THE NEUROLOGICAL ASPECT OF AUTISM

4th National Early Childhood Intervention Conference. 7th -9th June 2012

Sibu, Sarawak, Malaysia

The Early Brain Growth

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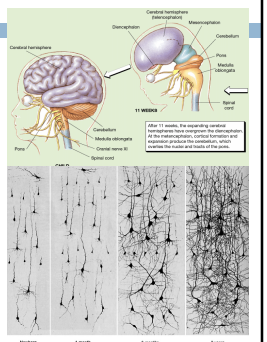
- During the first 2 years of life, there is genetically determined sequential growth, proliferation, and overproduction of axons, and synapses in different regions of the brain.



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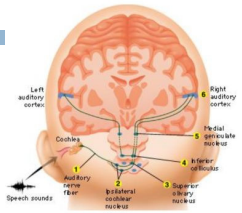
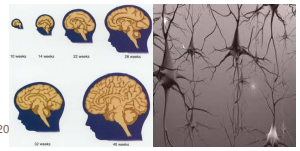
The determination of important synaptic connections is environmentally regulated and dependent on information received by the brain.

This period of plasticity has potential for change.





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- Synaptogenesis begins around the time of birth and increases to a peak level well above that observed in adults
- A key idea is that this "pruning" of synapses leaves intact those connections that have been most useful, and gets rid of connections that have been redundant or less useful.

Neuroscience Research in Autism

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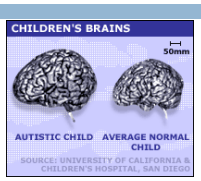
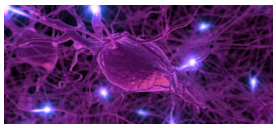
Beginning of life:

- Deviant brain growth in autism occurs at the very time when the formation of cerebral circuitry is at its most exuberant and vulnerable stage, and it may signal disruption of this process of circuit formation.
- The resulting aberrant connectivity and dysfunction may lead to the development of autistic behaviors





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- Slowing or arrest of growth during early childhood
- Some may have a third phase of degeneration in some brain region by preadolescence and continue to adulthood
- Enhanced reliance on visuospatial abilities for verbal and visual reasoning and reduced frontal systems connectivity (Minshew at al, 2010 Cur op in neurology)

What are the Evidence?

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1. Towards a neuroanatomy of autism:
   A systematic review and meta-analysis of structural magnetic resonance imaging studies (European Psychiatry 23 (2008) 289-299 Review)
2. The New Neurobiology of Autism
   Cortex, Connectivity, and Neuronal Organization
   (ARCH NEUROL/VOL 64 (NO. 7), JULY 2007) Neurological Review
3. Mapping Early Brain Development in Autism. Eric Courchesne et al. Neuron 56 Oct 25, 2007 Review Article

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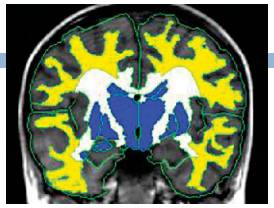
- Consistent evidence for an increase of the total brain volume in the cerebral hemispheres in autism
- The corpus callosum was relatively smaller in size



Yellow areas indicate the outer radiate white matter white zone, which are larger in volume. The white area represents bridging components, which did not differ in volume from controls. (Image courtesy of Martha Herbert, MD, PhD.*Arch Neurol*. 2007)

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- The increase in total brain volume was documented
- Beginning at 2 to 4 years of age, and persisted into childhood but not adolescence

Neuroradiology (2010) 52:3–14
Neuroimaging of autism
Judith S. Verhoeven et al

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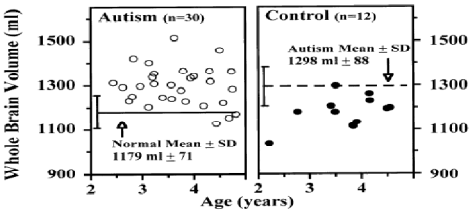

Fig. 1 Whole brain volume by age: 2- to 4-year-old autistic and normal boys are plotted showing overall whole brain enlargement of the youngest autistic children. As shown, 90% of the autistic boys had whole brain volumes larger than the normal mean. In contrast, only one normal boy in this age range exceeded the autism mean (from Courchesne, Neurology 2001 with permission)

Courchesne et al. 2007

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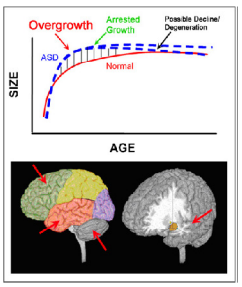
- Regional overgrowth in ASD include frontal and temporal cortices, cerebellum, and amygdale
- In some regions and individuals, the arrest of growth may be followed by degeneration,



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- Are the neural systems that fail to provide those fundamental skills so early in neurobehavioral development also the ones that undergo abnormal overgrowth?

