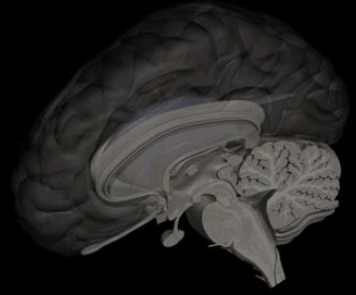
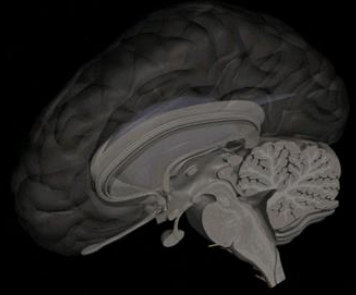


TRASTORNOS DEL ESPECTRO AUTISTA

DR. PATRICIO GUERRA
NEURÓLOGO INFANTIL Y ADOLESCENTES
MAGÍSTER NEUROCIENCIAS
DIPLOMADO TRASTORNOS DEL ESPECTRO AUTISTA
ESCUELA DE MEDICINA UNIVERSIDAD SAN SEBASTIÁN PUERTO MONTT



CLASE TRASTORNOS DEL ESPECTRO AUTISTA:
OBJETIVOS A DOMINAR POR LOS ESTUDIANTES

-ENTENDER CONCEPTUALMENTE LA TERMINOLOGÍA ASOCIADA A ESTE TIPO DE TRASTORNOS DEL NEURODESARROLLO

-SER CAPAZ DE IDENTIFICAR LOS SÍNTOMAS TEMPRANOS DE PRESENTACIÓN

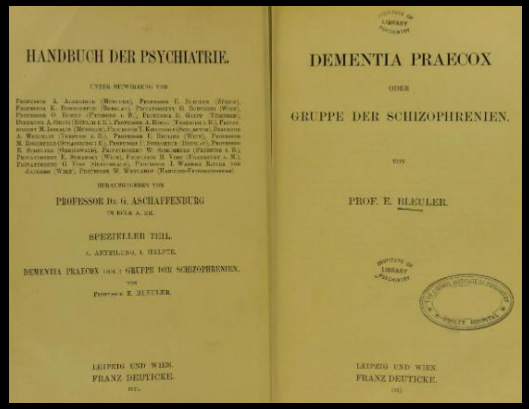
-CONOCER LAS HERRAMIENTAS DE TAMIZAJE POBLACIONAL

-CONOCER LAS HERRAMIENTAS DIAGNÓSTICAS DE LOS TEA

-IDENTIFICAR ELEMENTOS CLÍNICOS QUE HACEN PENSAR QUE UN TEA ESTÉ RELACIONADO A UNA ENFERMEDAD ORGÁNICA DEFINIDA

-CONOCER LAS ESTRATEGIAS TERAPÉUTICAS DE USO HABITUAL EN TEA

-CONOCER LAS COMPLICACIONES ASOCIADAS A LOS TEA



HANDBUCH DER PSYCHIATRIE.

DEMENTIA PRAECOX

ODER

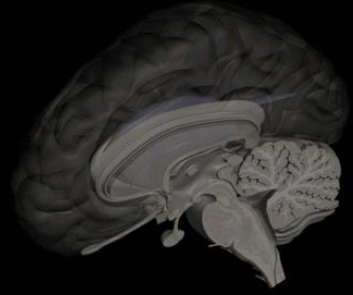
GRUPPE DER SCHIZOPHRENIEN.

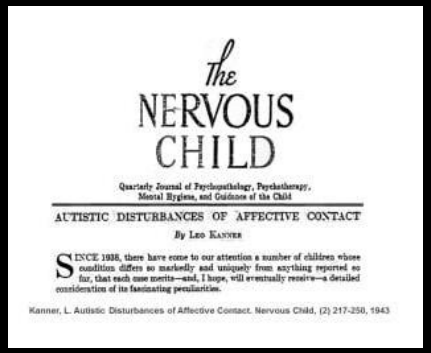
VON

PROF. E. BLEULER.

SPEZIELLER TEIL.

LEIPZIG UND WIEN.
FRANZ DEUTICKE.





The
NERVOUS
CHILD

Quarterly Journal of Psychopathology, Psychotherapy, Mental Hygiene, and Guidance of the Child

AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

By Leo Kanner

SINCE 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities.

Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child, (2) 217-250, 1943

Quelle: Archiv für Psychiatrie und Nervenkrankheiten 117: 76–136, 1994.
Springer, Berlin Heidelberg

(Aus der Wiener Universitäts-Kinderklinik [Vorstand: Prof. *Franz Hamburger*].)

Die „Autistischen Psychopathen" im Kindesalter[1].

Von

Doz. Dr. **Hans Asperger,**

Leiter der Heilpädagogischen Abteilung der Klinik.

(Eingegangen am 8. Oktober 1943.)

Problemstellung.

Ordnung und Erkenntnis des Aufbaues der Dinge ist eines der letzten Ziele der Wissenschaft. In der Fülle der Erscheinungen des Lebens, die voller Gegensätze sind, die mit verschwimmenden Grenzen in einander übergehen, sucht der denkende Mensch dadurch einen festen Standpunkt zu finden, daß er den einzelnen Erscheinungen einen Namen gibt, sie abgrenzt gegen die anderen Erscheinungen, Zusammenhänge, Ähnlichkeiten und Gegensätze feststellt, kurz, die Dinge in eine Ordnung, in ein System bringt. Diese Arbeit ist eine wesentliche Voraussetzung des Erkennens.

Die Wissenschaft vom Menschen mußte ähnliche Wege gehen. Nirgendwo aber sind die Schwierigkeiten größer als hier:

Jeder Mensch ist ein einmaliges, unwiederholbares, unteilbares Wesen („In-dividuum"), darum auch letztlich unvergleichbar mit anderen. In jedem Charakter finden sich einander scheinbar widersprechende Züge — gerade aus Gegensätzen und Spannungen lebt ja das Leben.

Endlich ist der Mensch das rätselhafteste Geschöpf auf Erden; das innerste Wesen einer Persönlichkeit wird weder dem offenbar, der sich selbst zu erkennen sucht, noch auch dem Blick des Gegenübertretenden, der in einen andern eindringen will.

Trotz oder vielleicht gerade wegen dieser Schwierigkeiten ist es das heiße Bemühen denkender Menschen seit je, die Menschen zu erkennen und auch, sie einzuordnen, eine Reihe von Bildern menschlicher Charaktere aufzustellen und gegeneinander abzugrenzen, also zu einer *Typologie* zu gelangen, welche der Vielfalt des Lebens gerecht wird.

Versuche zu einer Einordnung der menschlichen Erscheinungen

To understand and measure emotional qualities is very difficult. Psychologists and educators have been struggling with that problem for years but we are still unable to measure emotional and personality traits with the exactness with which we can measure intelligence.

—Rose Zeligs in *Glimpses into Child Life

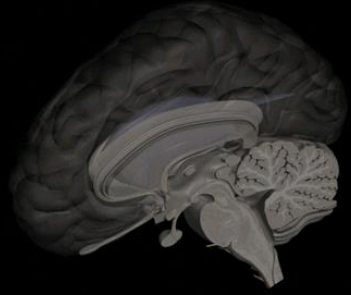
AUTISTIC DISTURBANCES OF AFFECTIVE CONTACT

By Leo Kanner

SINCE 1938, there have come to our attention a number of children whose condition differs so markedly and uniquely from anything reported so far, that each case merits—and, I hope, will eventually receive—a detailed consideration of its fascinating peculiarities. In this place, the limitations necessarily imposed by space call for a condensed presentation of the case material. For the same reason, photographs have also been omitted. Since none of the children of this group has as yet attained an age beyond 11 years, this must be considered a preliminary report, to be enlarged upon as the patients grow older and further observation of their development is made.

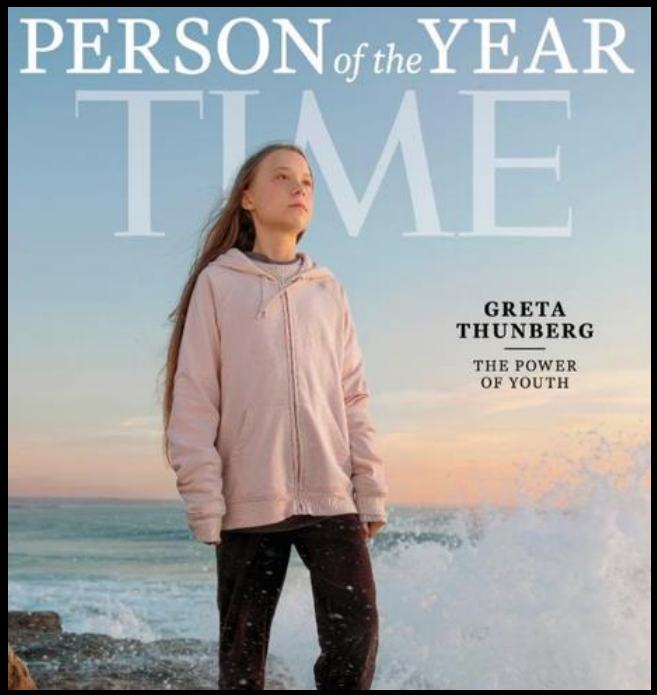

RAIN MAN

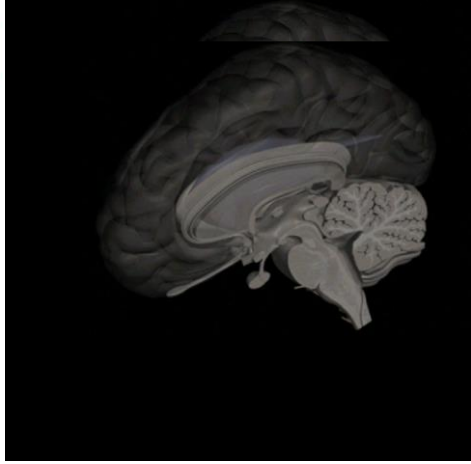

the BIG BANG THEORY




the Good Doctor


NORMAL IS OVERRATED
A NETFLIX ORIGINAL SERIES
ATYPICAL
NETFLIX | AUGUST 11


PERSON of the YEAR
TIME
GRETA THUNBERG
THE POWER OF YOUTH



In 2021, the CDC reported that approximately 1 in 44 children in the U.S. is diagnosed with an autism spectrum disorder (ASD), according to 2018 data.

- 1 in 27 boys identified with autism
- 1 in 116 girls identified with autism

Boys are four times more likely to be diagnosed with autism than girls.

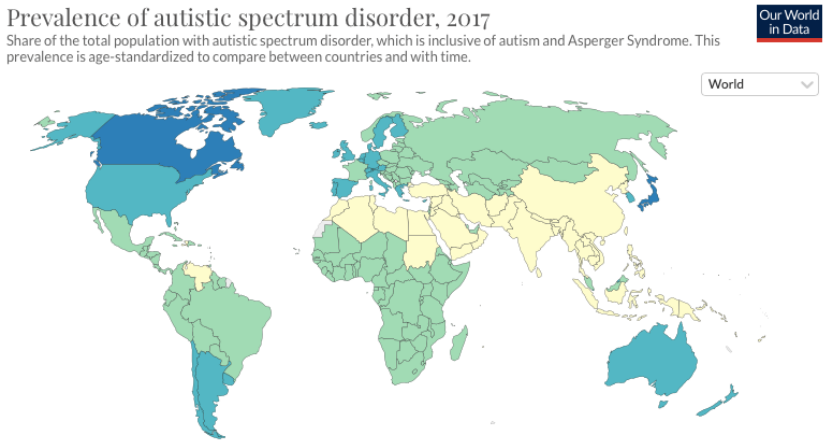
Most children were still being diagnosed after age 4, though autism can be reliably diagnosed as early as age 2.

31% of children with ASD have an intellectual disability (intelligence quotient [IQ] <70), 25% are in the borderline range (IQ 71–85), and 44% have IQ scores in the average to above average range (i.e., IQ >85).

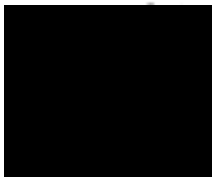
Autism affects all ethnic and socioeconomic groups.

Minority groups tend to be diagnosed later and less often.

Early intervention affords the best opportunity to support healthy development and deliver benefits across the lifespan.



Discussion | Using nationally representative data in the US, the estimated ASD prevalence was 3.14% among children and adolescents in the US in 2019 and 2020. This finding was higher than the reported prevalence from the NHIS in 2014 to 2016 (2.47%),[2] Autism and Developmental Disabilities Monitoring

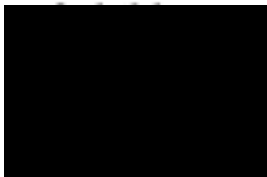


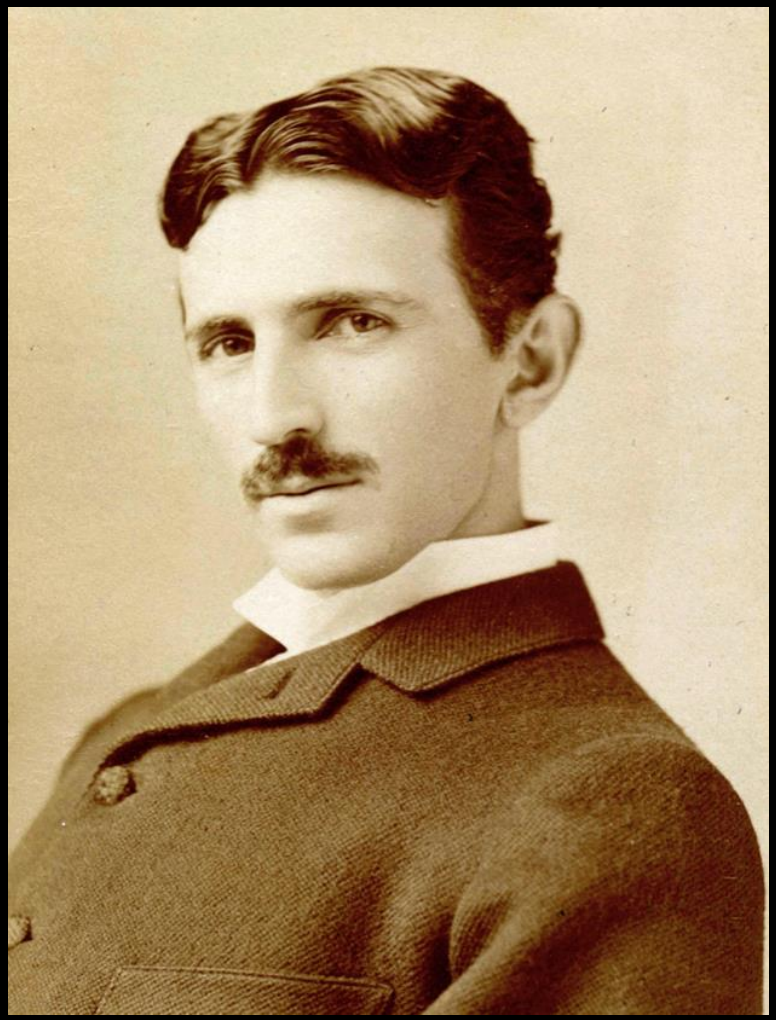
July 5, 2022

Prevalence of Autism Spectrum Disorder Among Children and Adolescents in the United States From 2019 to 2020

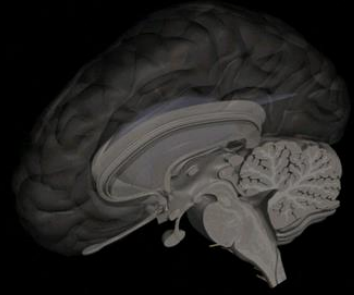
Qian Li, MM[1]; Yanmei Li, MM[1]; Buyun Liu, MD[2]; et al

Author Affiliations





CORRESPONDENCE



Autism, inflammatory bowel disease, and MMR vaccine

Sir—We are concerned about the potential loss of confidence in the mumps, measles, and rubella (MMR) vaccine after publication of Andrew Wakefield and colleagues' report (Feb 28, p 637),[1] in which these workers postulate adverse effects of measles-containing vaccines. As a result, we fear there may be a reduction in vaccine uptake in the UK and elsewhere. The main thrust of the report is to add to the record 12 possible cases of bowel disease associated with developmental regression (including autism), which is a useful contribution to research. However, an association was also alluded to between these two factors and environmental triggers such as receipt of MMR vaccine.

