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Genetic-Environmental Components Associated with the Etiology of Autism Spectrum Disorder

Prof. Lydia Castro Núñez[1], Manuel Ojea Rúa, PhD[2]
[1]Biology teacher at secondary school,
Student of Educational and Behavioural Sciences Doctoral Programme at the University of Vigo (Spain)
ORCID: https://orcid.org/0000-0002-0921-1846
[2]PhD in Psychology, Pedagogy of the Education and Behavioural Sciences Doctoral Programme at the University of Vigo (Spain)
ORCID: https://orcid.org/0000-0002-9787-2520

ABSTRACT

The conceptual evolution of autism spectrum disorder (ASD) from a propositional configuration is defined as a multilateral process of neurodevelopment, based on a particular process determined by the presence of pyramidal neurons, which show a dendritic increase of alterations in the system of neuronal connections, which form a regulatory network of pyramidal glutamatergic activity. The etiology is basically due to multiple possible genetic mutations or environmental processes which, in turn, may cause specific neuronal remodeling, determined by certain psycho-organic conditions, whose consequences are observed in the GABAergic cerebral connexional pathways.

The scope of this study is to verify the significance of factorial clustering that directly or indirectly affect the genetic mutation process as an explanatory basis for the etiology of autism spectrum disorder and, consequently, to be able to establish major empirical predictions about the presence of this disorder associated cluster.

A total of 116 participants with autism have collaborated in this study, elaborated from the *factorial dimensional reduction* of the independent variables, which have been factorially reduced to two factors: "Disease" and "GENETIC", as explanatory dimensions of the etiology of the autistic disorder formed by the variable "level" (levels 1-2-3) (American Psychiatric Association [APA], 2013) of the disorder. The study forms the analysis of groupings of belonging of the cases, according to the parametric statistical technique of *hierarchical clustering* through the *Ward* method, contrasted by means of an *ordinal regression* analysis of the *logit* link in order to elaborate the grouping of cases according to their particularities, which are corroborated by an ordinal regression analysis according to the *logit* calculation for the basic conceptual variable that configures the current neuropsychological development of autism, in relation to the capacity of elaboration of neural networks or nodes during information processing, which has been operationalized with the name of "nodes". Finally, comparative *t-studies* of the findings in both factors in relation to the variables sex and age of the participants were carried out.

The results concluded with the configuration of three differential clusters, which have been corroborated by a *one-factor ANOVA* analysis, which has indicated significant critical levels for the two factors (sig: .00). The contrasts of the *ordinal regression analysis* corroborated the goodness of fit of the factors as explanatory components of the etiology of the disorder (sig: .00), which have been duly corroborated by the ordinal regression analysis for these same etiological factors and the consequent statistical process of neural networks by means of the *multilayer perceptron* procedure. Likewise, no significant differential comparative *t* levels have been observed in the predictive results referring to the levels of the explanatory variance of the etiology of the diagnosis of autism as a function of the variables sex and age.

Key words: autism spectrum disorder, autism etiology, autism diagnosis, neuronal nodes, genetic, neuronal remodeling

INTRODUCTION

From a conceptual perspective, the diagnostic group of ASD is defined as a set of specific multivariate global neurodevelopmental particularities, with a wide prevalence, which may affect 1/54 persons at birth (Centers for Disease Control and Prevention [CDC], 2012). The current international classification of the American Psychiatric Association [APA] (2013) groups the symptoms of the disorder around developmental-behavioral components, which makes up two basic groups: 1) deficits in the area of social skills and social communication concurrent with linguistic communication, that may or may not be impaired, and 2) the presence of highly restrictive hyper sensory behaviors and the presence of stereotyped behaviors in greater or lesser intensity. However, the scientific evolution of the disorder has shown that many cases were, on the one hand, were left aside of the diagnosis because the developmental-behavioral components were not present highly enough during the diagnostic observation. However, the compatible symptoms start to appear lately due to a poor executive brain functioning; or, on the contrary, they could be diagnosed within the disorder group due to the evident observation of behavioral symptomatology that, subsequently, evolved favorably, due to the adjusted cognitive systemic functioning, leaving that individual aside of the initial diagnostic conclusion. From this systemic perspective, therefore, the evolutionary-behavioral symptomatic groups have to be complemented with the sensory-perceptual-cognitive components that facilitate cognitive performance. This configures the neuropsychological processing of information, from the initial phase of stimulus input (collected by the sensory-perceptual memory), to the comprehensive development of this stimulus, through the working memory. This kind of memory includes the development of connexional relationships of the incoming information with the previously stored information with semantic content and the corresponding conceptual categorization, in order to proceed to facilitate the access of the new information with semantic content to the long-term memory. Information will be then recovered by the same mechanisms by which it was stored through the working memory. The whole of this executive relational system requires a synaptic connectional functioning that allows the information to be fluently communicated, otherwise, any severe limitation or break in the interconnection process will simply cause information to be lost or to remain mechanically inaccessible without the possibility to create new pathways of knowledge.

