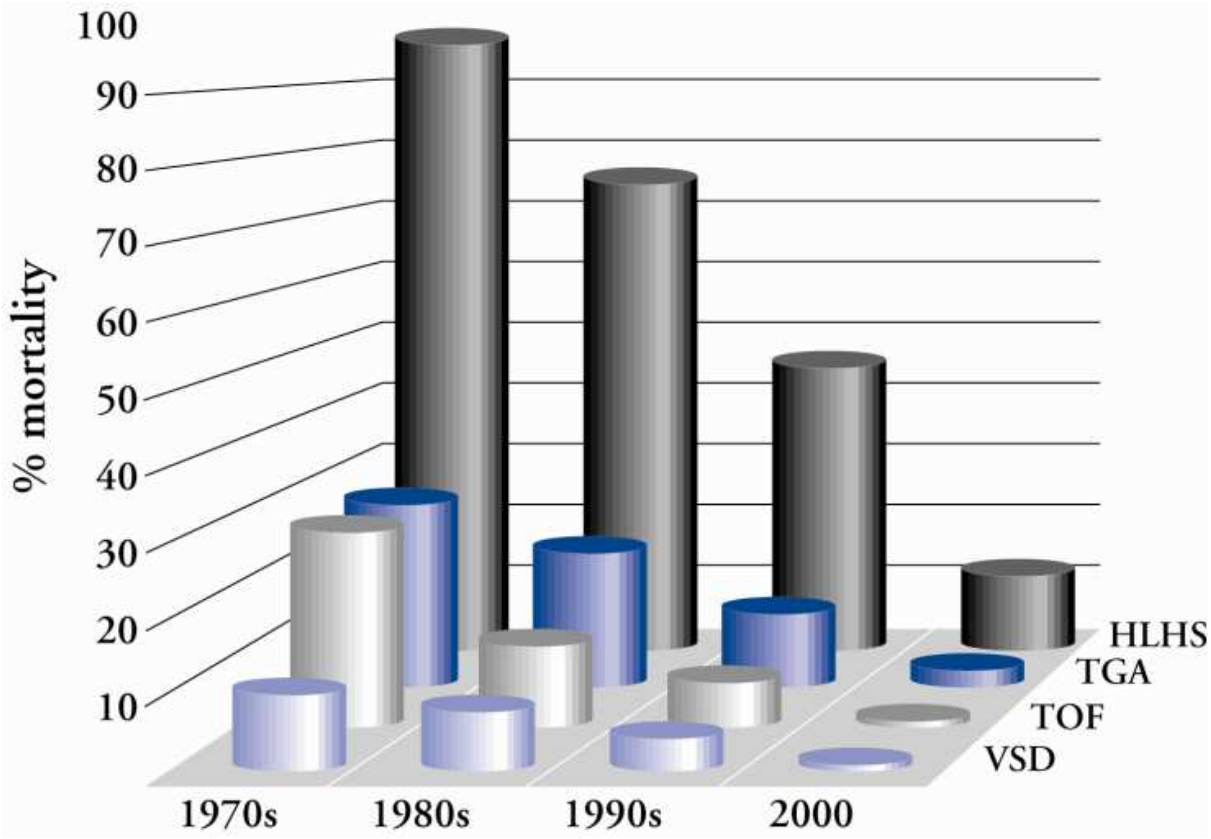
Concerns About Neurodevelopmental Outcomes

Jane W. Newburger, MD, MPH
Associate Cardiologist-in-Chief, Academic Affairs
Boston Children's Hospital

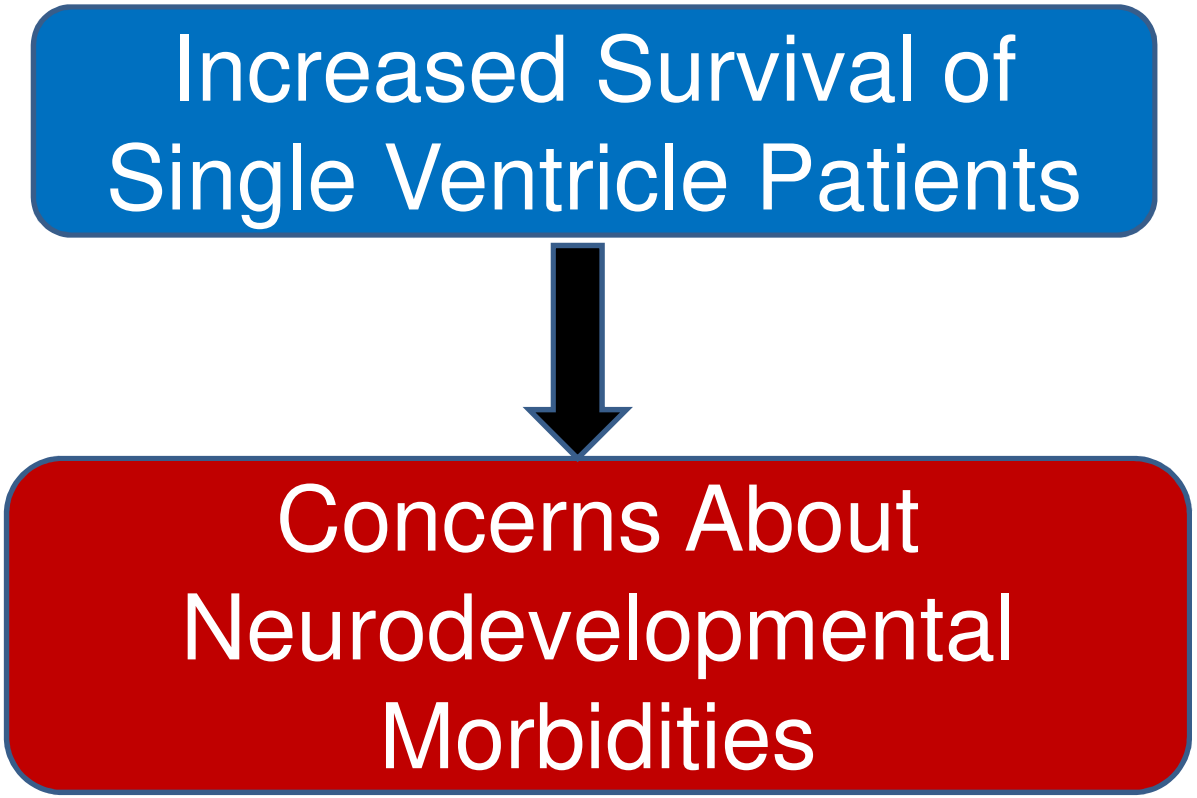
Boston Children's Hospital
Heart Center

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Improving Early Postoperative Results



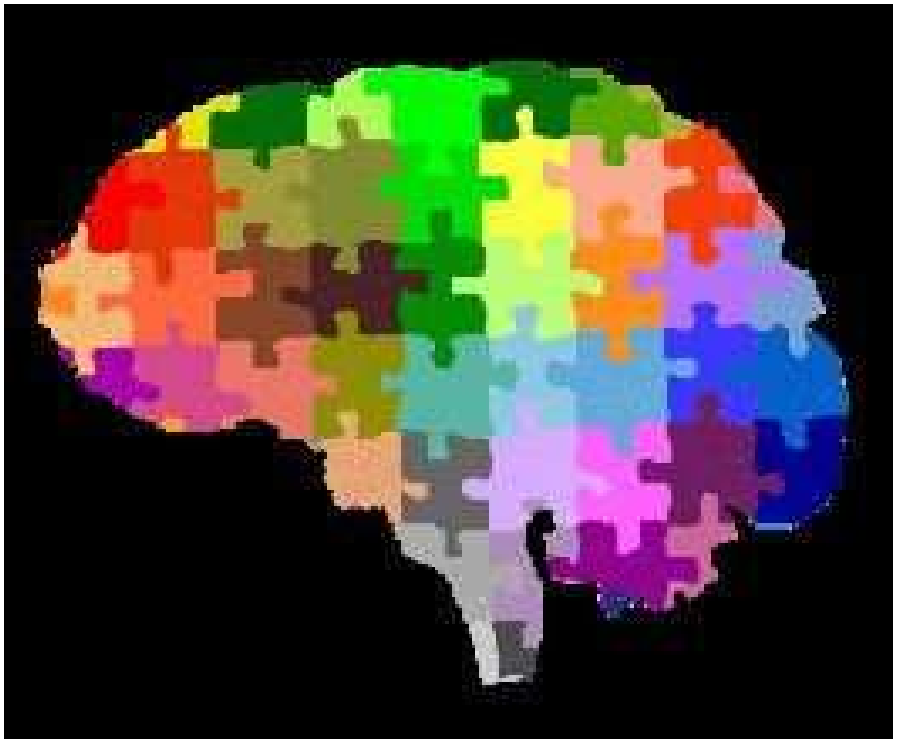
Courtesy of Wernovsky G


Increased Survival of Single Ventricle Patients
Concerns About Neurodevelopmental Morbidities

Topics For This Talk

- What causes neurodevelopmental problems in children with single ventricle?
- What sorts of neurodevelopmental challenges are Fontan patients prone to?
- What can we do to make things better?