Wakefield and co-workers state "We did not prove an association between measles, mumps, and rubella vaccines and the syndrome described". However, there are enough references in the text to lead the reader to the assumption that there is sufficient evidence provided by the study, and by other scientific publications, to suggest that there is a likely (although as yet unproven) link.

The study suggests a temporal relation between the so-called autism-bowel syndrome and administration of MMR in eight of the 12 cases. However, the interval between receipt of vaccine and onset of symptoms is provided in only five cases (1–14 days), and the age at which the vaccine was given was provided in only three (15 months, 16 months, and 4·5 years). Parents identified MMR to be the immediate precursor of developmental delay in eight of the 12 children, but developmental delay is likely to be detected by a gradual awareness over a period of time, not on a particular day. Although autism is rarely diagnosed before 18 months, the insidious onset of symptoms often predates the diagnosis by many months. As described by Wakefield, parents had trouble making a temporal link between the onset of autism and the onset of gastrointestinal symptoms for similar reasons. We therefore question the conclusion that there was a temporal association of the autism-bowel syndrome and MMR.

To prove a causal relation is much harder—it requires a selection of patients and matched controls, and a sample size that is capable of detecting a statistically significant difference between the two groups. The investigators may need to be blinded for such aspects as clinical assessments and laboratory tests. How does Wakefield's study match up? There was no patient selection other than 12 patients referred to him. There were no controls. There was no blinding of investigators. The accompanying commentary by Robert Chen and Frank DeStefano[2] elegantly explains the difference between temporal and causal association. We concur with them that Wakefield's study fails at every level to make a causal association.

Is it possible that we are confronted by a genuine causal association which has shown up by chance in these eight cases? Is it possible that these cases have brought to light a previously unnoticed association? Wakefield claims that the association between autism and MMR has been documented in the past—an important point to clarify. However, the two references they cite from Fundenburg and Gupta (refs 16 and 17 in their report) need further scrutiny. The first deals mainly with the association of autism and transfer factor (DLyE) and also mentions "live rubella immunization at 15 months has precipitated fever convulsions followed by autistic symptoms; so has live hepatitis B vaccine in 2 infants at 2 years". These anecdotal associations do not advance the argument for causality. We could not obtain the Gupta reference through usual library channels.

Wakefield and colleagues' findings confront us with a new hypothesis—that measles-containing vaccine may trigger developmental regression. It is known that such speculation may seriously damage important public health programmes, causing a decline in vaccine uptake and a rise in the target disease.[3] We can now expect such damage to occur in many countries. We question the merit of publishing this particular study.

Publication of this study is especially tragic because WHO and all consulted national public health authorities agree that it does not alter in any way the continued recommendation to use measles-containing vaccines throughout the world. Current measles containing vaccines are highly safe and effective.

*J W Lee, B Melgaard, C J Clements, M Kane, *E K Mulholland, J-M Olivé*

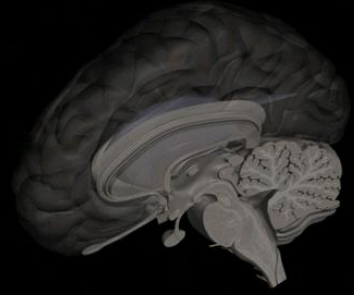
Expanded Programme on Immunization, Global Programme for Vaccines and Immunization, World Health Organization, Geneva 1211, Switzerland

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351:** 637–41.

2 Chen RT, DeStephano F. Vaccine adverse events; causal or coincidental? *Lancet* 1998; **351:** 611–12.

3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; **351:** 356–61.

Sir—Andrew Wakefield and colleagues[1] report a case series of 12 patients and use this to generate a hypothesis that gastrointestinal disease and an associated developmental disorder may be related to MMR. This research was widely reported in the mass media and has generated considerable public concern, despite the weight of evidence supporting the efficacy and safety of MMR vaccination discussed by Robert Chen and Frank DeStefano.[2] Previous experience suggests that adverse publicity about vaccination, even though subsequently shown to be exaggerated or unfounded, results in reduced vaccine coverage with serious public health consequences.[3] The



Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Summary

Background We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods 12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Findings Onset of behavioural symptoms was associated by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and a low serum IgA in four children.

Interpretation We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

Lancet 1998; **351:** 637–41
See Commentary page

Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology (A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath) **and the University Departments of Paediatric Gastroenterology** (S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP,), **Child and Adolescent Psychiatry** (M Berelowitz FRCPsych), **Neurology** (P Harvey FRCP), **and Radiology** (A Valentine FRCR), **Royal Free Hospital and School of Medicine, London NW3 2QG, UK**

Correspondence to: Dr A J Wakefield

Introduction

We saw several children who, after a period of apparent normality, lost acquired skills, including communication. They all had gastrointestinal symptoms, including abdominal pain, diarrhoea, and bloating and, in some cases, food intolerance. We describe the clinical findings, and gastrointestinal features of these children.

Patients and methods

12 children, consecutively referred to the department of paediatric gastroenterology with a history of a pervasive developmental disorder with loss of acquired skills and intestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance), were investigated. All children were admitted to the ward for 1 week, accompanied by their parents.

Clinical investigations

We took histories including details of immunisations and exposure to infectious diseases, and assessed the children. In 11 cases the history was obtained by the senior clinician (JW-S). Neurological and psychiatric assessments were done by consultant staff (PH, MB) with HMS-4 criteria.[1] Developmental assessments included a review of prospective developmental records from parents, health visitors, and general practitioners. Four children did not undergo psychiatric assessment in hospital; all had been assessed professionally elsewhere, so these assessments were used as the basis for their behavioural diagnosis.

After bowel preparation, ileocolonoscopy was performed by SHM or MAT under sedation with midazolam and pethidine. Paired frozen and formalin-fixed mucosal biopsy samples were taken from the terminal ileum; ascending, transverse, descending, and sigmoid colons, and from the rectum. The procedure was recorded by video or still images, and were compared with images of the previous seven consecutive paediatric colonoscopies (four normal colonoscopies and three on children with ulcerative colitis), in which the physician reported normal appearances in the terminal ileum. Barium follow-through radiography was possible in some cases.

Also under sedation, cerebral magnetic-resonance imaging (MRI), electroencephalography (EEG) including visual, brain stem auditory, and sensory evoked potentials (where compliance made these possible), and lumbar puncture were done.

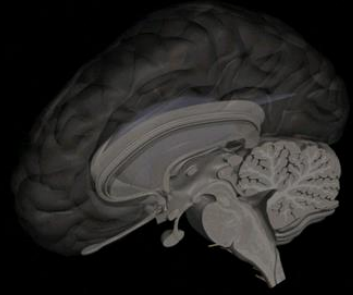
Laboratory investigations

Thyroid function, serum long-chain fatty acids, and cerebrospinal-fluid lactate were measured to exclude known causes of childhood neurodegenerative disease. Urinary methylmalonic acid was measured in random urine samples from eight of the 12 children and 14 age-matched and sex-matched normal controls, by a modification of a technique described previously.[2] Chromatograms were scanned digitally on computer, to analyse the methylmalonic-acid zones from cases and controls. Urinary methylmalonic-acid concentrations in patients and controls were compared by a two-sample *t* test. Urinary creatinine was estimated by routine spectrophotometric assay.

Children were screened for antiendomyseal antibodies and boys were screened for fragile-X if this had not been done

AUTISMO

“Autos”: uno mismo; “Ismos”: modo de estar



TÉRMINO CLÍNICO BASADO EN CONDUCTAS

INICIO EN LA INFANCIA

CAMBIOS CONCEPTUALES EN EL TIEMPO

CONCEPTO ACTUAL: TRASTORNO ESPECTRO AUTISTA

AUMENTO MARCADO PREVALENCIA EN ÚLTIMOS AÑOS (1,8%)

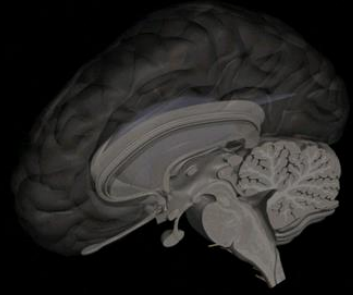
SIGNIFICATIVA “CARGA DE ENFERMEDAD” FAMILIAR Y SOCIAL

ALTERACIÓN DEL NEURODESARROLLO, ANATÓMICO Y FUNCIONAL

ENGLOBA MÚLTIPLES CUADROS DE ORIGEN DIVERSO

CONCEPTO DE UN “CONTÍNUO” DE SIGNOS Y SÍNTOMAS

TRASTORNOS DEL ESPECTRO AUTISTA



-¿QUÉ LO DEFINE EN LO NEUROBIOLÓGICO?

ALTERACIÓN DE MECANISMOS CEREBRALES QUE NOS PERMITEN ENTENDER LAS NECESIDADES DE LOS DEMÁS, COMUNICARNOS Y POR ENDE, MEJORAR NUESTRAS CAPACIDADES DE TRABAJAR EN GRUPO Y SOBREVIVIR

CAPACIDADES DESARROLLADAS EVOLUTIVAMENTE A TRAVÉS DE MILLONES DE AÑOS COMO ESPECIE

LAS PERSONAS AUTISTAS SON MUY DIFERENTES EN ASPECTOS CENTRALES DE LA VIDA HUMANA, GENERANDO LIMITACIONES Y CONSECUENCIAS EN SU GRUPO FAMILIAR Y LA SOCIEDAD

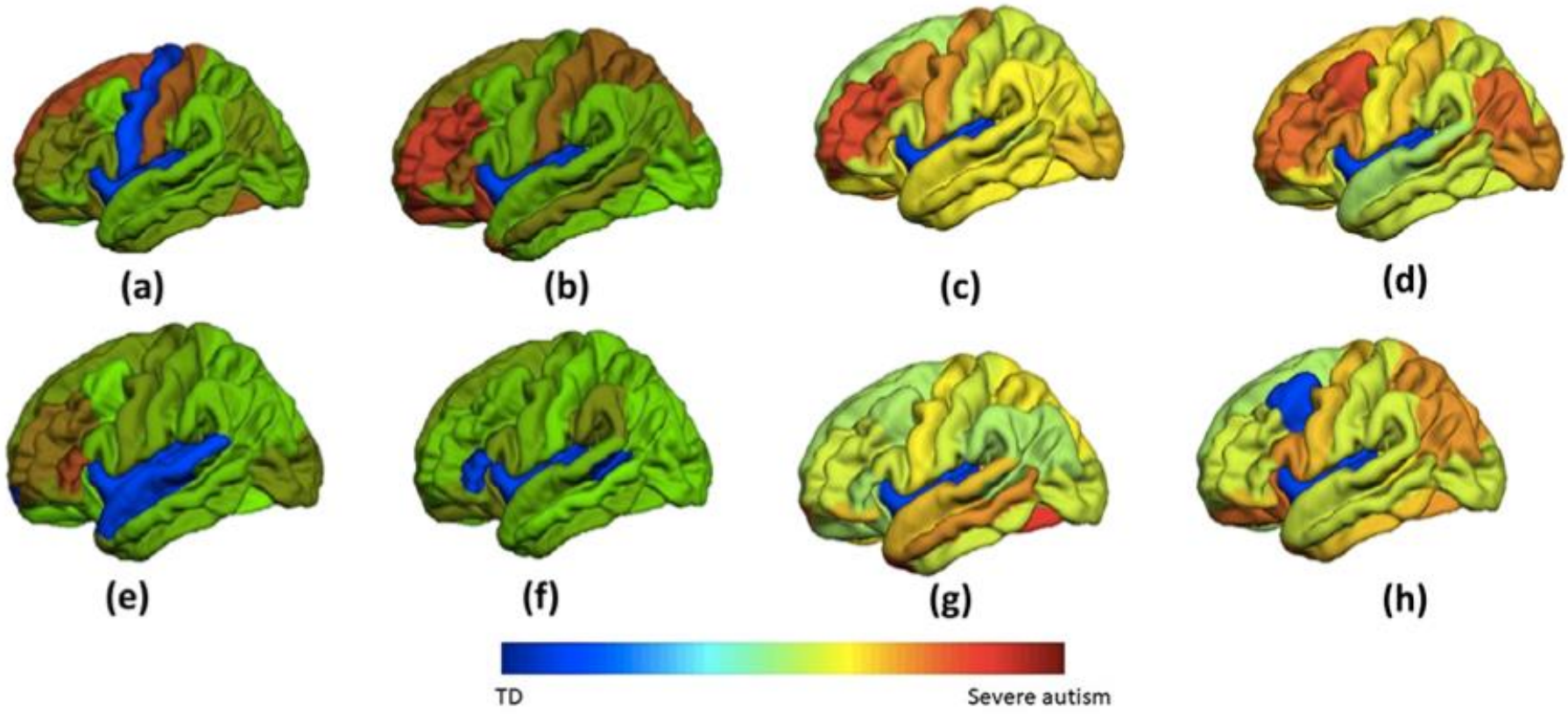


Figure 5 A sample of the generated personalized maps for 8 subjects: (a, b) are the personalized maps of 2 ASD subjects obtained from sMRI local classification, (c, d) are the personalized maps of 2 ASD subjects obtained from fMRI local classification, (e, f) are the personalized maps of 2 TD subjects obtained from sMRI local classification, and (g, h) are the personalized maps of 2 TD subjects obtained from fMRI local classification. (Color version of figure is available online.)

