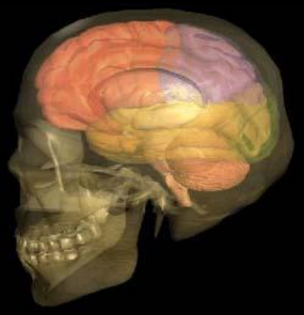
Reading Disability Alone and Reading Disability Alongside Giftedness: An Overview on Genetics and Neurology for Practitioners

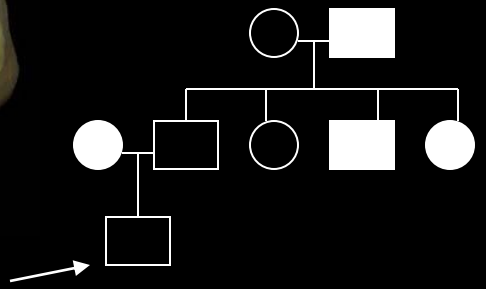
The Help Group *Summit 2013 Advances and Best Practices in Autism-Learning Disabilities-ADHD*

Jeffrey W. Gilger, PhD
October, 2013
University of California, Merced
Email = jgilger@merced.edu

Outline

1. **Review of Concepts**
2. **Family Studies of Dyslexia/Developmental Reading Disorder (RD) Genetics**
3. **Complex Associations: RD and Nonverbal or Spatial Giftedness (2e)**
4. **Closing Comment on Future Work and Clinical Implications**

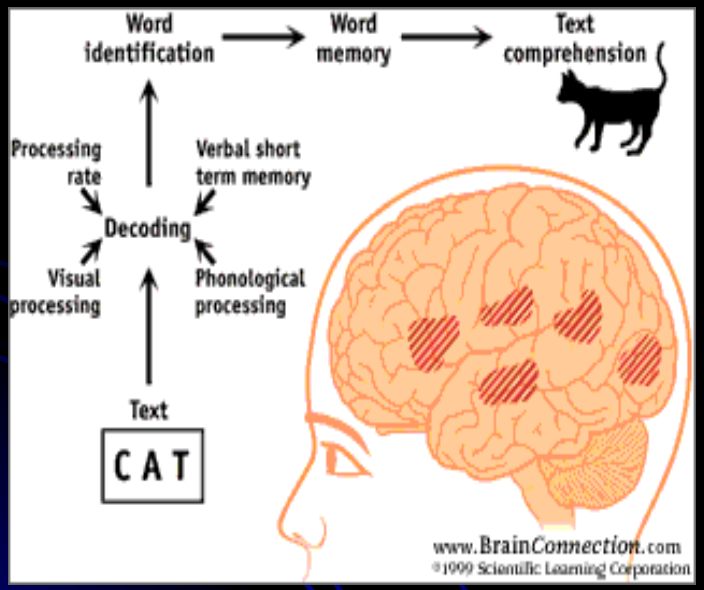




Learning Disorders Can Take Different Forms

- Reading or Dyslexia
- Attention and/or Activity
- Motor Coordination
- Math
- Language
- Writing
- Memory
- Nonverbal
- Comorbidity & Other

Dyslexia (RD) is an unexplained inability to learn to read (write, spell) in accordance with age and/or IQ expectations



Developmental Reading Disorder (RD)

- Prevalence is 5%-10%
- Sex ratio is 3.5:1 in clinical samples and 1.5:1 in samples controlling for ascertainment biases
- Associated with: language, math, verbal memory, attention disorders, self esteem, comprehension, etc.

Review

Definition of a Gene

- …a transmissible unit of inheritance that occupies a specific locus on a chromosome and that directly or indirectly influences phenotypes, the expression of other genes, and/or the development and modification of proteins...

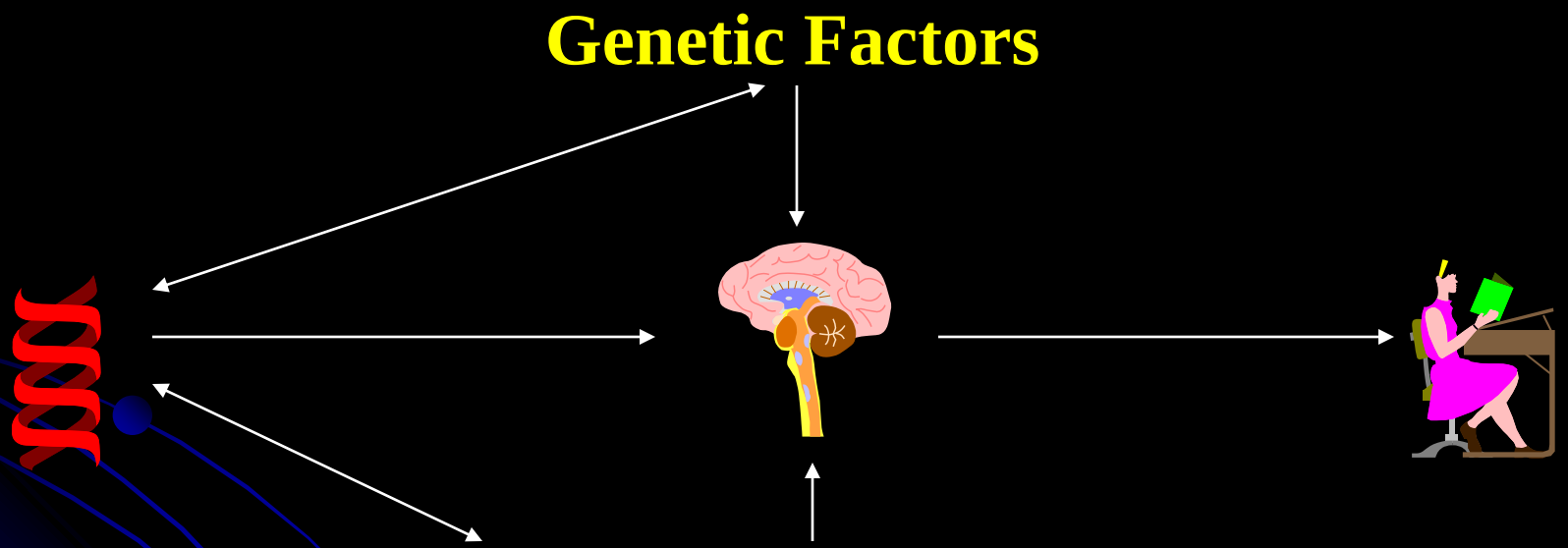
Who Cares?

- Etiology
- Diagnosis and prognosis
- Research of the learning process
- Differential diagnosis
- Remediation implications

Risk

- Risk is a probabilistic statement
- Risk can fluctuate over time
- Risk varies as a function of environmental and genetic factors
- Risk can shift person-to-person, place-to-place

A Behavior Like Reading is a Complex Cognitive Phenomenon That Involves Many Genetic and Nongenetic Factors ...



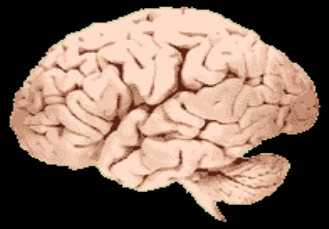
Conception….Childhood….Adulthood

Facts about the Human Genome

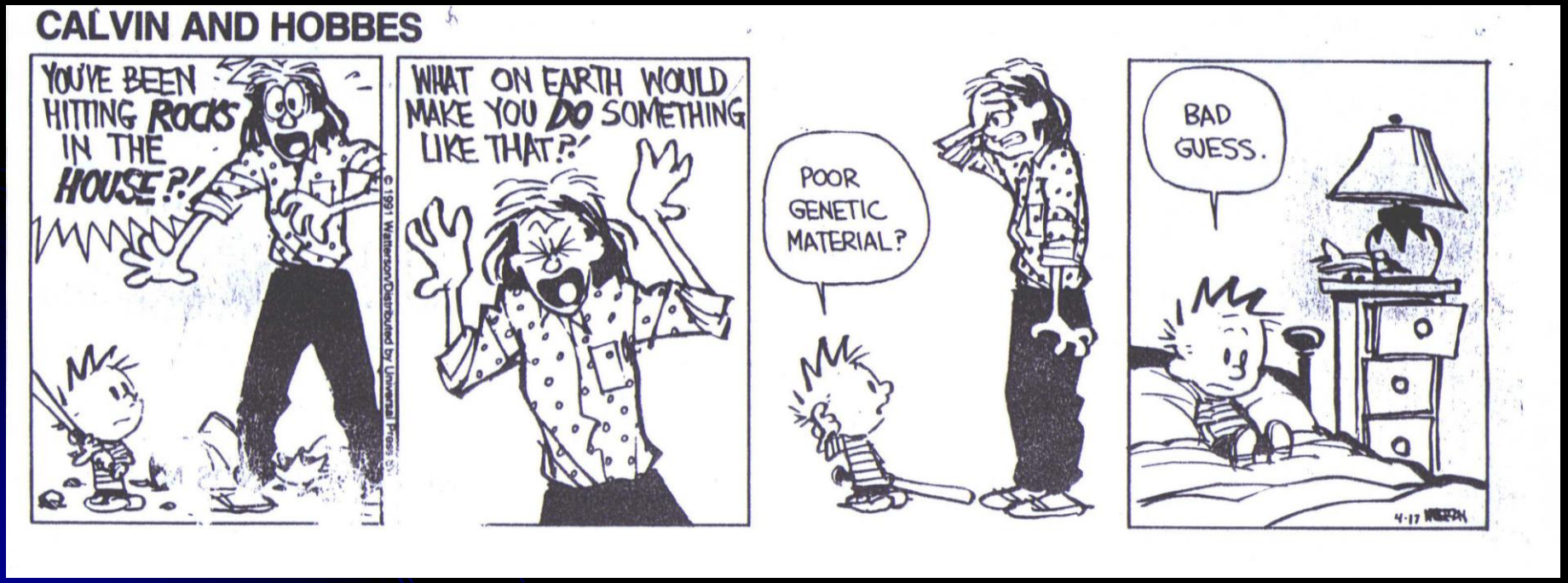
- 3 billion base pairs
- **22,000** or so nuclear genes
- 30% unique to the CNS
- Remaining 70% in CNS and elsewhere

- “Complete” map exists
- As organic beings all behaviors have a genetic component

The Brain is the Basis of All Behavior

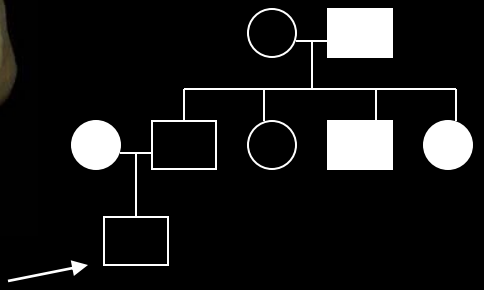


- **Genetic effects have been empirically identified for a variety of complex human traits**



Outline

1. Review of Concepts
2. **Family Studies of Dyslexia/Developmental Reading Disorder (RD) Genetics**
3. Complex Associations: RD and Nonverbal or Spatial Giftedness (2e)
4. Closing Comment on Future Work and Clinical Implications



Types of Questions

Simple Etiology

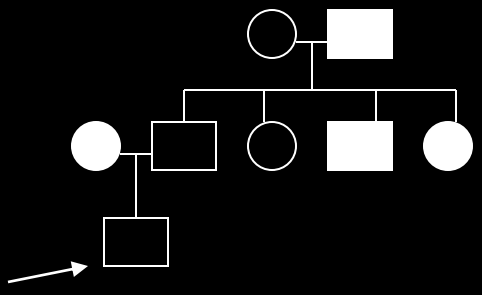
- Is it genetic?
- Where/what are the genes for it?
- What are the nongenetic factors?

Theory Driven

- What is the best definition or assessment?
- What accounts for comorbidity?
- How do genes and environments influence specific components of reading?

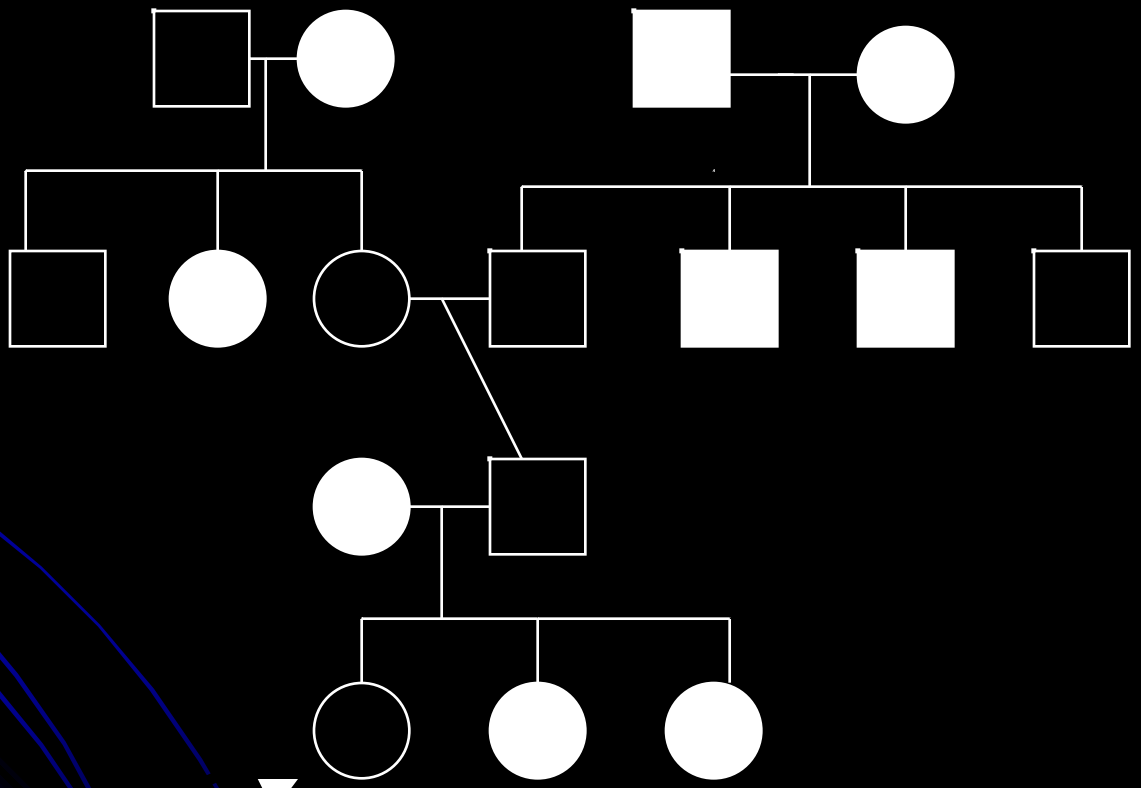
Basic Questions in Simple Genetics

- **Is the trait familial?**
- **Is this familial aggregation genetic?**
- **What is the mode by which this genetic factor (s) is transmitted?**
- **Where is the gene located and how can it be characterized?**



Is RD Familial?