Synaptic pathways can be affected by both organic and environmental factors. It has been already published that mutations in some genes involved in synaptic processes are related to autism development (Giannandrea et al., 2010; Weiss, 2009). Autism symptomatology can be due to point mutations in a single gene, but also organic and environmental factors can produce a specific neuronal remodeling that also affects the gene expression, such as alterations during the pre-neonatal process (Croen et al., 2011; Patterson, 2009; Ploeger et al., 2010), as well as the presence of specific diseases that may occur during evolutionary development, for instance blood infections, encephalitis, meningitis or the recurrent presence of seizures, especially of epileptic type (Courchesne et al., 2011), which can generate cognitive sequelae that specifically affect the GABergic pathway leading to a progressive confluence with the symptomatic group of ASD (Chao et al., 2010; Pizzarelli & Cherubini, 2011). Likewise, a good GABA functioning can cause initially compatible symptoms to be overcome autonomously by the individual during the social interactive development, which should not be understood as a cure of the symptoms, but as a clear error of the initial diagnosis.

Precisely, due to the limitations or malfunctioning of the GABA pathways (Hadjikhani et al., 2015; Lisman & Idiart, 1995) the learning processes of people belonging to the ASD diagnosis-group can be carried out relatively well within mechanical contexts, which do not require the elaboration of higher cognitive processes. Within this context, social skills, social communication, stereotyped or restrictive behaviors can be of high intensity or be very limited,

to the point that, in some level-1 cases, they could be practically unobservable and yet be concurrent with the disorder group.

And, precisely for this reason, the diagnosis of ASD is almost always comorbidly associated with other disorders related to GABA pathways, as it has been already shown by the presence of attention deficits and hyperactivity (Nardou et al., 2011), anxiety or medium depressive processes and, above all, the recurrent presence of epilepsy (Dzhala et al., 2005) or, especially, the presence of connotations compatible with schizotypal traits (Hurst, Nelson-Gray, Mitchell & Kwapil, 2007; Russell-Smith, Bayliss & Maybey, 2013). This related comorbidity is shaping into a highly specific feature. It is very common that, the greater the disruption of the GABA pathway is, the bigger is the effect on the whole functional neurological system of connectivity.

It has been already shown that, the systemic functionality of brain connectivity plays a major explanatory component of the variance of ASD diagnosis, precisely due to the interconnectivity of brain areas, which are mutually affected by mutational alterations, although these have a more local affectation. Lawrence et al. (2022), called this process brain prominence network, which plays a fundamental role in the connectivity between the areas of the brain itself, in relation to the connectionist pathways that affect the initial perceptual-attentional process characterized by an inductive lack of semantic processing compared to the group of neurotypical pairs that could perform these more fluid and immediate semantic-perceptual associations leading to the understanding of the incoming target-stimulus.

The basic neuropsychological assumptions of information processing initiate their systemic function with the input of the stimulated sensory processing (Horder et al., 2014; Robertson & Simmons, 2013), which, in ASD diagnosed people has initially a global attribution, but its content has a very slight semantic quality due to the lack of immediate execution of relations with other related contents. This is going to influence the whole subsequent cognitive executive process that needs to elaborate the working memory, so it configures an atypical processing mode, characterized by a second attribution too localistic, which is going to involve a significant effort of the working memory to achieve the conceptual categorization of the content (Chamak et al., 2008; Roberston & Simmons, 2013; Robertson & Baron-Cohen, 2017). The process of conceptual categorization is completely necessary due to the limited attribution of the permanent memory, which cannot hold the amount of stimuli perceived daily. This requires a categorial process based on the similarities and differences of stimuli, in order to build a specific space in the long-term memory related to comprehensive semantic levels that will now be retrieved when the context demands it. This process will be of greater or lesser level of limitation depending on the distribution of the different levels of the disorder continuum (Colvert et al., 2015; Neufled et al., 2021), although the differences between the current levels are not as strict as indicated by the current international classification. It depends more on the severity of the brain synaptic disturbance, which may result in differences belonging to more or less classification levels than the ones currently considered. Amina et al. (2021), Ariza et al. (2018), DeFelipe et al. (2013), and Hashemi et al. (2017) have identified the interneurons that influence the synaptic connective process of the GABAergic pathway that affects the executive-cognitive symptomatic group of ASD, which have been located as neocortical inhibitory neurons of very different subtypes. This forms a wide network that regulates the entire local glutamatergic-pyramidal projective process, producing a modulating process that affects and facilitates the different synaptic pathways, connecting the information in a fluid and automatic way.

With the new contributions to the conceptualization of the disorder (Dufour et al., 2023), it is clear that the finding of differences can be so great that the limitation to only three specific levels of ASD seems to be an increasingly distant option from the new experimental findings that form more appropriate multilevel connotations depending on the multiple combinations

and intensities between the multiple neocortical neuronal subtypes, which, in turn, give rise to very different GABergic interneuronal patterns.