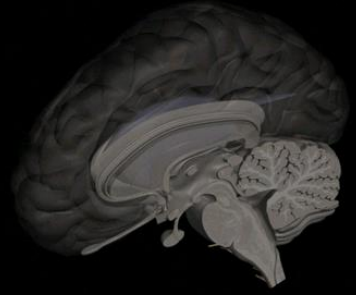
A Comprehensive Framework for Differentiating Autism Spectrum Disorder From Neurotypicals by Fusing Structural MRI and Resting State Functional MRI

Omar Dekhil, MSc,[*,a] Mohamed Ali, MSc,[*,a] Reem Haweel, PhD,[*] Yaser Elnakib, PhD,[*] Mohammed Ghazal, PhD,[†] Hassan Hajjdiab, PhD,[†] Luay Fraiwan, PhD,[†] Ahmed Shalaby, PhD,[*] Ahmed Soliman, PhD,[*] Ali Mahmoud, PhD,[*] Robert Keynton, PhD,[*] Manuel F. Casanova, PhD,[‡] Gregory Barnes, PhD,[§] and Ayman El-Baz, PhD[*]

Autism spectrum disorder is a neurodevelopmental disorder characterized by impaired social abilities and communication difficulties. The golden standard for autism diagnosis in research rely on behavioral features, for example, the autism diagnosis observation schedule, the Autism Diagnostic Interview-Revised. In this study we introduce a computer-aided diagnosis system that uses features from structural MRI (sMRI) and resting state functional MRI (fMRI) to help predict an autism diagnosis by clinicians. The proposed system is capable of parcellating brain regions to show which areas are most likely affected by autism related abnormalities and thus help in targeting potential therapeutic interventions. When tested on 18 data sets (n = 1060) from the ABIDE consortium, our system was able to achieve high accuracy (sMRI 0.75-1.00; fMRI 0.79-1.00), sensitivity (sMRI 0.73-1.00; fMRI 0.78-1.00), and specificity (sMRI 0.78-1.00; fMRI 0.79-1.00). The proposed system could be considered an important step toward helping physicians interpret results of neuroimaging studies and personalize treatment options. To the best of our knowledge, this work is the first to combine features from structural and functional MRI, use them for personalized diagnosis and achieve high accuracies on a relatively large population.

Semin Pediatr Neurol 34:100805

TRASTORNOS DEL ESPECTRO AUTISTA

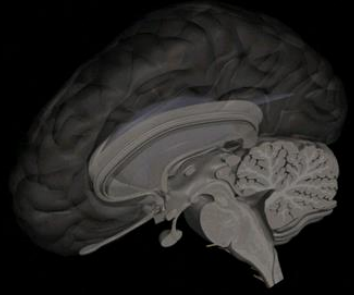


DEFINICIÓN SEGÚN DSM V

-COMPROMISO SIGNIFICATIVO DE LA INTERACCIÓN Y COMUNICACIÓN SOCIAL

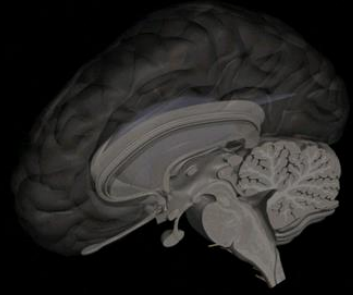
-PATRÓN DE CONDUCTAS E INTERESES RESTRICTIVOS Y REPETITIVOS

-HABITUALMENTE RELACIONADOS A ELEMENTOS NEUROSENSORIALES



Hand flapping

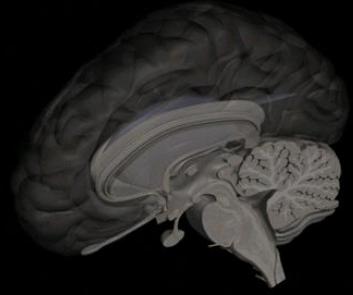
TRASTORNOS DEL ESPECTRO AUTISTA



SÍNTOMAS Y SIGNOS DE PRESENTACIÓN (Y DETECCIÓN) TEMPRANA

-FALTA DE CONTACTO VISUAL (PERMANENCIA EN LA MIRADA)
-TRASTORNOS DEL SUEÑO
-RETRASO DE LENGUAJE
-TERQUEDAD
-DEPENDENCIA DE OBJETOS O RUTINAS ESPECÍFICAS
-INTOLERANCIA A RUIDOS
-RECHAZO A TEXTURAS-COLORES-OLORES (OLER A PERSONAS)
-USO DE FRASES ESTEREOTIPADAS
-HIPERACTIVIDAD
-IRRITABILIDAD PERSISTENTE
-INTENCIÓN COMUNICATIVA CENTRADA EN SUS INTERESES PARTICULARES
-QUIEBRES COMUNICACIONALES
-MEMORIA VISUAL EXACERBADA
-FOBIAS O MIEDOS INUSUALES
-OBSESIONES O RITUALES

CONCEPTO DE SÍNDROME



-CONJUNTO DE SÍNTOMAS Y SIGNOS CLÍNICOS

SÍNDROME CONVULSIVO

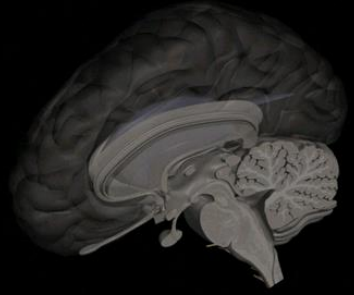
SIGNO CENTRAL

MÚLTIPLES CAUSAS

-CONCEPTO DE “UN CONTÍNUO”

RASGOS DE TEMPERAMENTO ⟷ PSICOPATOLOGÍA

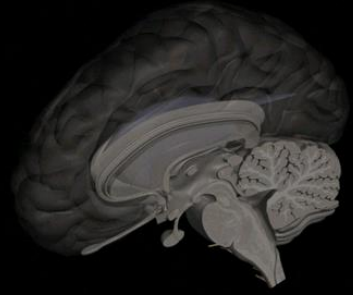
DISTRACTIBILIDAD ⟷ DÉFICIT ATENCIONAL



TRASTORNOS DEL ESPECTRO AUTISTA

- RELACIÓN A PREMATUREZ EXTREMA
- ERRORES INNATOS DEL METABOLISMO
- EXPOSICIÓN A TÓXICOS AMBIENTALES IN ÚTERO
- ENFERMEDAD MATERNA EN EL EMBARAZO
- ALTERACIONES ANATÓMICAS DEL CEREBRO
- CUADROS METABÓLICOS
- SECUELAS PERINATALES
- CUADROS GENÉTICOS

TRASTORNOS DEL ESPECTRO AUTISTA



ORIGEN DEL CUADRO

-BASE GENÉTICA (GEMELOS DICIGÓTICOS 20%-MONOCIGÓTICOS 70%)

-FACTORES DE MODULACIÓN AMBIENTAL DE LA EXPRESIÓN GÉNICA (EPIGENÉTICA)

-¿FACTORES AUTOINMUNES INFLAMATORIOS?

-NEUROIMÁGENES REVELAN ANATOMÍA Y FUNCIÓN DIFERENTE CEREBRO

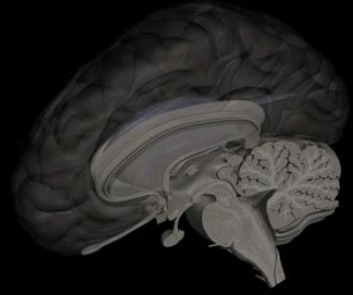
-FACTORES PREDISPONENTES IDENTIFICADOS

-RIESGO RECURRENCIA HERMANOS (TEA)

-AUMENTO DE FRECUENCIA ¿FACTORES VIDA MODERNA?

TRASTORNOS DEL ESPECTRO AUTISTA

PREVALENCIA: EXPLICACIONES AUMENTO



-MAYOR AMPLITUD DEL CONCEPTO DIAGNÓSTICO

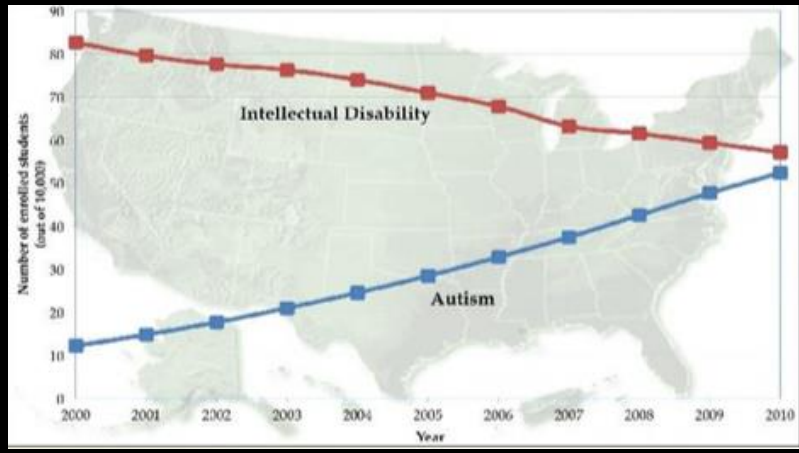
-MAYOR CONOCIMIENTO DEL CUADRO

-MAYOR BÚSQUEDA DE ÉSTE

-FACTORES BIOLÓGICOS
(EDAD DE PADRES)

-FACTORES AMBIENTALES (TÓXICOS)

-FERTILIZACIÓN IN VITRO



-FACTORES DESCONOCIDOS O HIPOTETIZADOS

-MAYOR SOBREVIDA DE NIÑOS CON PATOLOGÍA DE BASE QUE ORIGINE SÍNTOMAS O SIGNOS DE TIPO AUTISTA

TRASTORNOS DEL ESPECTRO AUTISTA

PREVALENCIA

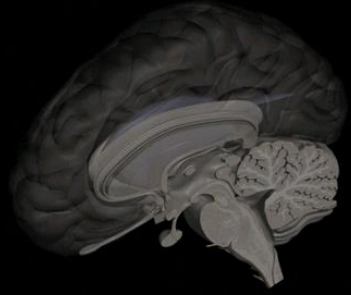
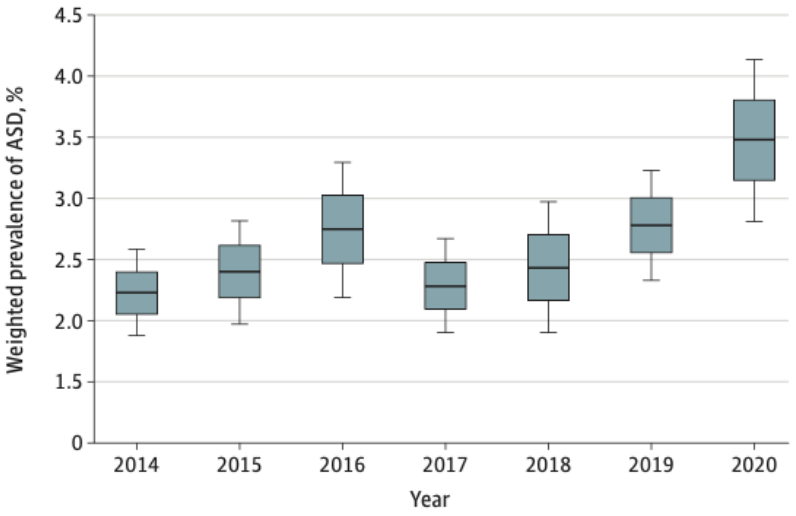


Figure. Trend in Prevalence of Autism Spectrum Disorder (ASD) in Children and Adolescents in the US From 2014 to 2020



The number of participants (n = 57 392) was 11 082 in 2014, 10 183 in 2015, 9237 in 2016, 7397 in 2017, 6939 in 2018, 7684 in 2019, and 4870 in 2020. The weighted prevalence of ASD was 2.24% (95% CI, 1.89%-2.59%) in 2014, 2.41% (95% CI, 1.98%-2.84%) in 2015, 2.76% (95% CI, 2.20%-3.31%) in 2016, 2.29% (95% CI, 1.91%-2.68%) in 2017, 2.44% (95% CI, 1.91%-2.98%) in 2018, 2.79% (95% CI, 2.34%-3.24%) in 2019, and 3.49% (95% CI, 2.82%-4.15%) in 2020 (*P* for trend = .31).

JAMA Pediatrics September 2022 Volume 176, Number 9

TRASTORNOS DEL ESPECTRO AUTISTA

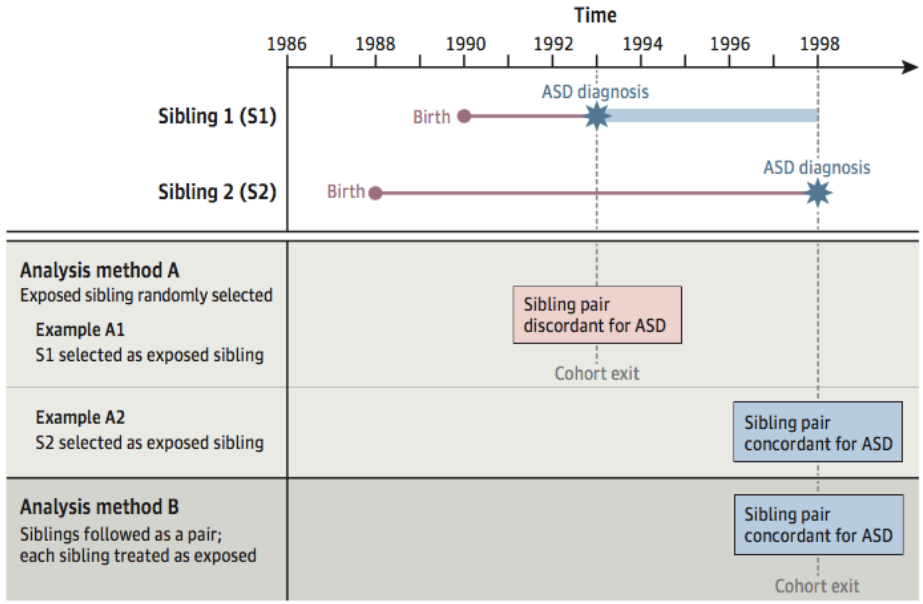
FACTOR GENÉTICO V/S AMBIENTAL

SUECIA COHORTE RN 1982-2006, SEGUIMIENTO 2009: 37.570 GEMELOS, 2.642.064 HERMANOS, 432.281 HERMANOS MATERNOS, 445.531 HERMANOS PAT.