What Causes of Neurodevelopmental Disabilities



Causes of Neurodevelopmental Disabilities

- Genetic abnormalities
- Fetal or in-utero environment
- Multiple catheterizations and operations
- Unstable state before and after cardiac surgery
- Long hospital length of stay
- Risks of heart disease itself (cyanosis, malnutrition, stroke, cardiac arrest)

Genetic Disorders Affect Both the Heart and Brain

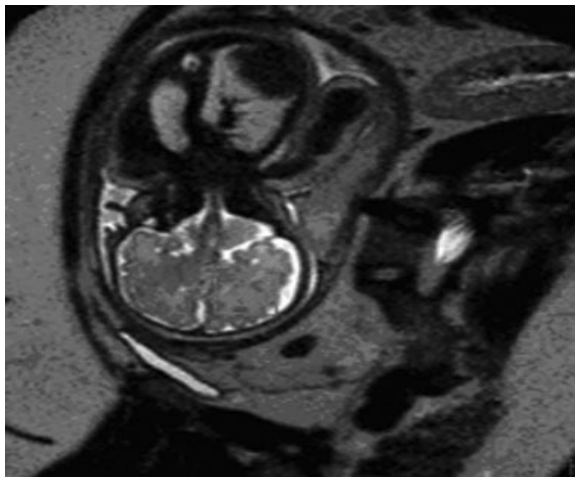
~40% of congenital heart defects are caused by genetic abnormalities

- Extra copy of a whole chromosomes (e.g., aneupoidies, Down's)
- Missing or extra parts of chromosomes (e.g., copy number variants like VCF)
- Single gene disorders
  - *De novo (n*ew, not in parents*)* point mutations contribute to 10% of severe CHD in whole exome analysis

Fetuses with single ventricle have lower oxygen supply to the brain

- Reduced cerebral oxygen delivery to the fetus affects
  - Brain growth
  - Maturation
  - Metabolism

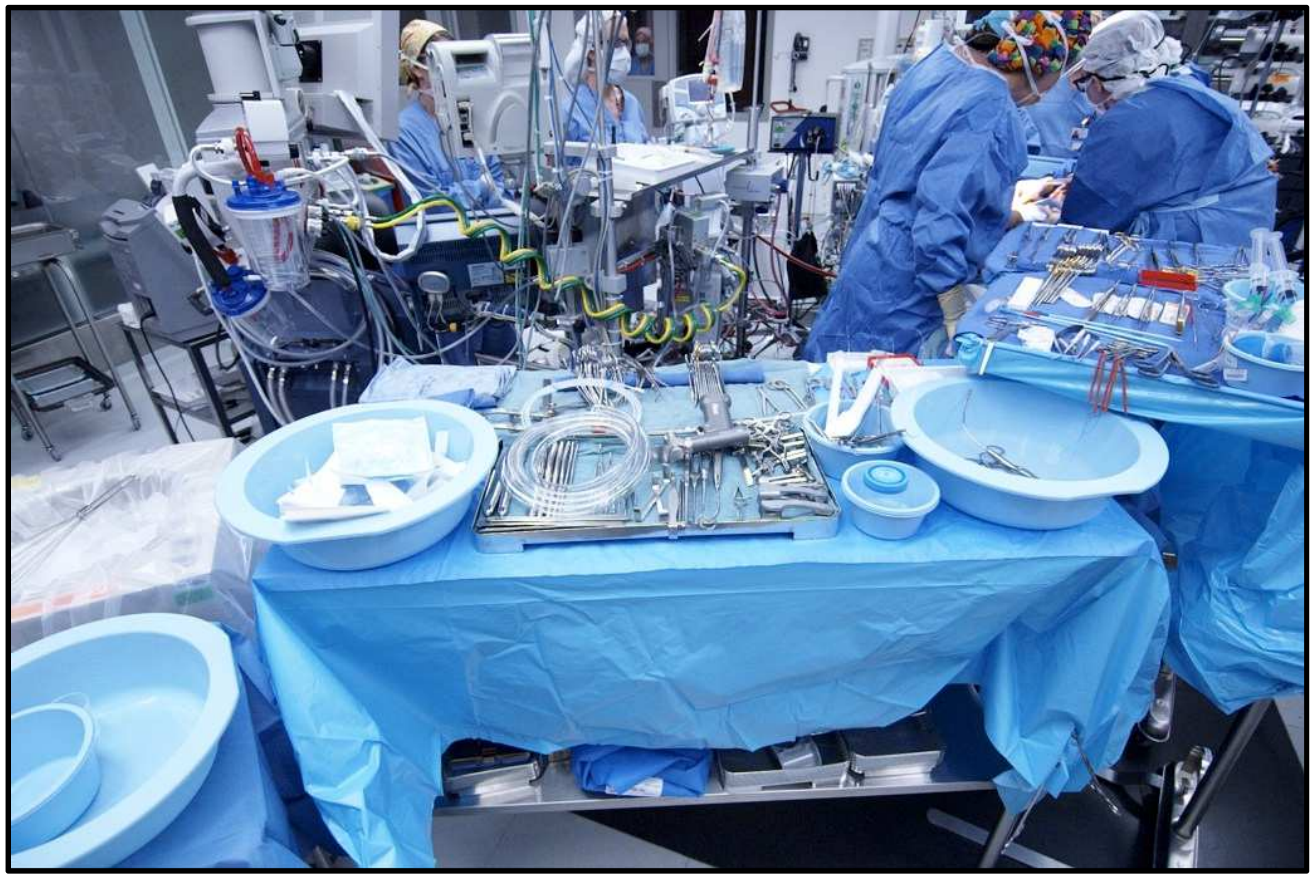
Fetuses with HLHS demonstrate differences in cortical folding and growth



Limperopoulos et al., 2010, Clouchoux et al., 2012

- Delayed cortical gyrification patterns as early as 25 wks
- Progressive fall-off of cortical and subcortical gray matter and white matter volume after 25 weeks.
- Low cerebro-placental resistance ratio and absence of anterograde arch flow associated with greater volume differences.

