Autism Update: New research, evidence-based intervention

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Selected New References

- Bourgeron, Thomas (2015) From the genetic architecture to synaptic plasticity in autism spectrum disorder. NATURE REVIEWS NEUROSCIENCE, VOLUME 16, SEPTEMBER 2015, 551-563
- Foxe, J. et al. (2013) Severe Multisensory Speech Integration Deficits in High-Functioning School-Aged Children with Autism Spectrum Disorder (ASD) and Their Resolution During Early Adolescence. *Cerebral Cortex Advance Access* published August 28, 2013
- Herbert, Martha (2014) Autism Brain Origins-Environment and Physiology Really Matter. Blog post July 2014 and summarized on Autism Speaks Website
- Jeste & Geschwind (2014) From Genes to Behaviour- a conceptual framework. *Nature Reviews Neurology* Volume: 10, Pages:74–81
- Krumm, N. et al., (2014) A *de novo* convergence of autism genetics and molecular neuroscience. *Trends Neurosci.* 2014 February ; 37(2): 95–105.
- Stoner, R., Chow, M. and Boyle, M. et al (2014) Patches of Disorganization in the Neocortex of Children with Autism. *New England Journal of Medicine*, **370**(13): 1209-1219
- Whitehouse, Lynn (2013) *Rethinking Autism.* New York: Academic Press

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Autism Prevalence

1 in 68 in US

1 in 45 in NJ

CDC 2014

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IDENTIFIED PREVALENCE OF ASD
ADDM Network 2000-2010
Combining Data from All Sites

Surveillance Yr	Birth Yr	#ADDM Sites	1 in X children
2000	1993	6	1 in 166
2001	1994	14	1 in 150
2004	1996	8	1 in 125
2006	1998	11	1 in 110
2008	2000	14	1 in 88
2010	2002	11	1 in 68

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ASD PREVALENCE
ADDM –Surveillance year 2010, Report year 2014

- Prevalence 5x more common in boys
  - 1:42 boys
  - 1:189 girls
- White > Black 30% higher
- White > Hispanic 50% higher

R. Huron, M.D. May, 2014

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So what is going on? What we know.

- Autism spectrum disorders are one of several neurodevelopmental disorders
  1. There are patches of disrupted cortical tissue
  2. There are problems with brain connectivity
  3. There is an imbalance in neural excitation and inhibition
  4. There are pruning deficits (over and under pruning)
  5. There are multisensory integration problems
- ASD's are polygenetic – meaning there are complex inherited and mutant genetic changes associated with ASD (and other neurodevelopmental disorders like seizure disorders, ID, and perhaps learning disabilities)
- ASD's are very heterogeneous disorders with tremendous diversity in severity and symptoms

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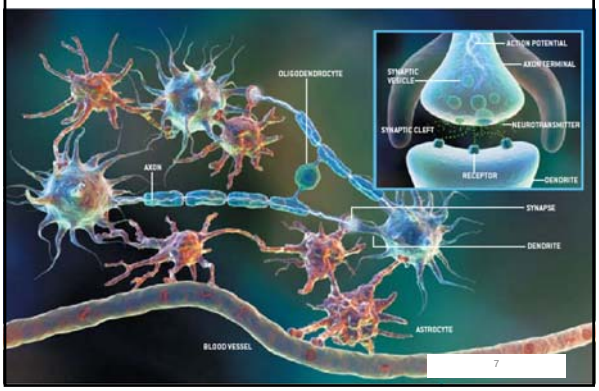
Reminder – How Synapses Work



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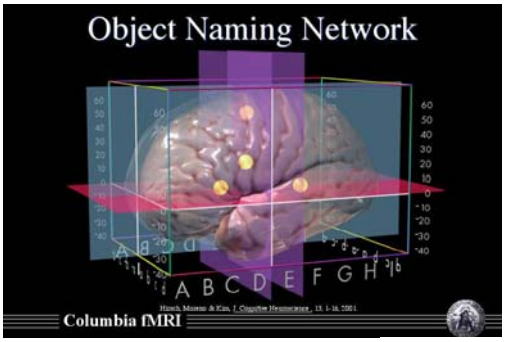
Reminder - Neurons that fire together wire together in networks