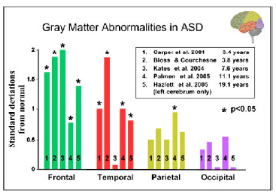

Figure 5. Summary of Observed Gray Matter Abnormalities (Standard Deviations from Normal) from Studies of Children and Adolescents with ASD.Note the general gradient of abnormality, with frontal and temporal regions most profoundly enlarged.(References: 1, Carper et al., 2002; 2, Bloss and Courchesne, 2007; 3,Kates et al., 2004; 4, Palmen et al., 2005; 5, Hazlett et al., 2005.)

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- What is the underlying cause of overgrowth? Excess neuron? glia cell? Synapses?
- Some reports on post-mortem studies of autistic individuals with megalencephaly, **cortical thickening** and an **increase in cerebral neuronal density.**
- Increased numbers of smaller and less dense cortical minicolumns. (vertical chains of cells extending through the cortical layers thought to be functional sub-units of cortex)

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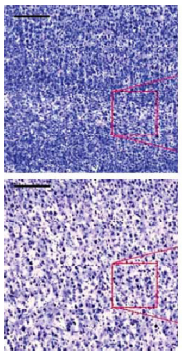
Autism



Micrographs of Brodmann area 4, lamina III
Insets highlight the cores of minicolumn fragments identified by a software program, illustrating the reduction in minicolumnar width in autism. Image courtesy of Manuel Casanova

A larger less well organised cerebral cortex possibly lead to

•Inefficient connectivity
•less integration of dispersed brain regions

Supported by a variety of functional neuroimaging studies.

Control B (age matched)

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- **Excess neuron numbers cause** defects in neural patterning and wiring.
- Exuberant local and short-distance cortical interactions **impeding** the function of large-scale, **long distance interactions** between brain regions.
- Large-scale networks underlie socio-emotional and communication functions. These changes could relate to the early clinical manifestations of autism. (Courchesne et al Neuron 2007)

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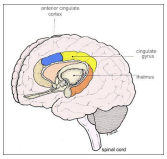
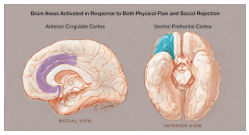
- This phenomenon showed predilection for the prefrontal areas and the anterior cingulate cortex (Casanova, 2006b; Buxhoeveden et al., 2006).
- **The** anterior cingulate cortex **(ACC) is involved in processing and modulating expression of emotional nuances, with which autistic individuals have considerable difficulties.**
- **The ACC is paramount in the formation of long-term attachments and maternal behavior.**





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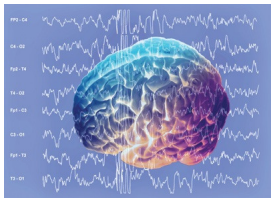
- The narrowing of the minicolumns was largely related to a reduction in the neuropil space occupied by unmyelinated projections of inhibitory interneurons(GABA)
- A deficit in cortical inhibition was hypothesized and proposed to explain the 30% prevalence of seizures and the sensory sensitivities



Autism and epilepsy are comorbid phenomena.

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- Mismatch in excitatory and inhibitory neurons may results in
- - excessive and less controlled excitability
- -reduced selective responsiveness
- -disorganized cortical assemblies

Functional magnetic resonance imaging (fMRI) studies Marcel Adam Just et al, 2004

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- The brain activation of a group of high-functioning autistic participants was measured using functional MRI during sentence comprehension
- Results compared with those of a Verbal IQ-matched control group.

-Example of task: The cook thanked the father. Who was thanked? cook – father

-An example of a passive sentence and probe is The editor was saved by the secretary. Who was saving?

-Sentences of the same type were presented in epochs of five items.

BROCA'S AREA , WERNICKE'S AREA, AND OTHER LANGUAGE-PROCESSING AREAS IN THE BRAIN

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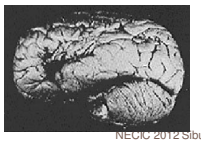
French neurosurgeon-Paul Broca

A diseased patient :

Able to understand spoken language. He could neither speak a complete sentence nor express his thoughts in writing

Only articulate sound he could make was the syllable "tan", which had come to be used as his name.



