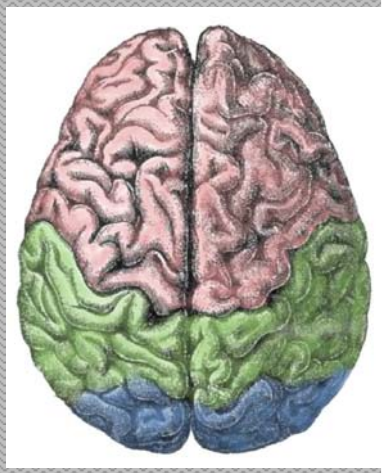

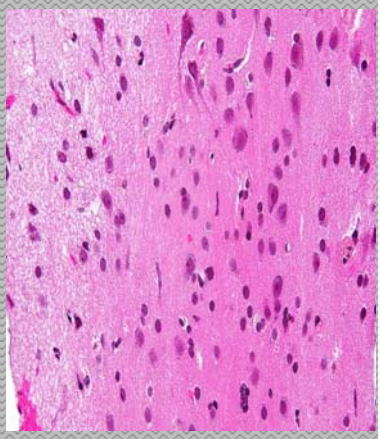

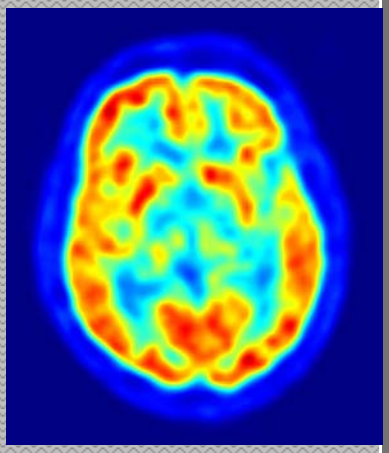

EMGEN Newsletter

Vol. 5, Issue 11

IN THIS ISSUE:

Eastern Mediterranean Health Genomics and Biotechnology Network (EMGEN) was created in 2004 with collaboration of representatives of selected centers of excellence in (health related) molecular biology, biotechnology & genomics in the Eastern Mediterranean region by recommendations and efforts of WHO/EMRO. Sponsored by Iran Biotechnology Development Council.

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AUTISM

Autism spectrum disorder is one of the neurodevelopmental disorders that characterized by:

1) Failure In Communication Contacts
2) Social Interactions
3) Intellectual Disability
4) Repetitive Behaviors
5) Failing To Develop Relationships
6) Severely Limited Activities.

Patients with classical autism have intensive disability in:

1) Both verbal and nonverbal correlations
2) Social interactions
3) Behaviors
4) Lack of unanimity
5) seizures

Figure 1. Repetitively arranging or adjusting objects is related with autism.

ASD can be associated by other symptoms such as sleep and gastrointestinal perturbations. Some of these children have borderline IQ. However, other are normal. In addition, autism has extensive variability in intensity of symptoms, even within the DSM-IV-TR categories, which demonstrates that there may be additional subtypes with common behaviors.

Clear symptoms slowly begin after six-month years old, become accepted by age nearly three years. Studies show that boys are four to five times more susceptible than girls for autistic disorders. Many of these children have unusual capacities in optical skills, music and art.

Several activities can help children with autism and learn them social and communication skills:

1) Early behavioral interventions
2) Music therapy
3) Working closely with a team
4) Give a proper therapy in a specialized center

Although there is no well-known treatment there have been reported several of them returned to normal life most of the autistic children cannot live alone after reaching adulthood. Each autistic individuals (child or adult) are distinctive thus. Each autism treatment plan should be appropriate to compensate specific necessities.

Epidemiology studies in all of worlds illustrates that the spread of autism is more than before. Classical autism is an earlier inception disorder so that the age of detection is before 3. Autism also known as an undoubtedly dependent on a number of factors. There is extensive heterogeneity , with hundreds of genetic and environmental factors involved.

Nevertheless, hereditary factors and mutations in a couple of significant genes are more prominent, although the genetic factors of autism are complex and sometimes with unclear effects. Complexity occurs because of interactions between a number of genes, the environment, and epigenetic factors. Many genes have been associated with autistic behaviors via sequencing the genomes of ASD patients and their parents.

