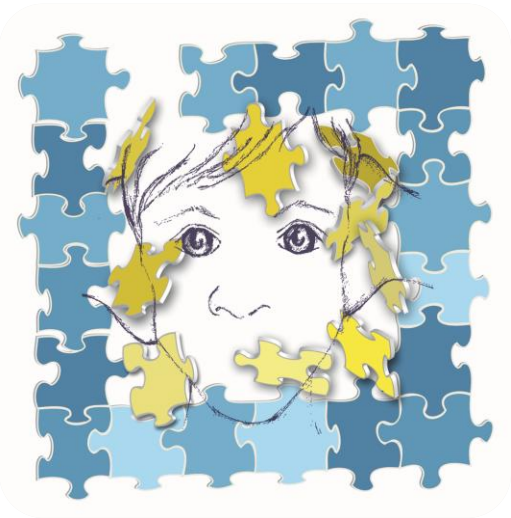
Neurobiologia dell'Autismo e cenni di epidemiologia



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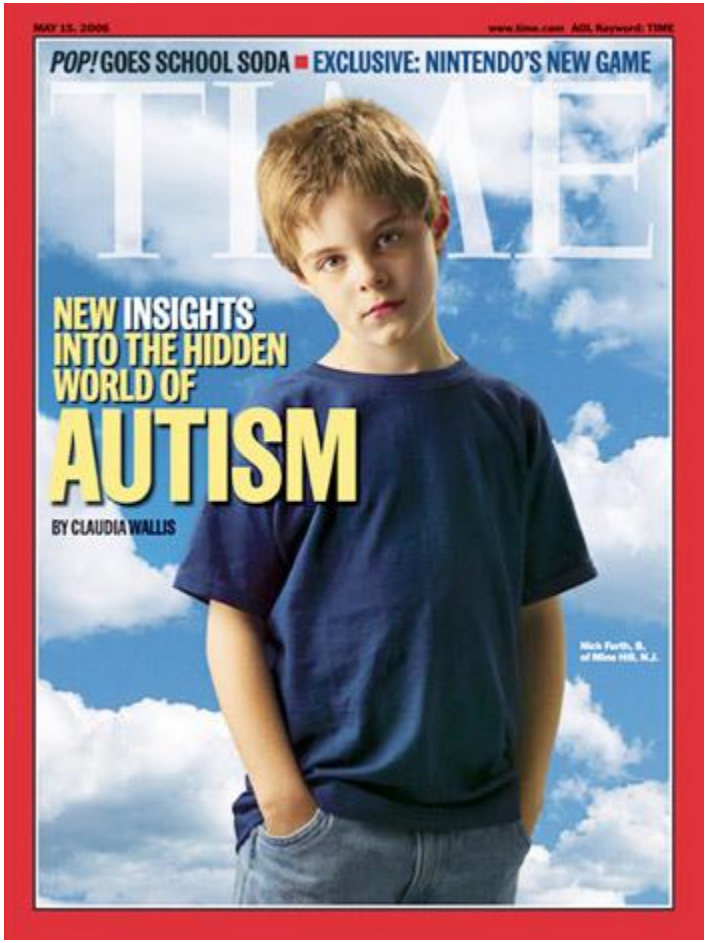
Special Issue November 2011



"I bambini del nostro gruppo hanno manifestato la loro profonda solitudine dall'inizio della loro vita, non rispondendo a niente che provenisse dal mondo esterno"

Leo Kanner,
Johns Hopkins University
Autistic disturbances of affective contact
Nervous Child 2:217-250, 1943

Un pò di storia…

1943: Leo Kanner

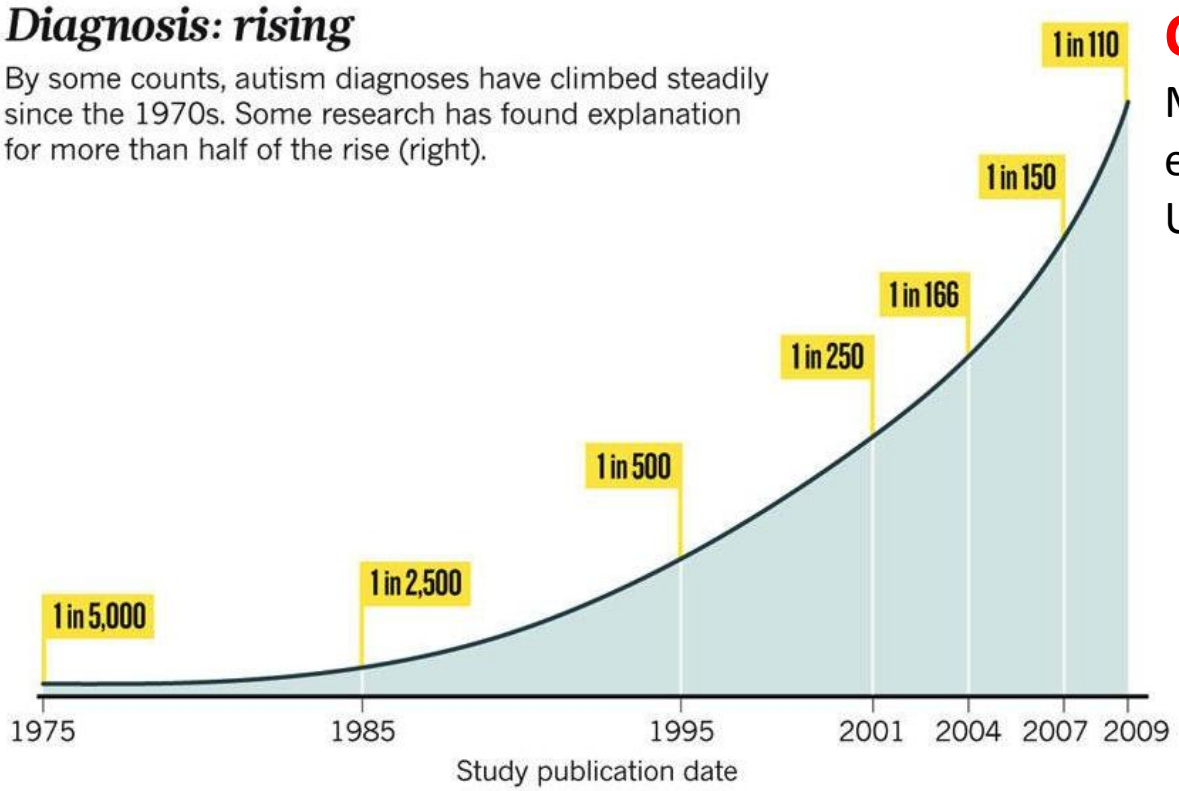
1952: Early-onset schizophrenia

1980: Infantile autism

1987: Autism Disorder

2000: Autism Spectrum Disorders: autism disorder, Asperger's syndrome, Rett Syndrome and pervasive developmental disorder not otherwise specified' (PDD-NOS)

Epidemiologia



CDC:

More than 90 in 10000 eight-year-olds in the United States had autism

King, M. & Bearman P. P.Int J Epidemiol (2009); King M. & Bearman P. Am. Soc.Rev. (2011)

Epidemiologia

"Current US prevalence for autism is low because they don't look at the entire population. Many US studies are based on diagnosed cases of autism",

Grinker, 2001

SOUTH KOREA: 1 in 38

In the 1980s, he had found Korean families generally unwilling to admit that anything might be wrong with their children, because of the stigma attached. But when he undertook the latest study, attitudes had changed. Families in Ilsan, a stable, residential community on the outskirts of Seoul, welcomed information about autism, which in this study was offered confidentially.

His team screened more than **55,000 children born between 1993 and 1999**, and came up with an estimated prevalence for ASD of 1 in 38.

Kim, Y. S. et al. Am. J. Psychiatry **168, 904–912 (2011)**

Epidemiologia

Alcuni studi evidenziano come la prevalenza è sempre stata alta

1) Terry Brugha, a psychiatrist at the University of Leicester, UK

His team knocked on more than 7,000 doors across England: he calculated a prevalence of autism in adults of **9.8 in 1,000** — close to the frequency found in US children.

Brugha, T. S. *et al. Arch. Gen. Psychiatry* ***68, 459–465 (2011).***

2) Christopher Gillberg, child and adolescent psychiatry at the University of Gothenburg in Sweden

He found a prevalence of autism of **0.7%** among seven-year-old Swedish children in 1983 and **1%** in 1999.

Gillberg, C. *J. Child Psychol. Psychiatry* ***24, 377–403 (1983).***
Kadesjö, B., Gillberg, C. & Hagberg, B. *J. Autism Dev. Disord.* ***29, 327–331 (1999).***

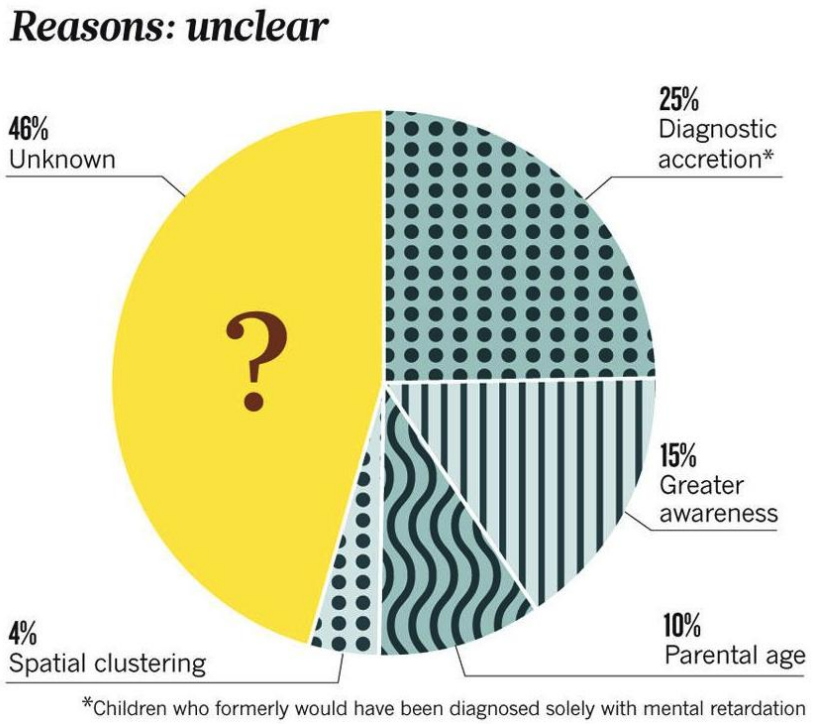
Epidemiologia

Peter Bearman, a sociologist at Columbia University in New York:

He analyzed nearly 5 million California birth records and 20,000 records from the state's department of developmental services

By linking **birth** with **detailed diagnostic data** he was able to generate a rich picture of the demographics and life history of those with autism, which yielded clues to the social factors that influence diagnosis.

Epidemiologia



He still cannot explain 46% of the increase in autism: new environmental pollutants?

King, M. & Bearman P. P.Int J Epidemiol (2009);
King M. & Bearman P. Am. Soc.Rev. (2011)

Environment?

During the past decade:

- **the US federal goverment has spent about:**

-$1 billion researching the genetics of autism

-$40 million on studies of possible environmental factors

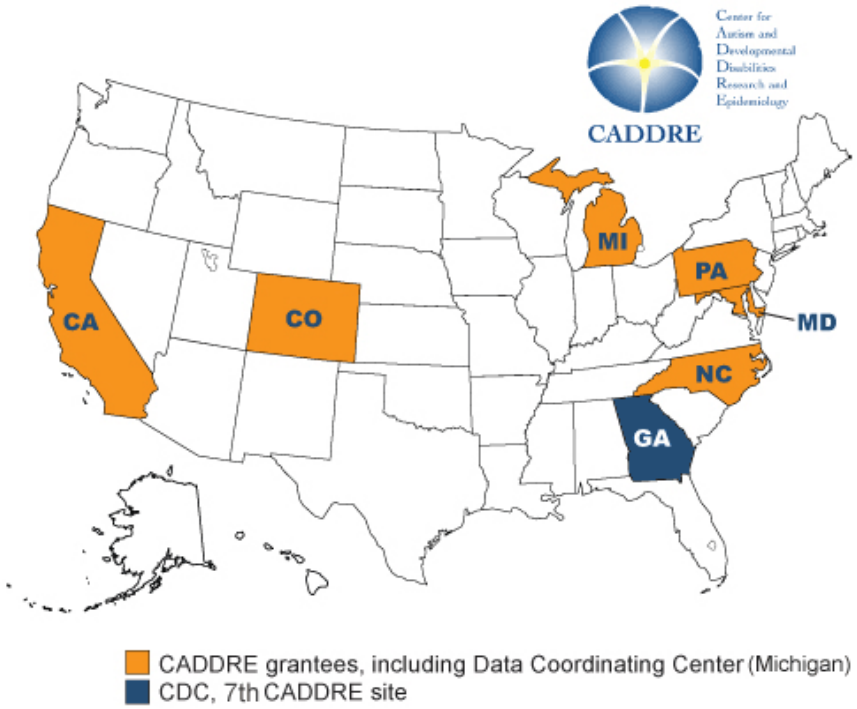
SEED

Under the auspices of CDC, began recruiting about 2700 children aged two to five

The study includes developmental evaluations, questionnaries, a review of medical records and analysis of blood, cheek-cell and hair-samples to examine genetic make-up exposures to environmental chemicals

SEED

The six SEED study sites and a data coordinating center are part of the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network.



EARLI

Funded by NIH is enrolling up to 1200 families that have a child with autism and are preparing to have another baby

The study intends to look for any interplay between environmental factors and genetic susceptibility that might contribute to autism risk in their next child

Geni e ambiente

COMPONENTE AMBIENTALE	DISTURBI DELLO SPETTRO AUTISTICO	COMPONENTE GENETICA

ESPOSIZIONE IN UTERO A:

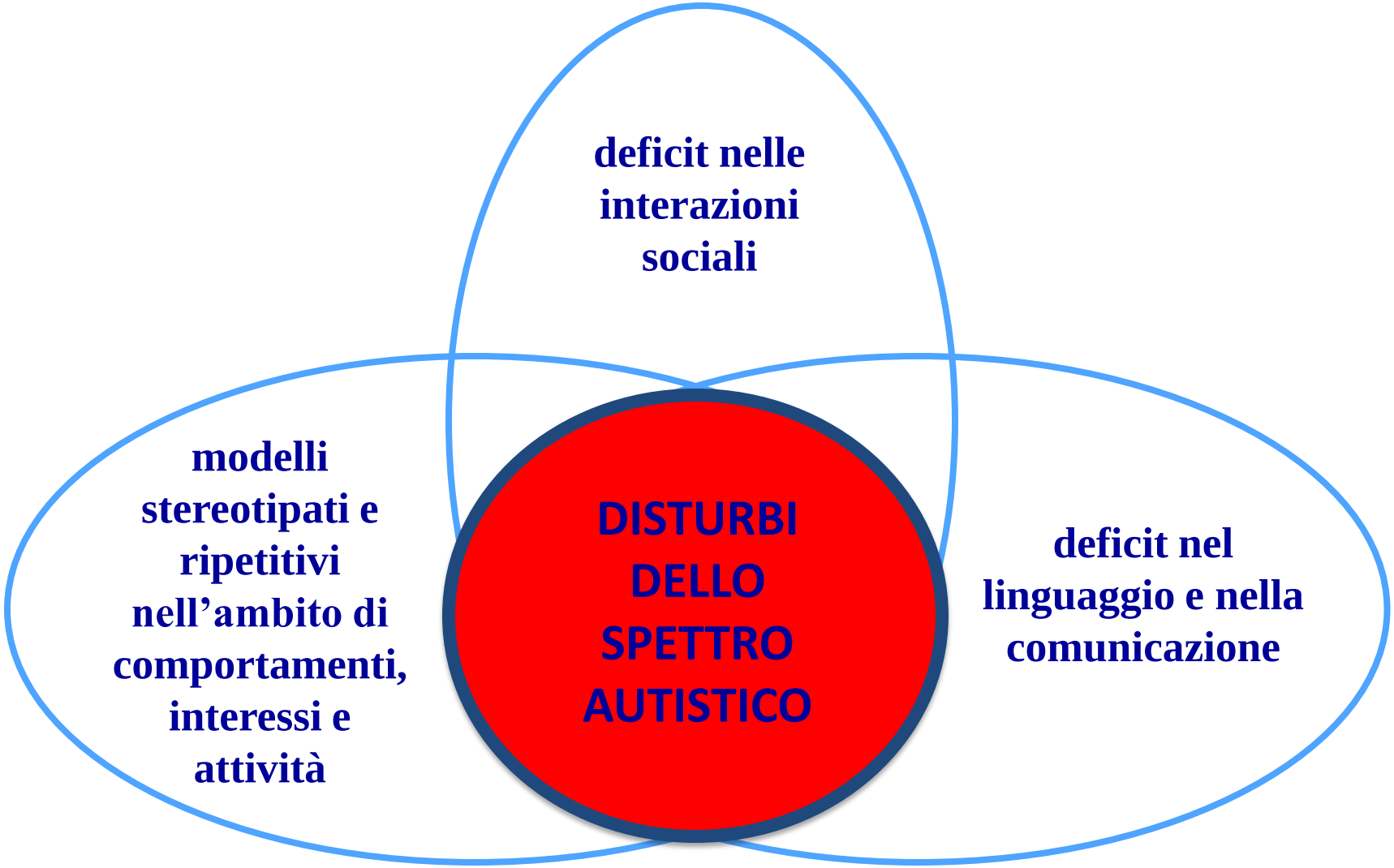
- **Virus della rosolia**
- **Elevati livelli di testosterone**
- **Sostanze che causano difetti alla nascita: alcool etilico, acido valproico** (farmaco antiepilettico)**, talidomide** (farmaco tranquillante ed antiematico)
- **Sono in studio gli organofosfati** (sostanze comunemente usate come pesticidi in agricoltura e come insetticidi in ambito domestico)

