Queenstown ACHD meeting 2017

Neurocognitive outcomes and interventions in ACHD survivors

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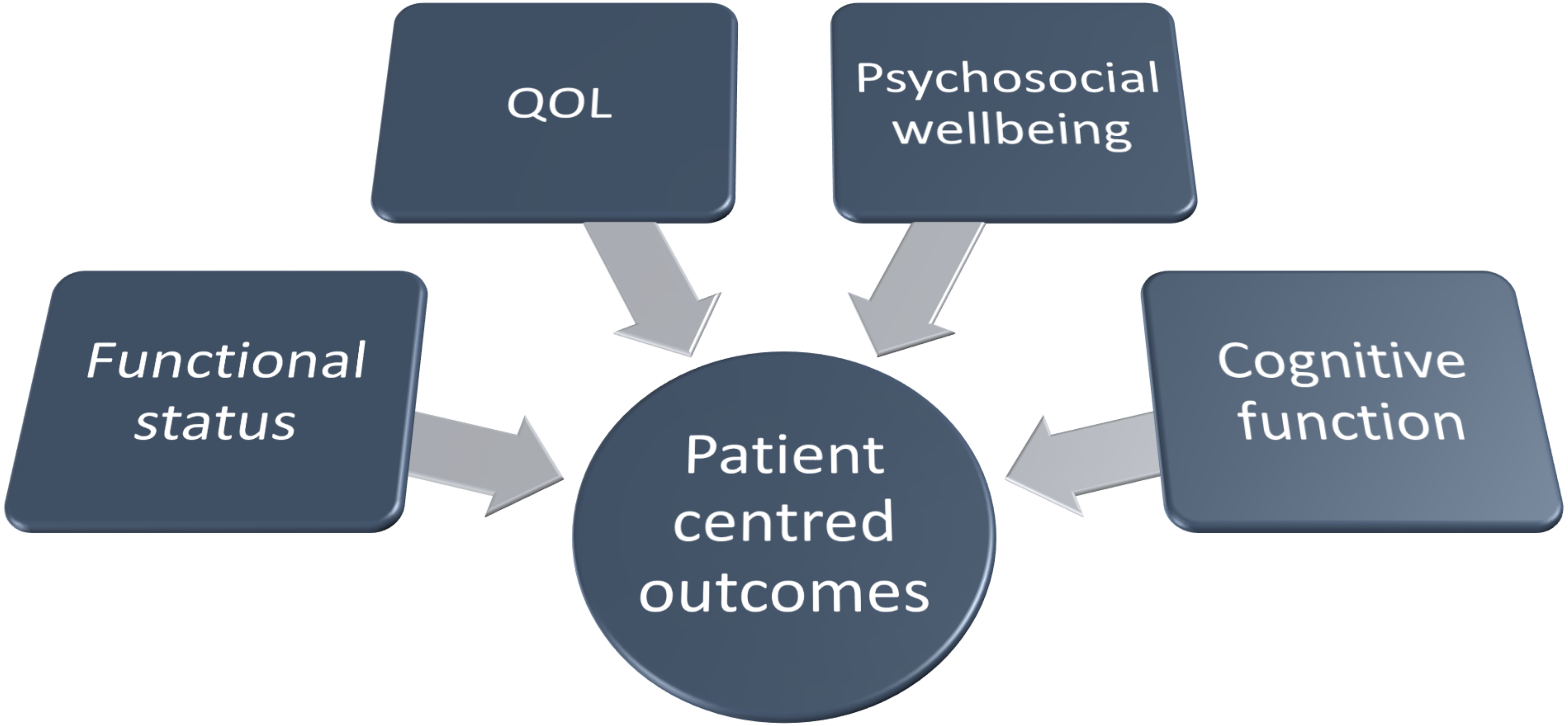
TORONTO CONGENITAL CARDIAC CENTRE FOR ADULTS

