 18 лет с ХРД или впервые выявленной ПД. Психическое состояние оценивали с использованием 12-пунктового «Опросника общего здоровья» (12-item General Health Questionnaire, GHQ12) и «Госпитальной шкалы тревоги и депрессии» (Hospital Anxiety Depression Scale, HADS), которая включает подшкалы тревоги (HADS-A) и депрессии (HADS-D). Качество жизни измеряли с помощью опросника «Дерматологический индекс качества жизни» (Dermatology Life Quality Index, DLQI).

РЕЗУЛЬТАТЫ: Было обследовано 166 пациентов: 104 — с ХРД и 62 — с впервые выявленной ПД. У пациентов с ХРД отмечалось статистически значимое снижение показателей психического благополучия и качества жизни по сравнению с пациентами с ПД. Особенно выраженные различия были у пациентов, набравших чрезвычайно высокие баллы по DLQI, что отражает наиболее тяжелое влияние заболевания на их повседневную жизнь (p<0,05). Наибольшие межгрупповые различия зафиксированы в доменах «симптомы и эмоциональное состояние» и «повседневная деятельность». По результатам многомерного логистического регрессионного анализа значимыми предикторами ХРД были площадь поражения кожи (в процентах от общей площади поверхности тела) и показатель тревоги по подшкале HADS-A.

ЗАКЛЮЧЕНИЕ: У пациентов с ХРД наблюдались более высокие уровни психологического стресса и тревожности, а также более выраженное ухудшение качества жизни по сравнению с пациентами со впервые выявленной ПД.

Keywords: *chronic and recurrent dermatophytosis; superficial dermatophytosis; quality of life; mental health*
Ключевые слова: *хроническая и рецидивирующая дерматофития; поверхностная дерматофития; качество жизни; психическое здоровье*

INTRODUCTION

Superficial fungal infections of the skin, hair, and nails by dermatophytes are among the most common infective dermatoses seen in humans, with an estimated prevalence of 37–78% in India [1].

In the Indian subcontinent, the incidence of chronic and recurrent dermatophytosis (CRD) is around 65% and 35% respectively [2], and it has risen to epidemic proportions over the years [3]. Most cases of dermatophytosis have turned into a therapeutic challenge due to various host, environmental, and etiological agent factors such as immunocompromised state, atopy, diabetes, change in host dressing habits, such as tight clothing and occlusive footwear, topical steroid abuse, high temperature and relative humidity, atypical presentations, change in dermatophyte strains and emergence of resistant strains [4, 5].

In the present scenario, CRD has posed a significant burden on patients (especially when they pay for their dermatophytosis treatment themselves with no insurance coverage). Even after treatment, CRD has a huge mental health impact on patients, as persistent and severe pruritus (cutaneous itching), extreme distress in their routine activities, especially social life and sexual activities, and also occupational health issues [6]. Since CRD runs a chronic course, it might have a significant impact on patients' mental well-being, and stress can adversely affect the patients' immunity, which could further impair the rate of recovery from the chronic infection [7]. Thus, it is important to address the mental health and quality of life of patients along with the recommended antifungal treatment.

Only a few studies [8, 9] have drawn attention to assessing mental health and quality of life in patients with CRD using the Dermatology Life Quality Index (DLQI) [10], the 12-item General Health Questionnaire (GHQ12) [11, 12], and the Hospital Anxiety and Depression Scale (HADS) [13, 14]. Since only a few studies [15] have been conducted in North India in this area and to our best knowledge, no studies have evaluated quality of life and mental health in patients with CRD in comparison with SDI (using DLQI, HADS, and GHQ12).

Hence, we aimed to study the quality of life and mental health burden in patients with CRD as compared to those presenting with first-episode superficial dermatophytic infection (SDI).

METHODS

Study design

A cross-sectional study was conducted. Patient record forms were used to obtain sociodemographic data (sex, age, education, marital and socioeconomic status), medical history and predisposing factors.

Setting

This study was conducted from July to December 2022 in the outpatient departments (OPDs) of dermatology and psychiatry at the Dr. Ram Manohar Lohia Institute of Medical Sciences (Lucknow, India).

Eligibility criteria

Inclusion criteria

Patients aged over 18 years presenting with CRD or first episode of SDI.

All study participants presenting with itchy annular lesions underwent cutaneous examination. The clinical diagnosis of dermatophytosis was based on clinical history (history of itchy, red lesions over the groin region, face, etc.) and cutaneous examination (annular lesions with erythematous raised borders and central clearing). In doubtful cases, a microscopic examination of the potassium hydroxide mount of scrapings from lesions was performed. Disease severity was measured by body surface area (BSA) involvement based on the "rule of nines" and itch severity on a scale of 1 to 10 using the Visual Analog Scale (VAS) [13].

We defined first-episode dermatophytosis as an infection in a treatment-naive patient with a duration of less than 6 weeks. When patients suffered from dermatophytosis for more than 6 months, with or without recurrence, despite being adequately treated, it was termed chronic dermatophytosis. Adequately treated was defined as having received a tablet of terbinafine 250 mg once a day for 4 weeks and/or a tablet of fluconazole 150 mg once a week for at least 8 weeks and/or a capsule of itraconazole 100 mg twice a day for at least 2 weeks. Recurrence of the disease (lesions) within 6 weeks after completion of treatment was defined as recurrent dermatophytosis [14].

Exclusion criteria

Patients with concomitant illnesses such as cardiovascular disease, hepatic disease, renal disease, and central nervous system disease, previously diagnosed psychiatric illnesses (which were identified using medical records and medical history), other dermatological conditions that could influence their quality of life, and those who had suffered a recent serious life event were excluded from the study.

Sample size

The required sample size was not calculated when planning the study.

Data collection methods

The enrolled patients were assessed for the DLQI [8], the GHQ12 [10], and the HADS [11, 12] questionnaires. DLQI was used for quality of life assessment, and the overall level of mental health distress was assessed using GHQ12 and HADS scores. HADS was used to differentiate between anxiety (HADS-A) and depression (HADS-D).

DLQI comprised 10 questions related to symptoms, feelings, daily activities, leisure, work, school, personal relationships, and treatment (in relation to participants' perception over the last week). Questions were scored from 0 to 3, and the final score ranges from 0 (no impact on quality of life) to 30 (maximum impairment). The cutoff score for DLQI is considered to be ≥2 [9].

The GHQ12 consists of 12 items and assesses the severity of mental problems over the past few weeks using a 4-point Likert-type scale (from 0 to 3). The final score ranges from 0 to 36, with higher scores indicating poorer mental health. The cut-off score is considered to be ≥4 [12].

The HADS comprises questions (items) related to mental health, which are scored using a 4-point Likert scale (range 0–3). It comprises 14 questions, with 7 related to anxiety (HADS-A) and 7 to depression (HADS-D). The total score is the sum of the 14 items range from 0 to 21, with the threshold value for each subscale being ≥11 [11].

Survey administration

All these psychometric tools were self-assessment forms which were completed in Hindi or English according to patient convenience after written informed consent was obtained in the dermatology and psychiatry OPDs.

The authors conducted the adaptation of the questionnaires into the local language (Hindi) themselves, which was not validated. The three questionnaires were handed over to the patients at once by the researcher (questions were explained in the local language to them) and they filled them in a separate room in the presence of a doctor (in the outpatient department). Patients were free to clarify any doubts regarding the questionnaires, and illiterate patients (n=10) were helped by an attendant to complete the questionnaires.

All authors discussed the procedures as a research team before performing the sample survey. The assisting doctor received prior training from the researcher on conducting the survey, including questionnaire details and a demonstration. The physicians participating in the survey did not receive any additional training beyond this.

Statistical analysis

Statistical analysis was carried out using R version 4.3.2. Continuous variables were summarized as median (Me) and interquartile range (Q1; Q3). Comparison between the two groups (CRD and SDI) was done using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. A p-value<0.05 was considered statistically significant.

Univariate analysis was performed for all relevant clinical and demographic variables (age, sex, socioeconomic status, marital status, occupation, education, family history of dermatophytosis, atopy, frequency of bathing, change of undergarments, sharing of clothes, clothes washed separately, tight clothing, and BSA, number of sites, clinical type, morphology of lesions, inflammation, seasonal exacerbation, DLQI score, GHQ12 score, HADS-A score, HADS-D score) to assess their association with the outcome variable (CRD). Variables with a p-value<0.05 in the univariate analysis were considered for inclusion in the multivariate model to ensure that potential confounders were not overlooked. For the multivariate analysis, a binary logistic regression model was used with CRD as the outcome variable. A stepwise selection algorithm was employed. The entry and removal criteria were based on significance levels (typically p<0.05 for entry and p>0.10 for removal), and the model fit was assessed using the Akaike Information Criterion (AIC) and/or McFadden's pseudo R^2. This value was calculated using R software with the pscl library. The analysis is presented in terms of estimated coefficients, standard errors, Z-values, p-values, and odds ratios (ORs) with 95% confidence intervals (CI).

Ethical considerations

The study was conducted after approval by the Ethics Committee of the Dr. Ram Manohar Lohia Institute of Medical Sciences (Lucknow, India). Date of approval by the ethics committee: 14/06/22. Protocol Number: IEC 10/22. Reference No. of protocol: RC 356/RMLIMS/2022. Patients were included in the study after providing written informed consent.

All study participants were asked to complete the questionnaire papers in a separate room in the OPD and patient data were kept confidential. Several measures were implemented throughout the survey to ensure anonymity and confidentiality. Anonymity measures included the collection of no personally identifiable information (e.g., names, addresses, or contact details). Responses were aggregated for analysis, preventing individual identification. Confidentiality measures, such as all survey data, were stored in a secure, protected database that was accessible only to authorized researchers. Participants were informed that their responses would be kept strictly confidential and used solely for research purposes.

RESULTS

Participant flow

After screening over six months, 250 patients attending the dermatology OPD were diagnosed with dermatophytosis. All of them were over 18 years of age. Of these, 69 patients were excluded due to the presence of concomitant illnesses (cardiovascular illness, hepatic, renal, and central nervous system diseases, previously diagnosed psychiatric illnesses, other dermatological conditions). Out of these patients, 15 patients refused to provide written consent and were excluded. Finally, 166 patients completed the full survey after consent: 104 patients with CRD and 62 with SDI.

Patient characteristics

The CRD group showed a significantly older and more often married demographic with less frequent use of tight clothing compared to the SDI group (Table 1). Other variables did not show statistically significant differences.

Clinical variables of the patients in the CRD and SDI groups were summarized in Table 2. The majority of patients had 0–5% BSA involvement and multiple anatomical sites involved in both groups, and there were significant differences between the groups. Overall, tinea cruris (code 1F28.3, International Classification of Diseases 11th Revision) was the predominant presentation, followed by tinea corporis in single-site disease as well as in multiple-site disease in both groups. Classical lesion morphology had a higher proportion, with significant differences between groups. Inflammation among participants in both groups was equally observed. Seasonal exacerbation among participants in both groups was equally affected.

Main findings

Patients with CRD reported significantly higher impairment in quality of life, greater psychological distress, and higher levels of anxiety compared to those with SDI (Table 3). In the domains of DLQI, significant differences were noted in the "symptoms and feelings" domain, with higher median scores in the CRD group compared to the

Table 1. Demographic variables of study participants

Variables	CRD, *n*=104	SDI, *n*=62	*p*-value
Age, Me (Q1; Q3)	32 (25; 41)	27.5 (21; 34)	**0.011**
Sex, *n* (%)			
Male	76 (73.1)	49 (79.0)	0.389
Female	28 (26.9)	13 (21.0)	
Marital status, *n* (%)			
Married	72 (69.2)	32 (51.6)	**0.023**
Unmarried	32 (30.8)	30 (48.4)	
Occupation*, *n* (%)			
Field worker	8 (7.7)	4 (6.5)	0.516
Outdoor occupation	8 (7.9)	8 (12.9)	
Indoor occupation	59 (56.7)	39 (62.9)	
Housewife	23 (22.1)	8 (12.9)	
Unemployed/Retired	6 (5.8)	3 (4.8)	
Socio-economic status, *n* (%)**			
Upper	2 (1.9)	3 (4.8)	0.566
Middle	75 (72.1)	43 (69.4)	
Lower	27 (26.0)	16 (25.8)	
Education, *n* (%)			
Graduate and above	40 (38.5)	27 (43.5)	0.133
High school and Intermediate	37 (35.6)	27 (43.5)	
Junior school and below	27 (26.0)	8 (12.9)	
Family history of dermatophytosis*, *n* (%)**	44 (42.3)	18 (29.0)	0.087
Atopy, *n* (%)	29 (85.6)	13 (21.0)	0.321
Frequency of bathing, *n* (%)			
Daily	85 (81.7)	57 (91.9)	0.070
Less frequently	19 (18.3)	5 (8.1)	
Change of undergarments, *n* (%)			
Daily	79 (76.0)	54 (87.1)	0.082
Less frequently	25 (24.0)	8 (12.9)	
Sharing of clothes, *n* (%)			
Absent	68 (65.4)	34 (54.8)	0.176
Present	36 (34.6)	28 (45.2)	
Clothes washed separately, *n* (%)			
Yes	71 (68.2)	37 (59.7)	0.261
No; together with family member	33 (31.8)	25 (40.3)	
Tight clothing, *n* (%)			
No	59 (56.7)	22 (35.5)	**0.008**
Yes	45 (43.3)	40 (64.5)	

Note: *Field worker: farmer, forest worker, pesticide worker, security guard; Outdoor occupation: washer man, mechanic, carpenter, labourer, food seller, security guard; Indoor occupation: shopkeeper, student, clerk, businessman, officer worker, ward boy, salesman, teacher, advocate, driver, accountant, pharmacist; **Kuppuswamy socio-economic status scale based on education status, occupation and per capita family income per month; middle class includes upper middle and lower middle; lower class includes upper lower and lower; ***History of similar dermatophytosis in family members (close contacts) of the patient. CRD — chronic and recurrent dermatophytosis; SDI — superficial dermatophytic infection. Significant *p*-value is highlighted in bold.

Table 2. Clinical variables of study participants

Variables	CRD, *n*=104	SDI, *n*=62	*p*-value
BSA, *n* (%)			
0 to 5%	62 (59.6)	57 (91.9)	**<0.001** (df=2)
5 to 10%	31 (29.8)	4 (6.5)	
>10%	11 (10.6)	1 (1.6)	
Number of sites, *n* (%)			
Single	10 (9.6)	17 (27.4)	**0.002**
Multiple	94 (90.4)	45 (72.6)	
Clinical type, *n* (%)			
Classical	25 (24.0)	28 (45.2)	**0.009**
Mixed	79 (76.0)	34 (54.8)	
Classical, *n* (%)			
T. corporis	8 (32)	8 (28.58)	0.977 (df=3)
T. pedis	2 (8)	2 (7.14)	
T. cruris	14 (56)	18 (64.28)	
T. faciei	1 (4)	0	
Mixed, *n* (%)			
T. corporis + T. cruris	40 (50.64)	22 (64.70)	0.685 (df=7)
T. corporis + T. cruris+ T. faciei	22 (27.85)	4 (11.77)	
T. corporis + T. faciei	5 (6.33)	5 (14.70)	
T. corporis + T. pedis	2 (2.54)	0	
T. corporis + T. cruris + T. pedis	4 (5.06)	0	
Extensive Tinea	1 (1.26)	0	
T. cruris + T. faciei	4 (5.06)	3 (8.83)	
T. corporis + T. cruris + + T. faciei + T. pedis	1 (1.26)	0	
Morphology of lesion, *n* (%)			
Classical	47 (45.2)	42 (67.7)	**0.001** (df=2)
Atypical*	29 (27.9)	14 (22.6)	
Combination	28 (26.9)	6 (9.7)	
Inflammation, *n* (%)			
Inflammatory	70 (67.3)	43 (69.4)	0.784
Non-inflammatory/Dry	34 (32.7)	19 (30.6)	
Seasonal exacerbation, *n* (%)			
None	30 (28.8)	27 (43.5)	0.167 (df=3)
Summer	56 (53.8)	30 (48.4)	
Winter	11 (10.6)	3 (4.8)	
Monsoon	7 (6.7)	2 (3.2)	

Note: *papulosquamous, eczematous, pustular, lichenoid. BSA — body surface area; CRD — chronic and recurrent dermatophytosis; SDI — superficial dermatophytic infection. Significant *p*-value is highlighted in bold.

SDI group. In the multivariate logistic regression analysis included age, marital status, clinical type, BSA involved, tight clothing, number of affected sites, lesion morphology, DLQI score, GHQ12 score, HADS-A score (anxiety) and HADS-D score (depression). We found that patients' BSA and HADS-A score whereas DLQI, GHQ12, and HADS-D scores were not associated with CRD (Table 4).

DISCUSSION

On conducting multivariate logistic regression, only BSA and HADS-A scores were statistically significant predictors of CRD. In various previous studies, BSA involvement emerged as a significant predictor of CRD compared to SDI [15, 18–20]. CRD patients have higher odds of suffering from anxiety in concordance with the study by Das et al. [17]. Our study showed a higher HADS-A score, suggesting the need to investigate more about the health-related discomfort and dissatisfaction experienced by patients with CRD (as it is one of the most common skin conditions). It implies that in CRD, mental health morbidity is negatively affected, i.e., chronicity and recurrence are related to anxiety. Addressing the mental health aspect of this disease through such detailed studies and thorough patient counseling can go a long way toward risk factor prevention as well as treatment compliance in such patients. A brief review of the previously conducted studies regarding mental health in chronic dermatophytosis in India has been compiled in Table S1 in the Supplementary.

In a cross-sectional study by Narang et al. [15], 196 patients with first-episode, chronic, and recurrent dermatophytosis were recruited. The median DLQI for SDI and chronic and recurrent dermatophytosis was 13, 13 and 11.5 among the three groups (the differences were insignificant). Although the median DLQI in the present study was slightly higher for the CRD group (Me=15) as compared to the SDI group (Me=12), the difference was not found to be statistically significant. Most of the previous cross-sectional studies have calculated the mean DLQI (Table S1 in the Supplementary). Except for the studies by Das et al. [17] and Shivani et al. [24] where the mean CRD DLQI was 21.4 and 15.98, DLQI in most studies ranged from 12.12 to 14.28 [18–23] which is lower than the DLQI of our study CRD group. In almost all the previous studies, the main questionnaire items most influenced by the disease were "symptoms and feelings", followed by "daily activities" (Table S1 in the Supplementary). In previous studies, age was noted [15], involvement of >10% BSA [15, 17, 20, 21],

Table 3. Comparative analysis of DLQI, GHQ12 and HADS scores between study groups

Variables	CRD, *n*=104	SDI, *n*=62	*p*-value
DLQI			
DLQI score, Me (Q1; Q3)	15 (9.8; 20)	12 (7.2; 16)	**0.020**
Domains of DLQI, Me (Q1; Q3)			
Symptoms & Feeling (0–6)	5 (3; 6)	3 (2; 4.75)	**<0.001**
Daily Activities (0–6)	3 (1; 4)	2 (1; 4)	0.057
Leisure (0–6)	2 (1; 4)	2 (1; 3)	0.135
Work & School (0–3)	3 (0; 3)	1 (0; 3)	0.310
Personal Relationships (0–6)	1.5 (0; 4)	1 (0; 3)	0.239
Treatment (0–3)	1 (0; 2)	1 (0; 2)	0.082
Categories of DLQI score, *n* (%)			**0.331** (df=4)
Extremely large (21–30)	24 (23.1)	6 (9.7)	
Very large (11–20)	48 (46.2)	31 (50)	
Moderate (6–10)	22 (19.4)	12 (21.2)	
Small (2–5)	10 (9.6)	12 (19.4)	
No effect (0–1)	0	1 (1.6)	
GHQ12 score			
GHQ12 score, Me (Q1; Q3)	15 (10; 19)	11 (7.2; 16.5)	**0.011**
Categories of GHQ12, *n* (%)			0.700
≥4	97 (93.3)	56 (90.3)	
<4	7 (6.7)	6 (9.7)	
HADS			
HADS-A			
HADS-A score, Me (Q1; Q3)	7 (4; 11)	6 (2; 8)	**0.016**
Categories of HADS-A score, *n* (%)			0.063 (df=2)
Abnormal (11–21)	27 (26.0)	8 (12.9)	
Borderline abnormal (8–10)	23 (22.1)	11 (17.7)	
Normal (0–7)	54 (51.9)	43 (69.4)	
HADS-D			
HADS-D score, Me (Q1; Q3)	7 (4; 9)	6 (2; 9)	0.210
Categories of HADS-D score, *n* (%)			0.549 (df=2)
Abnormal (11–21)	18 (17.3)	7 (11.3)	
Borderline abnormal (8–10)	26 (25.0)	18 (29.0)	
Normal (0–7)	60 (57.7)	37 (59.7)	

Note: DLQI — Dermatology Life Quality Index; GHQ12 — 12-item General Health Questionnaire; HADS — Hospital Anxiety Depression Scale. Significant *p*-value is highlighted in bold.