MICROARRAY

Copy number variations (CNVs) (Delezione o duplicazione di piccoli segmenti di DNA)

Mutazioni puntiformi (SNPs) (Polimorfismo di un singolo nucleotide)

Sintomi (DSM-IV)



Causes of Autism Spectrum Disorders: strongest evidence is genetic

- 4:1 frequency ratio boys:girls in ASD (8:1 in AS e 1:1 quando QI<50)
- Concordance is 60-80% for monozygotic twins
- Concordance is 20-30% in dizygotic twins
- Linkage analyses indicate many genes underlying Autism Spectrum Disorders, including linkages at chromosomal loci 15q11-q13, 16p11.2, 22q13, X-linked
- Multiple putative candidate genes include *GABA-β3*, *5-HTT*, *MET, PTEN*, *En2*, *UBE3a*, *CNTNAP2*, neurexins, neuroligins, shanks, SYN-1 and genes for comorbid neurodevelopmental disorders including *FMR1, MECP2, TSC*

High risk infants

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Baby Siblings Research Consortium Study

finanziato da AUTISM SPEAKS

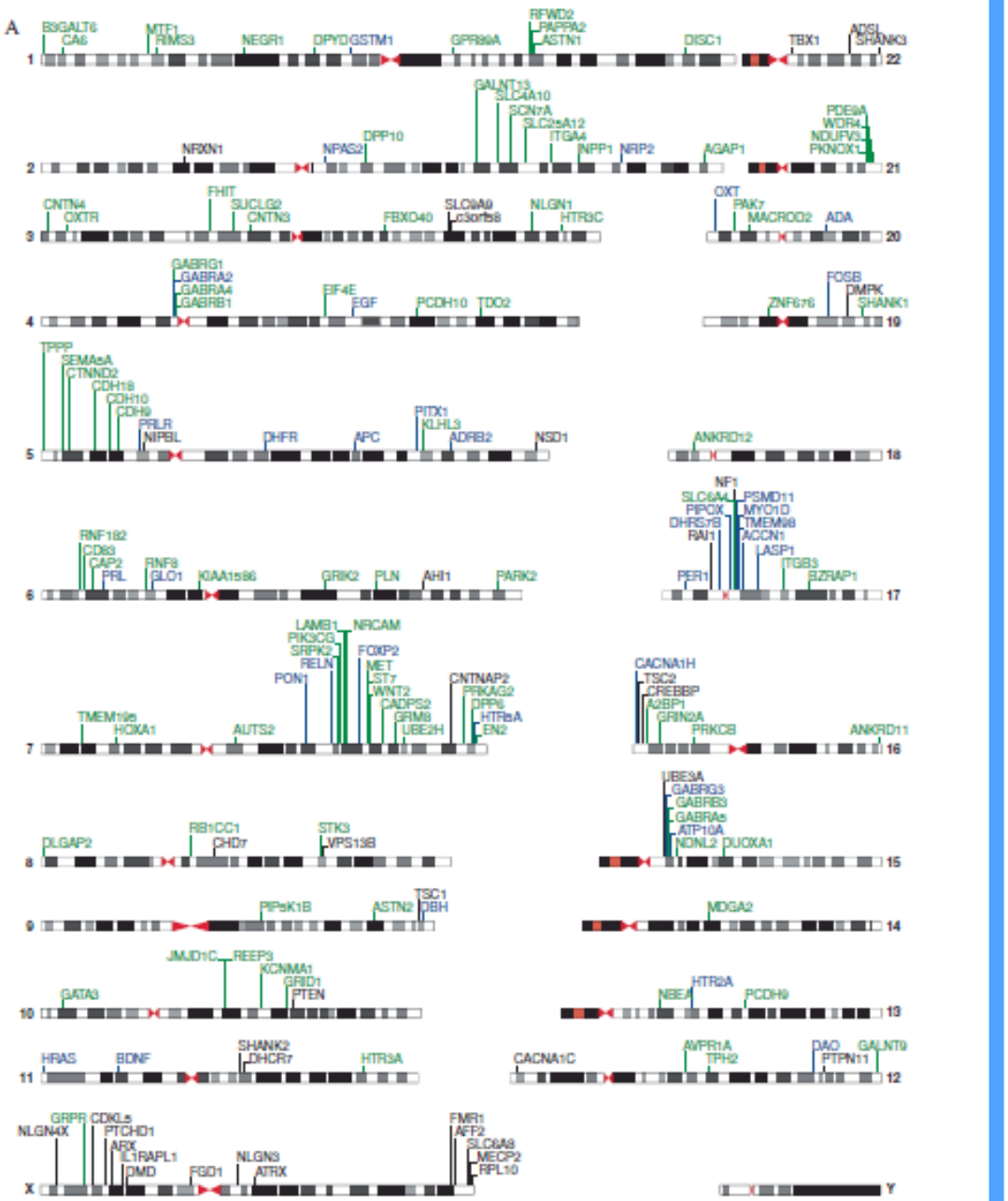
- **12 siti negli Stati Uniti**

- **664 bambini ad alto rischio reclutati e seguiti fino ai 36 mesi**

- **132 bambini diagnosticati con DSA (41% autismo; 59% con Disturbi generalizzati dello sviluppo non altrimenti specificati)**

RISCHIO SALITO AL 18% (25.9% nei maschi e 9.6% nelle femmine)

La complessità della genetica alla base dei DSA



ASD candidates

Genes showing association with ASD

ASD genes

Holt and Monaco, EMBO Mol Med. 2011

Mendelian Syndromes

12p13.33 (CACNA1C) Timothy Syndrome
15q11.2 (UBE3A) Angelman Syndrome
Xq27.3 (FMR1) Fragile X Syndrome
Xq28 (MECP2) Rett Syndrome

increase in risk for ASDs

Rare variants

2p16.3 (NRXN1) ASD, ID, language delay, SCZ
3p13 (FOXP1) ID, ASD
22q13.33 (SHANK3) ASD
Xp22.32-p22.31 (NLGN4X) ASD, ID, TS, ADHD
Xq13.1 (NLGN3) ASD

Common Alleles

1q42.2 (DISC1)
7q22.1 (RELN)
7q36.3 (EN2)

SnapShot: Genetics of Autism

Neuron

Kimberly A. Aldinger, Jasmine T. Plummer, Shenfeng Qiu, and Pat Levitt
Keck School of Medicine of USC, Los Angeles, CA, 90089, USA

	CHR GENE	PROTEIN FUNCTION	HUMAN PHENOTYPE (MUTANT MOUSE PHENOTYPES)
Mendelian Syndromes[1]	6q23.3 (AHI1*)	Jouberin; interacts with β-catenin in cilia	**Joubert syndrome.** (Reduced brain and body size. Cerebellar, retinal, and kidney defects. Most die by P10. Neuron-specific loss leads to depressive-like phenotypes.)
	7q35-q36.1 (CNTNAP2*)	Caspr2, a neurexin family member; clusters voltage-gated K+ channels	**Recessive EPI syndrome, ASD, ADHD, TS, OCD.** (Neuronal migration defects. Reduced GABAergic neurons and decreased cortical synchrony. Seizures. Deficits in social, repetitive behaviors, and USV.)
	9q34.13 (TSC1)	Hamartin, a growth inhibitory protein that negatively regulates the mTOR pathway	**Tuberous Sclerosis type I.** (Liver and neural tube defects. Die by E12. Abnormal kidney and liver growth in heterozygotes. Variable brain structure, function and behavior abnormalities in conditional mutants. Die at various postnatal ages. Neuron-specific loss causes abnormal spine morphology and cortical excitability. Loss of LTD.)
	10q23.31 (PTEN)	Protein tyrosine phosphatase; negatively regulates the mTOR pathway	**Cowden disease.** (Placenta and germ cell defects. Die by E9.5. Neuron-specific loss alters synaptic physiology. Heterozygotes have prostate, skin and colon defects, and spontaneous tumors. Macrocephaly, neuronal hypertrophy, abnormal social interaction, and increased survival in conditional mutants.)
	11q13.4 (DHCR7)	Final enzyme in cholesterol biosynthetic pathway	**Smith-Lemli-Opitz syndrome.** (Craniofacial and lung abnormalities. Die by P1. Abnormal cholesterol regulation and enlarged bladders. Hypomorphic mutants are viable and fertile. Compound mutants have fused toes, enlarged ventricles, and 25% embryonic lethality.)
	12p13.33 (CACNA1C)	α-1 subunit of a voltage-dependent Ca2+ channel	**Timothy syndrome.** (Die embryonically. Impaired pancreatic function. Motor defects and antidepressant-like behavior in heterozygotes; anxiety-like deficits in females. Neuron-specific loss, impaired cognition and LTP.)
	15q11.2 (UBE3A)	Ubiquitination ligase; targets protein degradation system	**Angelman syndrome.** (Small brain, seizure susceptibility, motor and learning deficits. Reduced spine density and impaired LTP. Impaired synapse maturation and plasticity.)
	16p13.3 (TSC2)	Tuberin; which negatively regulates the mTOR pathway	**Tuberous Sclerosis type II.** (Heart, neural tube, and motor defects. Purkinje cell death. Die by E12. Various tumors and axon guidance defects in heterozygotes. Dominant-negative mutant has enhanced anxiety-like behaviors; motor, learning, social behavior deficits.)
	17q11.2 (NF1)	Neurofibromin; a GTPase activator and negative regulator of RAS signaling	**Neurofibromatosis.** (Macrocephaly, small eyes, and heart defects. Delayed organ development. Embryonic lethal. Increased astrocytes and tumor susceptibility. LTP and learning and memory deficits in heterozygotes.)
	Xp21.2 (DMD)	Dystrophin; cytoskeletal protein bridging ECM	**Duchenne muscular dystrophy.** (Muscle and heart defects in hemizygous males and homozygous females. Reduced fertility. Abnormal retinal electrophysiology and synapse organization, density, and maturation.)
	Xp21.3 (ARX)	Aristaless-related homeobox protein TF	**LIS, XLID, EPI, ASD.** (Hemizygous males die perinatally. Decreased inhibitory synaptic transmission. Males hemizygous for point mutations or triple repeat expansions have seizures. Defects in behavior and GABAergic neuron generation and migration.)
	Xq27.3 (FMR1)	Fragile X mental retardation protein; an RNA-binding protein that traffics mRNA	**Fragile X syndrome.** (Seizures. Enlarged testes in males. Learning and social behavior defects. Dendritic spine abnormalities. Enhanced LTD and impaired LTP. Altered cortical drive and E/I neuronal cortical networks.)
	Xq28 (MECP2)	MeCP2; involved in transcriptional regulation and chromatin organization	**Rett syndrome.** (Brain, breathing, and motor defects in hemizygous males. Mild cognitive and anxiety-like phenotypes in heterozygous females. Various conditional loss and postnatal reduction mimic null phenotypes in adult hemizygous males. Impaired excitatory synapses and spine morphology. Increased neuronal connectivity.)
Rare Variants	2p16.3 (NRXN1)	A neurexin; forms intracellular junctions through neuroligin binding	**ASD, ID, language delay, SCZ.** (Reduced startle and PPI. Enhanced anxiety-like behavior and motor learning. Impaired spatial memory. Defective LTP. Defects in excitatory synaptic strength and diminished NMDA/AMPA receptor current.)
	3p13 (FOXP1)	A forkhead box TF	**ID, ASD, SLI.** (Cardiovascular defects. Die embryonically.)
	6q16.3 (GRIK2*)	A postsynaptic glutamate receptor subunit	**Recessive ID.** (Increased sensitivity to drug-induced seizures. Elevated startle and pain threshold. Impaired synaptic plasticity and inhibitory transmission.)
	7q31.1 (FOXP2)	A forkhead box TF	**SLI.** (Growth retardation, reduced USV, cerebellar, motor and neurological defects. Perinatal death. Impaired LTD and plasticity.)
	15q11-q13		**ASD, EPI, ID.** (Cleft palate in deletion mutants; die by P3; motor, and cognitive defects. Seizures. Increased newborn USV in maternal heterozygotes. Reduced activity, social interactions, and USV; increased anxiety-like behavior in duplications.)
	16p11.2		**ASD, ADHD, ID, EPI, SCZ.** (Mild structual brain defects and gene dose-dependent behavioral phenotypes.)
	17q11.2 (SLC6A4)	5-HT transporter	**ASD, OCD.** (Heart defects. Hyperactive, aggressive, anxiety-like behaviors, and learning deficits.)
	22q11.21		**DiGeorge syndrome, SCZ, ASD, ID.** (Sensorimotor, learning, and memory deficits. Hyperactivity. Increased anxiety-like behavior.)
	22q13.33 (SHANK3)	A PSD scaffold protein	**ASD.** (Variable phenotypes including excessive grooming, anxiety-like behavior, and disrupted social interactions. Abnormal dendritic spines. Reduced synaptic transmission, LTP, LTD, and NMDAR-dependent responses.)
	Xp22.32-p22.31 (NLGN4X)	A neuroligin; ligand for β-neurexins	**ASD, ID, TS, ADHD.** (Reduced brain size. Social interaction and USV deficits.)
	Xq13.1 (NLGN3*)	A neuroligin; ligand for β-neurexins	**ASD.** (Reduced brain size. Abnormal learning, social behavior, USV, and olfaction. Hyperactivity, altered E/I balance shift caused by increased inhibitory synaptic transmission.)
Common Alleles	1q42.2 (DISC1)	Large transmembrane protein involved in neurite outgrowth and brain development	(Region-specific changes in neuronal morphology. Homozygote and heterozygote learning and memory deficits. Reduced neurogenesis and altered neuron distribution. Abnormal dendritic spines. Reduced short-term plasticity.)
	2q31.1 (SLC25A12)	Mitochondrial Ca2+-binding carrier	(Growth retardation. Tremors, myelination and motor defects. Die E18–P15.)
	3p25.3 (OXTR)	GPCR for oxytocin	(Abnormal maternal behavior. Hypoactivity, increased aggression and USV in males. Social memory defects. Fewer GABAergic synapses.)
	7q31.2 (MET)	Receptor tyrosine kinase	(Muscle, axon guidance, placenta, and liver defects. Die by E14. Abnormal cortical dendrites/spines and hyperconnectivity of local circuits in conditional mutant.)
	7q22.1 (RELN)	Large secreted ECM protein involved in cell-cell interactions	(Reduced body size and premature death in some mutants. Retinal, olfactory, and fertility defects. Various neuron structural, functional, and localization abnormalities. Impaired PPI and LTP and reduced inhibitory tone in heterozygotes.)
	7q36.3 (EN2)	Homeobox TF critical for hindbrain patterning	(Deficits in cerebellar development. Altered DA neuron generation and degeneration. Hyperactivity. Motor, learning, and grooming impairments.)
	12q14.2 (AVPR1A)	GPCR for arginine vasopression	(Impaired spatial memory and reduced PPI. Social deficits in females. Reduced anxiety-like behaviors in males.)
	17q21.32 (ITGB3)	Mediates platelet cell adhesion and cell-surface signaling	(Platelet defects, anemia, internal bleeding, increased bone mass, hypocalcemia, and premature death. 50% die embryonically from placental defects. Altered social and repetitive behaviors.)