Open Heart Surgery



Courtesy of Gil Wernovsky

All Anesthetics Can Have Effects on the Brain

List of General Anesthetic and Sedation Drugs Affected by this Label Change*

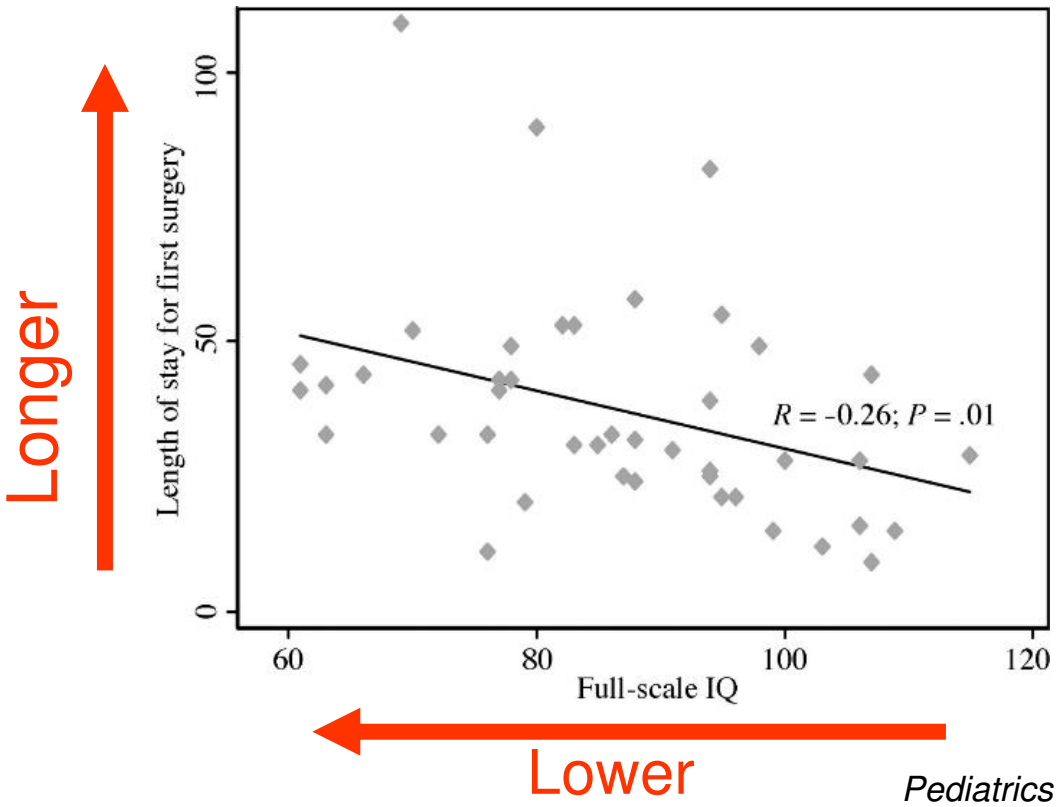
Generic Name	Brand Name
desflurane	Suprane
etomidate	Amidate
halothane	Only generic is available
isoflurane	Forane
ketamine	Ketalar
lorazepam injection	Ativan
methohexital	Brevital
midazolam injection, syrup	Only generic is available
pentobarbital	Nembutal
propofol	Diprivan
sevoflurane	Ultane, Sojourn

Courtesy Andreas Loepke

Environment in the Cardiac ICU

- Noise
- Pain
- Exposure to phenols and phthalates

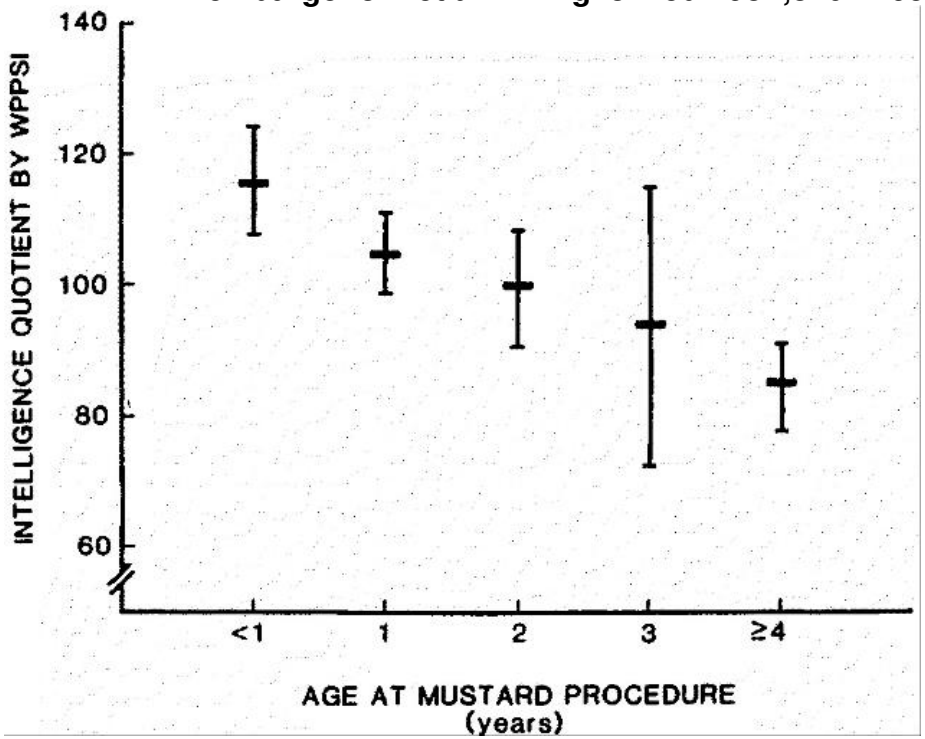
IQ in children with HLHS following either transplantation or Norwood



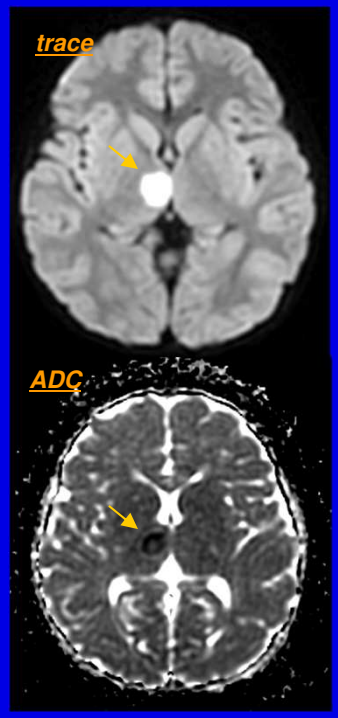
Mahle et al
Pediatrics 2006;117:e90

Profound hypoxia over years is associated with diminished cognitive ability

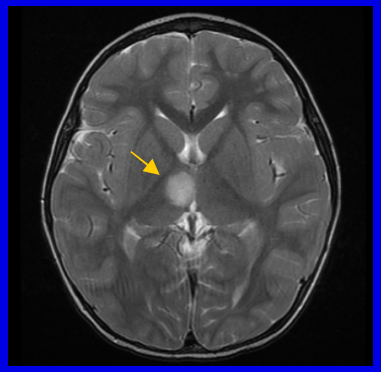
Newburger JW et al. N Engl J Med 1984;310:1495-1499.



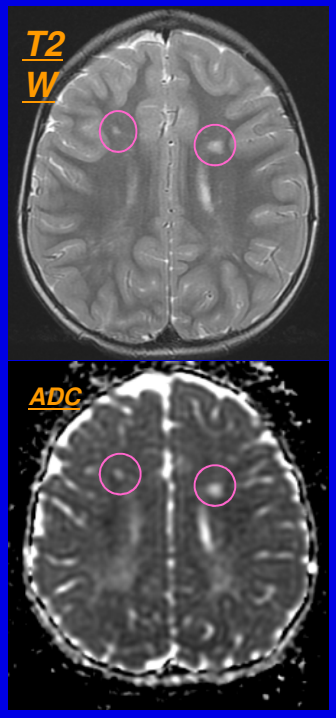
New Stroke in an 8-year Old Boy with Fenestrated Fontan



