Autismo ed educazione:

mai troppo presto, mai troppo tardi, mai troppo gravi

BOLOGNA, 23 Aprile 2016, TEATRO DUSE

Lo sviluppo del Sistema Nervoso: quando nasce l'autismo

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DSM-5

Autism Spectrum Disorders must meet criteria 1, 2, and 3:

- **1. Clinically significant, persistent deficits in social communication and interactions, as manifest by all of the following:**
- a. Marked deficits in nonverbal and verbal communication used for social interaction:
- b. Lack of social reciprocity;
- c. Failure to develop and maintain peer relationships appropriate to developmental level
- **2. Restricted, repetitive patterns of behavior, interests, and activities, as manifested by at least TWO of the following:**
- a. Stereotyped motor or verbal behaviors, or unusual sensory behaviors
- b. Excessive adherence to routines and ritualized patterns of behavior
- c. Restricted, fixated interests
- **3. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)**

Prima infanzia

- Lo sviluppo del bambino nei primi tre anni di vita è costituito dal susseguirsi di ***armonici apprendimenti***, che coinvolgono il sistema motorio, gli organi di senso, la comunicazione
- Lo ***sviluppo*** è legato a fattori genetici e ambientali (per es. anche aspetto educativo), alla plasticità cerebrale

Tutto questo può subire modificazioni generazionali influenzate anche dalla cultura, dalle mode e da differenti correnti di pensiero

- Tali ***apprendimenti*** sono legati temporalmente, per le necessità crescenti del bambino di autonomia e di strutturazione di relazioni sociali via, via più complesse

Modello del network neurale

- Cohen (1994, 1998)
- Modello matematico di simulazione al computer che tiene conto della popolazione neuronale e delle sinapsi
- Modificazioni neuronali e sinaptiche da stimolazioni ambientali che determinano l'apprendimento
- Modello di Kohonen dei circuiti laterali con stretta connessione di una cellula all'altra, equilibrio tra stimolazioni inibitorie ed eccitatorie, stabilità o instabilità $\rightarrow$ percezioni errate nel bambino con autismo
- Modello colonna neuronale con neuroni organizzati in strati perpendicolari alla superficie corticale. Colonna "ampia" (molte sinapsi, molti neuroni attivata da molti stimoli) faciliterà la generalizzazione, una colonna "stretta" la discriminazione

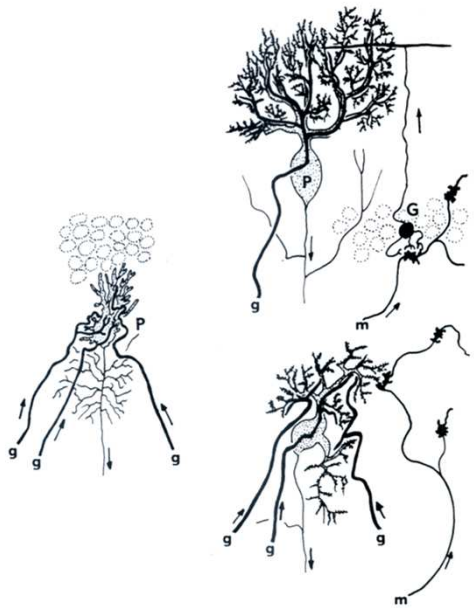
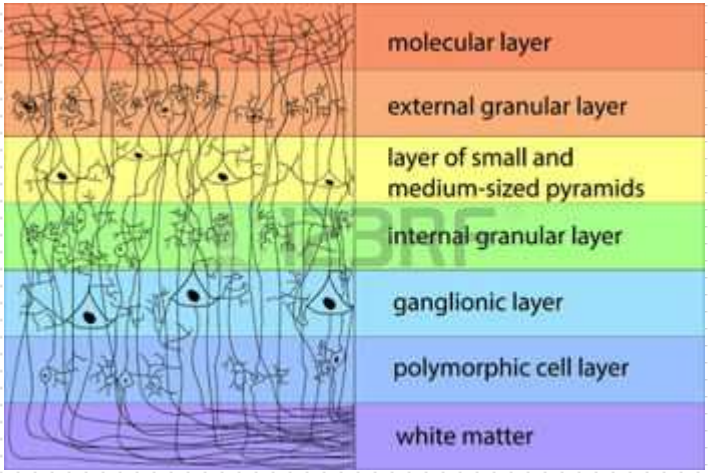
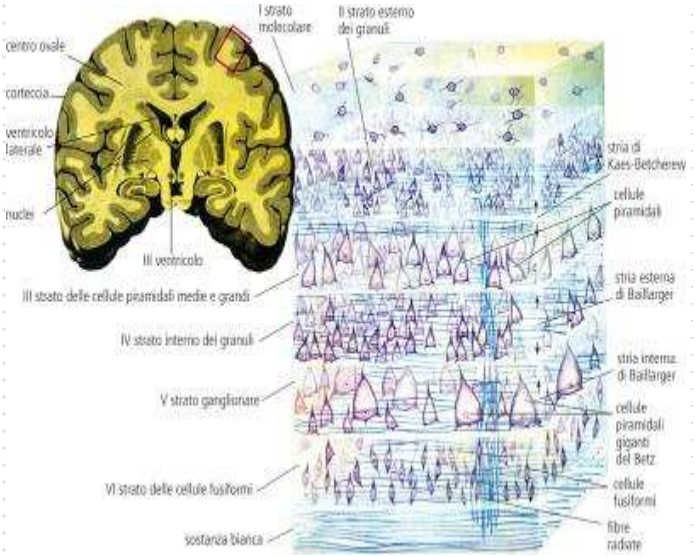
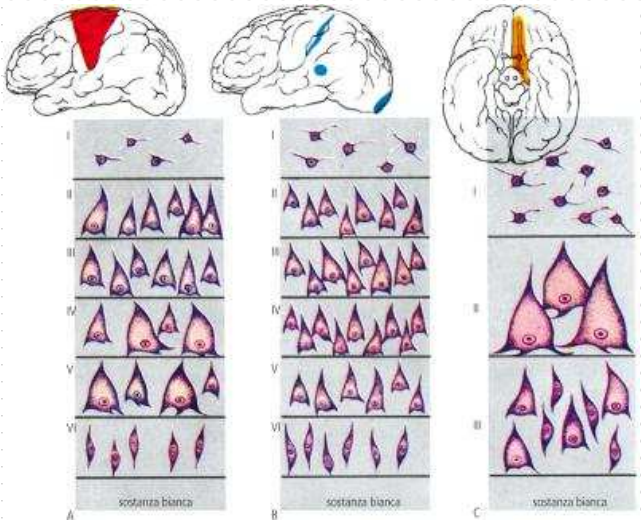


Fig. 1.8. Fenomeni regressivi collegati allo sviluppo delle sinapsi : formazione dei contatti sinaptici nel cervelletto di topo dopo la nascita.
A sinistra topo neonato; P: cellule del Purkinje; g: fibre rampicanti.
A destra (alto) topo adulto: aumento arborizzazione dendritica delle cellule del Purkinje e riduzione a 1 fibra rampicante (da Changeux J.P., op. cit.).