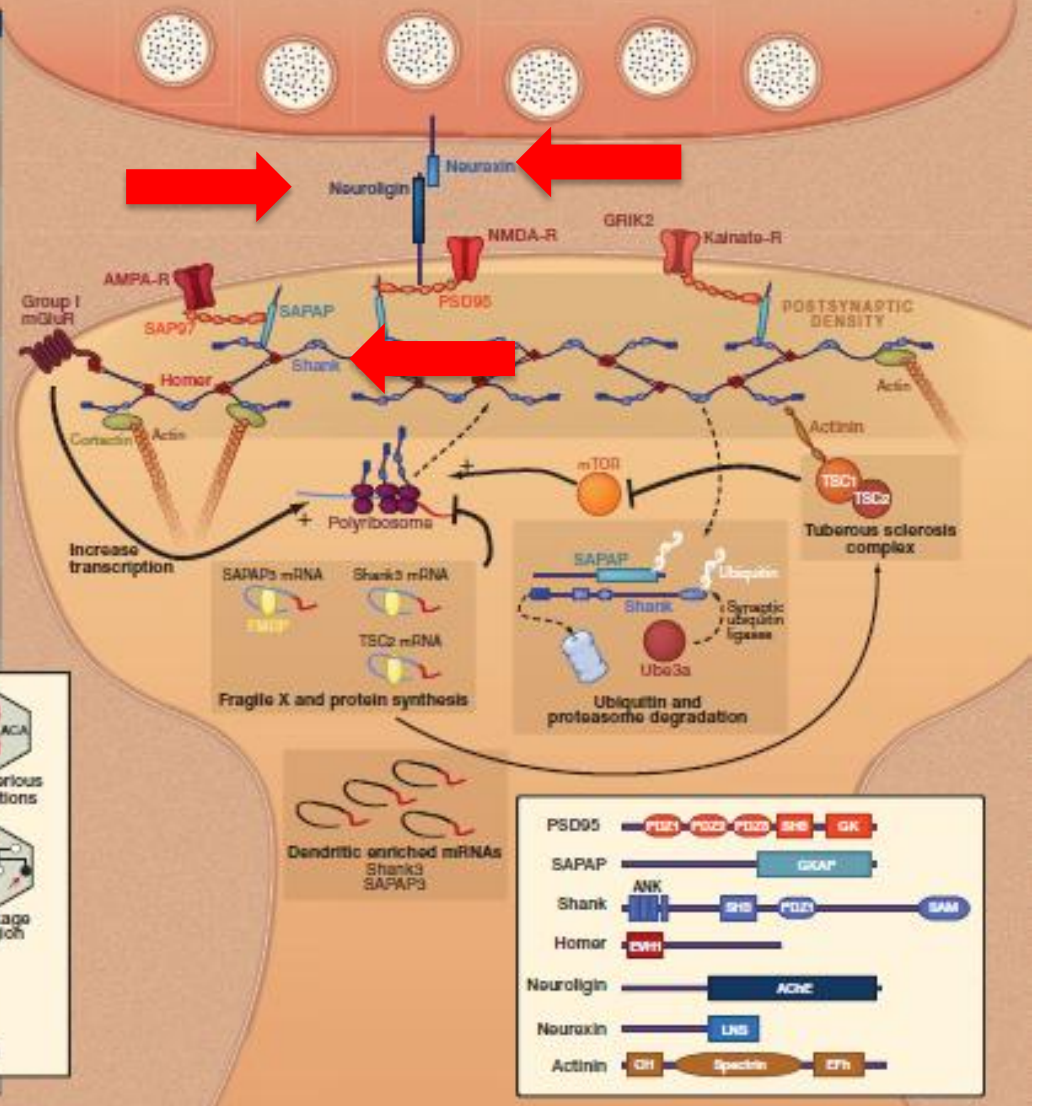
SnapShot: Autism and the Synapse

João Peça,[1] Jonathan Ting,[1] and Guoping Feng[1]
[1]McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Cell

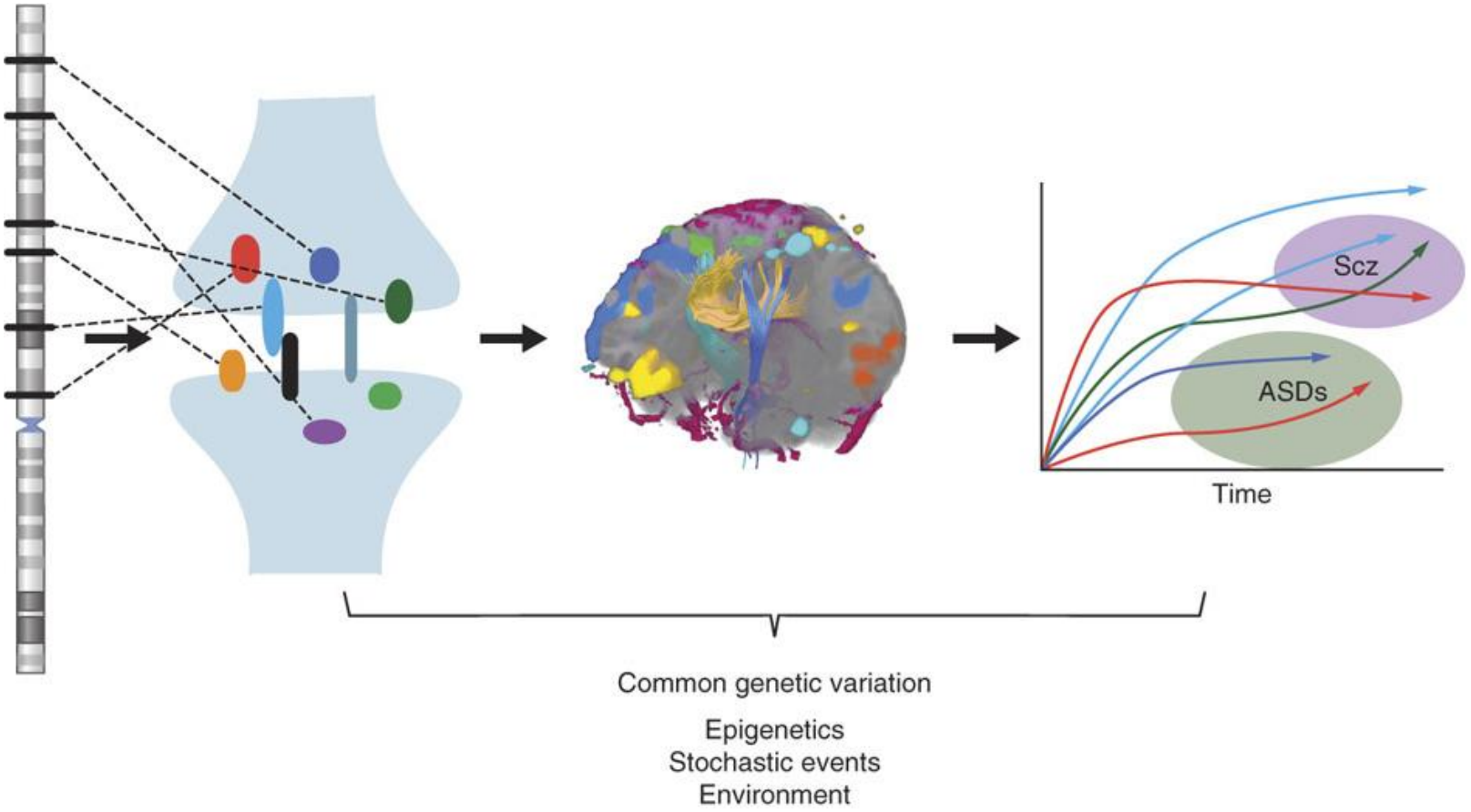
Gene/Protein	Locus	Evidence
PROSAP2/ Shank3 Phelan-McDermid syndrome	22q13	Schizophrenia
PROSAP1/ Shank2	11q13	
DLG1/SAP97 3q29 deletion syndrome	3q29	Autism and schizophrenia + Schizophrenia
DLG4/ PSD95	17p13	Schizophrenia
DLGAP2/ SAPAP2	8p23	Schizophrenia
DLGAP3/ SAPAP3	1p34	OC-Spectrum disorders
GRIK2/ GluR6	6q16	Intellectual disability
NRXN1/ Neurexin1	2p16	Schizophrenia
NRXN2/ Neurexin2	11q13	
NLGN1/ Neuroligin1	3q26	
NLGN3/ Neuroligin3	Xq13	
NLGN4X/ Neuroligin4	Xp22	
TSC1/hamartin tuberous sclerosis complex	9q34	
TSC2/tuberin tuberous sclerosis complex	16p13	
FMR1/FMRP fragile X syndrome	Xq27	
UBE3A/E6AP Angelman syndrome	15q11	

Genetic syndrome
Deleterious mutations
Copy number variations
Linkage region
SNP association



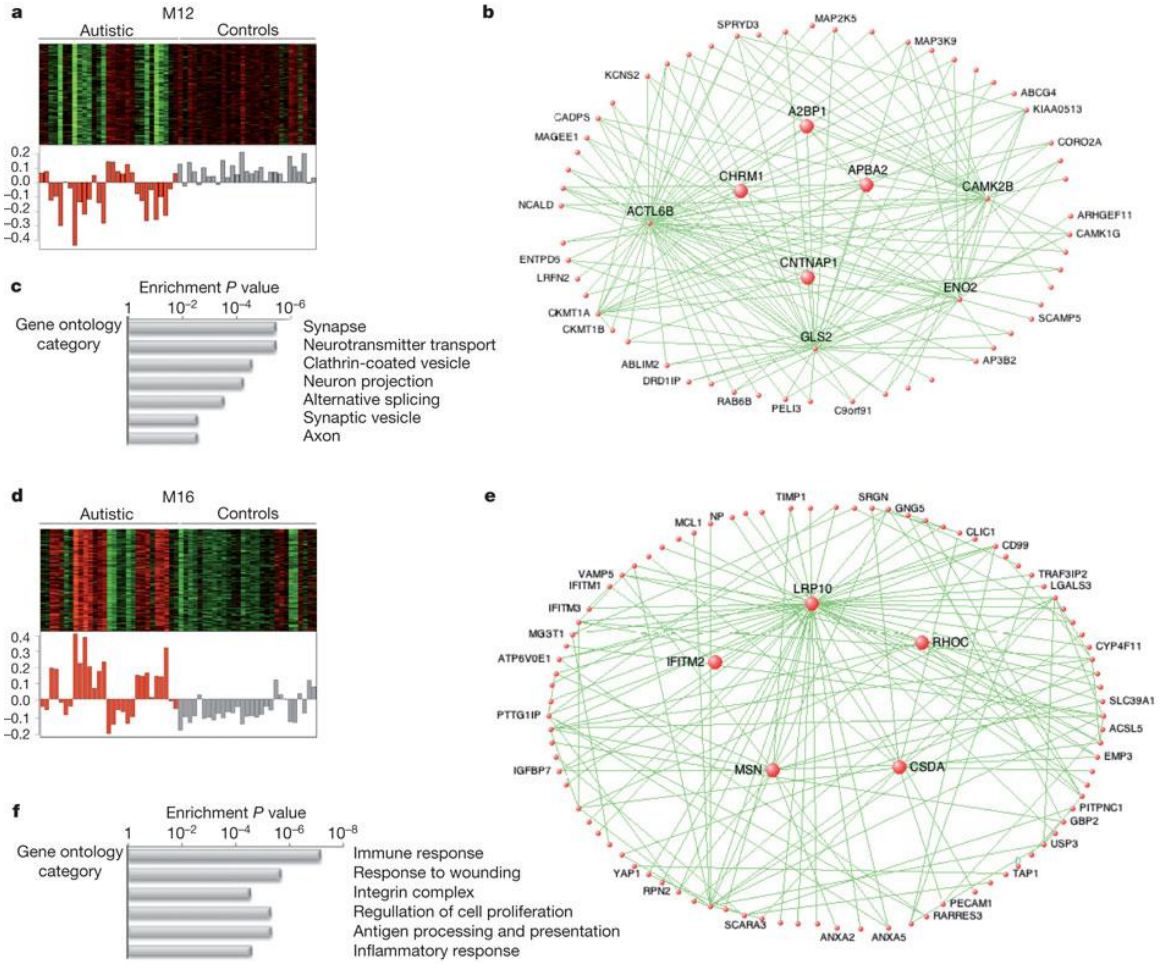
See online version for legend and references.

Geni della funzionalità sinaptica



Matthew W State & Pat Levitt, Nature, 2011

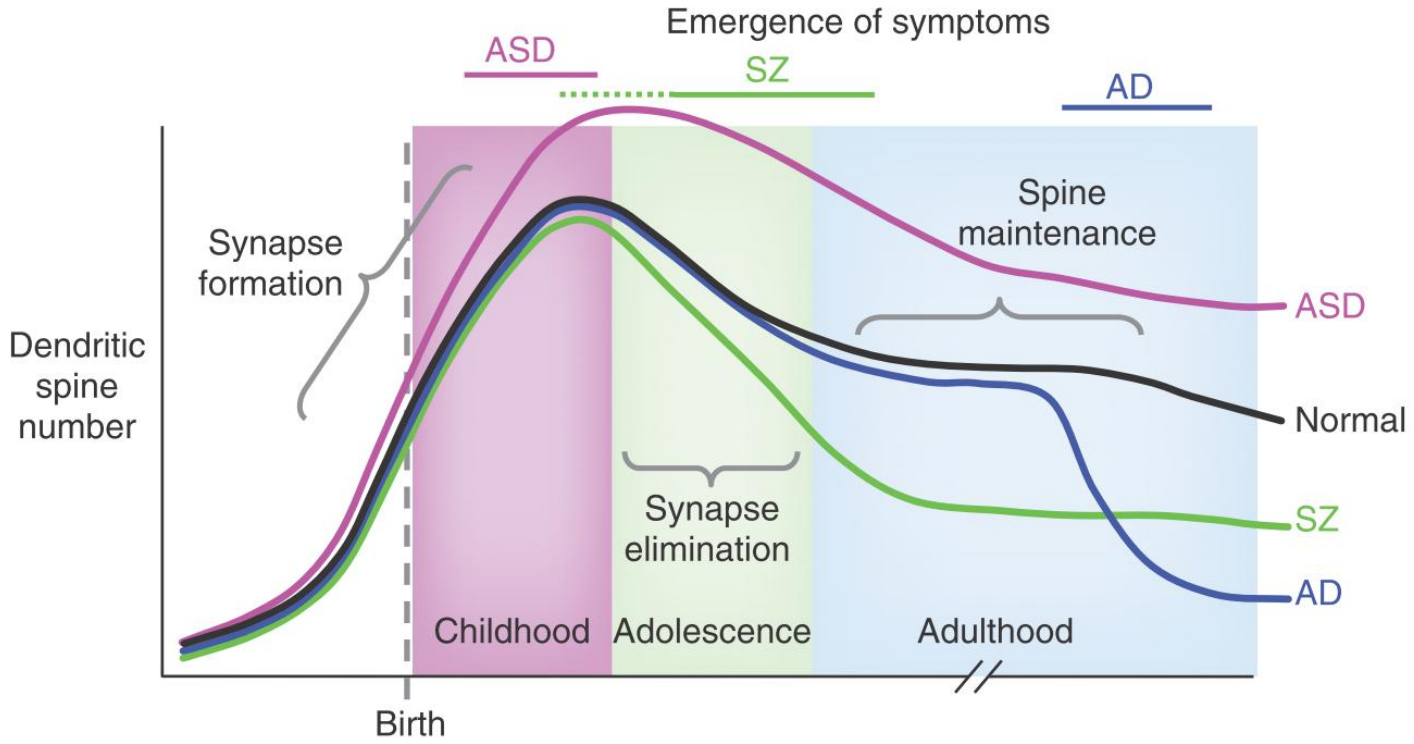
Analisi dei trascritti (trascrittomica)