Table 4. Logistic regression to assess the association of CRD with study variables

Variables	Estimate (β)	Std. Error	Z-value	*p*-value	OR (Exp (β))	Lower 95% CI	Upper 95% CI
(Intercept)	–2.090	1.169	–1.787	0.073	0.12	0.01	1.17
Age	0.029	0.023	1.246	0.212	1.03	0.98	1.08
Marital status	0.033	0.493	0.068	0.945	1.03	0.39	2.76
Tight clothing	–0.512	0.432	–1.185	0.236	0.60	0.25	1.39
BSA	1.389	0.503	2.760	**0.005**	4.01	1.62	11.91
Number of sites	0.319	0.537	0.595	0.552	1.38	0.48	4.04
Clinical type	0.024	0.046	0.537	0.591	1.03	0.94	1.12
Morphology of lesion	0.090	0.060	1.493	0.135	1.09	0.98	1.24
DLQI score	0.0176	0.035	0.496	0.619	1.02	0.95	1.09
GHQ12 score	0.0172	0.036	0.479	0.631	1.02	0.95	1.09
HADS-D score	–0.0603	0.065	–0.923	0.356	0.94	0.83	1.07
HADS-A score	0.1376	0.061	2.248	**0.024**	1.15	1.02	1.30

Note: BSA — Body Surface Area; CI — Confidence Interval; DLQI — Dermatology Life Quality Index; GHQ12 — 12-item General Health Questionnaire; HADS-D/A — Hospital Anxiety Depression Score (Depression/Anxiety).

Clinical type category: classical, mixed. Morphology of Lesion category: classical, atypical, combination. Statistics of the multivariate model: Null deviance: 219.38 (df=165). Residual deviance: 177.40 (df=154); Akaike Information Criterion (AIC): 201.4; McFadden R^2=0.1913; McFadden R^2≈0.15–0.4 is considered a good fit in logistic regression. Significant *p*-value is highlighted in bold.

>2 affected sites [17, 18, 20, 21], gender, education, and socioeconomic status [18] were associated with a significantly worsened DLQI. The DLQI score in our study was not significant; hence, we did not assess the factors influencing DLQI.

GHQ12 was studied in three previous studies so far in relation to chronic and recurrent dermatophytosis [15, 23, 24]. In both the studies by Anushree et al. and Narang et al. the GHQ12 cutoff score was set at 12 to assess mental health distress, whereas the cutoff was two and four in the studies by Saini et al. and ours, respectively. In the study by Narang et al. GHQ12 was found to have a significant correlation with DLQI, although it didn't show any significant difference between the SDI and CRD groups under this study. The mean GHQ12 was lower in the study by Saini et al. [24] as well as Anushree et al. [23] compared with the present study.

The study was limited by a possible selection bias (all patients were recruited from a tertiary care center). Also, the site of the dermatophytic infection (subtypes of tinea based on site) was not individually assessed for correlation with the HADS, DLQI, and GHQ12. The adapted questionnaires in the local language (Hindi) were not validated. In this study, the required sample size was not precalculated. However, a previously published article [16] reported that the mean and standard deviation of DLQI (μ±σ) score was 10.01±5.01 in 328 patients. Using the Cohen's sample size calculation:

$$n = \frac{Z^2_{1-\alpha/2}\sigma^2}{d^2},$$

where $Z_{1-\alpha/2}$=1.96 at a 5% significance level, σ=5.01, and *d* (margin of error) was set at 5.2% of the mean DLQI score, the required sample size was calculated to be 250 patients.

The study had a varied patient profile. As it was a tertiary care center, patient coverage included distant areas of North India (with patients referred from other hospitals). Hence, the results of the study are applicable to a larger population.

CONCLUSION

Chronic and recurrent dermatophytosis was associated with deteriorated mental health in patients. HADS-A showed significant differences between CRD and SDI. On multivariate logistic regression, HADS-A showed significantly elevated anxiety levels and a more pronounced decline in quality of life among the CRD group. The disease variable, i.e., BSA, was seen to be associated with the CRD group. Hence, a multidisciplinary approach involving counselling by psychiatrists along with treatment by a dermatologist is required in the management of CRD patients.

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Exploring Visual Representations of Safety in Virtual Relaxation Content: A Correlational Study

Изучение образных представлений о безопасности для подбора виртуального релаксационного контента: корреляционное исследование

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Original research

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ABSTRACT

BACKGROUND: Anxiety disorders are the most common mental disorders, yet only about a quarter of affected individuals receive treatment. This necessitates the development of high-technology care approaches, including virtual reality.

AIM: To analyze mental imagery associated with psychological safety and inner comfort to optimize the selection of relaxation content for virtual reality.

METHODS: Participants completed standardized questionnaires: the Social Readjustment Rating Scale, the Well-being, Activity, Mood questionnaire, and a Safe Place interview. Statistical analysis included significance testing and one-way analysis of variance. Descriptions of safe places underwent qualitative analysis to identify the frequency of key semantic categories.

RESULTS: A total of 192 respondents (18–82 years) were stratified into three age groups: 18–39 (*n*=97), 40–49 (*n*=55), and 50 years and older (*n*=40). Age was negatively correlated with overall stress levels and positively correlated with emotional well-being. The highest stress levels were in the 18–39 age group. For safe place imagery, most descriptions (68.2%) were of natural landscapes, followed by urban motifs (22.9%); intrapsychic and spiritual symbols accounted for 8.9%. Within natural landscapes, water-related images were most frequent (39.5%). The image of a confined personal space was 2.4 times more common in participants aged 50 years and older.

CONCLUSION: The highest distress levels were observed in individuals under 40, indicating a greater need for relaxation interventions. Across all age groups, images of water associated with a safe place, while participants aged 50 years and older more frequently preferred personal spaces. The identified semantic categories can form a basis for thematic catalogs in virtual relaxation libraries.

АННОТАЦИЯ

ВВЕДЕНИЕ: Тревожные расстройства являются наиболее распространенными психическими нарушениями, однако лечение получают лишь около четверти пациентов. Это создает потребность в разработке высокотехнологичных подходов к помощи, включая виртуальную реальность.

ЦЕЛЬ: Изучить образные представления о психологической безопасности и внутреннем комфорте у людей для оптимизации подбора релаксационного контента для виртуальной реальности.

МЕТОДЫ: Участники заполнили стандартизированные опросники: «Шкала оценки социальной адаптации», «Самочувствие, активность, настроение» и «Безопасное место». Были использованы статистические методы для оценки значимости различий и однофакторный дисперсионный анализ. Описания безопасных мест подверглись качественному анализу для определения частоты ключевых смысловых категорий.

РЕЗУЛЬТАТЫ: В исследовании участвовали 192 респондента (18–82 года), разделенные на три возрастные группы: 18–39 (*n*=97) лет, 40–49 (*n*=55) и 50 лет и старше (*n*=40). Возраст отрицательно коррелировал с уровнем стресса и положительно — с эмоциональным благополучием. Самый высокий уровень стресса был в группе 18–39 лет. Среди образов безопасного места большинство описаний относились к природным ландшафтам (68,2%), далее следовали урбанистические мотивы (22,9%); внутрипсихические и духовные символы составили 8,9%. Среди природных образов наиболее частыми были изображения, связанные с водой (39,5%). Образ ограниченного личного пространства встречался в 2,4 раза чаще у участников 50 лет и старше.

ЗАКЛЮЧЕНИЕ: Наивысший уровень дистресса наблюдался у лиц младше 40 лет, что указывает на их большую потребность в релаксации. Во всех возрастных группах чаще безопасное место ассоциировалось с водоемом, а люди старше 50 лет отдавали предпочтение личному пространству. Выявленные смысловые категории могут лечь в основу тематических каталогов библиотек виртуальной релаксации.

Keywords: *psychological safety; image of a safe place; virtual content; anxiety disorders*
Ключевые слова: *психологическая безопасность; образ безопасного места; виртуальный контент; тревожные расстройства*

INTRODUCTION

According to the World Health Organization (WHO), anxiety disorders are the most common mental disorders worldwide, affecting more than 300 million people [1]. These disorders lead to impaired functioning, reduce quality of life, and increase the risk of somatic diseases, including cardiovascular and cerebrovascular diseases [1]. However, only about a quarter of individuals having anxiety disorders receive treatment [1].

Study results indicate an age-related pattern in the manifestation of anxiety disorders. Adolescence and young adulthood are characterized by an increased incidence rate reflecting ongoing psychophysiological changes and personality development [2–5]. The incompleteness of self-identification processes weakens adaptive capabilities, contributing to the emergence of anxiety-related psychopathological symptoms [6].

According to the literature, anxiety disorders are diagnosed less frequently in older adults. Nevertheless, as the WHO notes, "around 14% of adults aged 60 and over live with a mental disorder; <...> the most common mental health conditions for older adults are depression and anxiety"[1]. There is evidence that anxiety symptoms often manifest in a physical (somatic) form in later life, being a part of anxiety-depressive states [7].

Treatment of anxiety disorders typically involves a combination of psychotherapy and pharmacotherapy [8]. Modern virtual reality (VR) technology enables the creation

[1] World Health Organization. Mental health of older adults [Internet]. Geneva: World Health Organization; c2025 [cited 2025 Nov 11]. Available from: https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults

of immersive relaxation environments that can be incorporated into psychotherapeutic interventions [9]. Such environments may enhance the sense of safety, reduce stress, and facilitate reflection and re-evaluation of negative experiences [10].

Despite substantial empirical evidence on the use of VR technologies in education and medicine among non-clinical and clinical populations in various age groups [11–15], research on their application in the prevention and treatment of stress and anxiety remains limited. These works mainly focus on assessing the effects of various immersive technologies, the classification and technical characteristics of VR tools [16, 17], as well as the analysis of the technical solutions themselves. Criteria for selecting specific content (plot) are rarely defined in experimental studies, and as a result, content selection is often insufficiently justified and based primarily on available virtual libraries.

Some studies have demonstrated individual differences in responses to virtual content [18]. However, many relaxation techniques are based on the activation of a patient's mental representation of a safe place and internal visualization of it [19]. This emphasizes the need for a deeper study of the impact of the specific content of VR environments on the subjects interacting with it. An empirical study of unique and characteristic ideas about psychological safety and inner comfort should be conducted for a more conscious and effective use of relaxation practices using VR. The results of such a study can form the basis for the development of personalized intervention programs.

This study analyzes mental imagery associated with psychological safety and inner comfort to optimize the selection of relaxation content for virtual reality devices.

METHODS

Study design

A correlational study was conducted.

Setting

The study was conducted in Moscow in September and October 2024.

Participants

A simple random sampling method was used.

The inclusion criteria were: aged over 18, living in Moscow, voluntary participation, and cognitive integrity at the level of understanding the instructions and conscious independent completion of psychodiagnostic questionnaires.

The exclusion criterion was non-cooperation in the process of psychodiagnostic research.

Data sources

Participants were asked to answer questions from three tools:

1. The Social Readjustment Rating Scale (SRRS) questionnaire, modified to reflect contemporary conditions[2] [20, 21]. The instrument yields a stress score for the preceding year (the higher the score, the higher the stress level). According to current research, this is one of the most common tools for assessing critical life events [22].
2. The Well-being, Activity, Mood (WAM) questionnaire [23], designed to assess current functional state. Higher scores indicate more favorable conditions, and low scores indicate less favorable ones.
3. The Safe Place semi-structured interview, developed to address the study objectives based on the relaxation technique of the same name [24]. Respondents were asked to imagine a place where they feel safe and can be alone. They first gave a brief general description of this place, and then elaborated on the image and described everything that happens there, paying special attention to the details, multisensory sensations, and the feelings experienced.

Statistical analysis

Statistical analyses were performed in the STATISTICA v12.0 (StatSoft, USA) software package and using Microsoft Excel. The following analyses were used: descriptive statistics data (measures of range and measures of central tendency), assessment of distribution normality using the Kolmogorov–Smirnov D-statistic, data weighting procedure, Spearman's rank correlation coefficient (the value of the correlation coefficient R), one-way analysis of variance ANOVA (the F-statistic and the level of significance), the significance of differences in independent groups using the Kruskal–Wallis and Mann–Whitney tests, the proportional representation of a binary variable in independent groups using the F-test. Statistical significance was set at $p \leq 0.05$.

[2] The modification consisted in adding fear for the life and health of a loved one due to the lack of news about them to the list of stressors.

The data weighting procedure used the Russian Population Census 2020 as a reference distribution for the age composition of the urban population[3]. Weighting coefficients were calculated as the ratio of the proportion in the target population (urban population of the Russian Federation) to the proportion in the surveyed sample (*n*=192).

Descriptions of the safe place were subjected to qualitative analysis in terms of the main semantic categories and the frequency of their occurrence. The analysis was conducted as follows: the results of the Safe Place semi-structured interview of each respondent were studied and then consolidated into a single text, which was assigned a single thematic category.

The categorization was based on both denotative and connotative meanings. Denotation, or denotative meaning, refers to the objective correlation between a word and the object or situation it designates, whereas connotation, or emotive (connotative) meaning, denotes the meaning arising from the emotionally expressive and evaluative reflection of objects and phenomena in the external world, shaped through their subjective interpretation [16]. The category and theme of a safe place were identified not only based on the direct denotation, but also the available details that clarify the connotation of the image. For example, the word "bedroom", which lacks a detailed description or a precise denotative reference, was interpreted as an intrapsychic image when it evoked an image of a safe place associated with feelings of peace and recovery. By contrast, the description "a safe place is my apartment where I live right now, a bedroom where I sleep, preferably with curtains closed" was categorized as an urban motif, as it refers to a concrete, physically situated environment. Similarly, a safe place described as "the city of St. Petersburg" or "my favorite city", when accompanied by specific details, was classified as an urban motif, whereas the phrase "the city where I spent my childhood" was treated as an intrapsychic image. Further classifications followed this same analytical logic.

Ethical considerations

Ethical principles were met by meeting the following conditions: the survey was anonymous and voluntary; all respondents had the opportunity to opt out at any stage. No approval from the local ethics committee was obtained for the study.

RESULTS

Participants

The study sample comprised 192 Moscow residents selected at random, including 134 women (69.8%) and 58 (30.2%) men; the number of years spent on education was 13.3±2.2 years. The age of the subjects included in the sample ranged from 18 to 82 years, while the interquartile range (50% of the surveyed sample) fell within the interval of 20 to 49 years; the median value was 39 years. Thus, the distribution was left-skewed and allowed the sample to be divided into three age strata: from 18 to 39 years (*n*=97), from 40 to 49 years (*n*=55), and 50 years and older (*n*=40).

Main results

According to the results of the SRRS questionnaire, the highest level of stress was observed in the 18–39 age group. The results of the one-way analysis of variance ANOVA include the main resultant indicator (F-statistic) and the level of significance (*p*)) is presented in Table 1.

Indicators of current functional state also differed across age strata. According to the results of the Kruskal–Wallis test, the characteristics of the WAM questionnaire showed statistically significant differences between age groups for the well-being (*p*=0.001), activity (*p*=0.003), and mood (*p*=0.02) domains. Primary differences observed in the 18–39 age group showed slightly reduced scores of the current emotional state; this group experienced higher stress levels, which is confirmed by pairwise comparison using the Mann–Whitney test (Table 2).

Table 1. Comparison of stress level across age groups based on the SRRS

Age groups	Stress level (scores)		F	df	*p*
	Mean (M)	Standard deviation (SD)			
18–39 years	216.8	138.7	3.53	2	0.03
40–49 years	166.1	116.5			
50 years and older	170.8	111.0			

Note: df — degrees of freedom; F — the value of F-test; *p* — *p*-significance level (*p*-value); SRRS — Social Readjustment Rating Scale.

[3] [The results of the VPN2020. Volume 2. Age and gender composition and marital status] [Internet]. Moscow: Federal'naja sluzhba gosudarstvennoj statistiki; c2022 [cited 2024 Nov 11]. Russian. Available from: https://rosstat.gov.ru/vpn/2020/Tom2_Vozrastno_polovoj_sostav_i_sostoyanie_v_brake

Table 2. Comparison of WAM Subscales scores across groups

WAM		Mediana	Q_1	Q_3	H	df	*p*
Well-being							
Age groups	18–39 years	45.0	36.0	52.0	14.7	2	0.001
	40–49 years	51.0	44.0	57.0			
	50 years and older	51.5	44.0	57.0			
Activity							
Age groups	18–39 years	43.0	33.0	49.0	11.52	2	0.003
	40–49 years	47.0	38.0	55.0			
	50 years and older	47.0	38.5	57.0			
Mood							
Age groups	18–39 years	52.0	43.0	59.0	7.83	2	0.02
	40–49 years	54.0	49.0	59.0			
	50 years and older	56.5	50.0	62.5			

Note: df — degrees of freedom; *p* — *p*-significance level (*p*-value); WAM — Well-being, Activity, Mood Questionnaire Subscales.

Sex and educational level were not significantly associated ($p>0.05$) with the total stress level score and the characteristics of the current functional state. The age of the surveyed sample was negatively correlated with the total stress level score (R=–0.17, $p=0.02$) and positively with the characteristics of the current emotional state (well-being R=0.25, $p=0.001$; activity R=0.21, $p=0.01$; mood R=0.17, $p=0.02$). Taking the results of the SRRS questionnaire in the surveyed sample into account, the stress score decreases with age, while a lower prevalence of unfavorable functional states decreases across these domains.

Correlations between the WAM questionnaire subscales and the total stress level score were weak: for the well-being and activity subscales, R=–0.14, $p=0.05$; for the mood subscale, R=–0.18, $p=0.01$ due to the abnormal distribution of the age variable (d=0.19, $p\leq0.01$), which confirms the correct use of age stratification in this analysis.