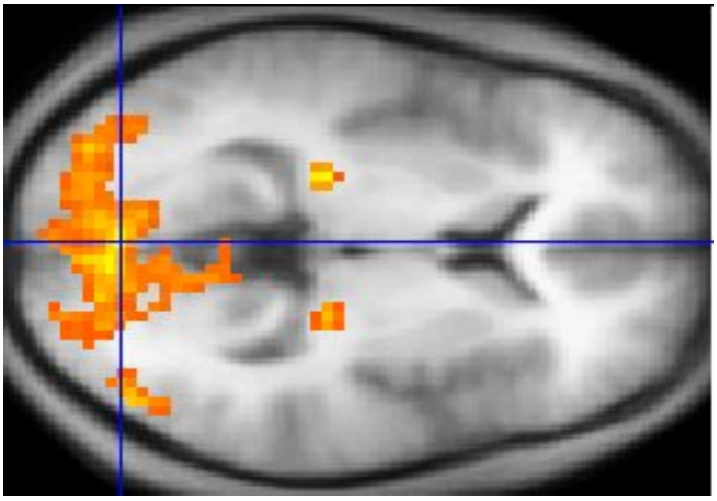

Figure 2. Functional magnetic resonance imaging

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7. https://en.wikipedia.org/wiki/File:Functional_magnetic_resonance_imaging.jpg

SIGNALING PATHWAYS IN AUTISM SPECTRUM DISORDERS

There is no wide study about autistic behaviors and their genetic factors in Iran (Except several studies in PTEN, MT DNA, SHANK genes in nowadays). Several main types of ASD are:

1) Autistic Disorder,
2) Cowden Syndrome
3) Bannayan-Riley-Ruvalcaba syndrome
4) Asperger Syndrome,
5) Rett Syndrome,
6) Childhood Disintegrative Disorder, Pervasive Developmental Disorder – Not Otherwise Specified (PDD -NOS).

These disorders are mostly related with essential functional impairments that often involved long-lasting meditation. Estimates from the Centers for Disease Control estimate that 1 in 88 children may be affected by ASD behaviors.

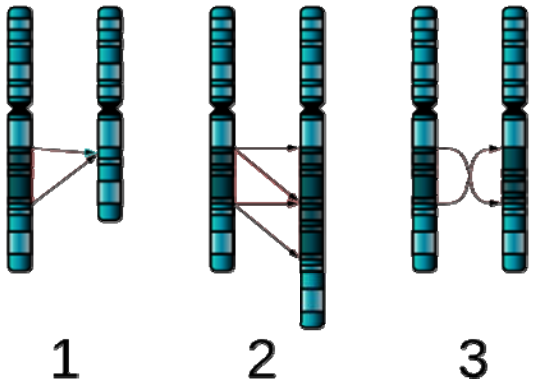

Figure 1. Deletion (1), duplication (2) and inversion (3) that have been involved in autism.

Autism-spectrum disorders speak on behalf of a group of developmental disorders with powerful genetic supporting. Several cytogenetic abnormalities, de novo mutations and signaling pathways' disruption, able to cause autistic behaviors and brain developmental abnormalities.

Nowadays studies show several signaling pathways and genes that are often disturbed in patients with ASD as well as autistic mouse models .(table 1 and 2)

Mammalian target of rapamycin (mTOR), Extracellular signal-regulated kinase (ERK1/2) signaling, Phosphatase and tensin homolog (PTEN) signaling pathway identifying how the downstream molecules correlate the growth pathways and which mutations or down regulations in these pathways disrupted brain development in ASD will give us a better autism classification.

