XXIII Congresso Nazionale SIPPS
Milano, 15-17 Settembre 2011

- FOCUS SULL'AUTISMO E SUL RITARDO MENTALE -

Novità in tema di patogenesi

Prof. Paolo Balestri

Direttore UOC di Pediatria
Università degli Studi di Siena

RITARDO MENTALE

DEFINIZIONE (ICD 10)

COMPROMISSIONE DELLE ABILITA' CHE SI MANIFESTANO DURANTE IL PERIODO EVOLUTIVO (18 anni) E CHE CONTRIBUISCONO AL LIVELLO GLOBALE DI INTELLIGENZA: COGNITIVE, LINGUISTICHE, MOTORIE, SOCIALI

AUTISMO

DEFINIZIONE (ICD 10)

COMPROMISSIONE DELLO SVILUPPO, CHE SI MANIFESTA PRIMA DEI 3 ANNI, CARATTERIZZATA DA ANORMALE FUNZIONAMENTO NELLE AREE DI:

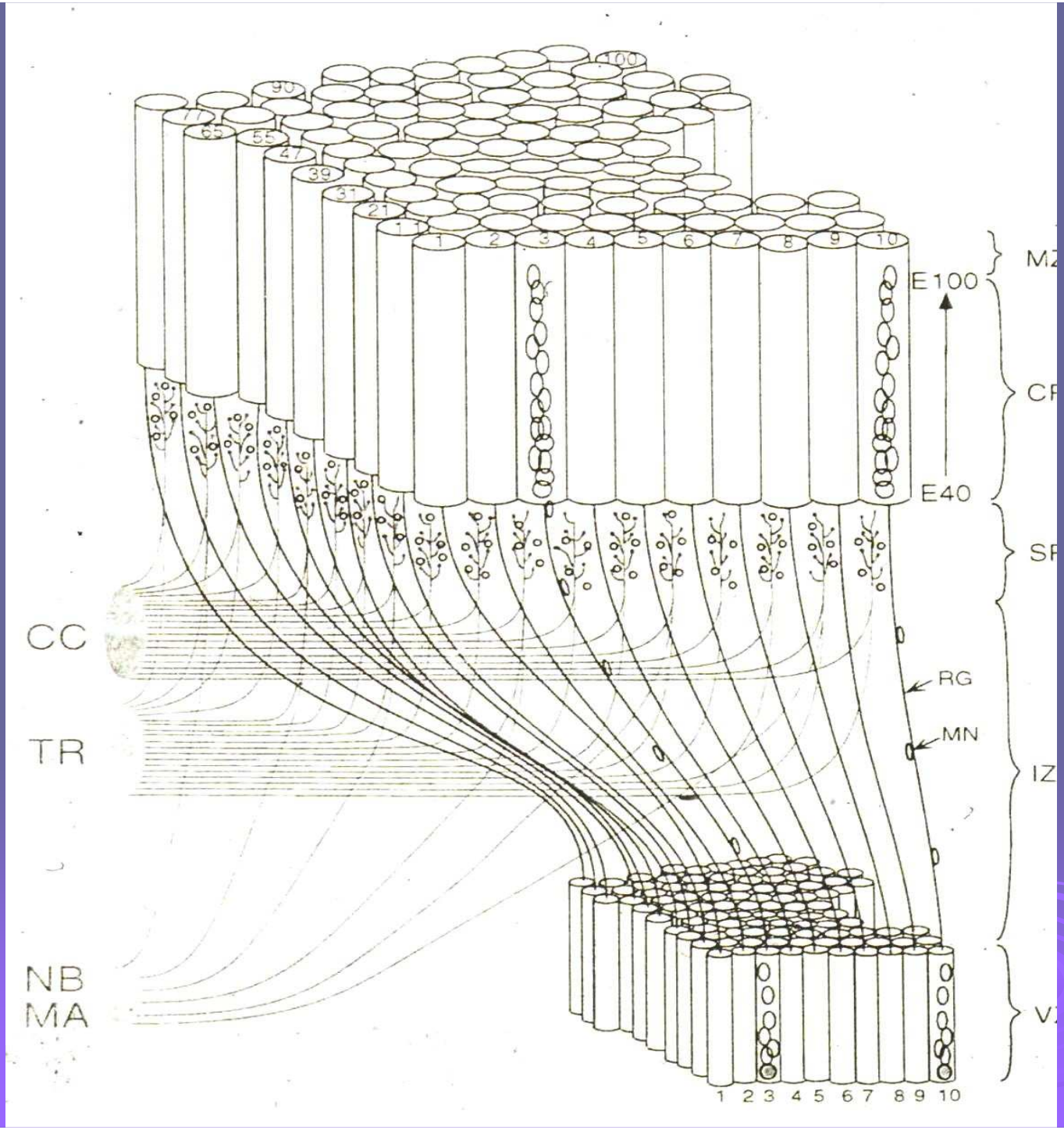
- *INTERAZIONE SOCIALE*
- *COMUNICAZIONE VERBALE E NON VERBALE*
- *COMPORTAMENTO (LIMITATO E RIPETITIVO)*

INCIDENZA R.M. e AUTISMO

- R.M. : 20 - 30 / 1000
  M / F = 1,5 – 5 / 1
- AUTISMO : 0,5 – 5 / 1000
  M / F = 3 – 4 / 1
- AUTISMO + R.M. : 50 – 75 %