Overall, indicators of psychological well-being, as reflected in measures of current functional state, were consistent with the observed patterns of overall stress across all age groups.

The second stage was devoted to semantic analysis of the responses.

Analysis of thematic categorization of safe place images among respondents ($n=192$), the analysis showed that the vast majority of descriptions ($n=131$, 68.2%) were those of natural landscapes, followed by urban motifs ($n=44$, 22.9%) and a small number of intrapsychic images ($n=12$, 6.3%) or attributes and symbols of spirituality ($n=5$, 2.6%).

After applying age-based proportional weighting, the distribution of safe place image categories in the urban population of the Russian Federation (Table 3): the largest proportion of images are those of natural landscapes (39.5%), urban motifs account for half as many descriptions (17.2%), and a small percentage of cases contain intrapsychic images (3.4%) and attributes of spirituality (2.8%).

Comparative analysis of the proportional representation of safe place image categories across age strata, based on F-test results, revealed no significant between-group differences ($p>0.05$). The distribution of categories within each age group was consistent with that observed in the general urban population. The results are provided in Table 4.

A more detailed analysis of the content within thematic safe place categories revealed frequency differences depending on the age stratum. Specifically, the distribution of more narrowly defined safe place images within the broader categories (natural landscapes, urban motifs, intrapsychic images, and attributes of spirituality) was examined. Safe place images were most varied in the group of 18 to 39 years and least varied in the group of 50 years and older, with 18 and 8 distinct images identified, respectively. The described result could be explained by higher exploratory activity and less stable world views at an earlier age, as well as the factual diversity, variability, and heterogeneity of the environment that influenced the formation of the worldview of the younger generation.

The two most common categories (natural landscapes, urban motifs) were then examined in greater detail. The analysis of the frequency of image-related terms denoting images in these thematic categories allowed identification of the most common safe place images within them. The results are presented in Table 5.

In all age groups of the surveyed urban sample, a body of water image (sea, river, lake, ocean, fountain), categorized as a "natural landscape", was cited as a safe place with statistically similar frequency ($p>0.05$, pairwise Fisher's exact test). These percentages were 26.8% in the 18–39 age group, 36.4% in the 40–49 age group, and 20.0% in the 50 years and older group. The image of a body of water as a place associated with psychological safety

Table 3. Thematic content of safe place images (*n*=192)

No.	Category of images	Detailed content	Sample (%)	Proportionally weighted distribution of safe-place imagery categories (%)
1	Natural landscapes	An alley lined with trees, a swing in the garden, a hammock in the park, a forest, the edge of a forest, a field, a glade, a meadow, a lawn, a cottage, a summer house, a mountaintop, mountains, a beach, a body of water (a sea, a river, a lake, an ocean, a fountain), a quiet island, a fishing area, sunsets	68.2	39.5
2	Urban motifs	A city park, city streets, a car, a bus, a lake in the city, a guarded house or apartment, a gym, one's favorite city, a kitchen, a bathroom, my room	22.9	17.2
3	Intrapsychic images	A den; a soft sofa with 10 pillows; a bedroom; the city where I spent my childhood	6.3	3.4
4	Attributes of spirituality	A church, a temple, a cathedral, a mosque, a cemetery	2.6	2.9

Table 4. Representation of safe place image categories across age strata, abs. (%)

Category of images	18–39 years (*n*=97)	40–49 years (*n*=55)	50 years and older (*n*=40)
Natural landscapes	67 (69.1%)	38 (69.1%)	26 (65.0%)
Urban motifs	22 (22.7%)	11 (20.0%)	11 (27.5%)
Intrapsychic images	6 (6.2%)	4 (7.3%)	2 (5.0%)
Attributes of spirituality	2 (2.0%)	2 (3.6%)	1 (2.5%)

and inner comfort was reported, without age differences, by 54 people (28.1% of the cases), representing nearly one quarter of the sample.

Another frequently reported safe place image was a stable familiar, and habitually organized personal space: "my room", "a guarded house or apartment", "a cottage", "a summer house". The combination of these images explains the overlap between the selected "natural landscapes" and "urban motifs" categories, since "my room", "a guarded house or apartment", when included in the larger thematic categories, were classified as urban motifs, and "a cottage" and "a summer house" as natural landscapes. This image was reported by 53 respondents, comprising 27.6% of the cases, representing approximately one quarter of the sample.

As shown in Table 5, personal space images were reported in 15 of 97 cases (15.5%) in the 18–39 age group, 14 cases out of 55 (25.5%) in the 40–49 age group, and 24 cases out of 40 (60.0%) in the 50 years and older group. A comparative analysis of the proportional representation of this image in age groups using the F-test revealed personal space images statistically more often in the group aged 50 years and older (p=0.001) than in the younger age groups, 3.9 times when compared to the 18–39 age group and 2.4 times when compared to the 40–49 age group.

All other images in the described groups account for less than 10% and do not statistically significantly distinguish the age groups ($p \geq 0.05$ according to the F-test results). In the 18–39 age group, these include a "church", "favorite city", "a place of rest", "a health resort", "outdoors", "a glade", "a field", "a forest", "a car", "a swing", "a road", "a cottage", "mountains", "a bathroom", "a library"; in the 40–49 age group, "a forest", "a den", "a beach", "a glade", "a field", "a place of rest", "a church", "a car", "favorite city", "a kitchen", "a road", "a cemetery", "a house"; in the 50 years and older group, "a glade", "outdoors", "a gym", "a church", "a house", "an aircraft cabin".

Table 5. Differences in safe place image content across age strata

Image		Frequency, abs. (%)		
		18–39 years (*n*=97)	40–49 years (*n*=55)	50 years and older (*n*=40)
A body of water	A sea, a river, a lake, an ocean, a fountain	26 (26.8%)	20 (36.4%)	8 (20.0%)
Personal space	My room, a guarded house or apartment, a cottage, a summer house	15 (15.5%)	14 (25.5%)	24 (60.0%)

DISCUSSION

This study aims to identify and analyze mental imagery associated with psychological safety and inner comfort across different age groups to inform the selection of relaxation content for virtual reality devices [25].

A statistical analysis of the studied urban sample conducted during the first stage of the study suggested three age strata. This stratification may reflect the cultural and historical context that shaped the respondents' worldview. Individuals within the same age cohort tend to share patterns of beliefs, attitudes, values, and behaviors, since they grew up in the same historical environment[4]. Although there is no single, generally accepted time frame that defines generations at the moment [26] and researchers often hold different views [27], this must be considered when conducting the analysis. We believe that the obtained age division of the sample is determined by the following circumstances.

The worldview of the 18–39 age group (*n*=97) formed during the period of the most powerful scientific and technical breakthrough in the field of information technologies, the era of globalization and the change in forms of communication; the participants of the 40–49 age group (*n*=55) were shaped by a transitional historical period, and responders aged 50 years and older (*n*=40) were brought up on the traditional values of a more traditional sociocultural environment, they used books and official sources as ways of transferring knowledge and obtaining information, the speed and scope of communication were low.

The age groups identified in this study differ in the characteristics of psychological well-being, namely: the highest stress level was observed among the 18–39 age group while those aged 50 years and older were least susceptible to social stressors. Respondents in the 40–49 age group showed intermediate levels. It is possible that this case may reflect age-related differences in life fulfillment, since older generations have achieved key life goals and experience less external and internal pressure in this respect.

The lower stress level of the older generation may also be related to the cultural context of their upbringing, since their early childhood development was in a period characterized by greater social stability and a more consistent system of values and life goals. Intergenerational differences in the speed of scientific and technological progress, manifested in the constantly accelerating development of information and communication technologies, are undoubtedly important.

Assessment of the functional state of respondents in the selected age strata showed that current psychological well-being was associated with both social stress and age group. Respondents aged 18 to 39 experienced a greater level of stress compared to older respondents, which was reflected at the functional level by lower well-being, activity, and mood scores in the urban sample at the time of the survey. Similar data on the age-related pattern of psychological well-being in modern society have been reported in international studies [28].

The thematic content of relaxation images was grouped into four main categories: natural landscapes, urban motifs, intrapsychic images and attributes of spirituality. Typically, various natural landscapes are included in the virtual context libraries used in research [29], which appears appropriate for most users: our study showed that the safe place imagery most commonly includes natural landscapes (about 70% of cases), while solitary urban motifs are less common (about 20% of cases). However, the results show that individual differences in image selection may be important. Although no age-related differences were observed at the level of generalized thematic categories, there are differences between the safe place imagery among representatives of different age strata when comparing the frequency of occurrence of specific, rather than generalized thematic, images of psychological safety and inner comfort. Safe place images were most varied in the group of 18 to 39 years and least varied in the group of 50 years and older. The reduced variability of imagery at older ages can be explained by available results of studies of social activity at different ages, which confirm that social engagement in later life is often limited to the private family sphere [30–32].

Images of water and personal space or home are the most common safe place images (one in four urban residents). In older people, the range of images associated with psychological safety narrowed toward personal space and home: in the group aged 50 years and older, such images are much more common than in the younger age

[4] Hoover E. The Millennial Muddle. How stereotyping students became a thriving industry and a bundle of contradictions. The Chronicle of Higher Education [Internet]. 2009 Oct 11 [cited 2025 Aug 30]. Available from: https://web.archive.org/web/20110713233331/http://chronicle.com/article/The-Millennial-Muddle-How/48772

groups. Since personal space is, typically, an enclosed area with boundaries separating it from the outside world and is distinctly owned by an individual, preference for these images may reflect these types of safe places value isolation and a barrier between the internal (individual) and external worlds. Younger individuals appear to be more oriented toward interaction with the external environment.

These findings are consistent with existing literature on age-related narrowing of psychological space toward one's own territory or home with age as a resource for psychological security; younger individuals associate security with social resources (positive environment) and older adults with intellectual and personal means (experience, knowledge) [19].

Age differences do not affect the choice of various water bodies as a relaxation image of a safe place in the surveyed sample. This consistency may be explained by both the archetypal symbolism of the water itself and its physical properties: when an individual is submerged in water, this produces sensations of weightlessness and that one can immerse oneself in a state of harmony and complete relaxation. In culture, water has many mythological and sacred meanings. Across cultures, water carries diverse mythological and sacred meanings: for Buddhists, it symbolizes the eternal flow of the material world and life itself; in Christianity, it is associated with purification, renewal, and baptism. Although the characteristics of water are ambivalent (it is a sacred element endowed with cleansing and protective powers, both a means of healing and a source of danger, an instrument of sorcery), a modern stressed person, to find peace of mind, turns to water as a cleansing spring restoring psychological balance, evoking feelings of safety and calm [33].

This study will be extended to further explore the relationship between the selection of safety- and comfort-related images, and the level of stress and functional state. To support this analysis, verbal data units will first be identified and formalized, representing the next stage of the research.

The scientific novelty of the study lies in its attempt to systematize safe place imagery to develop an individual approach to the use of virtual reality in psychological care for anxiety disorders and comprehensive medical rehabilitation, including psychological rehabilitation [34]. In addition, the identified categories in this work can serve as the basis for filling thematic catalogs of virtual libraries. The identified facts and an attempt to classify them can be useful in the development of individualized algorithms and psychocorrective programs using immersive technologies: the identified age preferences, according to which psychological safety and internal comfort for people over 50 years of age are associated with an enclosed and secluded personal space, must be considered.

This study was exploratory in nature and had several limitations. In particular, the limited reproducibility may be related to the uneven age distribution in the analyzed sample. This factor may partly account for the weak correlations observed between age, stress levels, and indicators of well-being, activity, and mood.

Future research should employ a more rigorous experimental design with adequate representation of age ranges in the sample and direct testing of specific virtual environments. A similar study in specific clinical groups could also add to the studied safe place image phenomenology. The categories used in the content analysis of the subjects' reports can be further refined and formalized using assessment scales.

CONCLUSION

The presented results suggest that people in the age range up to 40 years experience the highest level of stress in the surveyed urban respondents, suggesting a greater need for relaxation interventions. The study also showed that the choice of theme and imagery for relaxation content can be directly related to age-specific characteristics of the target population in need of appropriate psychocorrection measures. Further research using a more rigorous design with balanced age representation, as well as studies involving clinical samples, is warranted.

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Prenatal Ultrasound–Detected Structural Anomalies Associated with Autism Spectrum Disorder: A Narrative Review

Структурные аномалии плода как ультразвуковые маркеры риска расстройства аутистического спектра: нарративный обзор литературы

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Review

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ABSTRACT

BACKGROUND: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition with a globally increasing prevalence. Early detection is crucial for effective intervention, yet current diagnostic methods often result in delays. Emerging research suggests that prenatal biomarkers, including structural anomalies detectable via ultrasound, may offer opportunities for earlier identification.

AIM: To synthesize current evidence on prenatal ultrasound-detectable anomalies associated with ASD and assess their potential as early predictors.

METHODS: A comprehensive literature search was conducted across PubMed, Scopus, and Google Scholar for studies published between 2007 and 2025. Keywords included “autism spectrum disorder”, “prenatal ultrasound”, “fetal anomalies”, “preeclampsia”, “neurodevelopment” and “biomarkers”. Priority was given to recent and high-quality studies, including systematic reviews and large cohort analyses. The selected articles were read in full, and their key findings were summarized in a narrative form. The synthesis focused on describing the scope of the existing evidence, the prenatal ultrasound findings reported in relation to ASD, and on highlighting recurrent patterns or notable differences between studies.

RESULTS: Several studies report associations between ASD and prenatal anomalies such as ventriculomegaly, increased biparietal diameter, hyperechogenic kidneys, and congenital heart defects. However, these findings are not specific to ASD and show inconsistent predictive performance. Sensitivity and specificity vary widely across studies, and ethical concerns about overdiagnosis and disparities in access to care persist.

CONCLUSION: Prenatal ultrasound may contribute to early ASD risk identification but lacks the accuracy required for standalone diagnosis. Integrating ultrasound findings with genetic and postnatal data, along with standardized protocols and further research, is essential to improve its predictive value and clinical application.

АННОТАЦИЯ

ВВЕДЕНИЕ: Расстройство аутистического спектра (РАС) представляет собой полиэтиологичное нарушение нейропсихического развития, распространенность которого в мире неуклонно растет. Ранняя диагностика имеет решающее значение для эффективного вмешательства, однако существующие методы часто не позволяют

своевременно выявить это заболевание. Данные современных исследований свидетельствуют, что пренатальные биомаркеры, включая структурные аномалии плода, выявляемые в ходе ультразвукового исследования (УЗИ), могут стать инструментом для более ранней оценки риска развития РАС.

ЦЕЛЬ: Обобщить современные данные о пренатальных аномалиях плода, выявляемых с помощью УЗИ и ассоциированных с РАС, и оценить возможность использования данных аномалий в качестве ранних предикторов.

МЕТОДЫ: Был проведен комплексный поиск литературы в научных базах данных PubMed, Scopus и Google Scholar за 2007–2025 гг. с использованием ключевых слов «расстройство аутистического спектра (autism spectrum disorder)», «пренатальное УЗИ (prenatal ultrasound)», «аномалии плода (fetal anomalies)», «преэклампсия (preeclampsia)», «нейроразвитие (neurodevelopment)» и «биомаркеры (biomarkers)». При отборе публикаций приоритет отдавался наиболее релевантным и методологически качественным работам, включая систематические обзоры и крупные когортные исследования. Отобранные статьи были прочитаны полностью, а их основные результаты обобщены в описательной форме. Синтез информации сосредоточен на области применения существующих данных, характеристике аномалий, выявляемых при пренатальном УЗИ, их связи с РАС, а также на согласованности и противоречиях в результатах различных исследований.

РЕЗУЛЬТАТЫ: Ряд исследований демонстрирует связь между повышенным риском РАС и такими аномалиями плода, как вентрикуломегалия, увеличение бипариетального диаметра, гиперэхогенные почки и врожденные пороки сердца. Однако эти маркеры неспецифичны для РАС, а их прогностическая ценность существенно варьирует. Чувствительность и специфичность методов диагностики в разных исследованиях также заметно различаются; кроме того, сохраняются этические вопросы, связанные с гипердиагностикой и неравным доступом к медицинской помощи.

ЗАКЛЮЧЕНИЕ: Пренатальное УЗИ обладает потенциалом для раннего выявления риска развития РАС, но его точность в настоящее время недостаточна для постановки диагноза. Для повышения прогностической ценности и клинической значимости данных пренатального УЗИ необходима их интеграция с результатами генетического тестирования и постнатального наблюдения, а также стандартизация протоколов и проведение дальнейших исследований в этой области.

Keywords: *autism spectrum disorder; prenatal ultrasound; fetal anomalies; early diagnosis; neurodevelopmental disorders; biomarkers*

Ключевые слова: *расстройство аутистического спектра; пренатальное ультразвуковое исследование; аномалии плода; ранняя диагностика; расстройства нейропсихического развития; биомаркеры*

INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), autism spectrum disorder (ASD) is a neurobehavioral condition marked by enduring impairments in social and communication functioning, difficulties in forming, comprehending, and sustaining relationships, and atypical and persistent interests and repetitive activities [1]. ASD is one of the most prevalent neurodevelopmental conditions in children, with males being four to five times more likely to develop it than females [2, 3]. According to a recent meta-analysis, approximately 0.77% of children globally are diagnosed with ASD, with boys accounting for 1.14% of this population [4]. Based on a 2022 report from the Autism and Developmental Disabilities Monitoring Network (ADDM Network)[1], focusing on the prevalence

[1] Autism and Developmental Disabilities Monitoring (ADDM) Network — the United States – based public health surveillance program that tracks the prevalence and characteristics of autism spectrum disorder and other developmental disabilities in children.

and characteristics of ASD among four- and eight-year-old children whose parents or guardians resided in 16 ADDM sites in the United States, one in 31 (3.2%) children aged eight years had ASD [2, 5].

This appears to result from interactions between genetic and environmental factors [1, 6, 7]. ASD significantly impacts society through high healthcare and education costs, caregiver stress, and reduced employment opportunities [8]. The lifetime cost per individual can exceed $2 million due to specialized services and lost productivity [8]. Families often face emotional and financial strain, while individuals with ASD encounter barriers to education, employment, and social inclusion. These challenges are especially pronounced in low-resource settings, highlighting the need for improved access to care, early intervention, and supportive public policies [8].

Early detection of ASD is essential for optimizing developmental outcomes, reducing long-term societal and economic burdens, and enhancing support for individuals and families. Research highlights that interventions initiated before age three can leverage neuroplasticity, leading to improvements in communication, social skills, and behavior, as well as significant gains in Intelligence Quotient (IQ) and adaptive functioning[2]. Early diagnosis may also substantially reduce lifetime costs, estimated at $461 billion annually in the U.S., potentially saving up to $1.2 million per individual by decreasing reliance on special education and healthcare services [3, 9, 10]. In addition, families benefit from early access to resources, which helps to alleviate stress and improve coping mechanisms [11]. However, challenges persist, including diagnostic delays, despite recommendations for screening at 18–24 months, and ongoing disparities, particularly among minority groups who demonstrate higher rates of severe ASD[2].