TEA: 14.516

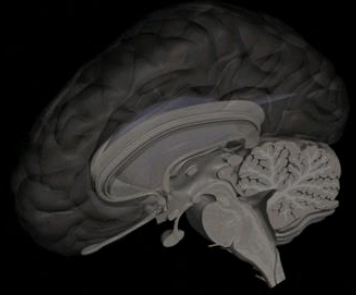
GENÉTICO: 83%

Figure. Examples of Methods for Defining ASD-Discordant and ASD-Concordant Sibling Pairs



The concordant or discordant status of the pair is determined at the end of follow-up of the exposed sibling (cohort exit).

ASD indicates autism spectrum disorder. Each sibling is followed from birth to end of follow-up (death, emigration, or end of follow-up) or ASD diagnosis. Analysis methods A and B agree for the clear majority of all sibling pairs. If S2 was not observed with ASD, the concordance or discordance status would be the same for both methods. In the Figure, for the family with 2 siblings where S1 is diagnosed with ASD in 1993 and S2 in 1998, the sibling pair (S1, S2) will be discordant in 1993 because S2 is censored at the ASD diagnosis of S1. However, the pair (S2, S1) will be concordant in 1998. The 2 pairs are 2 candidates representing the family. For calculating heritability, 1 of these representative sibling pairs was randomly selected. As a consequence, the algorithm led to a loss of about half of the concordant pairs compared with results under the assumptions and methods applied in the alternate method (analysis method B),[3] in which calculating heritability typically does not consider sibling pairs as both discordant or concordant depending on which sibling is considered dependent, but instead follows them as a pair.



Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study

Sally Ozonoff, Gregory S. Young, Alice Carter, Daniel Messinger, Nurit Yirmiya, Lonnie Zwaigenbaum, Susan Bryson, Leslie J. Carver, John N. Constantino, Karen Dobkins, Ted Hutman, Jana M. Iverson, Rebecca Landa, Sally J. Rogers, Marian Sigman and Wendy L. Stone

Pediatrics 2011;128;e488
DOI: 10.1542/peds.2010-2825 originally published online August 15, 2011;

1 HIJO TEA, RECURRENCIA 2º HIJO TEA: 18,7%
(26% DE RIESGO SI ES VARÓN, 9% SI ES MUJER)

2 HIJOS TEA, RECURRENCIA EN 3er HIJO: 32%

Werling and Geschwind *Molecular Autism* (2015) 6:27
DOI 10.1186/s13229-015-0004-5

Molecular Autism

RESEARCH Open Access

Recurrence rates provide evidence for sex-differential, familial genetic liability for autism spectrum disorders in multiplex families and twins

Donna M Werling[1] and Daniel H Geschwind[1,2,3,4,5*]

Abstract

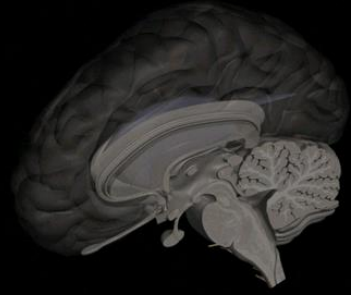
Background: Autism spectrum disorders (ASDs) are more prevalent in males, suggesting a multiple threshold liability model in which females are, on average, protected by sex-differential mechanisms. Under this model, autistic females are predicted to carry a more penetrant risk variant load than males and to share this greater genetic liability with their siblings. However, reported ASD recurrence rates have not demonstrated significantly increased risk to siblings of affected girls. Here, we characterize recurrence patterns in multiplex families from the Autism Genetics Resource Exchange (AGRE) to determine if risk in these families follows a female protective model.

Methods: We assess recurrence rates and quantitative traits in full siblings from 1,120 multiplex nuclear families and concordance rates in 305 twin pairs from AGRE. We consider the first two affected children per family, and one randomly selected autistic twin per pair, as probands. We then compare recurrence rates and phenotypes between males and females and between twin pairs or families with at least one female proband (female-containing (FC)) versus those with only male probands (male-only (MO)).

Results: Among children born after two probands, we observe significantly higher recurrence in males (47.5%) than in females (21.1%; relative risk, RR = 2.25; adjusted $P = 6.22e{-}08$) and in siblings of female (44.3%) versus siblings of male probands (30.4%; RR = 1.46; adj. $P = 0.036$). This sex-differential recurrence is also robust in dizygotic twin pairs (males = 61.5%, females = 19.1%; RR = 3.23; adj. $P = 7.66e{-}09$). Additionally, we find a significant negative relationship between interbirth interval and ASD recurrence that is driven by children in MO families.

Conclusions: By classifying families as MO or FC using two probands instead of one, we observe significant recurrence rate differences between families harboring sex-differential familial liability. However, a significant sex difference in risk to children within FC families suggests that female protective mechanisms are still operative in families carrying high genetic risk loads. Furthermore, the male-specific relationship between shorter interbirth intervals and increased ASD risk is consistent with a potentially greater contribution from environmental factors in males versus higher genetic risk in affected females and their families. Understanding the mechanisms driving these sex-differential risk profiles will be useful for treatment development and prevention.

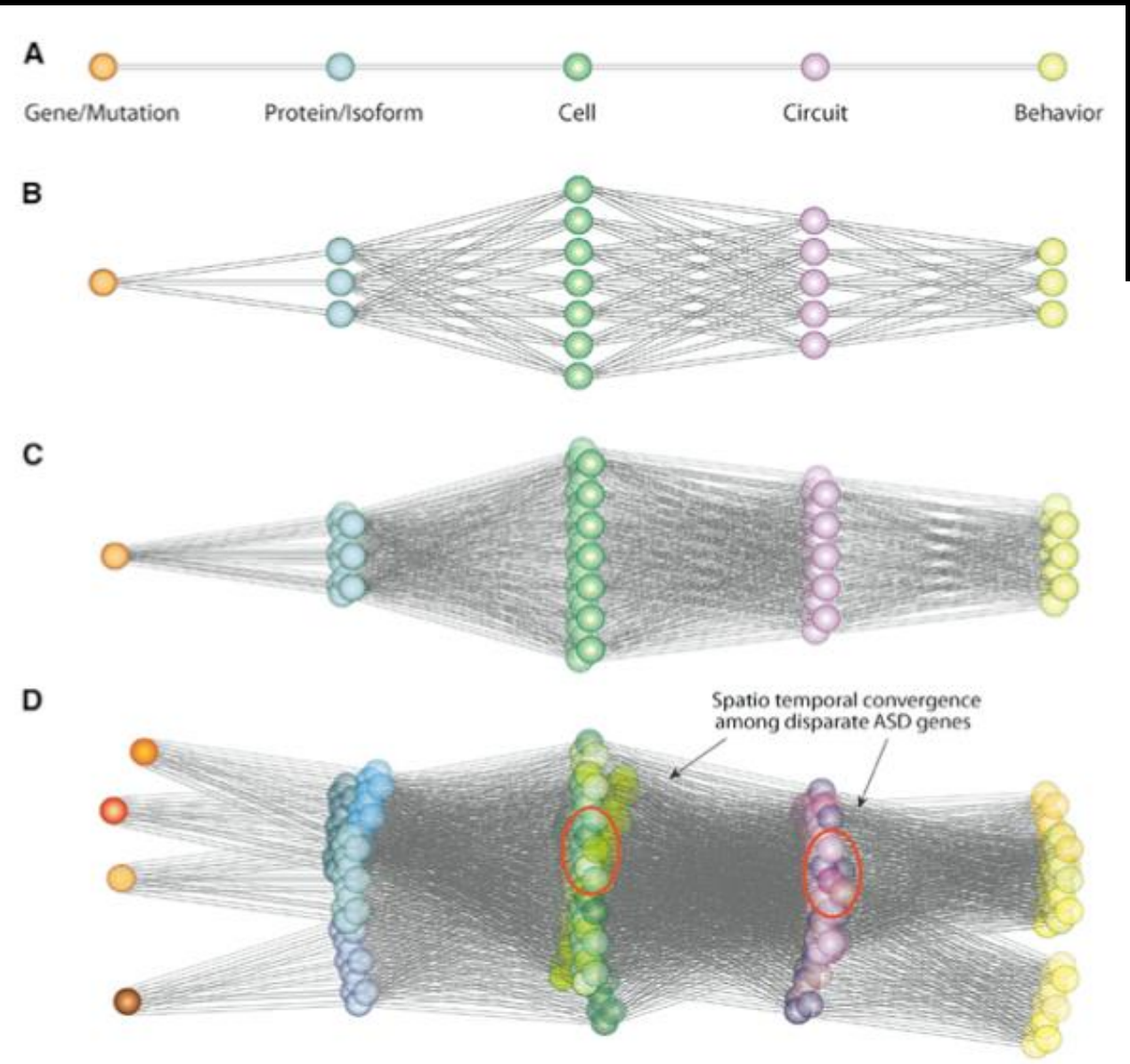
Keywords: Female protective model, Sex differences, Multiplex families, AGRE, Recurrence risk, Interbirth interval

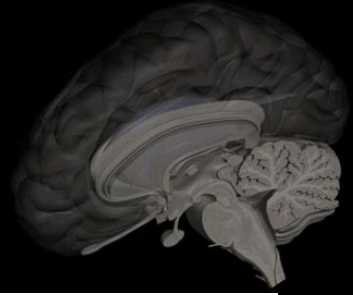


TEA 2 HERMANOS: RIESGO RECURRENCIA ENTRE 30-50%

EL RIESGO AUMENTA DE MANERA SIGNIFICATIVA SI EL CASO ÍNDICE ES DE SEXO FEMENINO

AUMENTAR EL PERÍODO INTERGESTACIÓN DISMINUYE RIESGO DE RECURRENCIA, PERO SÓLO EN HOMBRES, ¿FACTOR AMBIENTAL?, ¿MAYOR CARGA GENÉTICA EN MUJERES?





Neuron
Perspective

Lost in Translation: Traversing the Complex Path from Genomics to Therapeutics in Autism Spectrum Disorder

Nenad Sestan[1,2,*] and Matthew W. State[3,*]
[1]Department of Neuroscience and Kavli Institute for Neuroscience, Yale School of Medicine, New Haven, CT 06510, USA
[2]Departments of Genetics, of Psychiatry, and of Comparative Medicine, Program in Cellular Neuroscience, Neurodegeneration and Repair, and Yale Child Study Center, Yale School of Medicine, New Haven, CT 06510, USA
[3]Department of Psychiatry, Langley Porter Psychiatric Institute, Quantitative Biosciences Institute, Institute for Human Genetics, and Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA 94143, USA
*Correspondence: nenad.sestan@yale.edu (N.S.), matthew.state@ucsf.edu (M.W.S.)
https://doi.org/10.1016/j.neuron.2018.10.015

Figure 1. Spatiotemporal Convergence among High-Confidence ASD Risk Genes

(A–D) The figure provides a conceptual illustration of the path from risk genes to behavior in nsASD.

(A) An idealized path from genes to proteins to cells, circuits, and behavior. This is shown as a line connecting colored spheres representing the noted levels of analysis (orange, genes/mutations; blue, proteins; green, cells; purple, circuits; yellow, behaviors).

(B) Substantial complexity is introduced by isoform diversity and biological pleiotropy, with a single gene/mutation leading to multiple transcripts and proteins, corresponding to multiple cell types and circuits.

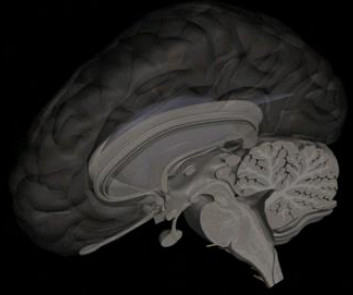
(C) Further complexity is added by spatial and temporal influences on gene expression and function during brain development. This is shown as a three-dimensional space connecting a single gene to multiple isoforms, proteins, cell types, and circuits. Sexual dimorphism adds yet another dimension of complexity (not shown).

(D) An example of a convergence strategy that leverages multiple independent risk genes in an effort to triangulate on specific cell types and circuits that show overlap among functionally diverse risk genes.

Neuron
Perspective

Lost in Translation: Traversing the Complex Path from Genomics to Therapeutics in Autism Spectrum Disorder

Nenad Sestan[1,2,*] **and Matthew W. State**[3,*]
[1]Department of Neuroscience and Kavli Institute for Neuroscience, Yale School of Medicine, New Haven, CT 06510, USA
[2]Departments of Genetics, of Psychiatry, and of Comparative Medicine, Program in Cellular Neuroscience, Neurodegeneration and Repair, and Yale Child Study Center, Yale School of Medicine, New Haven, CT 06510, USA
[3]Department of Psychiatry, Langley Porter Psychiatric Institute, Quantitative Biosciences Institute, Institute for Human Genetics, and Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA 94143, USA
*Correspondence: nenad.sestan@yale.edu (N.S.), matthew.state@ucsf.edu (M.W.S.)
https://doi.org/10.1016/j.neuron.2018.10.015



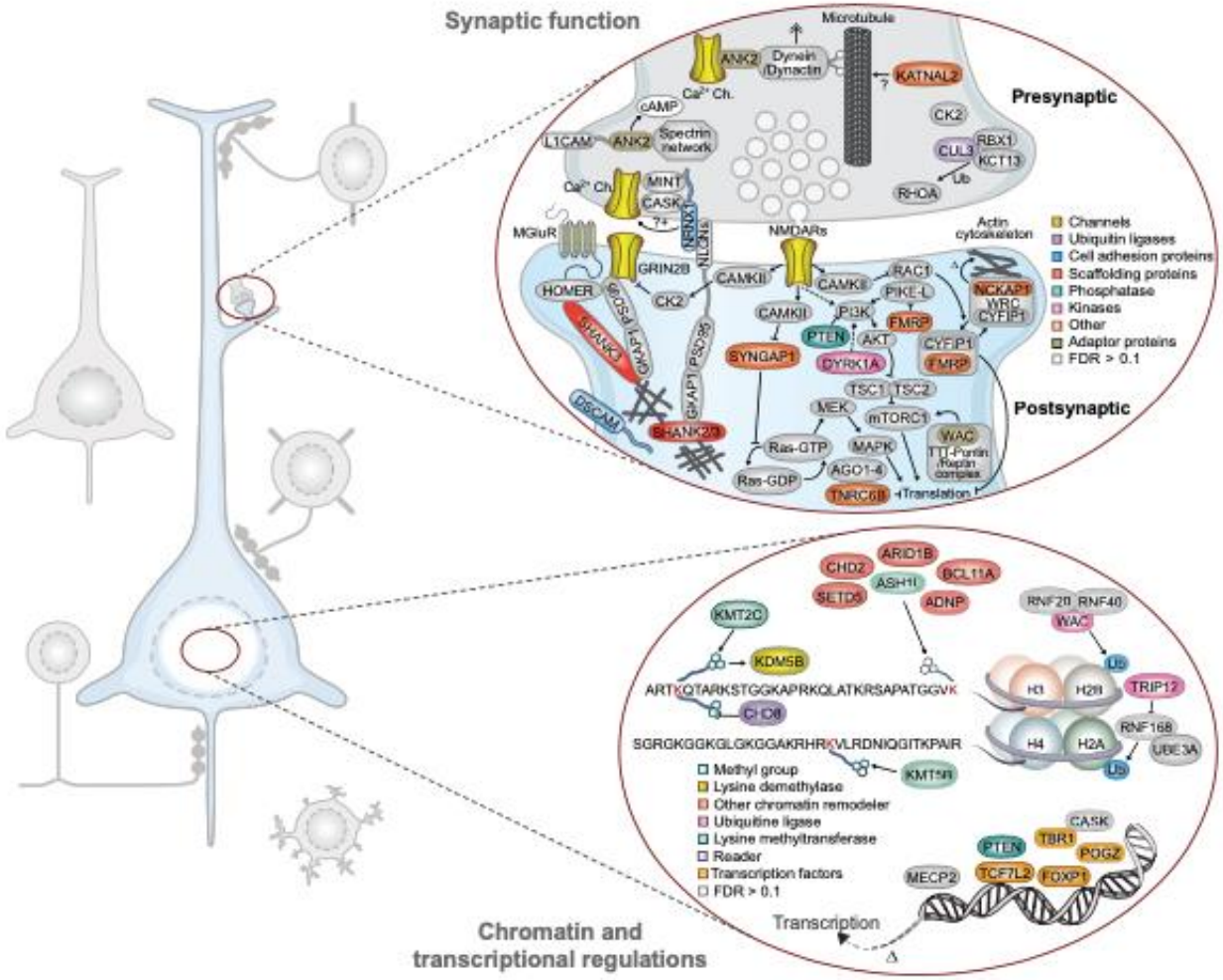
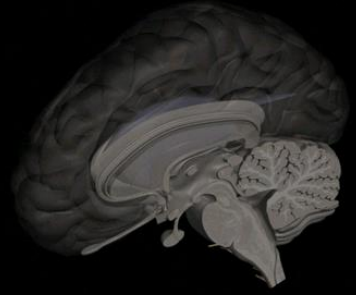