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Cognition 150 (2016) 181–199

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/COGNIT

Imagination in human social cognition, autism, and psychotic-affective conditions

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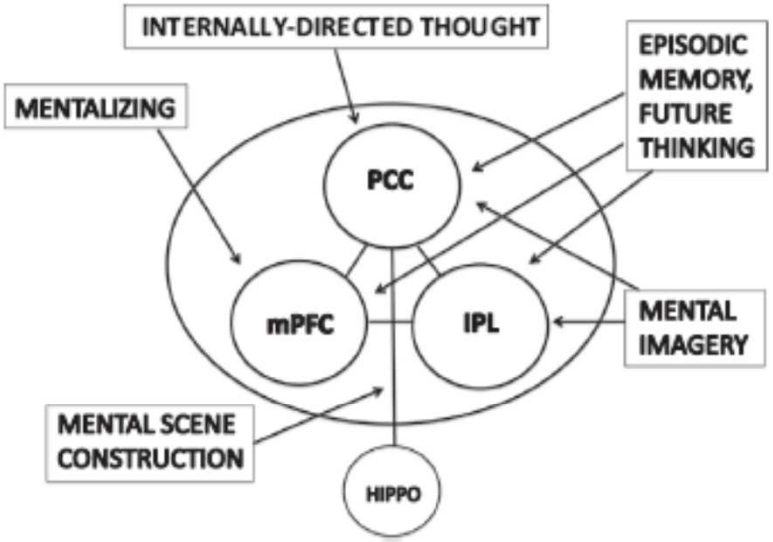

Fig. 2. The human default mode system comprises three main interacting hub regions, the posterior cingulate cortex (PCC) (including the precuneus), the medial prefrontal cortex (mPFC), and the inferior parietal lobe (IPL) (including the temporal-parietal junction), with core functions as depicted. HIPPO is the hippocampus. Arrows to specific regions represent documented functions of the region. The precise regions included in the default mode network, their specific functions, and their mediation of components of human imagination, remain active areas of research, but the primary roles of this network are well established.

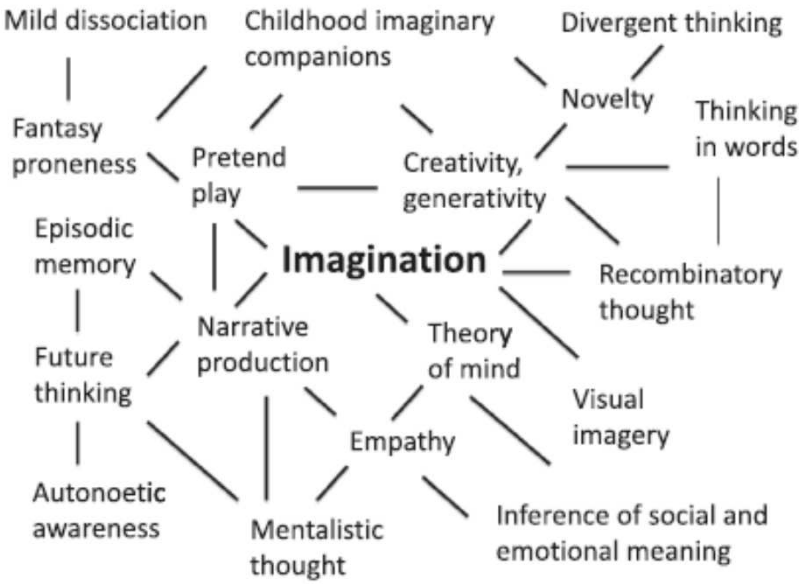

Fig. 1. Imagination, in neurotypical cognition, can be conceptualized in terms of a set of related phenomena that relate to core functions of the human brain.

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Unusual brain growth patterns in early life in patients with autistic disorder

An MRI study

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Article abstract—*Objective:* To quantify developmental abnormalities in cerebral and cerebellar volume in autism. *Methods:* The authors studied 60 autistic and 52 normal boys (age, 2 to 16 years) using MRI. Thirty autistic boys were diagnosed and scanned when 5 years or older. The other 30 were scanned when 2 through 4 years of age and then diagnosed with autism at least 2.5 years later, at an age when the diagnosis of autism is more reliable. *Results:* Neonatal head circumferences from clinical records were available for 14 of 15 autistic 2- to 5-year-olds and, on average, were normal (35.1 ± 1.3 cm versus clinical norms: 34.6 ± 1.6 cm), indicative of normal overall brain volume at birth; one measure was above the 95th percentile. By ages 2 to 4 years, 90% of autistic boys had a brain volume larger than normal average, and 37% met criteria for developmental macrencephaly. Autistic 2- to 3-year-olds had more cerebral (18%) and cerebellar (39%) white matter, and more cerebral cortical gray matter (12%) than normal, whereas older autistic children and adolescents did not have such enlarged gray and white matter volumes. In the cerebellum, autistic boys had less gray matter, smaller ratio of gray to white matter, and smaller vermis lobules VI–VII than normal controls. *Conclusions:* Abnormal regulation of brain growth in autism results in early overgrowth followed by abnormally slowed growth. Hyperplasia was present in cerebral gray matter and cerebral and cerebellar white matter in early life in patients with autism.