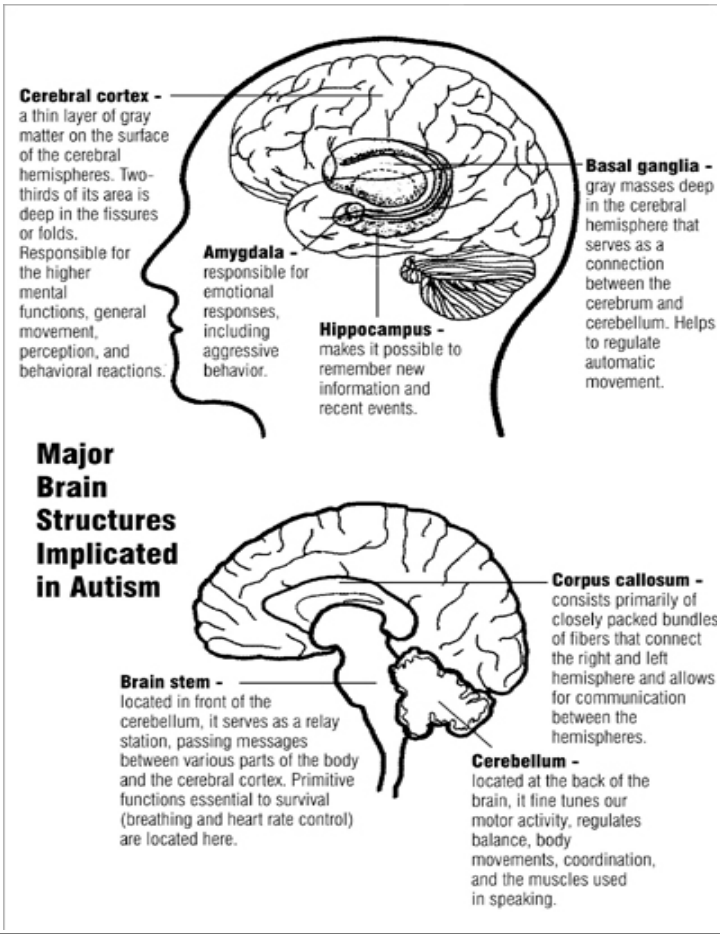

Figure 2. Many parts of the brain . amygdala and cerebellum in autistic patients

Table 1. Sevral gene associated with autism

Gene name	Gene name
UBE3A	HOXA1
TSC2	GRID2
TSC1	FOXP2
SHANK3	EML1
PTEN	CDKL5
MECP2	CACNA1C
MAPK3	ARX
OXTR	FMR1
SCL1A1	SCL1A2

Table 2. Novel InDels detected by Sanger sequencing of autism genes in 339 individuals with ASD (Christian P. Schaaf etal 2013).deletion and insertion of each individuals are different.

Gene name	Chr	Mutation type	Reference allele	Variant allele
HOXA1	chr7	Deletion	TGG	–
HOXA1	chr7	Insertion	–	TGG
HOXA1	chr7	Insertion	–	TGGTGG
HOXA1	chr7	Deletion	TGGTGG	–
TSC1	chr9	Insertion	–	CTG
UBE3A	chr15	Deletion	CTTTTC	–
HOXA1	chr7	Deletion	TGGTGGTGG	–
TSC2	chr16	Deletion	GCTGCCAAG	–
HOXA1	chr7	Frame shift deletion	C	–
FOXP2	chr7	Insertion	–	AGC
PTEN	chr10	Exon boundary deletion	TTAGT	–

Target-derived survival factors or neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) regulates many aspects of

1) Neuronal structure
2) Neuronal functions
3) Neurodevelopment
4) Differentiation
5) Synaptic plasticity and etc

Mammalian neurotrophins bind to and activate several members of the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases (TrkA, TrkB, and TrkC), leading to subsequent activation of other signaling molecular pathways such as phospholipase C (PLC), ERK1/2,phosphatidylinositol 3-kinase (PI3K), and mTOR signaling.

Moreover epigenetic, transcriptional, post-transcriptional, and post-translational change factors control the neurotrophin signaling. These controls are critical to cell fate decisions, axon and dendritic growth regulating.

Disruption in neurotrophin signaling leads to neurodegenerative disorders such as Alzheimer's, Huntington's disease, Parkinson's disease and also psychiatric disorders as well as autism.

mTOR is regulated by several downstream molecules and proteins such as PI3 kinase (PI3K),PDK1,PTEN, AKT, LKB1 and AMPK.