The Royal Melbourne Hospital

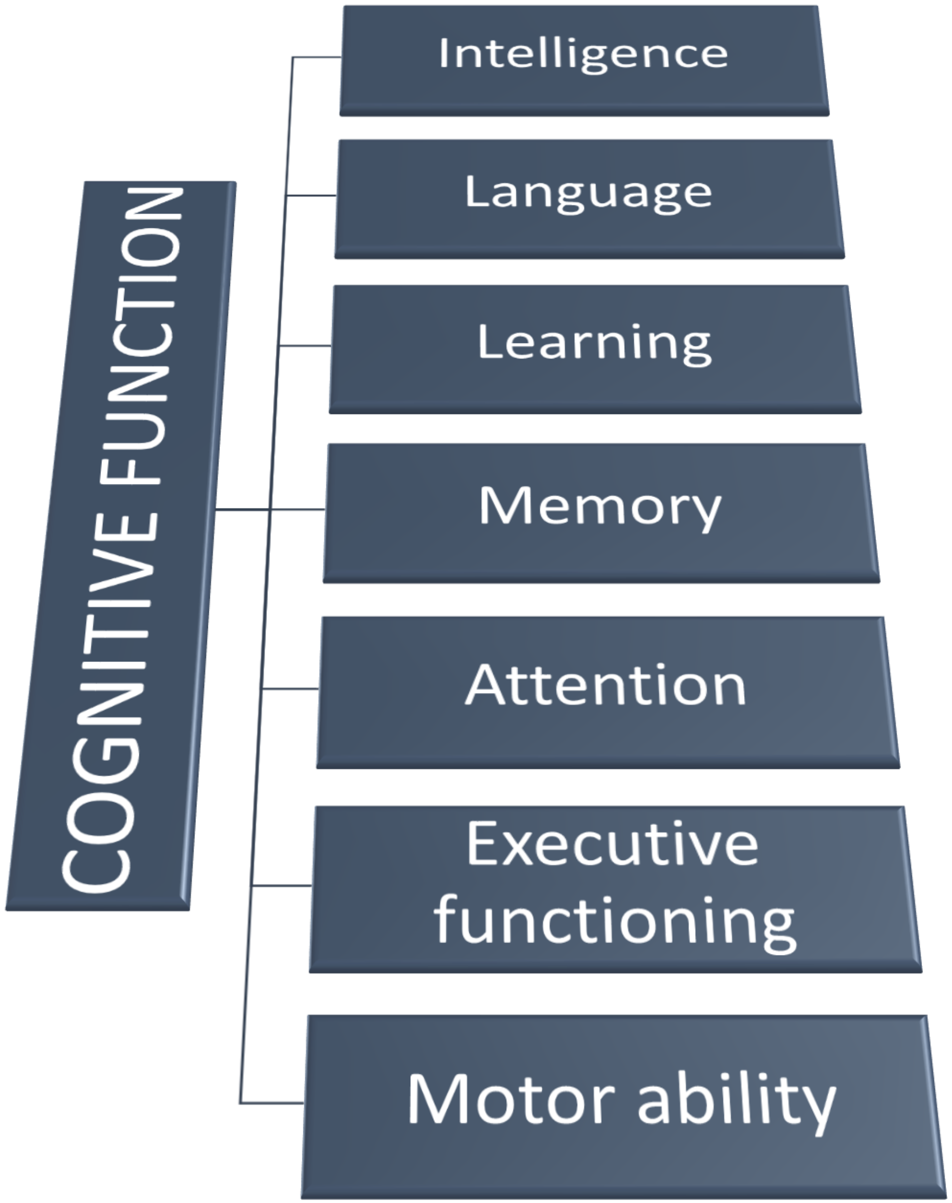
EXPANDED FOCUS:
Mortality → patient centred outcomes



Overview

1. What do mean by neurocognitive outcomes?
2. Why do we anticipate higher rates of neurocognitive difficulties in ACHD patients and what data is there available?
3. (How) can we intervene?

What do we mean by neurocognitive outcomes?


COGNITIVE FUNCTION
Intelligence
Language
Learning
Memory
Attention
Executive functioning
Motor ability