Preliminary studies (Arenalla et al., 2021; Ojea, 2020) confirm that it seems that a clear finding of scientific research that the etiology of ASD is supported by genetic consideration and concomitances that may affect the genetic consideration, affecting the connexional pathways, which, impact on the symptomatic groups currently collected by the APA (2013, *ob. cit.*), but not the only ones, which have been supported by multiple epidemiological and genomic analyses to justify the etiological contribution of the disorder. This justificatory expression, as stated by Tick et al. (2016), Lyall et al. (2014), Willsey et al. (2013) and Kim et al. (2021) not only depends on the presence of a specific karyotype, but also on an organic-environmental condition, produced already from the very process of pregnancy of the fetus, which can produce a neuronal remodeling that also affects the interneuronal process, giving rise to the diagnostic symptomatic group of the disorder, characterized by the behavioral evolutionary criterion items, socio-communicative and behavioral, sensitive and stereotyped, but also by the sensory-perceptual-cognitive criterion attributes, especially those components related to the creation of neural nodes or cognitive relationships during the process of knowledge creation and, consequently, favoring the global psycho-social development.

With these updated basic conceptual indicators about ASD, the aim of this study is to provide a significantly predictive basis in relation to the etiology of the diagnostic group of autism spectrum disorder empirically contrasted.

METHODS

Research Design

The design is based on an empirical study, based on the data obtained through structured interviews regarding to the questions of *ad hoc* questionnaire, which is made up of quantitative and qualitative variables, which were subsequently analyzed by means of statistical psychometric techniques duly adjusted to the objective of the study.

Participants

A total of 116 cases with an official diagnosis of ASD, corresponding to the three levels of the disorder (APA, 2013 ob. cit.), differentiated by sex and five age intervals, participated in the study (see Table I).

Table I: Participants.

Sex			Age					Total
			2.1-5 y-o	5.1-8 y-o	8.1-12 y-o	12.1-15 y-o	>15.1 y-o	
Guys	Level	Level 1	24	19	6	8	1	58
		Level 2	8	3	6	3	0	20
		Level 3	4	1	3	0	1	9
	Total		36	23	15	11	2	87
Girls	Level	Level 1	5	4	6	2	3	20
		Level 2	3	2	1	1	2	9
	Total		8	6	7	3	5	29
	TOTAL		44	29	22	14	7	116

As can be seen, a total of 87 male participants took part in the sample, of whom 58 were level 1, 20 level 2 and 9 level 3. For their part, 29 female participants took part, of whom 20 were level 1, 9 level 2 and 0 level 3. By age group, 44 participants belonged to the interval

between 2.1 and 5 years of age, 29 to the period between 6.1 and 8 years of age, 22 between 8.1 and 12 years, 14 between 12.1 and 15 years and 7 participants over 15.1 years of age.

Variables

The variables operationalized for the study are made up of a dependent variable (DV), which relates to the level of diagnosis of the disorder (1-2-3), five independent variables (IV) that explain the variance of the etiology found in the DV through a statistical classification process, a conceptual variable that explains the multilateral conceptual model of ASD, which is, in its case, determined by the goodness of fit of the two study factors and two comparative variables for the analysis of the study factors:

- DV is shaped by the variable "level", categorized by levels 1-2-3, according to the evidence of the current APA classification (2013, ob. cit.).
- The IVs operationalized for predictive analysis are as follows:
  - "comorbidity", which refers to comorbid conditions currently associated with the disorder, of which the following values have been established: 0 (no deficit), 1 (cognitive deficit), 2 (attention deficit and hyperactivity), 3 (anxiety, severe distress, mild depression), 4 (schizotypal components or features) and 5 (seizure processes or epilepsy).
  - "The values are: 0 (no deficit), 1 (premature), 2 (cesarean section), 3 (forceps), 4 (suction) or urgently induced processes, and 5 (several previous components combined).
  - "current diseases", relating to the presence of a clinical history of potentially influential diseases, whose values are: 0 (no deficit), 1 (encephalitis), 2 (meningitis), 3 (infections), especially of the blood type, 4 (seizures), especially in relation to epileptic components, and 5 (several previous elements combined).
  - "genes", in relation to the presence of an expressed genetic karyotype: 0 (no reference gene), 1 (gene 15q11-q13), 2 (gene 17q11-q22), 3 (gene 7q31-q33), 5 (gene SHANK2,3) AND 5 (several genes combined).
  - "family", in reference to the karyotypic history considered incident in first, second, third or other family generations of the case: 0 (no deficit), 1 (anxiety, severe distress), 2 (schizophrenia), 3 (severe depression), 4 (relevant organic diseases), and 5 (various combined).
- The basic conceptual explanatory variable of the neuropsychological model of the disorder:
  - "nodes", which refers to the capacity to elaborate neurocerebral relations with the processed information, with the following values: 0 (no deficit), 1 (no deficit), 1 (very slight deficit), 2 (slight deficit), and 3 (medium deficit), 4 (high deficit) and 6 (very severe deficit).
- The comparative variables for the conclusions of the analysis are:
  - "sex", in relation to the values: 0 (male) and 1(female).
  - "age", which relates to five age intervals: 0 (2.5-5 years), 1 (5.1-8 years), 2 (8.1-12 years), 3 (12.1-15 years) and 4 (>15.1 years of age).