NEUROLOGY 2001;57:245–254

RESEARCH ARTICLE

Longitudinal Volumetric Brain Changes in Autism Spectrum Disorder Ages 6–35 Years

Nicholas Lange, Brittany G. Travers, Erin D. Bigler, Molly B.D. Prigge, Alyson L. Froehlich, Jared A. Nielsen, Annahir N. Cariello, Brandon A. Zielinski, Jeffrey S. Anderson, P. Thomas Fletcher, Andrew A. Alexander, and Janet E. Lainhart

Since the impairments associated with autism spectrum disorder (ASD) tend to persist or worsen from childhood into adulthood, it is of critical importance to examine how the brain develops over this growth epoch. We report initial findings on whole and regional longitudinal brain development in 100 male participants with ASD (226 high-quality magnetic resonance imaging [MRI] scans; mean inter-scan interval 2.7 years) compared to 56 typically developing controls (TDCs) (117 high-quality scans; mean inter-scan interval 2.6 years) from childhood into adulthood, for a total of 156 participants scanned over an 8-year period. This initial analysis includes between one and three high-quality scans per participant that have been processed and segmented to date, with 21% having one scan, 27% with two scans, and 52% with three scans in the ASD sample; corresponding percentages for the TDC sample are 30%, 30%, and 40%. The proportion of participants with multiple scans (79% of ASDs and 68% of TDCs) was high in comparison to that of large longitudinal neuroimaging studies of typical development. We provide volumetric growth curves for the entire brain, total gray matter (GM), frontal GM, temporal GM, parietal GM, occipital GM, total cortical white matter (WM), corpus callosum, caudate, thalamus, total cerebellum, and total ventricles. Mean volume of cortical WM was reduced significantly. Mean ventricular volume was increased in the ASD sample relative to the TDCs across the broad age range studied. Decreases in regional mean volumes in the ASD sample most often were due to decreases during late adolescence and adulthood. The growth curve of whole brain volume over time showed increased volumes in young children with autism, and subsequently decreased during adolescence to meet the TDC curve between 10 and 15 years of age. The volume of many structures continued to decline atypically into adulthood in the ASD sample. The data suggest that ASD is a dynamic disorder with complex changes in whole and regional brain volumes that change over time from childhood into adulthood. ***Autism Res*** *2015, 8: 82–93.* © 2014 International Society for Autism Research, Wiley Periodicals, Inc.

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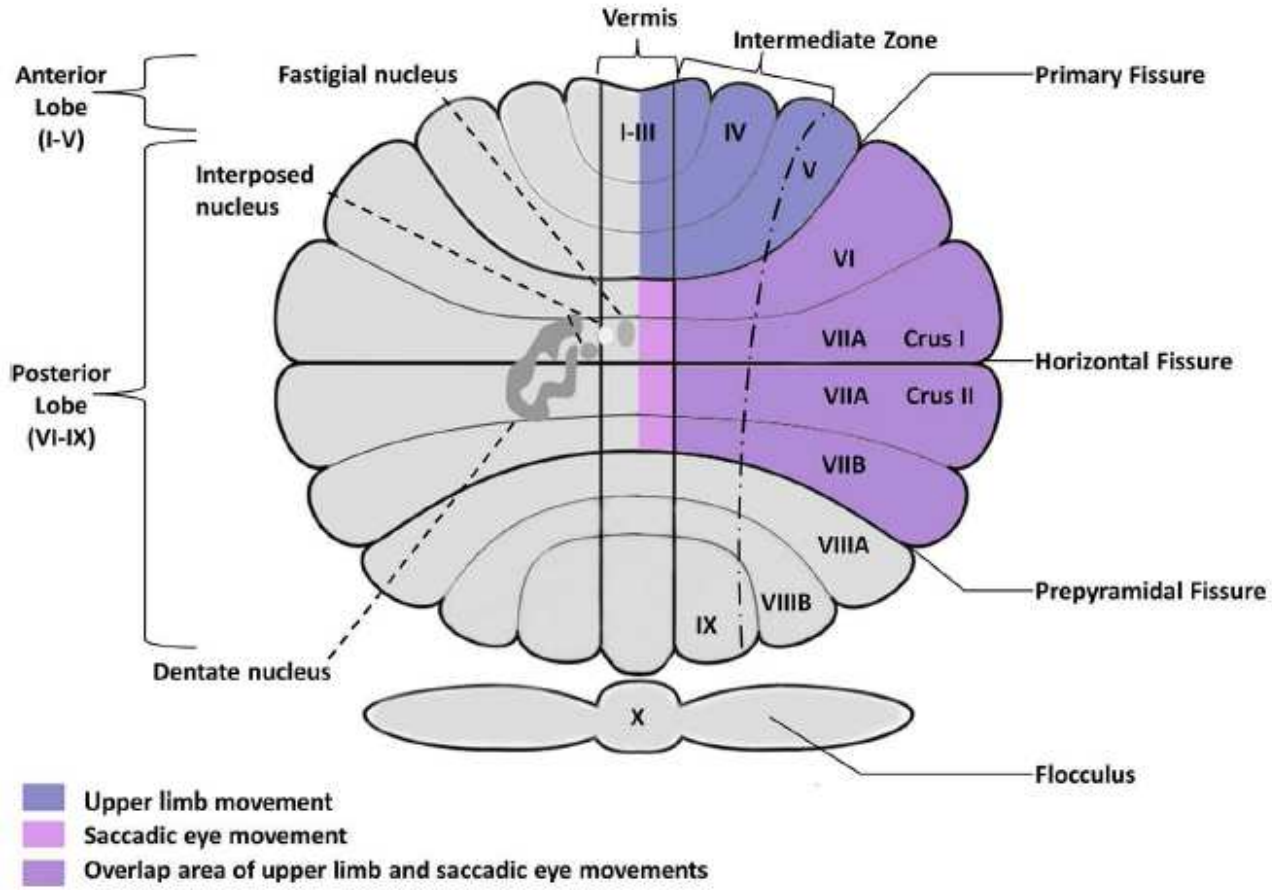

FIGURE 2 | Posterior view of the human cerebellum, showing the cerebellar fissure, lobular organization, and deep nuclei embedded within the cerebellar cortex. Deep nuclei are located bilaterally but shown only in the left hemisphere for clarity purposes. Saccadic and smooth pursuit eye movements are controlled by the oculomotor vermis including posterior lobules VI–VII, Crus I–II of the ansiform lobule, and their outputs in caudal fastigial nuclei. Upper limb movements primarily involve anterior lobules I–V as well as more lateral areas of lobules V–VI extending into Crus I–II. Cerebellar circuits involved in controlling balance and gait have been identified in the vermis and intermediate cerebellum (not shown).

