I disturbi dello spettro autistico

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Leo Kanner 1896-1981

La descrizione di Kanner (1)

- Kanner (1943) descrisse 11 bambini con “autistic disturbances of affective contact”
- Un disturbo caratterizzato da una mancanza profonda di attaccamento sociale fin dalla nascita o da poco dopo
- Una gamma di problemi di comunicazione e di risposte inusuali agli stimoli ambientali inanimati
- 3/11 bambini erano averbali, ma coloro che erano in grado di parlare, presentavano ecolalia e inversione pronominale

La descrizione di Kanner (2)

- I bambini in qualche caso potevano essere sottoposti a subtest cognitivi e di sviluppo, ottenendo buoni risultati
- Pertanto Kanner, tenendo anche conto dell'aspetto attraente dei bambini, ipotizzò che essi avessero un buon potenziale intellettivo
- Kanner osservò anche che in molti casi i genitori (soprattutto i padri) erano persone di successo e che le interazioni con i bambini apparivano strane
- D'altra parte, l'enfasi di Kanner sulla natura apparentemente congenita ("innate") del problema rendeva piuttosto difficile attribuire la sua genesi esclusivamente ad un disturbo genitore-bambino

La descrizione di Kanner (3)

- In sintesi, nella visione di Kanner, la caratteristica essenziale dell'autismo era l'incapacità di relazionarsi del bambino
- L'uso del termine "autismo" coniato da Bleuer (1911) per definire il pensiero idiosincrasico, centrato sul sé della schizofrenia, fu inteso per suggerire la nozione di un bambino che vive nel suo mondo
- L'uso della parola "autismo" e alcuni aspetti del suo lavoro originale si sono, purtroppo, rivelate delle false guide per la successiva ricerca


DSM-III
DSM-III-R
DSM-IV
DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
DSM-IV-TR
DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

→ **DSM-V (2012)**

DSM-IV (1994) and DSM-IV-TR (2000)

299.00 Autistic Disorder

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

(1) Qualitative impairment in social interaction, as manifested by at least two of the following:
(a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
(b) failure to develop peer relationships appropriate to developmental level
(c) lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
(d) lack of social or emotional reciprocity

(2) Qualitative impairments in communication as manifested by at least one of the following:
(a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
(b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
(c) stereotyped and repetitive use of language or idiosyncratic language
(d) lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level

(3) Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, as manifested by at least of one of the following:
(a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
(b) apparently inflexible adherence to specific, nonfunctional routines or rituals
(c) stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole body movements)
(d) persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play

C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

299.80 Pervasive Developmental Disorder Not Otherwise Specified (including Atypical Autism)

- This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interests, and activities are present, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder or Avoidant Personality Disorder. For example, this category includes "atypical autism"— presentations that do not meet the criteria for Autistic Disorder because of late age at onset, atypical symptomatology, or subthreshold symptomatology, or all of these

Disturbo multisistemico di sviluppo (Class. Diagn. 0-3)

- Disturbo significativo, ma non assenza completa, della capacità di entrare in relazione emotiva e sociale con i genitori (cioè, pur mostrandosi evitanti o senza scopi possono manifestare forme sottili di relazione o possono relazionarsi in modo abbastanza affettuoso, ma intermittente)
- Disturbo significativo nella capacità di formare, mantenere e/o sviluppare una comunicazione. Con il termine comunicazione si intende ogni forma di comunicazione, sia essa di tipo gestuale o preverbale e non verbale (ad es., figurativa)
- Disfunzione significativa nell'elaborazione delle informazioni uditive (cioè, nella percezione e nella comprensione)
- Disfunzione significativa nell'elaborazione di altre sensazioni: sono inclusi l'iper- e l'ipo-reattività (in relazione all'input visuo-spaziale, tattile, propriocettivo e vestibolare) e le difficoltà nell'elaborazione legata alla pianificazione motoria (ad es., di sequenze di movimenti)

AMERICAN PSYCHIATRIC ASSOCIATION

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Report of the DSM-V Neurodevelopmental Disorders Work Group

November 2008
Susan Swedo, M.D.

The Neurodevelopmental Disorders (ND) work group's discussions have focused on three areas:

1) Possible modification of ADHD criteria to allow for co-morbidity of autism and ADHD (currently excluded). The ADHD & Disruptive Behavior Disorders Work Group has agreed to consider this possibility.

2) Discussion of the validity of Rett's disorder as a separate disorder and inclusion of a new modifier within the Autism Spectrum Disorders (ASD), which might include genetic and medical disorders and other biologically-definable conditions.

3) How to address Pervasive Developmental Disorders – Not Otherwise Specified (PDD-NOS). The individuals currently diagnosed with PDD-NOS may still be described in DSM-V, but the work group will discuss whether they can redefine ASD in such a way that the PDD-NOS diagnosis isn't necessary, as this diagnosis currently captures a very heterogeneous group of individuals.

Report of the DSM-V Neurodevelopmental Disorders Work Group

Questions still under active discussion for ASD include:

1) How to describe the "spectrum" of disorders now known as ASD (e.g., how many domains will define the disorder);

2) What is the specificity of repetitive behaviors in ASD and how might they be better defined;

3) Whether Childhood Disintegrative Disorder (CDD) is a unique and separate disorder, and if so, what are its defining characteristics;

4) Whether autism is a life-long diagnosis or whether it is possible to recover/remit to the point where the diagnosis is no longer applicable;

5) Whether Asperger's disorder is the same as "high-functioning autism";

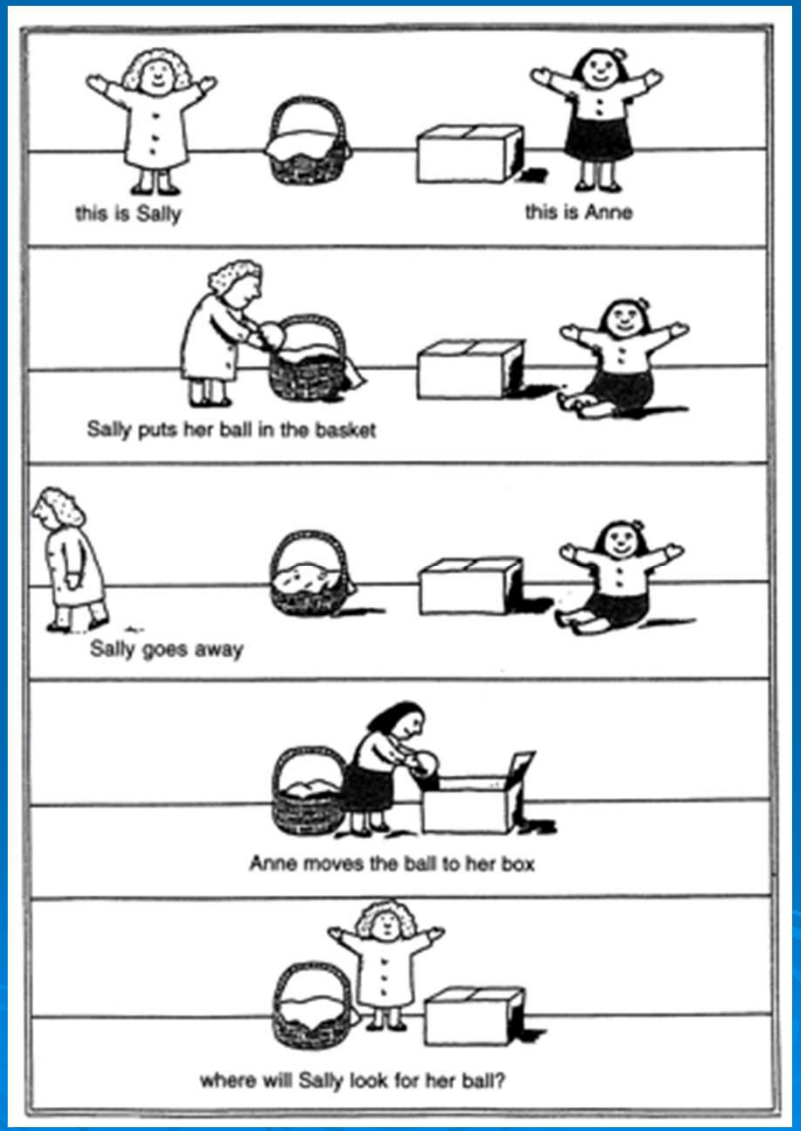
6) How the DSM-V can alert clinicians to common medical comorbidities (including genetic disorders, epilepsy/EEG abnormalities and sleep, or GI problems) and potential biomarkers;

7) How to include consideration of severity and impairment in diagnosis (currently defined as "qualitative impairments") and how to integrate these with the overall structure of DSM-V; and

8) How/where to discuss cultural influences on diagnosis (e.g., Korean use of reactive attachment disorder rather than ASD to avoid family stigmatization).