Procedure

Once the values corresponding to all the variables were obtained, the VI were reduced to two weighted dimensional factors, using the factor-dimensional reduction procedure: I) "DISEASE", which includes the variables "comorbidity" and "pre-neonatal" and "previous diseases"; and a second factor II) "GENETIC", which includes the variable related to the presence of a certain type of gene "genes" and the family karyotype: "family".

With the factorization of the process, we proceeded to the analysis of the statistical data predictive of the etiology of the disorder. Subsequently, we proceeded to determine the level of explanatory variance between the dimensional factors and the variable "nodes", in order to corroborate the importance, if applicable, of the etiological process.

Finally, we analyzed the possible comparative differences in the process according to the variables "sex" and "age" for the study as a whole.

Data Analysis

The data analysis is made up of several steps of the study: 1) a factorial dimensional reduction analysis for the calculation of the two factors that include the five variables considered predictors of the etiology of the disorder; 2) the cluster classification analysis to agglomerate the cases according to the similarities and differences in relation to the explanatory factors of the etiology of autism, which has been complemented with one-factor ANOVA levels for the classified data, 3) the contrastation of the above data by ordinal logistic regression analysis, through the logit link for the regression setup of the dimensional analysis of the two factors in relation to the diagnostic level: "level" and the fundamental neuropsychological conceptual variable: "nodes". Finally, a comparative *t-analysis* is performed for the two dimensional factors as a function of the variables "sex" and "age" of the participants.

RESULTS

The frequencies grouped in relation to the study variables making possible to delimit the effective conclusions if the objective of the study had been empirically confirmed by the regression contrast of the clusters formed, as the hypothesis of the study, in the sense that these variables related to the genetic mutation processes are the main explanatory components of the etiology of ASD (see Table II).

Table II: Frequencies grouped according to the values of the operationalized variables.

Comorbidity	No deficit	Cognitive deficit	Attention deficit and hyperactivity	Anxiety, anguish, mild depression	Schizotypal	Epilepsy
1 level	13	10	23	21	3	8
2 level	1	5	4	8	3	6
3 level	2	1	2	3	0	1

Pre-neonatal	No deficit	Premature	Cesarean	Forceps	Suction	Various
1 level	35	3	13	1	9	16
2 level	12	0	5	0	1	10
3 level	5	0	1	1	0	2

Previous illnesses	No deficit	Encephalitis	Meningitis	Infections	Convulsions	Various
1 level	32	9	9	9	1	18
2 level	13	6	1	3	1	4
3 level	4	2	1	2	0	0

Gene type	No deficit	15q11-q13	17q11-q22	7q31-q33	SHANK2,3	Various
1 level	51	13	1	1	3	9
2 level	13	12	0	2	0	2
3 level	3	5	0	0	0	1

Associated family disease	No deficit	Anxiety, anguish	Schizophrenia	Depression	Organic	Various
1 level	57	3	8	3	5	2
2 level	16	3	2	3	4	1
3 level	7	0	1	0	0	1

From the analysis of the frequencies observed in the individual variables as a function of the cases or "level" variable, according to the values previously assigned, we immediately proceeded to generate the two dimensions: "DISEASE" and "GENETIC", through dimensional reduction by factors.

And it is precisely these two factors that have configured the formation of the groupings or clusters by similarities or differences between the 116 cases, depending on the process of calculating the classification of clusters, through the hierarchical cluster classification procedure.

To carry out this analysis, Ward's method has been chosen, in order to corroborate the explanatory variance of the DV by the clusters formed, following the statistical procedure of Euclidean distance, with the transformation measure of the scale to the range 0-1, so that the closer to 1 the clusters formed from the clustering process will be more distant, while the closer to 0 the level of proximity between them will be closer in similarity, so that the clustered cases with greater similarities will be contrasted in the process of analysis of the factors considered to predict with greater guarantees of empirical criteria the diagnostic group of ASD.

According to the distance (1)-proximity (0) procedure, clusters of clusters are formed by similarities between cases, separated, in turn, from other clusters by their differences, which will make it possible to establish a deductive predictive system of the etiology of a given case in accordance with the basic principles of the factors of the analysis.

Thus, for example, in the cluster matrix, case 1 is very likely to form a cluster group with case 2 (.07), with case 3 (.16), with case 20 (.04) and so on, due to their proximity, while it will have no chance of forming the same cluster with case 38 (.55), case 60 (.78), case 61 (.62) or case 107 (.72) due to their remoteness or proximity to 1.

This history already allows us to make empirical predictions about the situation of a given case depending on the stage at which it entered the cluster, as indicated by its clustering history. Thus, e.g., case 68 associated with cluster 1 and case 88 associated with cluster 2 in the first agglomeration stage, could be joined by case 65 in the next conglomeration stage, so that a prediction of belonging to a certain group can be established according to the proximity or remoteness to the study factors of the analysis, which, in this case, is the prediction of the OER diagnostic group.

The output obtained from the procedure of classifying hierarchical clusters, linked to the Ward method, in the 0-1 rank system, which has been used for the progressive formation of clusters, as an explanatory method of the variance of the factors generated, can be seen in the dendogram shown in Figure I.