Gene ontology category	p-value
Down-regulated genes (N=209)	
Synapse	4.48E-08
Axon	5.07E-07
Neuropeptide hormone activity	2.62E-06
Synaptic transmission	9.96E-07
Synaptic vesicle	2.98E-04
Up-regulated genes (N=235)	
Immune response	5.59E-09
Regulation of cell proliferation	6.96E-08
Cell adhesion	3.34E-06
Negative regulation of cell death	6.86E-06
Inflammatory response	7.73E-06
Immunoglobulin domain	4.12E-04

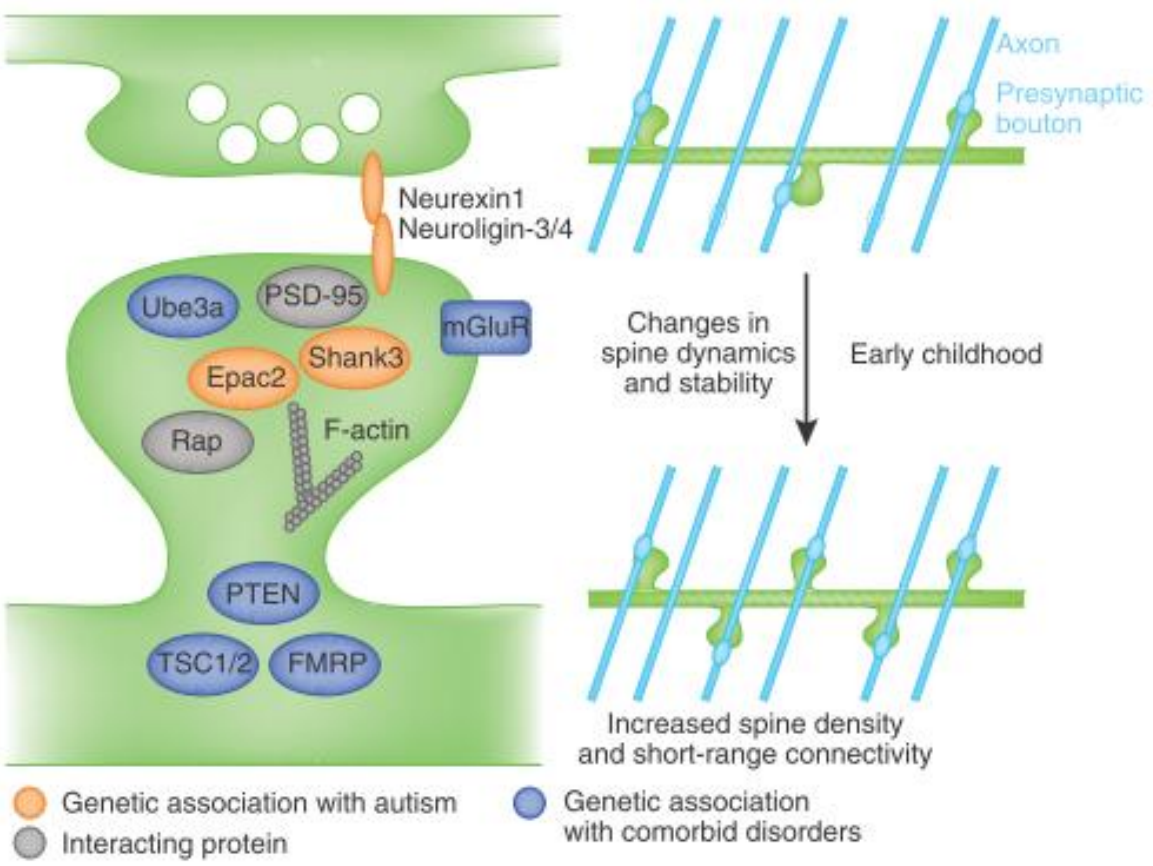
Voineagu I *et al. Nature*, 1-5 (2011)

Dendritic spine pathology in neuropsychiatric disorders



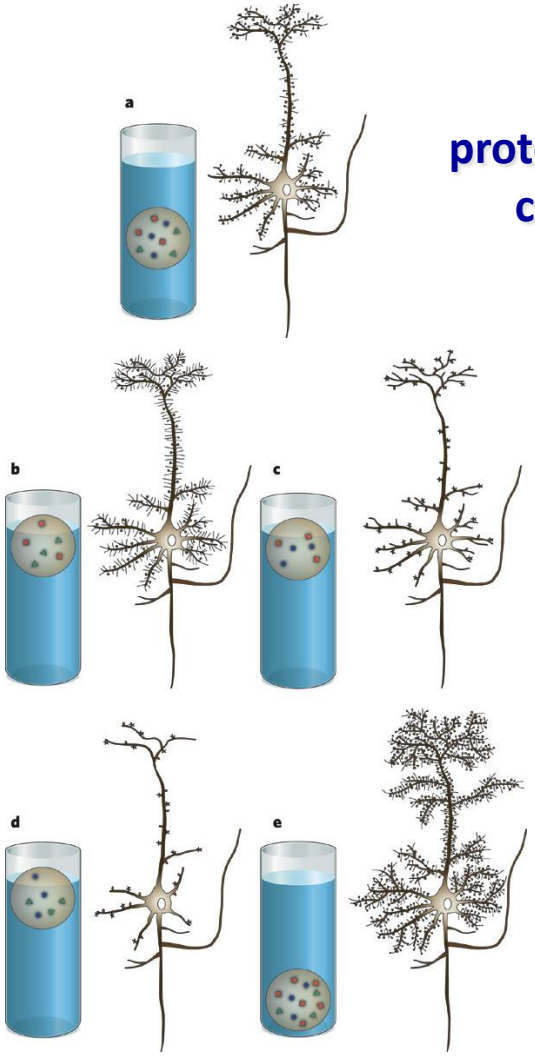
Penzes et al., Nat Neuroscience 2011

Dendritic spine pathology in ASD



Penzes et al., Nat Neuroscience 2011

Neuroni e spine dendritiche



Neurone di controllo:
proteine in equilibrio derivate da un corretto livello di espressione

Sindrome dell' X fragile:
normal dendrites but an increased density of longer, thinner, immature-appearing dendritic spines

Sindrome di Angelman:
normal dendrites but a decreased density of, and abnormally shaped, dendritic spines

Sindrome di Rett :
(Mecp2-null mice)
decreased density of dendrites and decreased density of, and abnormally shaped, synapses (represented by dendritic spines)

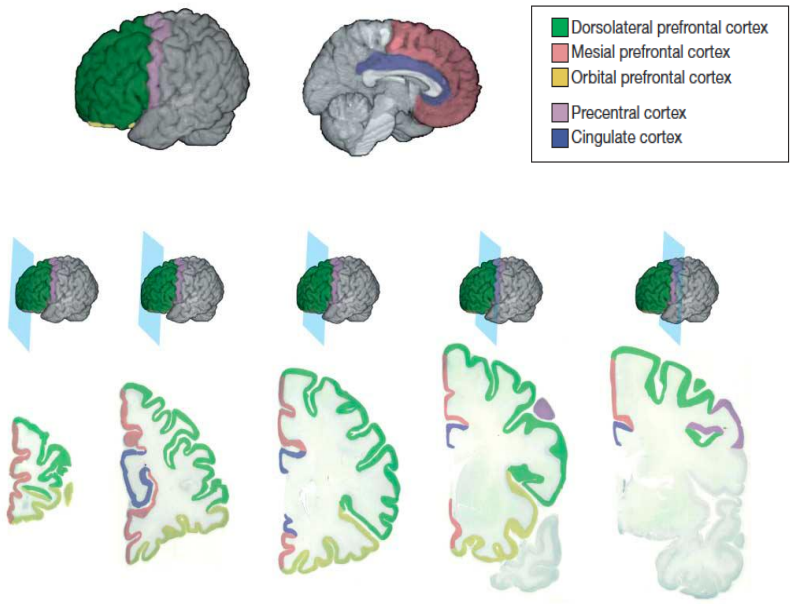
Sindrome di Rett :
(Mecp2 is duplicated)
increased density of synapses (represented by increased density of dendrites and dendritic spines)

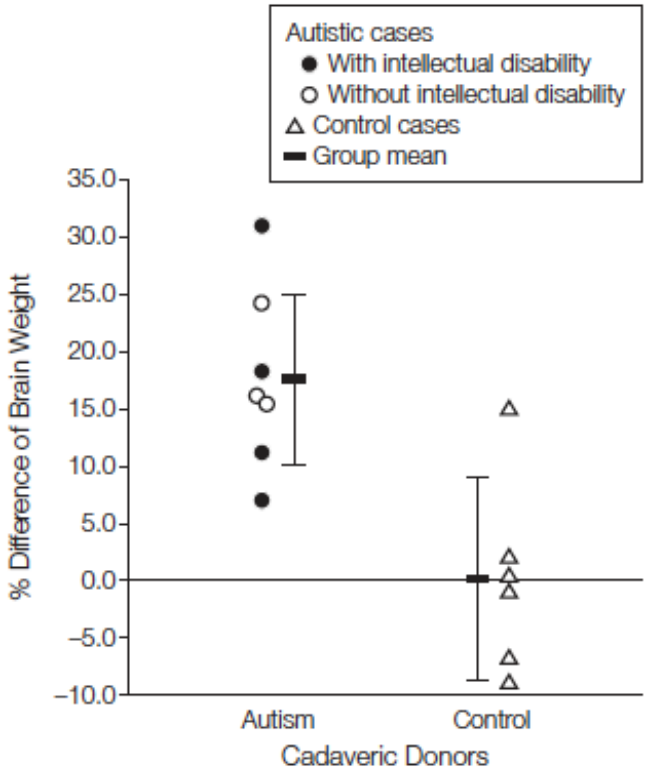
Melissa B. Ramocki & Huda Y. Zoghbi; Nature; 2011

Variazioni anche nel numero di neuroni

Il peso del cervello è maggiore nei bambini autistici

Corteccia prefrontale:





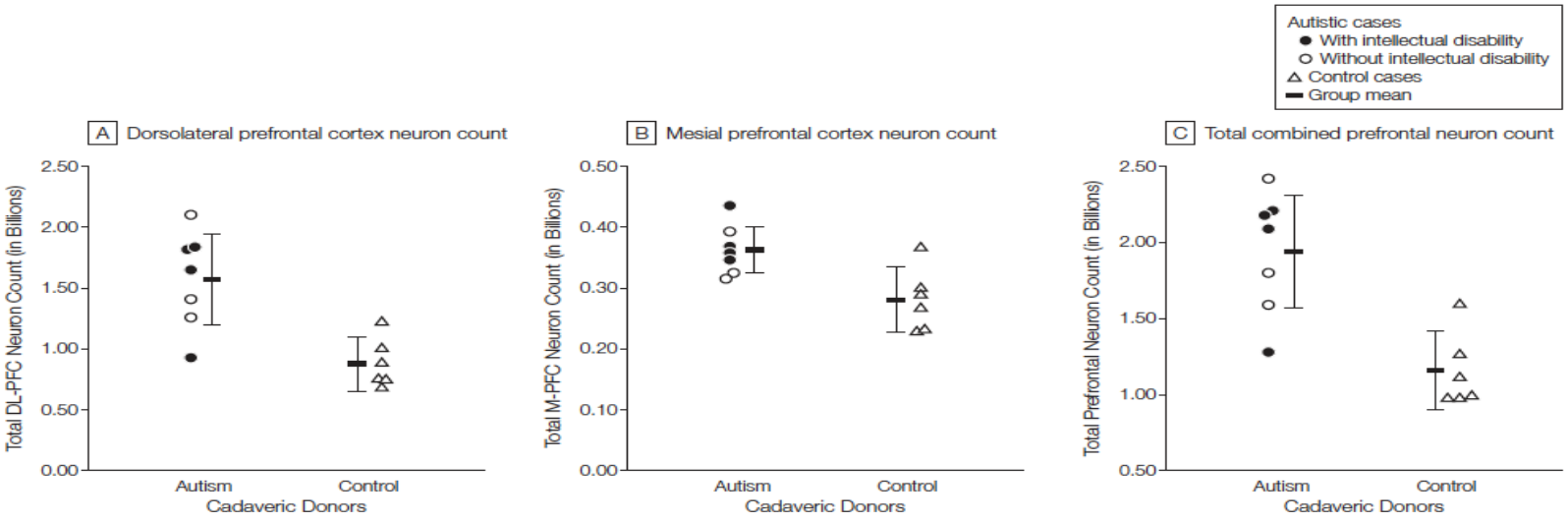
n = 7 n = 6

tra i 2 e i 16 anni

Courchense E. et al, Jama, 2011

Variazioni anche nel numero di neuroni

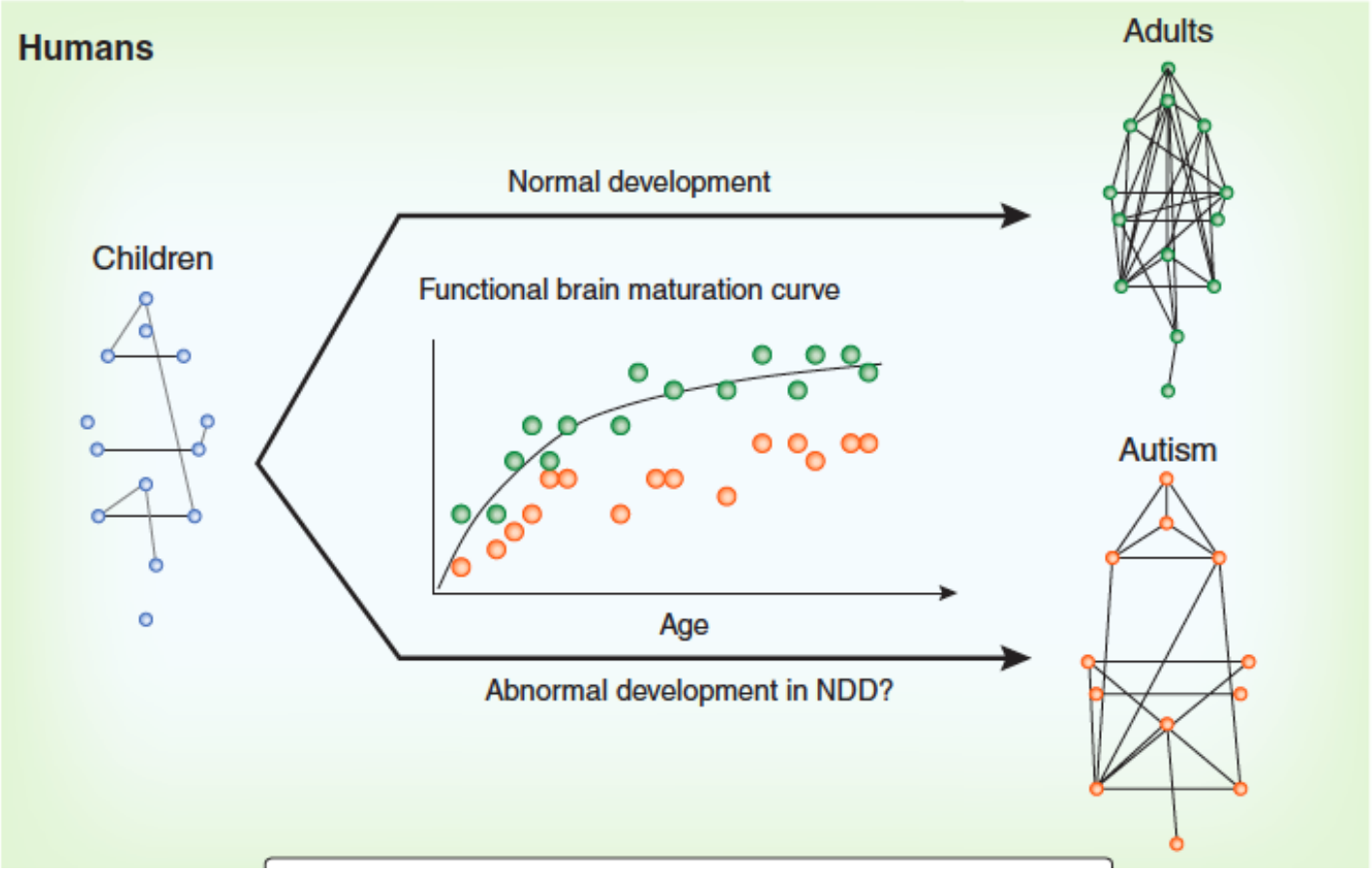
Nella corteccia prefrontale si osserva un maggior numero di neuroni