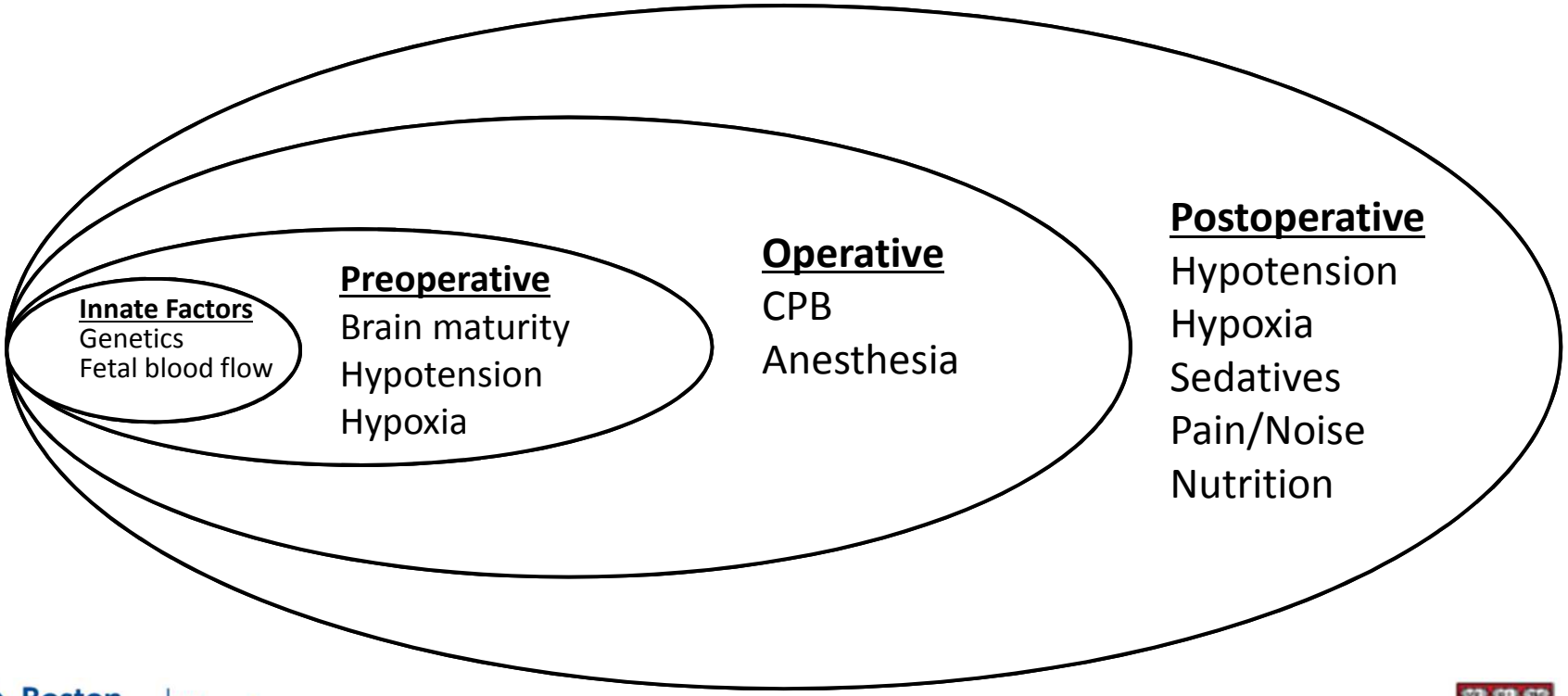
DWI



T2W



Risk Factors are Additive and Interactive



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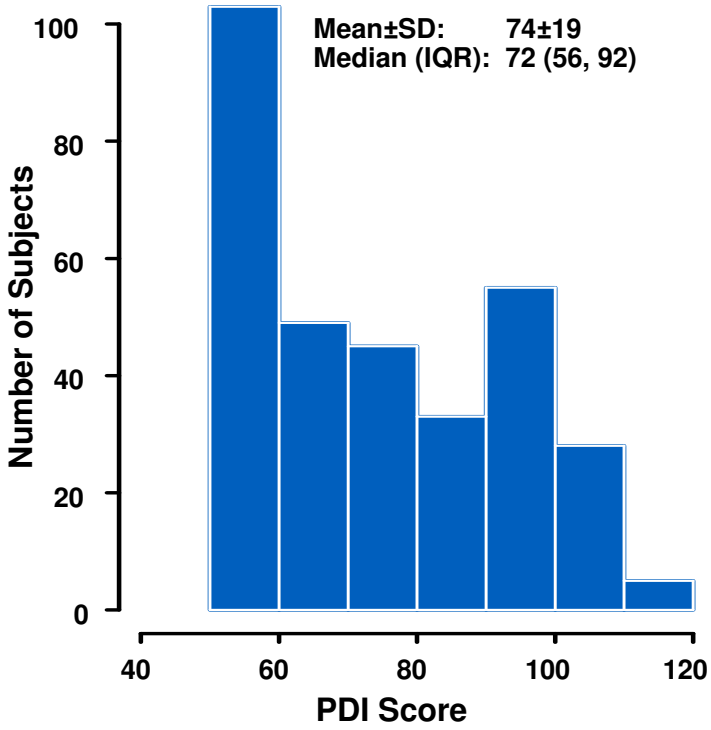
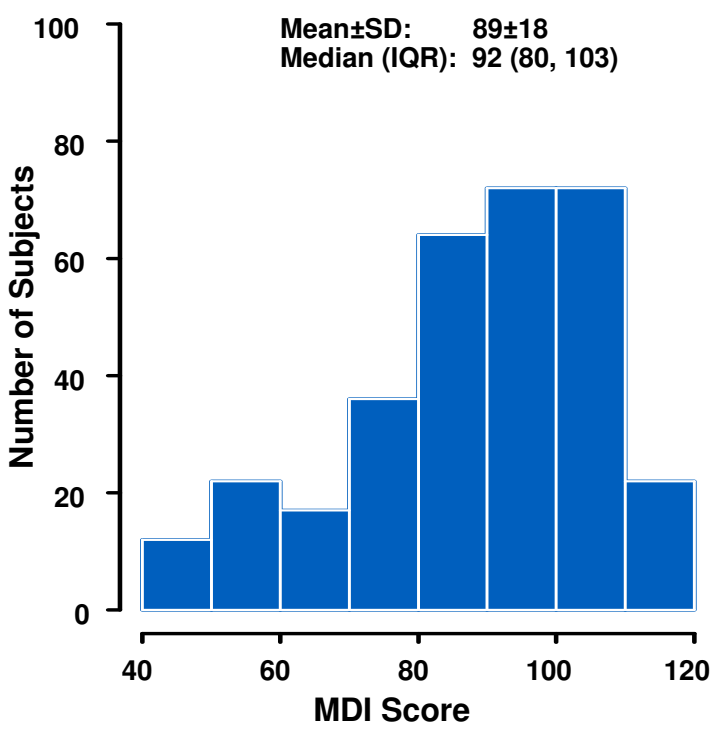
Until every child is well™

SVR Trial: Bayley II Scores at 14 months





What is Development Like in Pre-Teens and Teenagers After the Fontan?

ND Function in 156 Fontan Adolescents

(Bellinger et al, JAHA 2015)

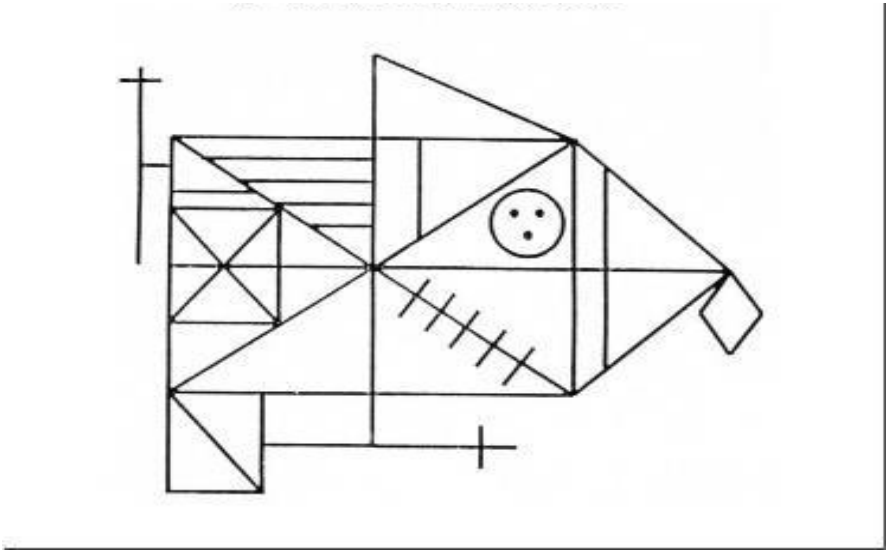
- Seizures: 23 (15%)
- Stroke: 19 (12%),
- Previous dx of ADHD: 34 (22%)
- Previous dx of learning disability: 57 (37%)
- Medications
  - *Stimulants: 15 (10%)*
  - *Psychotropic agents : 13 (8%)*
  - *Both: 3 (2%)*

Neurodevelopmental Signature

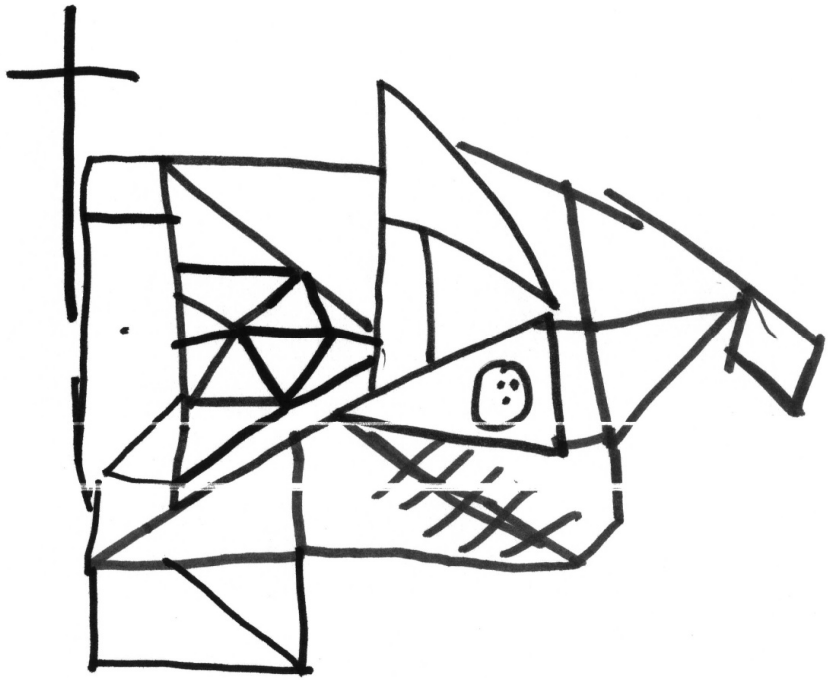
- IQ is generally good.
- Fontan patients have particular weaknesses
  - **Visual-spatial** function
  - Vigilance and sustained **attention**
  - **Executive function** and working memory
  - **Social cognition**.