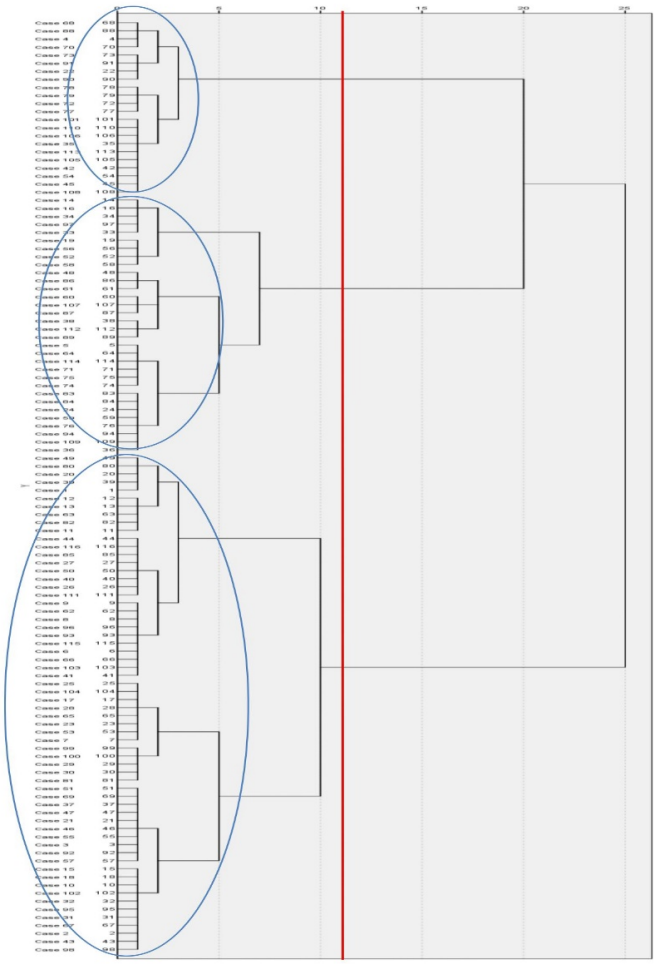

Figure I: Dendogram.

Therefore, in order to respond to the premises of proximity and remoteness, i.e. that there are groups with a high level of similarity, which, in turn, are relatively distant from the other groups of clusters, it has been decided to delimit the cut-off point in 12.3 for the formation of the groupings of cases, which have given rise to the constitution of three clearly differential clusters and, in turn, each of them implies a great similarity between them, giving rise, then, to the three clusters, which are indicated according to the OER level, which has formed the diagnostic variable of grouping "level", associated with each of the clusters of membership:

1. *CLUSTER 1:*

1.1. level 1: {1,2,3,6,8,9,10,11,12,13,15,17,18,20,21,26,27,31,37,39,40,41,43,44,46,47,50,51,53,55,57,63,65,67,69,82,85,93,95,96,98,102,111}.

1.2.level 2: {7,23,29,30,32,49,62,66,80,81,92,99,103}.

1.3.level 3: {28,100,104,115,116}.

2. *CLUSTER 2:*

2.1.level 1: {4,42,45,54,54,68,70,73,77,78,79,91,105,108,113}.

2.2.level 2 {22,35,72,88,90,101,106}.

2.3.level **3** {33,34,36,110}.

3. *CLUSTER 3:*

3.1.level 1: {5,14,16,19,24,52,58,61,83,83,86,87,89,94,112,114}.

3.2.level 2: {33,34,36,59,60,64,71,97,107}.

3.3.level 3: {84}.

Indeed, this formation or grouping of these clusters is empirically contrasted with the comparative analysis of a factor, which reflects the goodness of fit of the number of clusters considered by the cut-off and formed by the single determinant solution for the number of clusters considered by their membership according to the measurement cut-off (12.2) between three clusters of membership of the cases existing between the general intervals 0-25 of the hierarchical cluster classification analysis (see Table III).

Table III: One-factor comparative ANOVA.

		Sum of squares	df	Root mean square	F	Sig.
DISEASE	Between groups	61.70	2	30.85	65.40	.00
	Within groups	53.29	113	.47		
	Total	115.00	115			
GENETIC	Between groups	89.40	2	44.70	197.32	.00
	Within groups	25.59	113	.22		
	Total	115.00	115			

As can be seen, the critical prevalence is highly significant for the two factors: "DISEASE" (sig: .00, F: 65.40) and "GENETIC" (sig: .00, F: 197.32), so there are statistically significant differences between both factors in relation to the variability found in the "level" diagnostic group.

Well, with the statistical consideration of the three clusters, in fact, the old dialog box graph by the simple dispersion method, establishing marks according to the Ward method, which has been selected for the classification analysis of the study, allows obtaining the following distribution of clusters (see Figure II).