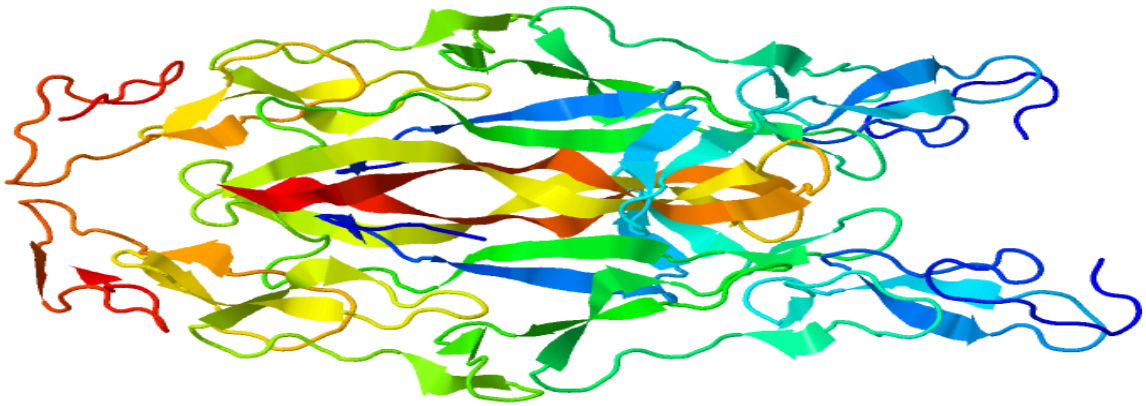

Figure 3. Monomer Front View of Neurotrophin

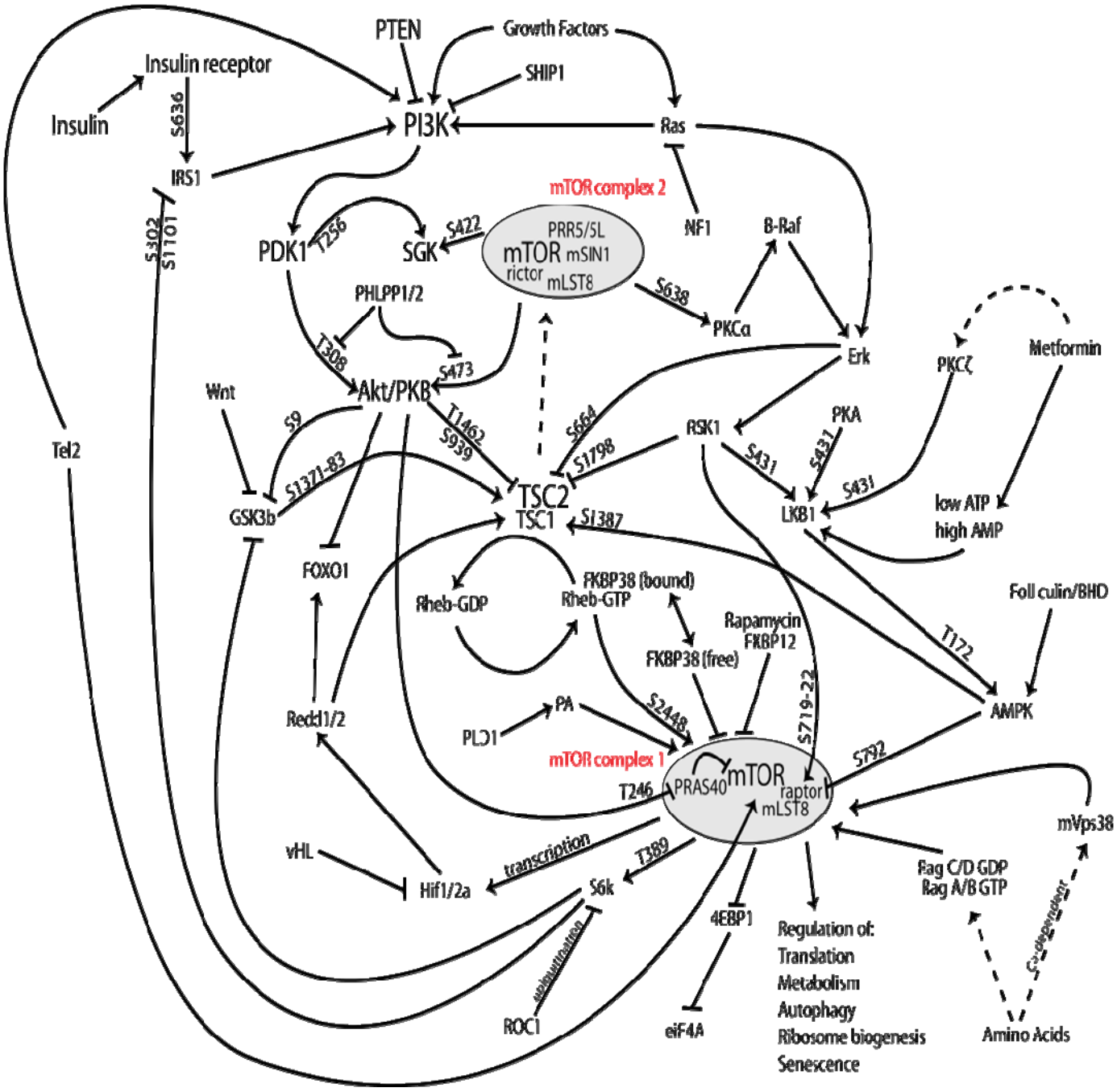

Figure 4. mTOR signaling pathway

Investigation of mTOR signaling in these disorders indicated loss-of-function of essential genes encoding mTOR blocker proteins such as TSC1, TSC2, PTEN and STRADa has been recently linked to developmental brain malformations associated with epilepsy, autistic behaviors and neurobehavioral disorders.

The idea that PTEN gene plays a risky role in autism spectrum disorder has appeared nearly decades. Phosphatase and tensin homolog (PTEN) is an important protein that encoded by the PTEN gene on chromosome 10 in human. This protein is a phosphatidylinositol-3, 4, 5-trisphosphate 3-phosphatase. Furthermore, The PTEN protein can dephosphorylate phosphatidylinositol (3,4,5)-trisphosphate.

PTEN negatively controls the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway with Its lipid phosphatase activity.

Somatic or germline Mutations and deletions in PTEN gene leading to inactivate its enzymatic activity and increased cell proliferation. Inactivation of PTEN or reduced its expression arises in glioblastoma, lung cancer, breast cancer, endometrial cancer, and prostate cancer and in many other tumor types.

Human genetic studies showed that PTEN plays an important role in brain development and its germline mutations leading to macrocephaly, seizures, and mental retardation in autistic children.