ASD is usually diagnosed through postnatal behavioral markers such as language delay, social difficulties, and repetitive behaviors [12, 13], often assessed with tools like the Autism Diagnostic Observation Schedule (ADOS). However, reliance on these signs delays diagnosis until ages four to five, limiting early intervention [14]. Early behavioral markers — including reduced social attention, delayed joint attention, diminished response to name, and decreased positive affect — can be observed at 6–12 months using eye-tracking or the Autism Observation Scale for Infants (AOSI) [15], while neuroimaging and EEG evidence of atypical connectivity and rapid cranial growth indicate an early neurodevelopmental origin [16, 17]. Hybrid behavioral–biological models achieve up to ~80% predictive accuracy in high-risk groups, though generalizability, limited sensitivity (50–70% for eye-tracking), and ethical issues remain [18]. Additional postnatal indicators include increased head circumference, atypical sensory responses, and delayed motor milestones [19, 20]. Overall, converging evidence suggests ASD originates prenatally but manifests behaviorally in the first year, underscoring the need to integrate early postnatal and prenatal risk markers for more timely diagnosis.

While postnatal behavioral indicators such as delayed language development and repetitive behaviors are traditionally used for diagnosis [12, 13], emerging research suggests that prenatal biomarkers, including those detectable via ultrasound, may offer earlier identification opportunities.

This article presents a narrative review of current evidence on prenatal structural anomalies associated with ASD, highlighting the role of ultrasound in detecting these abnormalities during fetal development. By synthesizing findings from clinical, genetic, and imaging studies, this review aims to assess the predictive value of ultrasound-detectable anomalies and highlight key gaps for future research.

METHODS

Information sources

A broad literature search was conducted using PubMed, Scopus, and Google Scholar, covering publications from 2007 to 2025.

Search strategy

Search terms included “autism spectrum disorder”, “prenatal ultrasound”, “fetal anomalies”, “biomarkers”, “preeclampsia”, and “neurodevelopment”.

Selection process

Articles were selected based on their relevance to prenatal indicators of ASD, with priority given to systematic reviews, meta-analyses, large cohort studies, and recent original

[2] Centers for Disease Control and Prevention. (2025, April 15). Data and statistics on autism spectrum disorder. Available from: https://www.cdc.gov/autism/data-research/index.html

research. The focus was on articles published in the past five years; however, older articles were considered if they addressed key research questions. Studies focusing exclusively on postnatal diagnosis were included only if they provided an essential context for understanding early developmental markers.

Data analysis

The findings from each study were extracted and thematically organized by type of anomaly (e.g., brain, cardiac, renal) and other relevant prenatal risk factors. The synthesis adopted a descriptive approach, summarizing reported associations and identifying recurring patterns.

RESULTS

This section is organized into three main parts. First, we review prenatal indicators identified in the literature, including genetic, metabolic, and structural markers. Second, we examine structural anomalies detectable by prenatal ultrasound, grouped into brain, cardiac, and other organ systems. Finally, we discuss the diagnostic potential of prenatal ultrasound and its limitations.

Prenatal indicators of Autism Spectrum Disorder

Jensen et al. (2022) present a comprehensive review of modern biomarkers for ASD, emphasizing their potential to advance diagnosis and treatment [21]. The authors considered genetic biomarkers such as mutations in the SH3 and multiple ankyrin repeat domains 3 (*SHANK3*) gene, which encodes a scaffolding protein critical for synapse formation and function, and the chromodomain helicase DNA-binding protein 8 (*CHD8*) gene, which encodes a chromatin remodeler regulating gene expression during brain development. These biomarkers are implicated in up to 20% of ASD cases and offer insights into its molecular mechanisms, including altered synaptic signaling, disrupted chromatin remodeling, and dysregulated neurodevelopmental pathways. Epigenetic markers, such as DNA methylation patterns, reflect gene-environment interactions and may serve as indicators of ASD risk [21]. While these biomarkers show promise for improving early and accurate diagnosis, their clinical application is constrained by individual variability, underscoring the need for integrated, multi-omics approaches to address the heterogeneity of ASD and inform targeted interventions [21].

Regarding metabolic biomarkers, disruptions in folate and mitochondrial pathways have been associated with biochemical imbalances observed in approximately 30% of individuals with ASD [21]. Neuroimaging research has revealed structural and functional brain differences in ASD, including rapid amygdala overgrowth during the first two years of life [22, 23]. Behavioral biomarkers such as atypical eye-tracking patterns, evident as early as six months old, also capture early deviations in social attention [24, 25]. Although these signs emerge postnatally during infancy or early childhood, they may reflect neurodevelopmental alterations originating prenatally. Therefore, although they are observed after birth, their underlying causes can be linked to prenatal brain development.

Parellada et al. (2023) underscore the potential of prenatal biomarkers to identify ASD risk before birth, highlighting maternal immune activation (MIA) as one such marker due to elevated levels of pro-inflammatory cytokines such as IL-6 during pregnancy, observed in approximately 20% of mothers of children with ASD [26]. Hormonal imbalances, such as elevated prenatal testosterone levels in amniotic fluid, are also noted as potential predictors, with studies showing a correlation with later ASD traits in male offspring [26]. The authors also point to genetic biomarkers detectable prenatally, such as copy number variants (CNVs) and *de novo* mutations in genes such as *CHD8*, which may be identified through prenatal genetic testing in high-risk families. Structural brain anomalies, detectable via prenatal MRI, such as early overgrowth in regions like the amygdala, are also considered, though their specificity to ASD remains limited [26]. These prenatal biomarkers hold promise for identifying at-risk fetuses, yet the authors caution that their predictive accuracy is constrained by the complexity of the etiology of ASD, necessitating further research to refine their clinical application [26, 27].

Prenatal structural anomalies detectable by ultrasound in Autism Spectrum Disorder

Brain anomalies

Evidence from multiple studies indicates that specific prenatal brain anomalies, detectable by ultrasound or MRI, may be associated with a later ASD diagnosis, although the nature, timing, and specificity of these findings differ.

Zamłyński et al. provided a comprehensive review showing that mild-to-moderate ventriculomegaly (10–15 mm), even when isolated (not accompanied by other anomalies), is associated with increased risks of neurodevelopmental disorders, including ASD, language delays, and learning difficulties [28]. This is attributed to possible altered brain maturation or undetected genetic or metabolic abnormalities [28].

Aydin et al. examined 219 singleton pregnancies, using 2D ultrasound at 12, 20, and 26–30 weeks to measure head circumference (HC), ventricular atrium (VA), and transcerebellar diameter (TCD) [29]. Follow-up of 179 children at 18–20 months using The Quantitative Checklist for Autism in Toddlers (Q-CHAT) tool [30] revealed that larger TCD at 20 weeks and greater HC at 28 weeks were correlated with higher autistic traits. These associations persisted after adjusting for sex, maternal age, and birth weight, suggesting that atypical prenatal brain growth — especially in the cerebellum — may be linked to early ASD markers [29].

Hobbs et al. analyzed ultrasound data from children who were later diagnosed with ASD and typically developing controls [31]. The study found that while overall fetal HC did not differ significantly, children with ASD showed relatively larger biparietal diameter (BPD) and a trend toward increased HC during the second and third trimesters [31]. These findings suggest subtle prenatal brain overgrowth in ASD [31]. Decreased abdominal circumference (AC) was noted in multiplex ASD cases, and renal anomalies such as pyelectasis were more common [31]. The study concluded that atypical brain and organ development may begin prenatally in ASD, highlighting ultrasound's potential as an early screening tool [31].

When comparing Aydin et al. (2024) and Hobbs et al. (2007), both studies point to subtle prenatal brain overgrowth in ASD; however, the specific measurements and emphasis differ: Aydin et al. highlight cerebellar growth and HC increases in late gestation, while Hobbs et al. emphasize changes in BPD and co-occurring systemic anomalies [29, 31]. Differences in gestational timing of measurements, follow-up age, and diagnostic tools may account for these discrepancies.

Adding another dimension, Frye et al. synthesized neuroimaging and physiological evidence from prenatal studies, identifying structural anomalies such as deviations in cortical development, white matter organization, and cerebellar morphology through prenatal MRI [14]. These markers may reflect early neurodevelopmental disruptions and atypical connectivity patterns that persist postnatally, offering a window into the fetal origins of ASD. However, Frye et al. caution that these markers are preliminary and lack diagnostic specificity [14].

Regev et al. linked fetal structural anomalies to genetics, finding that 34.1% of children with ASD in their sample exhibited at least one prenatal anomaly [32]. These cases were significantly more likely to carry loss-of-function mutations, particularly in genes expressed across fetal tissues during organogenesis. This association underscores a possible shared basis for head, brain, and systemic anomalies [32].

Supporting earlier observations, a smaller study presented at the International Congress of the Royal College of Psychiatrists (RCPsych) in 2014 compared the head and abdominal diameters of 40 fetuses who were later diagnosed with ASD with 120 controls at 20 weeks' gestation. The ASD group had larger measurements in both parameters, echoing findings from Aydin et al. (2024) and Hobbs et al. (2007) that cranial and somatic growth patterns may diverge prenatally in ASD cases[3].

In summary, while these studies collectively suggest that certain prenatal brain anomalies, such as ventriculomegaly, enlarged BPD, increased HC, and greater TCD, are more common in fetuses who are later diagnosed with ASD, the variations in study design, measurement timing, and associated systemic findings highlight the need for standardized protocols. The convergence of structural imaging, genetic evidence, and multi-organ involvement suggests a complex developmental trajectory, but predictive accuracy for ASD remains limited.

Cardiac Anomalies

Popa et al. (2025) highlight the potential link between prenatal detection of cardiac anomalies and an increased risk of ASD through associated genetic conditions [33]. In the first trimester, 13 cases of cardiac anomalies were associated with genetic syndromes such as Down syndrome, Edwards syndrome, and Turner syndrome, all of which have

[3] Brauser D. Routine ultrasounds may detect autism in utero. In: International Congress of the Royal College of Psychiatrists (RCPsych). London, United Kingdom: Medscape Psychiatry; 2014. Available from: https://www.medscape.com/viewarticle/827333?form=fpf

a higher incidence of ASD [33]. Choroid plexus cysts and abnormal tricuspid valve flow were identified as potential indicators of underlying genetic conditions associated with neurodevelopmental disorders, including ASD [33]. A second-trimester diagnosis of DiGeorge syndrome, a condition strongly correlated with ASD, was observed [33]. These findings suggest that early detection of cardiac anomalies and related markers could aid in identifying pregnancies at higher risk for ASD due to the genetic syndromes involved [33]. Other common findings include increased biparietal diameter, hyperechogenic kidneys, and cardiac malformations. Congenital heart disease (CHD), in particular, has been repeatedly associated with ASD, potentially due to shared genetic and developmental pathways between the heart and brain [29, 34–39].

Other prenatal risk factors

A meta-analysis by Dachew et al. (2018) examined the association between intrauterine exposure to preeclampsia and the risk of ASD in offspring [40]. The pooled results showed a statistically significant 32% increase in relative risk (RR) of ASD among children exposed to preeclampsia prenatally (RR=1.32; 95% CI: 1.20–1.45). Sensitivity analyses confirmed the robustness of the findings, with relative risks ranging from 1.30 to 1.37. This study concluded that preeclampsia is a significant prenatal risk factor for ASD and emphasized the importance of early developmental screening in this high-risk population [40].

Zhang, Jin, and Liu (2022) presented a systematic review and meta-analysis examining the association between preeclampsia and ASD [41]. Their findings showed that exposure to preeclampsia was associated with an approximately 30% increased odds for ASD compared to women with normal pregnancies [41]. This analysis pooled the results of multiple studies and demonstrated a significant positive association, further supporting preeclampsia as a prenatal risk factor for neurodevelopmental disorders [41].

A large retrospective cohort study by Carter et al. examined 308,536 mother—child pairs and found that maternal obesity, diabetes, preeclampsia, and asthma during pregnancy were each significantly associated with increased odds of ASD in offspring, particularly when co-occurring with gastrointestinal disturbances (GIDs) [42]:

- ASD with gastrointestinal disturbances (GIDs): Offspring exposed to maternal preeclampsia during pregnancy exhibited a 63% higher likelihood of developing ASD with GIDs compared to unexposed children (OR=1.63; 95% CI: 1.36–1.95).
- ASD without GIDs: The effect was smaller and non-significant, with an 18% increased odds (OR=1.18; 95% CI: 1.00–1.38).
- GIDs without ASD: There was a 19% increased likelihood of gastrointestinal disturbances without ASD among offspring exposed to preeclampsia (OR=1.19; 95% CI: 1.14–1.24).

Importantly, when comparing ASD with GIDs to ASD without GIDs, preeclampsia exposure conferred 38% greater odds of ASD accompanied by gastrointestinal disturbances (OR=1.38; 95% CI: 1.09–1.75) [42].

Diagnostic role of prenatal ultrasound

Prenatal ultrasound has emerged as a widely accessible and non-invasive tool for monitoring fetal development, offering the possibility of detecting structural anomalies associated with increased ASD risk. However, its diagnostic value is challenged by variability in anomaly types, timing of detection, and limited specificity.

Population-level studies provide important baseline estimates of anomaly prevalence. Regev et al. (2022), in a retrospective case-sibling-control study of 659 children, reported that ultrasound-detected fetal anomalies (UFAs) were present in 29.3% of ASD cases compared with 15.9% of typically developing siblings and 9.6% of unrelated controls [43]. The most common anomalies involved the urinary system, heart, and brain [43]. Similar findings were observed by researchers at Ben–Gurion University of the Negev, where mid-gestation fetal anatomy surveys showed anomalies in approximately 30% of fetuses who later developed ASD — three times the prevalence in the general population. Both studies highlight that multi-organ anomalies, rather than single-system findings, may indicate broader developmental disruptions, though these patterns are not unique to ASD.

Cardiac anomalies have been a particular focus due to shared developmental pathways between the heart and brain. Popa et al. demonstrated that first-trimester ultrasound can detect cardiac defects, some linked to genetic syndromes (e.g., Down syndrome, Edwards syndrome, DiGeorge syndrome, Fragile X syndrome) with elevated ASD incidence [33]. Genetic syndromes such as Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), DiGeorge syndrome (22q11.2 deletion), and

Fragile X syndrome (FXS) are known to carry an increased risk of ASD. For instance, congenital heart disease — frequently present in Down syndrome — has been linked to higher ASD probability [44, 45]. Approximately 30–40% of individuals with DiGeorge syndrome meet diagnostic criteria for ASD [46]. FXS, the most common inherited cause of intellectual disability, is also strongly associated with ASD, with prevalence estimates indicating that around 50% of males and 16% of females with FXS receive an ASD diagnosis or treatment history (Centers for Disease Control and Prevention, 2020), and peer-reviewed studies report even higher rates: 60–75% in males and 20–41% in females [47]. Their cohort of 8,944 pregnant women included 37 first-trimester CHD cases, with early diagnosis enabling genetic testing and timely intervention [33, 39].

Similarly, Bottelli et al. (2023) assessed 7,080 pregnancies and found major CHD detection rates of 58.3% in low-risk and 93.5% in high-risk populations [48]. Ling et al. (2023) evaluated a four-section ultrasound approach (upper abdominal, four-chamber, three-vessel–trachea, bilateral subclavian artery views) in 9,533 fetuses, achieving 67% sensitivity and 99.96% specificity for CHD [49]. Yang et al. (2025) reported similar sensitivity (70.5%) in a cohort of over 77,000 fetuses, but stressed that early detection should complement, not replace, second-trimester echocardiography [39, 50]. Across these studies, early cardiac anomaly detection is feasible, yet the low specificity of CHD for ASD limits its predictive value [50].

Brain anomalies are also well-documented. Zamłyński et al. emphasized the diagnostic role of ultrasound in isolated fetal ventriculomegaly, defined as an atrial diameter >10 mm, often detected during second-trimester scans [28]. While associated with neurodevelopmental disorders, including ASD, ventriculomegaly also occurs in other conditions, limiting specificity [28]. Fulceri et al. (2018), in a systematic review of 26 studies, found that recurrent markers such as enlarged lateral ventricles and increased nuchal translucency (>99th percentile) were associated with higher ASD risk (OR=2.48) [51], but methodological heterogeneity and small sample sizes limited definitive conclusions.

Comparative analysis of patterns suggests that the greatest strength of prenatal ultrasound lies in identifying combinations of anomalies. Isolated findings — such as ventriculomegaly, mild head size increases, or single cardiac defects — appear in many neurodevelopmental conditions and even in typically developing children, leading to high false-positive rates. In contrast, concurrent anomalies across the brain, cardiac, and renal systems [43] may point toward underlying genetic or developmental disruptions relevant to ASD. Despite advances in high-resolution imaging and extended protocols (e.g., 3D/4D ultrasound), prenatal ultrasound remains an adjunct rather than a standalone diagnostic tool for ASD. Its predictive value is constrained by low specificity, operator-dependent variability, and the absence of standardized ASD-specific screening protocols.

Future improvements may come from integrating ultrasound with genetic and biochemical markers (e.g., those described by Regev et al. [32]), as well as longitudinal studies validating anomaly combinations as early biomarkers.

Doppler ultrasound has also been investigated for its potential to detect early pregnancy complications that may indirectly increase ASD risk through adverse prenatal environments. For example, Oancea et al. (2020) evaluated first-trimester uterine artery Doppler parameters — pulsatility index (PI) and presence of a diastolic notch — between 11 and 14 weeks in 120 at-risk pregnancies. PI alone predicted later preeclampsia (PE) with moderate accuracy (sensitivity=61.5%, specificity=63.8%), and adding a bilateral notch slightly improved performance [52]. Lai et al. (2022) similarly found that uterine artery PI at 19–23 weeks detected preterm PE with 75.6% sensitivity; combining Doppler findings with angiogenic markers such as PlGF and sFlt-1 improved predictive accuracy [53]. Although these studies focused on PE rather than ASD directly, PE is a known prenatal risk factor for neurodevelopmental disorders, including ASD [40, 41, 54]. Thus, Doppler ultrasound — particularly when integrated with biochemical markers — may have value in identifying pregnancies with altered placental perfusion that could impact fetal brain development. However, current evidence is indirect, and no large-scale prospective studies have established Doppler parameters as reliable standalone predictors of ASD. In conclusion, while current evidence supports the role of prenatal ultrasound in identifying structural anomalies associated with ASD risk, clinical translation requires standardized protocols, integration with multimodal data, and clear guidelines to manage the ethical implications of probabilistic prenatal findings.

DISCUSSION

Overall, the evidence for prenatal markers of ASD combines structural abnormalities detectable by prenatal imaging and broader prenatal risk factors. In the genetic, metabolic, and epigenetic domains, several biomarkers (e.g., *SHANK3*, *CHD8*, folate and mitochondrial abnormalities, DNA methylation) have been implicated, highlighting the molecular underpinnings of prenatal origins of ASD. Prenatal ultrasound findings suggest that atypical neurodevelopment associated with ASD may begin in utero, with structural and systemic anomalies observed across multiple studies. Enlarged ventricles, accelerated cerebellar and cranial growth, altered biparietal and abdominal measurements, and co-occurring renal or cardiac abnormalities have all been reported in fetuses who were later diagnosed with ASD [28, 29, 31, 32, 44, 45]. These anomalies are frequently linked with genetic variants affecting organogenesis, reinforcing the view that ASD arises from complex prenatal interactions between genetic vulnerability and developmental trajectories. Neuroimaging evidence of altered cortical development and amygdala overgrowth further supports this interpretation [14].