The Rey Osterreith Complex Figure

- Tests visual-spatial-motor function
- Requires integration of many sections of the brain.



Rey-Osterrieth Complex Figure at 16 Years



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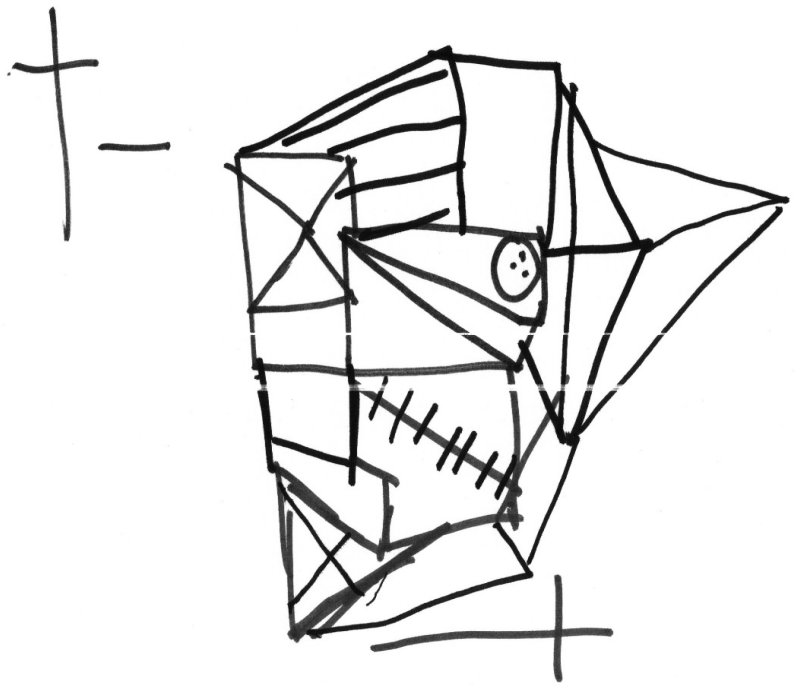
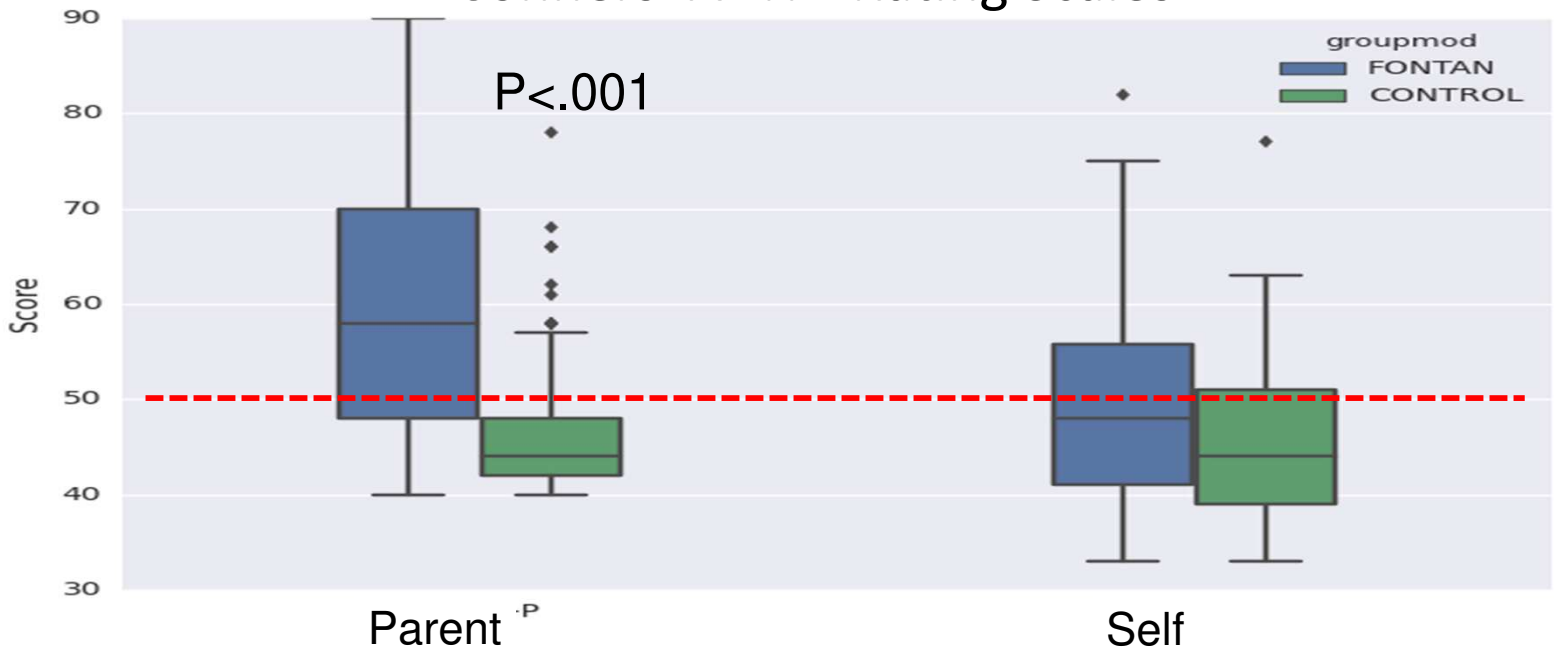