Pedigree Showing RD Aggregation

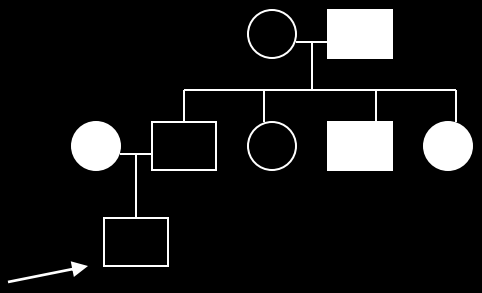


Summary: RD Family Risk Studies

- Population risk = 5%-10%
- 20%-60% rates in first degree relatives (50% average)
- Compensation effects: parents who had compensated reduced the risk for RD in their offspring by half
- More girls than boys “compensate” for their childhood reading problem, and overall, roughly 20% Of RD children “compensate” with age

Basic Questions in Simple Genetics

- Is the trait familial? YES!
- Is this familial aggregation genetic?
- What is the mode by which this genetic factor (s) is transmitted?
- Where is the gene located and how can it be characterized?



Is Familial Transmission Genetic? Summary: Twin Studies

- **Heritabilities for RD or reading-related abilities approximate .50**

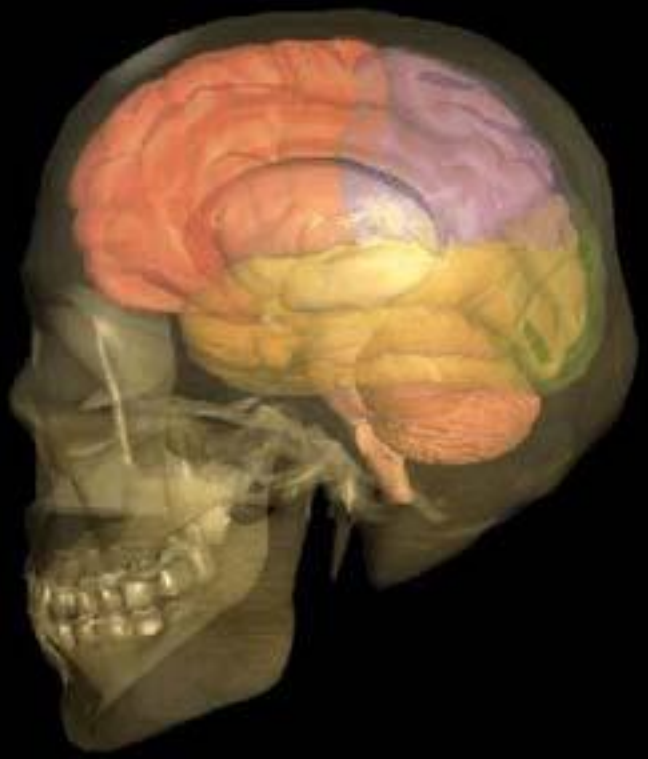
- **Some suggestion that different components of reading are differentially influenced by genes and environments**

Dizygotic Twins = 50% Genetic Similarity

Monozygotic Twins = 100% Genetic Similarity

Environment

Nothing

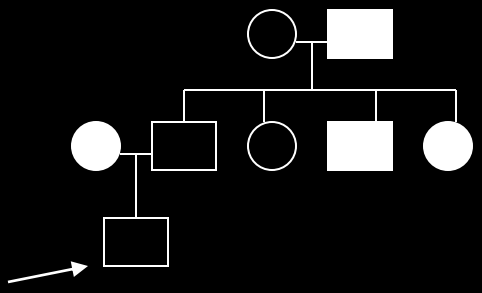


Nothing

Genetics <= 50% and Environment <= 50%

Basic Questions in Simple Genetics

- Is the trait familial? YES!
- Is this familial aggregation genetic? YES!
- What is the mode by which this genetic factor (s) is transmitted?
- Where is the gene located and how can it be characterized?



If Genetic, How is The Risk Factor Transmitted?

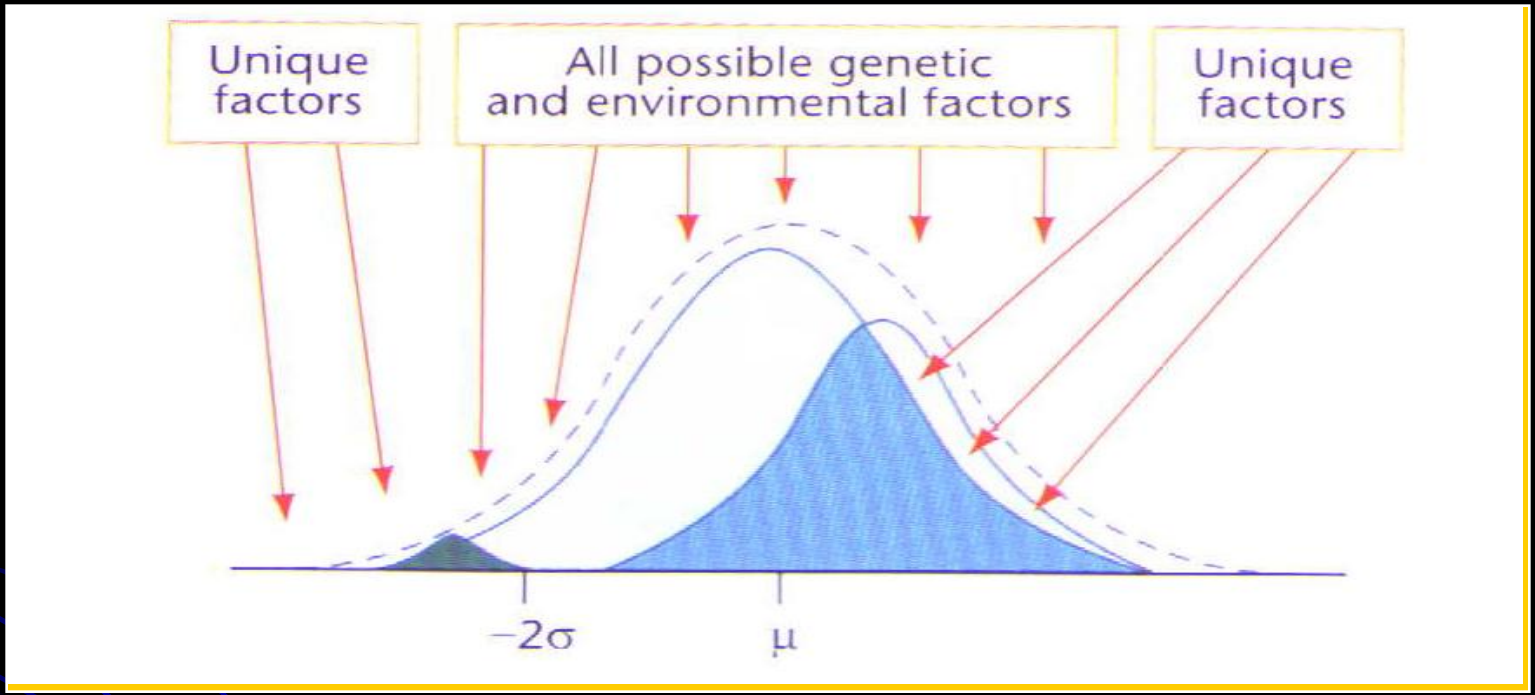
Summary of Segregation Studies

Major genes or limited number of genes
Not polygenic

Some variable expressivity

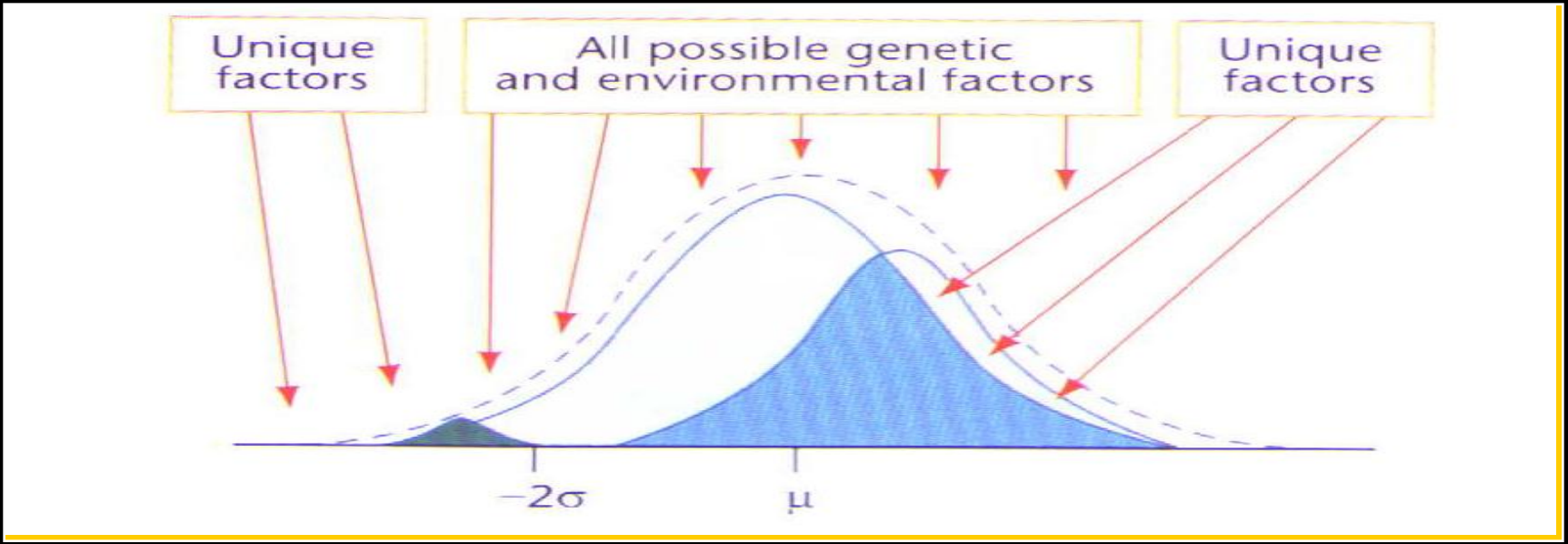
Some reduced penetrance

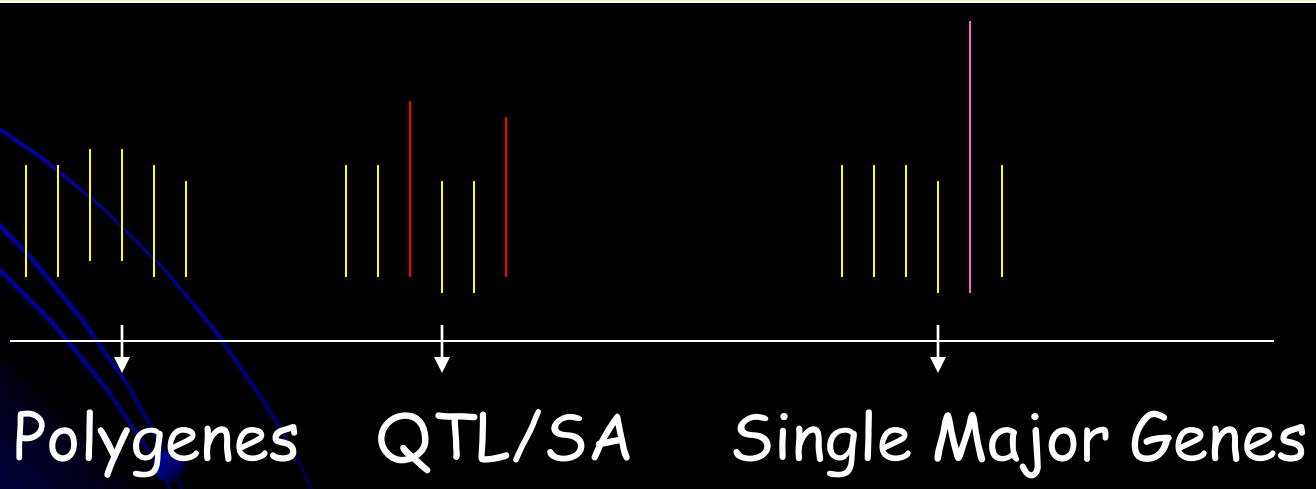
Similar parameters for families ascertained through normal readers



Distinct Etiology?

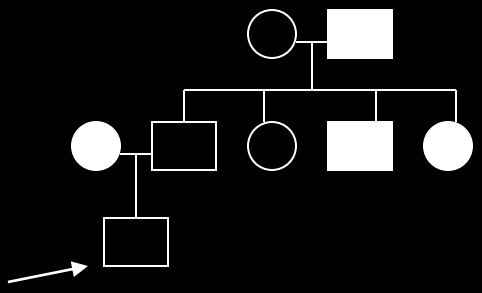
Implications of Gene Searches: Variance Added to the Continuum by QTL or Susceptibility Alleles





Basic Questions in Simple Genetics

- Is the trait familial? YES!
- Is this familial aggregation genetic? YES!
- What is the mode by which this genetic factor (s) is transmitted? One or More Significant Genes!
- Where is the gene located and how can it be characterized?



What and Where Are the Specific Risk Genes for RD?