The diagnostic value of ultrasound remains contested. Many of the reported anomalies — such as ventriculomegaly or increased biparietal diameter — occur not only in ASD but also in other neurodevelopmental disorders or even in typically developing fetuses, producing high false-positive rates [51]. Conversely, some individuals with ASD show no detectable anomalies on ultrasound [55]. This dual limitation restricts the role of ultrasound to surveillance rather than diagnosis. Inconsistencies across studies, influenced by variability in operator expertise, gestational timing, and technology, further reduce predictive reliability. Reported sensitivities range from ~58% in low-risk pregnancies to over 90% in high-risk groups, underscoring the uneven performance of current methods [48, 50].

Beyond methodological issues, ethical and clinical concerns must be considered. Prenatal labeling based on nonspecific anomalies risks unnecessary parental anxiety, stigmatization, or misguided decision-making. Equitable access is another challenge; advanced imaging modalities remain unavailable in many low-resource settings, potentially widening disparities in early identification and intervention.

Progress will require large, prospective cohort studies to validate markers and standardize protocols. Combining ultrasound with genetic, epigenetic, and metabolic data offers a path toward more reliable prediction models, while emerging imaging technologies such as 3D/4D ultrasound and Doppler may improve detection of subtle anomalies. Ultimately, ultrasound should not be viewed as a standalone diagnostic test for ASD but rather as one component in a multimodal framework aimed at earlier recognition and targeted intervention.

Although these findings suggest that prenatal ultrasound can detect developmental deviations potentially linked to ASD, their diagnostic specificity remains limited. Many of the identified markers — such as ventriculomegaly, increased HC, or renal anomalies — are nonspecific and may occur in fetuses without later neurodevelopmental disorders [56, 57]. This highlights the need for cautious interpretation and underscores that such features should not be considered definitive prenatal predictors of ASD. For example, ventriculomegaly is a relatively common finding with varied outcomes, ranging from normal development to intellectual disability or motor impairment [58]. Similarly, increased HC may also reflect constitutional growth patterns or benign familial macrocephaly [59]. The co-occurrence of non-CNS anomalies, such as pyelectasis or congenital heart disease, may indicate broader developmental disturbances, but these are also seen in other genetic and metabolic conditions unrelated to ASD. It is also important to note that the literature to date predominantly comprises retrospective analyses or small prospective cohorts, often limited by selection bias and variability in ultrasound protocols. While certain brain and organ anomalies were replicated across studies, methodological heterogeneity — differences in gestational age at assessment, imaging resolution, and diagnostic criteria — limits cross-study comparability. Only a few studies integrate genomic analysis alongside prenatal imaging, despite growing evidence that combined phenotypic and genotypic data could enhance early risk stratification [32, 60]. Taken together, current evidence suggests that prenatal ultrasound can provide valuable but indirect signals of ASD risk, and its greatest utility will probably emerge when used with genetic and longitudinal data rather than as a standalone predictive tool.

A key strength of this review lies in its comprehensive scope. By synthesizing findings from multiple disciplines — including obstetrics, genetics, and neurodevelopmental

research — it provides a broad overview of prenatal ultrasound findings potentially linked to ASD. The search strategy covered major databases (PubMed, Scopus, Google Scholar) across an extended time frame (2007–2025), and priority was given to systematic reviews, meta-analyzes, and large cohort studies, which improves the reliability of the synthesis. Another strength is the explicit focus on structural anomalies detectable by prenatal ultrasound, addressing a clinically relevant and under-explored domain that bridges obstetric practice with early neurodevelopmental risk assessment.

However, several limitations must be acknowledged. First, as a narrative review, the study is subject to selection bias in the choice of included articles and may not capture all available evidence. Second, the review did not employ formal quality assessment tools, and therefore, its findings should be interpreted with caution due to the varying quality of the included studies. Finally, the heterogeneity across the included studies limits the generalizability of the conclusions.

Despite these limitations, this review provides an important foundation for future systematic investigations and highlights the need for integrated, multimodal approaches to improve the predictive value of prenatal ultrasound in ASD risk assessment.

Future research may need to prioritize large, multicenter prospective studies incorporating standardized imaging protocols, comprehensive postnatal follow-up, and integration with genomic, biochemical, and neurobehavioral data. Such multimodal approaches may improve the predictive accuracy of prenatal ultrasound findings for ASD while clarifying their specificity relative to other neurodevelopmental disorders. Until then, prenatal ultrasound should be considered a screening adjunct — identifying fetuses who may benefit from closer developmental monitoring — rather than a standalone diagnostic tool.

CONCLUSION

Prenatal ultrasound demonstrates the potential for detecting structural anomalies, such as ventriculomegaly, atypical brain growth patterns, and certain extracranial malformations, that may later be associated with ASD. However, these findings are not specific to ASD and may also occur in a range of other neurodevelopmental or genetic conditions, limiting the diagnostic precision of ultrasound as a standalone tool. Therefore, prenatal ultrasound should be regarded as a supportive screening method rather than a definitive diagnostic technique. To improve early detection and risk stratification, future research should focus on integrating prenatal imaging with genetic, metabolic, and other biological markers. Such a multimodal approach could enhance both the sensitivity and specificity of early ASD risk assessment, enabling more timely interventions during critical developmental windows. Large, prospective, and diverse cohort studies will be essential to validate these combined screening strategies and determine their feasibility for routine clinical practice.

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Transition from Illness Anxiety Disorder to Delusional Disorder: A Case Series

Переход от ипохондрического расстройства к бредовому расстройству: серия клинических случаев

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Case report

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ABSTRACT

BACKGROUND: Illness anxiety disorder, also known as hypochondriasis, is characterized by excessive worry about having or developing a serious medical condition and has rarely been associated with delusional disorder.

CASE SERIES PRESENTATION: Two middle-aged patients with illness anxiety disorder gradually developed somatic-type delusional disorder. The first, a 45-year-old woman, had a two-and-a-half-year history of health-related fears involving her throat — an ulcer for six months, a cyst for one year and a tumor for one year. She initially showed improvement with fluoxetine over two months, but after discontinuing the medication for three months, developed a fixed delusion that she had throat cancer, accompanied by aggression and poor self-care. She responded to risperidone within three weeks, though symptoms relapsed after discontinuing the treatment at six months. The second patient, a 45-year-old man with anxious traits and a family history of psychosis, had a five-year history of concerns about having a gastric ulcer and liver failure despite repeated normal medical evaluations. He subsequently developed a delusional conviction of liver failure for three months and showed improvement within two weeks with cariprazine treatment. He remained stable for four months but relapsed after stopping the treatment. Upon restarting cariprazine, he achieved sustained remission for six months.

CONCLUSION: The factors leading to the transition of illness anxiety-related ideas into delusions require further study in the context of poor treatment adherence. It is equally important to distinguish delusional disorder from hypochondriasis, particularly in patients with poor or absent insight.

АННОТАЦИЯ

ВВЕДЕНИЕ: Тревожное расстройство, связанное со здоровьем (или ипохондрия), характеризуется чрезмерным беспокойством о наличии или развитии серьезного заболевания и лишь в редких случаях ассоциируется с бредовым расстройством.

ОПИСАНИЕ СЕРИИ КЛИНИЧЕСКИХ СЛУЧАЕВ: У двух пациентов среднего возраста с тревожным расстройством, связанным со здоровьем, постепенно развилось соматическое бредовое расстройство. У первого пациента, 45-летней женщины, в анамнезе выявлены продолжавшиеся 2,5 года ипохондрические опасения, связанные с областью горла, которые последовательно проявлялись страхом наличия язвы (в течение 6 месяцев), кисты (1 год) и опухоли (1 год). Первоначально отмечалась положительная динамика на фоне 2-месячной терапии флуоксетином, однако после 3-месячного перерыва в терапии препаратом у нее сформировался фиксированный бред о наличии рака горла, сопровождавшийся агрессивным поведением и социально-бытовой дезадаптацией.

Лечение рисперидоном в течение 3 недель дало положительный эффект, хотя после отмены препарата симптомы вернулись через 6 месяцев. Второй пациент, мужчина 45 лет с тревожными чертами личности и семейным анамнезом психоза, в течение 5 лет испытывал беспокойство по поводу наличия у себя язвы желудка и печеночной недостаточности, несмотря на неоднократное получение нормальных результатов анализов. Впоследствии у него развилось бредовое убеждение о наличии печеночной недостаточности, которое длилось 3 месяца. После терапии карипразином в течение 2 недель было достигнуто клиническое улучшение, которое сохранялось 4 месяца. Отмена препарата привела к рецидиву. Повторное назначение карипразина позволило достичь стойкой ремиссии, которая длилась 6 месяцев.

ЗАКЛЮЧЕНИЕ: Факторы, которые приводят к переходу ипохондрических идей в бред, требуют дальнейшего изучения в свете низкой приверженности лечению. Не менее важной остается дифференциальная диагностика между бредовым расстройством и ипохондрией, особенно у пациентов со сниженной или отсутствующей критикой к своему состоянию.

Keywords: *delusion; hypochondriasis; illness anxiety; obsessive compulsive disorder; psychosis; somatic disorders*
Ключевые слова: *бред; ипохондрия; тревожное расстройство, связанное со здоровьем; обсессивно-компульсивное расстройство; психоз; соматические расстройства*

INTRODUCTION

Illness anxiety disorder (IAD) is characterized by excessive worry about having or developing a serious undiagnosed medical condition for at least six months, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1]. The International Classification of Diseases 11th Revision (ICD-11) describes a similar condition as hypochondriasis [2]. This disorder is clinically significant because of its chronic course, distress, functional impairment, and high utilization of health care resources. Both classifications note frequent comorbidity with anxiety and depression. The ICD-11 highlights the risk of progression to somatic delusional disorder, which makes early recognition and adherence to treatment crucial [1, 2]. Delusional disorder is characterized by persistent delusions typically lasting one to three months or longer in the absence of other core psychotic features, with functioning relatively preserved apart from the impact of the delusion. In the somatic subtype, the fixed belief centers on bodily functions or illnesses, such as infestation, organ failure, or foul odor, despite contrary medical evidence [1, 2]. Hypochondriasis should be differentiated from delusional disorder since some patients with hypochondriasis with poor or absent insight may have beliefs that appear to be delusional or are overvalued ideas [2, 3]. The beliefs are more likely to be delusional if there is a greater level of conviction and fixity, and if the clinical presentation is less medically plausible [2, 3].

To our knowledge, the transition from hypochondriasis to delusional disorder is rarely reported. One previously reported case involved a patient with hypochondriasis who developed a monosymptomatic hypochondriacal delusion [4]. In addition, a systematic review showed that approximately 22% of patients with delusional disorders have at least one comorbid anxiety disorder, and anxiety disorders may precede delusional disorders [5]. However, there is a lack of data regarding factors that lead to this transition, which warrants further study to enable earlier recognition and treatment. In this case series, we describe two unique cases of IAD who developed related somatic delusions.

CASE SERIES PRESENTATION

All patients in this case series were diagnosed with the somatic-type delusional disorder according to the DSM-5 [1] and ICD-11 [2]. There was no history of mood, psychotic, or anxiety disorders, nor any chronic medical illness. The study is reported in accordance with the CARE guidelines [6].

Case 1

Patient information

A 45-year-old married female from a low socioeconomic background presented with a two-and-a-half-year history of persistent health concerns regarding a serious throat condition. She initially reported having a deep ulcer that had lasted for approximately six months. This was followed

by a year-long preoccupation with the belief that she had a cyst in her throat. Over the following year this progressed to a belief that she had a tumor, triggered by occasional tickling sensations in her throat. She frequently examined her throat in the mirror and repeatedly gargled to check for swelling or redness. She had previously been evaluated by multiple otorhinolaryngologists, and had undergone a recent clinical examination and laryngoscopy, all of which were within normal limits.

Clinical findings (initial)

On examination, the patient appeared anxious and preoccupied with the belief that she had a tumor in her throat. She also demonstrated poor insight into her condition.

Diagnostic assessment (initial)

The patient was diagnosed with IAD (care-seeking type) based on the DSM-5 criteria, and correspondingly with hypochondriasis according to the ICD-11 criteria.

Therapeutic intervention (initial)

Pharmacotherapy and psychotherapy options were discussed with the patient; however, she refused to accept the diagnosis yet insisted on receiving medication. Fluoxetine was initiated and titrated from 20 mg to 40 mg once daily.

Follow-up and outcomes (initial)

Follow-up over two months showed a significant reduction in her checking behaviors and a decrease of her concern about having a tumor in her throat, as reported by her husband; however, she did not engage in psychotherapy.

Diagnostic Assessment (re-assessment at 6 months)

The patient was brought to the emergency department approximately six months later with a one-month history of verbal and physical aggression toward her husband, after he repeatedly refused to take her for evaluation of possible throat cancer. She had discontinued her medications three months earlier.

On examination, she was poorly groomed, irritable, and expressed a firm belief that she had a tumor in her throat, as no sputum was being expelled while coughing or gargling. She believed that the sputum was being absorbed by the tumor, which was causing her throat to decay, unlike before, when she could occasionally expectorate. Her husband reported multiple crying spells along with reduced self-care and food intake over the preceding month. Because the duration of the symptoms was less than three months, she was diagnosed with delusional disorder, somatic type, based on the DSM-5 criteria, and with delusional disorder, unspecified, based on the ICD-11 criteria.

Therapeutic intervention (re-assessment at 6 months)

In the emergency department, she was given intramuscular haloperidol (5 mg) and promethazine (25 mg). She was initiated on risperidone (2–6 mg daily), with improvement in symptoms over three weeks.

Follow-up and outcomes (long-term)

The improvement was sustained over three months while she remained on medication. However, her symptoms relapsed one month after discontinuing medication, at the six-month follow-up (approximately one year and two months after the initial presentation).

Case 2

Patient information

A 45-year-old married man from a low socioeconomic background, with premorbid anxious personality traits, a family history of unspecified psychosis in a second-degree relative, and nicotine dependence with abstinence for three years, with no history of chronic medical illness, presented with a five-year history of persistent concerns about having a stomach ulcer and liver failure, triggered by occasional abdominal fullness, discomfort and decreased appetite. He had previously consulted multiple physicians, surgeons, and gastroenterologists and was extensively investigated, including four upper gastrointestinal endoscopies, two colonoscopies, four ultrasound scans of the whole abdomen, and one contrast-enhanced computed tomography of the abdomen — all of which were within normal limits. The patient had been advised to consult a psychiatrist or psychologist. He was diagnosed with hypochondriacal disorder by a physician and was prescribed escitalopram (10 mg) and clonazepam (0.5 mg twice daily), and later sertraline (50 mg) with clonazepam (0.5 mg twice daily). The duration of medication use ranged from two weeks to three months, with some reduction in health-related concerns, but complete relapse of symptoms occurred within months of discontinuation.

Clinical findings

The patient was presented to the outpatient clinic with a firm belief that his liver had failed and that, due to this failure, air from the surrounding environment was being absorbed into his body, polluting it and causing reduced appetite over the past three months. He often became irritable and aggressive when family members or neighbors repeatedly rejected his explanation, and he expressed sadness that none of the doctors he had consulted had addressed his concerns.

Diagnostic assessment

The patient was diagnosed with delusional disorder, somatic type according to DSM-5 criteria and delusional disorder according to ICD-11 criteria.

Therapeutic interventions

Treatment with cariprazine (1.5–3 mg daily) was initiated, resulting in symptomatic improvement within two weeks.

Follow-up and outcomes

The improvement was maintained over four months, but symptoms relapsed within two weeks of discontinuing medication. On restarting cariprazine at 3 mg, his symptoms resolved completely and remained stable for six months, up to the last follow-up.

Informed consent

Written informed consent for publication of clinical details was obtained from the patients, as well as for the publication of any data in this article that could potentially identify them.

DISCUSSION

Both patients were initially diagnosed with IAD and hypochondriasis, and as their illnesses progressed, they began to experience somatic delusions involving the same bodily systems previously associated with IAD. In both cases, the beliefs about having a serious illness, such as a tumor in the throat and liver failure, persisted for more than a month and were held with a strong conviction. These beliefs were implausible and illogical, involved constant preoccupation throughout the day, and were accompanied by low mood and aggression towards others when contradicted. These beliefs also interfered with daily functioning, indicating that they were delusional [6]. The delusions were limited to bodily concerns, without any other symptoms of schizophrenia, and were therefore diagnosed as delusional disorder [1, 2].

A previous case study reported a woman who initially had hypochondriasis and later developed the delusion that "her gastric mucosa dried out and she had a rotten tube in her throat". She responded to electroconvulsive therapy [4]. Our cases differ from this report. In Case 1, the beliefs about having a throat tumor evolved into a delusion after treatment discontinuation, whereas in Case 2, the patient presented with a delusional conviction of liver failure. The factors leading to the transition from hypochondriasis to somatic delusions remain difficult to determine. However, reasoning biases and a tendency to jump to conclusions may contribute to this progression [7]. Previous studies have shown that anxiety disorders may precede delusional disorders [5], and a case series also demonstrated that four patients with delusional disorder had a prior diagnosis of social anxiety disorder [8]. Dopamine dysregulation and amygdala-prefrontal dysfunction may be contributing neurobiological factors [5, 8]. In addition, poor treatment compliance may play a role, requiring further investigation. Moreover, a family history of psychosis, as seen in Case 2, is a known risk factor for developing psychotic disorders [9]. A similar transition — from distorted health-related ideas to somatic delusions involving the genital organs (Dhat delusion) — has also been described in the literature [10]. This case series highlights the uncommon transition from IAD to somatic-type delusional disorder, contributing to the limited literature on this phenomenon. The detailed timelines illustrate how prolonged health-related worries can evolve into fixed delusional beliefs, emphasizing diagnostic challenges and the importance of treatment adherence. The cases also demonstrate the effectiveness of antipsychotic medications and highlight potential vulnerability factors, such as premorbid anxious traits and family history of psychosis. However, the small sample size, lack of standardized assessments, short follow-up duration, and differing treatment approaches limit generalizability, and causality for the transition remains speculative.

Both patients and their family members acknowledged the importance of treatment adherence. They also reported that relapses were marked by poor self-care, emotional distress, and strained family relationships, whereas sustained treatment led to symptomatic remission.

CONCLUSION

In the context of poor treatment adherence and a family history of psychosis, the cases show how hypochondriacal thoughts may evolve into somatic delusions. It is also critical

to distinguish delusional disorder from hypochondriasis, particularly in cases with poor or absent insight. Further research is needed to explore the factors that may predispose patients with hypochondriasis and poor treatment adherence to develop delusional disorder or other psychotic disorders.

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Hypothyroidism-Induced Psychotic Disorder with Prolonged Antipsychotic Treatment: A Case Report

Длительное лечение антипсихотиками индуцированного гипотиреозом психотического расстройства: клинический случай

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Case report

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ABSTRACT

BACKGROUND: Hypothyroidism, a common thyroid disorder, is typically associated with affective and cognitive symptoms. However, up to 15% of patients may also present psychotic symptoms, which represents a relatively rare and poorly understood manifestation. Existing literature on this condition consists primarily of isolated case reports, which describe short courses of antipsychotic treatment. In contrast, the present case illustrates a prolonged and more complex trajectory, contributing to a better understanding of the psychiatric presentations of hypothyroidism and their management.