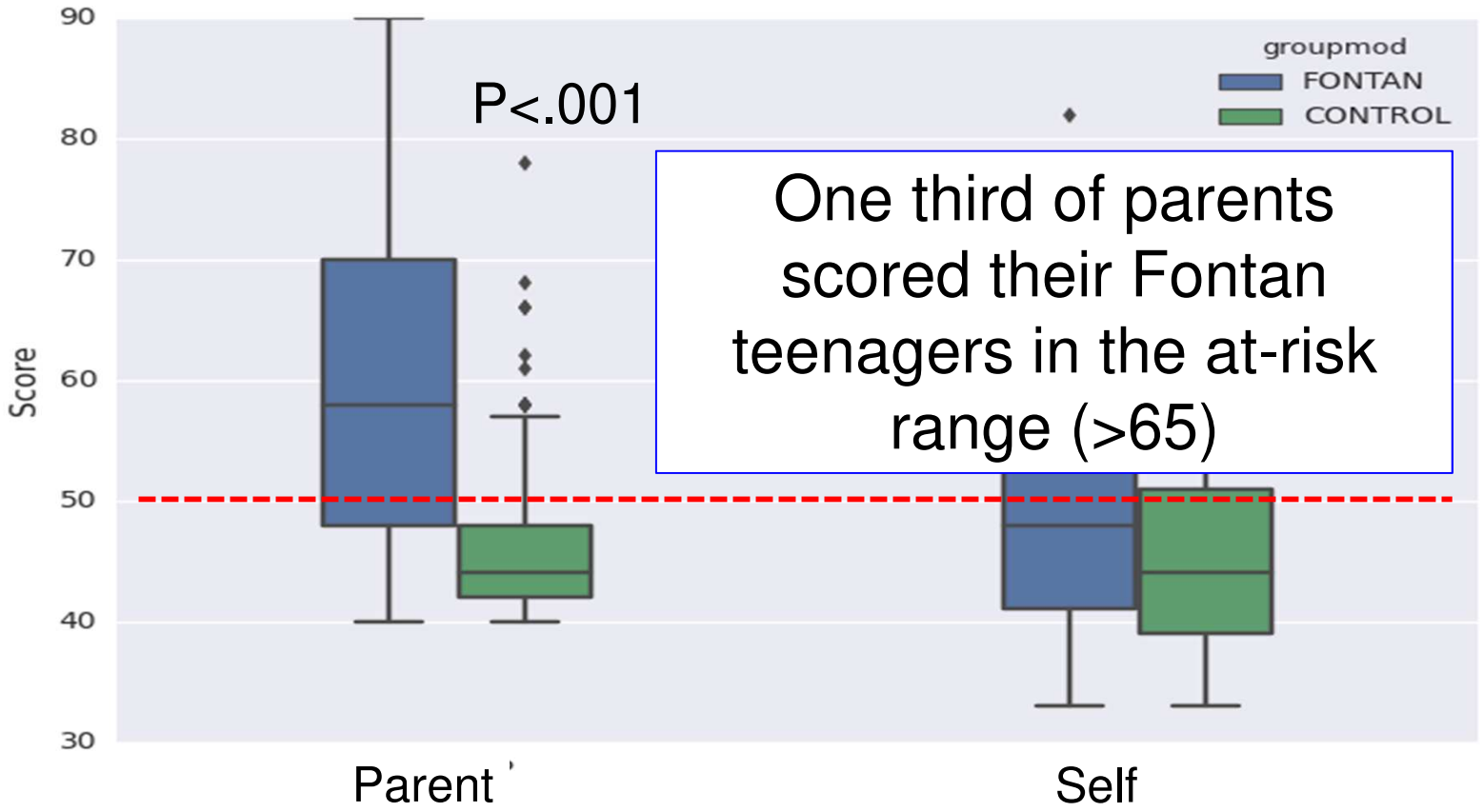
immediate recall

Conners' ADHD Rating Scales



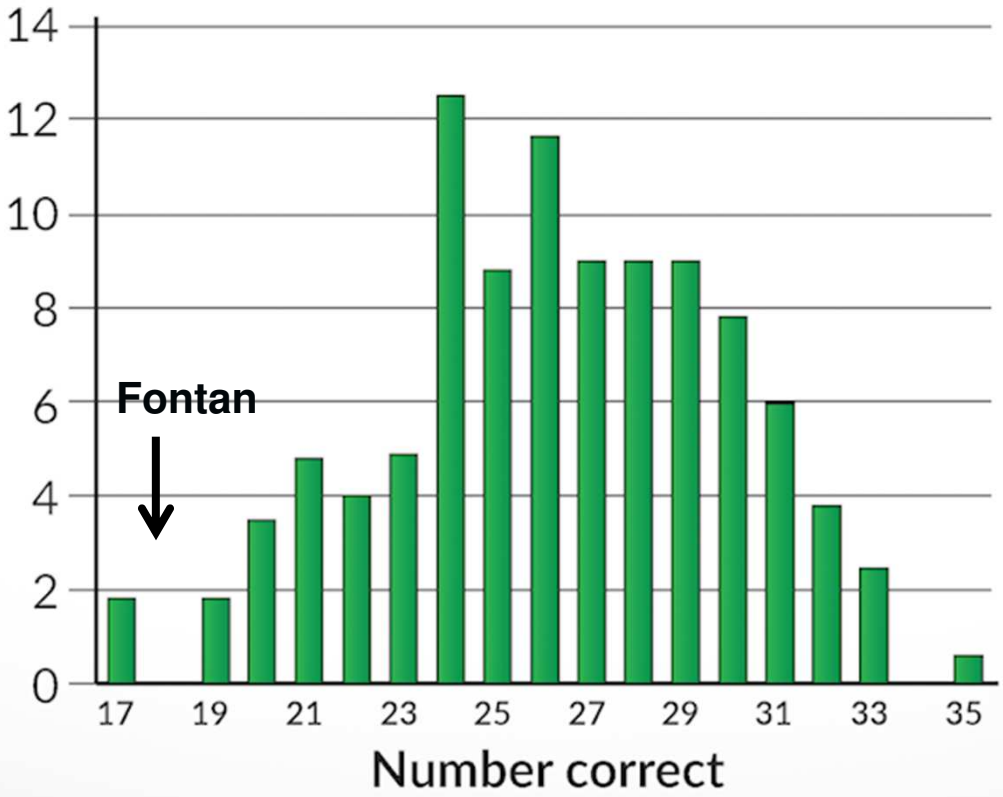
Bellinger et al. JAHA 2015

Conners' ADHD Rating Scales



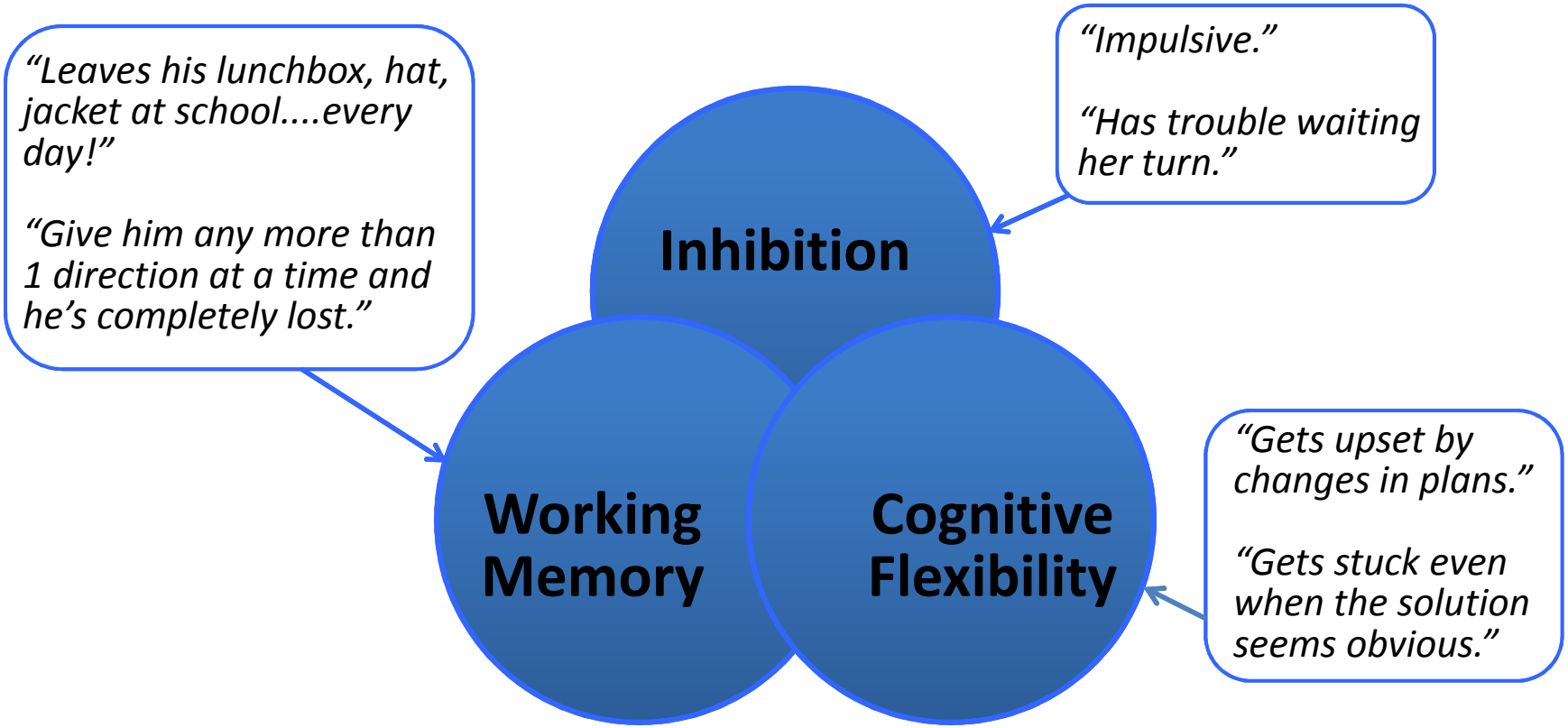
Bellinger et al. JAHA 2015

Reading the "Mind in the Eyes" Test

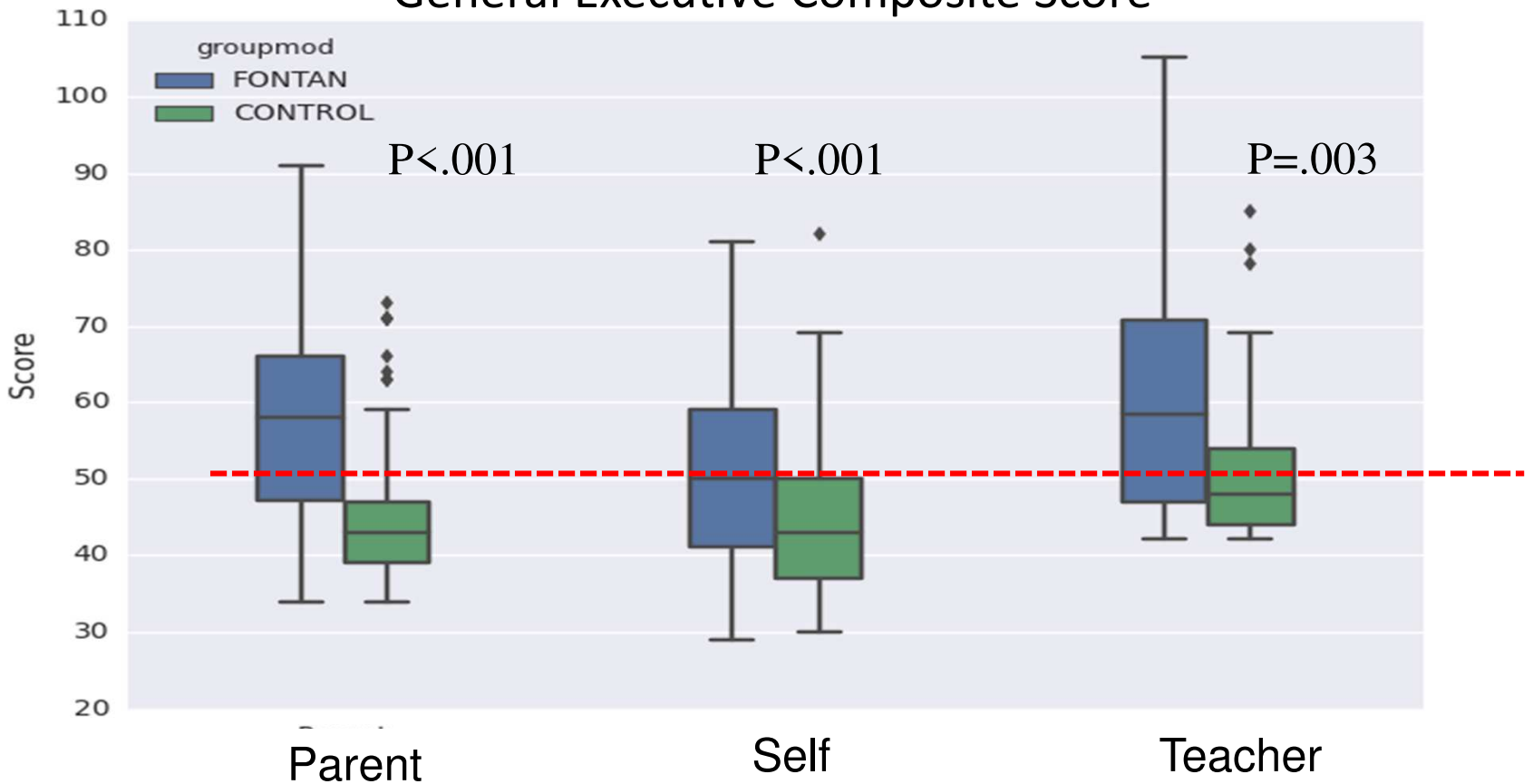


Data source: Khorashad BS, Baron-Cohen S, Roshan GM,et al. The "Reading the Mind in the Eyes" Test: Investigation of Psychometric Properties and Test-Retest Reliability of the Persian Version. J Autism Dev Disord. 2015;45(9):2651-66.

1. *What do we mean by "EF"?*



Behavior Rating Inventory of Executive Function
General Executive Composite Score