Several essential roles of the PTEN signaling pathway in neuronal network:

1) Role of the PTEN Pathway in Neuronal Fate Determination and Differentiation
2) Role of the PTEN Signaling Pathway in Synaptic Plasticity
3) Role of the PTEN Signaling Pathway in Dendritic and Synaptic Development
4) PTEN protein phosphatase activity maintains neural stem cells in a progenitor state
5) Pten-deficient neural stem cells differentiate precariously into neurons
6) Expression of wide type PTEN rescues the precocious differentiation induced by inactivation of PTEN protein phosphatase function
7) PTEN-dependent CREB (cAMP response element-binding protein is a cellular transcription factor) dephosphorylation is critical for neural stem cell differentiation

Conclusion

During the time that ASD has been shown to have important genetic etiological members, recent studies discovered approaching thousands genes associated with ASD risk. In addition, addition, these results do not even discuss the become visible role of non-coding RNA variants .

Many studies have shown that the PTEN /mTOR pathway is associated with ASD, although many other pathways could also lead to this syndrome and create the same behaviors. The effect of PTEN on neural stem cell development is quite complex.

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AUTISM AND ENVIRONMENTAL FACTORS

Autism's hypothesis of causation is not so informative and this disorder does not have a single cause, both environment factors and genetic are significant.