CASE PRESENTATION: We report the case of a 42-year-old man hospitalized for violent behavior toward others and overt psychotic symptoms in untreated hypothyroidism. Tests revealed elevated thyroid-stimulating hormone levels of 34.925 mIU/L. Clinical evaluation confirmed significant psychiatric disturbance necessitating inpatient care. A diagnosis of secondary psychotic disorder due to hypothyroidism was established. The patient required prolonged antipsychotic treatment, and an initial attempt to discontinue treatment was unsuccessful. A second withdrawal attempt made several months later was successful, with full recovery and complete remission of symptoms. This remission was maintained despite recurrent thyroid-stimulating hormone level elevation, while thyroxine hormone levels remained within the normal range.

CONCLUSION: This case illustrates the importance of ruling out non-psychiatric medical causes in the differential diagnosis of psychiatric symptoms. It also highlights the need for individualized treatment plans and sustained follow-up, particularly in rare and poorly understood conditions for which no formal guidelines or standardized management protocols exist.

АННОТАЦИЯ

ВВЕДЕНИЕ: Гипотиреоз — распространенное заболевание щитовидной железы, часто сопровождающееся аффективными и когнитивными нарушениями. Однако примерно у 15% пациентов заболевание может также проявляться психотическими симптомами. Это относительно редкое и малоизученное проявление гипотиреоза. На данный момент публикации, посвященные данному феномену, ограничиваются описанием отдельных клинических случаев, в которых преимущественно рассматривается краткосрочное применение антипсихотических препаратов. В отличие от ранее опубликованных, представленный случай демонстрирует более продолжительный и сложный клинический сценарий, что позволяет глубже изучить психические проявления гипотиреоза и оптимизировать подходы к терапии.

ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ: Авторы описывают случай 42-летнего пациента, госпитализированного с гетероагрессией и выраженными психотическими симптомами, которые развились на фоне нелеченого гипотиреоза с повышенным уровнем тиреотропного гормона (ТТГ) (34,925 мМЕ/л). Клиническое обследование подтвердило наличие серьезного психического расстройства, потребовавшего госпитализации. Пациенту был диагностирован вторичный психотический синдром на фоне гипотиреоза. Потребовалась длительная терапия антипсихотиками, при этом первая попытка отмены препаратов сопровождалась ребаунд-эффектом. Однако повторная попытка отмены, предпринятая спустя несколько месяцев, привела к полному восстановлению и стойкой ремиссии симптомов, даже несмотря на рецидивирующее повышение уровня ТТГ при стабильно нормальном уровне тироксина.

ЗАКЛЮЧЕНИЕ: Настоящий клинический случай указывает на важность исключения соматических причин при дифференциальной диагностике психических расстройств. Он подчеркивает необходимость длительного клинического наблюдения и индивидуализированного подхода к терапии, особенно при редких и малоизученных патологиях, в отношении которых отсутствуют официальные клинические рекомендации или стандартизированные протоколы лечения.

Keywords: *hypothyroidism; hallucinations; delusions; depression; case report*
Ключевые слова: *гипотиреоз; галлюцинации; бред; депрессия; клинический случай*

INTRODUCTION

Hypothyroidism is a common disorder, with a prevalence ranging from 0.2 to 1.3% in iodine-sufficient regions [1]. Among the psychiatric manifestations associated with hypothyroidism, cognitive and affective symptoms are the most frequently described, with estimated prevalences of approximately 27% and 60%, respectively [2, 3]. Less commonly, 5 to 15% of patients exhibit psychotic symptoms [4]. Historically, this condition was referred to as "myxedema psychosis" or "myxedema madness" [5]. The term "myxedema madness" was coined by Asher in a 1949 article describing 14 patients with myxedema and psychotic symptoms [5, 6].

This manifestation is sparsely described in the medical literature [5, 7], and no treatment guidelines are available. Clinical evidence is primarily limited to case reports, which indicate an average recovery time of about 2 weeks. Most patients require antipsychotic treatment for short periods, in addition to thyroid hormone replacement therapy. Although there is considerable heterogeneity in antipsychotic use, some patients were not treated with them at all.

Of the 75 cases included in a systematic review [7], only five required treatment longer than five months, two required 9 months, and none reached one year. In contrast, the present case involves a patient who required 12 months of antipsychotic treatment. An initial attempt to discontinue antipsychotic treatment was unsuccessful, but full symptom remission was achieved after prolonged therapy.

This case is presented under the CARE guidelines [8].

CASE PRESENTATION

Patient information

De-identified patient information and primary symptoms

We present the case of a 42-year-old Mexican man, divorced and unemployed at the time of evaluation. The patient exhibited delusional ideas of harm, persecution and guilt, accompanied by self-directed speech and passive suicidal ideation. Over time, these symptoms were compounded by apathy, loss of will (abulia) and social withdrawal, and neglect of personal hygiene. These features became prominent by July 2023. He also displayed aggressive behavior, including threatening a family member with a sharp object, which led to his psychiatric admission due to the severity of his hetero-directed aggression in August 2023.

Medical, family, and psycho-social history

The patient was diagnosed with hypothyroidism in November 2022, after nearly a year of physical symptoms, such as fatigue, weight gain, hair loss, and cold intolerance. He was prescribed levothyroxine 100 μg daily with inconsistent adherence. He had no history of surgeries, blood transfusions, allergies, or significant trauma. Family history included rheumatoid arthritis in his mother and hypothyroidism in his sister. There was no family history of mental disorders or suicide.

The patient had worked in the same administrative position for 25 years, resigning in November 2022 because

of diminished motivation and loss of interest. His history also included aggressive behavior during childhood and adolescence, directed toward both family members and partners. Depressive symptoms emerged in January 2021 in the context of financial problems and relationship issues. Occasional use of tobacco and alcohol was reported.

Relevant past interventions with outcomes

Between March and May 2023, the patient was admitted to a private clinic and treated with alprazolam and risperidone. While partial symptom relief was achieved during the stay, psychotic symptoms reappeared shortly after discharge.

Clinical findings

The patient appeared his stated age and had a mesomorphic build. He was uncooperative during the initial interview, without spontaneous speech. The patient was alert but drowsy, disoriented to time and situation, yet oriented to person and place. He answered questions in a sad tone, with decreased volume, limited verbal output, and speed.

His thought process was linear. The patient described delusions of harm and persecution. He did not report perceptual disturbances. He did not exhibit hallucinatory behavior at the time of the interview. However, he acknowledged having experienced auditory hallucinations with derogatory content in the preceding months. He described his mood as "tired". His affect was congruent and appropriate, though hypothymic and blunted. Overall mental functions appeared diminished. He was unaware of his illness.

Timeline

In Figure 1, a timeline of the patient's clinical case is presented graphically.

Diagnostic assessment

Upon admission, the initial diagnosis was schizophrenia. However, given the sudden onset of psychotic symptoms, the patient's age, and the absence of personal and family history of psychotic disorders, an underlying medical etiology was considered. Initial laboratory tests showed thyroid-stimulating hormone (TSH) levels at 34.925 mIU/L, free T_4 (FT4) of 0.51 ng/dL and total T_4 (TT4) of 3.05 µg/dL. During the first days of hospitalization, the patient had a score of 29 points on the Hamilton Rating Scale for Depression (HDRS), indicating severe depressive symptoms.

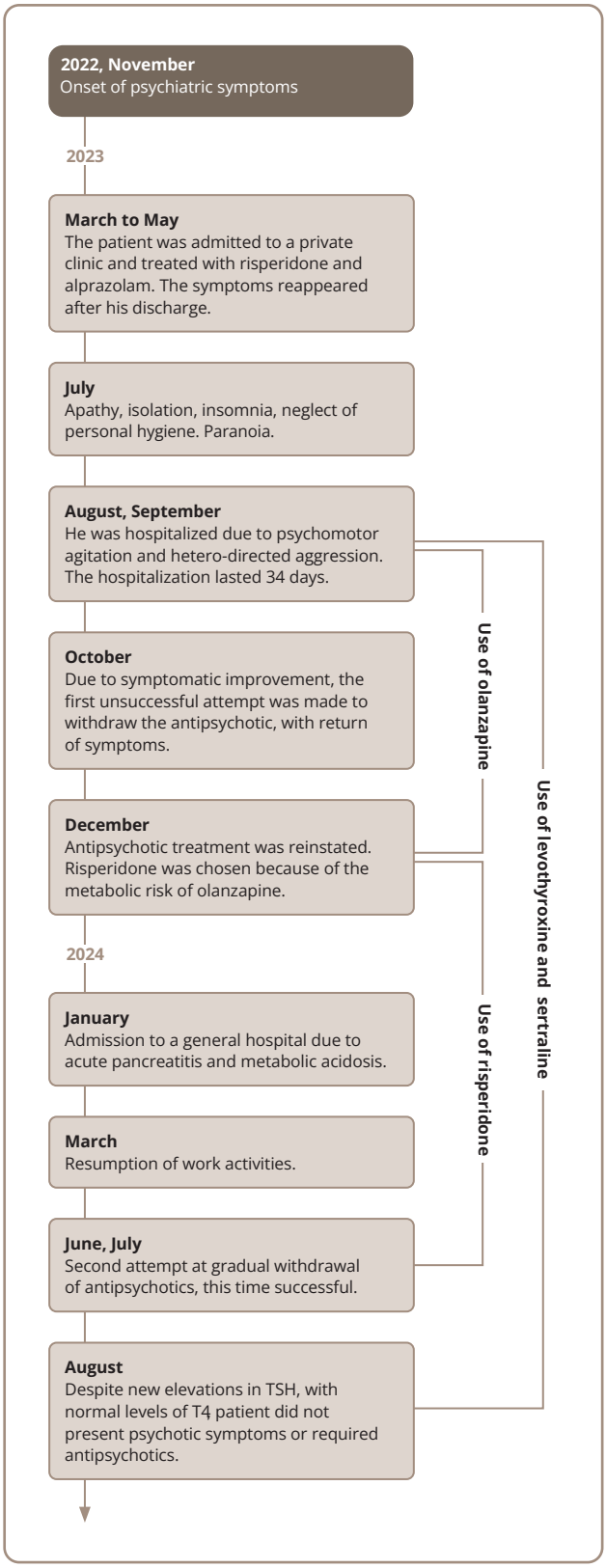

Figure 1. Clinical timeline of the patient's case.

Note: T_4 — thyroxine hormone; TSH — thyroid-stimulating hormone.

Source: López-Villa & Martín-Escoto, 2025.

Computed tomography (CT) and magnetic resonance imaging (MRI) were performed as outpatient procedures several weeks after hospitalization, as imaging services were unavailable at our center. CT revealed a thyroid nodule at the isthmus and hypotrophy of the right thyroid lobe. MRI (without contrast) showed findings consistent with the patient's age, according to the attending neurologist. An electroencephalogram (EEG) was also performed and reported within normal parameters.

Owing to diagnostic challenges, such as delayed radiologic studies and limited information, a provisional diagnosis of psychotic disorder under investigation was made, with the main hypothesis being psychotic disorder due to another medical condition (hypothyroidism).

Therapeutic interventions

The patient received pharmacologic treatment addressing both endocrine and psychiatric symptoms. In addition, he was also provided with multidisciplinary support, including assessment by internal medicine specialists, care from a nutritionist, social workers, nursing staff, and psychologists employing a cognitive-behavioral therapy approach.

Due to the significantly elevated TSH levels, levothyroxine was initiated at 150 μg daily (1.8 μg/kg/day). Likewise, olanzapine was prescribed at a dose of 10 mg per day for its sedative properties to manage psychotic symptoms and hetero-aggressive behaviour. For behavioral containment, benzodiazepine clonazepam was used at a dose 2 mg per day, and was gradually tapered prior to discharge.

For affective symptoms, the selective serotonin reuptake inhibitor (SSRI) sertraline was started at a dose of 50 mg daily. After 16 days, the dose was increased to 100 mg daily due to partial response. During the 34-day hospitalization, the patient experienced gradual improvement in psychotic and affective symptoms, with reduced social isolation, increased energy, and better interaction with family members.

Follow-up and outcomes

Clinician- and patient-assessed outcomes

During the follow-up, the patient showed a progressive reduction in affective symptoms and complete remission of psychotic symptoms. He could also reintegrate into his family life and resume caregiving responsibilities. By March 2024, the patient had returned to work and reported a good sleep pattern and functional recovery. In July 2024, he scored 4 points on the HDRS, indicating remission of affective symptoms.

Follow-up diagnostic

Serial laboratory monitoring showed a gradual decline in TSH levels (Table 1), particularly after increasing the dose of levothyroxine to 200 μg daily in March 2024. Despite a TSH level elevation in August 2024 (28.02 mIU/L), free and total T_4 levels (total 5.25 μg/dL and free 0.86 ng/dL) remained within the normal range, and no recurrence of psychotic symptoms was observed.

Intervention adherence and tolerability

The patient showed good adherence to pharmacological treatment. He tolerated levothyroxine, sertraline, and antipsychotics without significant side effects. Pregabalin (75 mg daily) was initially prescribed for sleep. A first attempt to withdraw olanzapine gradually between October and December 2023 led to recurrence of symptoms. Symptoms reappeared one week after discontinuation. The patient presented with social isolation, low energy, anhedonia, delusions of harm and insomnia. Due to this relapse, antipsychotic treatment was reinstated, with risperidone at 2 mg daily selected for its lower cardiovascular risk compared to olanzapine. Pregabalin was replaced with hydroxyzine at 25 mg daily for sleep. This adjustment led to renewed remission of psychotic symptoms.

In June 2024, a second attempt at gradual withdrawal of the antipsychotic was initiated. The dose was reduced to 1 mg, then to 0.5 mg one month later and, finally discontinued in August 2024, with a favorable clinical response. The antihistamine was also withdrawn at that time without adverse effects.

Table 1. Thyroid levels throughout patient follow-up

Date	TSH (mIU/L)	Free T_4 (ng/dL)	Total T_4 (μg/dL)	Free T_3 (pg/mL)	Total T_3 (ng/mL)
27.08.2023	34.925	0.51	3.05	1.23	0.38
05.09.2023	24.429	0.63	3.92	1.27	0.41
12.10.2023	9.59	0.86	5.22	1.82	0.43
16.11.2023	8.09	0.59	3.55	3.09	0.71
15.03.2024	11.75	0.68	4.51	—	0.58
30.04.2024	4.59	0.75	7.61	2.90	1.06
28.08.2024	28.02	0.86	5.25	1.33	0.32
14.04.2025	9.38	0.73	5.70	3.11	1.03

Note: T_3 — thyroxine hormone; T_4 — thyroxine hormone; TSH — thyroid-stimulating hormone.

Adverse and anticipated events

In January 2024, the patient presented polyuria, polydipsia, polyphagia, asthenia and adynamia, prompting admission to a general hospital. He was diagnosed with acute pancreatitis and metabolic acidosis, with triglyceride levels of 8,051.8 mg/dL. He received treatment with insulin and intravenous fluids and was discharged with a new diagnosis of type 2 diabetes mellitus, dyslipidemia, and hypertension, for which he continues treatment under internal medicine supervision.

Final clinical status

By August 2024, the patient remained clinically stable with no recurrence of psychotic or affective symptoms. The patient did not require further antipsychotic treatment, maintained functional stability, and remained on sertraline at 100 mg daily. He also remained under internal medicine follow-up for hypothyroidism and associated metabolic conditions.

Informed consent

All patient-identifying data have been omitted. In August 2024, informed consent for publication was obtained from both the patient and the primary caregiver.

DISCUSSION

The present clinical case illustrates psychotic symptoms induced by hypothyroidism, a rare and poorly understood manifestation. Case characteristics — such as the sudden onset, age at presentation, and the specific nature of the delusions — are consistent with descriptions in the medical literature. Based on these features, the diagnosis of secondary psychotic syndrome (ICD-11 6E61) due to hypothyroidism (ICD-11 5A00) was established.

The clinical course of the condition is distinct from schizophrenia and psychotic depression [9], particularly considering the rapid symptomatic improvement following initiation of levothyroxine with adequate adherence. Other distinguishing features included the absence of prior psychiatric history (except for brief situational affective symptoms) and the rapid functional decline coinciding with the abrupt onset of psychotic symptoms and markedly elevated TSH levels.

This case is notable for the necessity of prolonged antipsychotic use. An initial withdrawal was unsuccessful, but the patient later achieved complete and sustained remission and functional recovery, despite subsequent TSH elevations and normal T_4 levels. It also demonstrates the difficulties of treating rare conditions without formal guidelines, particularly regarding the duration of antipsychotic use.

The main limitation of this case is the inability to prove causality, despite the strong correlation observed between hypothyroidism and psychosis. Other limitations include the lack of objective measures of cognitive function and treatment adherence, with reliance instead on subjective reports from the patient and caregiver. This case's strengths are its long-term follow-up and structured treatment protocol.

The pathophysiology underlying psychotic symptoms in hypothyroidism remains unclear. Several hypotheses have been suggested, such as reduced cerebral metabolism [10], imbalance in tyrosine hydroxylase, altered serotoninergic neurotransmission, or increased T_3 receptor density in the amygdala and hippocampus [7]. Nevertheless, thyroid hormone replacement therapy — sometimes augmented with antipsychotics — remains the cornerstone of treatment.

There are documented cases in which psychotropic medications were not used, or were only prescribed for brief periods, particularly when hypothyroidism was identified and treated early [11, 12]. Symptomatic improvement typically occurs between one week and several months following the initiation of thyroid hormone replacement therapy [13]. Notably, the severity of thyroid dysfunction does not appear to correlate directly with the presence or intensity of psychiatric symptoms [14].

The clinical literature reflects high heterogeneity in reported cases, as demonstrated in two systematic reviews. Krüger et al. reported 52 cases, noting complete remission of psychotic symptoms in 82.7% of them; 40.4% of patients did not receive antipsychotic treatment [5]. The most frequently reported symptoms were delusions, perceptual disturbances, and formal thought disorders.

In contrast, Mohamed et al. reviewed 75 cases, with a mean age of 42 years and a female-to-male ratio of 2:1. Delusional thinking,especially paranoid and persecutory delusions, was the most common clinical presentation. Antipsychotics were used in 92% of cases, typically for a median duration of 1.8 weeks, and 93% of patients achieved remission. Only two of those cases underwent treatment lasting more than 9 months [7]. To the best of our knowledge, this is the clinical case with the longest reported antipsychotic treatment duration, totaling 12 months.

Establishing causality in cases of secondary psychosis can be challenging. However, three key elements are

considered helpful in this process: atypicality, temporality, and explicability. These criteria involve: (1) recognizing atypical features such as late-onset psychosis or unusual symptoms; (2) identifying a temporal association between psychotic symptoms and an underlying medical condition; and (3) excluding primary psychotic disorders as more likely explanations. Our patient met all three criteria.

A thorough diagnostic evaluation during the first episode is essential. This includes comprehensive history-taking, careful physical examination, and appropriate laboratory and imaging studies [15]. Certain symptom patterns may also suggest secondary psychosis. A systematic review and meta-analysis reported a significant association between visual hallucinations and secondary psychosis (OR 3.0, $p<0.001$; I^2 70%) [16].

Accurate diagnosis relies on diligent clinical investigation. Gama Marques (2020) retrospectively assessed 200 patients initially diagnosed with schizophrenia and found that 25% (50 patients) were later reclassified with a diagnosis of "organic psychosis". The average delay to correct diagnosis was 12 years [17]. Secondary psychosis is estimated to account for approximately 11% of psychosis cases, with roughly 10 patients needing to be evaluated to detect one such case. Approximately 5% of cases are due to an underlying non-psychiatric medical condition [18].