Molecular Genetic Work

Two Basic & Complimentary Methods

- Gene searches, mapping or linkage work
- Candidate gene searches

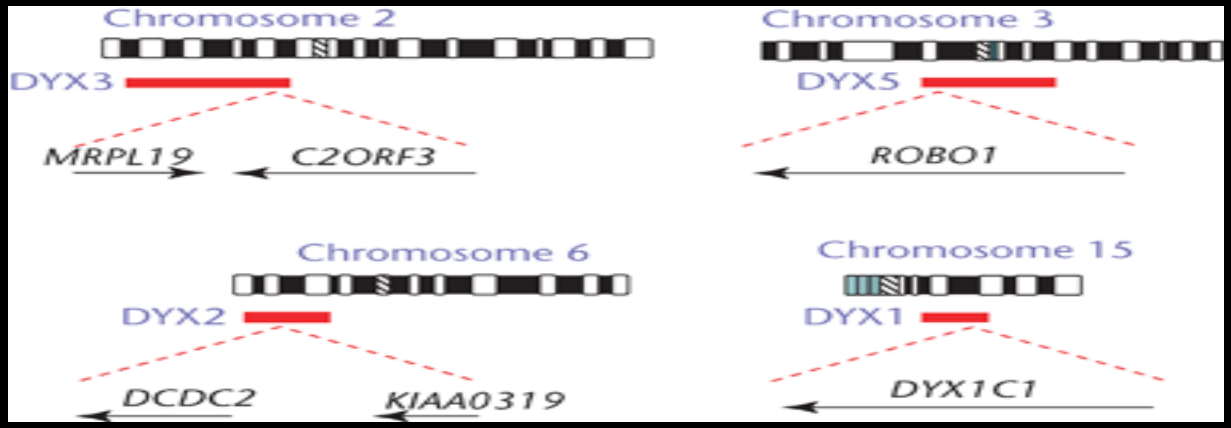
Summary: Linkage and Gene Characterization Studies for RD/LD

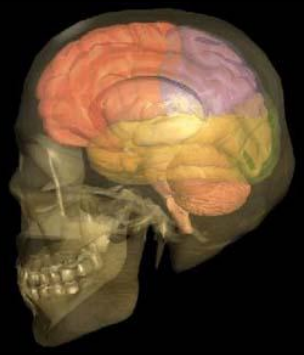
- Chromosome 1
- Chromosome 2
- Chromosome 3
- Chromosome 6
- Chromosome 7
- Chromosome 13
- Chromosome 15
- Chromosome 16
- Chromosome 18
- Chromosome 19
- Chromosome X
- Gene associations to specific cognitive traits

Locus	Region	Population	Phenotype
DYX8	1p36	N. Carolina	Phonological Decoding, RAN
DYX3	2p11	Norway	Reading and Spelling
DYX5	3c	Finland	Phonologic Awareness
DYX2	6p22	N. Carolina	Phonemic Awareness
		Colorado, UK	Orthographic Choice, Phonologic Decoding
DYX4	6q11-2	Canada	Phonologic Decoding
	7q32	Norway	Reading and Spelling
DYX7	11p15.5	Canada	Phonologic Decoding
DYX1	15q21	N. Carolina	Single Word Reading
		Germany	Spelling
		Norway	Reading and Spelling
DYX6	18p11	Colorado, UK	Single word reading, Orthographic Coding
DYX9	Xq27.3	Colorado, UK, Holland	Multiple phenotypes

Courtesy of Shelley Smith

Promising Gene Linkages and Gene Candidates





Promising Gene Linkages and Gene Candidates

- **Chromosome 3:**

  ROBO1: Axon guidance, across midline and hemispheres

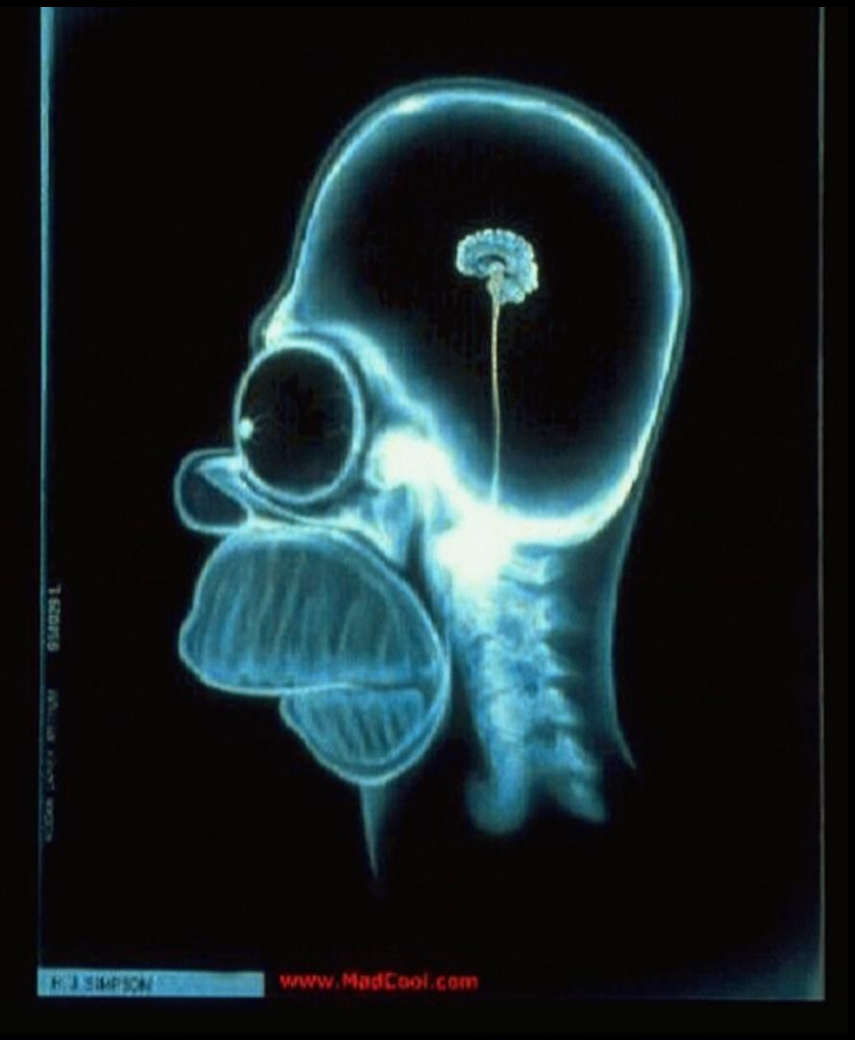
- **Chromosome 6:**

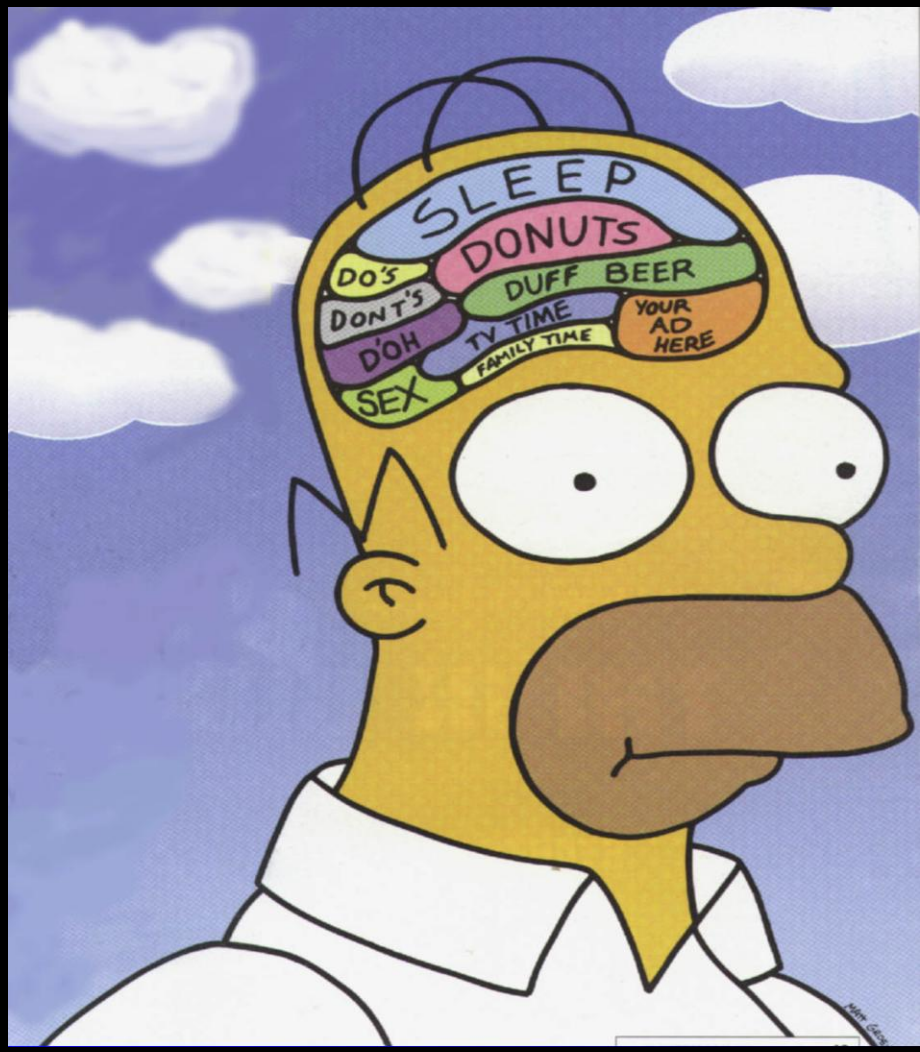
  DCDC2: Neuronal migration to cortex, expressed in thalamus as well

- **Chromosome 15**

  DYX1C1: Expressed in brain

Structural Imaging vs. Functional Imaging





Summary of Some Common Functional Findings

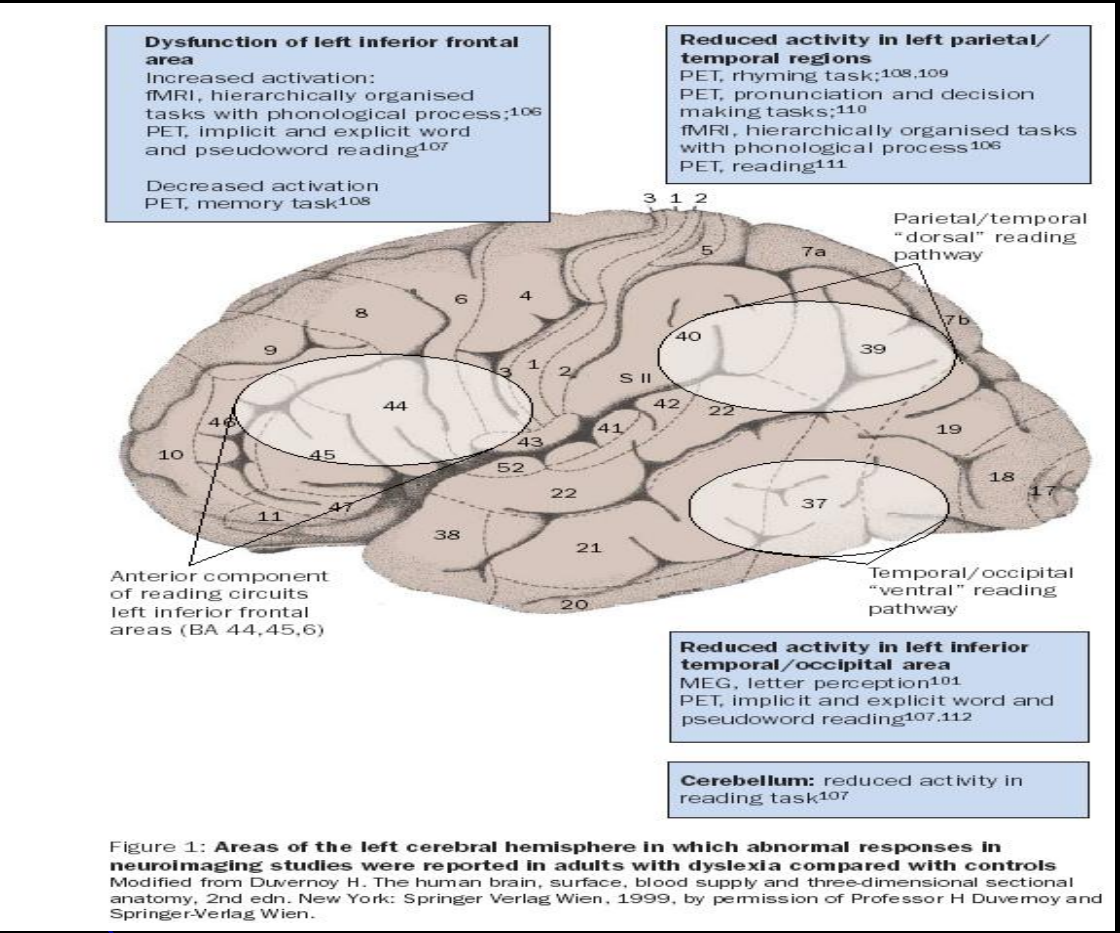
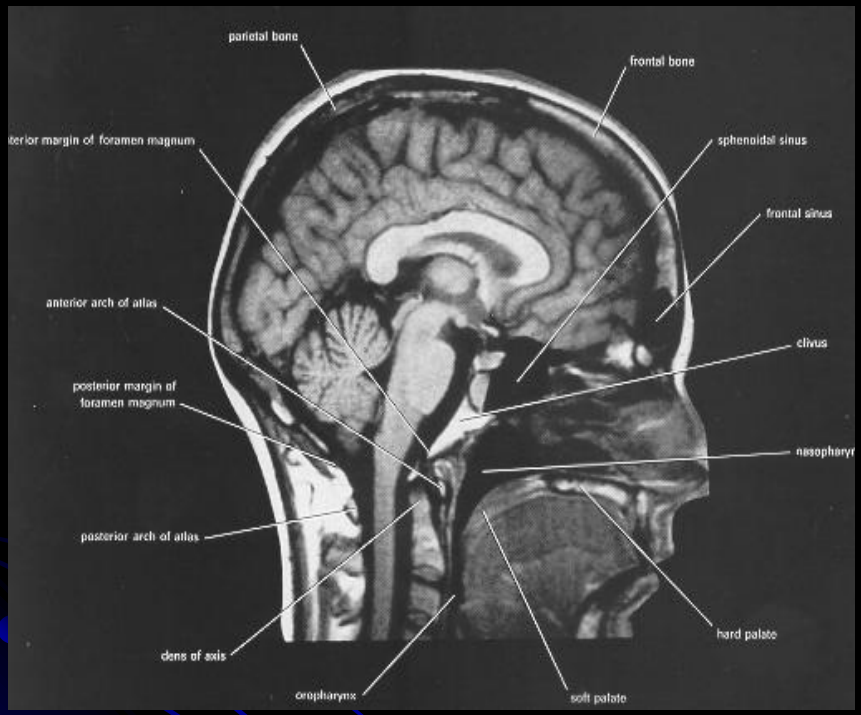


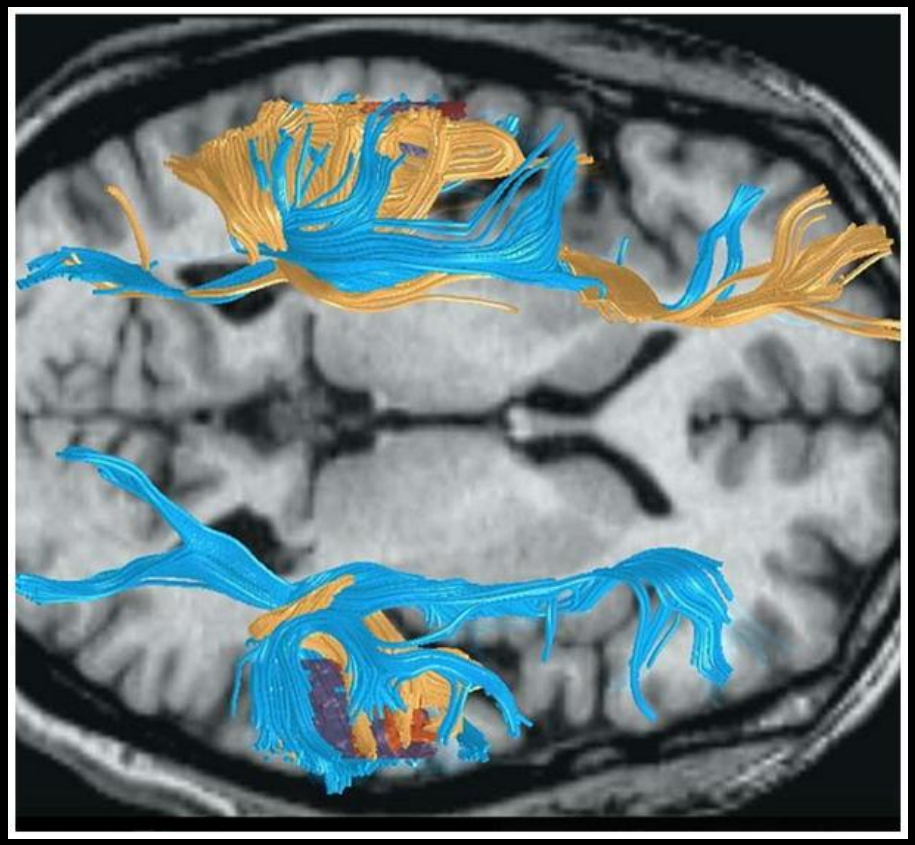
Figure 1: **Areas of the left cerebral hemisphere in which abnormal responses in neuroimaging studies were reported in adults with dyslexia compared with controls**
Modified from Duvernoy H. The human brain, surface, blood supply and three-dimensional sectional anatomy, 2nd edn. New York: Springer Verlag Wien, 1999, by permission of Professor H Duvernoy and Springer-Verlag Wien.