Figure 2. High-Confidence nsASD and Selected Syndromic Risk Genes Encode Synaptic Proteins and Chromatin and Transcriptional Regulators

Genetic studies have identified a large number of risk genes for ASD, many of which have pleiotropic functional properties. Synapse function, chromatin modification, and transcriptional regulation top the list of statistically enriched functional categories. On the left, a simplified schematic of the major cellular components of neural circuits in the cerebral cortex is shown: pyramid-shaped glutamatergic excitatory projection neurons, GABAergic inhibitory interneurons, and glial cells. On the right is shown the diverse intracellular distribution and pleiotropic roles of high-confidence (FDR < 0.1) nsASD risk genes (Sanders et al., 2015) and selected syndromic risk genes. Red outlined circles depict a view of the synapse with its many protein products of nsASD risk genes (top) and the nsASD proteins in the nucleus (bottom). Proteins in synaptic signaling pathways encompass cell adhesion, scaffolding, and signaling molecules. Nuclear protein products of nsASD risk genes are mainly associated with chromatin modification and transcriptional control, suggesting that alterations in chromatin structure and gene expression may contribute to ASD.

TRASTORNOS DEL ESPECTRO AUTISTA

ORIGEN DEL CUADRO: FACTORES AMBIENTALES



-FÁRMACOS EN GESTACIÓN (VALPROICO-MISOPROSTOL)

-DIABETES GESTACIONAL-PREECLAMPSIA

-AGROQUÍMICOS IN UTERO

-EXPOSICIÓN A PLOMO AMBIENTAL

-EDAD DE PADRES

-PREMATUREZ

-OBESIDAD MATERNA

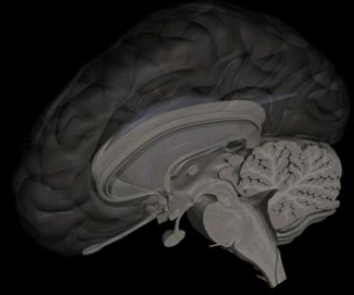
-ENFERMEDADES AUTOINMUNES MATERNAS

-¿FALTA DE ESTIMULACIÓN SOCIAL TEMPRANA?

JAMA Pediatrics | Original Investigation

Association of Early-Life Social and Digital Media Experiences With Development of Autism Spectrum Disorder–Like Symptoms

Karen Frankel Heffler, MD; Danielle M. Sienko, MS; Keshab Subedi, MS, MSc; Kathleen A. McCann, MPhil; David S. Bennett, PhD



IMPORTANCE Despite growing evidence that parent-child interactions and time viewing digital media affect child development, these factors have rarely been studied in association with autism spectrum disorder (ASD) symptoms.

OBJECTIVE To determine the association of experiential factors, including social activities and screen viewing in the first 18 months of life, perinatal factors, and demographic factors, with ASD-like symptoms and risk on the Modified Checklist for Autism in Toddlers (M-CHAT) at 2 years.

DESIGN, SETTING, AND PARTICIPANTS Data for this cohort study were derived from the National Children's Study, a US multicenter epidemiological study of environmental influences on child health and development. A total of 2152 children were enrolled at birth from October 1, 2010, to October 31, 2012. Data were analyzed from December 1, 2017, to December 3, 2019.

EXPOSURES Caregivers reported whether the child viewed television and/or videos (yes or no) at 12 months of age, hours of viewing at 18 months of age, time spent by the caregiver reading to the child (number of days per week compared with daily) at 12 months of age, and frequency of playing with the child (daily or less than daily) at 12 months of age. Prematurity, maternal age at birth, child sex, household income, race/ethnicity, and caregiver English-language status were included in analysis.

MAIN OUTCOMES AND MEASURES Significant association of exposures with ASD risk by M-CHAT and/or ASD-like symptoms assessed by revised M-CHAT (M-CHAT-R) total score in multiple regression models.

RESULTS Among the 2152 children included in the analysis (1099 boys [51.1%]), television and/or video viewing (yes or no) at 12 months of age was significantly associated with greater ASD-like symptoms at 2 years of age (change, 4.2%; 95% CI, 0.1%-8.3%) but not with ASD risk (risk prevalence rates, 8.3% vs 4.4%; adjusted odds ratio [AOR], 1.40; 95% CI, 0.86-2.29). Similarly, parent-child play daily compared with less than daily was significantly associated with fewer ASD-like symptoms at 2 years of age (change, −8.9%; 95% CI, −16.5% to −0.9%) but not with ASD risk (risk prevalence rates, 6.4% vs 14.0%; AOR, 0.58; 95% CI, 0.31-1.08). However, high screen viewing at 18 months of age was not significantly associated with ASD-like symptoms (change, 10.7%; 95% CI, −2.0% to 23.0%) or ASD risk by M-CHAT (AOR, 1.18; 95% CI, 0.56-2.49) at 2 years of age.

CONCLUSIONS AND RELEVANCE This cohort study found greater screen exposure and less caregiver-child play early in life to be associated with later ASD-like symptoms. Further research is needed to evaluate experiential factors for potential risk or protective effects in ASD.

Editorial

Supplemental content

Author Affiliations: Department of Ophthalmology, Drexel University College of Medicine, Philadelphia, Pennsylvania (Heffler); Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania (Sienko); Value Institute, Christianacare Health System, Wilmington, Delaware (Subedi); Social & Scientific Systems, Inc, Silver Spring, Maryland (McCann); Department of Psychiatry, Drexel University College of Medicine, Philadelphia, Pennsylvania (Bennett).

Corresponding Author: David S. Bennett, PhD, Department of Psychiatry, Drexel University College of Medicine, 4700 Wissahickon Ave, Philadelphia, PA 19144 (db36@drexel.edu).

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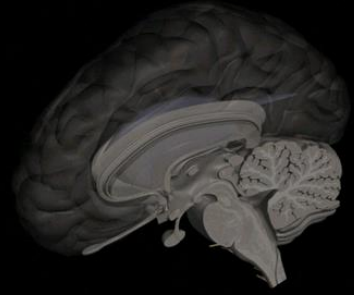


Six Developmental Trajectories Characterize Children With Autism

AUTHORS: Christine Fountain, PhD, Alix S. Winter, BA, and Peter S. Bearman, PhD

Paul F. Lazarsfeld Center for the Social Sciences, Columbia University, New York, New York

PEDIATRICS Volume 129, Number 5, May 2012

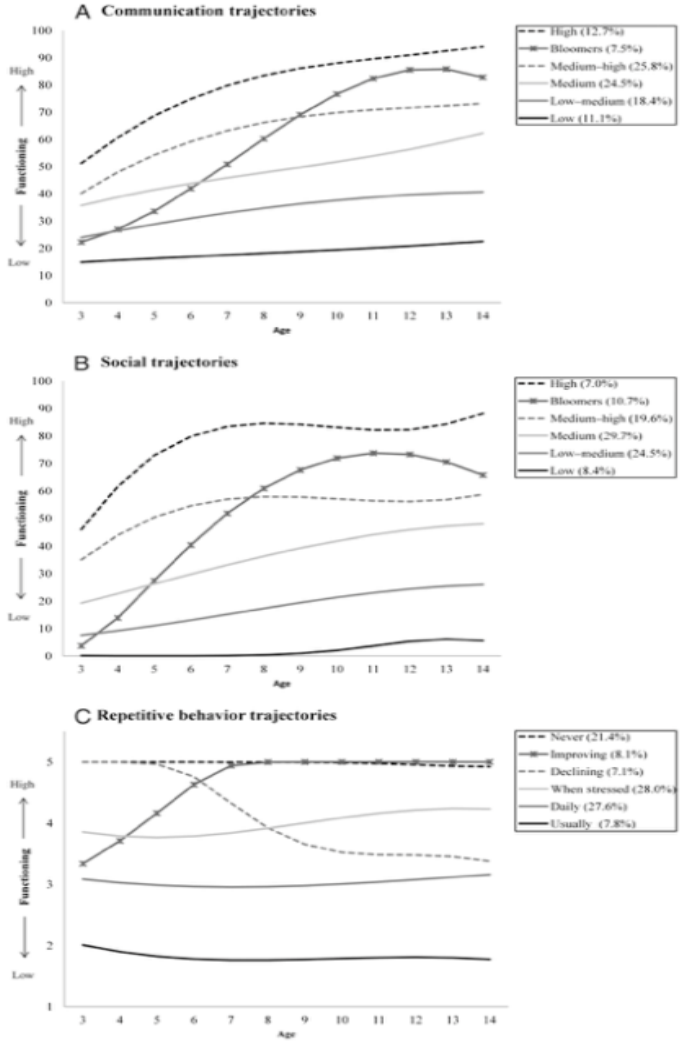


FIGURE 1
(A) Modeled communication, (B) social, and (C) repetitive behavior symptom trajectories based on CDER scores by age.

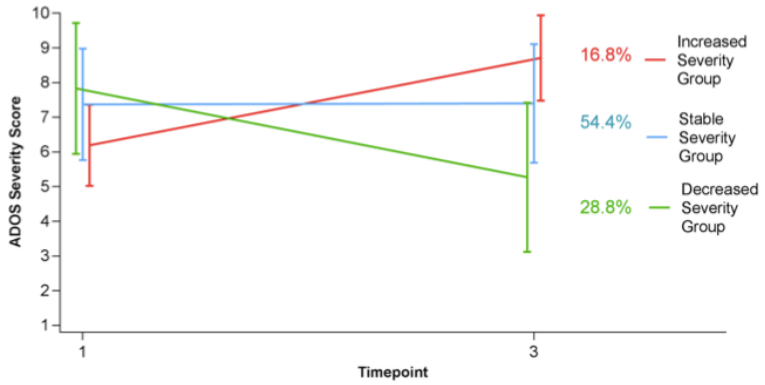
Journal of Autism and Developmental Disorders
https://doi.org/10.1007/s10803-020-04526-z

ORIGINAL PAPER

Trajectories of Autism Symptom Severity Change During Early Childhood

Einat Waizbard-Bartov[1,2] · Emilio Ferrer[1] · Gregory S. Young[2] · Brianna Heath[2] · Sally Rogers[2] · Christine Wu Nordahl[2] · Marjorie Solomon[2] · David G. Amaral[2]

Fig. 2 Group severity trajectories based on group ADOS CSS means at Time 1 and Time 3



Compensatory strategies below the behavioural surface in autism: a qualitative study

Lucy Anne Livingston, Punit Shah, Francesca Happé

Summary

Background Little is known about the compensatory profile in autism; that is, people with autism spectrum disorder who show few symptoms in their behavioural presentation, despite continuing to report autism-related cognitive difficulties or differences. Even less is known about the specific compensatory strategies that these individuals use to disguise autism at the behavioural surface, both in the clinic and everyday life. It is also currently unclear whether individuals without a formal autism diagnosis, but experiencing autistic-like difficulties, use similar compensatory strategies, potentially enabling them to sit below the diagnostic threshold. This study aimed to investigate social compensatory strategies, and their effect on diagnosis and clinical outcome, in adults with and without autism.

Methods In this study, individuals aged 18 years or older who responded to a study advert that was distributed worldwide via social media and the UK National Autistic Society formed a convenience sample. Participants self-reported their use and experiences of compensatory strategies using an online platform. Novel analyses, including a qualitative thematic approach, were used to interpret their responses and gain insight into compensatory strategies in autism.

Findings Between Oct 19, 2017, and Jan 2, 2018, 136 adults (58 had a clinical diagnosis of autism, 19 self-identified but were not formally diagnosed as autistic, and 59 were not diagnosed or self-identified, but nevertheless reported social difficulties) completed the online study questions. The findings suggested that there are multiple compensatory strategies with distinct characteristics, individual and environmental factors that modulate compensatory strategy use and success, positive (social relationships, independence, employment) and negative (poor mental health, late diagnosis) outcomes associated with compensatory strategy use, and that individuals without a diagnosis use compensatory strategies that are qualitatively similar to individuals with a diagnosis.

Interpretation Increased awareness and measurement of compensatory strategy use in autism should guide future diagnostic guidelines, towards improved diagnostic accuracy and support for people with autism spectrum disorder whose cognitive difficulties are not immediately evident in observable behaviour.