Le cause dell'aumento di neuroni sono da ricercare al livello prenatale

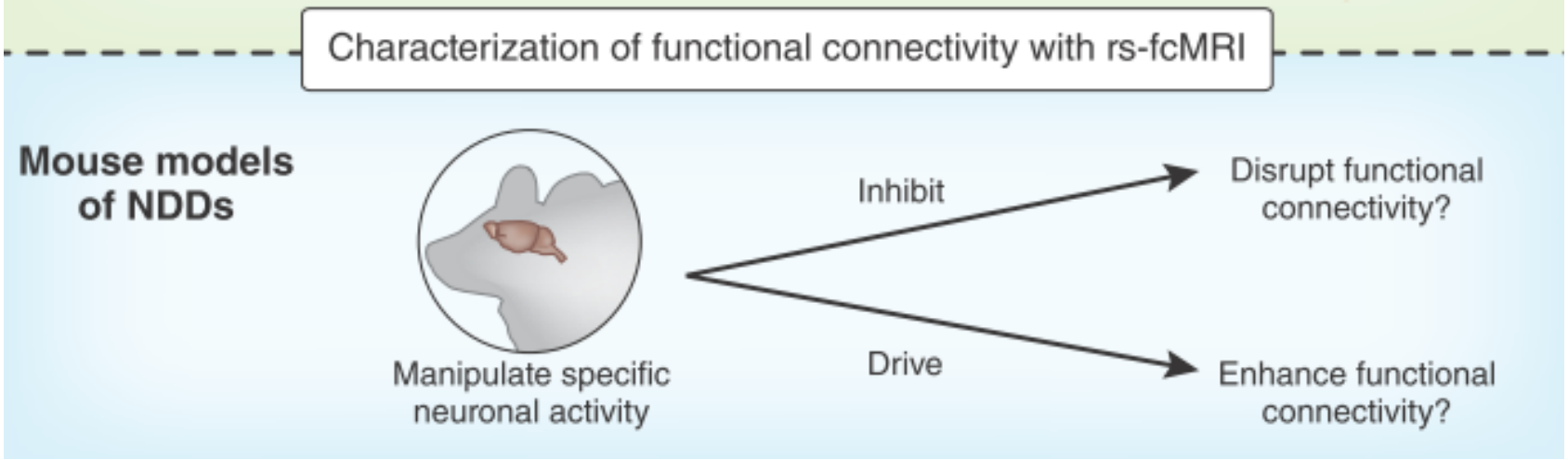
Courchense E. et al, Jama, 2011

Problemi di connettività

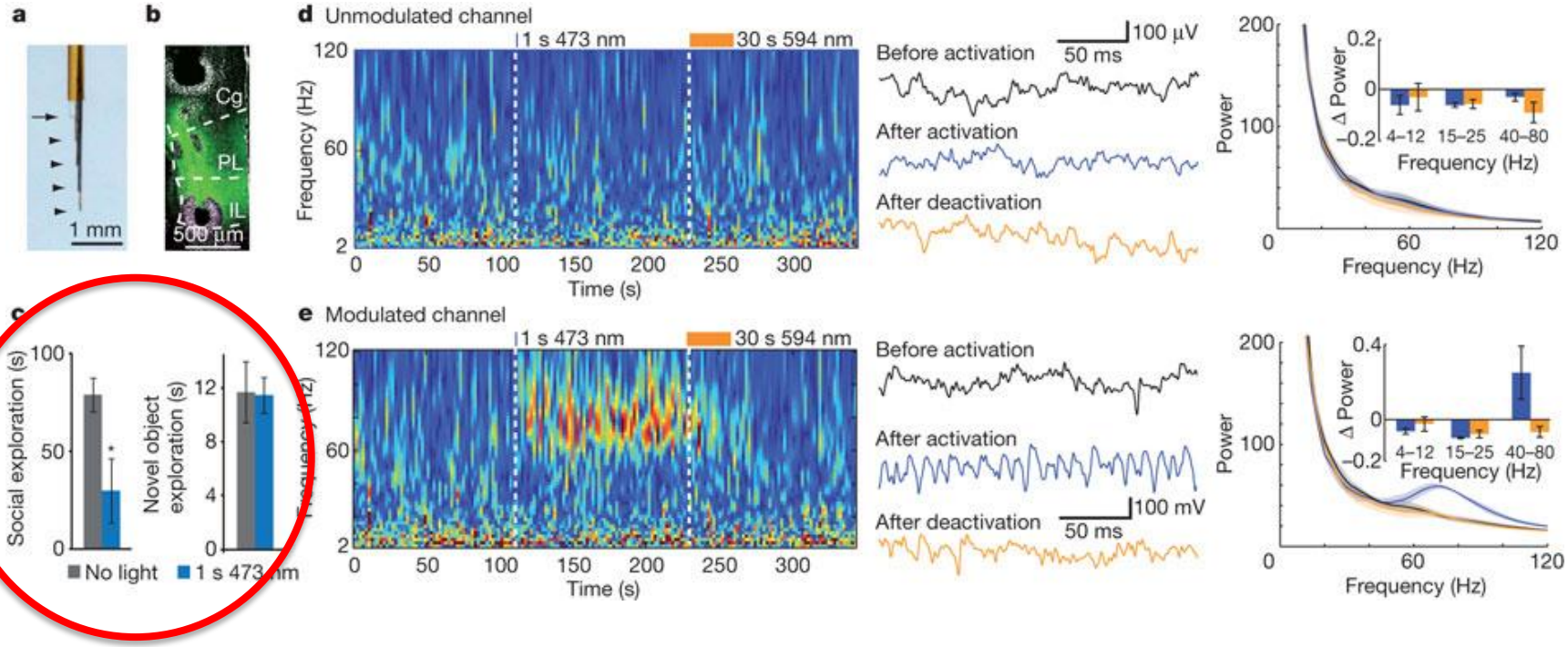


Neul JL, Nature 17 Nov 2011
Dosenbach, N.U. et al. Science 329, 1358–1361 (2010)

Problemi di connettività



Squilibrio eccitazione-inibizione

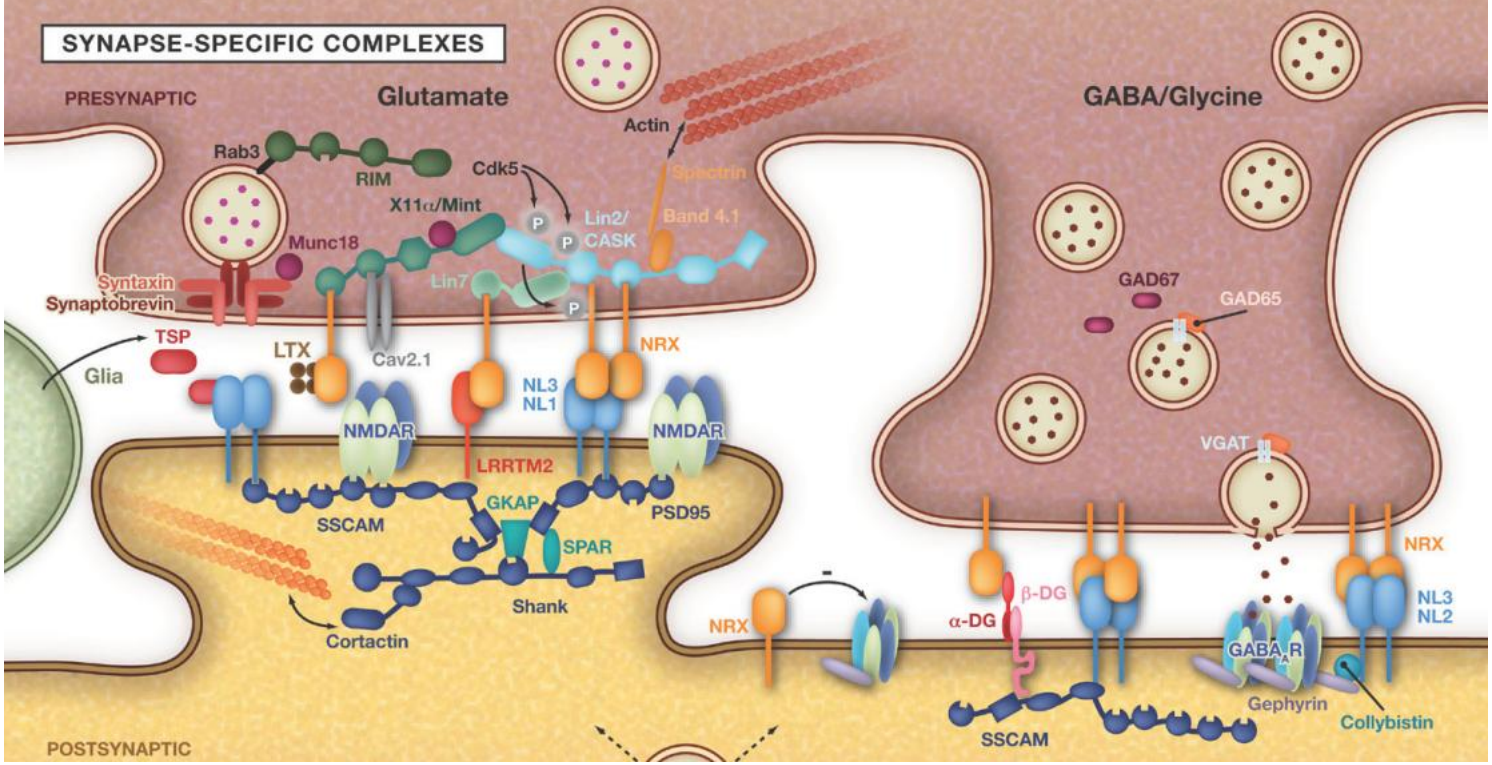


Yizhar O. *et al*. *Nature*, 1-8 (2011)

SnapShot: Neuroligin-Neurexin Complexes

Cell

Stéphane Baudouin and Peter Scheiffele
Biozentrum of the University of Basel, 4056 Basel, Switzerland

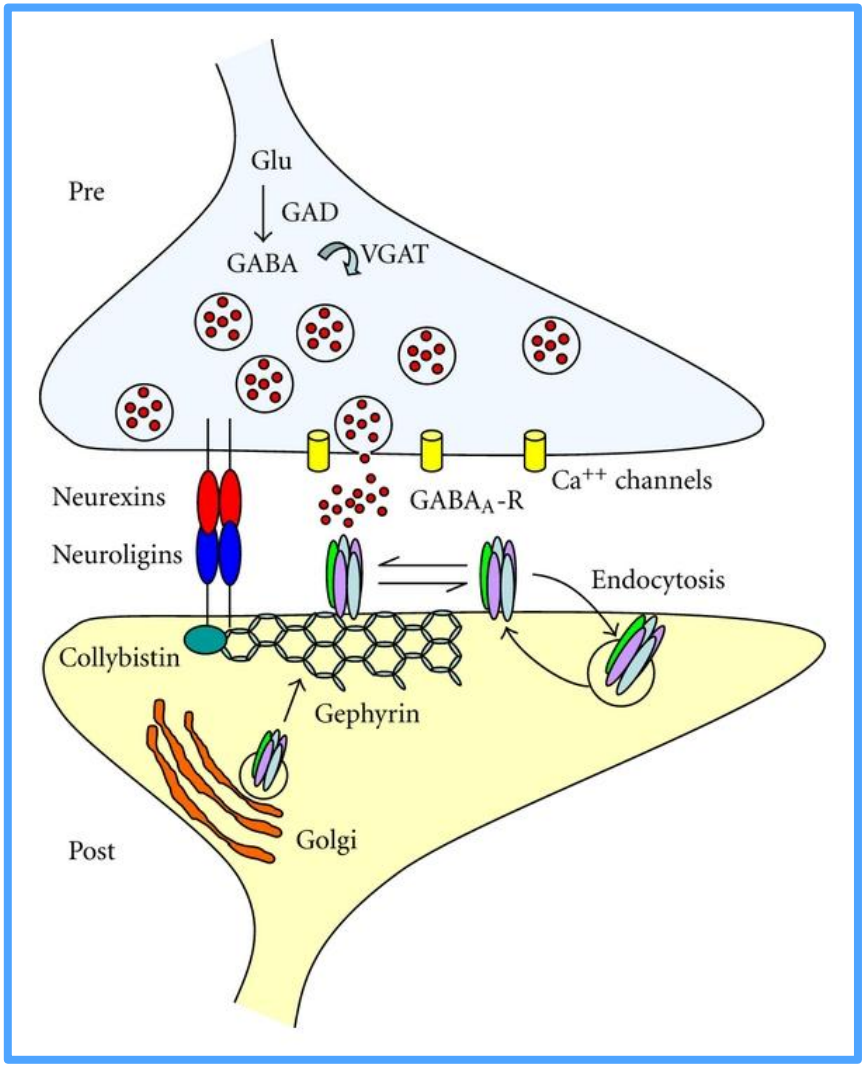


GABA

- in the **mature brain** GABA acts as an inhibitory transmitter
- during the **embryonic** and the **perinatal period**, this neurotransmitter depolarizes targeted cells and triggers calcium influx

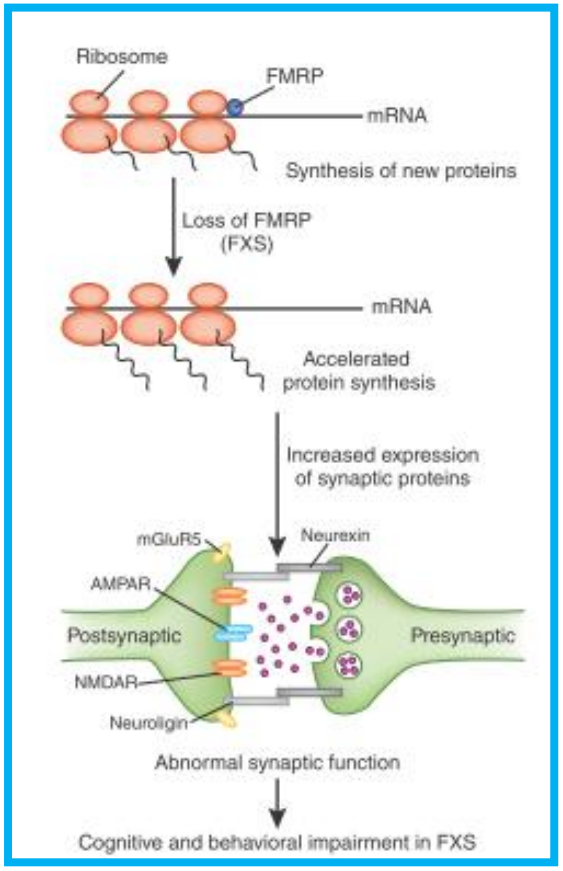
REGOLA molti processi durante lo sviluppo:

Proliferazione cellulare
Migrazione
Differenziamento
Maturazione sinaptica
Morte cellulare



Mouse model	Alterations in GABAergic signaling
Mecp 2-KO (Rett syndrome)	Reduced levels of GAD65 and GAD67 (*Viaat-Mecp2*$^{-/y}$)
	Reduced inhibitory quantal size in layer 2/3 pyramidal neurons of the somatosensory cortex
	The E/I balance is shifted to favor inhibition over excitation in cortical networks (*Mecp2*$^{2lox/x}$, *Nestin-Cre*)
	Reduced frequency of IPSC-based spontaneous rhythmic field potentials in the hippocampus (*Mecp2*$^{tm1.1Bird}$)
Fmr 1-KO (X fragile)	Down regulation of GABAA-mediated tonic inhibition in the subiculum
	Reduced expression of α5 and δ GABAA receptor subunits in the subiculum
	Increased frequency of sIPSCs and mIPSCs in the striatum
	Reduction in amplitude and frequency of sIPSCs and mIPSCs
	Reduced GABAA-mediated tonic inhibition
	Reduced GABAergic innervation in the amygdala
	Reduced expression of GABAA receptor subunits
Gabrb 3 KO	The E/I balance is shifted to favor excitation over inhibition in cortical networks (EEG recordings)
Dlx1/Dlx2 KO	Abnormal cell migration
	Reduction in the number of GABAergic interneurons in the cortex, olfactory bulb and hippocampus
Reln-KO	Reduced level of GAD67
	Decreased GABA turnover
En2-KO	Reduced expression of parvalbumin- and somatostatin-
	positive GABAergic interneurons in the hippocampus
	Increased susceptibility to seizures
Nlg3 R451C KI	Increased frequency of mIPSC
	Increased level of VGAT and gephyrin
	Asymmetric reduction of PV positive basket cells across cortical hemispheres
valproic acid	The E/I balance is shifted to favor excitation over inhibition in the lateral amygdala (multi electrode arrays)
	Asymmetric reduction of PV positive basket cells across cortical hemispheres