Functions Related to Reading in Adults and Children

Demonet, Taylor, & Chaix (2004). Lancet, 363, 1451-1460.

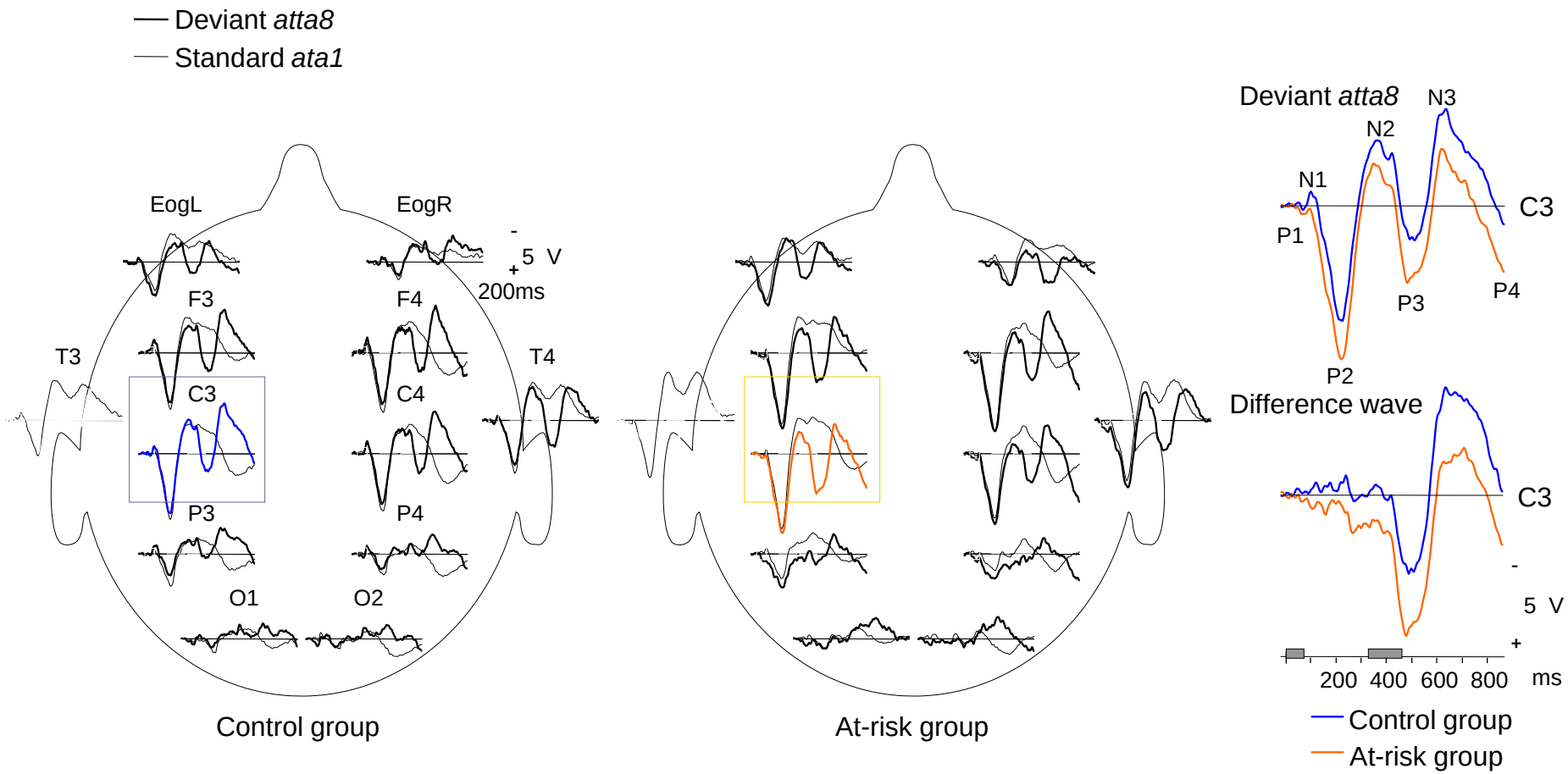
Summary of Some Structural Findings





Christiana M. Leonard, Mark A. Eckert (2008). Developmental Neuropsychology, 33 (6)

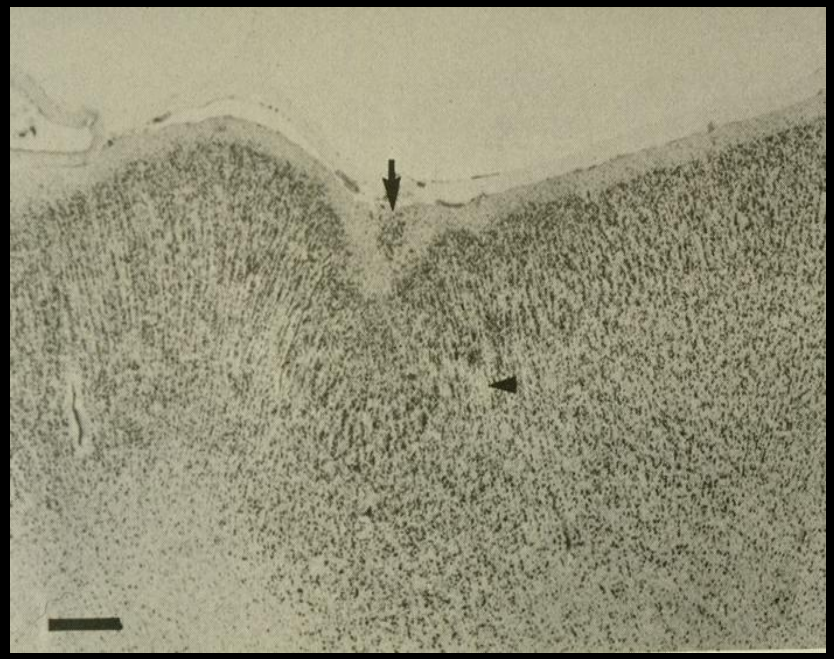
Evidence That Brain Differences Exist Early On



From Lyytinen & Leppanen

Even Before Birth: Structural Differences in Dyslexia

- An example from Galaburda et al. (1985) that shows a collection of neurons in Layer 1 of the cortex (cell free layer)
- These migration errors most likely occur in the 5 – 7th month of fetal development



Other structural differences as well!

How We Started Out & Where We Are Now

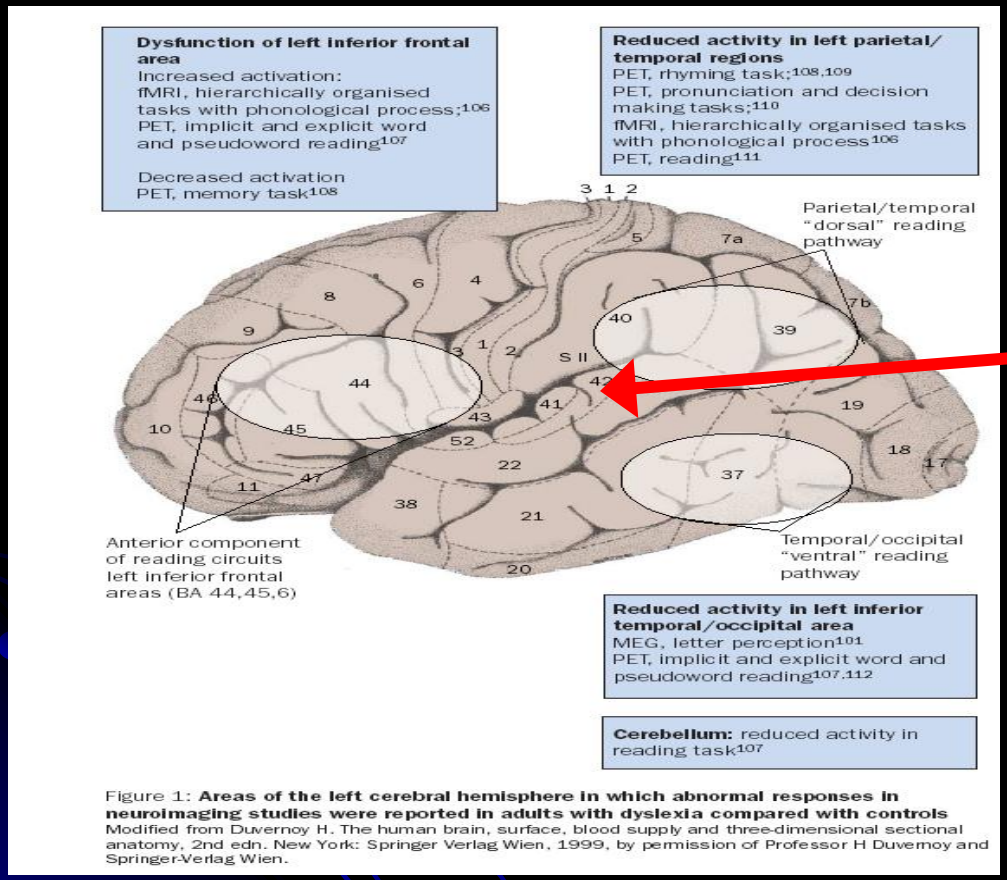


Figure 1: **Areas of the left cerebral hemisphere in which abnormal responses in neuroimaging studies were reported in adults with dyslexia compared with controls**
Modified from Duvernoy H. The human brain, surface, blood supply and three-dimensional sectional anatomy, 2nd edn. New York: Springer Verlag Wien, 1999, by permission of Professor H Duvernoy and Springer-Verlag Wien.

Demonet, Taylor, & Chaix (2004). Lancet, 363, 1451-1460.

Family Studies

Summary & Future Directions

- Theoretically possible to identify key genes
- Difficult task in identifying gene operations

Summary & Future Directions

- Unlikely (in near future) that a classic type of gene therapy will result
- Other therapies are more likely and best practices now involve certain reading remediation programs

A36 YT THE NEW YORK TIMES **NATIONAL** SATURDAY, OCTOBER 29, 2005

Scientists Tie Two Additional Genes to Dyslexia

By SANDRA BLAKESLEE

One year after scientists discovered a gene whose flaw contributes to dyslexia, scientists have now identified two more such genes.

The findings, described yesterday at a meeting of the American Society of Human Genetics in Salt Lake City, strongly support the idea that many people deemed simply lazy or stupid because of their severe reading problems may instead have a genetic disorder that interfered with the wiring of their brains before birth.

"I am ecstatic about this research," said Dr. Albert M. Galaburda of Harvard Medical School, a leading authority on developmental disorders who was not involved in the latest discoveries.

The findings, added to last year's, mean that for the first time, "we have a link between genes, brain development and a complex behavioral syndrome," Dr. Galaburda said.

As many as a dozen genes are probably involved in the disorder, he said, with each playing a role in the necessary migration of neurons as the brain's circuitry develops.

Researchers said a genetic test for dyslexia should be available within a year or less. Children in families that have a history of the disorder could then be tested, with a cheek swab, before they are exposed to reading instruction. If children carry a genetic risk, they could be placed in early intervention programs.

"Reading ability is a proxy for intelligence in American culture," said Dr. Sally E. Shaywitz of Yale University School of Medicine, a pediatrician who is an expert on dyslexia. The findings should help overcome stereotypes and get children the assistance they need, she said.

One of the genes newly linked to dyslexia is called DCDC2. It is active in reading centers in the human brain, said Dr. Jeffrey R. Gruen, a Yale geneticist who described the discovery at a news conference yesterday. Large deletions in a regulatory region of the gene were found in one of every five dyslexics tested, making it less active.

Fluent readers and dyslexics alike have the protein made by this gene, Dr. Gruen said, but it is less abundant in dyslexic brains. The function of the protein is not known, he said.

Rats also have the DCDC2 gene, so it should not be misconstrued as a spelling or reading gene, Dr. Gruen said. Rather, the gene supports the circuitry that underlies reading. When it was perturbed in unborn rats, he said, neurons migrated shorter distances, undercutting early brain development.

The second gene, called Robo1, was discovered by Dr. Juha Kere, a professor of molecular genetics at the Karolinska Institute in Stockholm. It is a developmental gene that guides connections, called axons, between the brain's two hemispheres, Dr. Kere said in an interview.

When the gene's activity is reduced, the number of finer connections, called dendrites, is reduced in brain areas involved in reading.

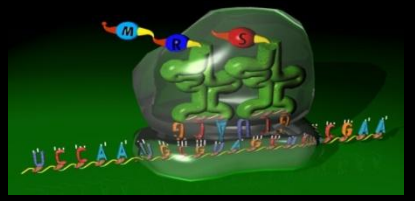
"You get the right signals going, but they do less well in terms of rapid processing," Dr. Kere said.