Lancet Psychiatry 2019

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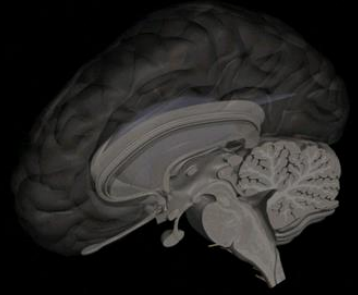
http://dx.doi.org/10.1016/S2215-0366(19)30296-2

Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK (L A Livingston MSc, Prof F Happé PhD); **and Department of Psychology, University of Bath, Bath, UK** (P Shah PhD)

Correspondence to:
Ms Lucy Anne Livingston, Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London SE5 8AF, UK
lucy.livingston@kcl.ac.uk



Autism and Physical Health Across the Lifespan

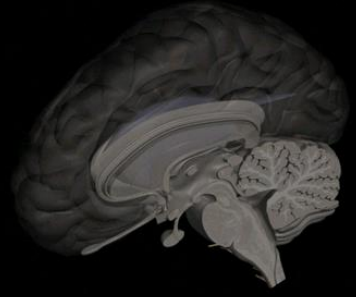
autism

Autism
1–14

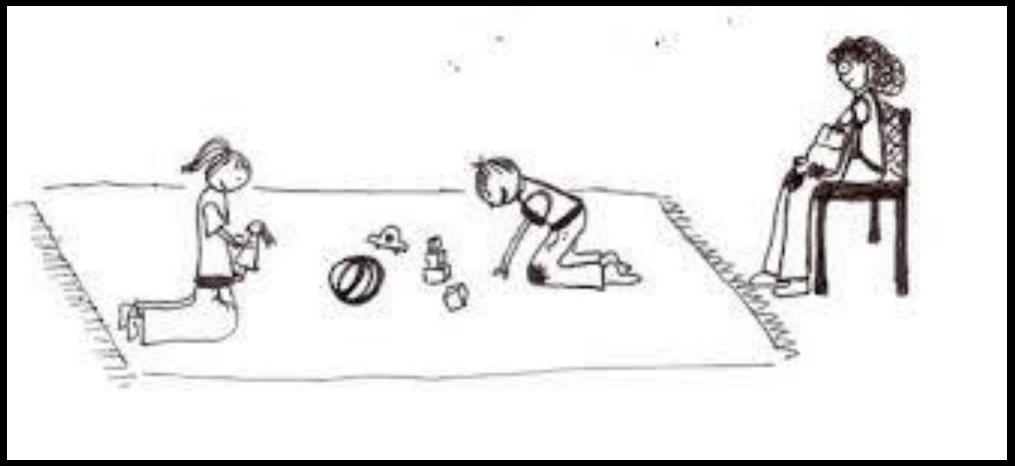
DOI: 10.1177/1362361320953652
journals.sagepub.com/home/aut
SAGE

Increased prevalence of non-communicable physical health conditions among autistic adults

Elizabeth Weir, Carrie Allison, Varun Warrier and Simon Baron-Cohen



¿CÓMO SE PUEDE DIAGNOSTICAR EL AUTISMO?

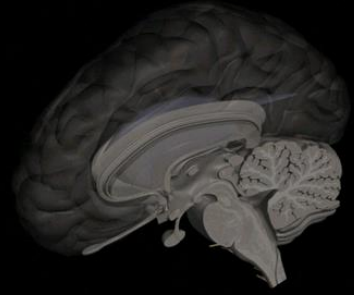


OBSERVACIÓN CLÍNICA
(HISTORIA DEL DESARROLLO-EXAMEN FÍSICO-OBSERVAR CONDUCTAS)
(TEST ESPECÍFICOS: ADI-R, ADOS 2)
SEGUIMIENTO CLÍNICO EN EL TIEMPO

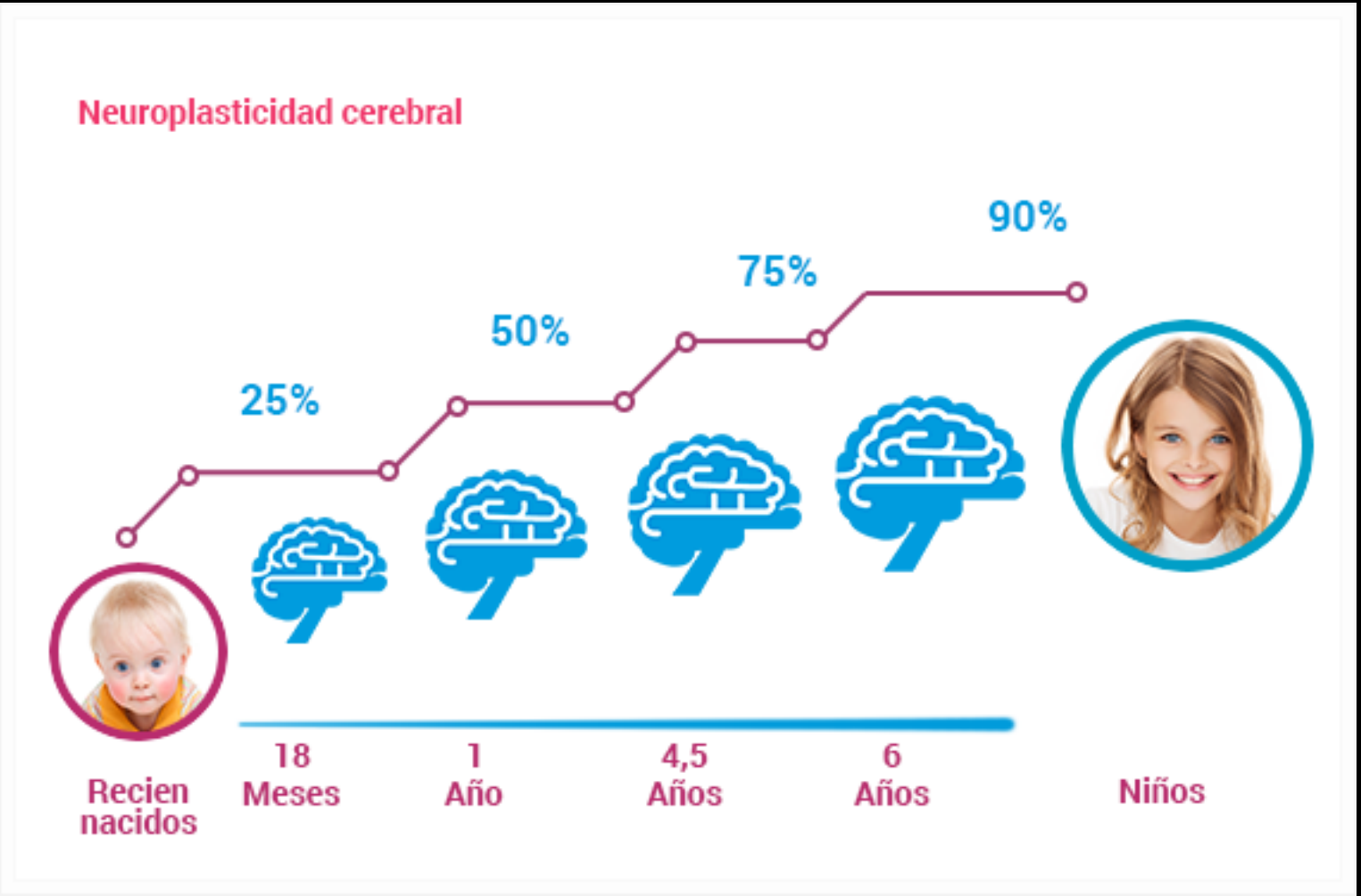
- CHILE ESTUDIO TARDANZA DIAGNÓSTICA 2016:

  PRIMERA SOSPECHA PADRES: 29 M DE EDAD

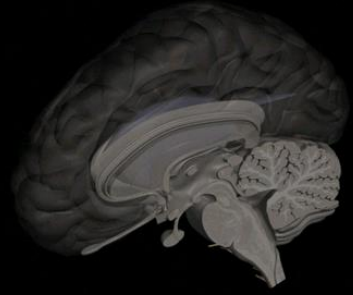
  DIAGNÓSTICO MÉDICO: 61 M DE EDAD



- ¿SIRVE DE ALGO DIAGNOSTICARLO EN FORMA TEMPRANA?



TRASTORNO DEL ESPECTRO AUTISTA

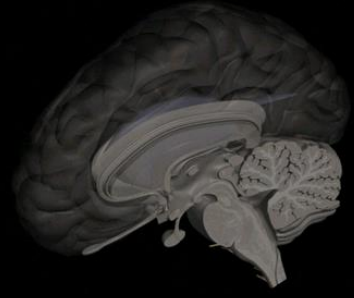


DIAGNÓSTICO
HERRAMIENTAS CLÍNICAS ESPECIALIZADAS

-ADOS 2: PROTOCOLO DE EVALUACIÓN CLÍNICA SEMI-ESTRUCTURADA
UTILIDAD DESDE EL AÑO DE VIDA
DURACIÓN 1,5 HRS
REQUIERE ALTO NIVEL DE ENTRENAMIENTO
"GOLD ESTÁNDAR" DE DIAGNÓSTICO CLÍNICO
APLICABLE DESDE EL AÑO DE VIDA
EVALÚA: LENGUAJE Y COMUNICACIÓN
INTERACCIÓN SOCIAL RECÍPROCA
CONDUCTAS RESTRICTIVAS Y REPETITIVAS

-ADI-R III: ENTREVISTA SEMIESTRUCTURADA A CUIDADORES DEL MENOR
SOBRE 18 M
93 ÍTEMS DE EVALUACIÓN

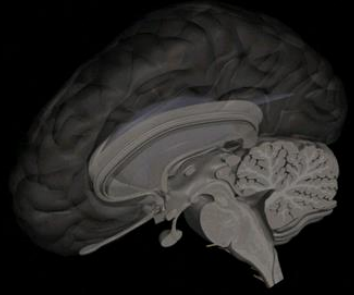
TRASTORNO DEL ESPECTRO AUTISTA



DIAGNÓSTICO
HERRAMIENTAS DE PESQUISA : M-CHAT 16-60 M
M-CHAT R/F validación 24m

		Sí	No
1	¿Le gusta que le balanceen, o que el adulto le haga el "caballito" sentándole en sus rodillas, etc.?	○	○
2	¿Muestra interés por otros niños o niñas?	○	○
3	¿Le gusta subirse a sitios como, por ejemplo, sillones, escalones, juegos del parque...?	○	○
4	¿Le gusta que el adulto juegue con él o ella al "cucú-tras" (taparse los ojos y luego descubrirlos; jugar a esconderse y aparecer de repente)	○	○
5	¿Alguna vez hace juegos imaginativos, por ejemplo haciendo como si hablara por teléfono, como si estuviera dando de comer a una muñeca, como si estuviera conduciendo un coche o cosas así?	○	○
6	¿Suele señalar con el dedo para pedir algo?	○	○
7	¿Suele señalar con el dedo para indicar que algo le llama la atención?	○	○
8	¿Puede jugar adecuadamente con piezas o juguetes pequeños (por ejemplo cochecitos, muñequitos o bloques de construcción) sin únicamente chuparlos, agitarlos o tirarlos?	○	○
9	¿Suele traerle objetos para enseñárselos?	○	○
10	¿Suele mirarle a los ojos durante unos segundos?	○	○
		Sí	No
11	¿Le parece demasiado sensible a ruidos poco intensos? (por ejemplo, reacciona tapándose los oídos, etc.)	○	○
12	¿Sonríe al verle a usted o cuando usted le sonríe?	○	○
13	¿Puede imitar o repetir gestos o acciones que usted hace? (por ejemplo, si usted hace una mueca él o ella también la hace)	○	○
14	¿Responde cuando se le llama por su nombre?	○	○
15	Si usted señala con el dedo un juguete al otro lado de la habitación... ¿Dirige su hijo o hija la mirada hacia ese juguete?	○	○
16	¿Ha aprendido ya a andar?	○	○
17	Si usted está mirando algo atentamente, ¿su hijo o hija se pone también a mirarlo?	○	○
18	¿Hace su hijo o hija movimientos raros con los dedos, por ejemplo, acercándoselos a los ojos?	○	○
19	¿Intenta que usted preste atención a las actividades que él o ella está haciendo?	○	○
20	¿Alguna vez ha pensado que su hijo o hija podría tener sordera?	○	○
		Sí	No
21	¿Entiende su hijo o hija lo que la gente dice?	○	○
22	¿Se queda a veces mirando al vacío o va de un lado al otro sin propósito?	○	○
23	Si su hijo o hija tiene que enfrentarse a una situación desconocida, ¿le mira primero a usted a la cara para saber cómo reaccionar?	○	○

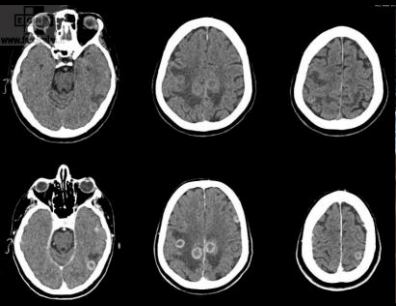
TRASTORNO DEL ESPECTRO AUTISTA

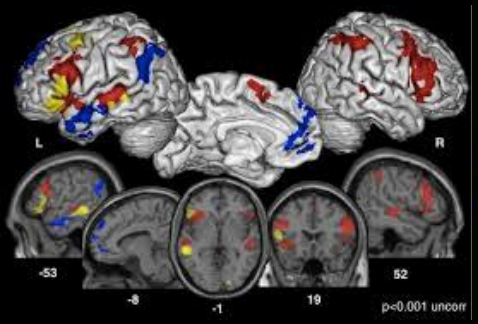


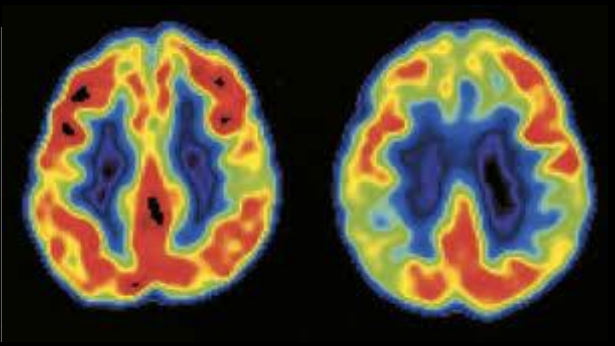
DIAGNÓSTICO

-EN BASE A LA CLÍNICA DEL PACIENTE

-SIN INDICACIÓN DE NEUROIMÁGENES







-ELECTROENCEFALOGRAMA UTILIDAD LIMITADA

-ESTUDIOS GENÉTICOS ¿CARIOGRAMA?
ESTUDIO SÍNDROMES ESPECÍFICOS
MICROARRAY CGH
ESTUDIO EXOMA COMPLETO
ESTUDIO GENOMA COMPLETO

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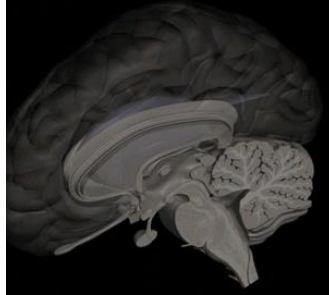
Seminars in
Pediatric
Neurology



State of the Art of Genetic Testing for Patients With Autism: A Practical Guide for Clinicians

Bracha L. Kreiman, BS,*,† and Richard G. Boles, MD*,†

The explosion in knowledge, technology, and clinical capabilities regarding genetics and genetic testing has expanded greatly in recent years, and these gains have rapidly been applied to individuals with autism spectrum disorder (ASD). However, most clinicians are unaware or confused in regards to whom to test, what tests to order, and how testing might alter management and improve outcomes. This review will address these issues. Research shows that ASD is highly genetic, and while monogenic cases are common, most patients have multiple genes interacting in disease pathogenesis. However, as genetics dictates disease risk, not outcomes, this does not exclude environmental factors. Clinically actionable genetics test results can be found across the phenotypically-heterogeneous ASD spectrum; thus recommendations are to test everyone. As ASD is also highly genetically heterogeneous, testing should address a wide range of variant types, including both large (historically detected by microarray) and small (detected by sequencing), at least across all genes (exome). Additional specialized testing important in ASD diagnostics includes fragile X, mitochondrial DNA, and pharmacogenetics; the latter often informative for which drug to order, at which dose. Recently, whole genome sequencing has emerged as a favorite since all of the above testing, and more, can be performed at a lower total cost than individual test orders. Trio (child plus parents) sequencing is often indicated, especially in more "severe" cases in order to find new (de novo) variants not present in either parent. Additionally, Angelman syndrome testing should be considered in appropriate cases. Current testing provides a precise diagnosis in many cases with ASD. Beyond diagnosis, genetic testing can oftentimes help elucidate potentially treatable risk factors that predispose the individual patient to develop disease. In this clinician's experience (RGB), this information leads to improved outcomes in as many as one-half of cases. Clinical improvement can occur in common associated ASD symptoms (attention, behavior, and anxiety) and/or in general systemtic symptoms (nausea, fatigue, pain), as demonstrated in brief case reports. Practical guidance is provided regarding assisting clinicians to choose the appropriate test (s) and laboratory, as well as how to get testing paid for. Recent cost reductions now allow for most families to benefit from genetic testing.