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cervelletto

TABLE 1
Cerebellar Involvement in Neurocognitive Functions

Cognitive domain	Function	Reference
Executive planning	Frontal problem solving	e.g., Grafman et al., 1992
	Cognitive planning	e.g., Grafman et al., 1992
	Sequencing of plans	e.g., Hallett & Grafman, 1997
Temporal sequencing	Judgment of time duration	e.g., Ivry & Keele, 1989
	Timing of plans and actions	e.g., Hallett & Grafman, 1997
	Judgment of velocity of movement	e.g., Ivry & Diener, 1991
	Discrimination of vowel duration	e.g., Ackermann et al., 1996
	Discrimination of VOT	e.g., Ackermann et al., 1996
Attention	Enhancement of neural responsiveness	e.g., Yeo et al., 1985
	Direction of selective attention	e.g., Akshoomoff et al., 1997
Visuoperception	Visuospatial processing	e.g., Silveri et al., 1997
	Visuoconstruction	e.g., Botez-Marquard et al., 1994
Learning	Motor skill learning	e.g., Marr, 1969; Tach, 1997; Poldrack & Gabrieli, 2001
	Procedural & associative learning	e.g., Bracke-Tolkmitt et al., 1989
Memory	Long-term memory	e.g., Appollonio et al., 1993
	Phonological short-term memory	e.g., Paulesu et al., 1993
Imagery	Visuomotor imagery	e.g., Decety et al., 1990

Note. VOT = voice onset time.

Cervelletto e loops cortico-pontino-cerebello-talamico-corticale

Circuiti cerebellari controllano diversi comportamenti sensorimotori: mantenere equilibrio, marcia, movimenti oculari, raggiungere e afferrare un oggetto.

Condizioni deficitarie nei soggetti con ASD

-Studi post-mortem: riduzione numerica e di dimensione c. Purkinje nei soggetti con ASD (soprattutto CRUS I e II)

-Riduzione del GABA

-Riduzione volume lobuli VI e VII

-Associazione TSC e ASD soprattutto per quei pazienti con i tuberi a livello cerebellare

-Sofferenza pre-peri-neonatale che determina lesioni cerebellari associata ad ASD

-Alterazione SB peduncolo cerebellare superiore (output) e medio (input)

Article

Differential Effects of Developmental Cerebellar Abnormality on Cognitive and Motor Functions in the Cerebellum: An fMRI Study of Autism

Greg Allen, Ph.D.

Eric Courchesne, Ph.D.

Objective: Recent years have seen a revolution in views regarding cerebellar function. New findings suggest that the cerebellum plays a role in multiple functional domains: cognitive, affective, and sensory as well as motor. These findings imply that developmental cerebellar pathology could play a role in certain *non*motor functional deficits, thereby calling for a broader investigation of the functional consequences of cerebellar pathology. Autism provides a useful model, since over 90% of autistic cerebella examined at autopsy have shown well-defined cerebellar anatomic abnormalities. The aim of the present study was to examine how such pathology ultimately impacts cognitive and motor function within the cerebellum.

Method: Patterns of functional magnetic resonance imaging (fMRI) activation within anatomically defined cerebellar regions of interest were examined in eight autistic patients (ages 14–38 years) and eight matched healthy comparison subjects performing motor and attention tasks. For the motor task, subjects pressed a button at a comfortable pace, and activation was compared with a rest condition. For the attention task, visual stimuli were presented one at a time at fixation, and subjects pressed a button to every target. Activation was compared with passive visual stimulation.

Results: While performing these tasks, autistic individuals showed significantly greater cerebellar motor activation and significantly less cerebellar attention activation.

Conclusions: These findings shed new light on the cerebellar role in attention deficits in autism and suggest that developmental cerebellar abnormality has differential functional implications for cognitive and motor systems.

(Am J Psychiatry 2003; 160:262–273)

frontiers in Neuroscience

REVIEW
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Cerebro-cerebellar circuits in autism spectrum disorder

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The cerebellum is one of the most consistent sites of abnormality in autism spectrum disorder (ASD) and cerebellar damage is associated with an increased risk of ASD symptoms, suggesting that cerebellar dysfunction may play a crucial role in the etiology of ASD. The cerebellum forms multiple closed-loop circuits with cerebral cortical regions that underpin movement, language, and social processing. Through these circuits, cerebellar dysfunction could impact the core ASD symptoms of social and communication deficits and repetitive and stereotyped behaviors. The emerging topography of sensorimotor, cognitive, and affective subregions in the cerebellum provides a new framework for interpreting the significance of regional cerebellar findings in ASD and their relationship to broader cerebro-cerebellar circuits. Further, recent research supports the idea that the integrity of cerebro-cerebellar loops might be important for early cortical development; disruptions in specific cerebro-cerebellar loops in ASD might impede the specialization of cortical regions involved in motor control, language, and social interaction, leading to impairments in these domains. Consistent with this concept, structural, and functional differences in sensorimotor regions of the cerebellum and sensorimotor cerebro-cerebellar circuits are associated with deficits in motor control and increased repetitive and stereotyped behaviors in ASD. Further, communication and social impairments are associated with atypical activation and structure in cerebro-cerebellar loops underpinning language and social cognition. Finally, there is converging evidence from structural, functional, and connectivity neuroimaging studies that cerebellar right Crus I/II abnormalities are related to more severe ASD impairments in all domains. We propose that cerebellar abnormalities may disrupt optimization of both structure and function in specific cerebro-cerebellar circuits in ASD.

Keywords: autism spectrum disorder, cerebellum, neuroimaging, diffusion tensor imaging, voxel based morphometry, resting state MRI, cerebo-cerebellar circuits, functional connectivity

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Antonia Parmeggiani, 23 aprile 2016

- Cervelletto in connessione con diverse aree cerebrali legate al movimento, attenzione, motivazione, linguaggio, memoria, funzioni esecutive, socializzazione

- Porzione anteriore collegata con l'area sensorimotoria, la parte posteriore con le aree cognitive prefrontali e parietali associative

- Cervelletto implicato nei ASD, ADHD e dislessia, disturbo di coordinazione
- Connettività anomala tra cervelletto e aree corticali/talamo

- Prevalenza di connessioni omolaterali tra emisfero cerebrale ed emisfero cerebellare dx anziché controlateralmente come dovrebbe essere $\rightarrow$ ***connettività extra***

Cerebro-cerebellar circuits in autism spectrum disorder

Anila M. D'Mello[1,2] *and Catherine J. Stoodley*[1,2]*

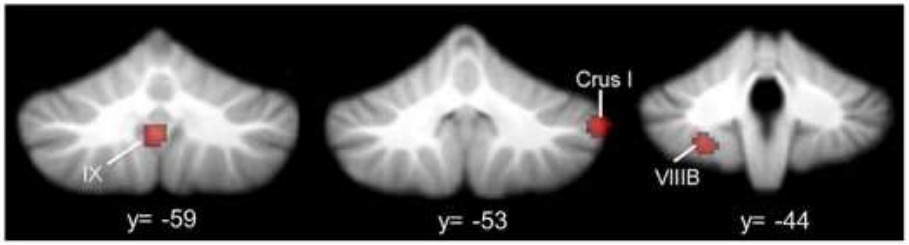

FIGURE 4 | Cerebellar gray matter reductions in autism. GM reductions in the cerebellum in ASD, based on a meta-analysis of voxel-based morphometry studies (Stoodley, 2014). Consistent GM reductions are evident in right Crus I, left VIIIB, and midline IX. Figure adapted from Stoodley (2014).