The patient shared the following regarding his experience with treatment: *"I'm doing very well with the treatment. Thank God I'm feeling better. So far, everything has gone well. I've been following the treatment to the letter"*.

CONCLUSION

This clinical case illustrates the crucial need for ruling out underlying non-psychiatric medical causes of psychiatric symptoms. We believe that our case report can help clinicians in recognizing the potential risk of relapses, the need for individualized care, and the value of long-term follow-up — particularly in rare conditions such as this one, where formal guidelines or standardized management protocols are lacking and reported cases show high variability.

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Proprioception and Cognitive Polarization in Autism: The Bipolar Tensile Model

Проприоцепция и когнитивная поляризация при аутизме: модель биполярного напряжения

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Discussion

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ABSTRACT

This article introduces the Bipolar Tensile Model, a neurosemiotic and integrative framework for understanding Autism Spectrum Disorder (ASD). The model reinterprets ASD not as a collection of deficits, but as the outcome of an unresolved tension between two complementary hemispheric cognitive modalities: symbolic-sequential and corporeal-perceptual. In typical development, these modalities are dynamically harmonized through an extended interhemispheric network, comprising the Default Mode Network, major cerebral commissures (corpus callosum, anterior and hippocampal), and the cerebellum.

In ASD, the instability of this mediating system disrupts proprioceptive integration and generates polarized cognitive configurations, such as operational rigidity, sensory disorganization, and repetitive behaviors. Proprioception is understood not as a peripheral sensory channel, but as a semiotic regulator of interhemispheric coherence and embodied self-awareness.

Drawing on a narrative synthesis of clinical, neuropsychological, and neurophysiological literature — and supported by representative clinical cases — the model highlights how interhemispheric disconnection and proprioceptive instability interact to shape atypical developmental patterns. It proposes compensatory adaptation, including local hyperconnectivity and symbolic overcompensation, as central mechanisms in the formation of ASD profiles.

By integrating insights from semiotics, systems neuroscience, and embodied cognition, the Bipolar Tensile Model provides new perspectives on diagnosis, clinical interpretation, and individualized therapeutic approaches, with particular attention to the early identification of proprioceptive dysfunction and the design of integrative rehabilitation protocols.

АННОТАЦИЯ

В настоящей статье представлена альтернативная теоретическая гипотеза, объясняющая расстройства аутистического спектра и описывающая модель биполярного напряжения — нейросемиотическую и интегративную концепцию, которая определяет расстройства аутистического спектра не как совокупность дефицитов, а как результат неразрешенного напряжения между двумя взаимодополняющими когнитивными модальностями полушарий головного мозга: символически-последовательной и телесно-перцептивной. При нормотипичном развитии эти модальности динамически гармонизируются посредством расширенной межполушарной сети, включающей сеть пассивного режима работы головного мозга (Default Mode Network, DMN), основные мозговые комиссуры (мозолистое тело, передняя комиссура и гиппокампальная комиссура) и мозжечок.

Нестабильность этой опосредующей системы при расстройствах аутистического спектра нарушает проприоцептивную интеграцию и порождает поляризованные когнитивные конфигурации, такие как поведенческая ригидность, сенсорная дезорганизация и повторяющееся поведение. Таким образом, проприоцепция позиционируется не как периферический сенсорный канал, а как семиотический регулятор межполушарной связи и телесного самосознания.

Разработанная на основе нарративного синтеза клинической, нейропсихологической и нейрофизиологической литературы и подкрепленная показательными клиническими случаями модель демонстрирует, как межполушарное разъединение и проприоцептивная нестабильность объединяются в формировании нетипичных функциональных траекторий. В качестве центральных механизмов формирования профилей расстройств аутистического спектра предлагается компенсаторная адаптация, включая локальную гиперконнективность и символическую сверхкомпенсацию.

Объединяя идеи семиотики, системной нейробиологии и воплощенного познания, модель биполярного напряжения открывает новые перспективы для диагностики, интерпретации и индивидуальных терапевтических стратегий, уделяя особое внимание раннему выявлению проприоцептивных дисфункций и разработке протоколов интегративной реабилитации.

Keywords: *proprioception; interhemispheric connectivity; autism spectrum disorder; embodied cognition; neurosemiotics*
Ключевые слова: *проприоцепция; межполушарные связи; расстройство аутистического спектра; воплощенное познание; нейросемиотика*

INTRODUCTION

Autism spectrum disorder (ASD) is commonly understood through spectrum-based models, designed to explain the phenotypic and symptomatic variability of the condition. While descriptively effective, these models often fail to capture the underlying functional and adaptive dynamics, particularly those related to sensorimotor integration and the development of bodily self-awareness.

This article introduces an alternative theoretical model, the Bipolar Tensile Model (BTM), developed within a neurosemiotic and informational framework. In this perspective, ASD is not viewed as a collection of traits or deficits, but as the result of an unresolved tension between two complementary hemispheric cognitive styles — symbolic-sequential and corporeal-perceptual — that, in neurotypical conditions, are harmonized by an interhemispheric system of integration.

When this mediation is unstable or ineffective, polarized cognitive patterns may emerge, leading to atypical functional profiles. In this model, proprioception plays a key role, not merely as a peripheral sensory channel, but as an indicator of coherence between cognitive systems and the efficiency of interhemispheric integration.

Despite the growing use of sensory and psychomotor approaches in ASD interventions, proprioceptive integration often remains limited, especially in high-functioning individuals. The proposed model provides an alternative framework for interpretation, suggesting that therapeutic efforts should focus on restoring postural and interhemispheric balance through proprioceptive stimulation, embodied narrative techniques, and integrative hemispheric training.

THEORETICAL FRAMEWORK

Neurosemiotic foundations

The hypotheses presented here draw upon two significant theoretical traditions. Yuri Lotman's neurosemiotic framework, developed from his seminal work "Culture as collective intelligence and the problem of artificial intelligence" [1], interprets cerebral asymmetry not merely as a biological fact, but as an epistemic structure of culture itself. The two cognitive hemispheres — logical-verbal and visual-holistic — operate through distinct codes and generate meaning through their confrontation and mutual tension. In this view, cultural and cognitive creativity emerges at the boundaries where these divergent systems meet and interact.

Giulio Tononi's Integrated Information Theory (IIT) [2] posits that consciousness emerges from the highest possible integration among highly differentiated systems. This view also reveals a structural paradox: the greater the specialization (and therefore asymmetry) of the systems involved, the greater the need for global mediation to prevent experiential fragmentation.

Hemispheric specialization and cognitive tension

The BTM places this tension at its core between differentiation and integration as its central organizing principle: cognitive and identity coherence arise from an unstable and dynamic equilibrium between specialized hemispheric poles, continually modulated through proprioceptive and embodied processes.

Although not directly derived from the work of Nikolai Bernstein [3], the model aligns closely with his conception of movement as a centrally regulated, goal-oriented

activity. Bernstein's distinction between anticipatory coordination and retroactive adjustment reflects a functional tension like that proposed here between conscious proprioception and motor automatism. From this perspective, the sensorimotor disturbances observed in ASD may not result from simple executive deficits, but from imbalances between these regulatory systems.

This view is consistent with recent models of distributed brain function, which conceptualize lateralization not as a static division of labor, but as a dynamic axis of specialization and integration — mediated by interhemispheric structures and the Default Mode Network (DMN).

METHODS

This study adopts a theoretical approach to construct an interpretative model that integrates neuroscientific evidence, clinical data, and semiotic perspectives. Its aim is to outline a heuristic framework for understanding the atypical cognitive and sensorimotor dynamics observed in ASD, with a particular focus on proprioception and interhemispheric connectivity.

The BTM was developed through a narrative review of the scientific literature to identify theoretical, clinical, and experimental contributions relevant to the model's core hypothesis. The literature search included peer-reviewed articles indexed in major international databases (PubMed, Scopus, PsycInfo), without rigid temporal restrictions, to include foundational studies on motor control and hemispheric lateralization. The main keywords used were: "ASD", "proprioception", "hemispheric connectivity", "interhemispheric integration", "default mode network", "motor planning", "sensorimotor integration", and "semiotics".

The inclusion criteria prioritized studies that:

- presented neuroimaging data (fMRI, DTI, EEG);
- included sensorimotor evaluations of individuals with ASD;
- explicitly addressed functional lateralization, motor regulation, or body perception.

A central element of the model is the concept of the Extended Default Mode Network, which encompasses not only the cortical areas of the classical DMN, but also the primary interhemispheric commissures (corpus callosum, anterior and hippocampal commissures) and the cerebellum, conceptualized as active nodes of cognitive compensation and integration.

The theoretical framework acknowledges the simplifications required when modeling a multifactorial condition such as ASD: other sensory or cognitive systems not directly related to proprioception have been intentionally omitted to maintain focus on the tensile dynamics of hemispheric processing. The model's heuristic validity is illustrated through three illustrative clinical cases drawn from the literature, each showing convergence between proprioceptive dysfunction, interhemispheric disconnection, and atypical neurofunctional profiles.

THE BIPOLAR TENSILE MODE

Interhemispheric disconnection and compensation

Numerous neuroimaging studies suggest that ASD is characterized by an atypical pattern of brain connectivity, with increased local intrahemispheric connectivity and reduced communication between homologous interhemispheric regions. These patterns are observable through fMRI, DTI, EEG, and MEG analyses. A significant reduction in interhemispheric connectivity, associated with social interaction deficits, has been reported [4]. Widespread alterations in functional brain connectivity have been confirmed using the ABIDE dataset [5]. A model based on local hyperactivity and weak global integration has been proposed [6], and reduced interhemispheric synchronization and more idiosyncratic processing styles have also been reported [7].

These dysfunctions support the hypothesis that each hemisphere processes information relatively independently, according to its own computational style. Local hyperconnectivity may thus be interpreted as a compensatory strategy, in which each hemisphere reinforces its internal coherence to compensate for weak bilateral integration. Within this dynamic, divergent cognitive profiles emerge: the left hemisphere favors symbolic-sequential processing, while the right hemisphere adopts corporeal-perceptual modes [8–10].

Based on this evidence, the BTM, rooted in semiotic-informational theory, views the heterogeneity of ASD as arising from a functional tension between two complementary cognitive modalities (Figure 1). The "bipolar" axis refers to the deviation from a dynamic equilibrium between hemispheric specializations. When interhemispheric connectivity weakens, each pole tends to amplify its characteristic processing style, leading to polarized cognitive patterns. Clinically, these configurations may manifest as operational rigidity, perceptual selectivity, motor stereotypies, or sensory disorganization.

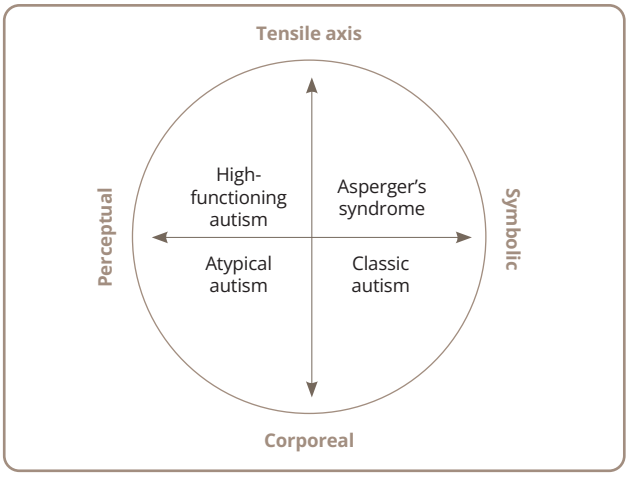

Figure 1. Axial representation of the Bipolar Tensile Model.

Source: Tensile Axis Image concept by M. Sanna, generated by ChatGPT (OpenAI, 2025).

Inspired by the neurosemiotics of Lotman [11] and IIT [2], the model proposes that cognitive lateralization is a plastic and dynamic process. The center of the axis represents a point of active tension in which the two hemispheres seek to integrate qualitatively distinct forms of processing. Hemispheric tension is not pathological per se, on the contrary, it can fuel cognitive creativity and coherence of self. It becomes clinically relevant only when integration fails, resulting in unbalanced profiles, such as disembodied verbalizations or disorganized motor behavior.

The model distinguishes between two semiotic modalities: the left hemisphere operates through discrete codes (analytical, symbolic, sequential), whereas the right hemisphere relies on continuous codes (perceptual, spatial, affective). These cognitive languages, though qualitatively divergent, are potentially integrable via a mediating function.

From this perspective, position along the tensile axis does not represent a rigid clinical typology, but rather indicates a degree of compensation in relation to the prevailing mode. For instance:

- a left-dominant profile may exhibit advanced linguistic abilities with pragmatic rigidity [12, 13];
- a right-dominant profile may be associated with sensory hypersensitivity and hyperverbality [14, 15].

The weaker the interhemispheric communication, the greater the profile's polarization. Conversely, effective integration of cognitive styles promotes flexibility and self-coherence, even in neurotypical individuals, who are not necessarily centered on the axis, given the high variability of functional asymmetry across individuals.

The compensatory instance

Within the framework of the BTM, we propose the existence of an intermediary neural function, a true mediating mechanism, that not only relay information between hemispheres, but actively regulates their functional tension, acting as a dynamic regulator between qualitatively distinct cognitive styles.

The main challenge of this mediation lies in the asymmetry of hemispheric codes: the left hemisphere processes information in discrete, segmented, and sequential formats; the right hemisphere, by contrast, operates through continuous, spatial, affective, and perceptual configurations. Integrating these heterogeneous cognitive languages requires an active process of recoding rather than direct translation.

Under neurotypical conditions, this mediating function supports adaptive plasticity, which supports the emergence of a coherent and flexible embodied self. In atypical profiles, such as in ASD, this mediation may prove unstable or inefficient, promoting cognitive and sensorimotor fragmentation.

This compensatory mechanism can be understood as an internal regulator of functional coherence, whose purpose is to optimize integration according to an individual's neurofunctional profile. Anatomically and functionally, the cerebral commissures are the primary structures likely to fulfill this role, primarily the corpus callosum, followed by the anterior and hippocampal commissures. These structures do not merely transmit signals: they modulate, filter, and transform information, actively contributing to the construction of cognitive unity.

As noted by Gazzaniga [16], the corpus callosum is essential for integrating interhemispheric consciousness; van der Knaap and van der Ham [17] further emphasize its selective and integrative function, well beyond simple information transfer.

Parallel research has associated disturbances in the DMN with impairments in self-integration in individuals with ASD. The DMN, comprising the medial prefrontal cortex, precuneus, posterior cingulate cortex, and limbic areas, plays a central role in self-representation and monitoring bodily intentions [18]. A meta-analysis by Wang et al. [19] identified systematic alterations in resting-state DMN connectivity in ASD populations. Similarly, Yao et al. [4] reported reduced connectivity within DMN regions, associated with social deficits.

He et al. [20] described topological changes in the network, affecting emotional regulation and behavioral adaptation.

Within interhemispheric mediation, the inferior parietal lobule (IPL) functions as a multisensory hub constructing the body schema. Under conditions of hemispheric disconnection, the IPL becomes vulnerable, disrupting the alignment between perception, intention, and action [21].

The anterior commissure connects limbic and temporoparietal areas and may influence sensory-affective coherence. The hippocampal commissure, involved in memory processing and autobiographical space, is part of both the limbic system and the Extended Default Mode Network, making it an integral component of this mediating mechanism.

This "third structure" can therefore be identified as a functionally integrated system comprising the Extended Default Mode Network and the major cerebral commissures. Together, these constitute the neurofunctional platform of hemispheric compensation.

In individuals with ASD, this integrated network is frequently compromised. Converging studies report reduced connectivity between DMN nodes and structural alterations in the cerebral commissures [22, 23]. This disconnection impairs interhemispheric coherence, resulting in asymmetrical management of information between the symbolic and perceptual poles. Clinically, this produces a persistent tensile imbalance, manifesting as sensorimotor disintegration, repetitive behaviors, and disturbances in the narrative construction of the self.

Within our model, dysfunction of the third structure compromises the system's central regulatory function, impeding the dynamic balance between complementary cognitive codes.

The heuristic potential of the BTM becomes particularly evident in this configuration: each new clinical profile is read not as a direct product of lesion or dysfunction, but as an adaptive trajectory along the tensile axis.

However, empirical validation of the model requires a cumulative and multidisciplinary approach. The model relies on adaptive axial logic rather than rigid typologies. Its application may initially target documented subgroups (e.g., individuals with marked lateralization or proprioceptive instability) and evolve alongside accumulating clinical and neurofunctional data. Its open structure enables continuous refinement, in line with the increasing complexity of scientific evidence.

IMPAIRMENT OF THE PROPRIOCEPTIVE SYSTEM

Conscious proprioception and automatic kinesthesia

Proprioception — a core function of the sensorimotor system — is not fully operational at birth. It develops gradually through embodied experience, following a trajectory that is initially lateralized and later integrated through interhemispheric transfer into a unified and conscious perception of the self in action [24]. This developmental path parallels Bernstein's distinction between anticipatory coordination and retroactive adjustment in motor control, which is also applicable to proprioceptive maturation [3].

Within the BTM, we propose, for heuristic purposes, a distinction between two functional modes of the sensorimotor system:

- conscious proprioception is the reflective and intentional perception of the body in action, corresponding to the body image described by Gallagher [25] and associated with analytical, linguistic, and representational functions;
- automatic kinesthesia is a form of embodied, fluid, and non-verbalized action regulated by sub-threshold proprioceptive, vestibular, and somatic signals. This corresponds to Jeannerod's motor intentionality [26] and Bernstein's implicit dynamic models [3].

This distinction is not intended to replace computational frameworks such as predictive coding, but instead offers an operational perspective for describing cognitive tensions involved in the self-regulation of bodily experience. It is also essential to understanding the dynamic role of the DMN, which is preferentially active during states of bodily automation and supports the narrative and interhemispheric integration of the self.

In neurotypical individuals, these two modes alternate fluidly, the body acts automatically while the DMN prepares subsequent action sequences. In novel or complex situations, the right hemisphere guides action planning, once the movement is stabilized, the left hemisphere automatizes and consolidates the movement. This cycle ensures motor fluidity, postural coherence, and identity continuity.

In individuals with ASD, this alternation is often disrupted: transitions between control and automation are often incoherent or blocked, manifesting clinically as motor hypercontrol, stereotypies, clumsiness, or unmodulated sensorimotor regressions. Such patterns reflect unregulated

tension between misaligned hemispheres, leading to failures in voluntary planning and the emergence of repetitive, non-intentional behaviors.

Neurofunctional studies indicate that individuals with ASD (in the presence of interhemispheric disconnection) often compensate for instability with excessive reliance on visual feedback, at the expense of proprioceptive modulation [27, 28]. This results in postural-tonic alterations, disorganized movement, and repetitive behaviors, interpretable as bodily attempts to stabilize an unstable or fragmented self [14, 29].

Numerous studies now support the central role of proprioception in a wide range of motor and cognitive processes [30, 31]. It is involved in both anticipatory (feedforward) and retroactive (feedback) regulation of movement, and is essential for motor learning, spatial planning, and environmental adaptation [32, 33].

In addition to its motor functions, proprioception also contributes to spatial working memory by providing dynamic representations of the body and its environment [34, 35]. Impairments in this system affect muscle tone, posture, and movement fluidity, with significant effects on daily functioning [36–39].