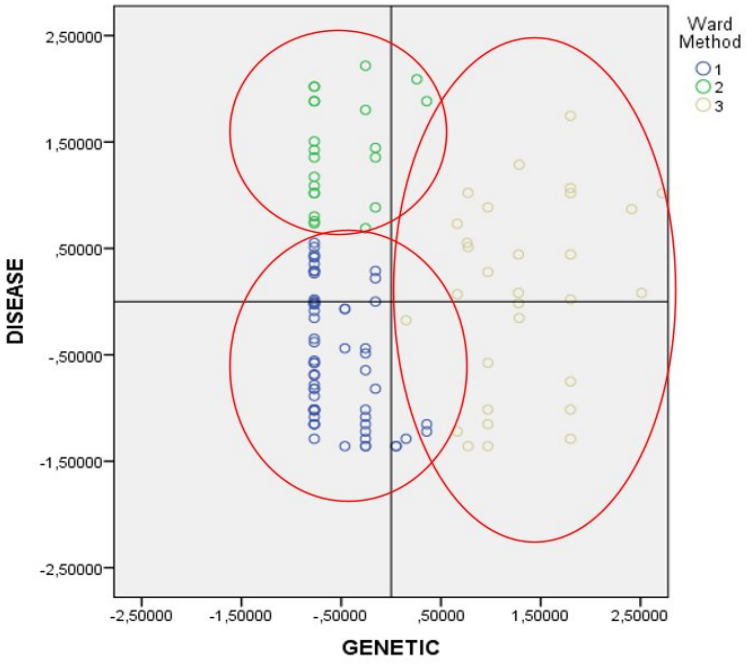

Figure II: Graphical dispersion of the three clusters.

As it can be seen, the graphical representation of the clusters makes highly defined agglomerations with a high level of precision, so that cluster 1 indicated with blue color groups the cases located within the "DESIRE" group, while cluster 2 indicated with green color groups

the cases explained by the "DISEASE" factor, while cluster 3 indicated with yellow color groups together most of the cases explained by the "GENETIC" factor, converging with the "DESIRE" factor in some cases of the study, which is logical, due to the interrelationships existing between both dimensions during a study of these characteristics.

Indeed, if a customized table is made for the two factors analyzed by the Ward method, it is possible to corroborate the arithmetic means found for the three clusters, in relation to the two factors of the analysis (see Table IV).

Table IV: Group arithmetic mean for the two study factors.

		DISEASE	GENETIC
		μ	μ
Ward Method	1	-.53	-.55
	2	1.41	-.51
	3	.06	1.42

The critical level found (sig: .00) shows, definitively, that the regression analysis for the two factors of the study is highly significant to establish an adjusted prediction and explanation regarding the percentage of variance that determines the type or group of diagnosis, represented by the variable "level" in this study.

These data have been highly corroborated by pseudo R-squared analysis, using the logit link function, which can be seen in Table V.

Table V: Pseudo R-squared.

Cox & Snell	.794
Nagelkerke	.989
McFadden	.978

In other words, the Pseudo R-squared statistics indicating the current of explanatory determination of the ordinal regression analysis are appreciably high with scores very close to statistical adequacy (.1), thus in the Nagelkerke test a score very close to 1 (.98) is found, as well as in the McFadden test (.97), so that the squared adjustment of the analysis can be considered highly explanatory for the predictive hypotheses of departure to analyze the main etiology of autistic disorder in this empirical study.

The ordinal regression analysis for the two factors in relation to the conceptual neuropsychological variable: "nodes" also indicates significant levels of incidence as observed in the model fit information, in which the intercept of the logarithm of verisimilitude-2 indicates a value of 199.30, which is equivalent to the final chi-square, which implies a significant critical level of explanation of both factorial dimensions on the variable "nodes" (sig: .00, for 80 degrees of freedom).

And, from the explanatory analysis of the factor variables, we conclude a significant critical level in relation to the explanatory variance of the scores found in the conceptual explanatory variable "nodes", which is corroborated in a particularly decisive way in the goodness-of-fit, in which the chi-square of the *Pearson* measure is 42.82 (being 1.00 its significance level, for a total of 217 degrees of freedom), which, contrary to other interpretations of the critical level, in this case implies an optimal value of explanation, as is the case with the measure of the *Deviance* test (chi-square: 35.16) with an optimal level of sig: 1.00 for 217 degrees of freedom.

The associated goodness-of-fit allows us to find maximum positive ideal scores to explain the explanatory regression of the two factors "DESIRE" and "GENETIC" in relation to the data found in the variable "nodes".

These considerations are logical if we consider that the brain works in a systematic way, organizing information through multiple neural complexes that shape the understanding of meanings, their conceptual categorization, the mnesic process and their retrieval, as can be seen in Figure III, taking the factorial dimensions themselves in relation to the variable "nodes", found through the calculation of neural networks by means of the *multilayer perceptron* test.