X-fragile



Fmr1(fragile X mental retardation 1): sul braccio lungo del cromosoma X (Xq27.3) codifica per la proteina FMRP

- mental retardation with language deficits,
- hyperactivity,
- autistic behavior
- seizures

the 'mGluR theory of fragile X'

In assenza di FMRP:

- attivazione recettori mGluR5 (recettori metabotropici del glutammato) conduce ad un'eccessiva sintesi di proteine sinaptiche
- impairment of GABAergic circuitry and a decreased expression of GABAA receptor subunits

Loss of GABAergic function = hyper excitability

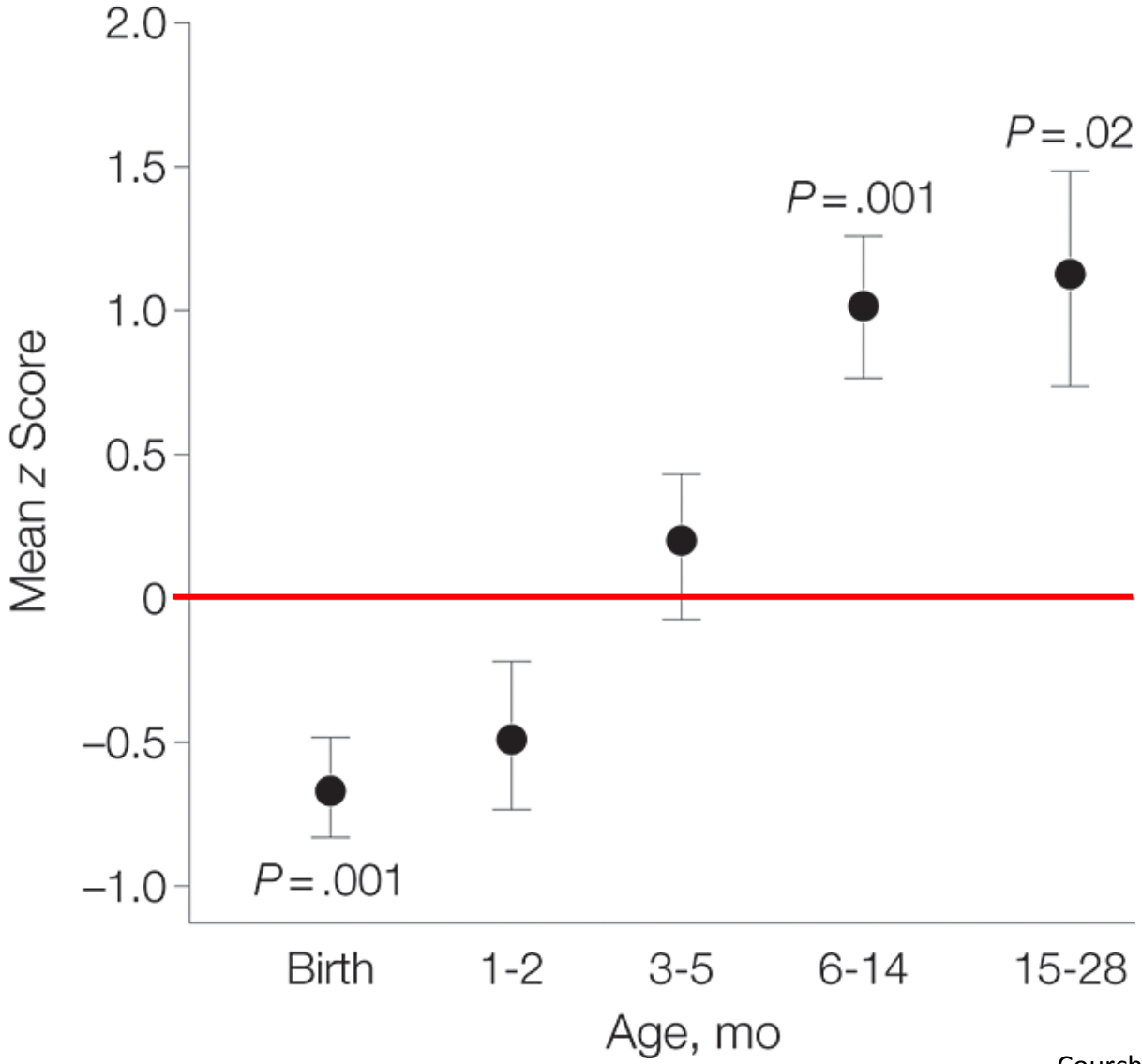
Nonostante tutte queste osservazioni non esistono dei marcatori precoci per l'autismo perchè:

- **Il disturbo si sviluppa tra il periodo pre-natale e la prima adolescenza quindi si possono sviluppare interazioni tra fattori di rischio multipli**
- **I pochi biomarcatori candidati non sono stati rilevati in tutti i pazienti autistici**
- **Biomarcatori trovati sono spesso associati con altri disturbi del neurosviluppo**

Biomarker type	Sample/measure
Gene expression profile	Blood samples
Proteomic profile	Serum samples
Metabolomic profile	Urine samples
Head size	Head circumference trajectory
Brain size and structure	MRI, DTI
Brain function	Functional MRI, EEG, ERPs
Eye movement	Looking measures, saccadic reaction time

DTI, diffusion tensor imaging; EEG, electroencephalography; ERPs, event-related potentials.

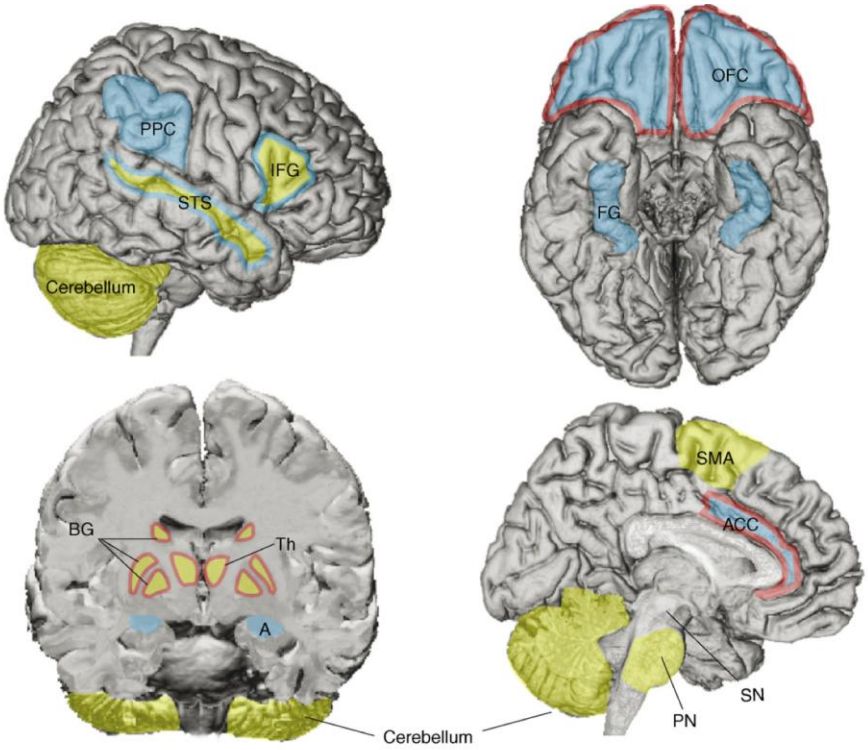
Crescita cerebrale anomala:



Circonferenza cranica: valore medio normale

Courchesne, E. et al. JAMA 2003;290:337-344

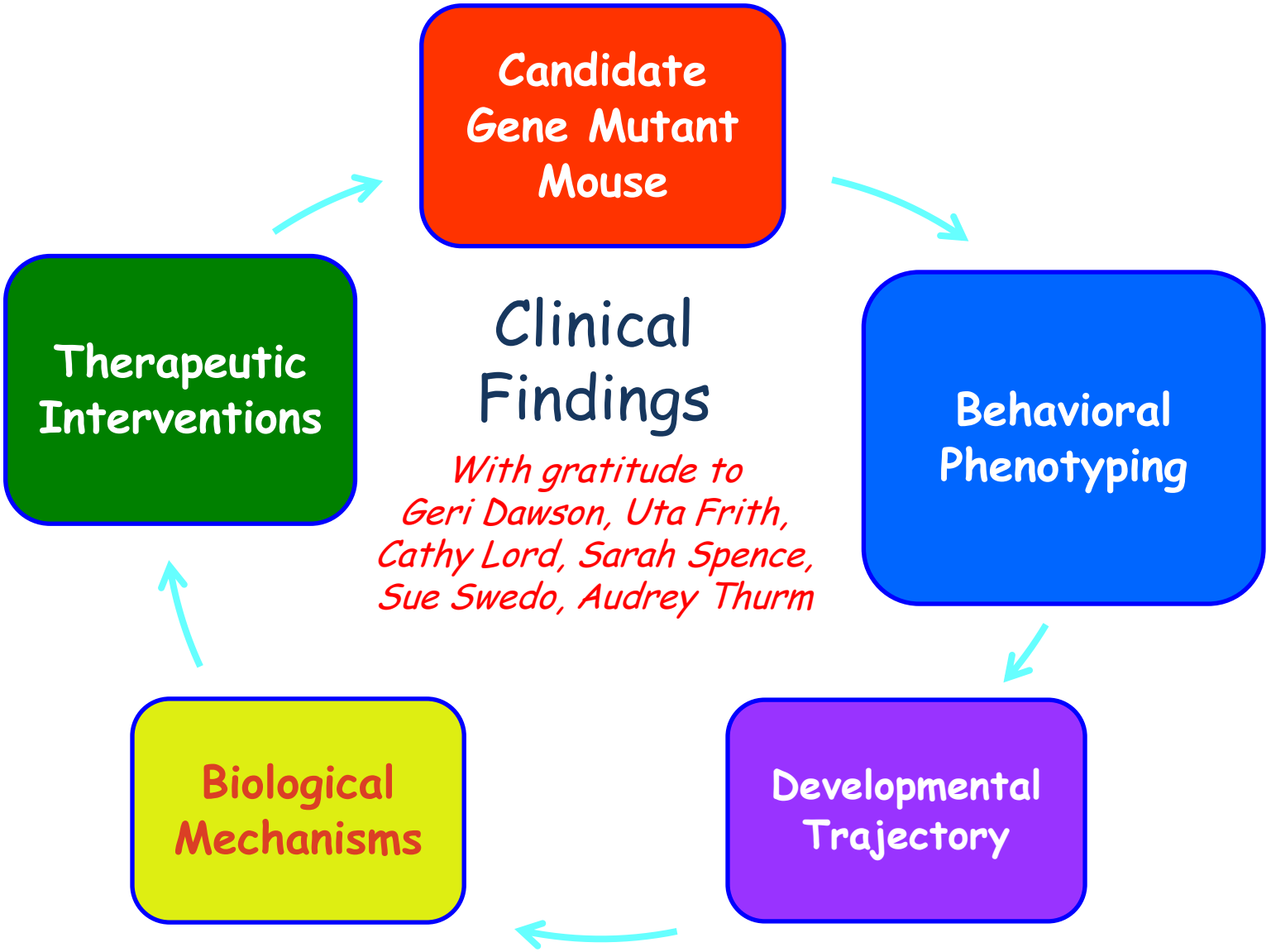
Quali sono le aree cerebrali coinvolte nell'autismo?



Social impairment	Communication deficits	Repetitive behaviors
OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex FG – Fusiform gyrus STS – Superior temporal sulcus A – Amygdala mirror neuron regions IFG – Inferior frontal gyrus PPC – Posterior parietal cortex	IFG- Inferior frontal gyrus (Broca's area) STS – Superior temporal sulcus SMA – Supplementary motor area BG – Basal ganglia SN – Substantia nigra Th – Thalamus PN – Pontine nuclei cerebellum	OFC – Orbitofrontal cortex ACC – Anterior cingulate cortex BG – Basal ganglia Th – Thalamus

Amaral et al., Trends Neurosci. 2008

ISS and NIMH STRATEGY
for testing genetic hypotheses about the causes of autism



Mouse Models with Mutations in Candidate Genes

Adapted from Abrahams and Geschwind, Nature Reviews Genetics 2008

Human Gene	Co-morbid Syndrome	Mutant Mouse
AVPR1a		Yes
CACNA1C	Timothy	Yes
CADPS2		No
CNTNAP2		Yes
DHCR7	Smith-Lemli-Opitz	Yes
EN2		Yes
FMR1	Fragile X	Yes
GABARβ2		Yes
ITBG3		Yes
MECP2	Rett	Yes
MET	(tumors)	Yes
NRXN1		Yes
NLGN3		Yes
NLGN4		Yes
OXTR		Yes
PTEN	(cancers)	Yes
RELN		Yes
SHANK3	22q13 deletion Phelan-McDermid	Yes
SLC6A4		Yes
TSC1, TSc2	Tuberous sclerosis	Yes
UBE3A	Angelman	Yes

Why are Mouse Models Useful?