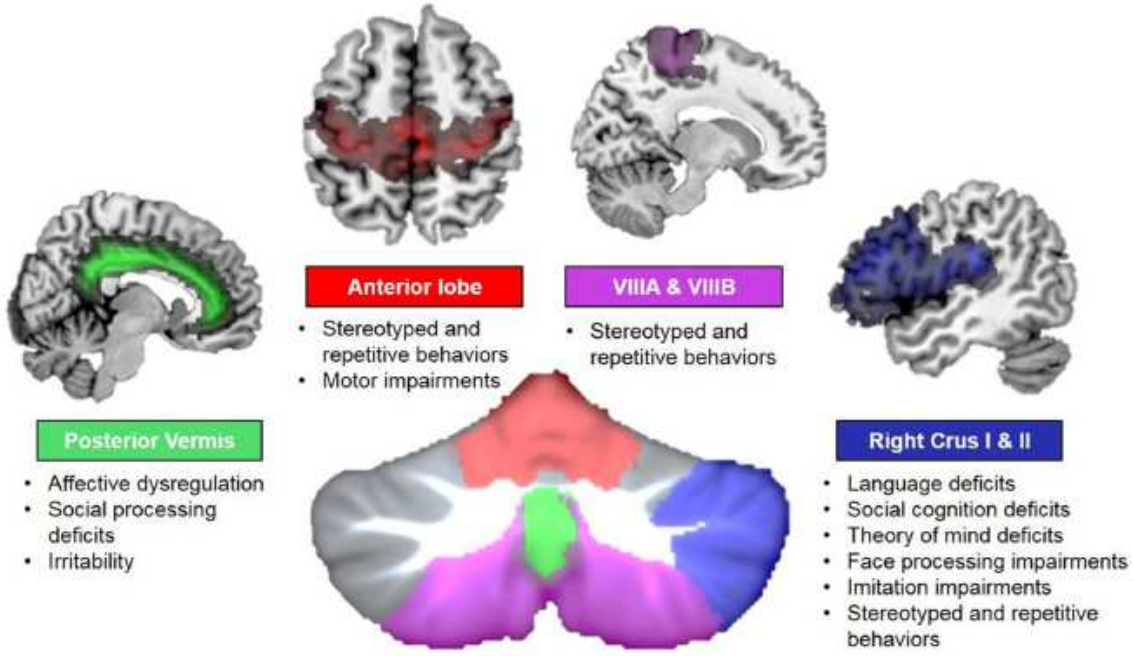

FIGURE 5 | Cerebro-cerebellar circuits in autism. Disruptions in specific cerebro-cerebellar circuits could result in different behavioral symptoms of ASD. Colors reflect connectivity of specific cerebellar regions: anterior lobe (red) and lobule VIII (violet) and somatomotor circuits; right Crus I and II (blue) and frontal language areas (among others); and posterior vermis (green) and limbic networks. Behavioral deficits associated with structural and functional disruptions in each circuit are noted.

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White Matter Integrity and Pictorial Reasoning in High-Functioning Children with Autism

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Neuroimaging of the Functional and Structural Networks Underlying Visuospatial versus Linguistic Reasoning in High-Functioning Autism

Chérif P. Sahyoun[a,b], **John W. Belliveau**[a,b], **Isabelle Soulières**[a,c], **Shira Schwartz**[a], and **Maria Mody**[a,b]

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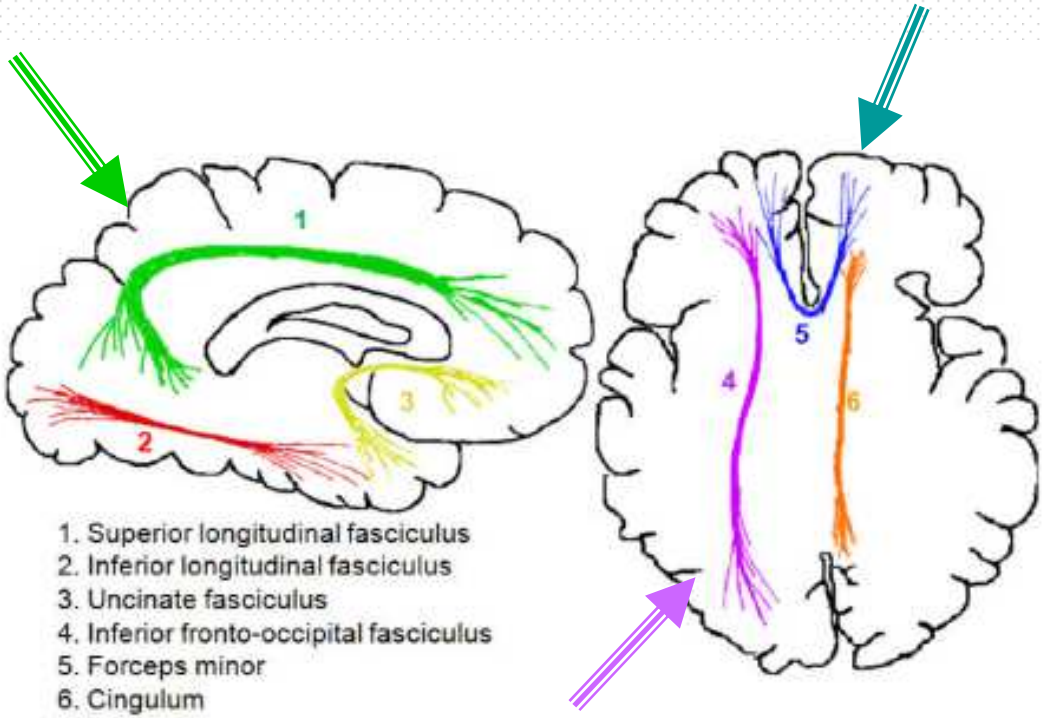


Figure 2.
Summary schematic of major white matter pathways found to be differentially implicated in HFA versus CTRL. Pathways were traced to reflect known anatomy in order to serve as a reference in interpreting results.