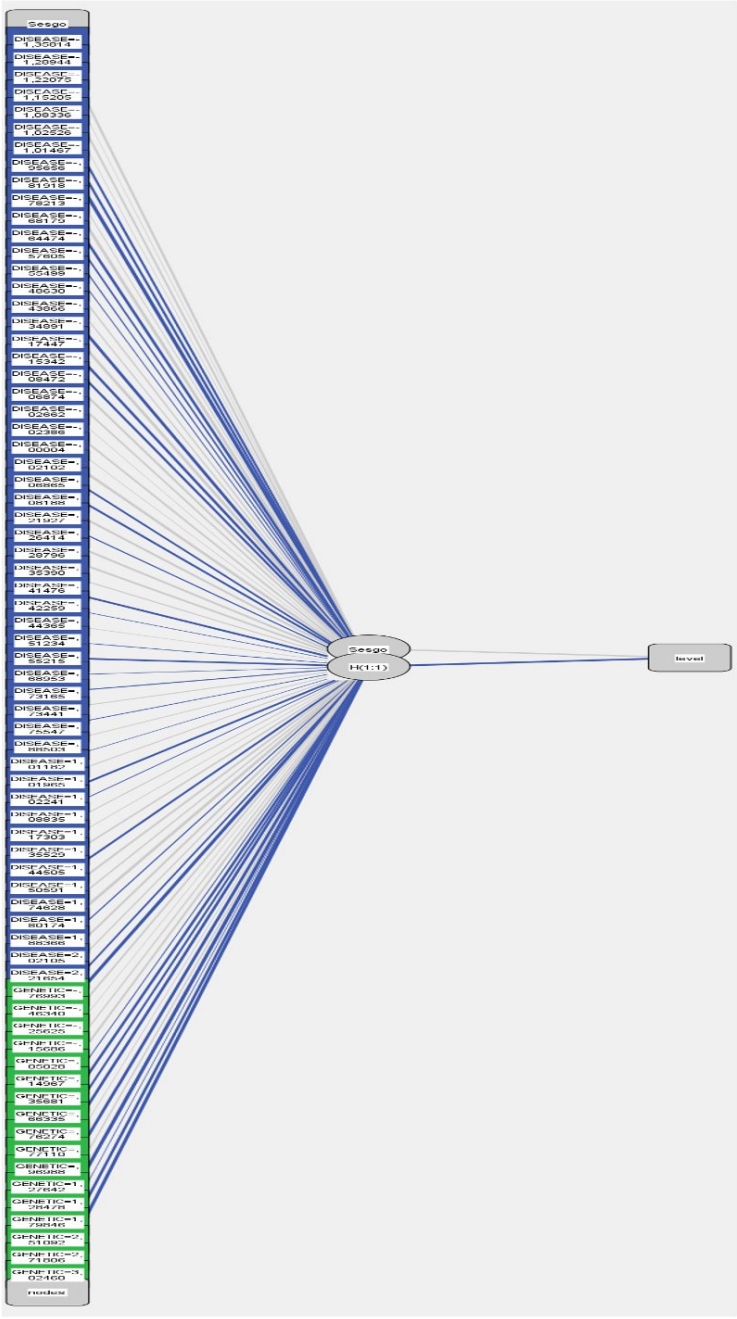

Figure III: Multilayer neural networks.

In fact, the variable "nodes" is influenced by the two factorial dimensions, being "DISEASE", the one indicated in blue color and "GENETIC" with green color, which continuously interact with the variable "nodes" to configure the diagnostic process "level", forming a highly related set of neural networks that give rise to human cognitive processing.

Finally, these statistical findings that allow significant prediction of the principal components of the causes of the disorder are independent of the type of sex or age intervals collected in the database.

Thus, the comparative *t-analysis* for sex* DISEASE presents a critical level that is not differentially significant (sig: .37), for an F: 1.09, just as no differences were observed in the classification and regression analyses for sex*GENETIC (sig: .35, F: 1.10).

Likewise, the comparative analysis for age in relation to the study factors, the data also do not allow us to deduce differences in the analysis according to the age intervals, thus for age*DISEASE we found a non-significant intergroup critical level (sig: .83, F: .36); while, for the comparative measure age*GENETIC, the intergroup level does not offer differential measures either (sig: .51, F: .81).

Hence, it can be concluded that the classification and regression analyses do not depend on the type of sex or age range in the predictive findings in relation to the three levels of ASD of the participants in the study sample.

CONCLUSION

Indeed, it is confirmed that the processes related to the genetic mutation affecting directly or indirectly the synaptic-GABAergic pathways, constitute an explanatory variance of significant critical level, in relation to the diagnostic level of the disorder. The cases are grouped according to these basic hypotheses, which form the membership clusters, aiming to predict the situation of a given case according to the basic starting hypotheses. In this sense, the cases clustered around the 15q11-q13 gene type of diagnostic levels 1-2-3 are up to a total of 30 cases (24.86% of the total cases analyzed) and the presence of several clustered genes is present in 12 cases, representing 7.75% of the total. Likewise, the frequency of diseases that can present secondary effects of significant neuronal remodeling is presented in the case of encephalitis in a total of 17 cases of the three diagnostic levels (14.65%), with blood type infections especially in 14 cases (12.06%), with meningitis in 11 cases (9.48%) and with several conditions produced that can cause mutant effects in 22 cases (18.96%). Strikingly, the agglomeration of the "GENETIC" factor, which is related to the presence of a particular family karyotype, so that in 11 cases there is a family history related to the process of schizophrenia (9.48%) and processes related to groups of severe anxiety and depression in 12 cases (10.34%).