NEURO-EMBRIOGENESI

- INDUZIONE NEURALE
- REGIONALIZZAZIONE DEL TUBO NEURALE
- NEUROGENESI E GLIOGENESI
- SOPRAVVIVENZA E APOPTOSI
- MIGRAZIONE CELLULARE
- CRESCITA ASSONAE
- SVILUPPO DENDRITICO
- FORMAZIONE DEI CIRCUITI (*PLASTICITA' CEREBRALE*)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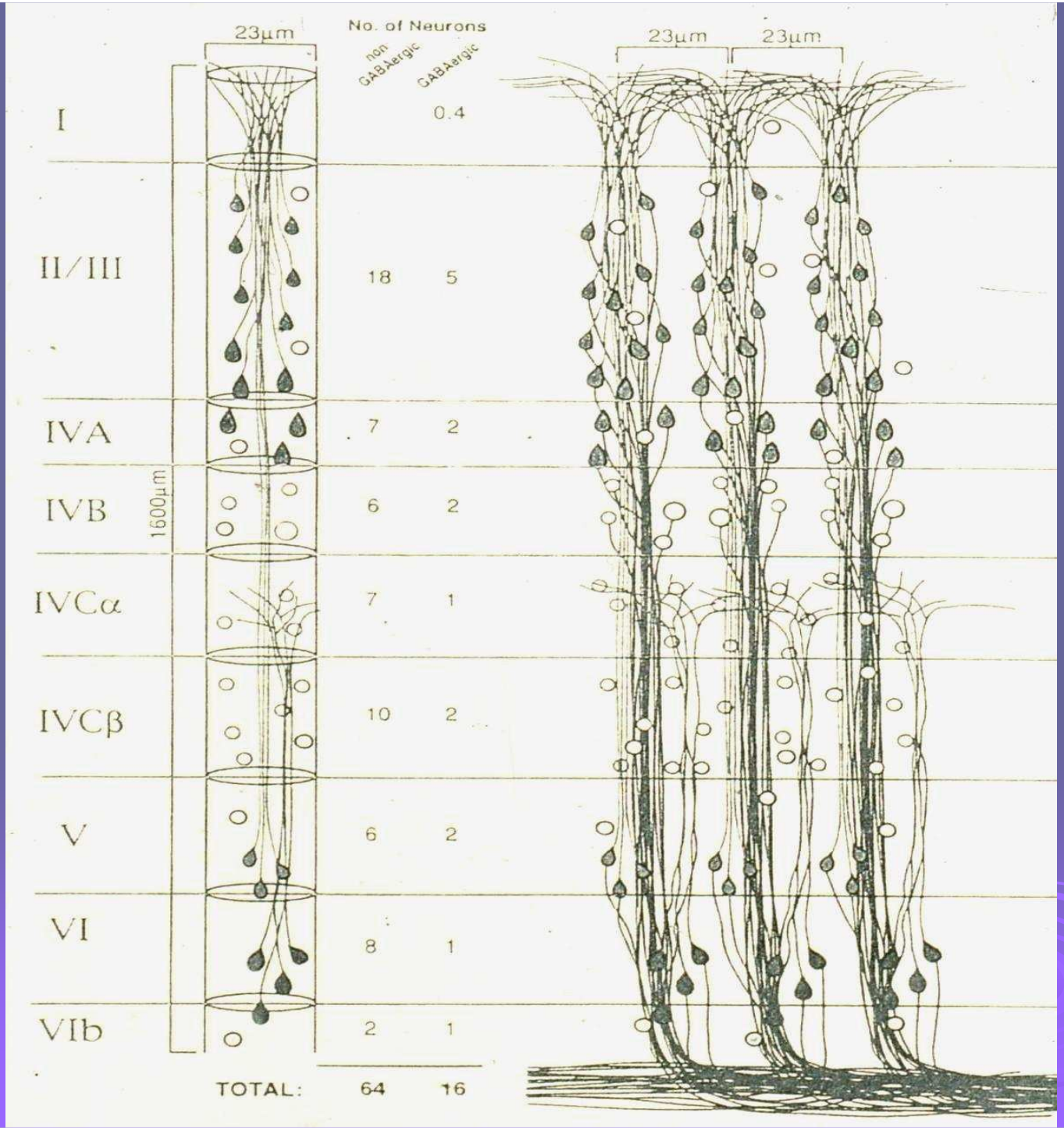
23µm
No. of Neurons
non GABAergic
GABAergic
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5
IVA
7
2
IVB
6
2
1600µm
IVCα
7
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IVCβ
10
2
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6
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VI
8
1
VIb
2
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TOTAL:
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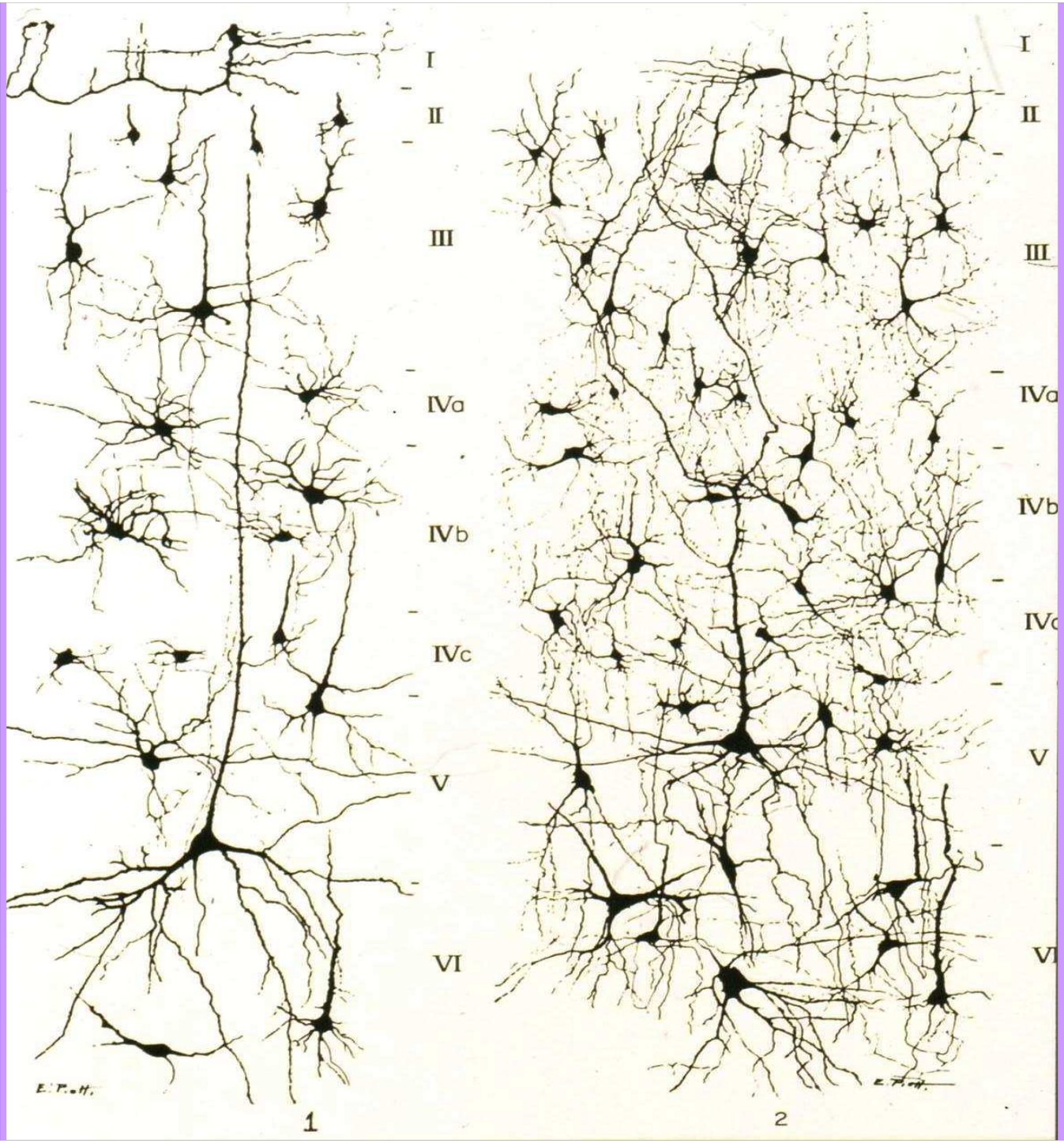