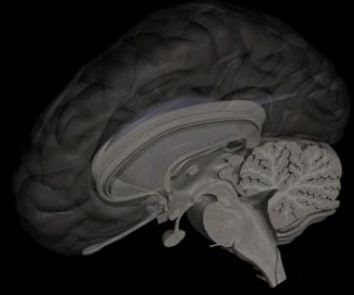
Semin Pediatr Neurol 34:100804

Reason for testing

Diagnostic test for a personal and family history of disease

Test performed

Sequence analysis and deletion/duplication testing of the 192 genes listed in the Genes Analyzed section.
Multiple panels/genes ordered: see Methods for complete list.



RESULT: POSITIVE

One Pathogenic variant identified in EEF1A2. EEF1A2 is associated with autosomal dominant early infantile epileptic encephalopathy.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
EEF1A2	c.364G>A (p.Glu122Lys)	heterozygous	PATHOGENIC
ATP1A2	c.1881C>T (Silent)	heterozygous	Uncertain Significance
ST3GAL5	c.922A>G (p.Ile308Val)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 192 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

ELSEVIER

Brain & Development 42 (2020) 77–82

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Mild epileptic phenotype associates with de novo *eef1a2* mutation: Case report and review

Marta De Rinaldis [a], Roberto Giorda [b], Antonio Trabacca [a,*]

[a] *Scientific Institute IRCCS "E. Medea", Unit for Severe Disabilities in Developmental Age and Young Adults (Developmental Neurology and Neurorehabilitation), Brindisi, Italy*
[b] *Scientific Institute IRCCS "E. Medea", Molecular Biology Laboratory, Bosisio Parini, LC, Italy*

Received 22 June 2019; received in revised form 7 August 2019; accepted 13 August 2019

Abstract

Background: Mutations in the elongation factor 1 alpha 2 (*EEF1A2*) gene have been recently shown to cause epileptic encephalopathy (MIM # 616409 EIEE33) associated with neurodevelopmental disorders such as intellectual disability, autistic spectrum disorder, hypotonia and dysmorphic facial features. EEF1A2 protein is involved in protein synthesis, suppression of apoptosis, regulation of actin function and cytoskeletal structure. To date, only sixteen patients with *EEF1A2* mutations have been reported.

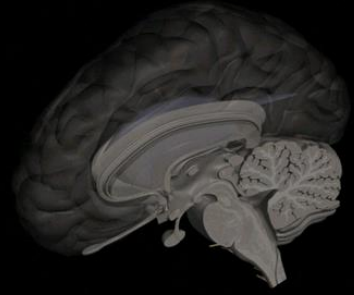
Case report: We described a new case, a boy with severe intellectual disability with absent speech, autistic spectrum disorder, mild dysmorphic facial features, failure to thrive and epilepsy associated to a de novo heterozygous missense mutation in *EEF1A2* (c.364G>A; p.Glu122Lys) identified by next generation sequencing; it was already reported in other studies. Most clinical features are shared by all individuals with *EEF1A2* mutation, but unlike others reports our patient showed a mild epileptic phenotype: epilepsy developed in late infancy and was well-controlled with antiepileptic drugs. Moreover, at the onset of epilepsy, interictal wake/sleep electroencephalograms showed typical pattern that disappeared with age.

Conclusion: This report focused that *EEF1A2* mutations should be considered not only in patients with epileptic encephalopathy, but also in those with less severe epilepsy. A typical EEG pattern may be a biomarker for *EEF1A2* mutation, but further investigations and longitudinal clinical observations are required.

Av El Líbano 5524
Casilla 138-11
Santiago - Chile
Fax : 56 (2) 98-1489
Fono : 56 (2) 98-1489

UNIVERSIDAD DE CHILE
INSTITUTO DE NUTRICION
Y TECNOLOGIA DE LOS ALIMENTOS
Laboratorio de Genética y Enfermedades Metabólicas
Neurogenética Molecular

Universidad de las
Naciones Unidas
Unidad de
Investigación
y Docencia



INFORME ESTUDIO MOLECULAR

HIBRIDACION GENOMICA COMPARADA MEDIANTE MICROARRAY (mCGH)

[redacted]

Muestra: Sangre	**Fecha Extracción**: 30/11/2016	**Fecha Informe**:09/01/2017
Examen Nº: CGH252		**Plataforma**: ISCA CGH Microarray, 8x60K
Array ID: 253174626851_2_1		**Genome assembly**: Feb. 2009 GRCh37/hg19

Técnica: Se realizó una hibridación genómica comparada o mCGH en la muestra con control masculino sobre la plataforma comercial (8x60K, Agilent). Para su análisis bioinformático se ha empleado el algoritmo Aberration Detection Methods 2 (ADM-2) y se ha establecido en 3 el número mínimo de oligos consecutivos para considerar una aberración en el número de copias. La resolución media del array de 1 clon cada 5 kb en las regiones de máximo interés, detectando pérdidas o ganancias de material genómico desde 25 kb.

Control de calidad de la muestra: DLRS (Dispersión derivada del logaritmo de ratio): 0,25 (<0,30)

RESULTADOS

Cromosoma y Banda	Categoría	Tipo	LogR	Pb Inicio	Pb Término	Tamaño (pb)	Genes OMIM*
12p12.1p11.1	Patogénica	Deleción	-0.72	21536497	34091162	12.554.666	*PYROXD1, GYS2, LDHB, ABCC9, SOX5, KRAS, BHLHE41, ITPR2, PTHLH, DDX11, FGD4, DNM1L, YARS2, PKP2*

* Causantes de enfermedad, a la fecha del informe.

RESULTADO ISCN 2016:
arr[hg19] 12p12.1p11.1(21.536.497_34.091.162)x1 dn

CONCLUSIÓN:
En todas las bases de datos de pacientes, así como en la literatura (Lu et al., 2009; Soysal et al., 2011) se describe esta deleción como patogénica. Además, la variante encontrada es similar a lo hallado en el cariotipo.
Se sugiere correlacionar las manifestaciones del paciente con lo descrito para esta deleción, así como con lo propuesto para la haploinsuficiencia del gen *SOX5* (Lamb et al., 2012) y del gen *PKP2* (Roberts et al., 2013), comprometidos en esta variante.

TRASTORNO DEL ESPECTRO AUTISTA

DIAGNÓSTICO
HERRAMIENTAS LABORATORIO: MARCADORES BIOLÓGICOS

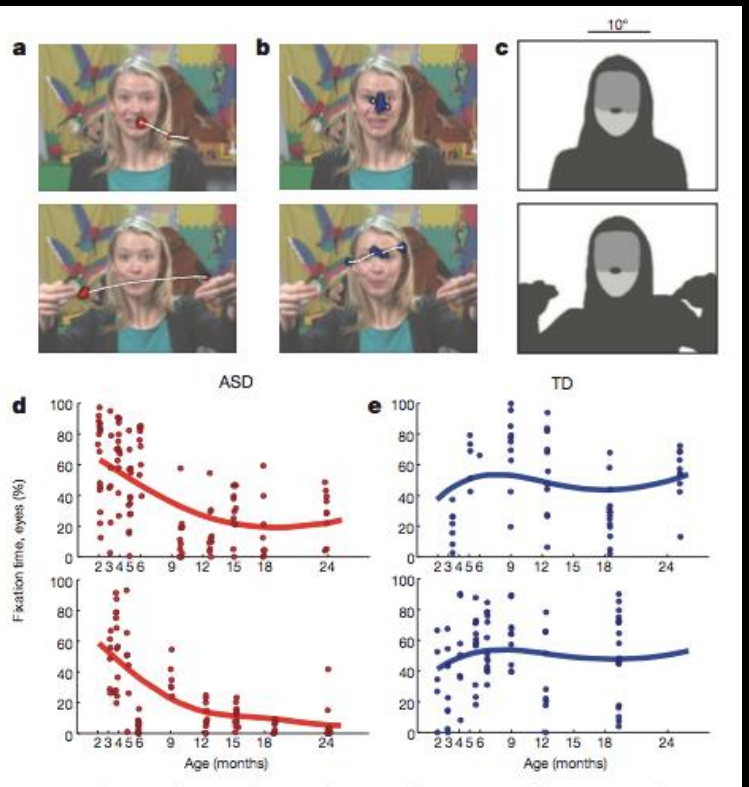
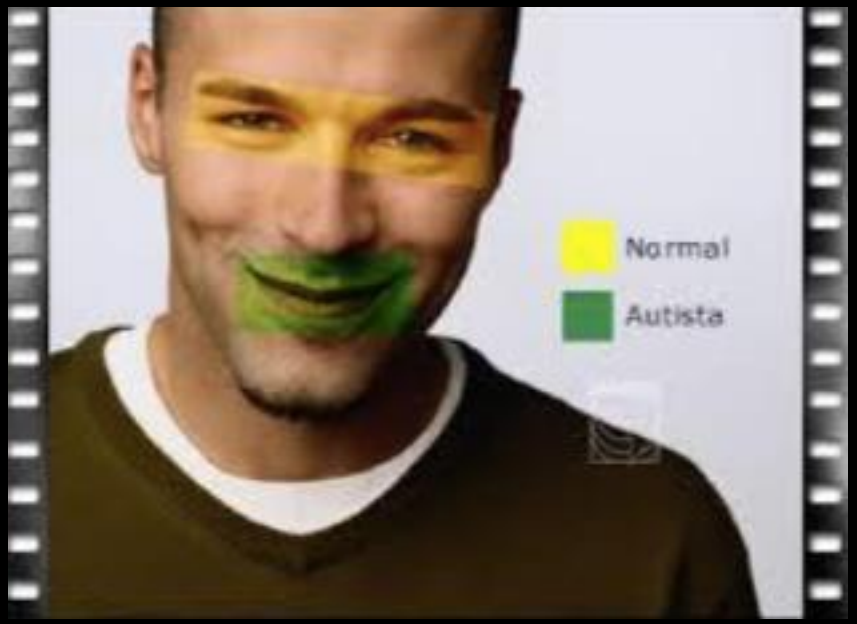
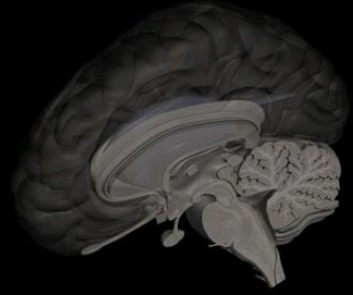


Figure 1 | Example stimuli, visual scanpaths, regions-of-interest, and longitudinal eye-tracking data from 2 until 24 months of age. **a**, Data from a 6-month-old infant later diagnosed with ASD, red. **b**, Data from a typically developing (TD) 6-month-old infant, blue. Two seconds of eye-tracking data are overlaid on each still image, onscreen at the midpoint of the data sample. Saccades are plotted as thin white lines with white dots; fixation data are plotted as larger coloured dots. **c**, Corresponding regions of interest for each image in **a** and **b**, shaded to indicate eye, mouth, body and object regions. **d**, **e**, Trial data with FDA curve fits plotting percentage of total fixation time on eyes, from 2 until 24 months of age, for two children with ASD (**d**) and two TD children (**e**).