IQ testing

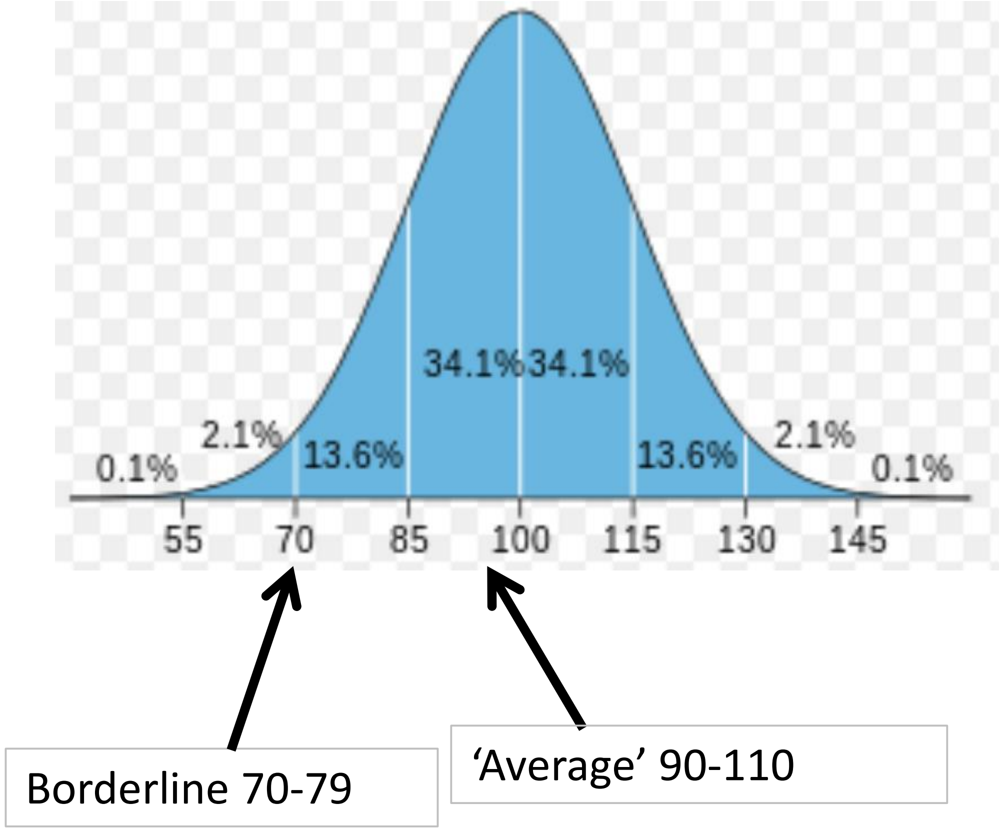
Several standardised tests available

- Most common: WAIS

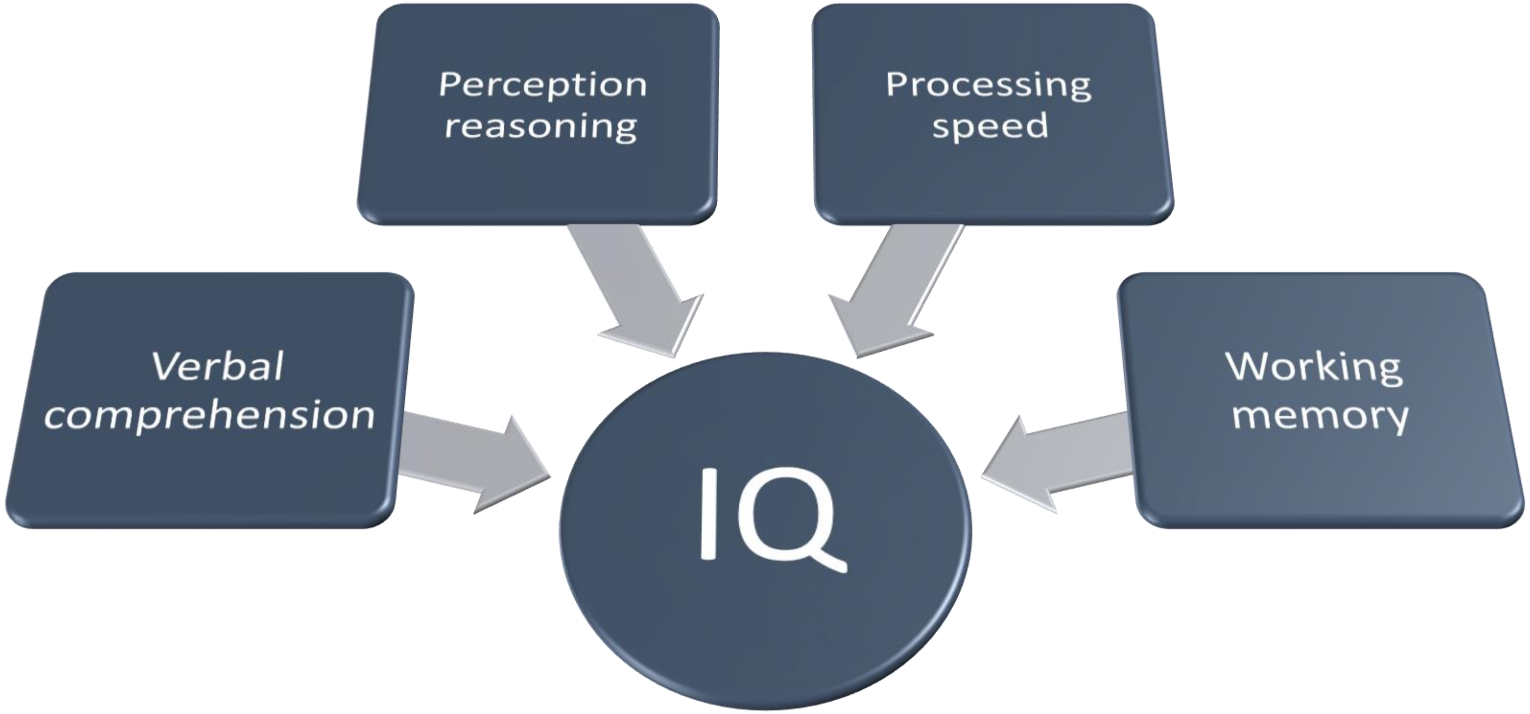
(Wechsler Adult Intelligence Scale)