23µm
23µm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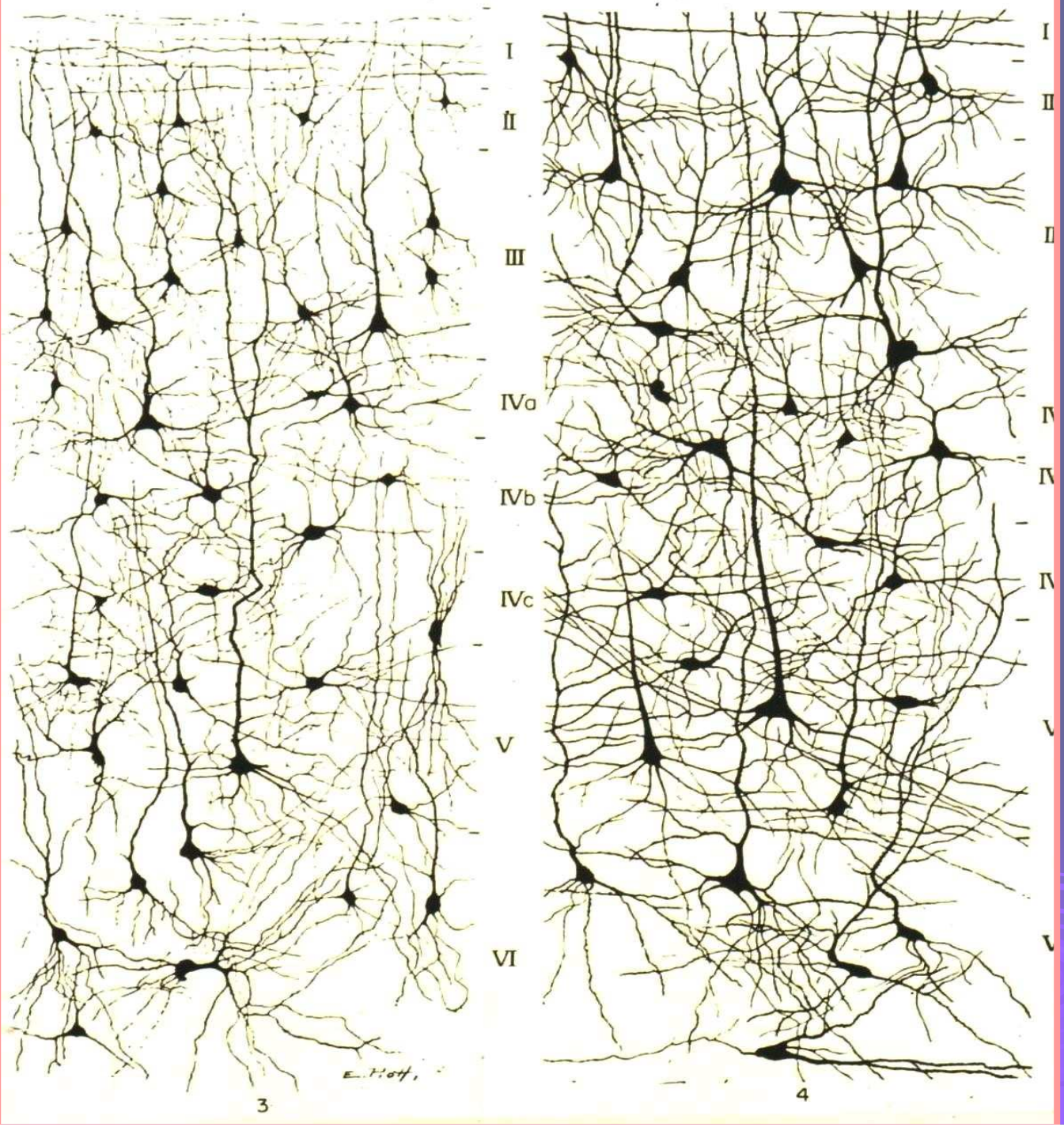
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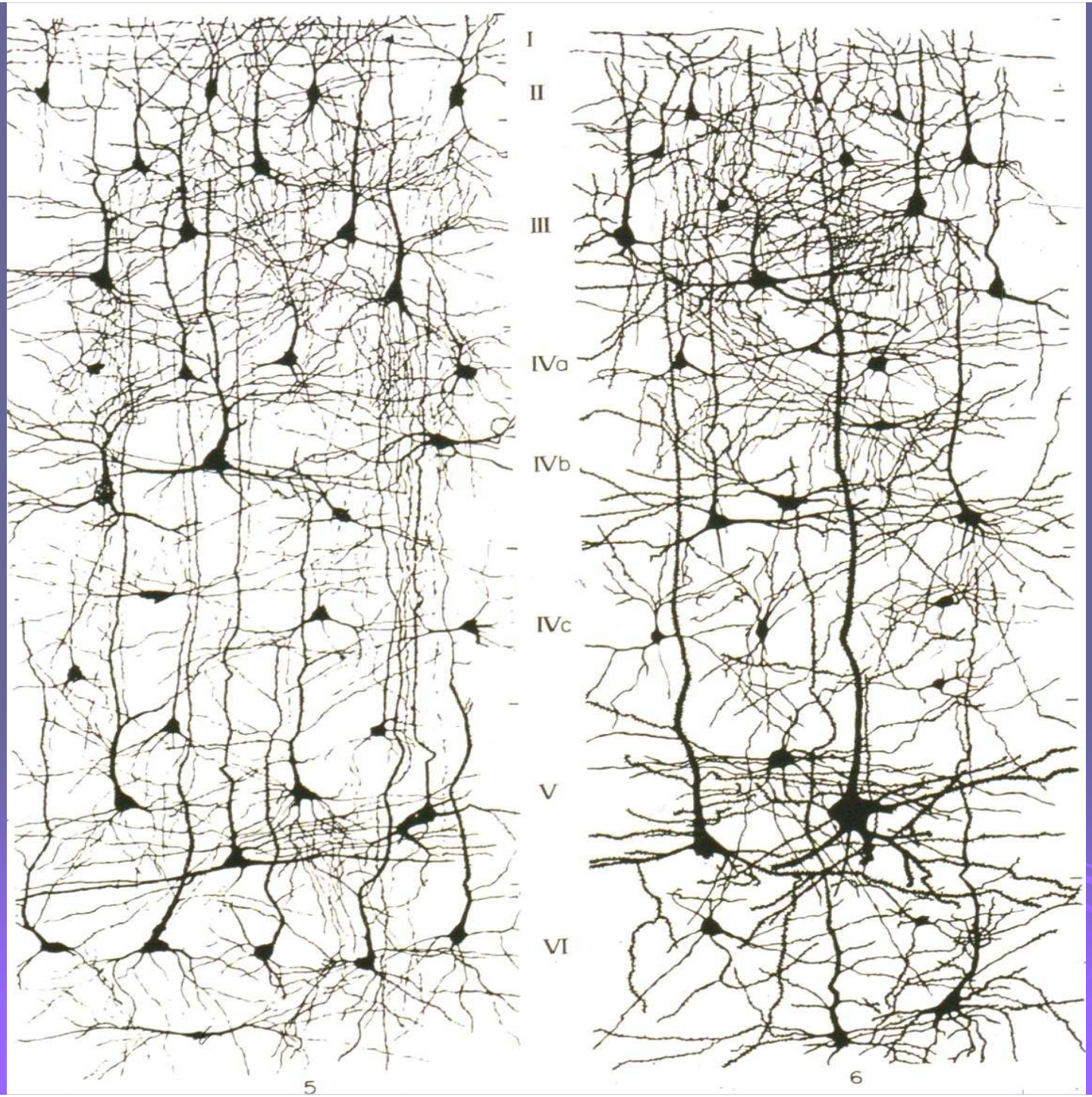
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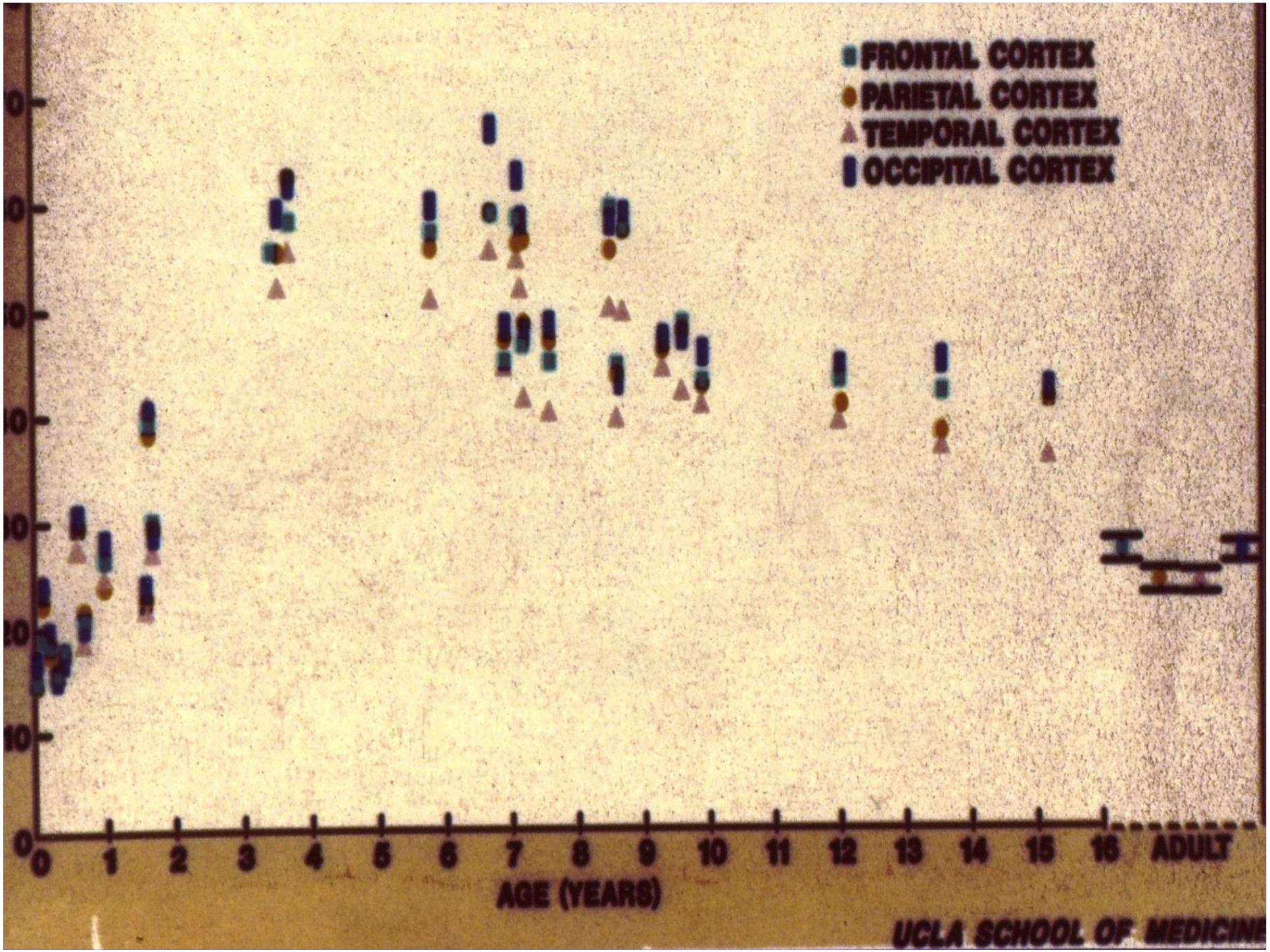
FRONTAL CORTEX
PARIETAL CORTEX
TEMPORAL CORTEX
OCCIPITAL CORTEX
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1
2
3
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9
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11
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13
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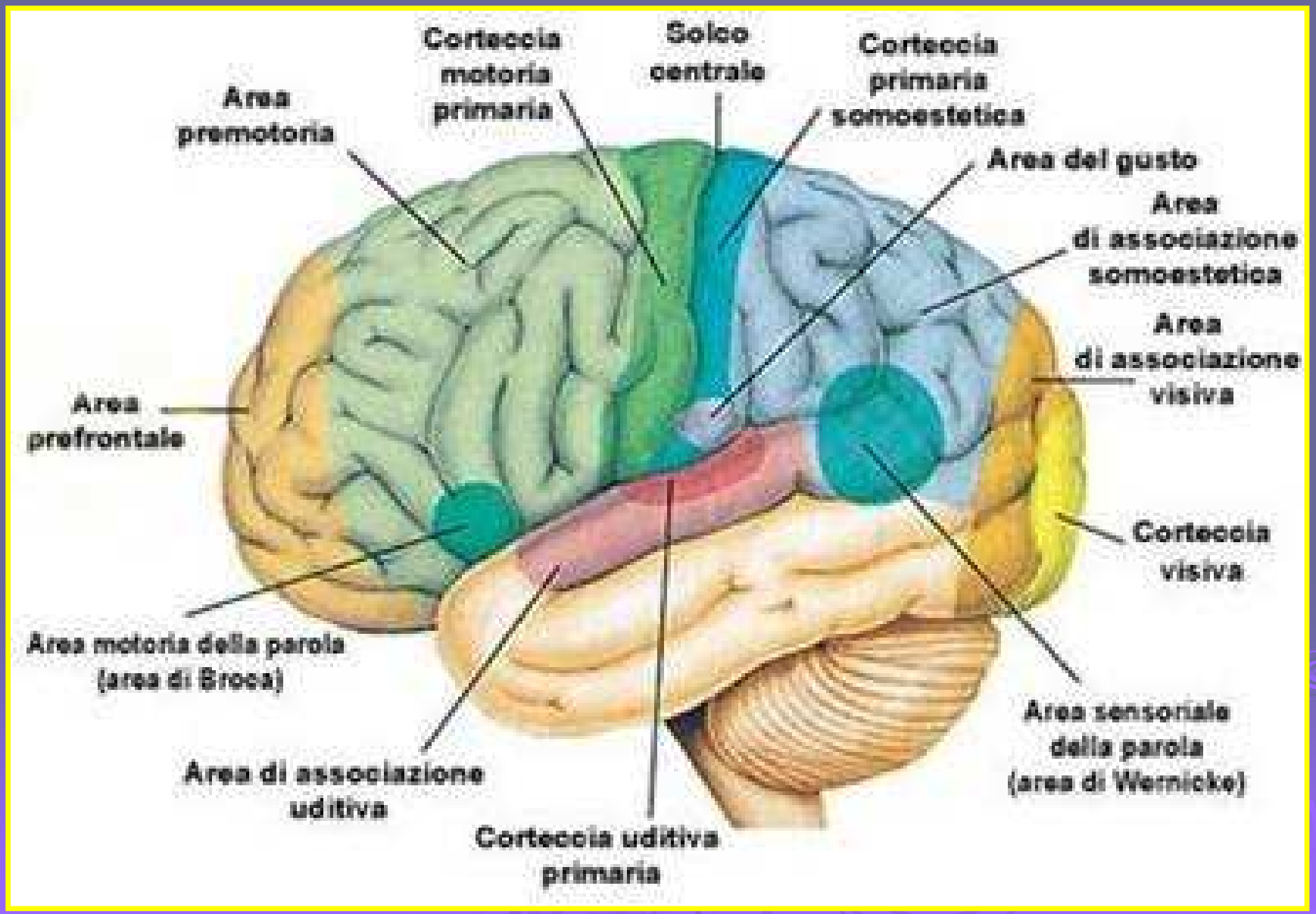
15
16
ADULT
AGE (YEARS)
UCLA SCHOOL OF MEDICINE