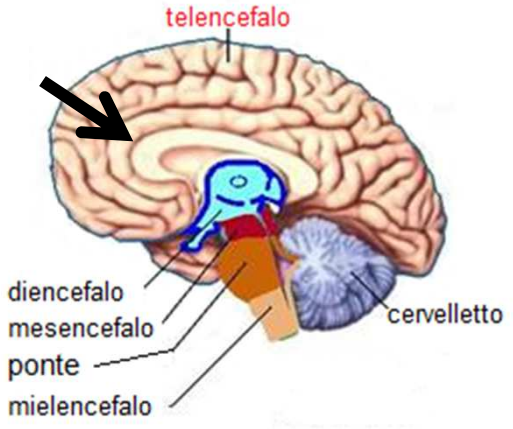
Our results appear to support a preferential use of linguistically-mediated pathways in reasoning by typically-developing children, whereas autistic cognition may rely more on visuospatial processing networks.

J Autism Dev Disord
DOI 10.1007/s10803-014-2096-8

ORIGINAL PAPER

Abnormal Corpus Callosum Connectivity, Socio-communicative Deficits, and Motor Deficits in Children with Autism Spectrum Disorder: A Diffusion Tensor Imaging Study

Ryuzo Hanaie · Ikuko Mohri · Kuriko Kagitani-Shimono · Masaya Tachibana · Junko Matsuzaki · Yoshiyuki Watanabe · Norihiko Fujita · Masako Taniike



Alterazioni strutturali a livello del CC relativamente alle fibre di connessione tra lobi frontali, parietali, occipitali, temporali (giro fusiforme, lobuli parietali sup. e inf.) → linguaggio, espressione volto, attenzione, empatia, comunicazione verbale e non verbale

Consapevolezza dei propri processi mentali per comprendere quelli altrui → **Teoria dello specchio rotto nei ASD**

Neuroni specchio che entrano in funzione quando viene compiuta un'azione ma anche quando la stessa azione viene compiuta dall'altro

Sono coinvolti nella comprensione delle azioni dirette ad un obiettivo, simulazione azioni, imitazione, ***empatia ???***

Localizzazione: **giro frontale inferiore, lobulo parietale inferiore** → "Sistema specchio" (connessione con altre aree corticali e sottocorticali)

- Minore attività dei neuroni specchio nei soggetti con ASD (deficit attenzione congiunta, imitazione, intersoggettività)
- *Alcuni studi non hanno documentato minore attività dei neuroni specchio, oppure ne hanno documentato maggiore attività*

Dapretto et al., 2005

- Soggetti con autismo ad alto funzionamento riconoscono e imitano espressione di alcune emozioni ma utilizzando circuiti cerebrali differenti
- Non utilizzato circuito mirror premotorio e ipoattivazione di insula ed amigdala
- Iperattivazione corteccia visiva

↓

Mancanza contenuto esperienziale al mondo affettivo altrui, rimane una semplice registrazione sensoriale di un evento esterno (Gallese, 2006)

online © ML Comm
ORIGINAL ARTICLE
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Print ISSN 1738-3684 / On-line ISSN 1976-3026
OPEN ACCESS

Abnormal Activation of the Social Brain Network in Children with Autism Spectrum Disorder: An fMRI Study

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Objective The aim of this study is to investigate abnormal findings of social brain network in Korean children with autism spectrum disorder (ASD) compared with typically developing children (TDC).

Methods Functional magnetic resonance imaging (fMRI) was performed to examine brain activations during the processing of emotional faces (happy, fearful, and neutral) in 17 children with ASD, 24 TDC.

Results When emotional face stimuli were given to children with ASD, various areas of the social brain relevant to social cognition showed reduced activation. Specifically, ASD children exhibited less activation in the right amygdala (AMY), right superior temporal sulcus (STS) and right inferior frontal gyrus (IFG) than TDC group when fearful faces were shown. Activation of left insular cortex and right IFG in response to happy faces was less in the ASD group. Similar findings were also found in left superior insular gyrus and right insula in case of neutral stimulation.

Conclusion These findings suggest that children with ASD have different processing of social and emotional experience at the neural level. In other words, the deficit of social cognition in ASD could be explained by the deterioration of the capacity for visual analysis of emotional faces, the subsequent inner imitation through mirror neuron system (MNS), and the ability to transmit it to the limbic system and to process the transmitted emotion.
Psychiatry Investig 2015;12(1):37-45

Key Words Autism spectrum disorder, Social brain network, Social cognition, fMRI.

RESEARCH ARTICLE

Motor Learning in Individuals With Autism Spectrum Disorder: Activation in Superior Parietal Lobule Related to Learning and Repetitive Behaviors

Brittany G. Travers, Rajesh K. Kana, Laura G. Klinger, Christopher L. Klein, and Mark R. Klinger

Motor-linked implicit learning is the learning of a sequence of movements without conscious awareness. Although motor symptoms are frequently reported in individuals with autism spectrum disorder (ASD), recent behavioral studies have suggested that motor-linked implicit learning may be intact in ASD. The serial reaction time (SRT) task is one of the most common measures of motor-linked implicit learning. The present study used a 3T functional magnetic resonance imaging scanner to examine the behavioral and neural correlates of real-time motor sequence learning in adolescents and adults with ASD ($n = 15$) compared with age- and intelligence quotient-matched individuals with typical development ($n = 15$) during an SRT task. Behavioral results suggested less robust motor sequence learning in individuals with ASD. Group differences in brain activation suggested that individuals with ASD, relative to individuals with typical development, showed decreased activation in the right superior parietal lobule (SPL) and right precuneus (Brodmann areas 5 and 7, and extending into the intraparietal sulcus) during learning. Activation in these areas (and in areas such as the right putamen and right supramarginal gyrus) was found to be significantly related to behavioral learning in this task. Additionally, individuals with ASD who had more severe repetitive behavior/restricted interest symptoms demonstrated greater decreased activation in these regions during motor learning. In conjunction, these results suggest that the SPL may play an important role in motor learning and repetitive behavior in individuals with ASD. ***Autism Res*** *2015, 8: 38–51.* © 2014 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism; motor learning; implicit learning; procedural learning; superior parietal; repetitive behaviors

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Article

Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits

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Dendritic Spine Pruning Defect in the ASD Brain

We assessed spine density across development and confirm an increase in basal dendrite spine density in layer V pyramidal neurons in ASD temporal lobe. Layer V pyramidal neurons are the major excitatory neurons that form cortical-cortical and cortical-subcortical projections. Basal dendrites receive excitatory and inhibitory inputs from local sources, and excitatory cell types target this compartment almost exclusively (Spruston, 2008). The increase in basal dendrite spine density suggests an enhanced local excitatory connectivity, a feature of ASD (Belmonte et al., 2004) proposed to cause failure in differentiating signals from noise, prevent development of normal long-range cortical-cortical and cortical-subcortical communications, and underlie neocortical excitation/inhibition imbalance (Sporns et al., 2000; Gogolla et al., 2009).