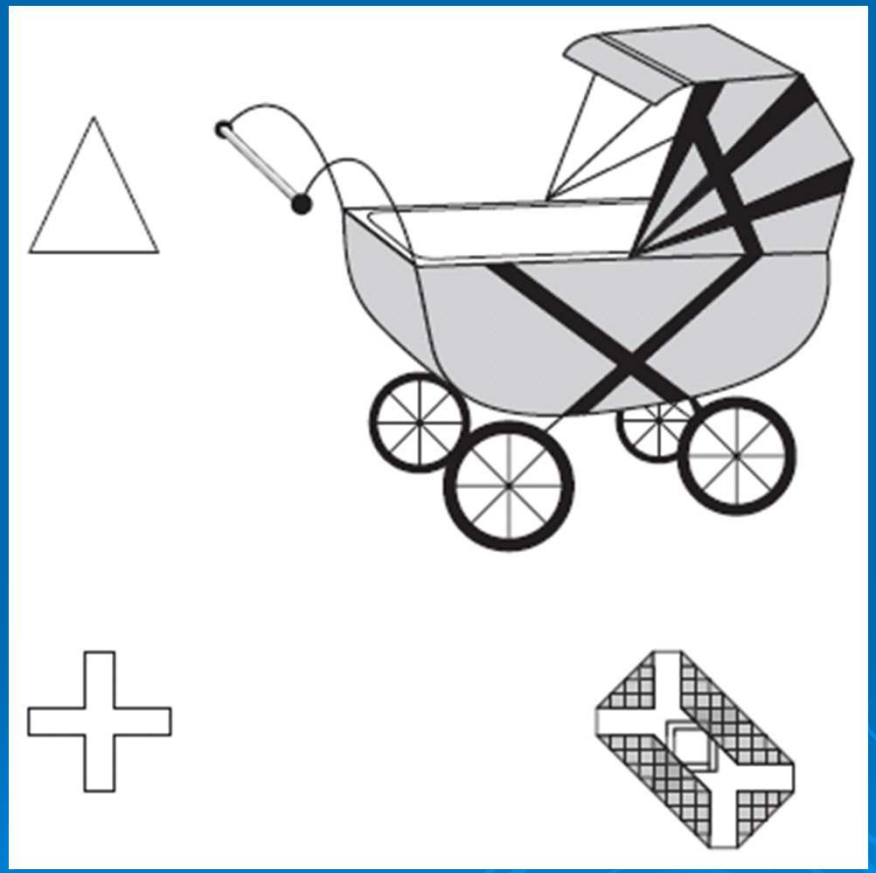
Teoria della mente

Soprattutto grazie ai contributi di Frith, Baron-Cohen e Happé, sono stati compiuti notevoli passi avanti nella comprensione delle problematiche cognitive dell'autismo. Questa sindrome è stata da questi Autori descritta in termini di cecità nei confronti della mente, ossia di incapacità a comprendere gli stati mentali altrui (emozioni, intenzioni, credenze).



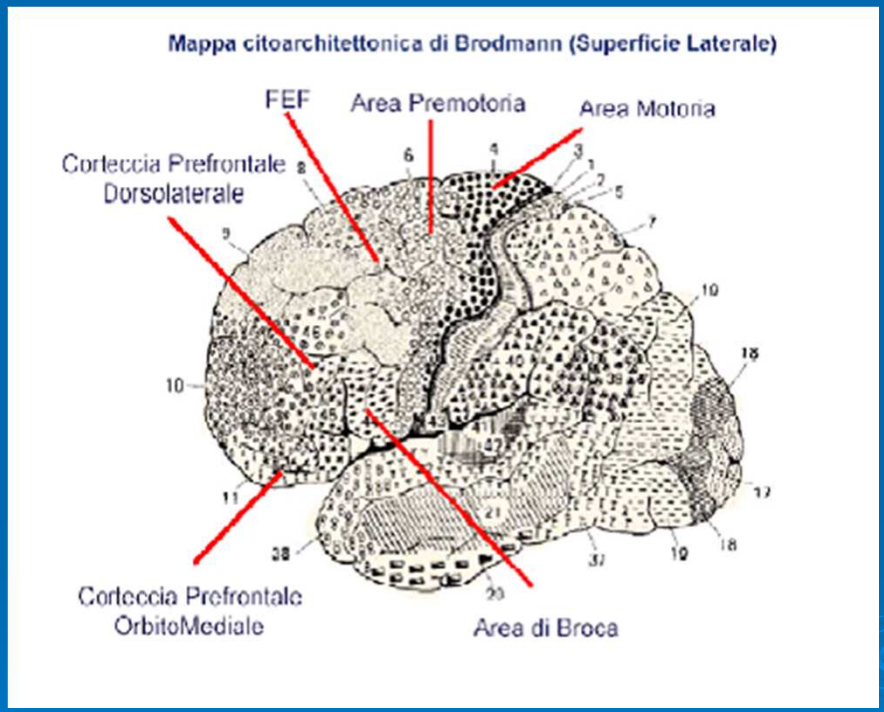
Teoria della coerenza centrale

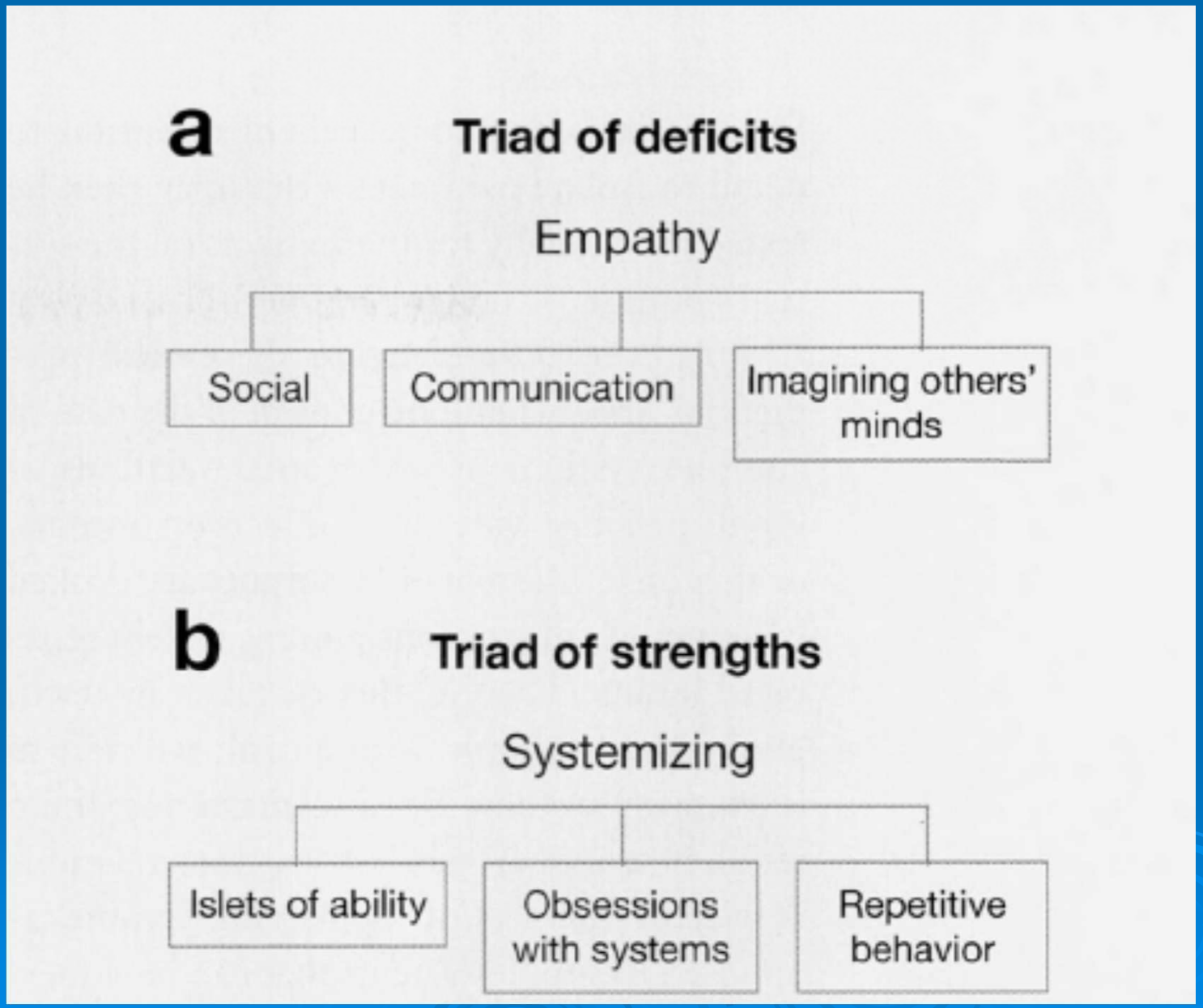
In base a questo modello teorico, le difficoltà delle persone con disturbo dello spettro autistico sono messe in relazione, non tanto alla teoria della mente, quanto ad una predisposizione cognitiva a focalizzare l'attenzione sui dettagli piuttosto che sulle figure/oggetti nella loro interezza.
Una conseguenza di questo stile cognitivo è che il cambiamento di un dettaglio in una situazione può comportare il non riconoscimento di una situazione come già sperimentata.