Carl Wernicke, a German neurologist

Discovered another part of the brain, this one involved in understanding language, in the posterior portion of the left temporal lobe.
People who had a lesion at this area could speak, but their speech was often incoherent and made no sense.

The language Loop

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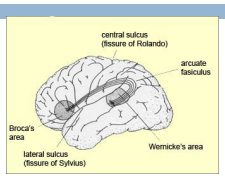
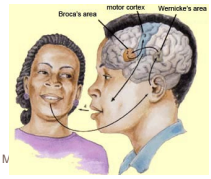
- At the frontal end of this loop lies **Broca's area. U**sually associated with the language outputs .
- In the superior posterior temporal lobe, lies **Wernicke's area,** which is associated with the processing of words that we hear being spoken
- Broca's area and Wernicke's area are connected by a large bundle of nerve fibres called the **arcuate fasciculus.**





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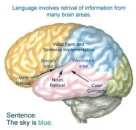
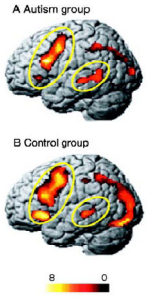
- The autistic participant perform the task less accurately.
- They also showed a reduced activation in Broca's area
- Increased activation in Wernicke's (processing of words that we hear) area compared to controls





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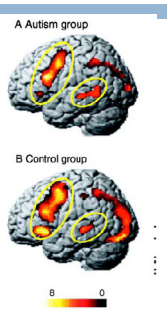
- The autistic participants engage in **more extensive** processing of the meanings of the individual words and manifested as more **Wernicke's areas activation.**
- The autistic participants showed **less activation in Broca's area** (associated with semantic, syntactic and working memory processes) which serve to integrate the meanings of individual words into a coherent conceptual and syntactic structure



Social interaction

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- The theory of mind (ToM) originated from a concept found in the pioneer works of Premack and Woodruff
- It refers to the ability to attribute to oneself and others mental states such as beliefs, intentions, memories and aspirations, and the ability to make use of these attributions in understanding and predicting behaviours of others
- A special class of motor neurons, the mirror neurons (Mn), would play a major role in this cognitive system.

Mirror Neurons

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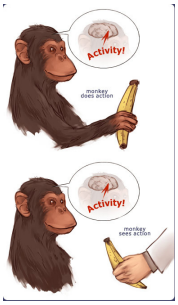

- **The discovery of mirror neurons in macaque monkey was actually an accident during research on the monkeys.**
- When placing peanuts in front of a monkey, a neuron would be fired whenever the monkey would reach for a peanut.
- However, when a researcher grabbed a peanut while the monkey was simply watching, the neurons were still fired, implying a neurological link between physical movement and observation.

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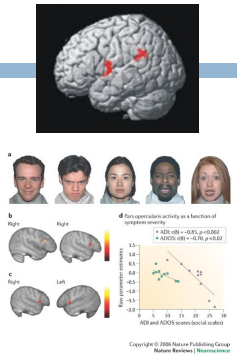
- Discovery of possible neuron mirror systems in the human brain have been found by the fact that areas in motor cortex become excited when a person observes another do an action
- function of mirror neurons in human brains is much more extensive.



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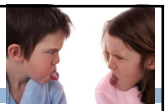

- **Function in terms of empathy:** mirror neurons are active when a person feels an emotion or witnesses another person expressing emotion, which could explain the feeling of empathy.
- **Function in terms of language:** Mirror neurons can be found near the language area of our brains, and could prove to be a valuable component of language learning.
- This discovery also supports the notion that language evolved from gesture understanding.

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- **Function in terms of planning:**
  Neurons' firing while observing an action can be helpful in planning one's actions, as the consequences of those actions can also be observed.
- **Function in terms of learning new movements**
  Mirror neurons in the pre-motor cortex are linked to neurons in the primary motor cortex, and by observing actions certain pathways between the mirror and motor neurons are strengthened.

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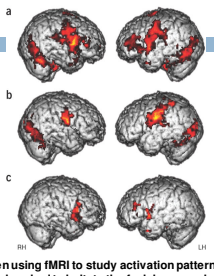
Study of the mirror neuron system in children with ASD compared with age- and IQ-matched typical children

- The children with autism showed **no mirror neuron activation** in the pars opercularis during either observation or imitation of emotional face expressions



When using fMRI to study activation patterns in people asked to imitate the facial expressions of others, control subjects (a) show markedly more activation than do ASD subjects (b). (C) represents areas where the differences in activation were significantly greater in controls, mainly the pars opercularis.