The risk of autism is linked with several different environmental risk factors including :

1) Use of psychiatric drugs in the mother during pregnancy
2) Prenatal viral infection
3) Advanced age in both mother and father
4) Maternal depression
5) maternal emotional strain
6) Urbanization of birth place
7) Contraception use prior to pregnancy
8) Vitamin D deficiency
9) Maternal asthma
10) Allergies
11) Maternal toxemia

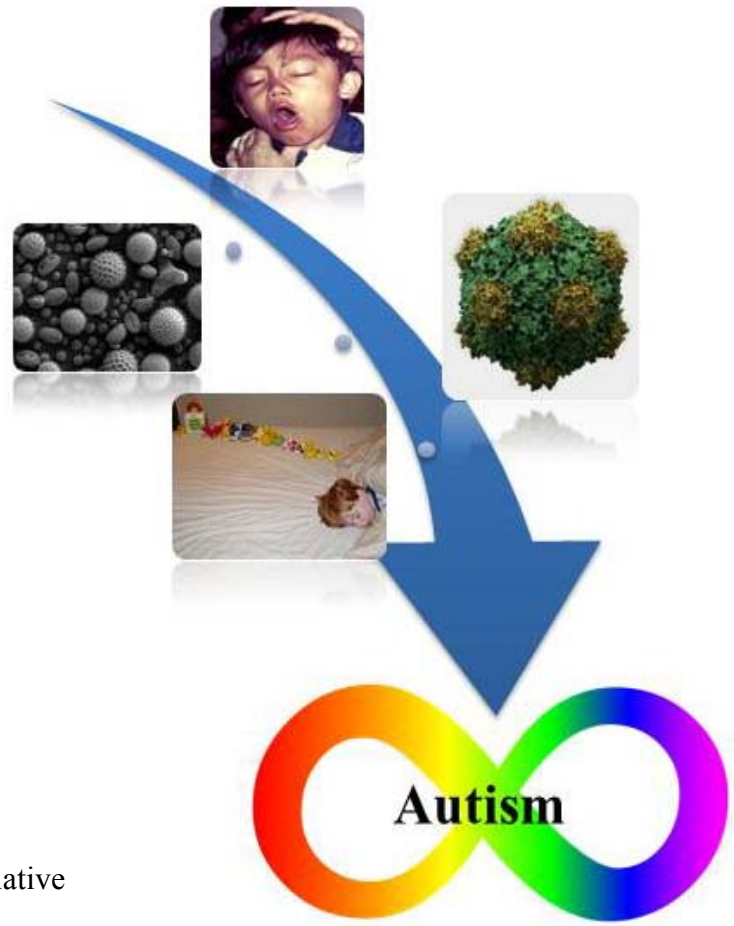

Figure 1. Environmental Factors in Autism Initiative

Last studies have shown that brain inflammation is associated with the caution of ASD. furthermore special kind of mast cell activation maybe associated with brain inflammation and neurodevelopmental problems. In addition following factors are significantly raised in autistic patient (tissue samples or cerebral spinal fluid):

1) interleukin-6 (IL-6)
2) tumor necrosis factor-α (TNF-α)
3) interferon-γ (IFN-γ)
4) IL-1β
5) IL-12p40
6) chemokine C-C motif ligand (CCL)-2

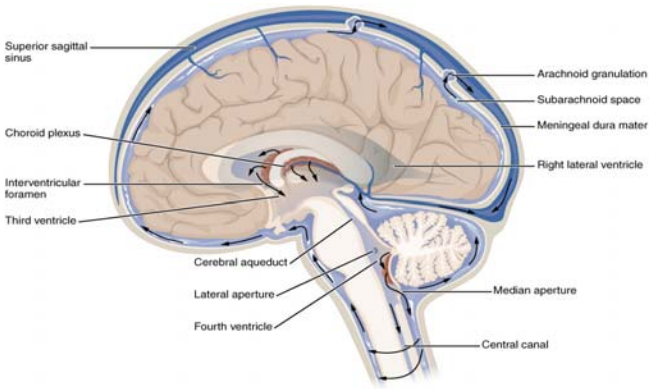

Figure 2. The cerebrospinal fluid (CSF) circulates

Cytokines such as IL-6 and TNF can disrupt the blood–brain barrier (BBB) which may be playing an important role in pathogenesis of ASD. Neurotensin (NT), corticotropin-releasing hormone (CRH), secreted under stress, stimulate mast cells and expansion vascular permeability and recently studies indicated these factors are associated with brain inflammation .