Teoria della funzione esecutiva

- Alcuni aspetti del disturbo autistico sembrano associati ad un danneggiamento neurologico della corteccia prefrontale. Questa area del cervello sembra essere coinvolta nelle capacità di pianificazione, controllo dell'impulso, memoria procedurale
- L'ingestibilità, soprattutto a livello emotivo, che deriva da queste disfunzioni ostacola una elaborazione efficace delle situazioni nel corso del loro svolgimento




a
Triad of deficits
Empathy
Social
Communication
Imagining others' minds
b
Triad of strengths
Systemizing
Islets of ability
Obsessions with systems
Repetitive behavior

La teoria del “cervello maschile estremo”

- *Type E* (E > S): individuals whose empathy is stronger than their systemizing
- *Type S* (S > E): individuals whose systemizing is stronger than their empathy
- *Type B* (S = E): individuals whose empathy is as good (or as bad) as their systemizing (B stands for balanced”)
- *Extreme Type E* (E ≫ S): individuals whose empathy is above average, but who are challenged when it comes to systemizing
- *Extreme Type S* (S ≫ E): individuals whose systemizing is above average, but who are challenged when it comes to empathy

Recently, the EMB theory has been extended to the level of neurology, with some interesting findings emerging (Baron-Cohen, Knickmeyer, et al. 2005).Regions of the brain that on average are smaller in males than in females (such as the anterior cingulate, superior temporal gyrus, prefrontal cortex, and thalamus) are even smaller in people with autism than in typical males. In contrast, in regions of the brain that on average are bigger in males than in females (including the amygdala, cerebellum, overall brain size/weight, and head circumference), these regions or measurements are even bigger in people with autism than in typical males. Also, the male brain is, on average, larger than the female, and people with autism have been found to have even larger brains than typical males. Not all studies support this pattern but

(Baron-Cohen, 2009)

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Autism: The first firm finding = underconnectivity?

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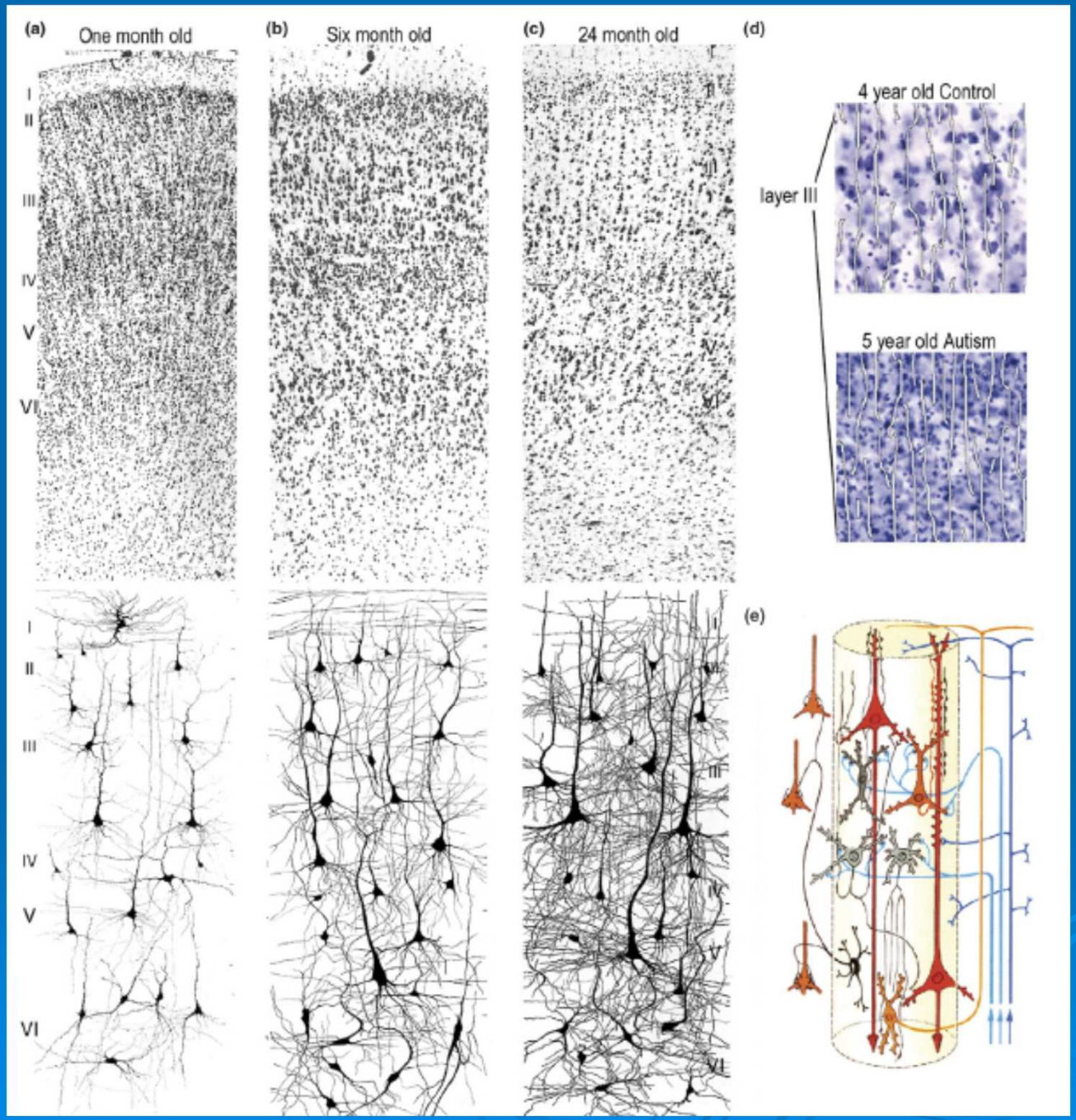
Available online 24 May 2007

Abstract

In January 2005, J.R. Hughes and M. Melyn published an electroencephalographic study on autistic children and found 46% with seizures and also a relatively high prevalence of 20% with epileptiform discharges but *without any clinical seizures* (Clin EEG Neurosci 2005;36:15–20). Because the discharges have always been viewed as focal events and the clinical seizures as requiring spread, the conclusion from these data was that children with autism may have a deficiency of corticocortical fibers. Since that time many MRI and functional MRI studies have been published confirming that one of the first findings in this devastating condition is underconnectivity. Specific findings are the thinning of the corpus callosum and the reduced connectivity, especially with the frontal areas and also the fusiform face area. Other studies involving positron emission tomography scans, magnetoencephalography, and perception have added to the evidence of underconnectivity. One final point is the initial overgrowth of white matter in the first 2 years of life in autistic children, followed later by arrested growth, resulting in aberrant connectivity; myelination of white matter will likely be significant in the etiology of autism.