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Early teens and Adolescent

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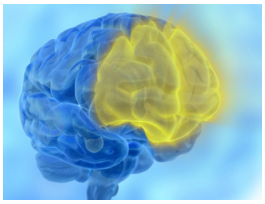
- During adolescence many other "executive functions" such as selective attention, working memory, problem solving, and multi-tasking improve steadily.
- Such executive functions are commonly related to the prefrontal cortex, fMRI studies indicate that broad networks of cortical regions are involved in these changes (e.g. Luna et al. 2004).



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Hadjikhani et al(2006)

- Detailed cortical map showing abnormally thin cortices in multiple superior parietal, temporal, frontal regions in adolescents with autism.
- These regions include the mirror neuron system

Second wave of deficits

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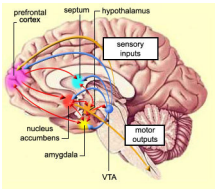
Functional MRI, and neuropsychologic studies of working memory and executive function in autism have revealed the emergence of new deficits in adolescence in autism, with the failure of frontal lobe skills to develop

- The higher order frontal lobe skills needed to cope with these life demands failed to develop in autism.



The Amygdala

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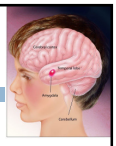

- Derived from the Greek for almond
- Amygdalae are essential to your ability to feel certain emotions and to perceive them in other people e.g fear
- It modulate our reactions to events that are very important for our survival.
- Also events that signal the presence of food, sexual partners, rivals, children in distress, and so on.

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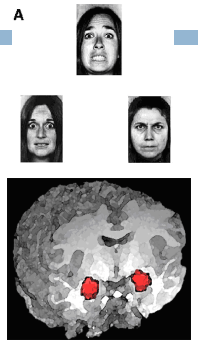
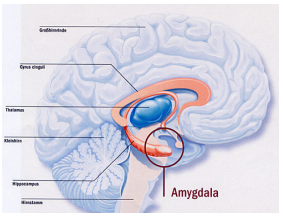
- Functional MRI studies indicate that the amygdala is involved in social cognition, in particular 'theory of mind' (the ability to attribute mental states to others)



The Amygdala

35

- Autistic individuals failed to show amygdala activation when required to interpret emotions based on the perception of another person's eye expression (Baron-Cohen et al.2000)
- A larger amygdala volume in 3-4 years old ASD has been found to predict worse social and communication skills several years later(Munson et al 2006, Arch Gen Psy)
- In adult ASD showed less functional neurons



The cerebellum

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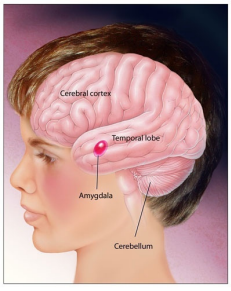
Cerebellum connects to cortical regions involved in emotional and cognitive functions.

- **A lack of integration and regulation of distributed brain functions** could lead to deficits in complex processes which require the recruitment of a variety of brain regions, such as language and social behaviour



The Cerebellum

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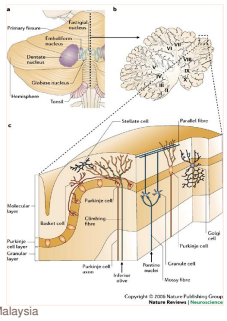
- Histological abnormalities of the cerebellum in ASD
- Recent meta-analysis evidence was found for **a global increase in cerebellum size in autistic individuals** (Stanfield et al., 2007).