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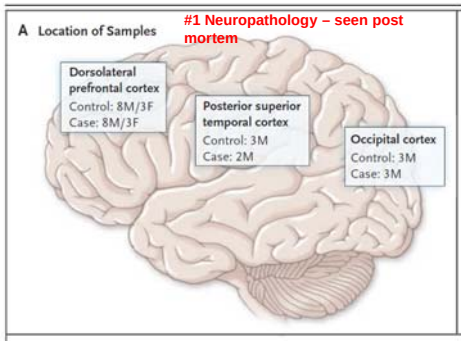

Stoner et al, 2014 findings : patches of disorganization in many areas of the neocortex (the outer layer of gray matter in the brain), though not the same from one person to the next.

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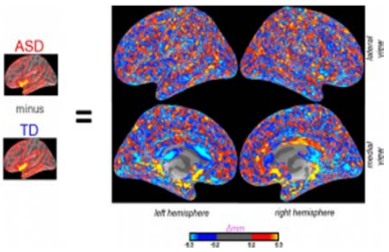
#1 Neuropathology (continued) - Seen on MRI (Herbert 2014)

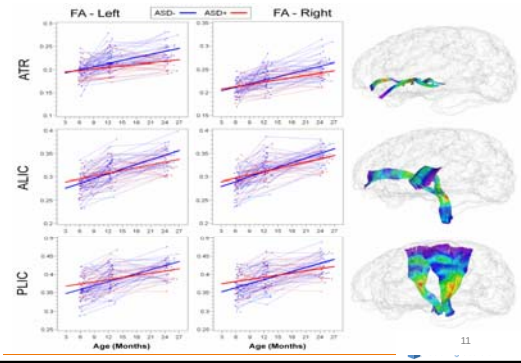


Herbert and colleagues have seen similar patches of cortical thinning and thickening on MRI images of children with ASD distributed all over the cortex (2014)

Neuropathology #2 – problems with connectivity

FIGURE 3.

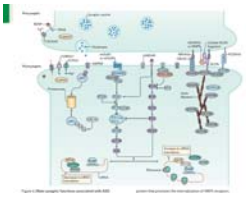
Trajectories of Mean Fractional Anisotropy for High-Risk Groups, Projection Fiber Tracts (Wolff, et al 2012)



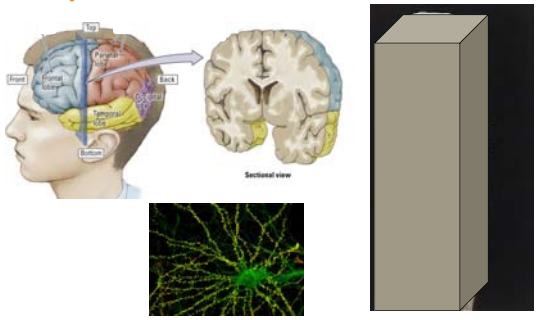
We have known about problems with excitation and inhibition for over a decade

- J. L. R. Rubensteinand M. M. Merzenich (2003) Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes and Behavior*
- Bourgeron 2015 Complex genetic mechanisms contribute to the disruption of synaptic homeostasis

- Figure 4 | **Main synaptic functions associated with ASD.**



Synaptic pruning fine-tunes *local* circuitry – over or under pruning would alter network development and function

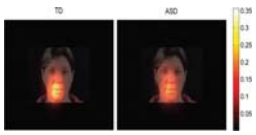


Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits

Tang, G. et. al. (2014) *Neuron* 83, 1–13, September 3

Multisensory integration problems

- Identified by OT's as sensory integration disorder
- Seen in speech integration with visual processing as well (Foxe et al, 2013)



Brief Primer on Genetics

- Genetic risk of autism increases with family history – prevalence of ASD-risk genes
- There are also more rare genetic mutations seen in individuals on the autism spectrum
- And, this is where is gets complicated – some genetic mutations may cause problems with neural connectivity by affecting synaptic plasticity