Mice and humans share 99% of their genes

Similar brain anatomy

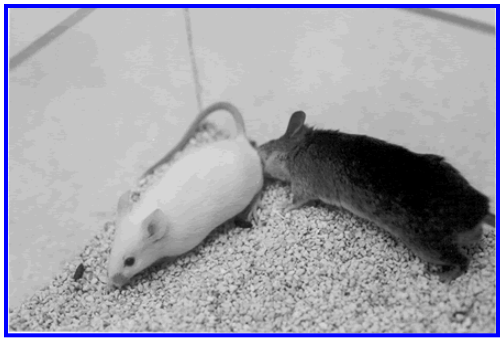
Similar biochemistry, neurotransmitters, receptors

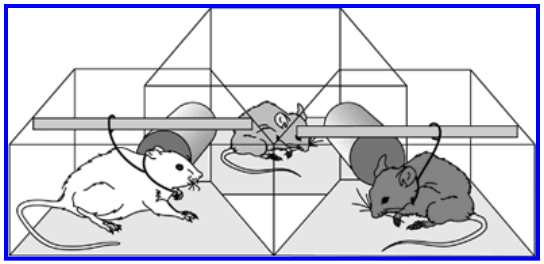
Similar physiology, brain electrophysiology

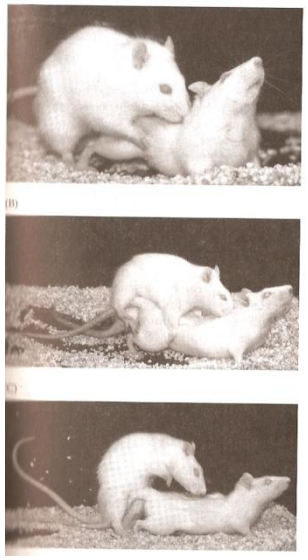
Analogous behavioral endophenotypes

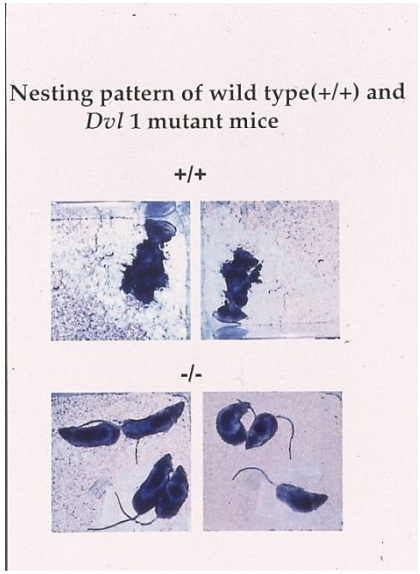
Mice are a social species

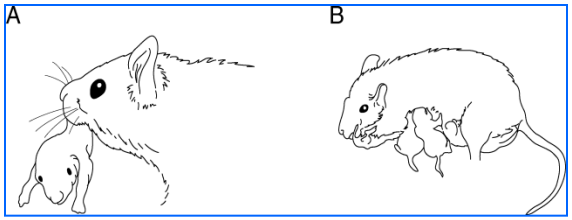
Some social behaviors of *Mus musculus*











La famiglia dei geni SHANK

Bozdagi *et al. Molecular Autism* 2010, **1**:15
http://www.moleculara utism.com/content/1/1/15

Molecular Autism

RESEARCH Open Access

Haploinsufficiency of the autism-associated *Shank3* gene leads to deficits in synaptic function, social interaction, and social communication

ARTICLE

doi:10.1038/nature09965

Shank3 mutant mice display autistic-like behaviours and striatal dysfunction

João Peça[1,2]*, Cátia Feliciano[1,3]*, Jonathan T. Ting[1], Wenting Wang[1], Michael F. Wells[1], Talaignair N. Venkatraman[4], Christopher D. Lascola[1,4], Zhanyan Fu[1,5,6] & Guoping Feng[1,6,7]

28 APRIL 2011 | VOL 472 | NATURE | 437

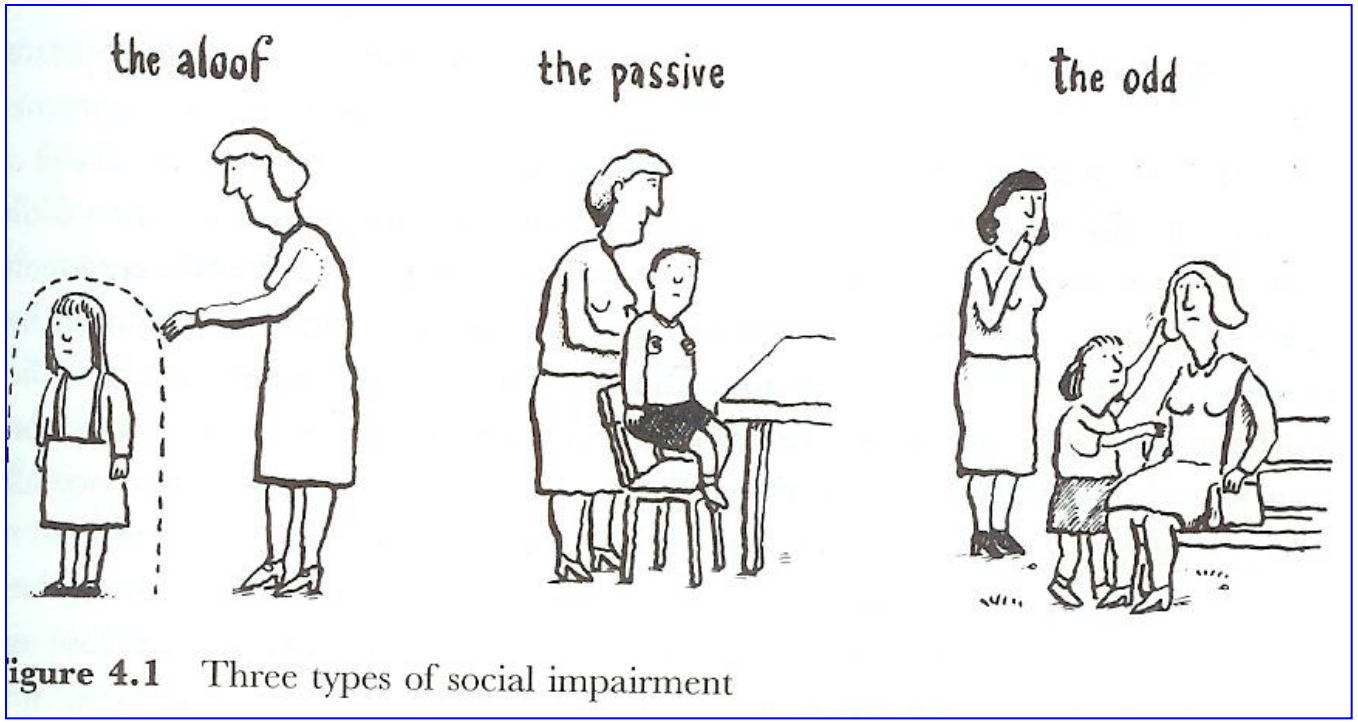
Autism is a neurodevelopmental disorder that is behaviorally defined by three core symptoms:

Animal Models of Autism

Core Symptom #1

Sociability Deficit

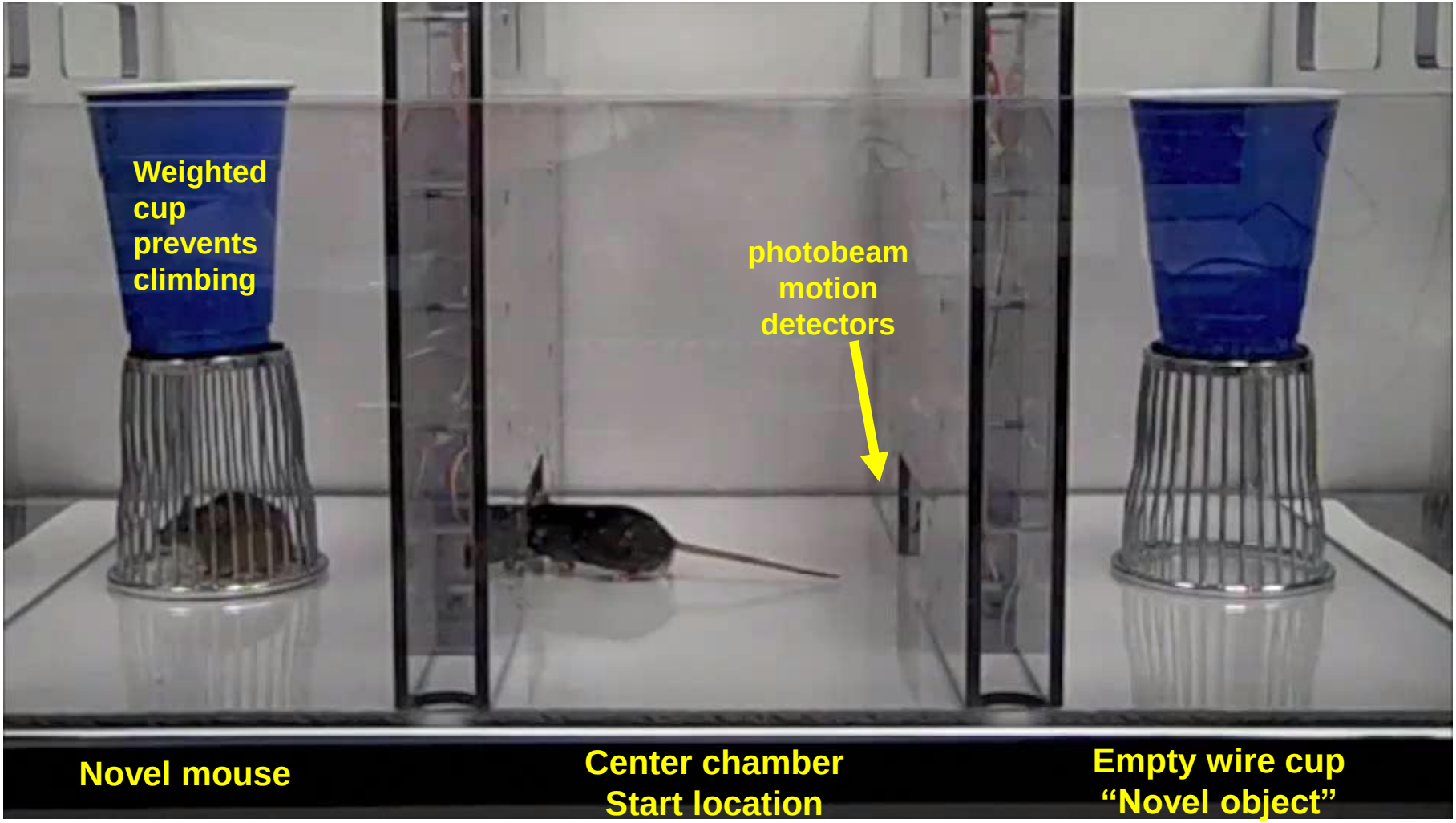
Abnormal reciprocal social interactions, with deficits in eye gaze, joint attention, empathy



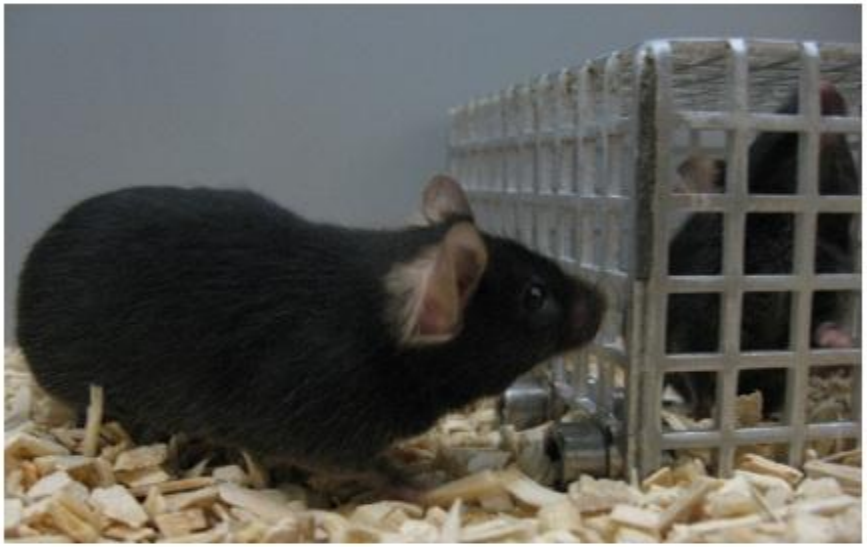
igure 4.1 Three types of social impairment

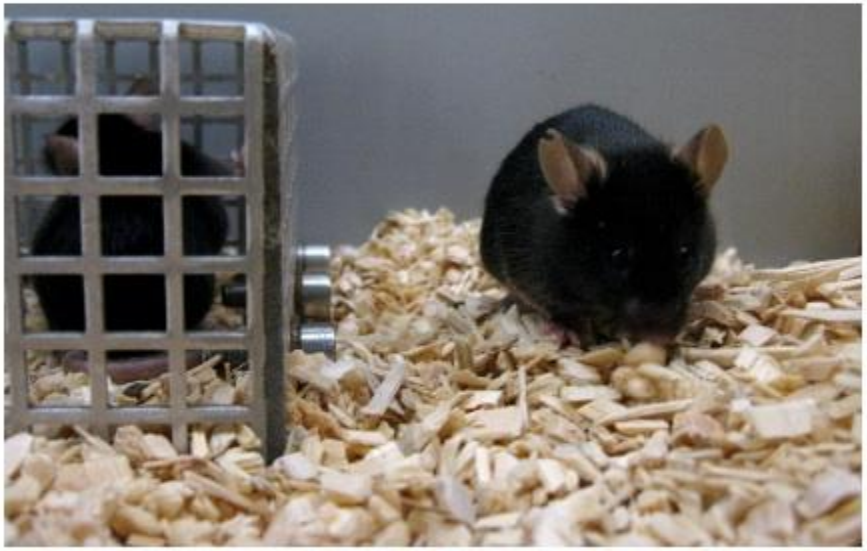
Uta Frith (2003) Autism: Understanding the Enigma

Sociability in Adult C57BL/6J (B6) Mice

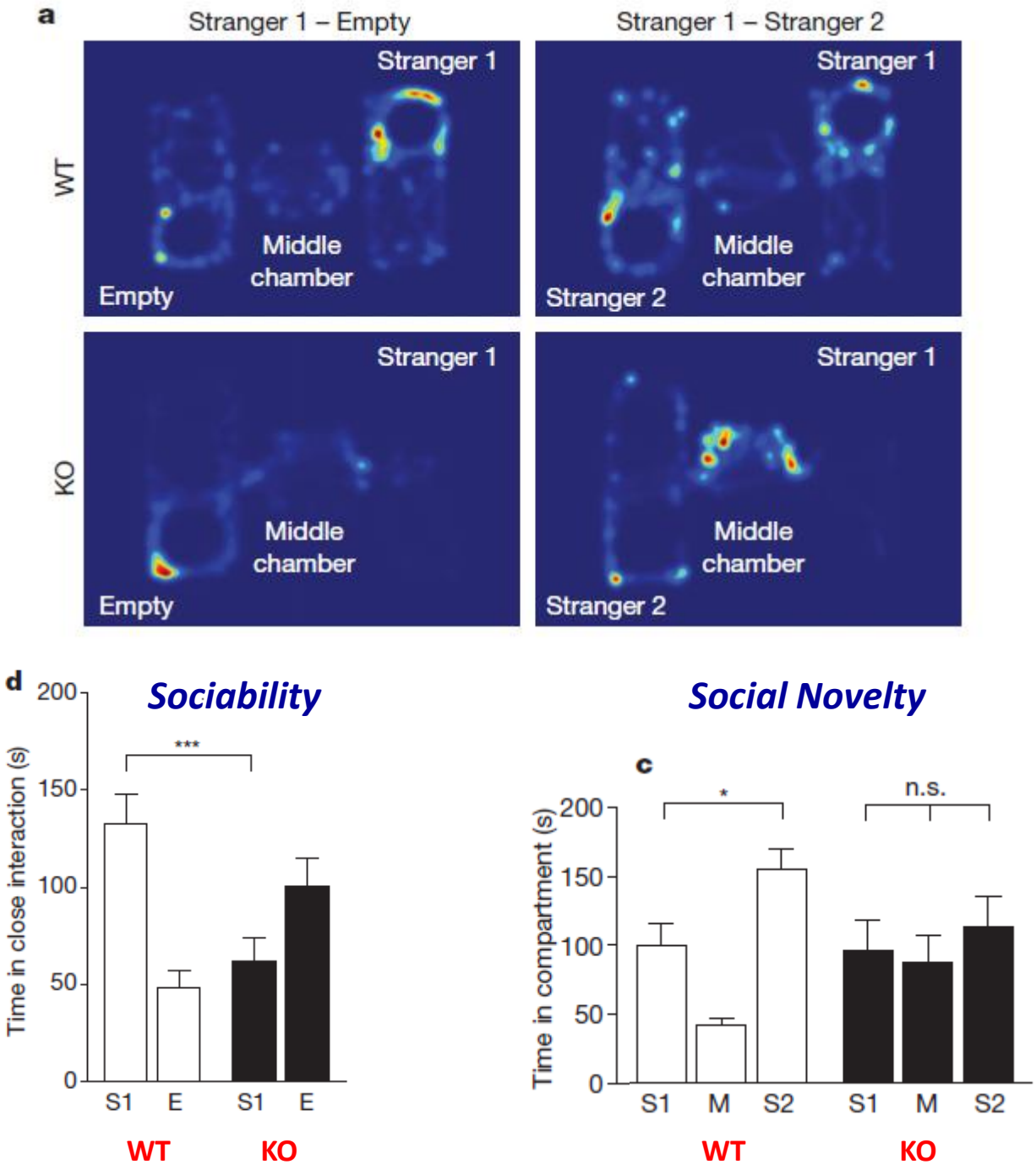


“Normal” mouse





“Autistic” mouse


a
Stranger 1 – Empty
Stranger 1 – Stranger 2
WT
KO
Stranger 1
Middle chamber
Empty
Stranger 2
d
Sociability
Social Novelty
Time in close interaction (s)
200
150
100
50
0
***
S1
E
S1
E
WT
KO
c
Time in compartment (s)
*
n.s.
S1
M
S2
S1
M
S2
WT
KO

Core Symptom #2

Impairment in Social Communication

delayed onset and lower frequency of babbling, grunting, extended humming, stereotypic squeals, or laughing inappropriately