Aree funzionali

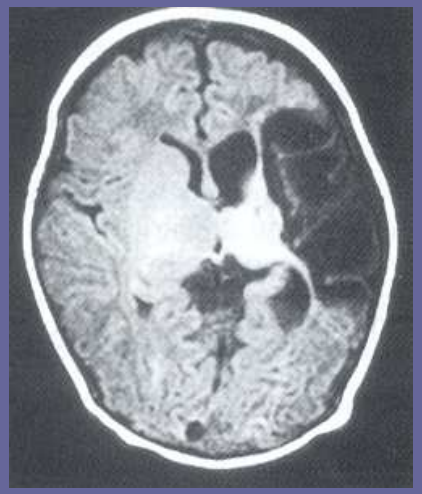


CAUSE di R.M.

- *PRE-NATALI:* genetiche (60 – 80 %)
  fattori materni
- *PERI-NATALI:* S. ipossico-ischemica (8 – 12 %)
- *POST-NATALI:* infezioni (10 %)
  altri eventi neurologici

S. anossico-ischemico-emorragica

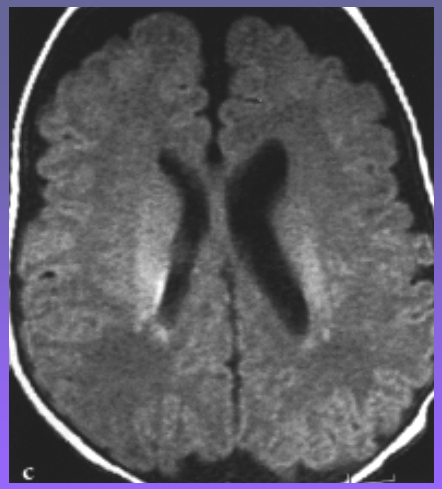
Prenatale: → porencefalia
idranencefalia



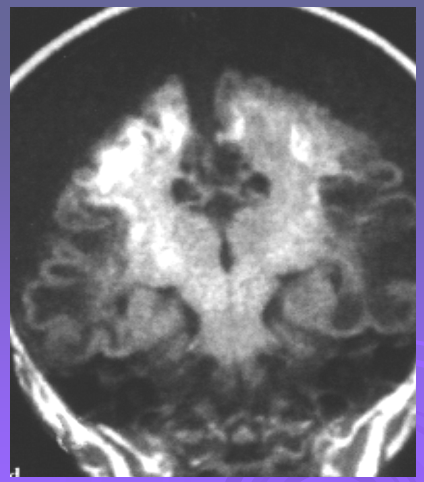
Perinatale

- leucomalacia periventricolare
  porencefalia postemorragica
- encefalopatia multicistica
  infarto zone di confine
  infarto bilat. n. della base

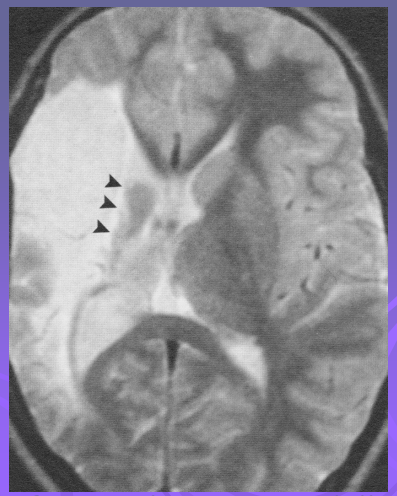
Postnatale: → leucomalacia sottocorticale