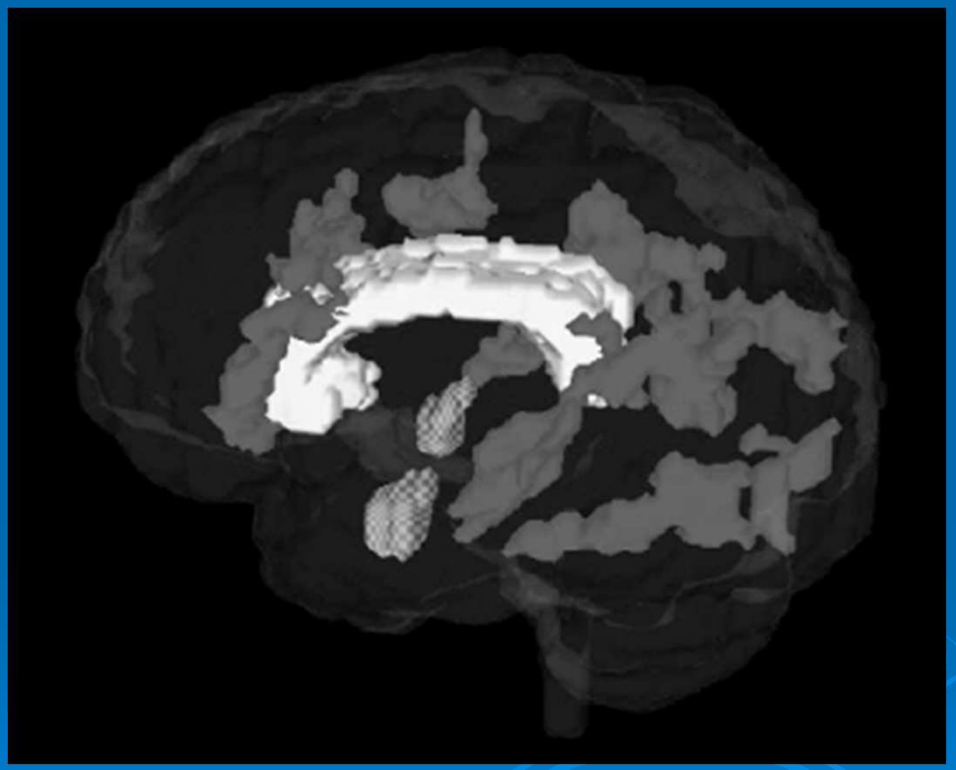


Amaral et al., 2008

Diffusion tensor imaging MRI

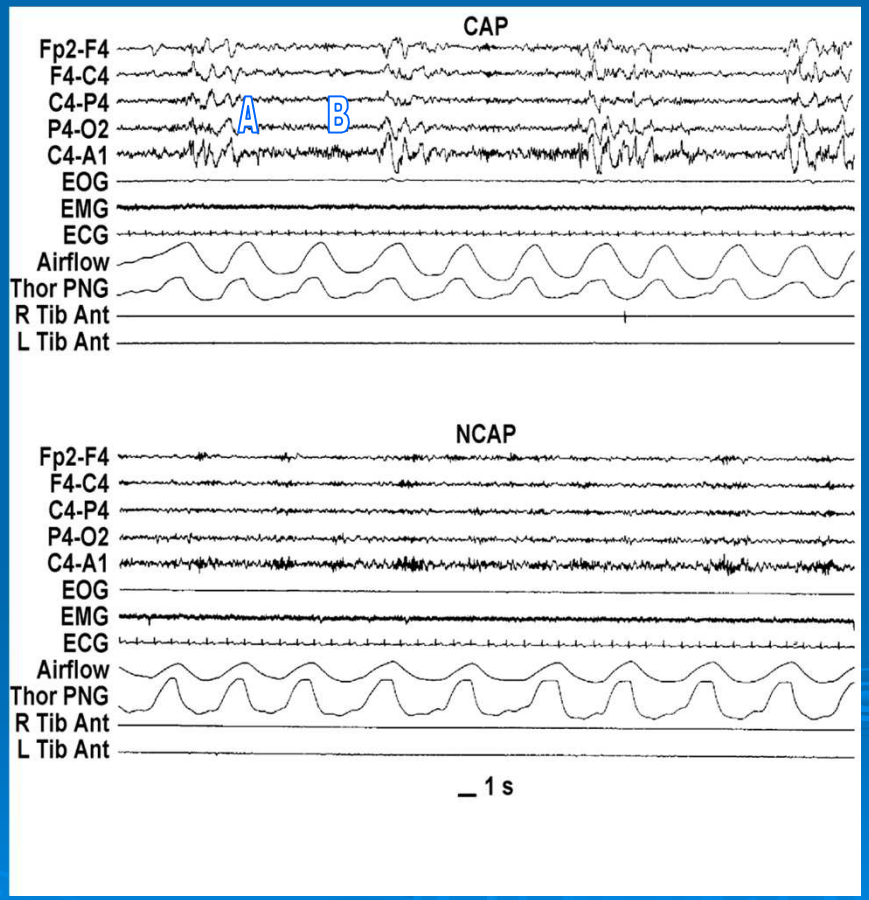
Alterazioni a carico della sostanza bianca adiacente alla corteccia prefrontale ventro-mediale, ai giri del cingolo anteriore e alla giunzione temporo-occipitale (regioni implicate nel “social functioning”)

(Barnea-Goraly et al., 2004)



Il sonno non-REM è caratterizzato da tre diversi livelli di vigilanza:

- Uno stato d'attivazione *(fase A)*
- Una stato di disattivazione *(fase B)*
- Uno stato stabile *(non- CAP)*



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Original Article

Sleep in children with autistic spectrum disorder: A questionnaire and polysomnographic study

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Available online 28 August 2007

Table 3
CAP parameters found in ASD children and normal controls

	Normal controls ($n = 18$)		ASD patients ($n = 16$)		Mann–Whitney U-test
	Mean	SD	Mean	SD	$p <$
Total CAP rate (%)	37.9	7.27	36.8	10.39	NS
In S1 (%)	33.5	21.48	39.4	18.64	NS
In S2 (%)	33.9	10.77	40.4	13.68	NS
In SWS (%)	47.3	8.67	33.9	15.47	0.02
A1 (%)	77.9	8.43	65.1	8.35	0.0004
A2 (%)	12.8	7.03	19.7	6.23	0.006
A3 (%)	9.4	3.02	15.1	6.16	0.002
A1 duration (s)	4.8	0.33	4.9	0.32	NS
A2 duration (s)	7.8	1.75	6.6	0.79	0.04
A3 duration (s)	15.3	4.83	12.5	1.51	NS
A1 index	47.0	10.67	38.2	10.12	0.04
In S1	33.2	20.93	25.5	20.49	NS
In S2	43.8	10.81	41.4	13.45	NS
In SWS	77.7	18.94	52.6	22.58	0.004
A2 index	8.7	6.38	12.3	6.52	NS
In S1	6.4	6.31	8.5	8.05	NS
In S2	11.2	8.15	19.3	9.65	0.02
In SWS	6.8	4.55	5.0	3.25	NS
A3 index	5.5	3.17	8.9	5.74	0.03
In S1	16.7	13.13	33.3	24.04	0.04
In S2	8.1	3.44	12.5	8.00	0.05
In SWS	2.6	1.72	4.6	3.85	NS
B duration (s)	20.7	4.14	19.5	2.30	NS
Sequence duration (s)	195.3	42.84	180.1	38.55	NS
No. of sequences	44.9	9.62	41.6	7.92	NS

CAP, cyclic alternating pattern; ASD, autistic spectrum disorder; SWS, slow wave sleep.

CAP, autismo e lobo frontale

- Il basso valore di CAP rate, statisticamente significativo solo in SWS, suggerisce una certa immaturità del SNC nel gruppo di soggetti con autismo presi in esame
- Questo si riflette sulla componente A1, caratteristica dei meccanismi protettivi del sonno che appaiono nell'autismo meno maturi ed efficienti
- Correlazione tra attività ad onde lente (CAP) e funzioni cognitive (lobo frontale)

Sleep Architecture and NREM Alterations in Children and Adolescents with Asperger Syndrome

Oliviero Bruni, MD[1]; Raffaele Ferri, MD[2]; Elena Vittori, MD[1]; Luana Novelli, PhD[1]; Manuela Vignati, MD[3]; Maria C. Porfirio, MD[3]; Debora Aricò, PsyD[2]; Paola Bernabei, MD[1]; Paolo Curatolo, MD[3]

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Study Objectives: To analyze sleep in children with Asperger syndrome (AS) by means of standard sleep questionnaires, to evaluate sleep architecture and NREM sleep alterations by means of cyclic alternating pattern (CAP) and to correlate objective sleep parameters with cognitive behavioral measures.

Design: Cross-sectional study involving validated sleep questionnaires, neuropsychological scales, and PSG recording.

Setting: Sleep medicine center.

Participants: Eight children with AS, 10 children with autism, and 12 healthy control children.

Interventions: N/A

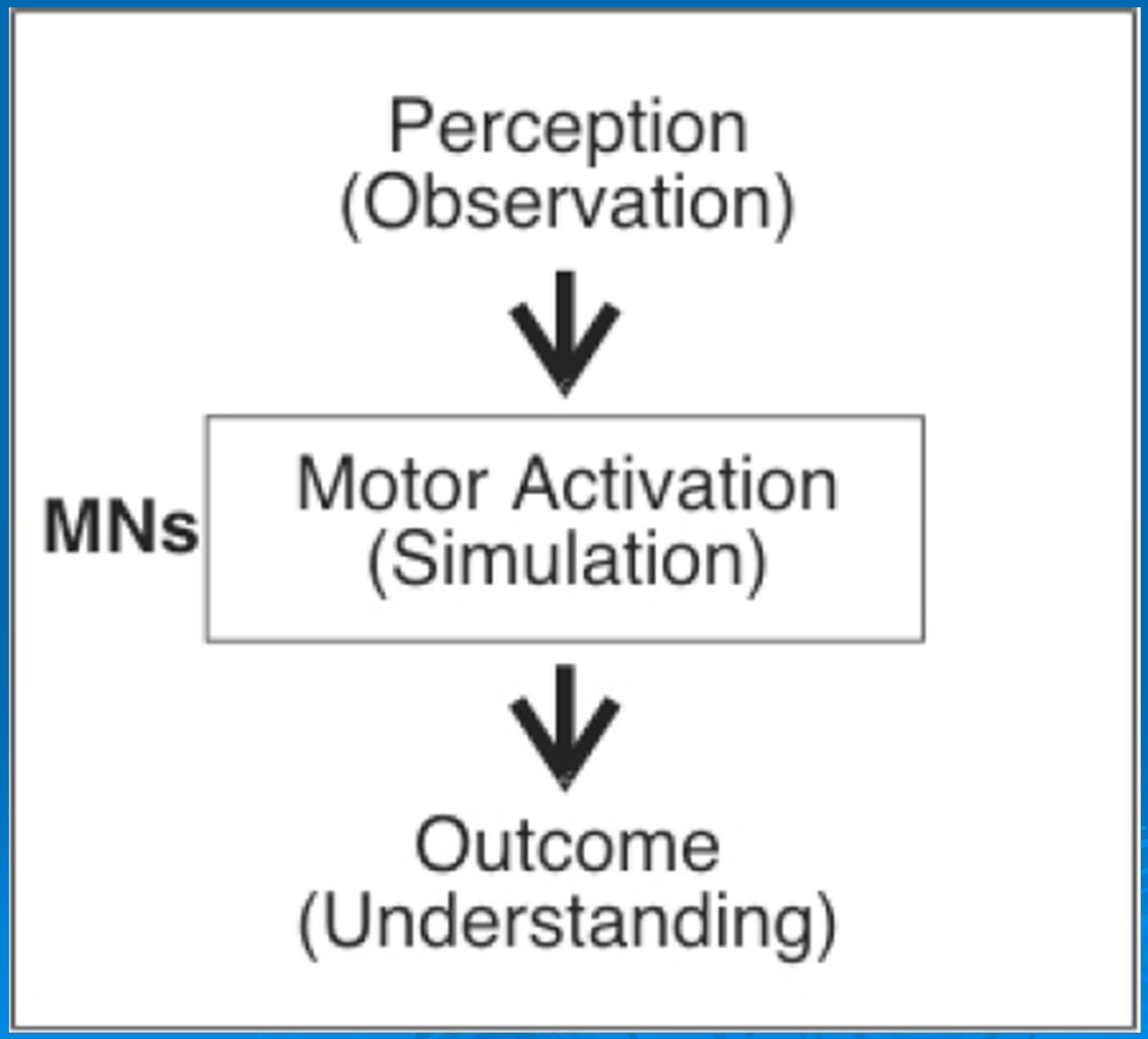
Measurements and Results: Children with AS had a higher prevalence of problems of initiating sleep and daytime sleepiness. Sleep architecture parameters showed minor differences between the 3 groups. CAP parameters showed an increased percentage of A1 and a decreased percentage of A2 subtypes in subjects with AS vs. controls. All A subtype indexes (number per hour of NREM sleep) were decreased, mostly in sleep stage 2 but not in SWS. With respect to children with autism, subjects with AS showed increased CAP rate in SWS and A1 percentage. In subjects with AS, verbal IQ had a significant positive correlation with total CAP rate and CAP rate in SWS and with global and SWS A1 index. The percentage of A2 negatively correlated with full scale IQ, verbal and performance IQ. CBCL total score correlated positively with CAP rate and A1 index while externalizing score correlated negatively with A3%.