Children with Critical CHD Struggle with *Social Cognition*

- Processing of social information
- Interpretation of social situations and relationships
- Ability to “read” the emotions of other people

terrified

upset

arrogant

annoyed

terrified

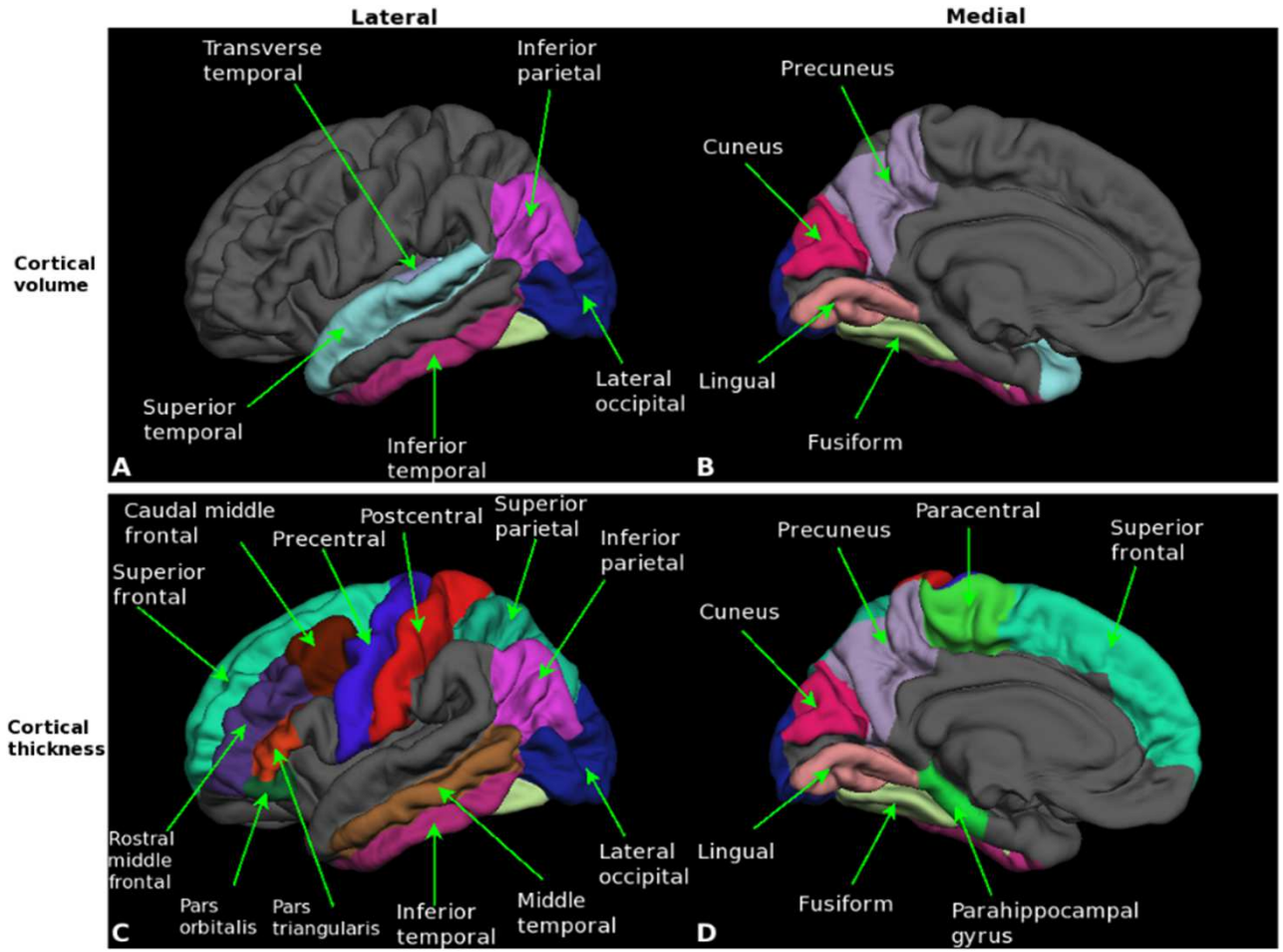
upset

arrogant

annoyed

Structural Brain MRI in Fontan Adolescents			
	Fontan (n =144)	Referents (n = 59)	P value
Any abnormality	66%	6%	**<0.001**
Focal or multifocal abnormality	60%	1%	**<0.001**
Infarction or atrophy	13%	0%	**<0.001**
Brain mineralization	54%	1%	**<0.001**
Diffuse Abnormality	9%	2%	**0.03**
Ventriculomegaly	2%	0%	0.27
Abnormal T2	7%	2%	0.12
Developmental abnormality	4%	4%	1.0