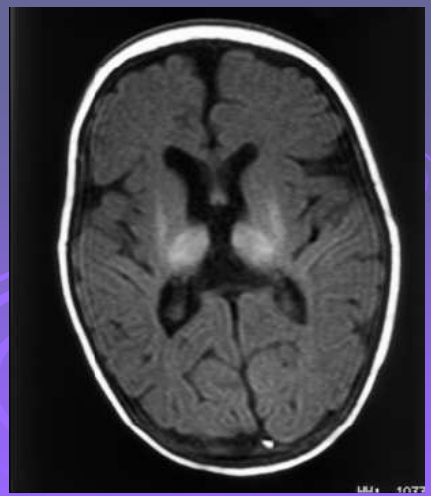
Leucomalacia periventricolare



Encefalopatia multicistica



Infarto nel territorio dell' arteria cerebrale media dx



Status marmoratus

CROMOSOMOPATIE

S. di Down	Trisomia 21	Ipotonia , bassa statura, **ritardo mentale**, cardiopatie, facies tipica
S. di Prader-Willi **S. di Angelman**	15q11-13 delezione cromosoma paterno/materno	- Ipotonia neon. grave, ROT, ipogonadismo, difficoltà di alimentazione (obesità), facies tipica, **ritardo mentale** - **Ritardo mentale**, epilessia, **autismo**
??	Micro-delezioni (Array-CGH)	**Ritardo psicomotorio**

FORME MONOGENICHE

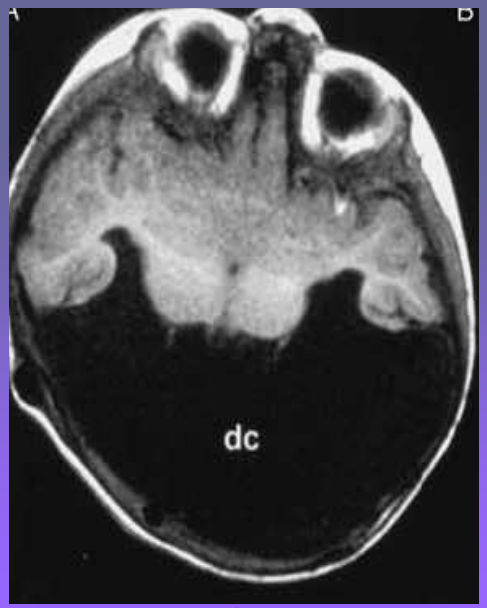
RITARDO MENTALE X-LEGATO

- S. di Martin-Bell (Fra-X): Ritardo mentale e tratti autistici nei maschi

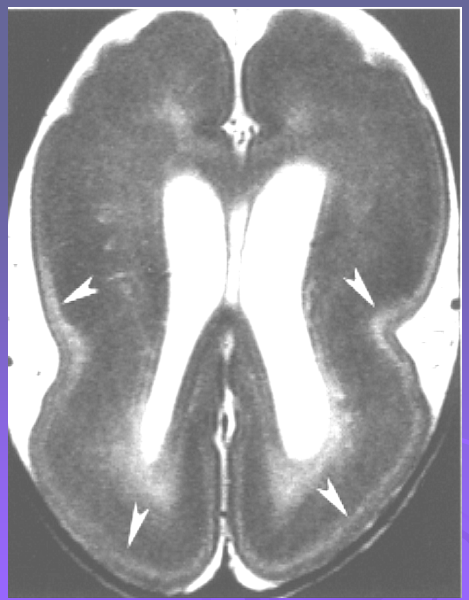
Fenotipo più lieve nelle femmine

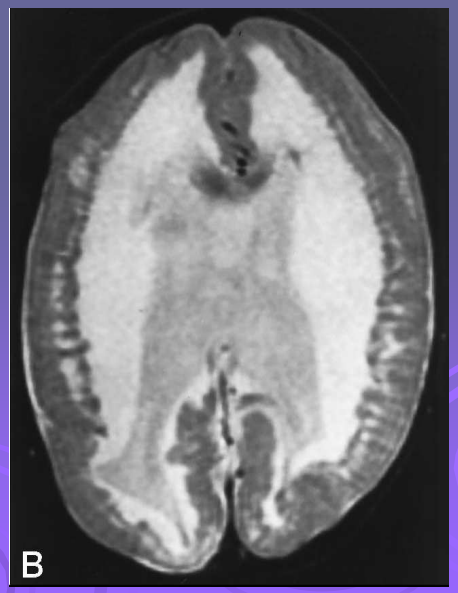
MALFORMAZIONI DEL SNC

OLOPROSENCEFALIA	Sindromica (tris. 13, del. 14…) o Non Sindromica	Grave ritardo mentale, epilessia farmacoresistente
LISSENCEFALIA CLASSICA Spettro agiria- pachigiria S. Miller-Diecker Lissenc. Isolata Lissencefalia Doppiacorteccia Lissencefalie cobblestone S.Normann Roberts	Del. 17p13.3 Mutaz. LIS 1 Xq22.3-23 (doppiacortina) POMT1, PMGNT1, Fukutina AR (reelina)	Grave ritardo mentale, epilessia FR
ETEROTOPIE PERIVENTR. NODULARI	X-linked (Filamina A)	Fenotipo più grave nei maschi

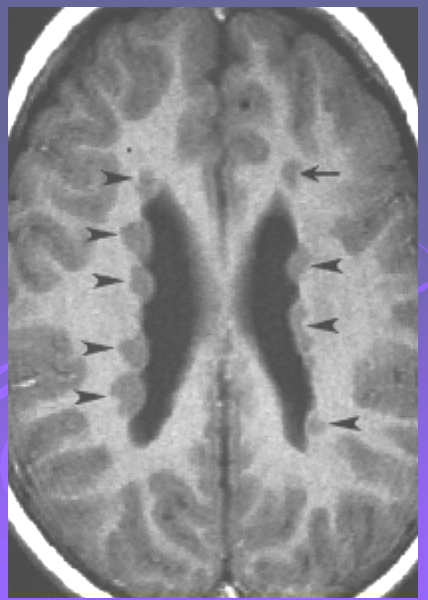


Oloprosencefalia alobare


Lissencefalia Classica



Cobblestone


Eterotopia subependimale

CAUSE di AUTISMO

1. *AUTISMO E RELATIVI PROBLEMI*

2. *GENETICA*

3. *CONTESTO PRE-NATALE*
   - 3.1 Età dei genitori
   - 3.2 Infezioni materne
   - 3.3 Diabete in gravidanza
   - 3.4 Teratogeni
   - 3.5 Pesticidi
   - 3.6 Problemi alla tiroide
   - 3.7 Acido folico
   - 3.8 Stress
   - 3.9 Testosterone fetale
   - 3.10 Ultrasuoni

4. *CONTESTO PERI-NATALE*

5. *CONTESTO POST-NATALE*
   - 5.1 Mercurio
   - 5.2 Vaccini
     - 5.2.1 Thimerosal
     - 5.2.2 Frode scientifica della falsa ipotesi vaccinale
   - 5.3 Malattia autoimmune
   - 5.4 Infezione virale
   - 5.5 Igiene eccessiva
   - 5.6 Stress ossidativo
   - 5.7 Neuroni dell'amigdala
   - 5.8 Neuroni specchio
   - 5.9 Locus ceruleus e noradrenalina
   - 5.10 Mancanza di vitamina D
   - 5.11 Piombo
   - 5.12 Leaky Gut Syndrome
   - 5.13 Paracetamolo
   - 5.14 Pioggia
   - 5.15 Affetto dei genitori
   - 5.16 Altre teorie psicogenetiche

AUTISMO

NEUROPATOLOGIA

a) **Precoce e aumentata crescita della massa cerebrale**

b) **Anomalie delle minicolonne**

c) **Difetti di neurogenesi, migrazione e maturazione neuronale**

AUTISMO

NEURO-IMMAGINI

MRI

a) accelerata crescita S.G. e S.B. (10 %) con picco 2-4 aa

b) riduzione C.C. (connettività interemisferica)

MRI-DTI

a) alterata organizzazione e traiettoria fibre di connessione

b) ispessimento S.G., atipica girazione, scarsa organizzazione S.B.

f MRI

a) ridotta connettività cortico-corticale (fibre Antero-Post)

b) aumentata connettività cortico-subcorticale

MRS

a) < NAA nella S.G., < NAA e mioinositolo nella S.B.

b) alterato rapporto eccitazione/inibizione

AUTISMO

NEURONI SPECCHIO

a) **Neuroni che si attivano sia quando effettuiamo un movimento, sia quando osserviamo lo stesso movimento fatto da altri**

b) **E' necessario non solo che il movimento venga simulato, ma venga riconosciuto e vi sia una risposta selettiva *(per evitare di attribuire scopi impropri a chi stiamo osservando)***

c) **fMRI: ridotta attività dei neuroni specchio negli autistici** osservando e imitando facce con differenti espressioni (Nature Science)

d) **fMRI: risposta intensa e selettiva delle aree specchio negli autistici** durante l'osservazione e l'effettuazione di movimenti (Neuron)