Conclusions: This study shows peculiar CAP modifications in children with AS and represents an attempt to correlate the quantification of sleep EEG oscillations with the degree of mental ability/disability.

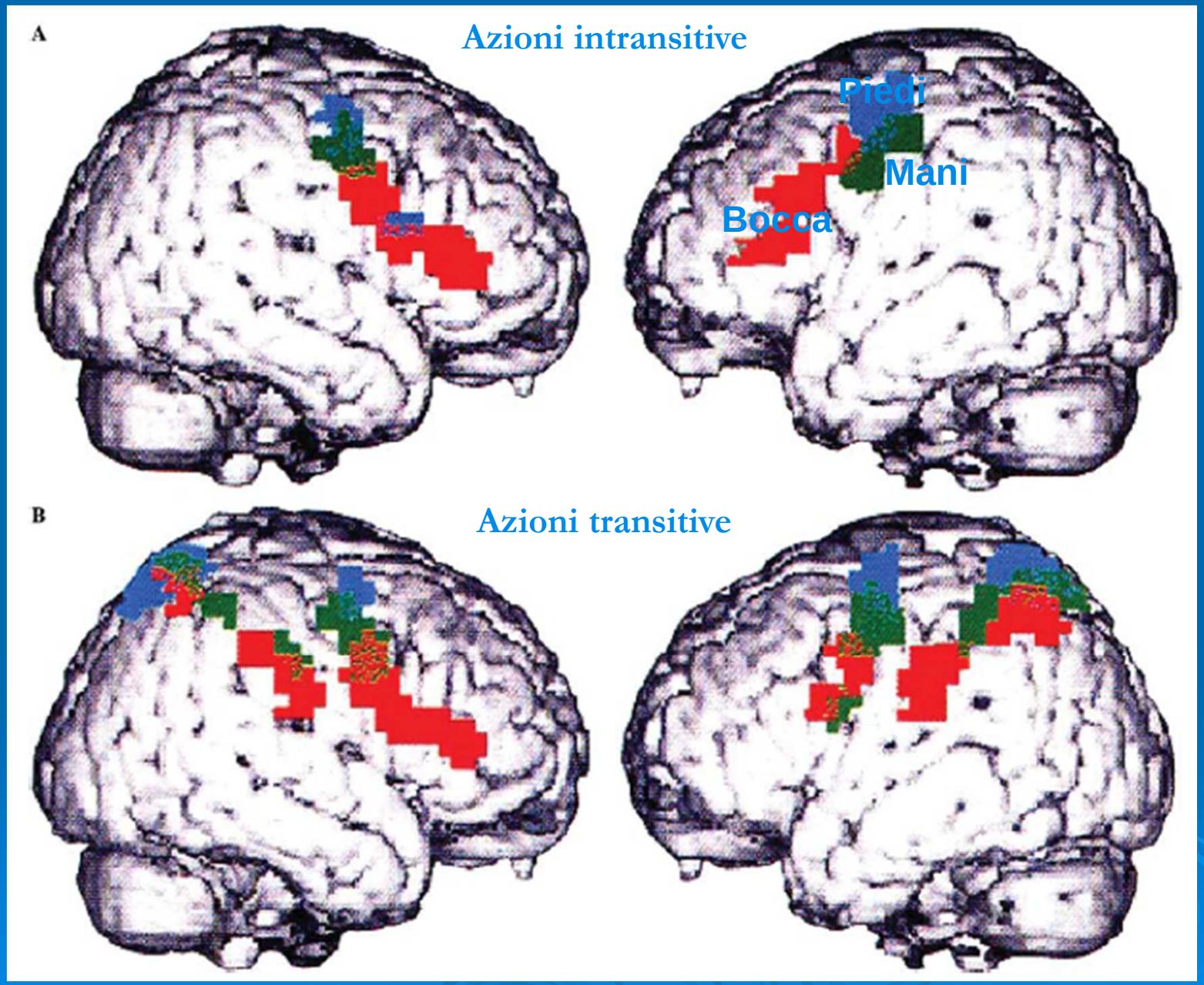
Keywords: Asperger syndrome, autism, sleepiness, polysomnography, child behavior checklist, autism diagnostic observation schedule, cyclic alternating pattern

Citation: Bruni O; Ferri R; Vittori E; Novelli L; Vignati M; Porfirio MC; Aricò D; Bernabei P; Curatolo P. Sleep architecture and NREM alterations in children and adolescents with asperger syndrome. *SLEEP* 2007;30(11):1577-1585.

Mirror neurons



(Fadiga L, Fogassi L, Pavesi G, & Rizzolatti G, 1995)