Likewise, the combination of the groupings is also related to the frequencies found in the pre-neonatal processes, especially related to the use of cesarean section, which is combined in 19 cases (16.38%) or the existence of several complications during the gestational and neonatal process, which occurs in 28 cases (24.13%). A specific symptomatic group is thus configured in which the connectivity process is affected. Significant empirical data can explain the variance corresponding to the etiology of autism. It is usual, therefore, that the presence of the symptomatic group is not presented alone but in comorbidity with other pathologies related to connectivity processes, such as attention deficit and hyperactivity, which occurs in 29 cases (25%), processes related to connotations of anxiety, anguish or mild depression in 29 cases (25%) or with cognitive deficit in 16 cases (13.79%). The presence of recurrent convulsive processes of epileptic type, was also present in 15 cases (12.93%).

From this perspective, it can be concluded that the factors considered for the study are highly significant of the etiology of the disorder, so that clinical predictions can be established, in relation to the possible presence of the diagnosis, so that they should be considered as criteria for analysis and exhaustive observation during the process of making the diagnosis, in order to delimit the scope of the synaptic limitations that affect the whole diagnostic group system, apart from the evolutionary-behavioral manifestations that also require necessary analysis.

DISCUSSION

In this study, the 15q11-q13 gene is most frequently associated with the diagnosis of autism and, indeed, this gene is associated with the coding of elements directly involved in brain synaptic regulation (Pramanik et al., 2018). Such affectation is relatively involved in Sartori cells (Schlicher et al., 2017), which may partly explain the higher prevalence existing among children with ASD in relation to females, however, it does not seem sufficient evidence to determine such a high level of proportion between both sexes and, although the prevalence between the sexes may be higher in favor of boys, no significant existing differences are demonstrated in relation to the sex type of the participants of our study, which is a relevant issue for the immediate future of scientific research.

In this same sense, the significant association of the presence of this type of genetic mutations especially affects social and behavioral processes. It can do so within a variety as large as genetic variations may occur, so reducing the diagnosis exclusively to the observation of the absence of social skills, deficits in social communication and the presence of specific behaviors of their own, constitutes a major risk that can lead to serious errors in the initial diagnosis of the disorder.

For this reason, scientific studies are currently emerging that corroborate the use of diagnostic scales that analyze executive dimensions weighted with developmental-behavioral criteria. Indeed, the integrated perceptual-cognitive scale of autism (Ojea, 2022), which analyzes the sensory-perceptual and cognitive-executive dimensions, places special emphasis on the type of development of neural nodes or relationships between informative contents, both between the incoming stimulus in relation to the information existing in the semantic memory, and between the semantic contents themselves existing in the permanent memory and the form of relational access to them.

The accuracy of the specific diagnosis is a crucial issue because it will determine the type of specific support needed to facilitate the evolution of their development, otherwise, completely wrong methods could be used that not only prevent a good development, but also hinder it and make it regress. In fact, within the inclusive didactic-methodological processes (Ilan et al., 2023), which have to program the development of cognitive, social, adaptive, and behavioral skills (Little, 2017; Zachor, Ben-Itzchak, Rabinovich & Lahat, 2007; Zachor & Ben-Itzchak, 2010) will have no effect if the designed processes of cognitive mediation is not carried out, in relation to the learning of mediated relationships between the learning-goal processes themselves, both intrinsically with the content, and, if necessary externally to it. The main goal would be to set up links and interrelationships between contents in which, people with ASD show important limitations to the extent of constituting the fundamental characteristic of their particular way of cognitive processing and, consequently, of the final process of their specific diagnosis (Talbott, Estes, Zierhut, Dawson & Rogers, 2016).

Therefore, it is essential to gain insight into these processes, in order, firstly, to complement the diagnostic processes to avoid classification errors and, secondly, to promote the implementation of programs designed through a process of continuous networking between cognitive content, to facilitate the formation of neural nexuses in which these people are deficient. The creation of networks must be configured as nexuses duly learned as one more content, but trying to strengthen the levels of progressive autonomy. In this way, ASD patients would become increasingly autonomous providing the learning process with semantic significance and globality for themselves. Thus, the mediation process has to start with a high intensity and be reduced to the extent that the acquired skills allow it.

LIMITATIONS OF THE STUDY

Logically, when working in the field of a specific determined need, as is the case of the study of people with a diagnosis of ASD, the length of the population obtained can always be considered a limitation for the general conclusions. However, these limitations must be overcome by the consideration of all the contrasted empirical contributions, which together with other scientific studies also deductive on these same issues, must complement their contributions, with the ultimate aim of adding up all the conclusions derived and duly corroborated, whose ultimate goal is to converge on those common aspects that favor the improvement of the quality of the diagnosis of people with ASD, as well as, consequently, of their quality of life.

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DATA AVAILABILITY STATEMENT

Data has been found and evaluated between the years 2021-2024. No potential conflict of interest was reported by the authors.

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