AUTISMO

EMPATIA

a) **Capacità di vedere le cose dalla prospettiva di un altro**

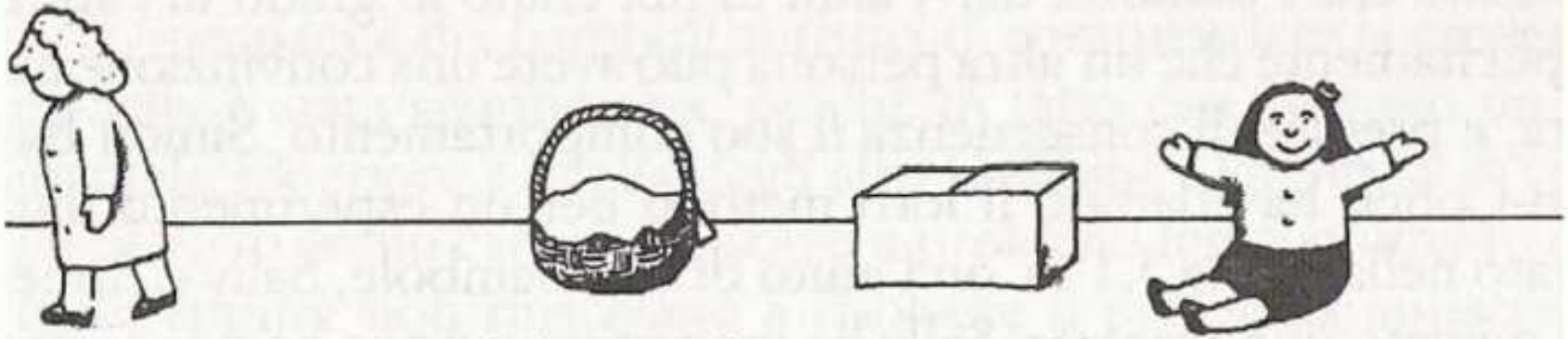
b) **Capacità di capire che cosa l'altro sta provando e condividerlo**

c) **Teoria della mente: l'esperimento di Sally e Anne**

Le prove empiriche della teoria della mente

L'esperimento di Sally e Anne

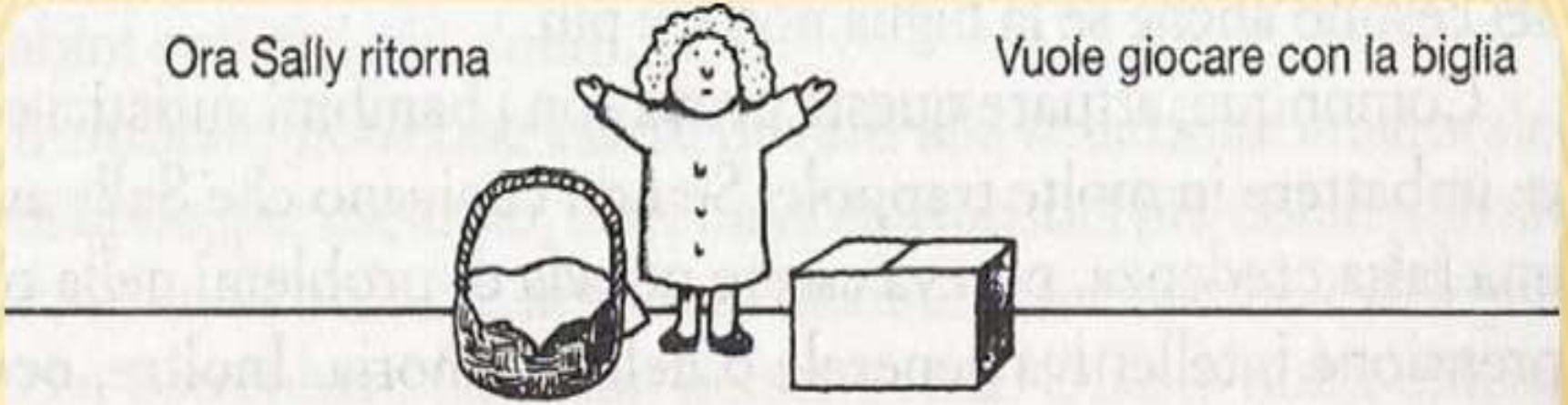

Questa è Sally
Questa è Anne
Sally ha un cestino
Anne ha una scatola
Sally ha una biglia e la mette nel cestino



Sally esce a fare una passeggiata

Anne prende la biglia e la mette nella scatola

Ora Sally ritorna



Vuole giocare con la biglia

Dove cercherà la biglia Sally?

AUTISMO

NEURO-BIOLOGIA

Hindawi Publishing Corporation
Neural Plasticity
Volume 2011, Article ID 297153, 12 pages

Review Article

Alterations of GABAergic Signaling in Autism Spectrum Disorders

Rocco Pizzarelli and Enrico Cherubini

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Autism spectrum disorders (ASDs) comprise a heterogeneous group of pathological conditions, mainly of genetic origin, characterized by stereotyped behavior, marked impairment in verbal and nonverbal communication, social skills, and cognition. Interestingly, in a small number of cases, ASDs are associated with single mutations in genes encoding for neuroligin-neurexin families. These are adhesion molecules which, by regulating transsynaptic signaling, contribute to maintain a proper excitatory/inhibitory (E/I) balance at the network level. Furthermore, GABA, the main inhibitory neurotransmitter in adult life, at late embryonic/early postnatal stages has been shown to depolarize and excite targeted cell through an outwardly directed flux of chloride. The depolarizing action of GABA and associated calcium influx regulate a variety of developmental processes from cell migration and differentiation to synapse formation. Here, we summarize recent data concerning the functional role of GABA in building up and refining neuronal circuits early in development and the molecular mechanisms regulating the E/I balance. A dysfunction of the GABAergic signaling early in development leads to a severe E/I unbalance in neuronal circuits, a condition that may account for some of the behavioral deficits observed in ASD patients.

AUTISMO
NEURO-BIOLOGIA

Table 1: Main alterations of GABAergic signaling present in different animal models of ASDs. For the Rett syndrome, different genotypes are expressed in brackets.

Mouse model	Alterations in GABAergic signaling	Ref.
Mecp 2-KO (Rett syndrome)	Reduced levels of GAD65 and GAD67 (*Viaat-Mecp2*$^{-/y}$)	[75]
	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*)	[79]
	Reduced frequency of IPSC-based spontaneous rhythmic field potentials in the hippocampus (*Mecp2*$^{tm1.1Bird}$)	[80]
Fmr 1-KO (X fragile)	Down regulation of GABAA-mediated tonic inhibition in the subiculum	[88]
	Reduced expression of α5 and δ GABAA receptor subunits in the subiculum	
	Increased frequency of sIPSCs and mIPSCs in the striatum	[89]
	Reduction in amplitude and frequency of sIPSCs and mIPSCs	[90]
	Reduced GABAA-mediated tonic inhibition	[84–87]
	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)	[56]
Dlx1/Dlx2 KO	Abnormal cell migration	
	Reduction in the number of GABAergic interneurons in the cortex, olfactory bulb and hippocampus	[97]
Reln-KO	Reduced level of GAD67	[103]
	Decreased GABA turnover	
En2-KO	Reduced expression of parvalbumin- and somatostatin-positive GABAergic interneurons in the hippocampus	[115]
	Increased susceptibility to seizures	
Nlg3 R451C KI	Increased frequency of mIPSC	
	Increased level of VGAT and gephyrin	[106]
	Asymmetric reduction of PV positive basket cells across cortical hemispheres	[108]
valproic acid	The E/I balance is shifted to favor excitation over inhibition in the lateral amygdala (multi electrode arrays)	[114]
	Asymmetric reduction of PV positive basket cells across cortical hemispheres	[108]

frontiers in
HUMAN NEUROSCIENCE

REVIEW ARTICLE
published: 21 December 2010
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The Intense World Theory – a unifying theory of the neurobiology of autism

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Autism covers a wide spectrum of disorders for which there are many views, hypotheses and theories. Here we propose a unifying theory of autism, the *Intense World Theory*. The proposed neuropathology is hyper-functioning of local neural microcircuits, best characterized by hyper-reactivity and hyper-plasticity. Such hyper-functional microcircuits are speculated to become autonomous and memory trapped leading to the core cognitive consequences of hyper-perception, hyper-attention, hyper-memory and hyper-emotionality. The theory is centered on the neocortex and the amygdala, but could potentially be applied to all brain regions. The severity on each axis depends on the severity of the molecular syndrome expressed in different brain regions, which could uniquely shape the repertoire of symptoms of an autistic child. The progression of the disorder is proposed to be driven by overly strong reactions to experiences that drive the brain to a hyper-preference and overly selective state, which becomes more extreme with each new experience and may be particularly accelerated by emotionally charged experiences and trauma. This may lead to obsessively detailed information processing of fragments of the world and an involuntarily and systematic decoupling of the autist from what becomes a painfully intense world. The autistic is proposed to become trapped in a limited, but highly secure internal world with minimal extremes and surprises. We present the key studies that support this theory of autism, show how this theory can better explain past findings, and how it could resolve apparently conflicting data and interpretations. The theory also makes further predictions from the molecular to the behavioral levels, provides a treatment strategy and presents its own falsifying hypothesis.