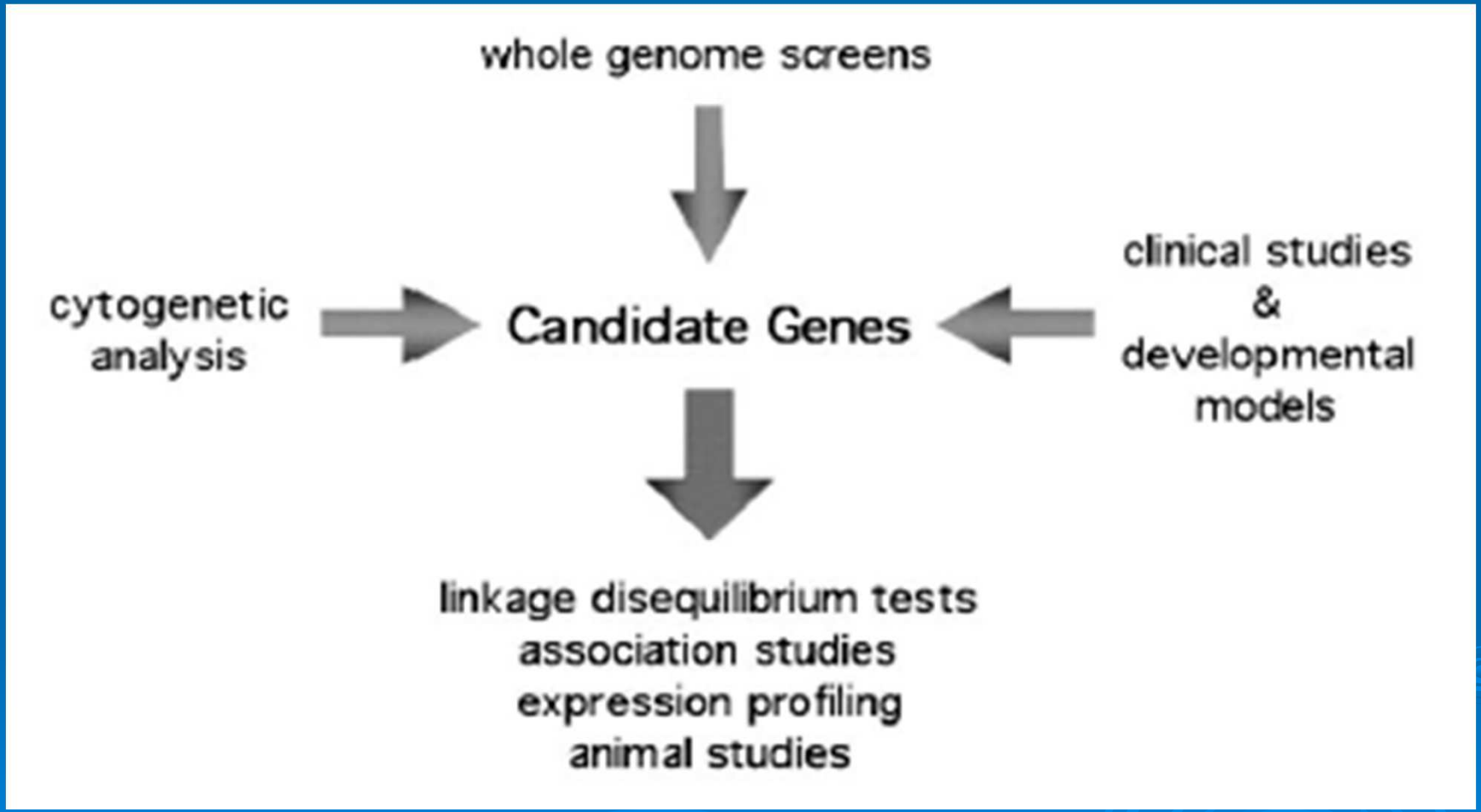


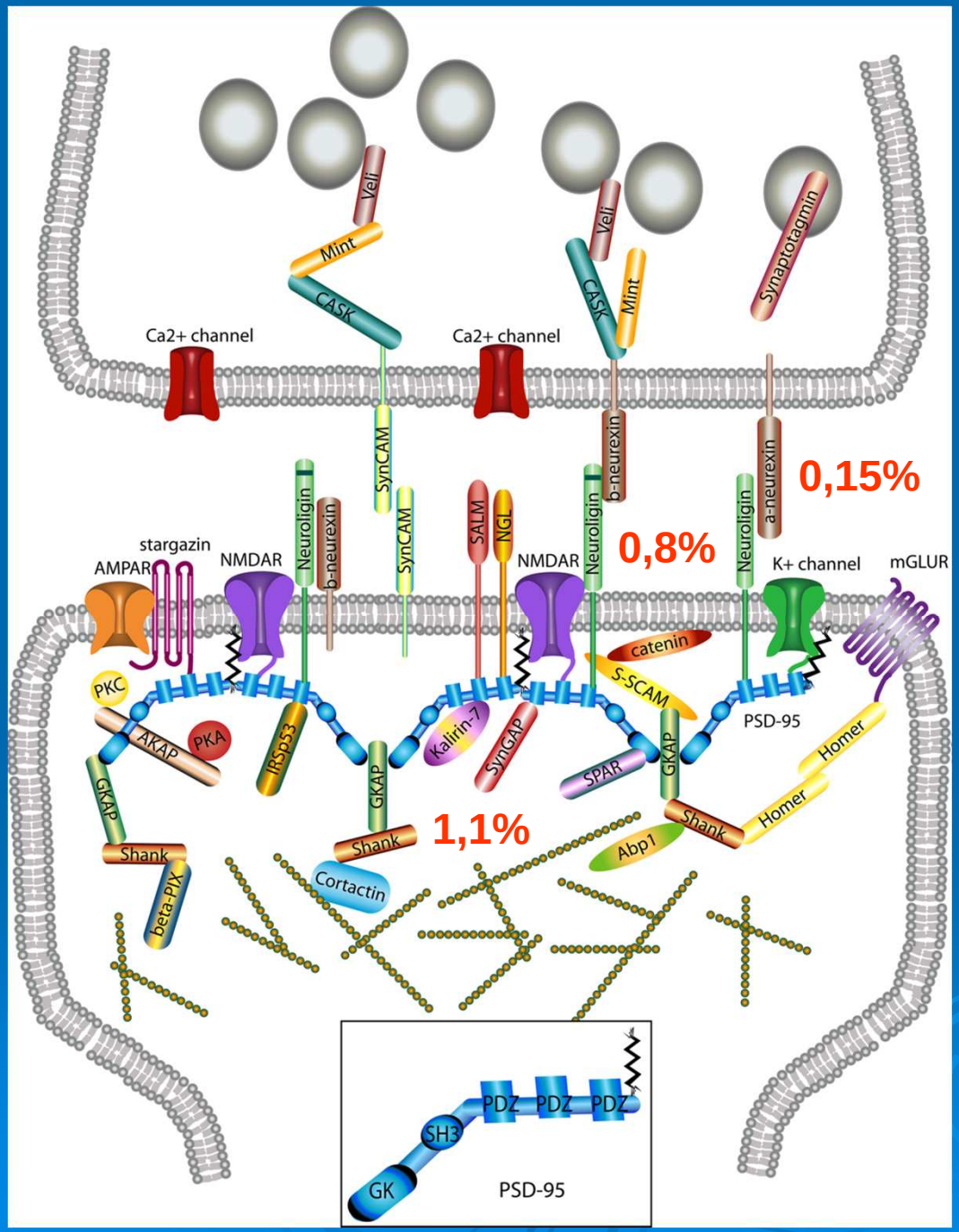
(Buccino et al., 2001)

I mirror neurons e l'autismo

- Per giudicare i movimenti di un'altra persona occorre forse eseguire una simulazione interna virtuale di ciò che l'altro sta facendo
- Tale simulazione interna implica l'attivazione dei mirror neurons
- I mirror neurons consentendo una simulazione virtuale delle azioni e delle intenzioni degli altri, consentono probabilmente di elaborare una "teoria della mente" (deficitaria nell'autismo)

La genetica dell'autismo: metodi di indagine




Veli
Mint
CASK
Ca2+ channel
Ca2+ channel
Veli
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Synaptotagmin
SynCAM
b-neurexin
a-neurexin
0,15%
Neuroligin
b-neurexin
SynCAM
SALM
NGL
NMDAR
Neuroligin
0,8%
Neuroligin
K+ channel
mGLUR
stargazin
AMPAR
NMDAR
catenin
S-SCAM
PKC
PSD-95
AKAP
PKA
IRSp53
Kallirin-7
SynGAP
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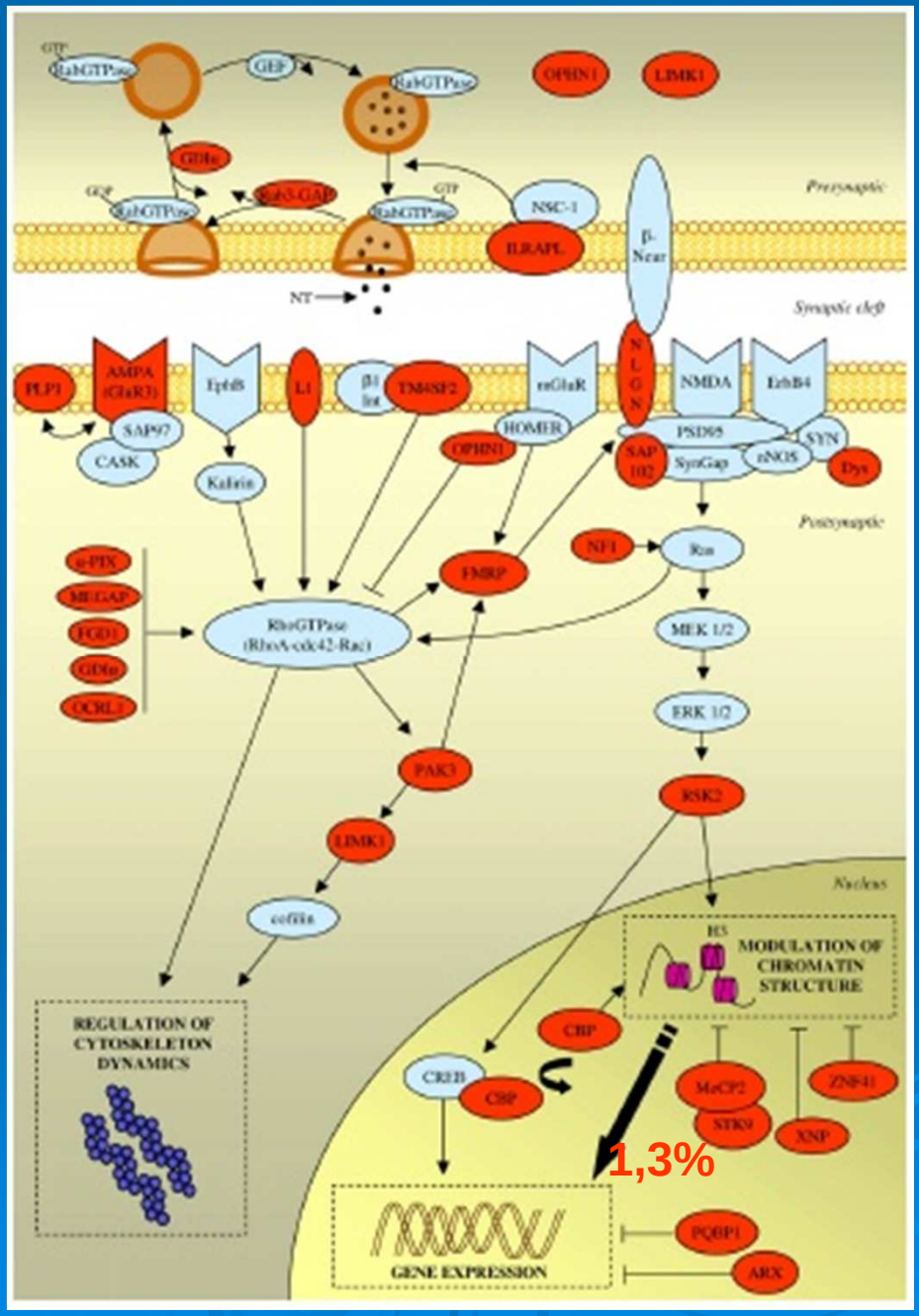
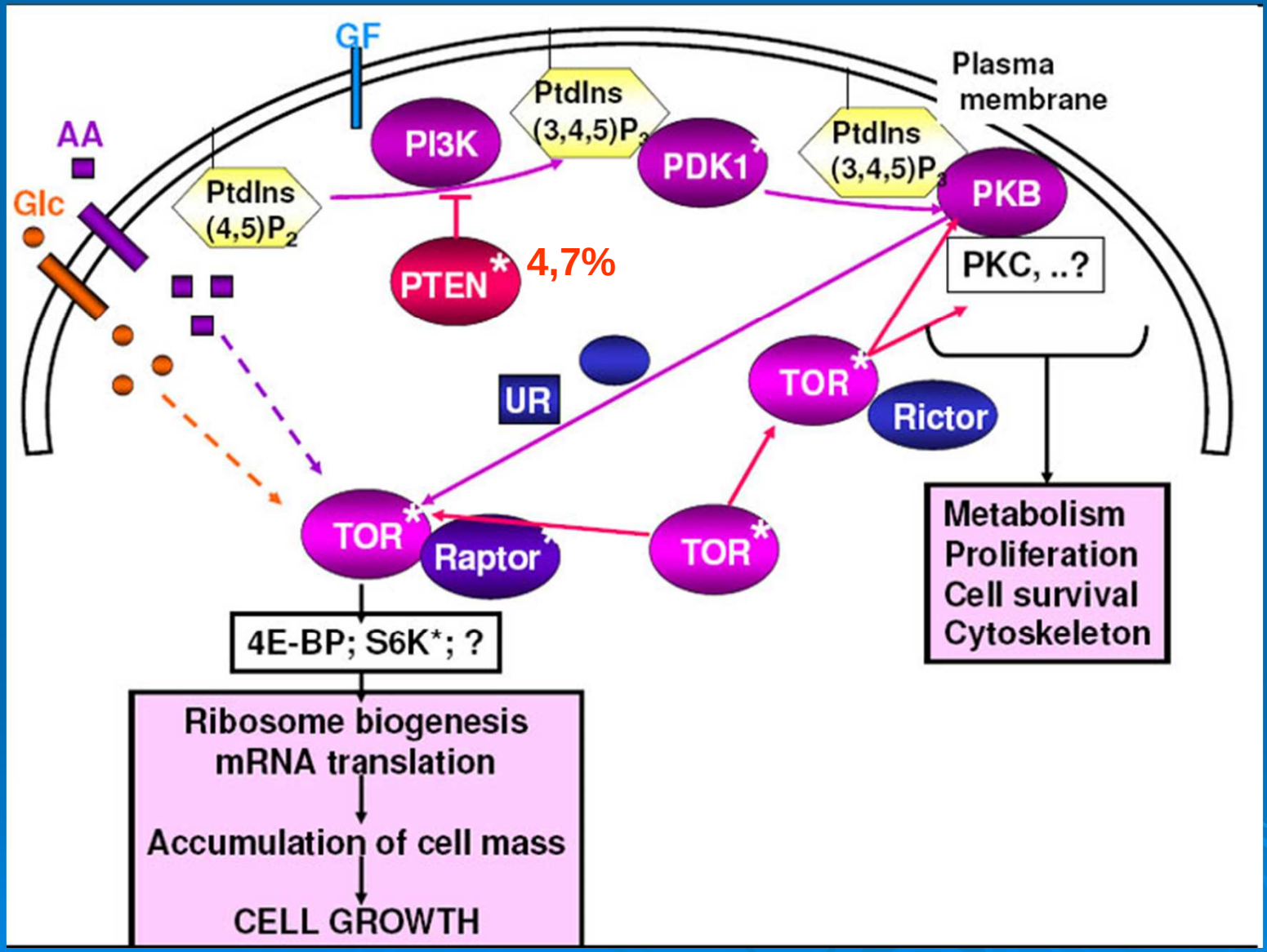
SH3
GK
PSD-95