Scores are age adjusted and converted to an IQ score

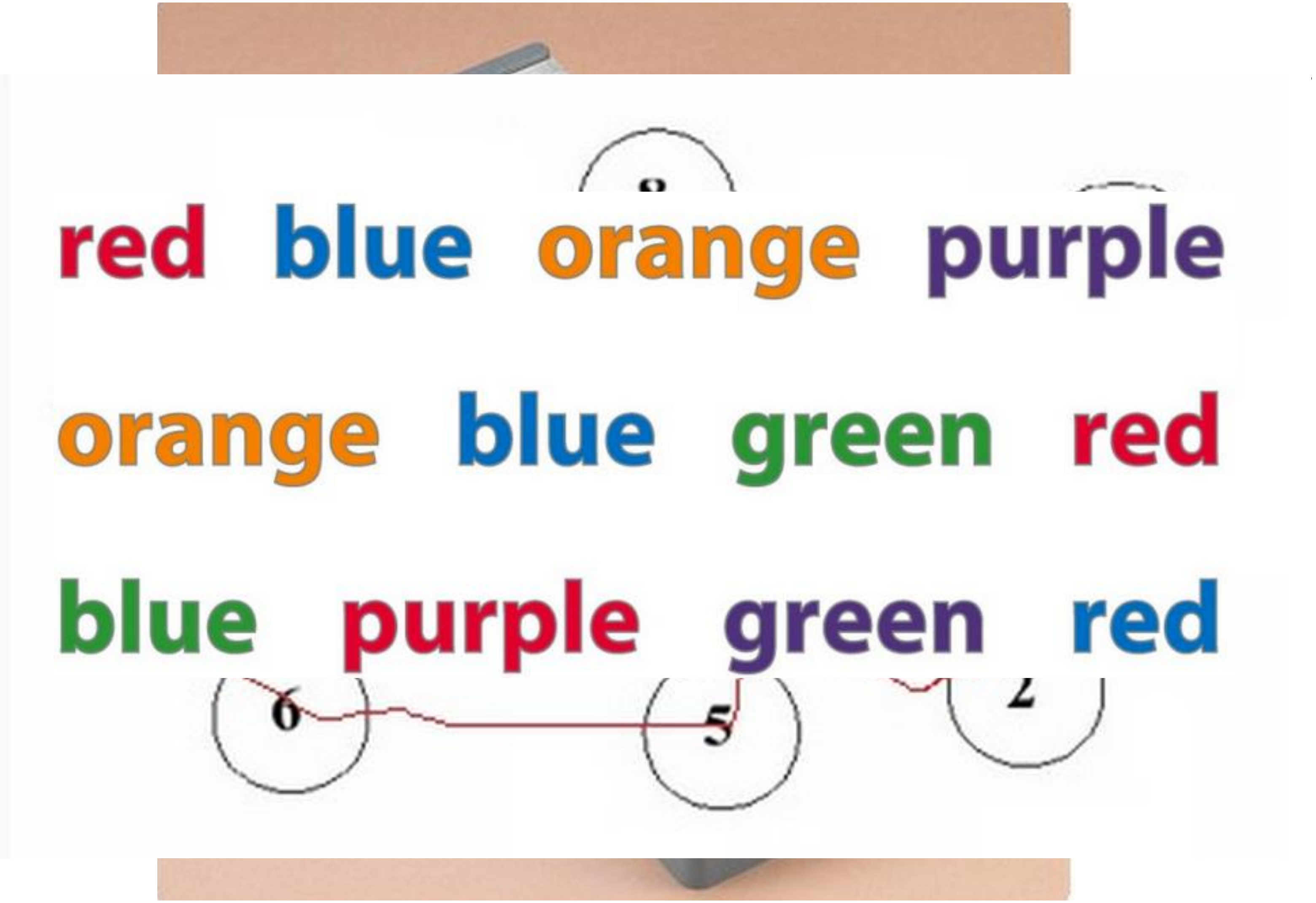
- Normalised distribution
- Not linear, not a percentage



Subscales of IQ score



Additional testing components?