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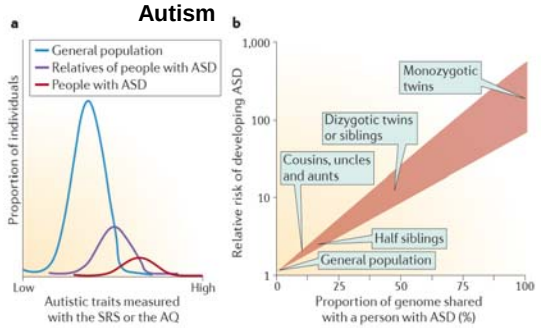
Genetic Risk of Autism



b | Twin and familial studies revealed that the relative risk of an individual developing ASD is proportional to the percentage of the genome shared with an individual diagnosed with ASD. Bourgeron 2015

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Understanding genetic mutations

- Genes are constantly replicating - gene copies are called ***Alleles***
- When genes replicate errors can occur
  - There are many potential sources of errors in replication and many potential diseases and disorders that result when replication goes awry
    - Cancer, for example, can result from replication errors that interfere with checks and balances in the cell that control proliferation.
  - *DeNovo (anew)* mutations in maternal or paternal cells, in stem cells, or during brain development, are seen in DNA samples of children with ASD

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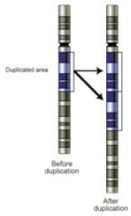
Copy Number Variations (CNV's) vs. Single Nucleotide Variants



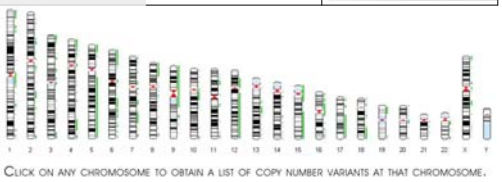
- This gene duplication has created a copy-number variation. The chromosome now has two copies of this section of DNA, rather than one
- CNVs may either be inherited or caused by ***de novo*** mutation (not inherited my mother or father)
- Contribute to risk of ASD's

https://gene.sfari.org/autdb/Welcome.do

Latest Statistics
(Updated June, 2015)

# of Genes: 740

EXPLORE COPY NUMBER VARIANTS



CLICK ON ANY CHROMOSOME TO OBTAIN A LIST OF COPY NUMBER VARIANTS AT THAT CHROMOSOME.

Studies of Autism Spectrum Disorders (ASD) have uncovered many potential candidate genes. The Human Gene module of SFARI Gene serves as a comprehensive, up-to-date reference for all known human genes associated with autism spectrum disorders (ASD). The content of the Human Gene module originates entirely from manual curation of published scientific literature by our expert researchers.

Figure 2 | **The interplay between rare mutations and genetic background**

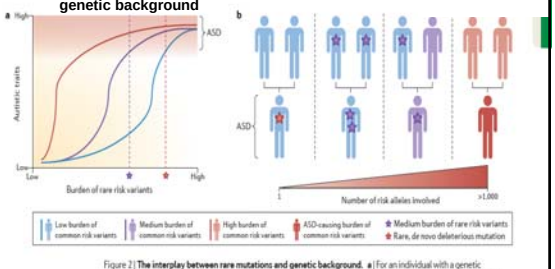


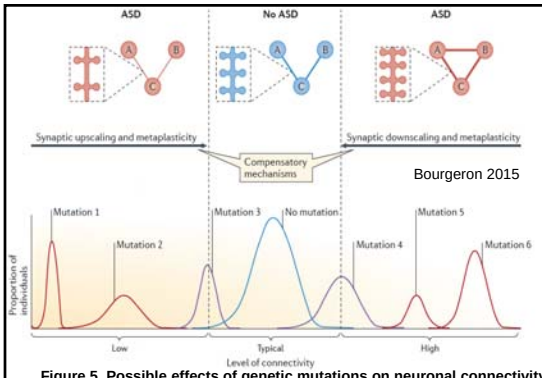
Figure 2 | **The interplay between rare mutations and genetic background.** **a** | For an individual with a genetic

b | The transmission of ASD may occur through one of various paths. A *de novo* highly penetrant mutation can cause ASD even in individuals with a high genetic buffer for ASD (far left).
ASD may also arise in children if both parents have a medium burden of rare variants (left-of-middle) or if one parent has a medium load of common risk variants for ASD and one has medium burden of rare risk variants (right-of-middle).
Finally, children might develop ASD if both parents have a hig
risk variants (far right)

Bourgeron 2015

Now the complicated part (Bourgeron, 2015)

- Neuronal genes are very large
- Neuronal activity regulates ASD-risk genes and the proteins they encode
- These proteins modulate synaptic plasticity
  - They increase or decrease the number and strength of synapses



Bourgeron 2015

Figure 5. Possible effects of genetic mutations on neuronal connectivity in ASD.