presynaptic
vesicle cycling

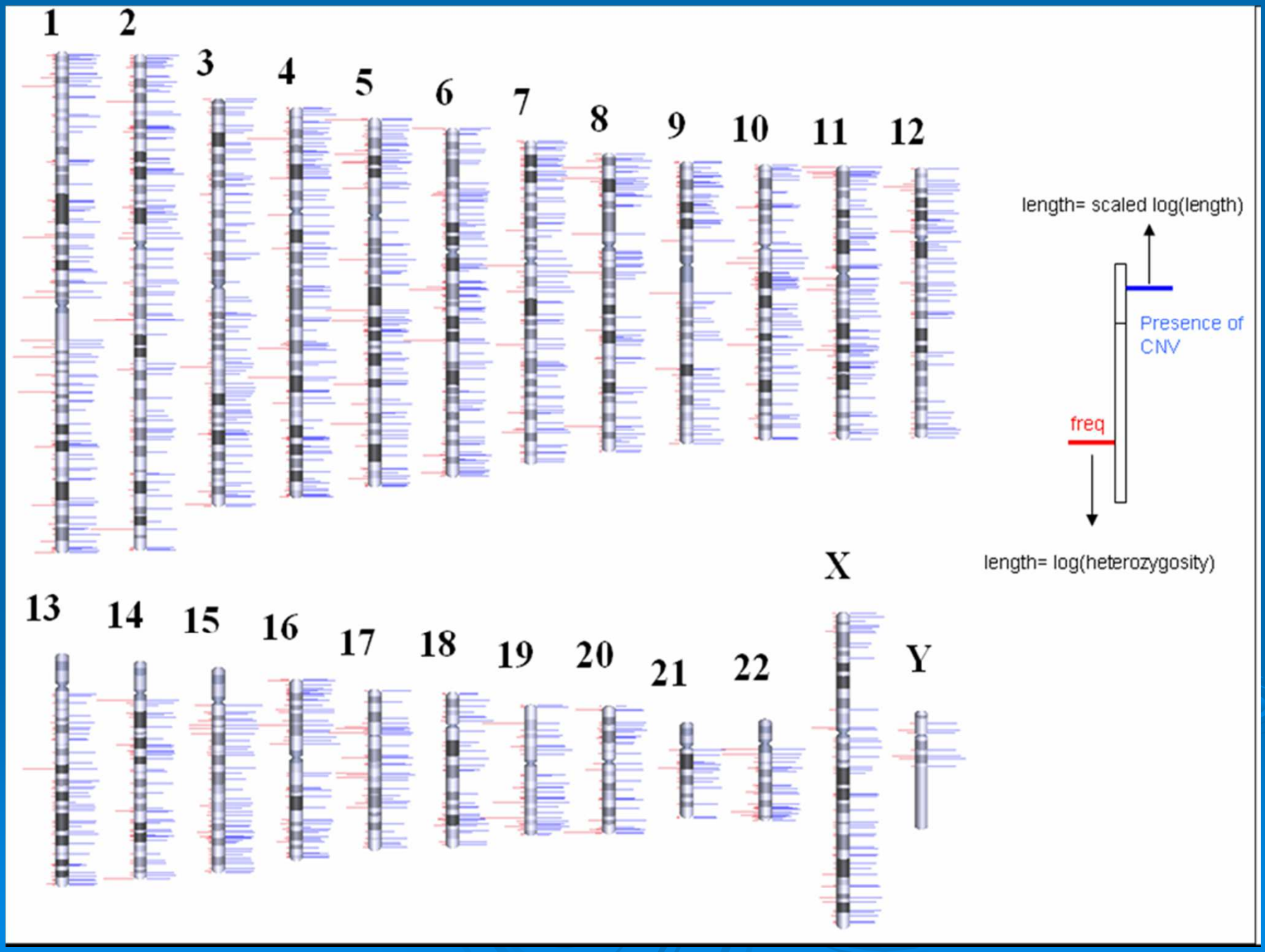
organization
of postsynaptic
protein complexes




GF
Plasma membrane
AA
Glc
PI3K
PtdIns (3,4,5)P3
PDK1*
PtdIns (3,4,5)P3
PKB
PtdIns (4,5)P2
PTEN*
4,7%
PKC, ..?
UR
TOR*
Rictor
TOR*
Raptor*
TOR*
Metabolism
Proliferation
Cell survival
Cytoskeleton
4E-BP; S6K*; ?
Ribosome biogenesis
mRNA translation
Accumulation of cell mass
CELL GROWTH

Copy number variation (CNV)

- Varianti genomiche strutturali nelle quali invece di un normale assetto diploide si hanno amplificazioni o perdite
- Molte di queste varianti si trovano nella popolazione generale e riguardano > 15% del genoma umano
- Il microarray è uno dei migliori metodi per identificarle
- Se la loro frequenza allelica nella popolazione > 1% vengono considerate un polimorfismo
- Rappresentano una delle maggiori fonti di diversità fenotipica e un formidabile motore per l'evoluzione
- Possono essere sia **benigne** che **estremamente deleterie**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11
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14
15
16
17
18
19
20
21
22
X
Y
length= scaled log(length)
Presence of CNV
freq
length= log(heterozygosity)

CNV già associate a diverse patologie

Fattori di suscettibilità

* Schizofrenia
*Obesità
* Disordine bipolare
* Malattia delle coronarie
* Diabete
* Morbo di Crohn
* Cancro
* Ipertensione
* Artrite reumatoide
*Diabete
* Psoriasi
* Lupus eritematoso sistemico
* HIV
* Parkinson

Fattori di rischio ad alta penetranza

* Ritardo Mentale
* Autismo
* Alzheimer
* Infertilità

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Copy number variation characteristics in subpopulations of patients with autism spectrum disorders.