Many dyslexia experts believe that reading problems stem from an inability to process the fast sounds of spoken words.

Gene-Based Therapies for RD

Treatments Operating on Different Levels of a Genetic System

DNA/Genes for Risk	←	Level 1 Gene Therapy
Gene Products Atypical Neurochemical Effects	↔	Level 2 Pharmacologic Therapy
RI or LI Clinical Symptoms	←	Level 3 Environmental & Instructional Therapy



Gilger, J. (I2013). In Handbook on Language and Literacy: Development and Disorders (2nd Ed.), Guilford Press.

Applications of Family History and Genetic Data

(see Gilger. J. W. (2004). From Mice to Men: The role of our genes on the risk for reading-related disorders. IDA Perspectives, Summer Issue; or go to www.interdys.org

Diagnosis

- Risk Prediction
- Differential Diagnosis

Prognosis

- Recovery or Compensation

Guide for Assessment & Therapy

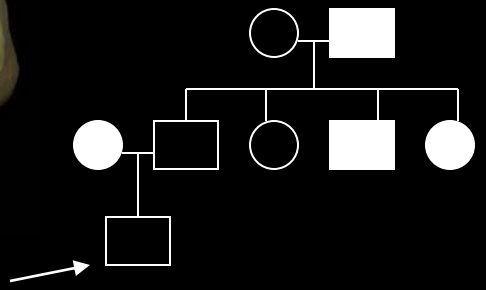
- Family Profiles and Interventions

Gene vs. Environment Question, Reactions & Attitudes

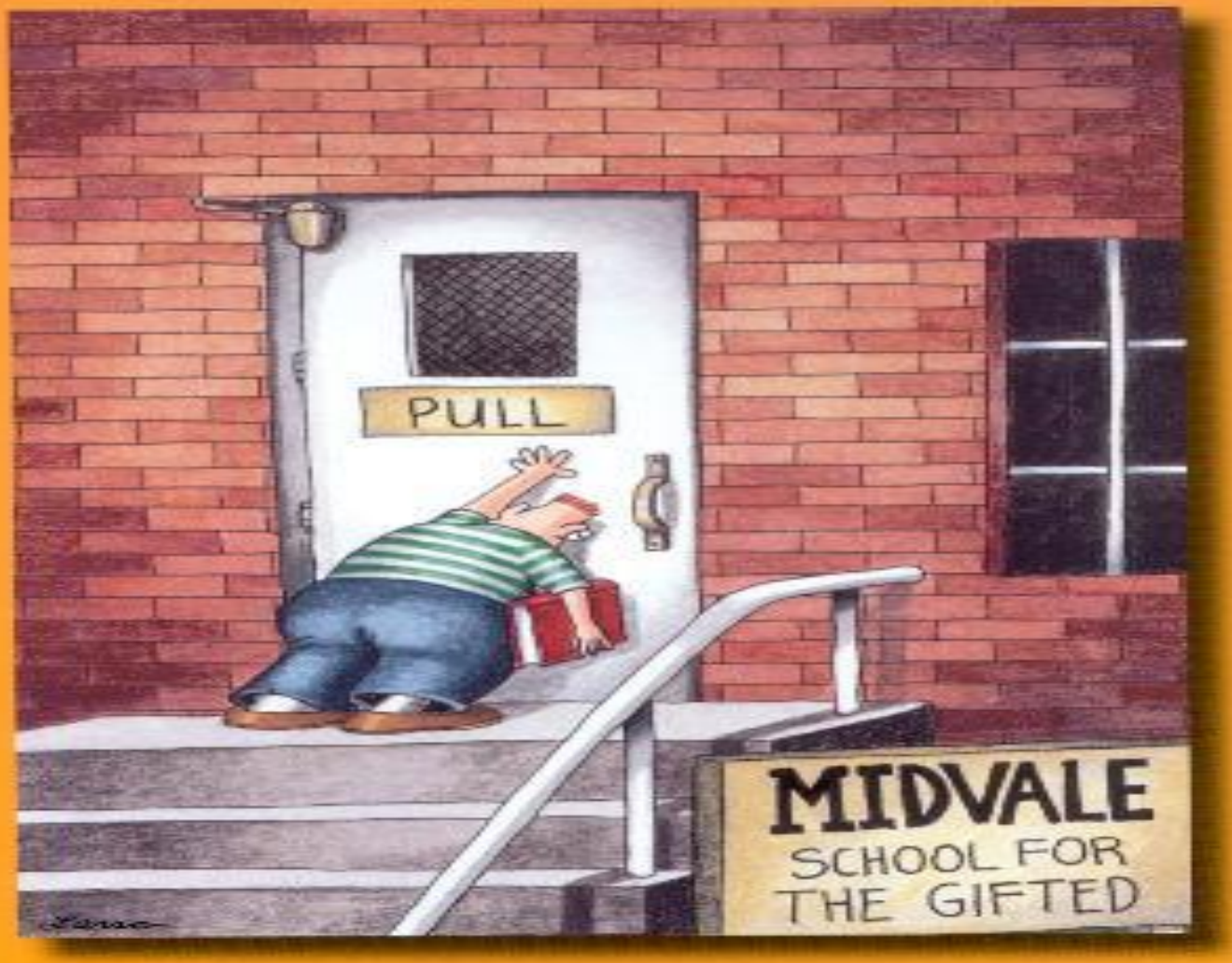
- Assignment of Etiological Blame
- Family/Therapist Dynamics and Attitudes

Outline

1. Review of Concepts
2. Family Studies of Dyslexia/Developmental Reading Disorder (RD) Genetics
3. **Complex Associations: RD and Nonverbal or Spatial Giftedness (2e)**
4. Closing Comment on Future Work and Clinical Implications



Even Gifted People Have “issues”



The Stereotype of the Gifted Youth

Precocious Compared to Peers

Advanced Motor Skills

Advanced Cognitive Interests

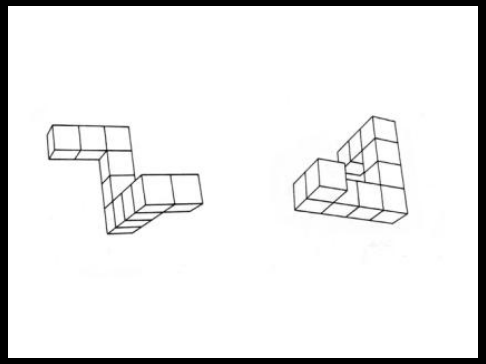
Advanced Ability to Deal With Complex Information

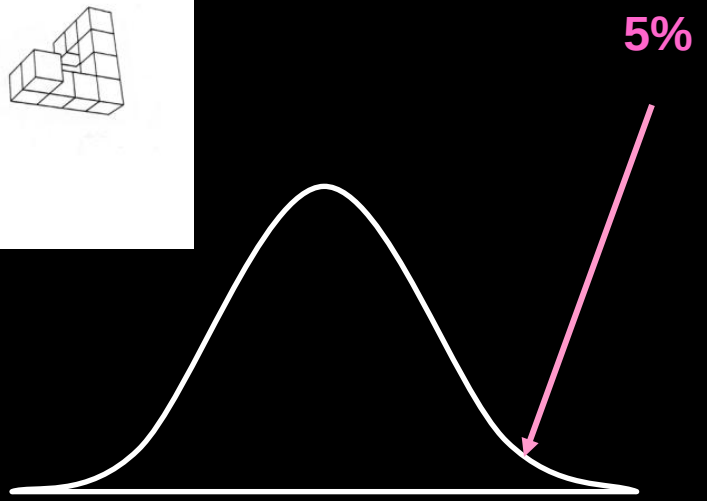
Some one's 2.5 year old child

Complex Associations: RD and Nonverbal or Spatial Giftedness (2e)

Nonverbal (spatial) abilities are those skills that involve mental manipulation of objects, forms or shapes, spatial coordination, nonverbally mediated Gestalt processing, visual memory, other

- Practice effects
- Genetics
- Hormones
- Gender
- Culture
- Etc.





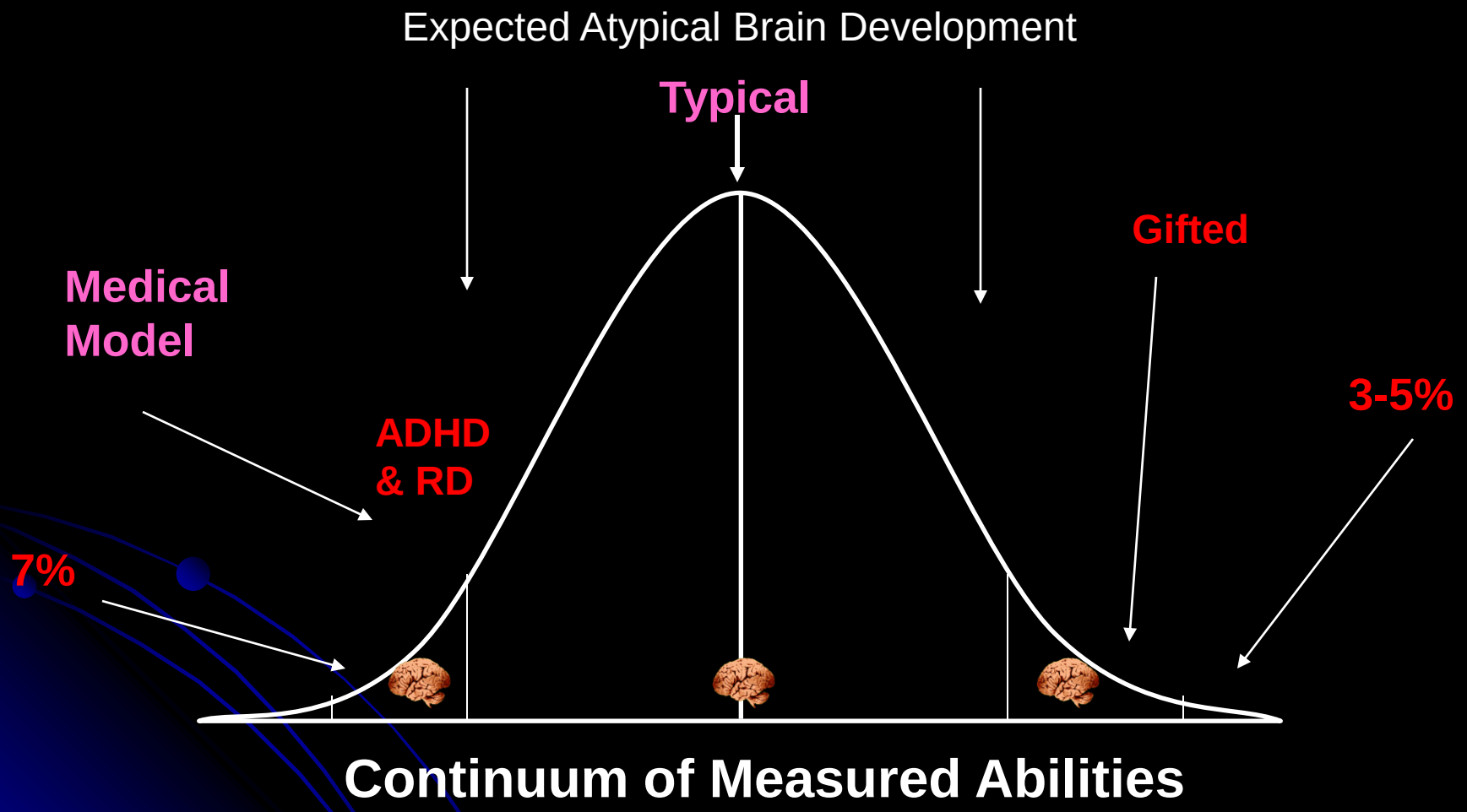
What We Are Not Talking About

- Rare and talented autistic, savant, or prodigy cases (Casanova et al., 2002; Cash, 1999; Butterworth, 2001; Deutsch & Joseph, 2003)

What We Are Talking About

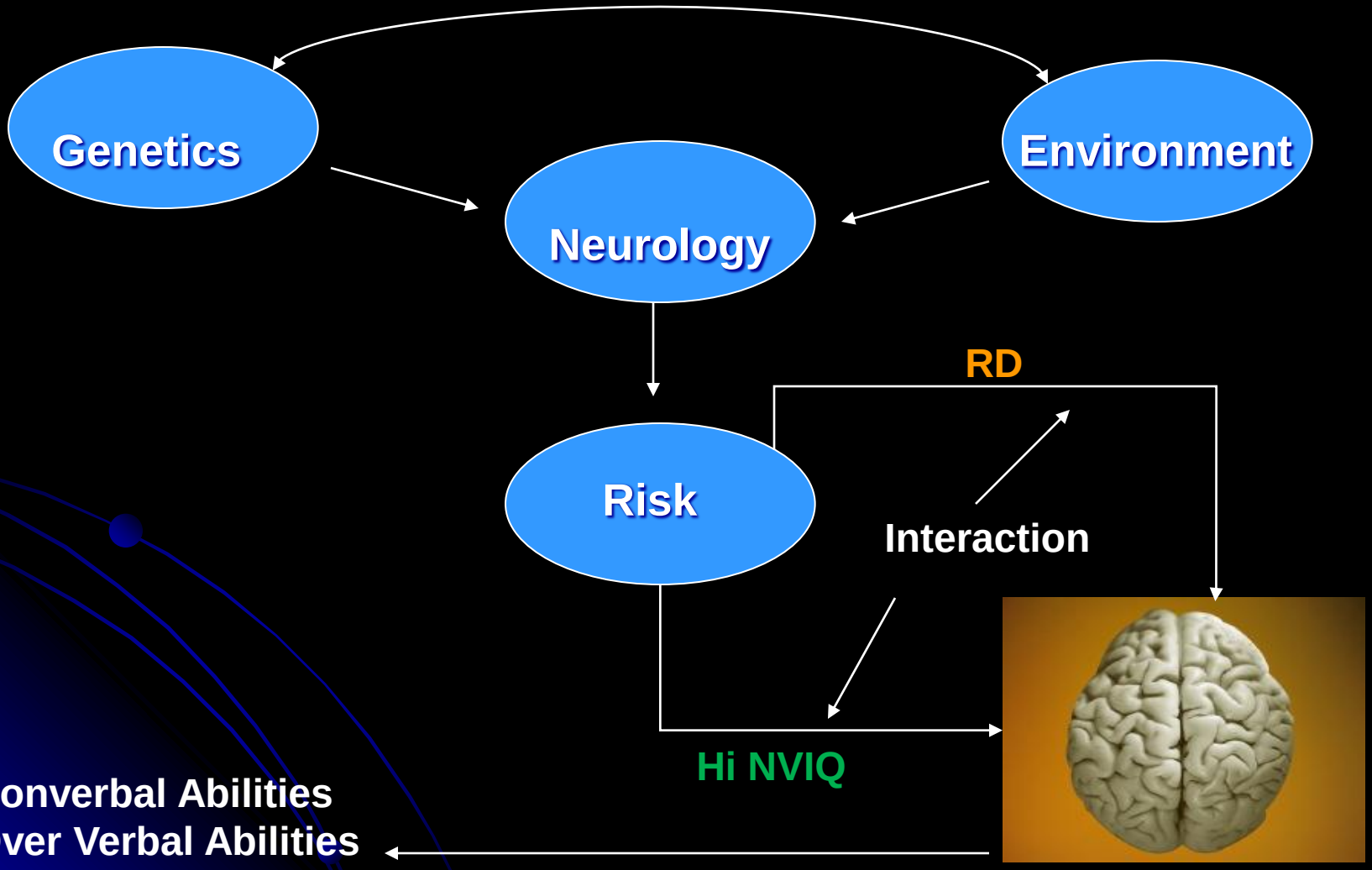
- Typical people who have a specific learning disorder (RD) concomitant with a superior NV skill/talent
- A specific form of giftedness to the neglect of many other possible forms

Normal Distribution of Learning Abilities or Learning Brains



See Gilger, J.W. & Kaplan, B. (2001). The neuropsychology of dyslexia: The concept of Atypical Brain Development. Developmental Neuropsychology, 20 (2) 465-481; Gilger, J., & Hynd, G. (2008). Neurodevelopmental Variation as a Framework for Thinking About the Twice Exceptional. Roeper Review, 30, 214-228.