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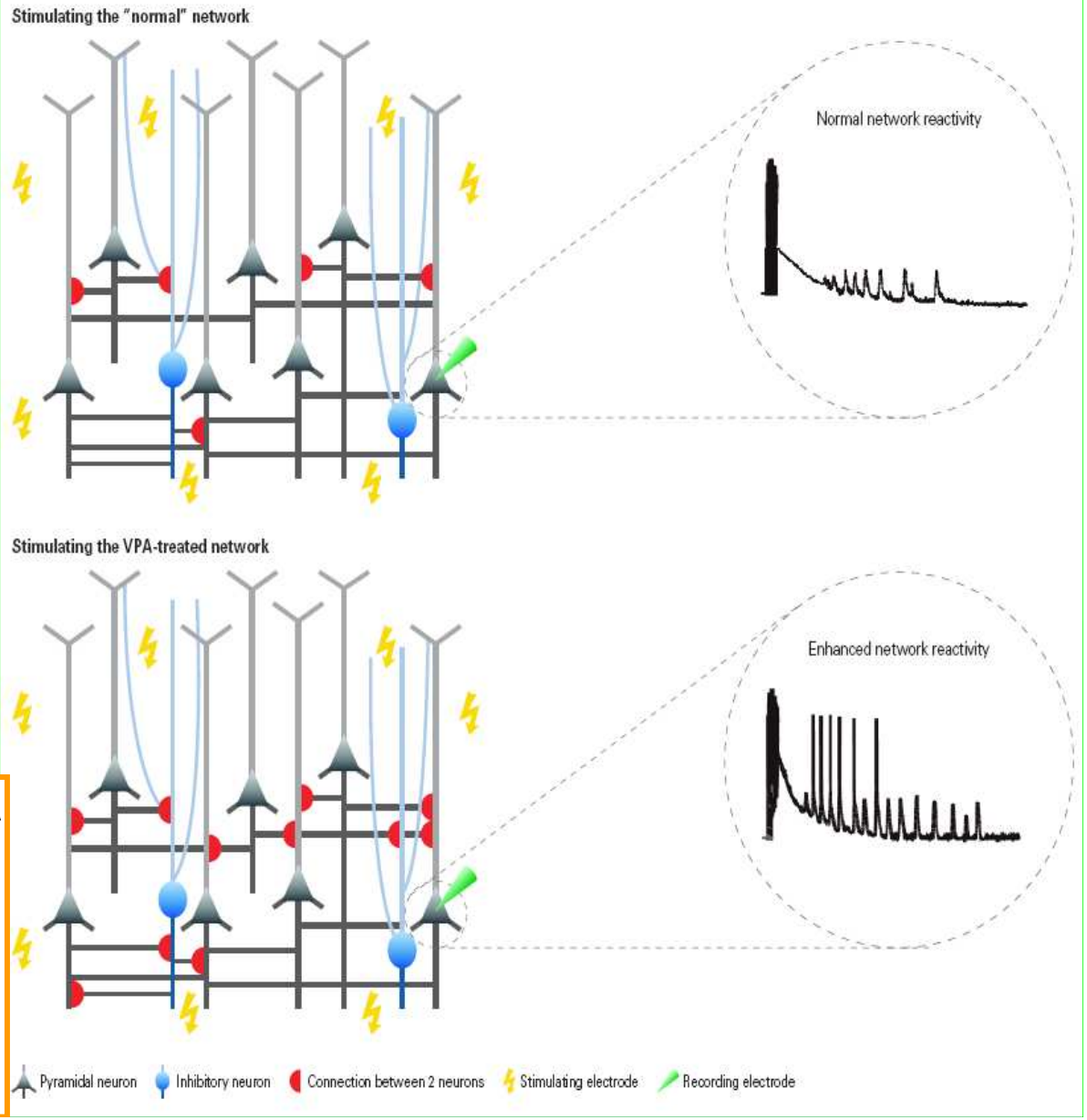

FIGURE 1 | Hyper-reactivity and hyper-connectivity in VPA-treated offspring. Depicted are schematic neural microcircuits from control (top) and VPA-treated offspring (bottom). Brain slices were electrically stimulated through multiple stimulation electrodes underneath the slice – a multi-electrode array. The responsiveness to this network stimulation was recorded from individually patched cells. In comparison to controls, neurons from VPA-treated offspring were excessively reacting to the stimulation as depicted in the exemplary voltage traces. Further examination by recording from pairs of neurons revealed that this hyper-reactivity was due to the excessive connectivity in VPA-treated microcircuits (schematically depicted by the red half-circles). The connection probability was increased by approximately 50% in microcircuits from VPA-treated offspring.

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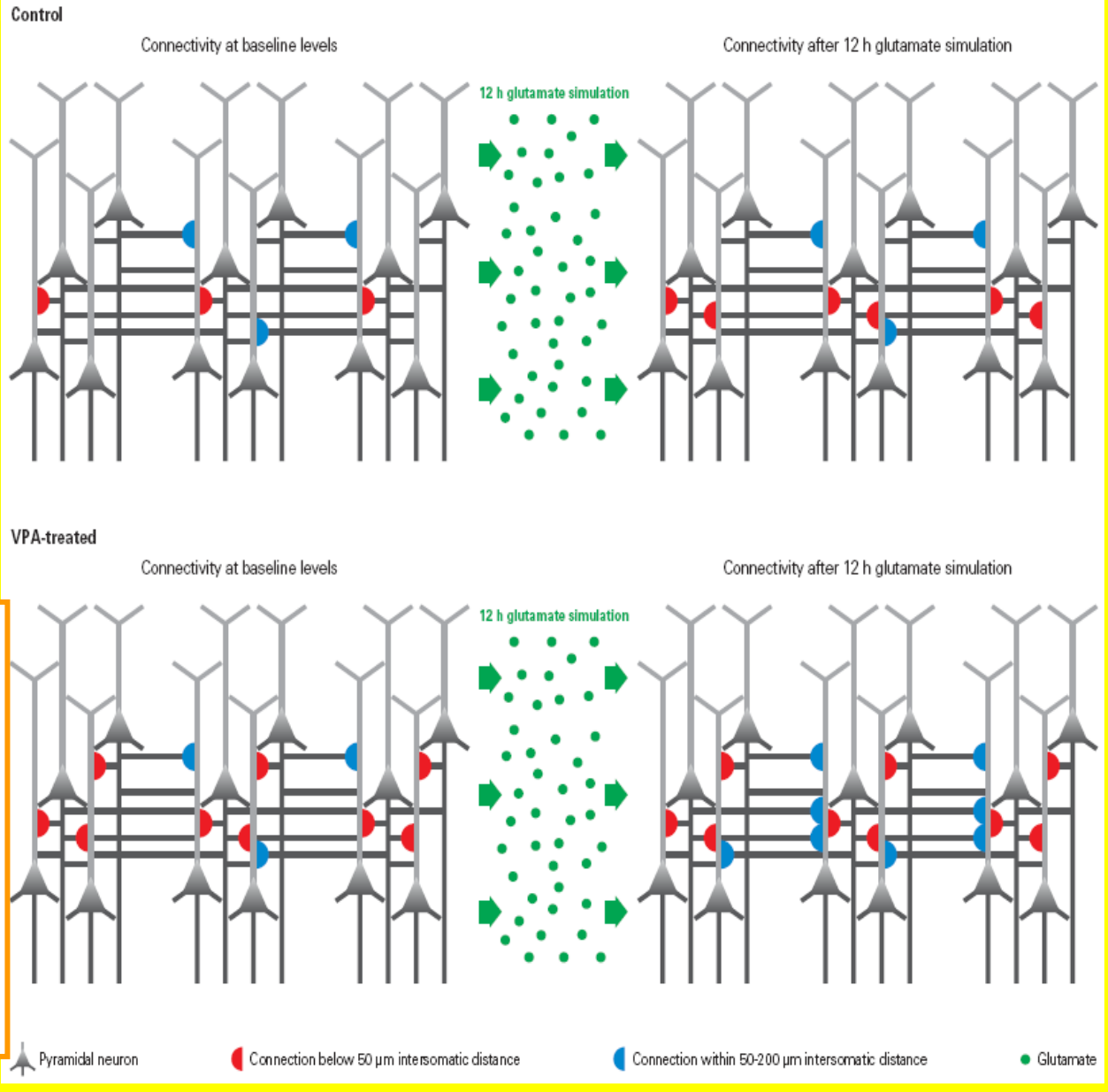