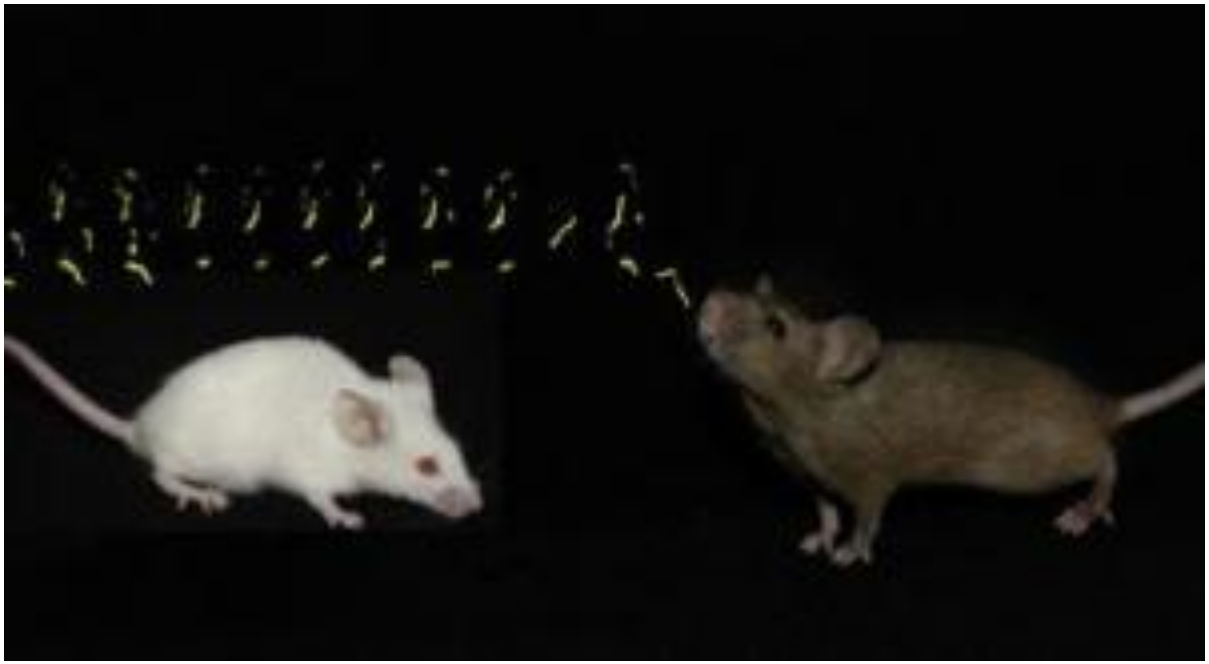
Mice communicate primarily with ultrasonic vocalizations

Proposed DSM-5 criteria:

two symptom criteria sets:

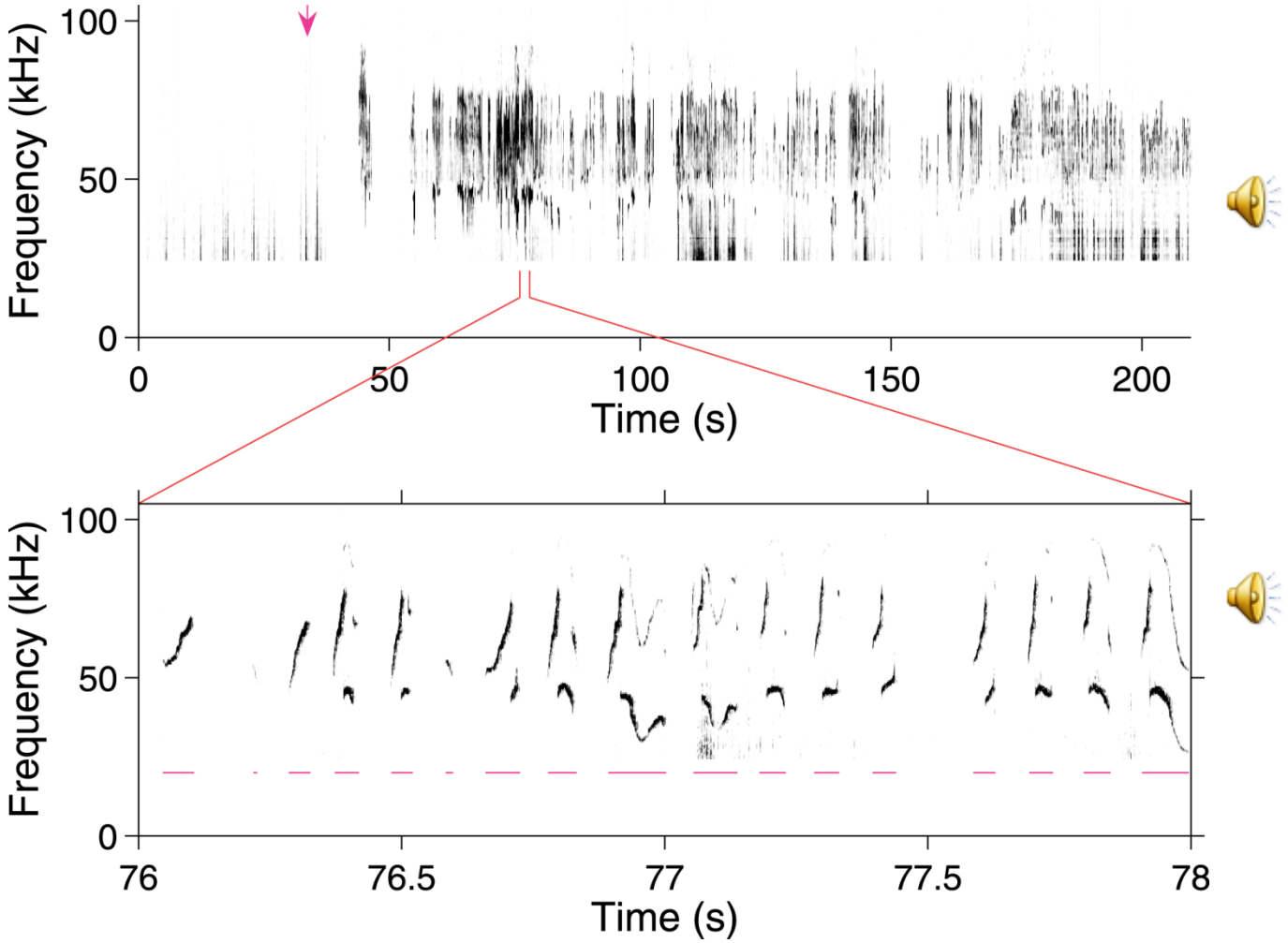
1) social communication and interaction

2) restricted, repetitive behavior



Adult Ultrasonic Vocalizations

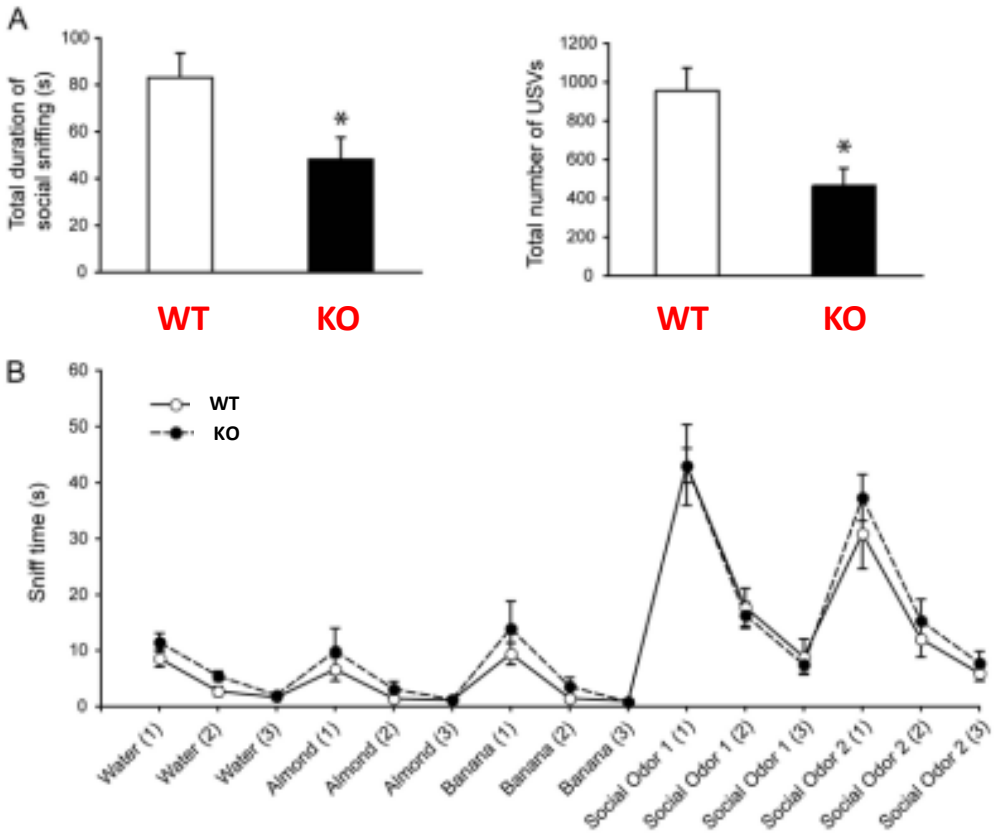
C57BL/6J male mouse



B6 male-female social interactions

BTBR male-female social interactions

Sociability deficit



Bozdagi *et al. Molecular Autism* 2010, **1**:15

Core Symptom #3

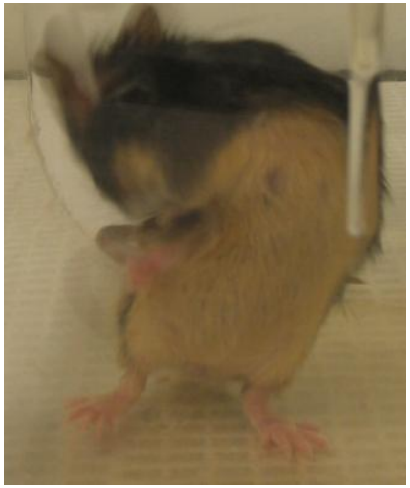
Stereotyped Repetitive Behaviors and Narrow Restricted Interests

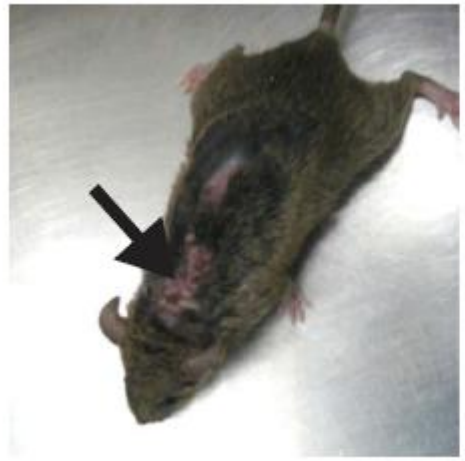
Videoscoring of spontaneous stereotyped jumping, grooming

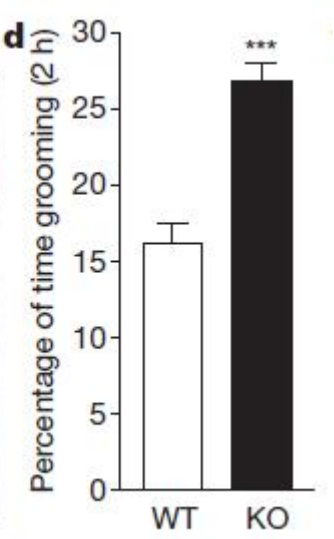
Perseveration as a failure to make a change in a search strategy, using Morris water maze and T-maze spatial tasks

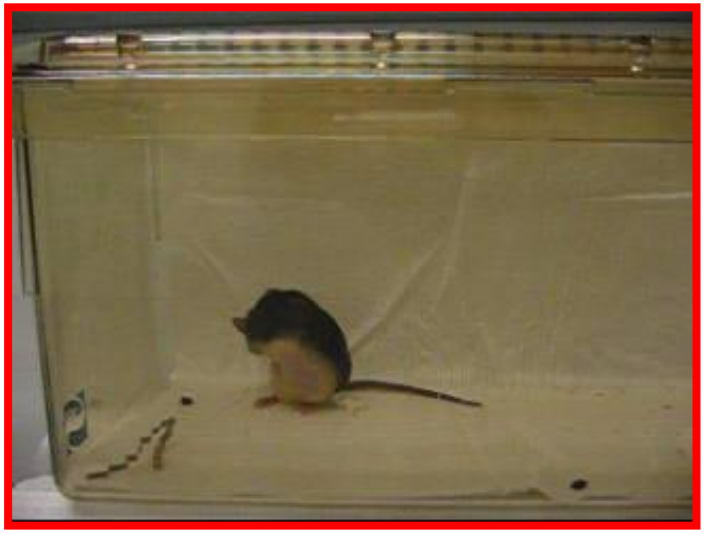
Restricted interests in a holeboard exploration task

Self-Grooming

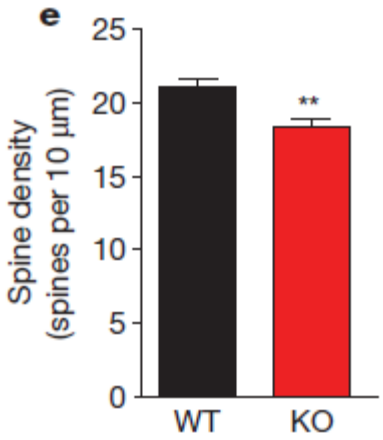


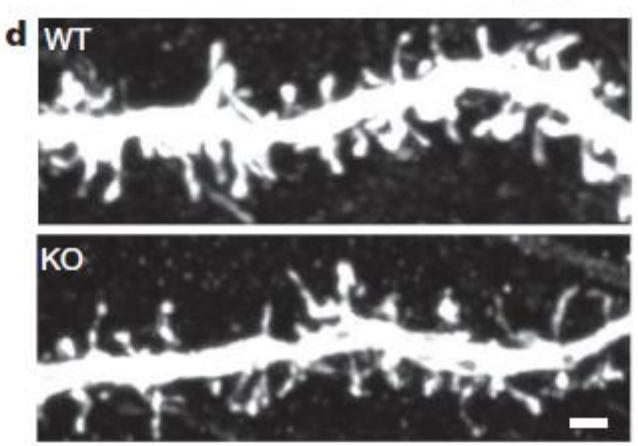






Densità sinaptica





SHANK3

Incorporate behavioral phenotypes for all 3 symptoms of autism

- Reduced sociability (social approach)
- Repetitive behaviors (greater self-grooming)
- Communication deficits (low number of ultrasonic vocalizations during male-female interaction)

Modelli animali transgenici:

- Valutare la complessa **interazione gene-ambiente**
- Studiare i **pathways neurobiologici** alla base dei tre sintomi principali dell'autismo
- Esplorare eventuali **interventi terapeutici/comportamentali**

Conclusioni

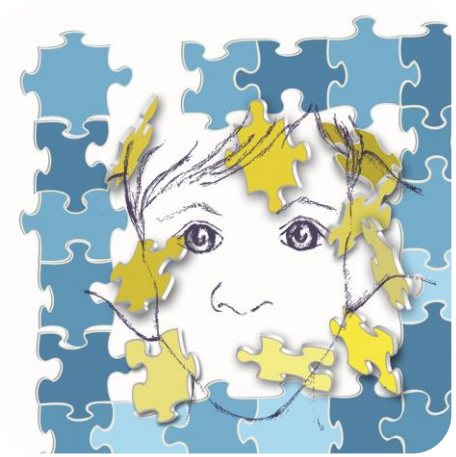
L'autismo è contraddistinto da una grande eterogeneità che rende difficoltosa la validazione di teorie eziopatologiche capaci di sintetizzare gli aspetti cognitivi, comportamentali e fisiologici.

Approssimativamente 67 milioni di persone nel mondo sono affette da autismo, più di quante ne colpiscano i tumori, il diabete e l'AIDS messi insieme.

Non esiste una cura per l'autismo ma la diagnosi e un intervento precoce ne migliorano l'esito

la figura del PEDIATRA è indispensabile

Grazie per l'attenzione



"Non-invasive tools for early detection of Autism Spectrum Disorders"

Ministero della Salute- Progetto Giovani Ricercatori 2008