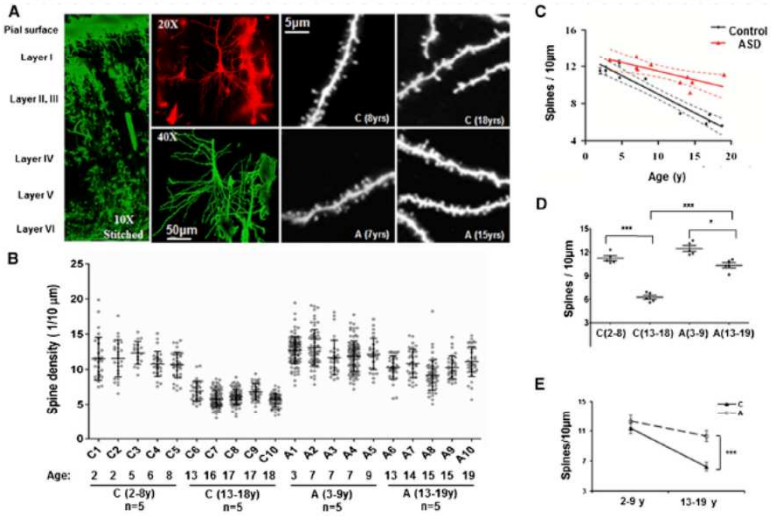

Figure 1. Dendritic Spine Pruning in Temporal Lobe of ASD Patients and Controls

(A) Representative Golgi images for postmortem human temporal lobe (left, 10×, stitched from nine separate image stacks), layer V pyramidal neurons with basal dendritic tree (top middle, 20×, pseudocolored in red; bottom middle, 40×, pseudocolored in green; scale bar, 50 μm). The right four panels (100×; scale bar, 5 μm) are representative images of proximal basal dendritic segments from two control subjects (C, aged 8 years and 18 years) and two ASD cases (A, aged 7 years and 15 years).

(B) Distribution of spine density (mean ± SD) in basal dendrites after the first bifurcation. Age and diagnosis are indicated for each sample. Controls aged 2–8 years [C(2–8 years)]: n = 5; controls aged 13–18 years [C(13–18 years)]: n = 5; ASD cases aged 2–8 years [A(2–8 years)]: n = 5; ASD cases aged 13–18 years [A(13–18 years)]: n = 5. Each point represents the average spine density for each individual neuron measured from each individual.

(C) A linear regression of spine density with age in the control subjects (n = 10) and ASD patients (n = 10). The number of spines per 10 μm was plotted against the age of each individual. Broken lines indicate 95% confidence intervals.

(D) Spine density (mean ± SD) for the controls and ASD patients in childhood and adolescence. Each point represents the mean spine density for an individual. Two-way ANOVA, Bonferroni post hoc test. ***$p < 0.001$, *$p < 0.05$.

(E) The decrease of spine density with age was greater in the controls than the ASD patients (mean ± SD). ***$p < 0.001$.

controls). From childhood through adolescence, dendritic spines decreased by ~45% in control subjects but only by ~16% in ASD patients (Figure 1E), demonstrating a developmental defect in net spine pruning in ASD.

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Altro…

- Sbilanciamento tra sistema eccitatorio ed inibitorio a livello cerebrale (Glutammato, GABA) → frequente comorbidità ASD con epilessia
- *Microglia* (cellule con azione fagocitaria per le cellule morte o sinapsi poco attive o malfunzionanti → malfunzionamento microglia → sbilanciamento processi inibitori ed eccitatori
- *Spine dendritiche in eccesso* in cervelli esaminati post-mortem di soggetti con ASD a livello delle c. piramidali del V strato del lobo medio superiore temporale
- Microglia con differente densità in regioni cerebrali del soggetti con ASD (area dorso laterale prefrontale, cervelletto)

Ipotesi: microglia non in grado di riconoscere le sinapsi da eliminare (rimangono le sinapsi eccitatorie? Oppure microglia iperattiva nell'eliminazione sinapsi inibitorie?

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Review article

Microglia in the pathogenesis of autism spectrum disorders

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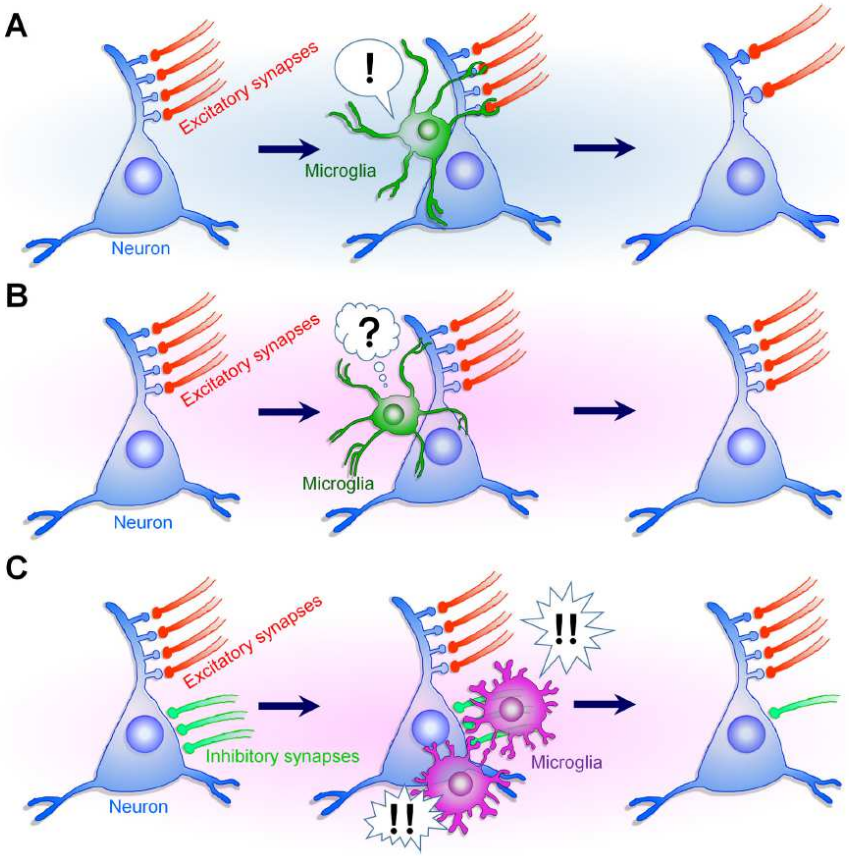