TRASTORNO DEL ESPECTRO AUTISTA

MANEJO TERAPÉUTICO



-PRIMERO CONSIDERAR QUE NO TODOS LOS PACIENTES SON IGUALES

-EVALUAR EN QUÉ PUNTO DEL ESPECTRO SE ENCUENTRA

-RECONOCER CUADROS SIMILARES EN LA FAMILIA

-LAS EXPECTATIVAS DEPENDERÁN DE LAS CONDICIONES DEL MEDIO SOCIAL

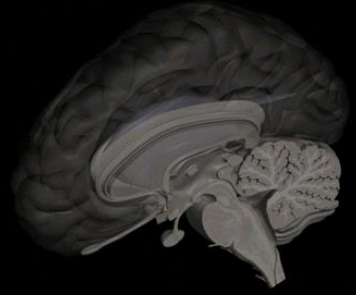
-NO EXISTE UNA CURA MILAGROSA

-LA TERAPIA CONSISTE EN POTENCIAR LAS ÁREAS EN FALENCIA Y HACER AL SUJETO FUNCIONAL AL MEDIO EN QUE SE DESENVUELVE

-MIENTRAS MÁS TEMPRANA LA DETECCIÓN DEL CUADRO, MEJOR EVOLUCIÓN

TRASTORNO DEL ESPECTRO AUTISTA

MANEJO TERAPÉUTICO



-TERAPIA NEUROSENSORIAL

-TERAPIA FONOAUDIOLÓGICA (COMUNICACIÓN)

-PSICOTERAPIA (HABILIDADES SOCIALES)

-RESPETO CICLOS BIOLÓGICOS

-FOMENTAR LA SOCIABILIZACIÓN

-USO RACIONAL DE PANTALLAS Y MEDIOS ELECTRÓNICOS

-TERAPIA FARMACOLÓGICA

NEUROLÉPTICOS
PSICOESTIMULANTES
ANSIOLÍTICOS
ESTABILIZANTES DE ÁNIMO
MANEJO SÍNTOMAS TOC
OCITOCINA INTRANASAL

Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism

Karen J. Parker[a,1], Ozge Oztan[a], Robin A. Libove[a], Raena D. Sumiyoshi[a], Lisa P. Jackson[a], Debra S. Karhson[a], Jacqueline E. Summers[a], Kyle E. Hinman[a], Kara S. Motonaga[b], Jennifer M. Phillips[a], Dean S. Carson[a], Joseph P. Garner[a,c], and Antonio Y. Hardan[a]

[a]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94305; [b]Department of Pediatrics, Stanford University, Stanford, CA 94305; and [c]Department of Comparative Medicine, Stanford University, Stanford, CA 94305

Edited by Michael L. Platt, University of Pennsylvania, Philadelphia, PA, and accepted by Editorial Board Member Michael S. Gazzaniga June 6, 2017 (received for review April 17, 2017)

Autism spectrum disorder (ASD) is characterized by core social deficits. Prognosis is poor, in part, because existing medications target only associated ASD features. Emerging evidence suggests that the neuropeptide oxytocin (OXT) may be a blood-based biomarker of social functioning and a possible treatment for ASD. However, prior OXT treatment trials have produced equivocal results, perhaps because of variability in patients' underlying neuropeptide biology, but this hypothesis has not been tested. Using a double-blind, randomized, placebo-controlled, parallel design, we tested the efficacy and tolerability of 4-wk intranasal OXT treatment (24 International Units, twice daily) in 32 children with ASD, aged 6–12 y. When pretreatment neuropeptide measures were included in the statistical model, OXT compared with placebo treatment significantly enhanced social abilities in children with ASD [as measured by the trial's primary outcome measure, the Social Responsiveness Scale (SRS)]. Importantly, pretreatment blood OXT concentrations also predicted treatment response, such that individuals with the lowest pretreatment OXT concentrations showed the greatest social improvement. OXT was well tolerated, and its effects were specific to social functioning, with no observed decrease in repetitive behaviors or anxiety. Finally, as with many trials, some placebo-treated participants showed improvement on the SRS. This enhanced social functioning was mirrored by a posttreatment increase in their blood OXT concentrations, suggesting that increased endogenous OXT secretion may underlie this improvement. These findings indicate that OXT treatment enhances social abilities in children with ASD and that individuals with pretreatment OXT signaling deficits may stand to benefit the most from OXT treatment.

autism | biomarkers | clinical trial | oxytocin | social functioning

Autism spectrum disorder (ASD) is a brain disorder of early childhood onset. ASD is characterized by core social communication impairments as well as restricted, repetitive behaviors, which jeopardize the development of appropriate social skills and the maintenance of social relationships (1). Despite being one of the most devastating childhood disorders in terms of prevalence [1 in 68 US children (2)] and societal cost [$236 billion expended annually in the United States (3)], ASD pathophysiology remains poorly understood. Consequently, there are no approved medications that enhance social abilities in individ-

OXT signaling through pharmacologic or genetic manipulation produces social deficits in rodents (11).

Studies of rodent models of human syndromes with high ASD penetrance (e.g., fragile-X syndrome, Prader–Willi syndrome, cortical dysplasia, and focal epilepsy syndrome modeled using CNTNAP2-knockout mice) have reported social impairments and diminished numbers of hypothalamic OXT-producing cells (12–14). This reduction in brain OXT has been associated with lower blood OXT concentrations in transgenic vs. wild-type animals, with social impairments ameliorated in transgenic animals following OXT treatment (13, 15). These preclinical findings suggest that the OXT signaling pathway may be a promising therapeutic target for improving social abilities in patients with ASD, particularly in those with OXT signaling deficits.

Multiple studies have shown that single doses of OXT administered to individuals with ASD improve processing of social information (16), emotion recognition (17), and social learning (18). However, evidence from OXT treatment trials in ASD patients is more equivocal: Several studies have reported that OXT administration improves social abilities in individuals with ASD (19, 20), but others have found no improvement in the trial's primary outcome measure (21–24). Interestingly, many OXT administration studies have documented significant

Significance

Autism spectrum disorder (ASD) is characterized by social deficits. Emerging evidence suggests that the neuropeptide oxytocin, which regulates mammalian social functioning, may be a promising treatment for ASD. However, prior oxytocin treatment trials in ASD patients have produced equivocal results, perhaps because of variability in patients' underlying neuropeptide biology. Here we provide evidence that oxytocin treatment improves social abilities in children with ASD and that individuals with the lowest pretreatment blood oxytocin concentrations benefit the most from oxytocin administration. These findings reveal a personalized component to oxytocin treatment which may have important implications for accurately testing oxytocin's therapeutic potential, both for ASD and for a broad range of developmental and psychiatric disorders in which patients exhibit social impairments.

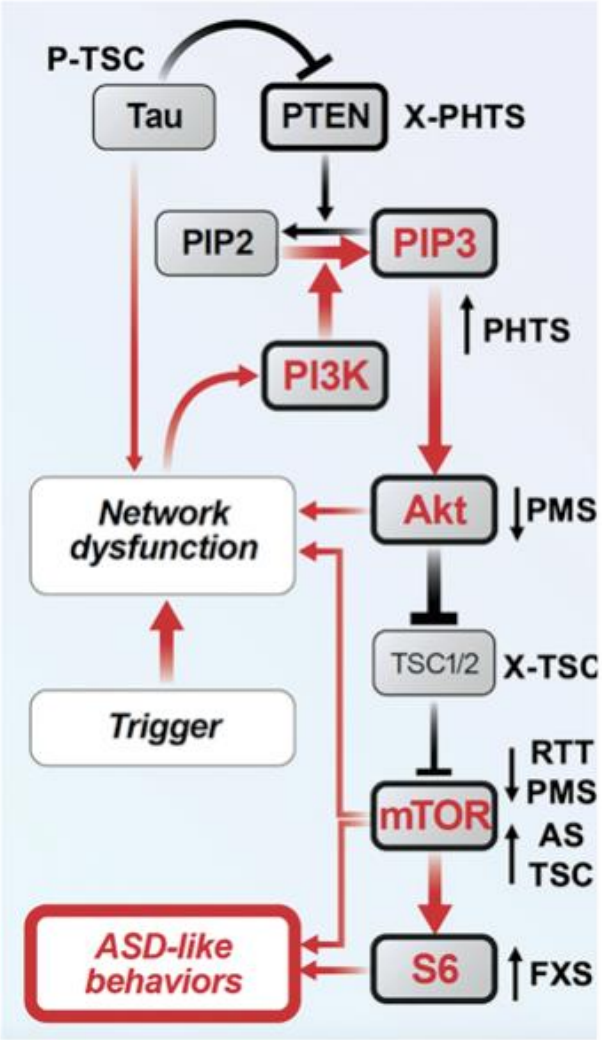
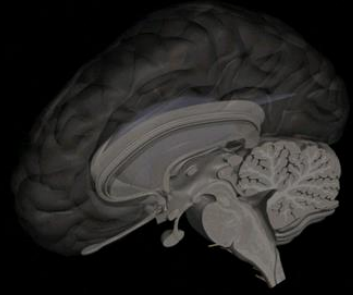


Figure 1. Autism-Related Syndromes Affected by mTOR Dysregulation

There are several genetically defined disorders that exhibit dysregulation of the PI3K/Akt/mTOR pathway. Based on the role of tau on the inhibition of PTEN described by Tai et al., the therapeutic approach of tau reduction could be applied to disorders with pathological upregulation of the pathway, including fragile X (FXS) and Angelman syndrome (AS). Rett (RTT) and Phelan-McDermid syndrome (PMS), though, exhibit pathological downregulation of the pathway and would not be amendable to this approach. mTORopathies defined by mutations directly within this pathway that include tuberous sclerosis complex (TSC) and PTEN hamartoma tumor syndrome (PHTS) similarly may not benefit from a tau reduction approach despite evidence of tau pathology because of the absence of the mediators of this response. ↑ indicates upregulation, ↓ indicates downregulation, "p" indicates phosphorylation. Figure modified from Tai et al. (2020).



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Tau: A Novel Entry Point for mTOR-Based Treatments in Autism Spectrum Disorder?

Meera E. Modi[1] and Mustafa Sahin[1,*]
[1]Translational Neuroscience Center, F.M. Kirby Neurobiology Center, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
*Correspondence: mustafa.sahin@childrens.harvard.edu
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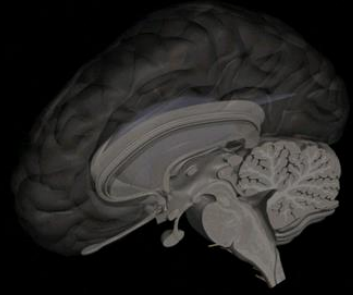
Dysregulation of the PI3K/Akt/mTOR pathway has become a point of convergence in autism spectrum disorder (ASD). In this issue of *Neuron*, Tai et al. (2020) identify a therapeutic role for tau reduction in downregulating this pathway and ameliorating ASD-like symptoms.

Tau Reduction Prevents Key Features of Autism in Mouse Models

Chao Tai,[1] Che-Wei Chang,[1] Gui-Qiu Yu,[1] Isabel Lopez,[1] Xinxing Yu,[1] Xin Wang,[1] Weikun Guo,[1] and Lennart Mucke[1,2,3,*]
[1]Gladstone Institute of Neurological Disease, Gladstone Institutes, San Francisco, CA 94158, USA
[2]Department of Neurology and Weill Institute for Neurosciences, University of California, San Francisco, San Francisco, CA 94143, USA
[3]Lead Contact
*Correspondence: lennart.mucke@gladstone.ucsf.edu
https://doi.org/10.1016/j.neuron.2020.01.038

TRASTORNO DEL ESPECTRO AUTISTA

MANEJO TERAPÉUTICO



-DESCARTAR COMORBILIDAD FRECUENTE: DIGESTIVO-TIROIDES

-DÉFICIT OLIGOELEMENTOS-DIETA RESTRICTIVA: HIERRO-ZINC-VIT D-B12

-CORREGIR ALTERACIONES DEL SUEÑO

-EVITAR FACTORES AGRAVANTES AMBIENTALES (“DROGAS”)

-AUMENTAR CONTACTO CON “LO NATURAL”

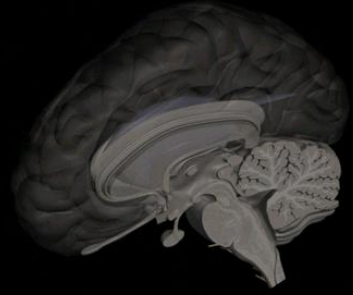
-¿PROBIÓTICOS?

-DESCARTAR FACTORES MÉDICOS-AMBIENTALES EN “DESCOMPENSACIONES”

-DESCARTAR TERAPIAS ALTERNATIVAS DE RIESGO PARA LOS NIÑOS

-SENADIS: MANEJO DE TRÁNSITO A LA VIDA INDEPENDIENTE

TRASTORNO DEL ESPECTRO AUTISTA



COMPLICACIONES-SECUELAS

-DEPENDIENTES DE COMORBILIDAD-ETIOLOGÍA

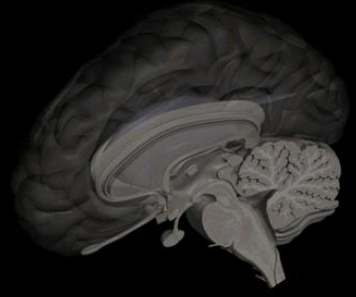
-PERSISTENCIA DE PROBLEMÁTICA CONDUCTUAL DISRUPTIVA EN EL TIEMPO

-EXCLUSIÓN DE SISTEMA ESCOLAR

-EVOLUCIÓN A CUADROS ESFERA PSIQUIÁTRICA (PSICOSIS, CUADROS ESQUIZOMORFOS)

-FALTA DE AUTONOMÍA EN LA VIDA DIARIA - ”DESGASTE PARENTAL”

-RIESGO DE INSTITUCIONALIZACIÓN



TRASTORNO DEL ESPECTRO AUTISTA

CONCLUSIONES DESDE LA NEUROBIOLOGÍA

-EL AUTISMO ES UN CUADRO DE ORIGEN BIOLÓGICO

-BASE GENÉTICA, MODULADO AMBIENTALMENTE

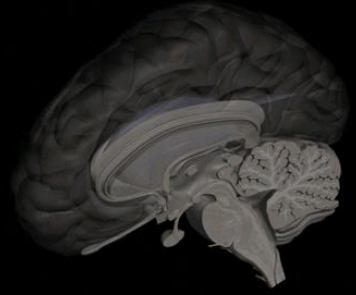
-SUS CEREBROS SON DIFERENTES

-GRANDES AVANCES EN COMPRENSIÓN DEL FENÓMENO

-CON LIMITADOS ALCANCES (AÚN) EN LO TERAPÉUTICO

-DESARROLLO HERRAMIENTAS DIAGNÓSTICAS TEMPRANAS
(MAYORES VENTANAS DE OPORTUNIDAD TERAPÉUTICA)

-REQUIERE EQUIPOS DE ESTUDIO Y MANEJO MULTIPROFESIONAL



CLASE TRASTORNOS DEL ESPECTRO AUTISTA:
OBJETIVOS A DOMINAR POR LOS ESTUDIANTES

-ENTENDER CONCEPTUALMENTE LA TERMINOLOGÍA ASOCIADA A ESTE TIPO DE TRASTORNOS DEL NEURODESARROLLO

-SER CAPAZ DE IDENTIFICAR LOS SÍNTOMAS TEMPRANOS DE PRESENTACIÓN

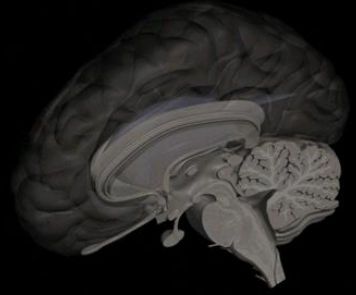
-CONOCER LAS HERRAMIENTAS DE TAMIZAJE POBLACIONAL

-CONOCER LAS HERRAMIENTAS DIAGNÓSTICAS DE LOS TEA

-IDENTIFICAR ELEMENTOS CLÍNICOS QUE HACEN PENSAR QUE UN TEA ESTÉ RELACIONADO A UNA ENFERMEDAD ORGÁNICA DEFINIDA

-CONOCER LAS ESTRATEGIAS TERAPÉUTICAS DE USO HABITUAL EN TEA

-CONOCER LAS COMPLICACIONES ASOCIADAS A LOS TEA



TRASTORNOS DEL ESPECTRO AUTISTA

PRESENTACIÓN DISPONIBLE EN
www.doctorpatricioguerra.cl

DR. PATRICIO GUERRA
NEURÓLOGO INFANTIL Y ADOLESCENTES
MAGÍSTER NEUROCIENCIAS
DIPLOMADO TRASTORNOS DEL ESPECTRO AUTISTA
ESCUELA DE MEDICINA UNIVERSIDAD SAN SEBASTIÁN PUERTO MONTT