Distortions in spatial estimation and trajectory prediction disrupt interaction with the environment, often leading individuals on the spectrum to engage in motor stereotypies, such as rocking or rhythmic movements, interpreted here as self-regulatory strategies aimed at re-establishing a minimal sense of bodily perceptual continuity [40].

Within the BTM, such behaviors are understood not as secondary symptoms but as central indicators of a systemic imbalance between conscious proprioception and automatic motor execution — a persistent tension between the poles of anticipation and action.

Poetic language as tensile synthesis: a semiotic analysis of the autistic body

Within the clinical framework of ASD, it is often observed that individuals present an uneven developmental profile, in which gross motor functions appear clumsy or unstable, while fine abilities, such as drawing, writing, or verbal composition, are remarkably well developed. This asynchrony, often dismissed as a functional paradox, can be reinterpreted through the lens of the BTM as the result of localized hemispheric compensation: the hyperfunctional left hemisphere attempts to counter proprioceptive instability by reinforcing symbolic-discrete structures capable of containing disorganized perceptual experience.

Proprioceptive deficiency manifests as a loss of axial alignment, hyporeactive posture, misalignment between intention and action, compensatory visual dependency, and an inability to adapt to new situations fluidly, which must be reconstructed each time, as if the body lacked a memory of experience. In these cases, sensory input fails to integrate into an embodied narrative, fragmenting instead into discontinuous episodes unanchored from the self.

Within this framework, expressive texts produced by individuals with ASD, whether graphic, verbal, or gestural, should be understood not merely as aesthetic exercises, but as attempts at symbolic stabilization. Highly detailed drawings, for instance, reflect an analytical compensatory strategy in response to a deficit in bodily anchoring; meticulous repetition of forms, strict segmentation of space, and focus on isolated elements all serve to reestablish perceptual control.

An emblematic example of proprioceptive and affective self-awareness in neurodivergent writing is Benjamin Giroux's poem "I Am Odd, I Am New" (2016)[1], composed when the author was ten years old.

The poem captures the embodied perception of difference and the oscillation between vulnerability and affirmation:

I am odd, I am new,
I wonder if you are too.
I hear voices in the air,
I see you don't, and that's not fair.
I feel like a boy in outer space,
I touch the stars and feel out of place.
I worry what others might think,
I cry when people just don't link.
I am odd, I am new,
I understand now that so are you.
I say I "feel like a castaway",
I dream of a better day.
I try to fit in, I hope that I do,
I am odd, I am new.

[1] National Autism Association [Internet]. Barrington (RI): National Autism Association; 2016 May 6. I'm odd, I'm new [Poem published online]. [cited 2025 Jan 14].
Available from: https://www.facebook.com/photo.php?fbid=10154112555864283&id=299524134282&set=a.41931544428
* Facebook (banned in Russia; owned by Meta Corporation, which is designated as extremist in the Russian Federation)

This text has been widely circulated as an authentic expression of autistic self-perception and proprioceptive dissonance, illustrating how internal bodily awareness (oddness, spatial dislocation, tactile imagery) becomes linguistic rhythm and poetic identity.

The poem's graphic layout, with the vertical alignment of the repeated "I am", visually evokes an ordering structure, functioning as a symbolic sensory axis functioning as a symbolic sensory axis that compensates for the absence of a proprioceptive one. A semiotic analysis of the text reveals sensory dysfunctions typical of ASD: "I hear voices in the air" expresses non-localized auditory hypersensitivity, lacking spatial anchorage; "I touch the stars and feel out of place" reflects a dissociation between tactile contact and proprioceptive feedback, where touching does not coincide with feeling grounded; "I feel like a boy in outer space" encapsulates a profound corporeal delocalization — a loss of narrative gravity and embodied weight.

The poem does not merely describe an emotional state but symbolically encodes a fragmented proprioceptive experience, rendering its sensory profile in metrical form. The symmetry of the phrases, the regularity of repetition, and the analytical segmentation of rhythm perform an ordering function, where the body cannot guarantee continuity, poetic form provides symbolic compensation.

In the BTM, such texts, whether poetic, graphic, or motoric, are interpreted as semiotic traces of adaptation: functional devices activated by the subject to cope with hemispheric asymmetry and loss of sensorimotor coherence. These are not merely expressive outputs, but clinically relevant data, capable of revealing deep dynamics of hemispheric polarization and the compensatory strategies employed.

Semiotic analysis of these texts makes it possible to identify cognitive configurations otherwise inaccessible through standard diagnostic tools. It offers a complementary interpretive resource grounded in an embodied reading of meaning. This approach strongly supports the inclusion of a semiotic perspective within clinical and neuropsychological contexts, underscoring the potential of sign theory to render intelligible the disorganized experiential world of autistic embodiment.

The axiality of the body

The poem analyzed in the previous section highlights a key element for the semiotic understanding of ASD: the absence of an internal bodily axis, that is, the lack of a stable perception of one's own spatial and identity-related positioning.

In the BTM, space is not understood as an objective structure, but as an active construction rooted in sensorimotor experience. The body does not simply occupy space; it generates it, by articulating referential axes, such as up/down, left/right, front/back; coordinates that are not innate but emerge through embodied interaction with the environment.

From the earliest months of life, the infant explores the world through early actions, such as head-lifting or declarative pointing, that imply bodily localization in relation to objects and others. These early acquisitions, which require precise integration of motor intentionality and proprioceptive feedback, can be interpreted, following Bernstein [3], as dynamic outcomes of the progressive interplay between anticipatory control and sensory retroaction. The pointing gesture, a precursor of symbolic communication [41], activates mirror neurons and reinforces the intersubjective dimension of the self [42].

In individuals with ASD, proprioceptive instability impairs the construction of personal space: postural disorganization, alterations in interpersonal distance regulation, gestural rigidity, and difficulties in intercorporeal coordination are frequently observed. Individuals may experience forms of bodily estrangement, such as the sensation of not inhabiting one's own body or lacking an "internal gravity" [43], which result in disorientation during interactions with the environment and with others [40].

As Merleau-Ponty [44] observed, space is constituted through the body: only a centered body can articulate intention, movement, and meaning. When this internal axis collapses, language itself loses its experiential foundation, becoming detached from action and lived experience.

From this perspective, proprioception is not merely a sensory system, but an embodied semiotic device: it is a condition of possibility for gesture, meaning, and the emergence of the self. In this light, the semiotic analysis of bodily texts, whether verbal, graphic, or behavioral, can meaningfully inform clinical practice, helping to identify the presence or absence of an internal axis and to interpret the symbolic strategies through which individuals attempt to reconstruct embodied centeredness.

TOWARD FUNCTIONAL SYNTHESIS: THE BIPOLAR TENSILE MODEL IN CLINICAL CONTEXT

In light of the conceptual, clinical, and neurofunctional evidence presented thus far, it is now possible to propose an interpretive synthesis. The goal is not

to close the theoretical discussion but rather to outline a possible direction, to reframe disparate elements — interhemispheric disconnection, proprioceptive alteration, and DMN dysfunction, within a unified framework capable of highlighting their dynamic interactions. In this sense, the BTM serves as a heuristic tool for understanding how, under conditions of functional disintegration, the brain can generate divergent compensatory strategies which, though adaptive, contribute to the emergence of the atypical profiles observed on the autism spectrum [45].

Regardless of the origin of commissural insufficiency, its effects depend on which hemisphere receives incomplete information. The contralateral hemisphere processes input unilaterally, according to its characteristic computational style, tends to compensate for the imbalance by enhancing local resources [7, 46]. While this mechanism is adaptive, it can foster the development of distinct cognitive and behavioral patterns in ASD [46, 47].

Research on high-risk infants shows that reduced interhemispheric connectivity is associated with increased reliance on local connections as early as the first year of life [48]. Such findings underscore the central role of cerebral plasticity in compensatory adaptation and help to explain the well-known heterogeneity observed across the spectrum.

In this context, proprioception emerges as a bridge between deep neural mechanisms and observable functional manifestations. More than a simple support for motor control, it is essential to intentional planning as well as cognitive and social competence [49]. Interhemispheric disconnection disrupts sensorimotor synchronization, thereby impairing the efficiency of the DMN — a network central to bodily self-integration.

To illustrate the heuristic validity of the BTM, three clinical cases from the literature are presented that consistently demonstrate a nexus between interhemispheric disconnection, proprioceptive alteration, and DMN dysfunction.

Hagemann [50] describes two children with ASD who exhibit pronounced proprioceptive deficits — poor awareness of the moving body, vestibular hyporesponsiveness, and disorganized gestures. Improvements following intensive sensorimotor training highlight the difficulty in transitioning from conscious proprioception to automatic fluidity.

Leisman et al. [51] report a case characterized by marked asymmetry of the corpus callosum and left-hemispheric dominance. The subject exhibits rich linguistic ability yet profoundly disembodied expression — a verbalization process unsupported by proprioceptive grounding, resulting in a disembodied sense of self.

Paquet et al. [39] examined 34 individuals with ASD, and found postural instability, poor spatial awareness, and uncertain lateralization. Functional asymmetry, confirmed by EEG and cognitive assessments, reflects impaired interhemispheric communication.

Together, these cases demonstrate how the interplay between interhemispheric disconnection, DMN dysfunction, and proprioceptive instability generates fragmented neurofunctional configurations that correspond to the tensile poles described in the model. Far from being merely correlative, this triadic configuration offers a coherent interpretive framework for differential analysis across the autism spectrum.

CONCLUSION

The BTM offers an alternative and integrative interpretation of ASD, grounded in the hypothesis that many clinical manifestations emerge from an unmediated functional tension between cognitive hemispheric specializations. Interhemispheric disconnection, dysfunction and proprioceptive dysregulation of the DMN are not viewed as isolated causes, but as interacting elements within a dynamic system governing self-regulation.

On an epistemological level, the model positions proprioception as a primary semiotic channel — crucial for the emergence of embodied consciousness and sensorimotor coherence. This perspective enables a shift beyond the conventional dichotomy between genetic explanations and phenomenological descriptions, drawing attention to the adaptive modes of atypical functioning.

From a diagnostic standpoint, the model promotes careful observation of subtle but significant bodily indicators; gesture quality, postural stability, motor fluidity, and coherence between intention and action. When integrated with neurofunctional tools, such signs may provide valuable insight into patterns of cognitive lateralization and their compensatory strategies.

Therapeutically, mapping an individual's tensile profile can guide more targeted interventions. In profiles marked by symbolic-verbal dominance, cognitive abilities may be grounded through proprioceptive stimulation and embodied narrative practices. Conversely, in profiles characterized by perceptual-sensorial dominance, symbolic elaboration of sensory experience may be supported.

A specific contribution of this work lies in its integration of a semiotic perspective: the analysis of verbal, graphic, or behavioral texts produced by individuals on the spectrum may reveal perceptual and tensile states that are otherwise unexpressed, uncovering adaptive strategies and meaning-making trajectories inaccessible to standard tests. This supports the inclusion of semiotic theory in clinical and neuropsychological contexts, filling interpretive gaps left by conventional frameworks.

Nonetheless, the model presents several limitations that must be acknowledged.

First, its nature is essentially theoretical and interpretive: it is not derived from original empirical data, and it does not currently rely on standardized assessment instruments. Second, the clinical cases discussed are illustrative rather than statistically representative, and should be interpreted accordingly. Third, the model does not attempt to claim predictive power or diagnostic classification, nor does it provide direct comparisons with other contemporary models of ASD — such as predictive coding frameworks, connectivist models, or cognitive-behavioral typologies. These comparisons lie beyond the scope of the present essay but remain essential for future validation.

Rather than proposing a definitive explanatory system, the BTM serves as a flexible heuristic framework, intended to generate new hypotheses and promote an embodied, context-sensitive understanding of autistic heterogeneity.

Its greatest strength lies in this adaptability: the axial structure of the model makes it possible to represent the spectrum's variability not as deviation from the norm, but as the outcome of differential hemispheric compensation trajectories. This perspective opens new avenues for the development of interpretive and rehabilitative protocols centered on corporeal and symbolic resources rather than deficit-based metrics.

Ultimately, the BTM serves as a theoretical and clinical framework for orientation, capable of embracing the complexity of autistic functioning and supporting therapeutic practices more attuned to the lived experience of the individual.

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Secondary Psychotic Syndromes Should Be Excluded before Assuming Idiopathic Digital “Folie à Trois”

Перед постановкой диагноза идиопатического виртуального folie à trois необходимо исключить вторичные психотические синдромы

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Letter to the editor

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Dear Editor, we were interested to read a recent article in your journal «Shared Psychotic Disorder in the Digital Age: A Case Series of Virtual “Folie à Trois”», dedicated to a case series of virtual *folie à trois*. The case series highlighted a novel manifestation of shared psychotic disorder in digital cohabitation, underscoring that psychological proximity, rather than physical closeness, may suffice for the transmission of delusional beliefs in the modern age [1]. The article was very interesting, but we have some questions to ask:

First, why did the author describe aripiprazole as a second-generation antipsychotic? Aripiprazole is widely accepted as a third-generation antipsychotic [2]. It is very important to be rigorous while classifying the drugs we use to treat our patients, in order to get a better theragnosis. Please allow me to remind you of a useful mnemonic for the most commonly used third-generation antipsychotics: ABC, for aripiprazole, brexpiprazole, and cariprazine [3].

Second, why did the author not introduce the World Health Organization’s International Classification of Diseases (ICD) codes for any of the three patients? Readers may easily assume that Case B (Recipient 1) and Case B (Recipient 2) suffered from shared psychoses. Induced delusional disorder, code F24, at ICD-10, or other specified primary psychotic disorder, code 6A2Y, at ICD-11, as the most recent nosology system do not have a specific code for these kinds of cases. But what about Case A (Inducer)? What was the diagnosis? Was it schizophrenia, code F20, at ICD-10, or code 6A20, at ICD-11? Or was it another psychosis? While the recipients may have schizophrenia, affective disorder, depression, dementia, or intellectual disability, the commonest diagnoses in the inducer are delusional disorders, schizophrenia and affective disorder [4].

Still, we have read cases of shared psychosis where the inducer had psychosis due to drug abuse [5, 6] or organic psychosis [7]. Again, it is obligatory to be specific while attributing labels to our patients to provide the most accurate diagnosis. Beware of secondary schizophrenia, pseudo-schizophrenia, and schizophrenia-like psychosis [8]!

Third, why did the author assume that all patients had a primary psychotic condition, and not a secondary psychotic condition, code F06, at ICD-10, or 6E61, at ICD-11? All the three patients should have been studied with, *exempli gratia*, brain magnetic resonance imaging to exclude encephalic anomaly, electroencephalogram to exclude signs of epilepsy, neuropsychological assessment to exclude intellectual impairment; lumbar puncture to exclude encephalitis; bloodwork to exclude hormonal, vitamin, infectious, auto-immune, and/or genetic causes; drug urinalysis to exclude cannabis, cocaine, amphetamine, ketamine, and/or phencyclidine misuse, *et cetera*. *Folie à trois* or schizophrenia can be imitated by many imitators that should be discarded before the clinician assumes the diagnosis of a primary/functional/idiopathic.

Remember: schizophrenia is one the greatest imitated syndromes of medicine [9].

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Response to the Letter to the Editor Titled «Secondary Psychotic Syndromes Should Be Excluded before Assuming Idiopathic Digital “Folie à Trois”»

Ответ на письмо в редакцию под названием «Перед постановкой диагноза идиопатического виртуального folie à trois необходимо исключить вторичные психотические синдромы»

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Authors' response

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We sincerely thank Prof. João Gama-Marques for thoughtful engagement [1] with our case series on digitally mediated shared psychotic disorder [2]. The opportunity to clarify methodological, diagnostic, and nosological aspects of our work is greatly appreciated. Our response below addresses the key concerns raised, while situating our interpretations within contemporary psychiatric literature.

On the classification of antipsychotic treatments

The correspondents note that aripiprazole is often described as a “third-generation antipsychotic” due to its partial dopamine D_2 agonism. We acknowledge this pharmacodynamic distinction. However, in many contemporary clinical contexts and guideline frameworks, aripiprazole continues to be grouped within the broader category of second-generation (atypical) antipsychotics when contrasted with first-generation agents [2]. Our use of terminology was therefore pragmatic. Importantly, this classification did not affect treatment rationale, clinical interpretation, or outcome reporting. The therapeutic response across cases was consistent with established evidence supporting dopamine-modulating agents in delusional and schizophrenia spectrum disorders [3, 4].

On ICD classification and diagnostic clarity

We agree that explicit diagnostic specifications enhance clarity. Shared psychotic disorder has historically occupied a complex nosological position. While Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition subsumed “shared psychotic disorder” under “other specified schizophrenia spectrum and other psychotic disorder”, the International Classification of Diseases 10th Revision (ICD-10) retains the entity of induced delusional disorder (F24), and ICD-11 continues to recognize related phenomena under schizophrenia spectrum conditions [5].

In our series, Case A most closely met criteria for a primary delusional disorder with persecutory themes rather than schizophrenia, given the absence of persistent negative symptoms, disorganization, or cognitive decline. Cases B and C demonstrated symptom emergence temporally linked to psychological dependence on Case A, with rapid partial remission following separation and treatment — features classically associated with induced psychosis [6]. This diagnostic reasoning aligns with prior systematic reviews showing that inducers most commonly have delusional disorder or schizophrenia spectrum conditions, while recipients exhibit suggestibility and psychological dependency [6, 7].

On exclusion of secondary psychotic syndromes

We fully concur that secondary causes must be excluded before attributing psychosis to a primary disorder. All three patients underwent comprehensive clinical evaluation, including metabolic screening, thyroid profiling, vitamin levels (with correction where indicated), substance use assessment, and neuroimaging where clinically warranted. No neurological signs, fluctuating consciousness, autonomic

instability, or systemic features suggestive of autoimmune or infectious encephalitis were present. Current guidelines emphasize a probability-guided diagnostic workup, reserving extensive investigations (e.g., lumbar puncture, neuronal antibody panels) for cases with red flags or atypical features [8]. In the absence of such indicators, our evaluation was consistent with accepted standards of care [8, 9].

On the conceptualization of "digital" shared psychosis

The correspondents question whether the diagnosis of idiopathic shared psychosis may be premature. We wish to clarify that our central claim was not that the disorder was idiopathic, but that the mechanism of delusional transmission occurred in the absence of physical proximity, mediated instead by sustained digital interaction. The possible intersections have been discussed in detail in our original paper. Shared psychosis has historically required prolonged interpersonal closeness; however, emerging literature in digital psychiatry demonstrates that immersive online environments can generate comparable emotional intensity, identity fusion, and reinforcement dynamics [10]. In this sense, our report extends, rather than replaces classical models of folie à deux by proposing that psychological proximity in the digital era may functionally substitute for geographical cohabitation.

On therapeutic separation and recovery

The improvement of recipients following temporary separation from the inducer is well documented in earlier and contemporary literature [6, 11]. In our cases, structured digital abstinence during the acute phase was associated with accelerated reduction in persecutory intensity in Cases B and C. While antipsychotic medication was administered in all three cases, differential trajectories of insight recovery support classical observations that recipients often demonstrate more rapid improvement once environmental reinforcement is interrupted [11].

In conclusion, we appreciate the authors' emphasis on rigorous differential diagnosis and nosological precision. Our intent was to contribute to the evolving understanding of how shared psychosis may manifest within digitally mediated social ecosystems. We hope this exchange stimulates further empirical research on the intersection between digital environments and psychotic phenomena.

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