Several roles of Neurotensin actions in autism spectrum disorder (ASD) :

1) Activation of mast cells of MT DNA
2) Disruption of gut-blood barrier
3) Mast cell stimulation in ASD children with allergic symptoms
4) Stimulation of glutamate receptors and Neuronal damage

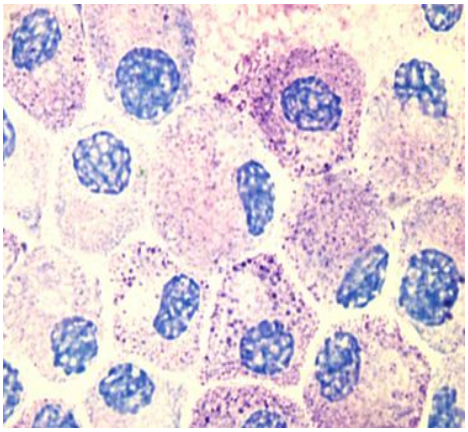

Figure 3. Mast cells

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PRENATAL EXPOSURE TO ACETAMINOPHEN AND AUTISTIC BEHAVIORS IN CHILDREN

A new study was published in *International Journal of Epidemiology* Has found that acetaminophen, which is used widely throughout gestation, maybe has a strong association with autistic behaviors in boys and for both genders maybe linked to hyperactivity symptoms.

2644 mothers and their child were recruited in a birth cohort study throughout gestation. 2 groups were analyzed :child with one years old 88 percent and 79.9 percent were analyzed when they were five years old. Mothers were asked about their use of acetaminophen during pregnancy .

43 per cent of children in group one and 41 per cent of individuals in group 2 were exposed to acetaminophen during the first 32 weeks of pregnancy.in this study children with five years old, were at higher risk of hyperactivity symptoms.in comparison between both gender, boys showed more autism spectrum symptoms than girls when exposed to acetaminophen for a long time during pregnancy.

Claudia Avella-Garcia (one of the authors in this article) believed that, The male brain may be more susceptible to injurious effects such as androgenic endocrine disruption during early life.

The conclusion of this study was the persistently exposure of infants to acetaminophen in utero during pregnancy could caution ADHD or autism spectrum behaviors. of course this study needs precise dosage measurements, and that the disadvantages versus advantages of acetaminophen use during pregnancy.

Reference: https://www.sciencedaily.com/releases/2016/07/160701095445.htm

AUTISM RESEARCH

Journal ISSN: 1939-3792

Autism Research will cover Pervasive Developmental Disorders (or autism spectrum disorders –ASDs). and encourages the submission of articles that take a developmental approach to the biology and psychology of autism.

Impact Factor:4.33

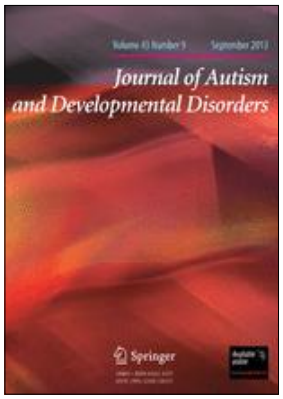
AUTISM

ISSN:1362-3613 (Print)
1461-7005 (Electronic)
1362-3613 (Linking)

Autism covers all areas of intervention, diagnosis, training, education and etc. in autism

Impact Factor: 3.170

JOURNAL OF AUTISM AND DEVELOPMENTAL DISORDERS



ISSN: 0162-3257 (Print)

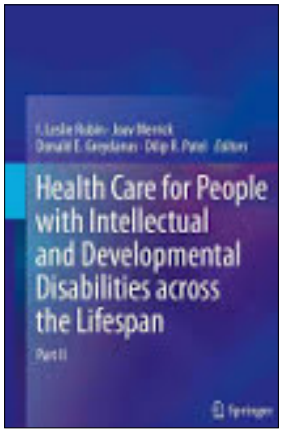
1573-3432 (Online)

Journal of Autism and Developmental Disorders Published monthly, covers genetic, immunological, environmental, diagnosis advancements and etc.