How Can Similar Factors "Misswire" the Brain to Have Both Deficits and Gifts?



LD, Gifts, and Twice Exceptionality (2e)

- Problems with research and diagnostics, but estimates ~ 2-5%
- In schools there are problems with identification & treatment
- Often missed via regular assessments and RTI
- May usurp "gifts" to compensate for weaknesses
- Complicates realization of potential
- May be more likely to be labeled with personality disorders, ADHD, other
- May have unique emotional needs and stresses

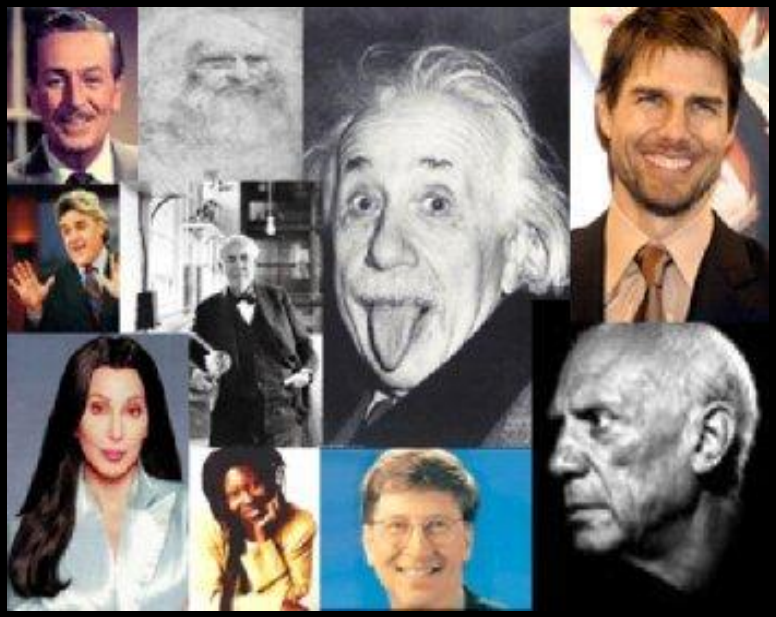
In summary:

2e are not RD and not gifted

They are their own category!

Stories Abound About Gifts and Twice Exceptionality

The "gift" of dyslexia?



- Some evidence that RDs are over represented in NV careers, creative fields, etc.

- Mixed, primarily negative results, that RDs are better at standardized NV assessments

Need more empirical research!

Four Studies

1. **MN Family Study**

   Craggs, Sanchez, Kibby, Gilger, & Hynd (2006). Cortex, 42, 1107-1118: *2e may run in families; correlated with unique brain morphology*

2. **Spatial Visualization in RD vs Control Students**

   Olulade, Gilger, Talavage, Hynd, & McAteer (2012). Developmental Neuropsychology, 37 (7), 617-635: *RD's may process spatial information uniquely although they may not show this behaviorally*

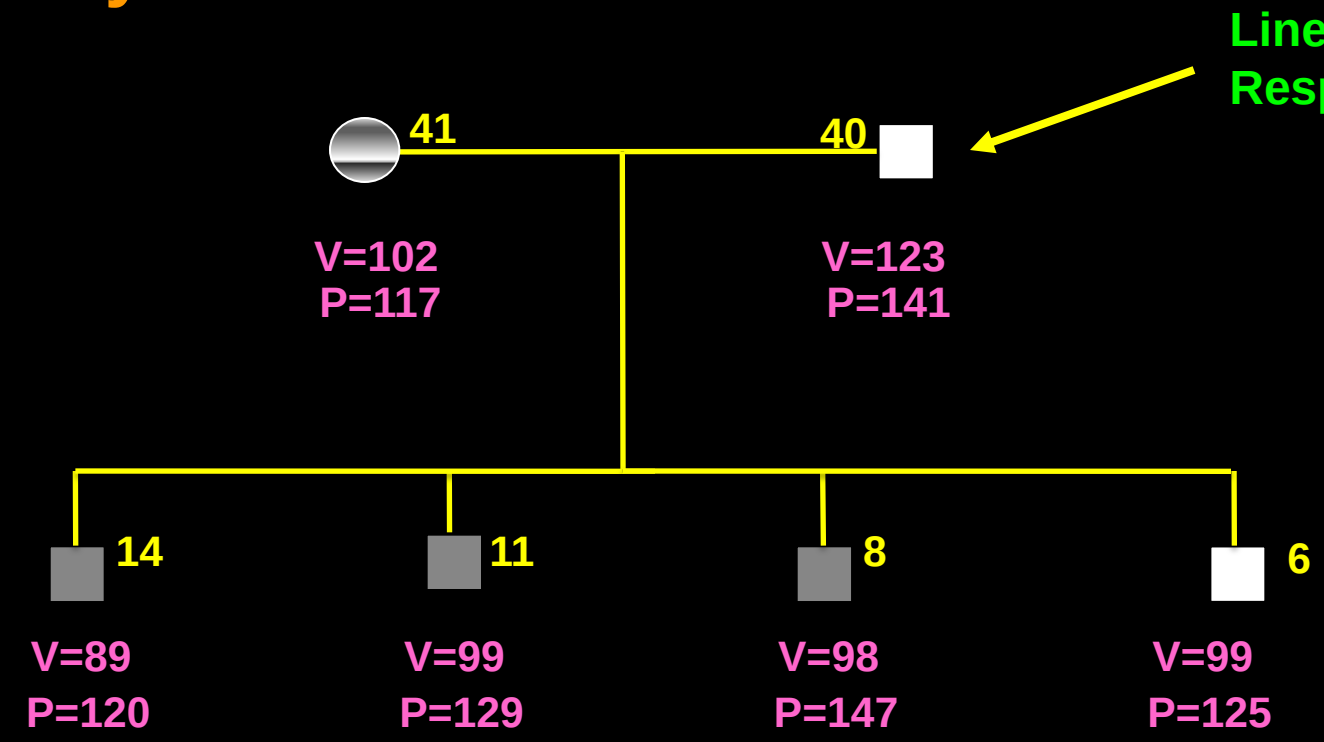
3. **Comparison of NV Gifted RD to RD, Gifted and Controls**

   Gilger, Talavage, & Olumide (2013). Frontiers Human Neuroscience, 7, 1-12: *2e adults may look neurologically like RDs due to life long compensation effects*

4. **Comparison of NV Gifted RD to Gifted**

   Gilger & Olumide (October, 2013). Roeper Review: *Gifted RDs might look the same on a NV test, but they process things differently*

MN Family Study



V = Verbal IQ

P = Performance IQ

Unaffected – No linguistic deficit

RD status unclear

RD/Verbal Deficit

MN Family Study

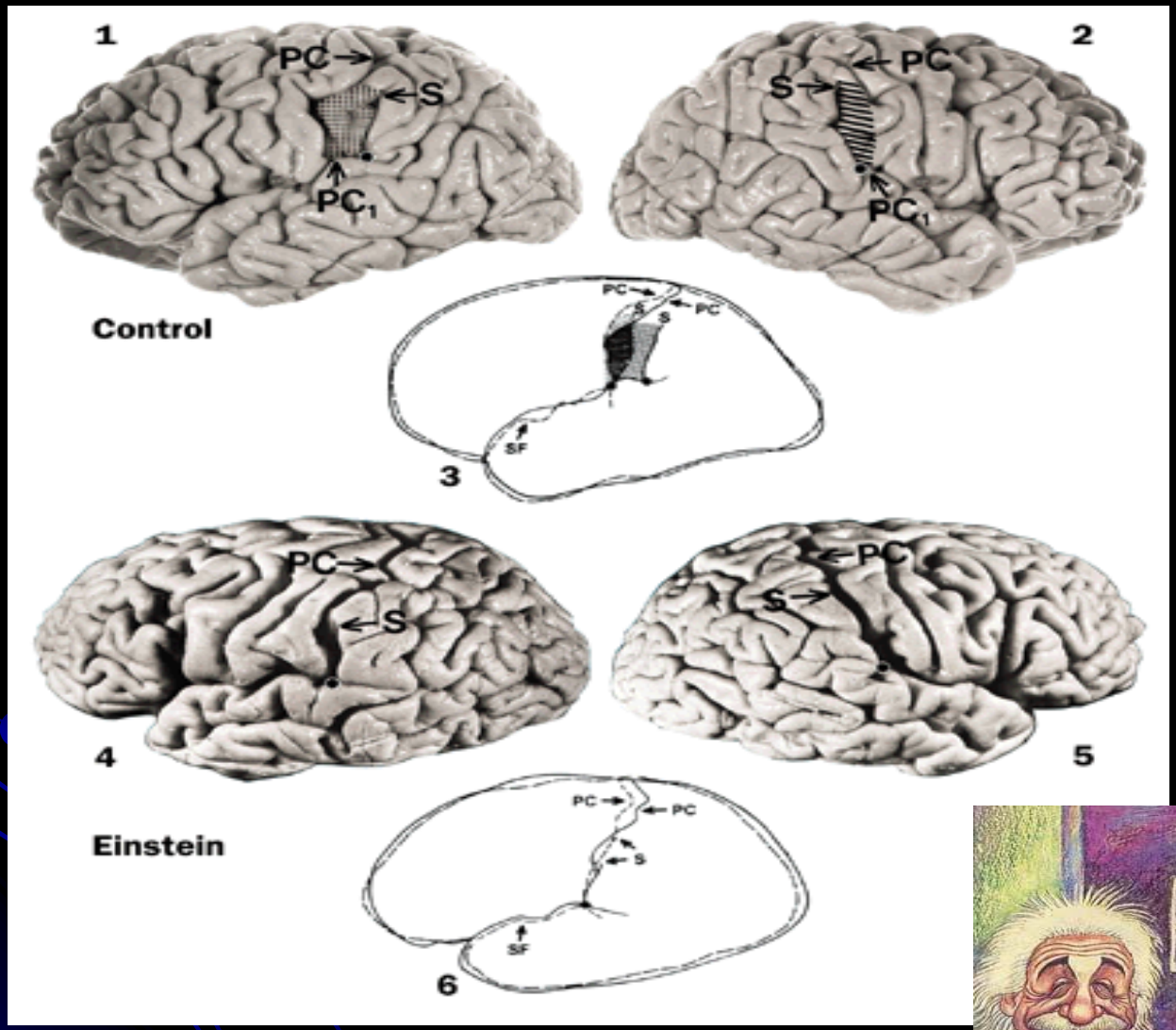
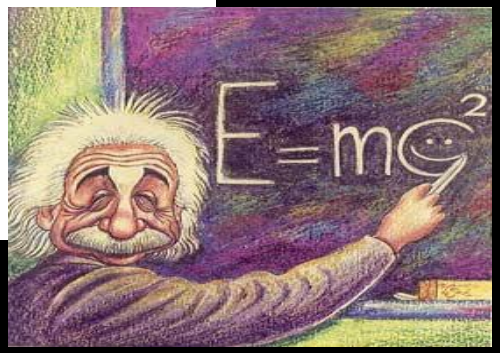
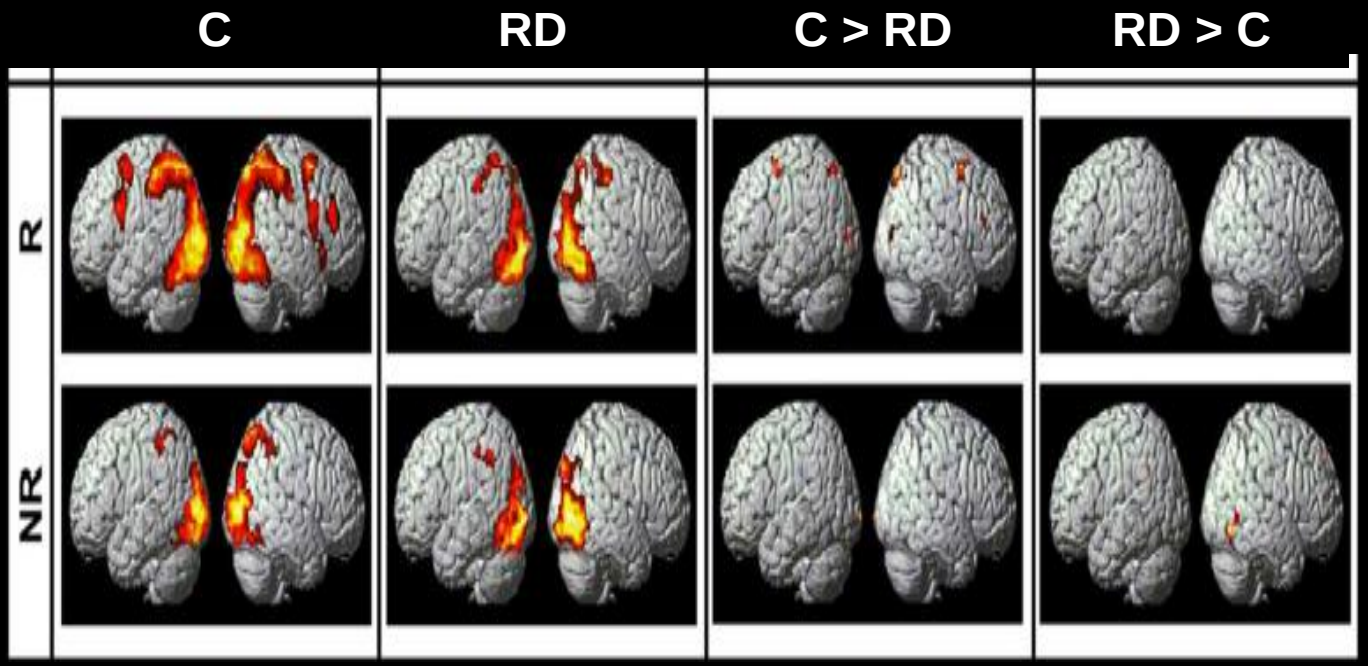