FIGURE 3 | Microcircuit hyper-plasticity in VPA-treated offspring. Depicted are schematic neural microcircuits from control (top) and VPA-treated offspring (bottom). In this experiment, brain slices were perfused for 12 h with a glutamate solution in order to stimulate the circuits and induce rewiring of connections (red and blue half-circles). The connectivity probability between neurons was accessed before (left panels) and after (right panels) the glutamate stimulation. In controls, the connection probability increased significantly within a range of less than 50 µm (red half-circles), which is the mini-columnar range, but did not change in ranges higher than 50 µm (measured up to 200 µm, blue half-circles), which is a increased within the short mini-columnar range (below 50 µm, red half-circles) before the glutamate stimulation and did not increase any further after the stimulation (right panel), because the connection capacity was already boosted and probably saturated to a maximum at baseline levels. Indeed, controls only reached a similarly high connectivity probability within the mini-columnar range as VPA-treated offspring already exhibited at baseline levels after the 12 h stimulation was applied. However, in VPA-treated offspring, the connectivity probability increased significantly at ranges above 50 µm (right panel, blue half-circles), revealing a further remarkable rewiring capacity at the columnar range due to stimulation – a feature "normal" control microcircuits did not exhibit.

frontiers in
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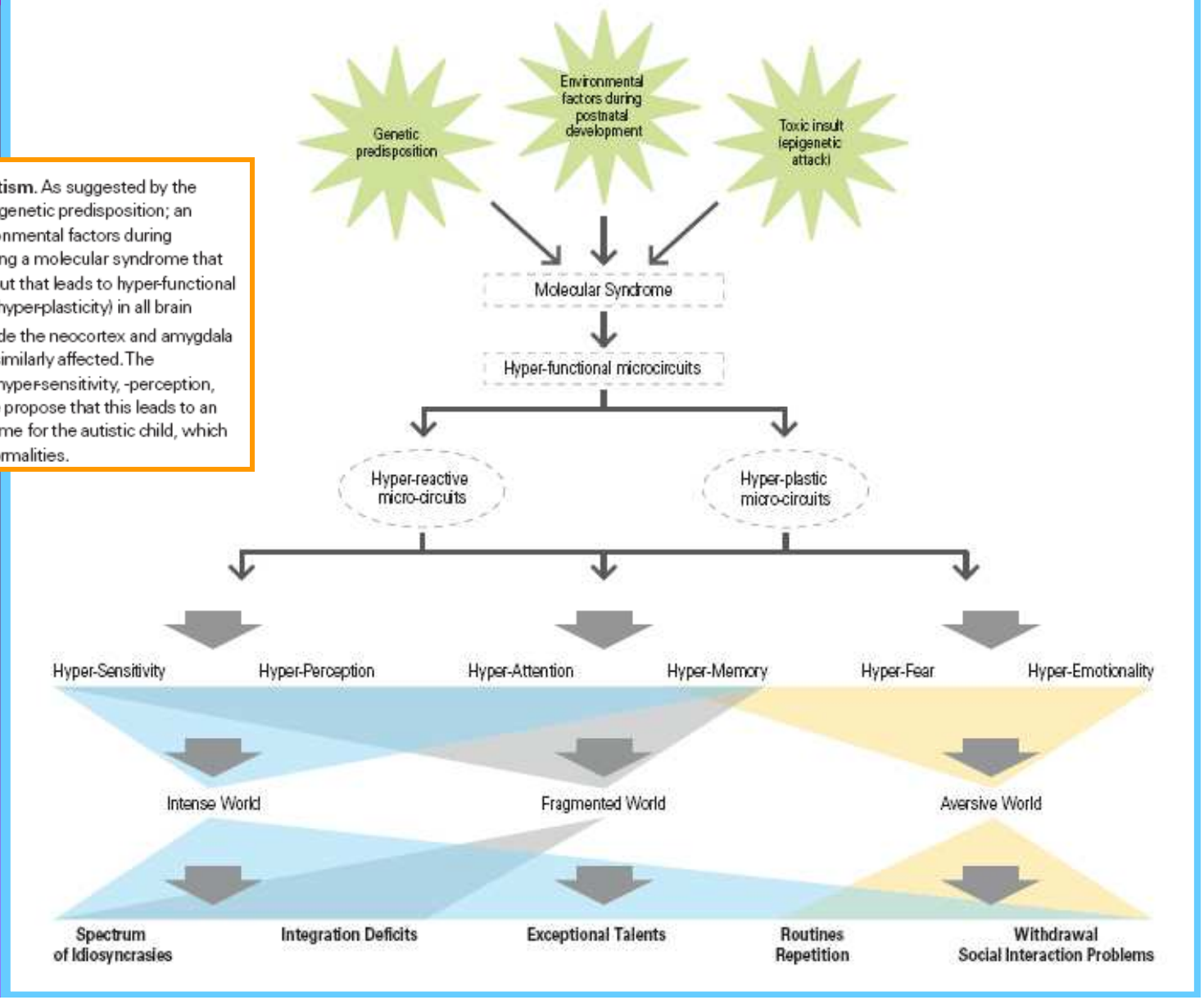

FIGURE 5 | The hyper-functional circuits in autism. As suggested by the *Intense World Theory* three etiological factors (a genetic predisposition; an epigenetics attack in form of a toxic insult; environmental factors during postnatal development) cause autism by activating a molecular syndrome that may be different across different brain regions, but that leads to hyper-functional microcircuits (expressed as hyper-reactivity and hyper-plasticity) in all brain regions. Two regions known to be affected include the neocortex and amygdala and we hypothesize that other regions may be similarly affected. The consequences on cognitive processing include hyper-sensitivity, -perception, -attention, -memory, -fear, and -emotionality. We propose that this leads to an intense, fragmented, and aversive world syndrome for the autistic child, which could account for a spectrum of behavioral abnormalities.

Transcriptomic analysis of autistic brain reveals convergent molecular pathology

Irina Voineagu, Xinchen Wang et al.

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Autism spectrum disorder (ASD) is a common, highly heritable neurodevelopmental condition characterized by marked genetic heterogeneity[1, 2, 3]. Thus, a fundamental question is whether autism represents an aetiologically heterogeneous disorder in which the myriad genetic or environmental risk factors perturb common underlying molecular pathways in the brain[4]. Here, we demonstrate consistent differences in transcriptome organization between autistic and normal brain by gene co-expression network analysis. Remarkably, regional patterns of gene expression that typically distinguish frontal and temporal cortex are significantly attenuated in the ASD brain, suggesting abnormalities in cortical patterning. We further identify discrete modules of co-expressed genes associated with autism: a neuronal module enriched for known autism susceptibility genes, including the neuronal specific splicing factor *A2BP1* (also known as *FOX1*), and a module enriched for immune genes and glial markers. Using high-throughput RNA sequencing we demonstrate dysregulated splicing of *A2BP1*-dependent alternative exons in the ASD brain. Moreover, using a published autism genome-wide association study (GWAS) data set, we show that the neuronal module is enriched for genetically associated variants, providing independent support for the causal involvement of these genes in autism. In contrast, the immune-glial module showed no enrichment for autism GWAS signals, indicating a non-genetic aetiology for this process. Collectively, our results provide strong evidence for convergent molecular abnormalities in ASD, and implicate transcriptional and splicing dysregulation as underlying mechanisms of neuronal dysfunction in this disorder.


Grazie