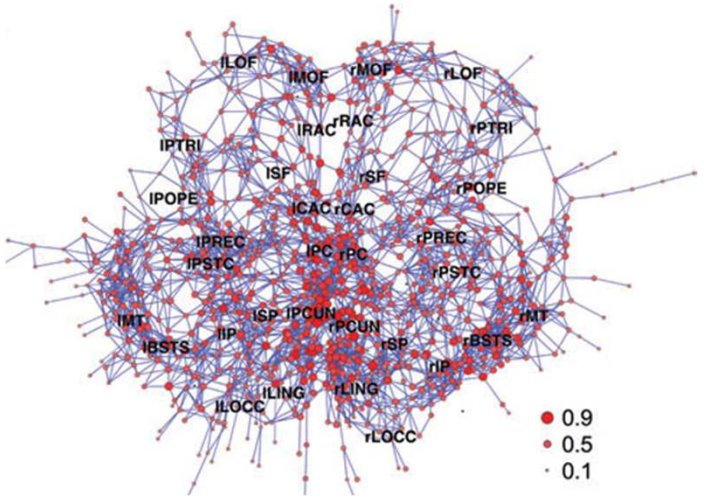
Bellinger et al. JAHA 2015

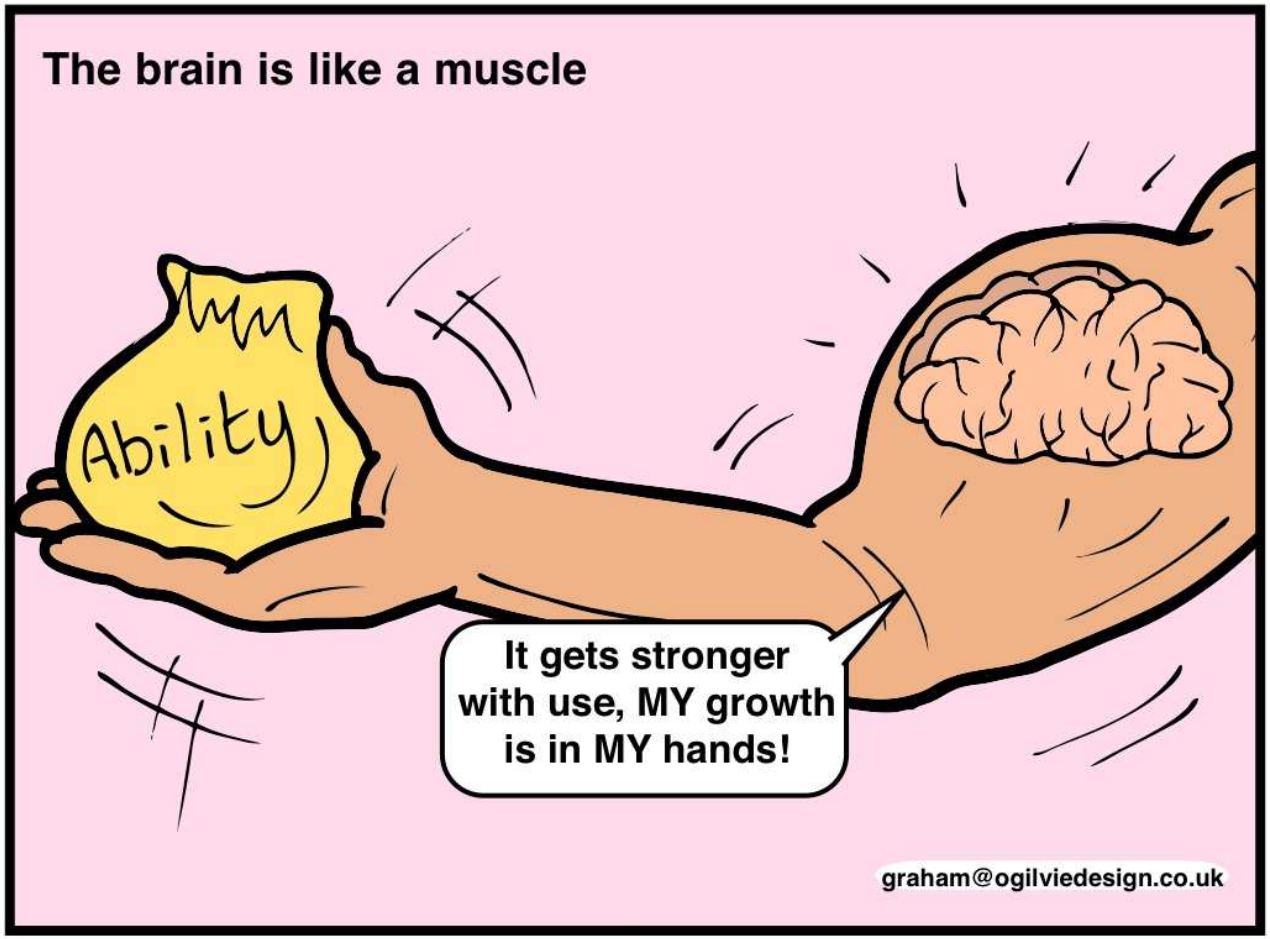

Lateral
Medial
Cortical volume
Transverse temporal
Inferior parietal
Precuneus
Cuneus
Superior temporal
Inferior temporal
Lateral occipital
Lingual
Fusiform
A
B
Cortical thickness
Caudal middle frontal
Precentral
Postcentral
Superior parietal
Inferior parietal
Superior frontal
Rostral middle frontal
Pars orbitalis
Pars triangularis
Inferior temporal
Middle temporal
Lateral occipital
Precuneus
Paracentral
Superior frontal
Cuneus
Lingual
Fusiform
Parahippocampal gyrus
C
D

But There Is Good News!
The Brain Has the Ability to Change with Learning

- **Plasticity:** The brain's ability to reorganize pathways in the brain throughout the lifespan, and especially in childhood, as a result of experience.
- The internal structure of neurons and synapses (their connections) can change.
- The number of synapses can increase.
  - 70% of synaptic connections change each day!

The CONNECTOME




The brain is like a muscle
Ability
It gets stronger with use, MY growth is in MY hands!
graham@ogilviedesign.co.uk

AHA Scientific Statement

Neurodevelopmental Outcomes in Children With Congenital Heart Disease: Evaluation and Management

A Scientific Statement From the American Heart Association

This statement has been approved by the American Academy of Pediatrics.

Bradley S. Marino, MD, MPP, MSCE, FAHA, Co-Chair; Paul H. Lipkin, MD; Jane W. Newburger, MD, MPH, FAHA; Georgina Peacock, MD, MPH; Marsha Gerdes, PhD; J. William Gaynor, MD; Kathleen A. Mussatto, PhD, RN; Karen Uzark, PhD, CNP, FAHA; Caren S. Goldberg, MD, MS; Walter H. Johnson, Jr, MD; Jennifer Li, MD; Sabrina E. Smith, MD, PhD; David C. Bellinger, PhD; William T. Mahle, MD, FAHA, Co-Chair; on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council

- Routine ND screening/testing of high-risk children with CHD
- Education of patients, families, schools

Recommendations for Children with CHD at Higher Risk for Developmental Disability

- Early intervention services or early childhood special education services
- Formal developmental and medical evaluation
  - 12-24 mos, 3-5 yrs, and 11-12 yrs of age
- After age 12 years, an evaluation plan should be determined at the discretion of the “medical home provider”
- Referral of young adults for higher education and/or vocational counseling

Conclusions

- Dramatic advances have occurred in the survival of patients with single ventricle.
- Improved survival of Fontan patients has produced new challenges for their cognitive, behavioral, and psychosocial health.
- With continued innovations, each child should reach his or her full neurodevelopmental potential.

Thank You!

Lawyer and Ethicist
HLHS/Fontan