The 'typical' neuronal network, neurons A and B are equally connected to neuron C (center). The presence of an autism spectrum disorder (ASD)-linked mutation may decrease (left) or increase (right) synaptic strength or efficacy

SO: ASD's are very heterogeneous

- But, what do all of these children have in common?
  - *Problems with synaptic plasticity and homeostasis*
  - For certain affecting regions of the temporal lobe and frontal lobe – probably more widely dispersed
- What can be done?
  - Behavioral treatments must be individualized to the child's specific problems
  - Exercises must be very repetitive to compete with non-adaptive networks
  - Neuroscience designed technological interventions designed to drive repetitive adaptive synaptic stimulation across overlapping cognitive domains will:
    - Create build and stabilize adaptive attention, social and language synaptic networks
    - Improve homeostasis

The ASD Research

- 34 professionals across the country
- 100 children
  - must have worked with Fast ForWord for at least 20 days
  - must have been diagnosed within the Autism Spectrum by a medical professional
- Two types of information
  - Age equivalent test scores before and after treatment
  - Results of a functional skills checklist

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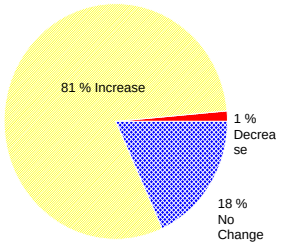
Changes in Attention After Fast ForWord Training

(73% response rate)



Attention

- for testing
- for computer activities
- for structured therapy activities
- for listening to stories
- for group activities

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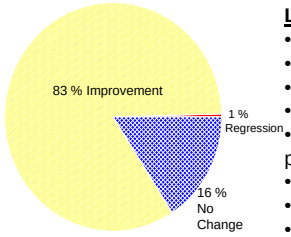
Changes in Language After Fast ForWord Training

(86% response rate)



Language

- response time
- following directions
- understanding humor
- overall comprehension
- imitation skills for words & phrases
- use of new vocabulary
- length in utterance
- answering questions - Y / N
- answering questions - WH
- verbal fluency - flow of speech
- overall expression

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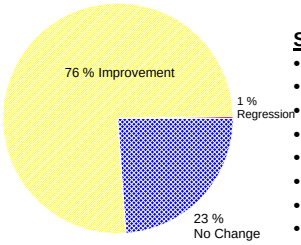
Changes in Social Skills After Fast ForWord Training
(88% response rate)



Social/Communication skills

- eye contact
- addressing people by name
- topic maintenance
- appropriate attention-getting
- greetings / closures
- appropriate protesting / refusal
- ability to verbally negotiate
- initiation of communication

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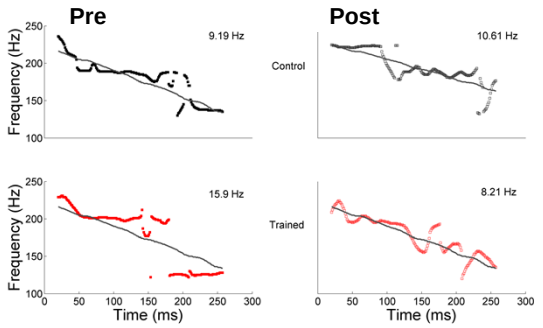
Russo, Hornickel, Nicol, Zecker, & Kraus, 2010

Improved pitch tracking



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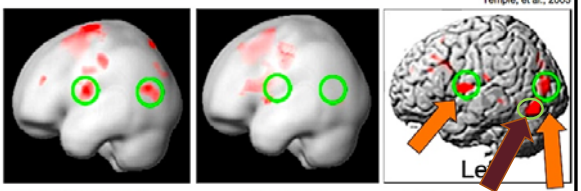
Reading Program Changes Activation of Specific Brain Areas

Brain Areas Critical For Reading

Temple, et al., 2003



Typical 7 year old reader

Struggling Reader

After Retraining

Six weeks - 90 min/day – five days a week

30

Reading results – fast.
Results that last.

Fast ForWord®

Language and literacy intervention that uses the principles of neuroplasticity to target the root cause of slow reading progress – for fast reading progress.

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