Fig from Witelson, et al., Lancet, 1999

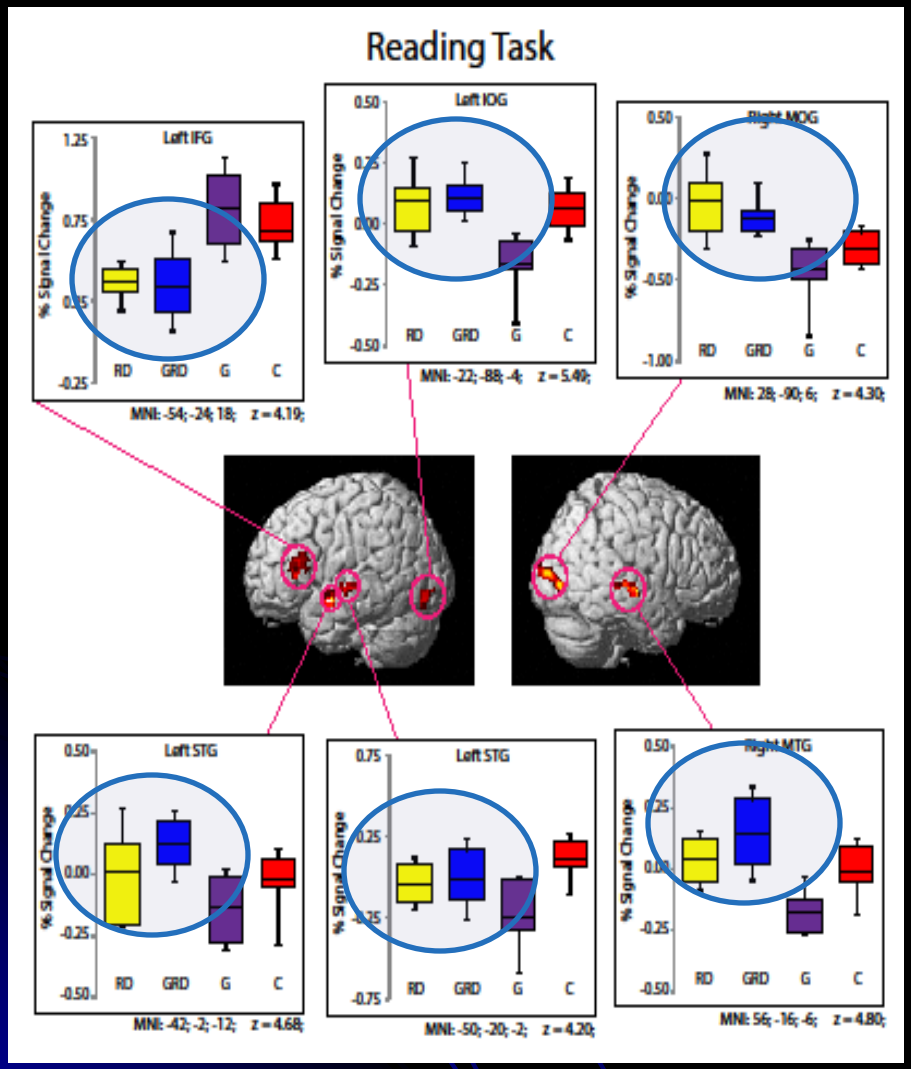


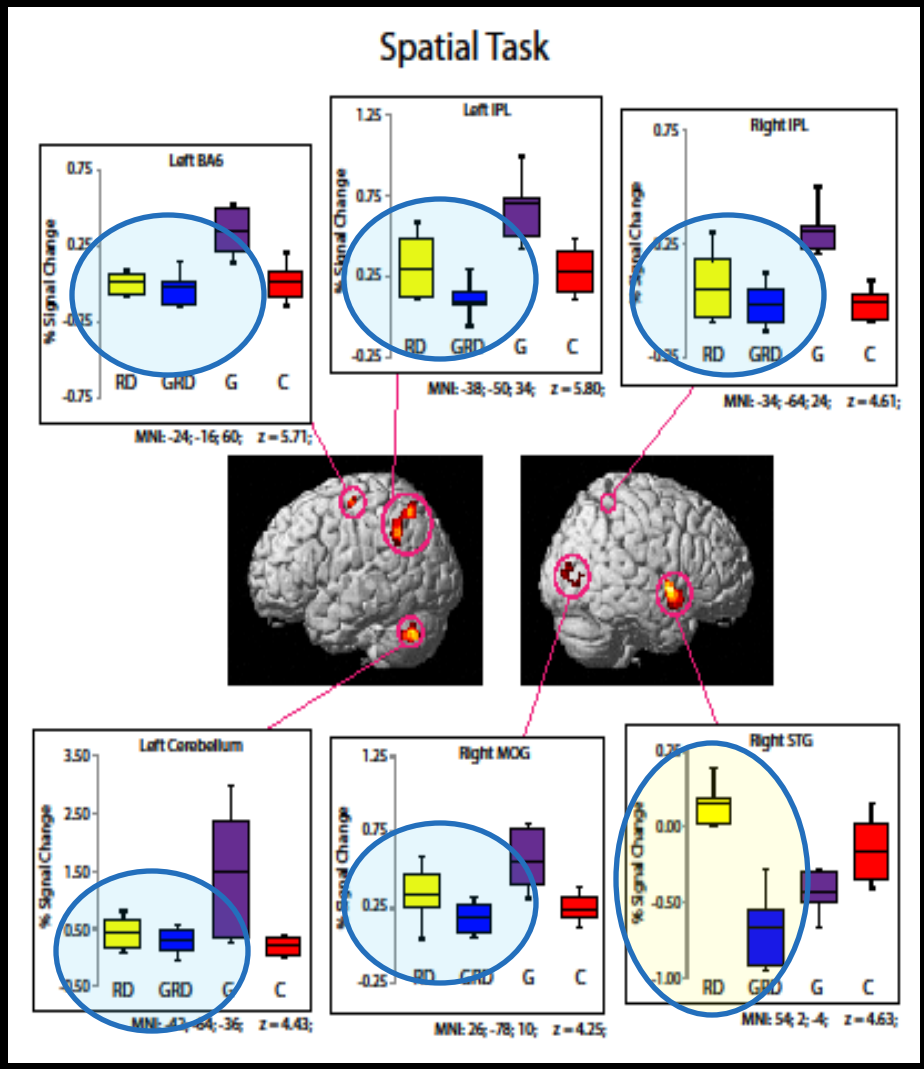
Spatial Abilities in RD Adults



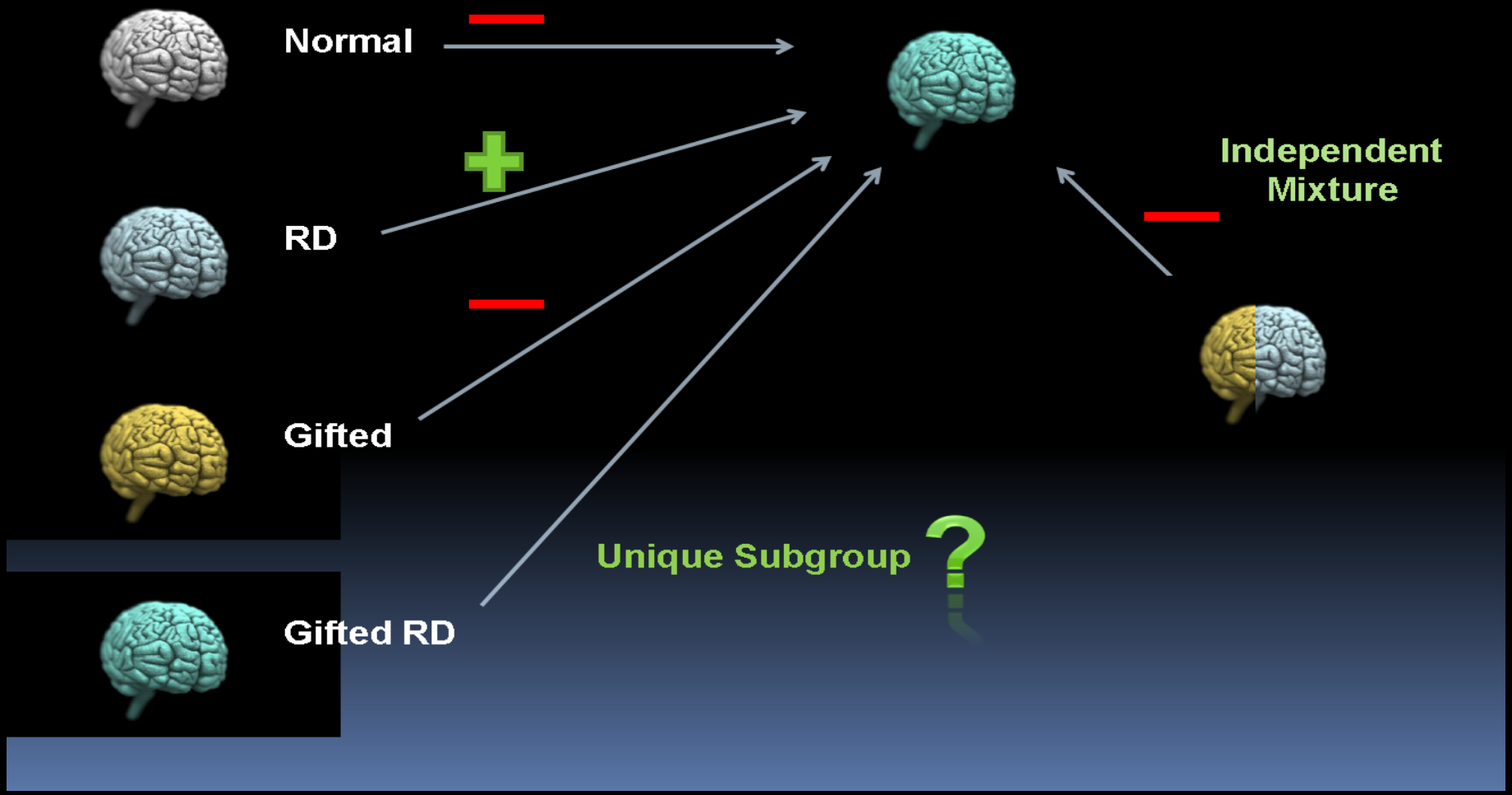
- As expected for verbal task
- Same behaviorally on spatial task
- Under/over activated different areas
- *Brain processes dynamic spatial info differently*