The Role of the Cerebellum in the Pathophysiology and Treatment of Neuropsychiatric disorders: A review

Sylco S. Hoppenbrouwersa, et al (BRAIN RESEARCH REVIEWS 59 (2008) 185–200)

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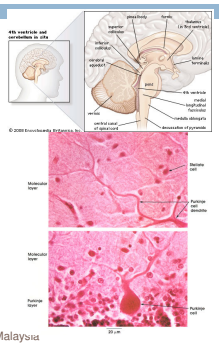
Clinical observations in patients with lesions confined to the cerebellum:

1) Executive dysfunction (e.g., working memory, planning)

2) visuo-spatial abnormalities (e.g., impairments in visual memory and visuo-spatial organization)

3) and linguistic dysfunction



The Basal Ganglia

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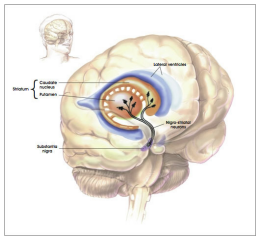
The basal ganglia as a whole are broadly responsible for **sensorimotor coordination,** including response **selection and initiation**

- An increase in volume was found in caudate volume.
- This finding was also recently reported in a study of individuals with autistic spectrum disorders in which the **size of the caudate** was found to correlate with the degree of restricted, repetitive behaviours



Corpus callosum

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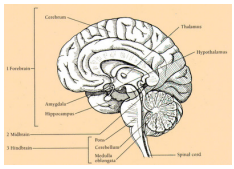
- The contrast between the increase in white matter volume and the decrease in corpus callosum size is notable.
- The neurobiological process affecting intra-hemispheric white matter spares inter-hemispheric white matter.
- The status of interhemispheric processing remains an unanswered but important research question.



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The structural imaging findings have led to the near general acceptance of autism as a disorder originating in the brain rather than in behavior, a subtle but significant distinction.

What causes it?

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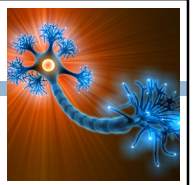
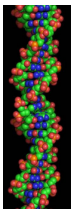
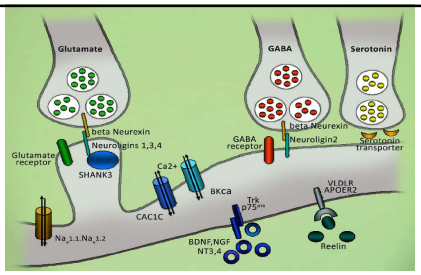


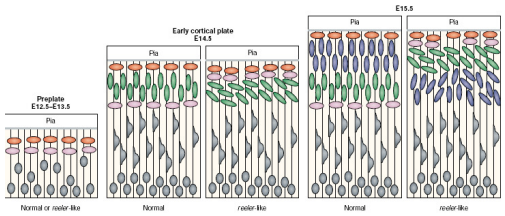


- Many molecular abnormalities observed in ASD patients impact on the **communication between neurons** and therefore support MBD (Multi-system Brain Disconnectivity-Dissynchrony) hypothesis of ASD.
- Genes implicated in synapse formation and synaptic plasticity.
- Neuroligins are cell adhesion molecules, localized post synaptically at glutamatergic or GABAergic synapses (Varoqueaux et al., 2006).



Selection of misexpressed genes in ASD brains. A subset of genetic abnormalities (reelin, neurotrophin family, etc.) impacts on neuronal migration and corticogenesis.

Another subset of genetic anomalies affects **synaptogenesis** (neuroligins, neurexins, Shank3) and **neurotransmission** (serotonin transporter, GABA and glutamate receptors, voltage-gated ion channels). As a consequence, neural networks and inter-neuron communication are disrupted



Schematic view of early cortical development in mice.

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Environmental Factor

- Environmental factors are suspected to disrupt the normal encephalogenesis by perturbing neurodevelopmental pathways and/or interacting with the neuroimmune system.
- Role of epigenetic misregulation not well studied

Gene & Environmental Interactions

Isaac et al

- Hereditary genetic vulnerability can amplify the adverse effect triggered by environmental exposures if both gene and environment converge to dysregulate the same neurotransmitter and/or signaling systems at critical times during development
- Pesticides- interfere with GABA-mediated neurotransmission
- A large number of priority chemicals of concern to human environmental health have been shown to affect the integrity of cellular Ca++ signals

- Children who are at risk of ASD (imbalance neuronal connectivity) are more susceptible to environmental triggers that affect the signaling pattern for neuronal connectivity, from early neuronal migration, axonal path finding to postnatal refining of neuronal connection

Gene & Environment

- Understanding on how low level chemical exposure influence molecular, cellular and behavioral outcomes relevant to the development of autism will enlighten geneticist, neuroscientist and immunologists about autism's complex etiology, and possibly yield novel intervention strategies

Neuroscience and Biobehavioral Reviews 33 (2009) 1227–1242

The comprehension of Neurobiology Neurophysio and Neuropsycho-pathology of ASD may open new avenue for the treatment of ASD

Thank You