Bremer A, Giacobini M, Eriksson M, Gustavsson P, Nordin V, Fernell E, Gillberg C, Nordgren A, Uppströmer A, Anderlid BM, Nordenskjöld M, Schoumans J.

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Abstract

Autism spectrum disorders (ASDs) are a heterogeneous group of disorders with a complex genetic etiology. We used high-resolution whole genome array-based comparative genomic hybridization (array-CGH) to screen 223 ASD patients for gene dose alterations associated with susceptibility for autism. Clinically significant copy number variations (CNVs) were identified in 18 individuals (8%), of which 9 cases (4%) had de novo aberrations. In addition, 20 individuals (9%) were shown to have CNVs of unclear clinical relevance. Among these, 13 cases carried rare but inherited CNVs that may increase the risk for developing ASDs, while parental samples were unavailable in the remaining seven cases. Classification of all patients into different phenotypic and inheritance pattern groups indicated the presence of different CNV patterns in different patient groups. Clinically relevant CNVs were more common in syndromic cases compared to non-syndromic cases. Rare inherited CNVs were present in a higher proportion of ASD cases having first- or second-degree relatives with an ASD-related neuropsychiatric phenotype in comparison with cases without reported heredity ($P = 0.0096$). We conclude that rare CNVs, encompassing potential candidate regions for ASDs, increase the susceptibility for the development of ASDs and related neuropsychiatric disorders giving us further insight into the complex genetics underlying ASDs.

Functional Annotation of Genes Overlapping Copy Number Variants in Autistic Patients: Focus on Axon Pathfinding

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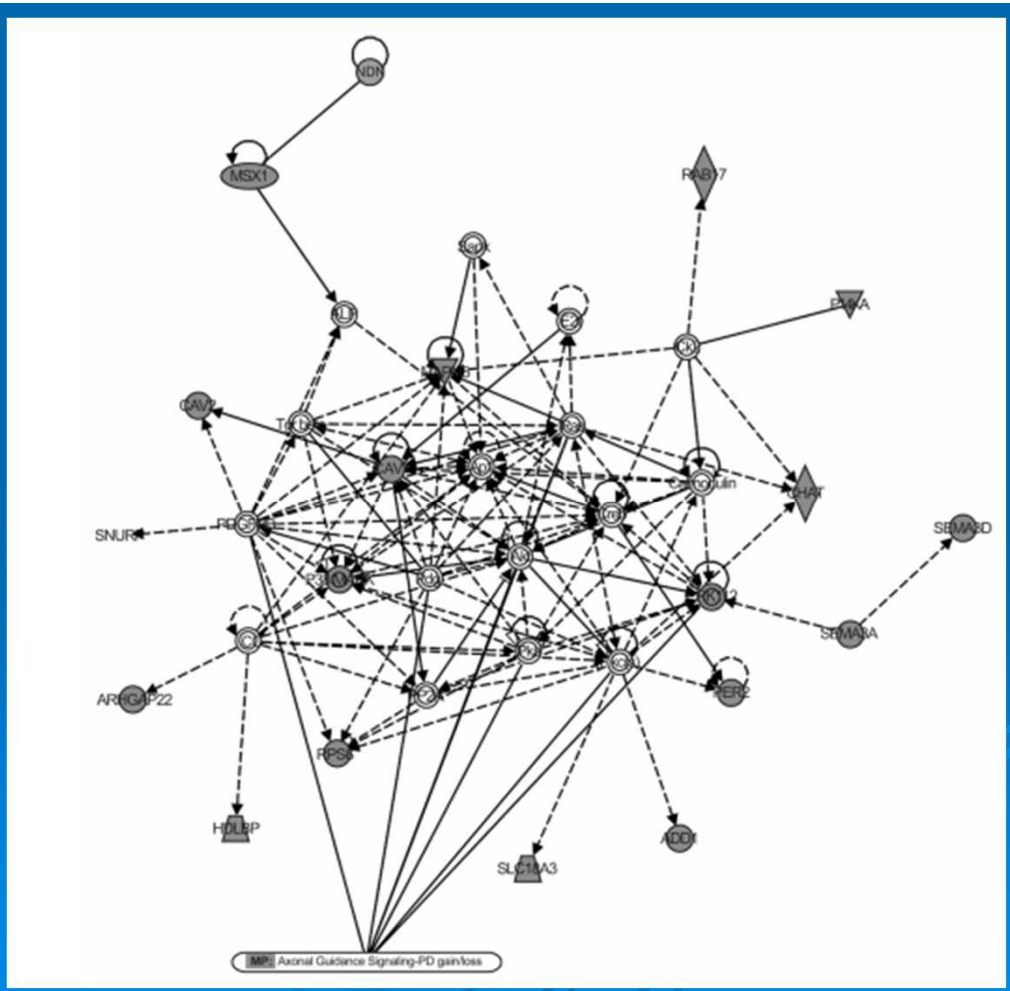

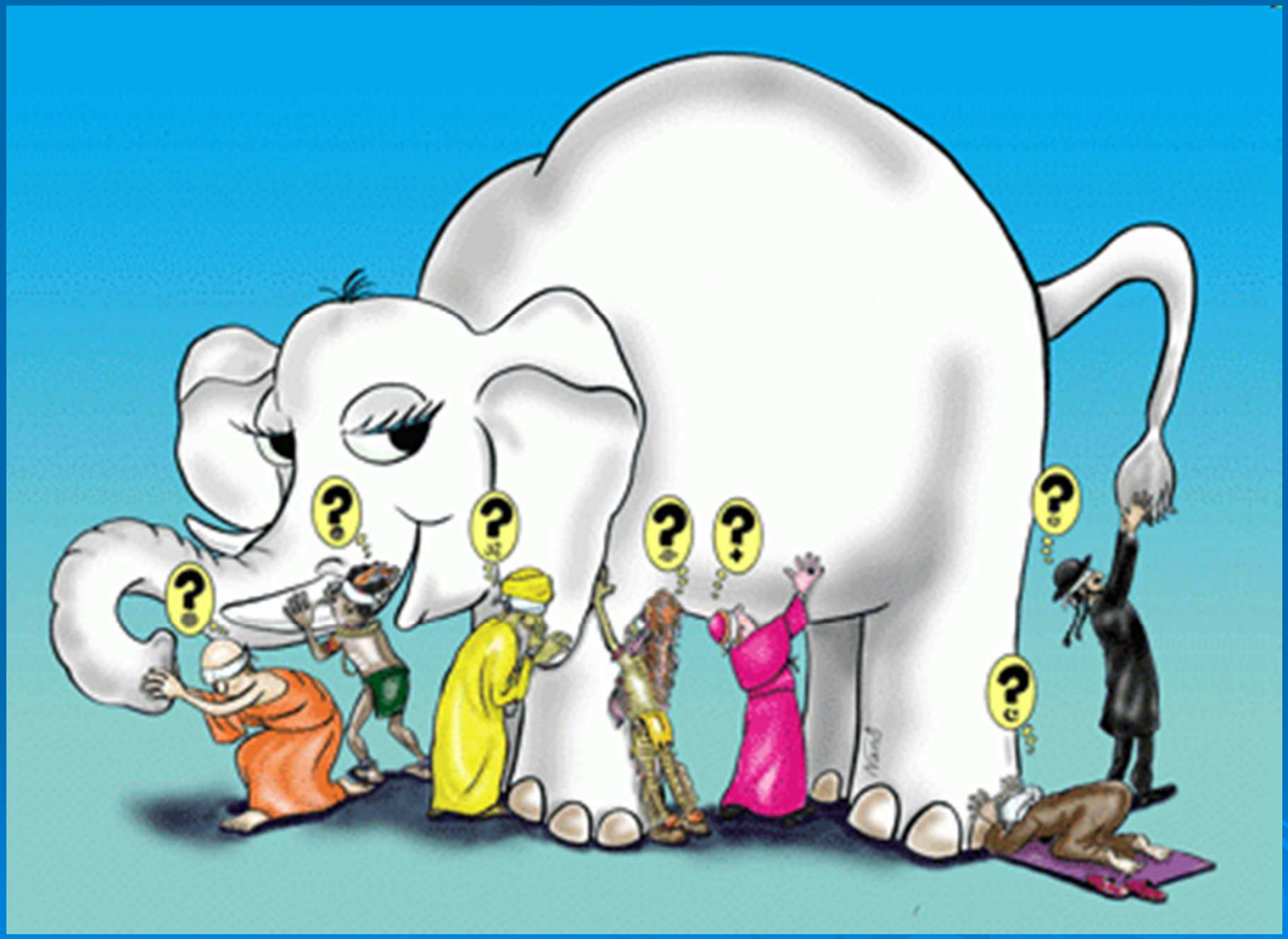

L’autismo, l’elefante, gli uomini ciechi e le sette verità…