fMRI Study of 4 Groups





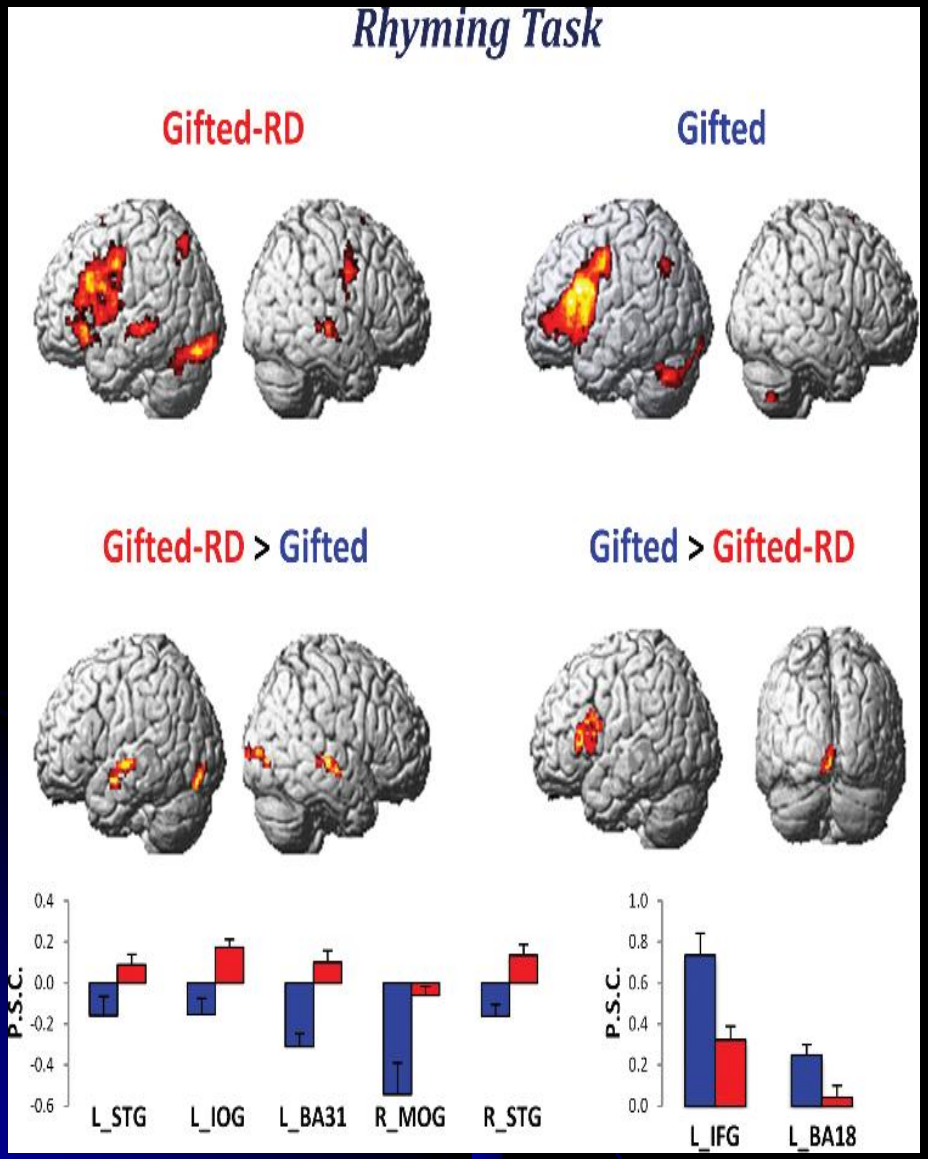
Complexities

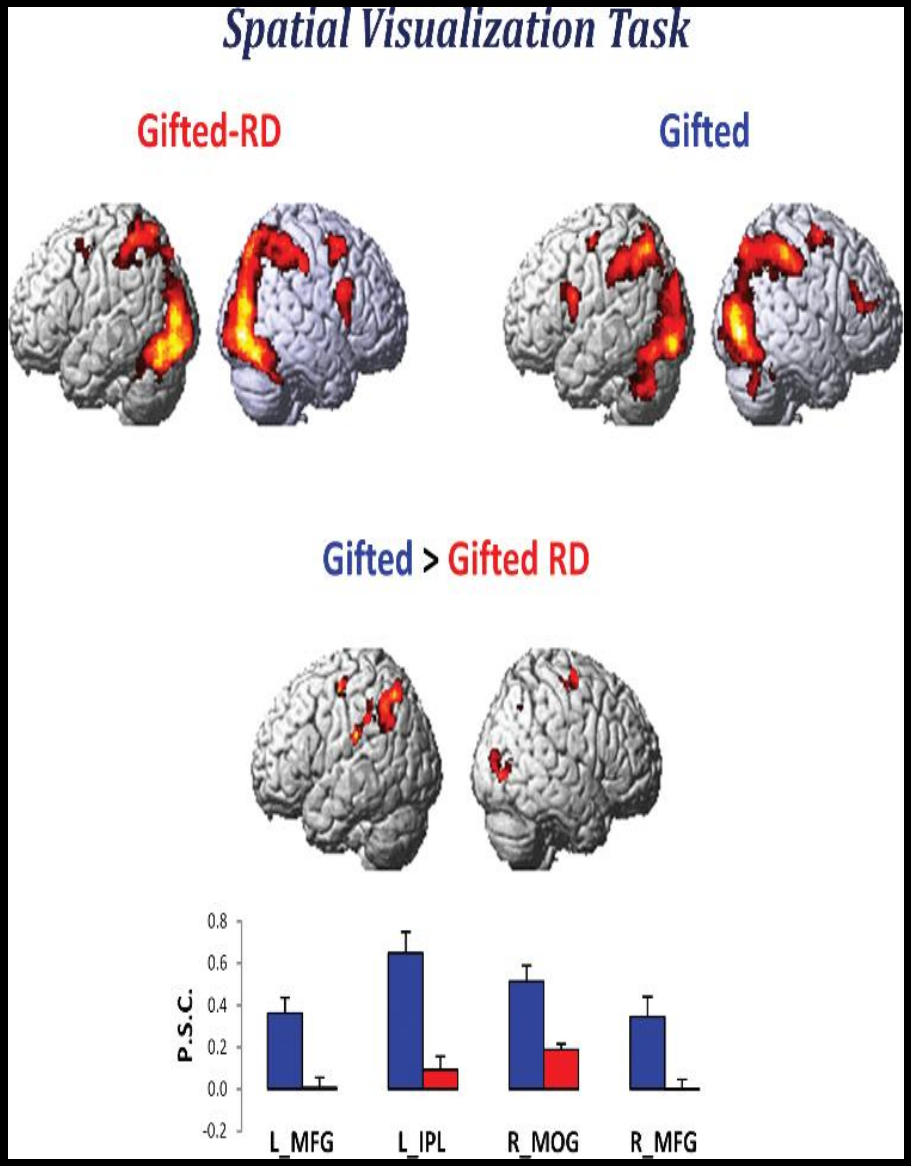


- Gifted RD brains act like RD brains
- *Could be due to long term interactions and compensations*

Complexities

fMRI Study of Gifted RD vs Gifted



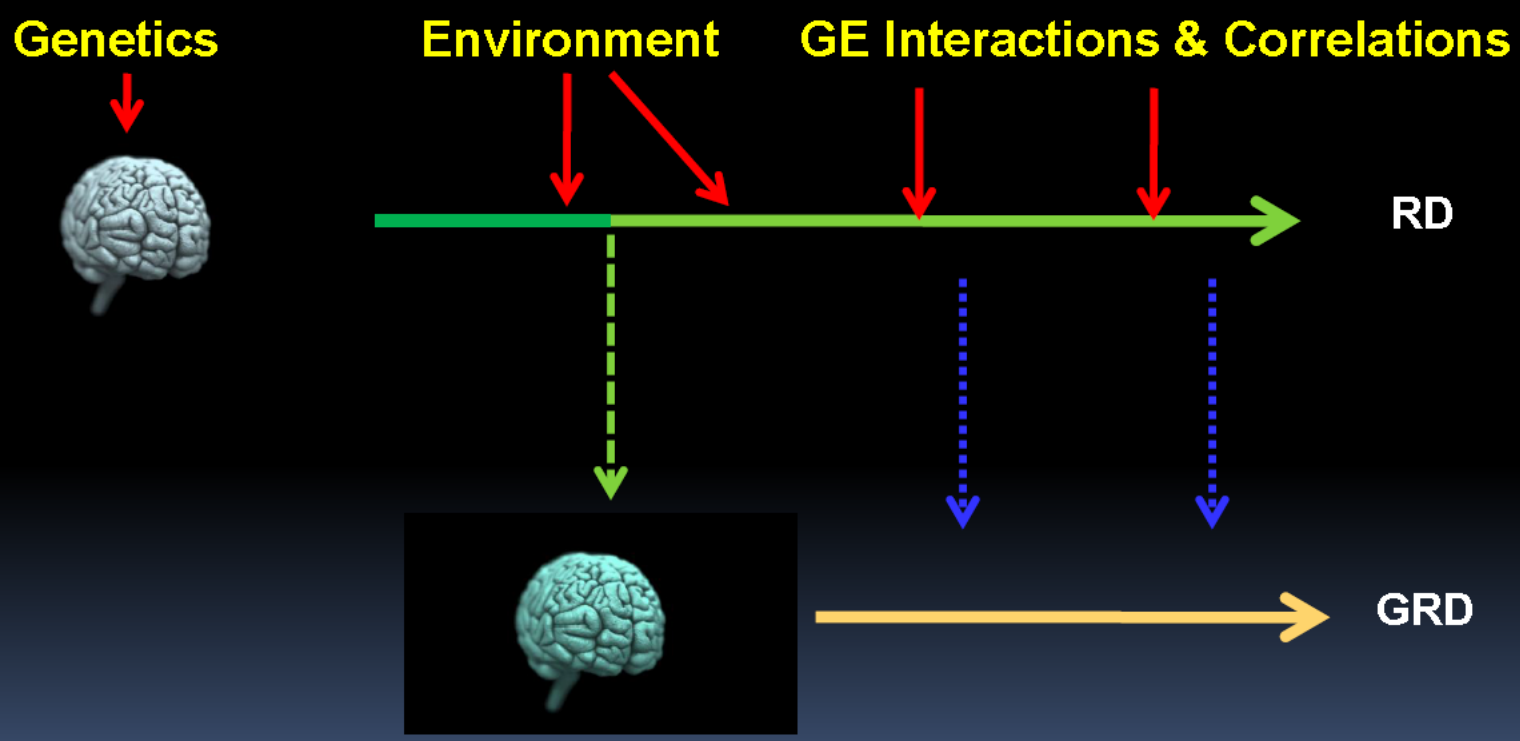


Complexities

fMRI Study of Gifted RD vs Gifted

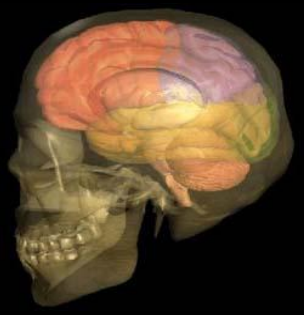
- Matched on NV IQ > 120
- Gifted RD performed worse than gifted on WJSR
- Gifted RD performed worse on spatial visualization task than gifted
- *Implications for diagnosis, placement and treatment*

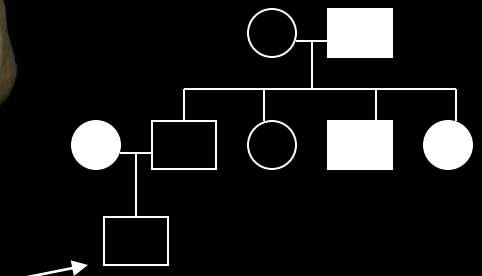
What Do These 4 Studies (and others) Suggest?



Outline

1. Review of Concepts
2. Family Studies of Dyslexia/Developmental Reading Disorder (RD) Genetics
3. Complex Associations: RD and Nonverbal or Spatial Giftedness (2e)
4. **Closing Comment on Future Work and Clinical Implications**





Results to Date

- RD is cognitively complex
- No single cognitive model fits all the data
- Individual variation
- RD is not necessarily a distinct from normal variation
- Some common functional brain patterns, but there is variability and nonspecificity
- Some common patterns of brain structure, but great variability and nonspecifcity
- “Many” genetic linkages
- Other

Central Lessons

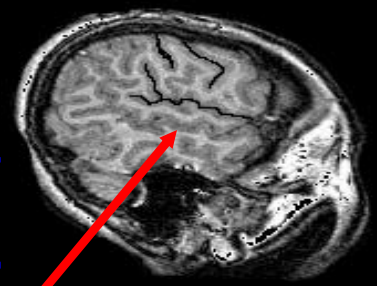
- Genes for RD risk = genes for atypical brain development (see Gilger et al, 2001; 2008)
- Risk genes for RD do not act in isolation
- A developmental perspective must be maintained—*throughout the lifespan*

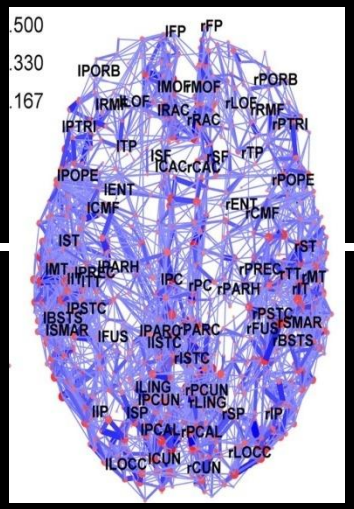
Central Lessons

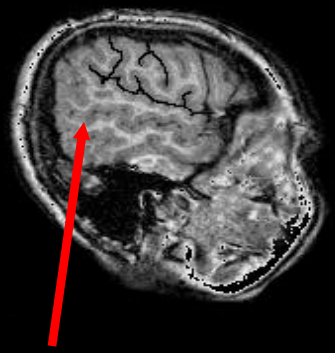
- Behavioral similarity does not insure neurological similarity
- Developmental and experimental studies of the whole brain are needed

A Developmental Model of Treatment

- What we do to the person effects the entire person
- Effect on one area may effect another
- Might do well to appreciate profiles and individual differences w/o need for “negative dx”







Left Hemisphere Reading Center

Right Hemisphere Visualization Center

Thank you!

Jeffrey W. Gilger
University of California
Psychological Sciences
5200 N. Lake Road
Merced, CA 95343-5603
jgilger@ucmerced.edu

http://faculty2.ucmerced.edu/jgilger/

Some References

Craggs, J. Sanchez, J., Kibby, M., Gilger, J. & Hynd, G. (2006). Brain morphological and neuropsychological profiles of a family displaying superior nonverbal intelligence and dyslexia. Cortex, 42, 1107-1118.

Rhee, S., Hewitt, J., Corley, R., Willicut, E. & Pennington, B. (2005). Testing hypotheses regarding the causes of comorbidity: Examining the underlying deficits of comorbid disorders. J. Abnormal Psychology, 114, 346-362.

Ramus, F. Neurobiology of dyslexia: A reinterpretation of the data. TINS, 27, 720-726.

Gilger, J. & Wilkins, M. (2008). Atypical Neurodevelopmental Variation as a Basis for Learning Disorders. In M. Mody & E. Sillliman (Eds.), Language Impairment and Reading Disability: Interactions Among Brain, Behavior, and Experience. (Series on Challenges in Language and Literacy). Guilford Press.

Smith, S.D. & Gilger, J.W. (2007). Dyslexia and other language/learning disorders. In Rimoin, Connor, Pyeritz & Korf (Eds.; 5th edition), Emory and Rimoin's Principles and Practices in Medical Genetics. Livingstone Churchill: NY.

Gilger, J.W. & Kaplan, B. (2001). The neuropsychology of dyslexia: The concept of Atypical Brain Development. Developmental Neuropsychology, 20 (2) 465-481.

Gilger, J., & Hynd, G. (2008). Neurodevelopmental Variation as a Framework for Thinking About the Twice Exceptional. Roeper Review, 30, 214-228.

Newbury, D. F. & & Monaco, A.P. (2008). The application of molecular genetics to the study of developmental language disorder. In *Understanding developmental language disorders: From theory to practice*. Psychology Press, NY, NY, 79-91.

References Continued

Gilger, J.W., Borecki, I., Smith, S.D., DeFries, J.C., & Pennington, B.F. (1996). The etiology of extreme scores for complex phenotypes: An illustration using reading performance. In C. Chase, G. Rosen, & G. Sherman (Eds.), Developmental dyslexia: Neural, cognitive and genetic mechanisms. Baltimore, MD: York Press.

Pennington, B.F., Gilger, J.W., Pauls, D., Smith, S.A., Smith, S.D., DeFries, J.C. (1991). Evidence for Major Gene Transmission of Developmental Dyslexia JAMA, 266(11),1527-1534.

Gilger, J.W., Borecki, I., DeFries, J.C., & Pennington, B.F. (1994). Commingling and segregation analysis of reading performance in families of normal reading probands. Behavior Genetics, 24, 345-355.

Hannula-Jouppi K, Kaminen-Ahola N, Taipale M, et al. (2005) The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia. PLoS Genetics, 1(4), 50.

Meyler, A., Keller, T.A, Cherhassky, V. L., Gabrieli, J.D.E., Just, M. A. (2008). Modifying the brain activation of poor readers during sentence comprehension with extended remedial instruction: A l longitudinal study of neuroplasticity. *Neuropsychologia, 46*, 2580-2592.

Nopola-Hemmi, J., Myllyluoma, B., Haltia, T., Taipale, M., Ollikainen, V., Ahonen, T., et al. (2001). A dominant gene for developmental dyslexia on chromosome 3. *Journal of Medical Genetics, 38,* 658–664.

Galaburda, A. M. (1992). Neurology of developmental dyslexia. *Current Opinion in Neurology and Neurosurgery, 5,* 71–76.