Impact Factor: 3.493

Book Alert

HEALTH CARE FOR PEOPLE WITH INTELLECTUAL AND DEVELOPMENTAL DISABILITIES ACROSS THE LIFESPAN



Editors: I. Leslie Rubin, Joav Merrick, Donald E. Greydanus, Dilip R. Patel

Publisher: Springer, 2016

ISBN: 3319180967, 9783319180960

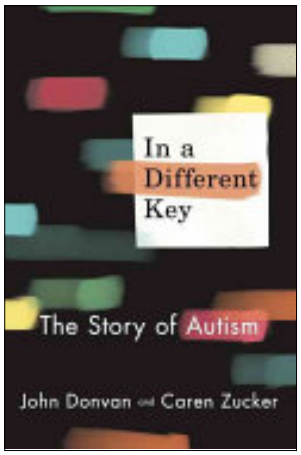
HEALTHCARE TECHNOLOGY INNOVATION ADOPTION

Authors: Tugrul U. Daim, Nima A. Behkami, Nuri Basoglu, Orhun M. Kök, Liliya Hogaboam

Publisher: Springer, 2016

ISBN: 3319179756, 9783319179759

IN A DIFFERENT KEY: THE STORY OF AUTISM



Authors: John Donvan, Caren Zucker

Publisher: Crown/Archetype, 2016

ISBN: 0307985679, 9780307985675

Announcements

http://www.apac17.org.au/

http://www.st.wsconf.com/

http://www.saco.ae/icps/index.php

CEREBRAL LOBES OF HUMAN BRAIN

The lobes of the brain are only an anatomical classification, but have been presented different functions of the brain. The telencephalon (cerebrum), the largest part of the human brain, is divided into lobes. In the indefinite expression of "lobes of the brain", "telencephalon" could be used.

The human cerebral cortex includes a thick layer of neural tissue that covers the two cerebral hemispheres that compose most of the brain. This layer is folded in a special manner. The amount of surface area is increased; therefore brain can fit into the volume available. Even though the pattern of folds is the same across individuals, it shows many small variations. The cortex is separated into four lobes – the frontal lobe, parietal lobe, temporal lobe, and occipital lobe. (in addition, Some classification systems name a limbic lobe and treat the insular cortex in place of a lobe.) Each lobe had many cortical areas, each related to a specific function, including vision, motor control, and language. The left and right hemispheres are generally analogous in shape, and most critical areas are copied on both sides. However, some areas show strong lateralization language is resulted of most areas of lobes. mostly the left hemisphere is a central part of language, with the right hemisphere playing only a slight role. There are other functions, such as visual-spatial ability, for which the right hemisphere is typically dominant.

Reference: https://en.wikipedia.org/wiki/File:Cerebral_lobes.png

MICROGRAPH OF GREY MATTER

Grey matter (or gray matter) is a main section of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and myelinated in addition to unmyelinated axons), glial cells (astroglia and oligodendrocytes), synapses, and capillaries. Grey matter is illustrated from white matter, in that it has abundant cell bodies and relatively few myelinated axons, whereas white matter contains relatively very few cell bodies and is composed mainly of long-range myelinated axon tracts. The color difference is caused mainly by the whiteness of myelin. In living tissue, grey matter actually has a very pale grey color with yellowish or pinkish types, which come from capillary blood vessels and neuronal cell bodies.

In this picture, HPS stain is used and micrograph presents grey matter, with the characteristic neuronal cell bodies (dark shade of pink), and white matter with its characteristic well mesh-work like form (left of image - lighter shade of pink).

Grey matter is existed in the brain, brainstem and cerebellum, and exist in the spinal cord. It includes regions of the brain participates in muscle control, and sensory perception such as seeing and hearing, memory, emotions, speech, decision making, and self-control.

Reference: https://en.wikipedia.org/wiki/File:Grey_matter_and_white_matter_-_very_high_mag.jpg

POSITRON EMISSION TOMOGRAPHY IMAGE OF THE HUMAN BRAIN

Positron emission tomography (PET) is a nuclear medicine, useful imaging technique that is used to detect metabolic processes in the body. The system distinguishes pairs of gamma rays produced indirectly by a positron-emitting radionuclide (tracer), which is presented in the body on a biologically active molecule. Three-dimensional images of tracer concentration inside the body are then created by computer analysis. In modern PET-CT scanners, three dimensional imaging are often achieved with the assistance of a CT X-ray scan performed on the patient during the same period, in the same machine.

Reference: https://en.wikipedia.org/wiki/File:PET-image.jpg