Fig. 1. Schematic diagrams showing the possible involvement of microglia in E/I imbalance in ASD. (A) In the healthy developing brain, firstly, excess number of immature excitatory synapses are formed. Secondly, inappropriate or less active synapses are pruned by microglia. Finally, strong mature synapses are maintained. It has not been concluded yet whether microglia are in a morphologically "activated" state or not when they engulf synapses in the healthy brain. (B) Hypothesis 1: In the ASD brain, microglia may fail to detect inappropriate or less active synapses, which results in the maintenance of excess number of excitatory synapses. The maintained excitatory synapses can be both immature and mature. (C) Hypothesis 2: In the ASD brain, microglia may be over-activated. It would be interesting if there are mechanisms by which over-activated microglia selectively prune inhibitory synapses.

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A Non-inflammatory Role for Microglia in Autism Spectrum Disorders

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In addition to providing trophic support to developing neurons, it has also been shown that microglial cells play a central role in the normal postnatal apoptosis and phagocytosis of neurons and their connections, which are naturally over-produced and then "pruned" away based on experience-dependent usage (17). Specifically, numerous studies over the last decade have shown that microglia are essential in both initiating cell death and phagocytizing dying neurons in the developing retina, spinal cord, cerebellum, hippocampus, and cerebral cortex (12, 18). It is

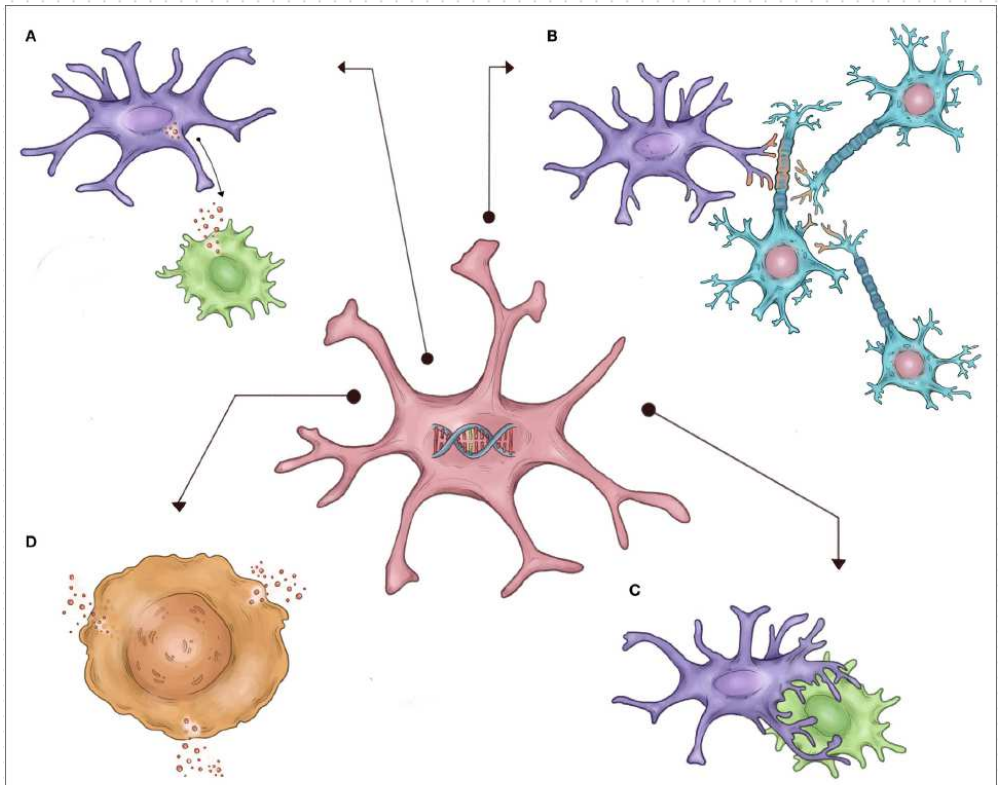

FIGURE 1 | Schematic representation of hypothesized non-immune microglial contributions to ASD, as described in the text. It is proposed that inherited defects in the microglial genome/epigenome in autistic patients (center) result in abnormal or exaggerated execution of normal developmental microglial functions, such as **(A)** abnormal secretion of trophic factors necessary for normal neuronal growth, **(B)** incorrect synaptic pruning, **(C)** failure of appropriate apoptosis of neurons, and **(D)** exaggerated activation and cytokine secretion.

the known genetic risk for ASD. Our hypothesis presented here would be further supported by these studies, in that the inherited risk for ASD could result in "primed" abnormal microglial cells that in individuals exposed to maternal inflammation or other factors results in an exaggerated/abnormal microglial response that perturbs normal neural network development (48).

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Involvement of synaptic genes in the pathogenesis of autism spectrum disorders: the case of synapsins

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Autism spectrum disorders (ASDs) are heterogeneous neurodevelopmental disorders characterized by deficits in social interaction and social communication, restricted interests, and repetitive behaviors. Many synaptic protein genes are linked to the pathogenesis of ASDs, making them prototypical synaptopathies. An array of mutations in the synapsin (Syn) genes in humans has been recently associated with ASD and epilepsy, diseases that display a frequent comorbidity. Syns are pre-synaptic proteins regulating synaptic vesicle traffic, neurotransmitter release, and short-term synaptic plasticity. In doing so, Syn isoforms control the tone of activity of neural circuits and the balance between excitation and inhibition. As ASD pathogenesis is believed to result from dysfunctions in the balance between excitatory and inhibitory transmissions in neocortical areas, Syns are novel ASD candidate genes. Accordingly, deletion of single Syn genes in mice, in addition to epilepsy, causes core symptoms of ASD by affecting social behavior, social communication, and repetitive behaviors. Thus, Syn knockout mice represent a good experimental model to define synaptic alterations involved in the pathogenesis of ASD and epilepsy.

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Grazie