Executive function:

Group of processes that control & regulate other cognitive processes

Inhibitory control

Behavioural regulation and control of attention

Working memory

Ability to keep information in mind and manipulate it

Cognitive flexibility

Ability to switch between tasks efficiently and consider information from a different perspective

Lezak et al.Neuropsychiatric Assessment 2004
Vogels et al. Eur J Heart Failure 2007
Calderon et al, Cardiol in Young 2015

Allows an individual to:

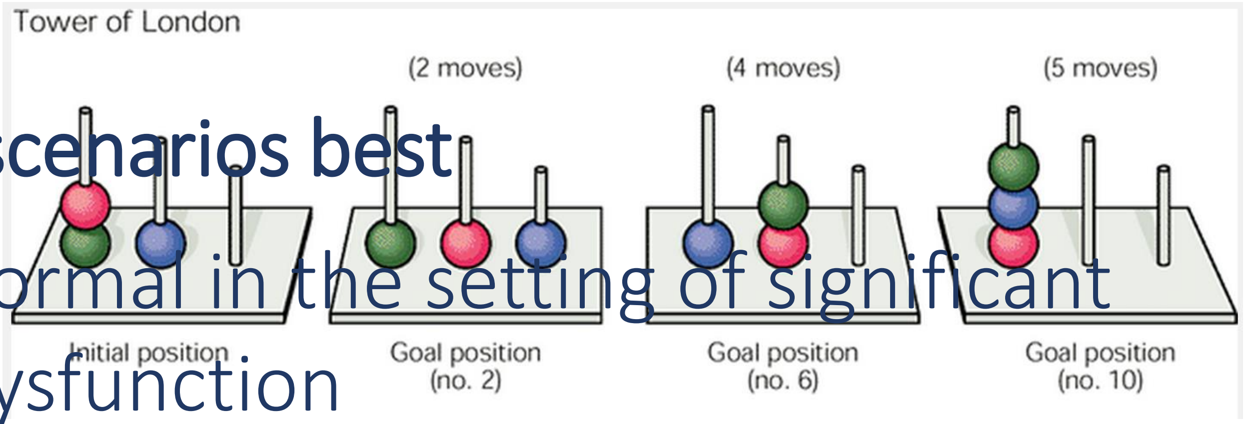
- Develop and carry out plans
- Solve problems
- Function in social structures
- Adapt to unexpected circumstances

If impaired:

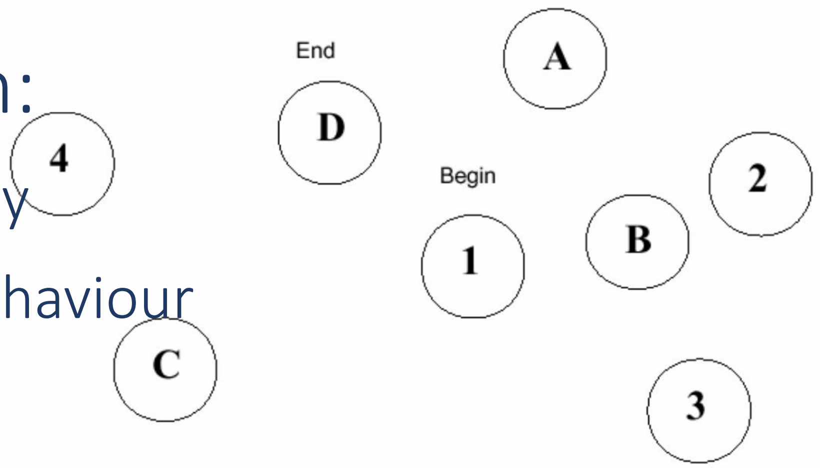
- Disorganised
- Impulsive
- Hyperactive

+- Aggressive

How to assess executive function?



- Real world scenarios best
- IQ can be normal in the setting of significant executive dysfunction
  - Clue: working memory subscale
- Impairments in:
  - set shifting ability
  - task-oriented behaviour



Why do we anticipate higher rates of neurodevelopmental difficulties in ACHD patients?

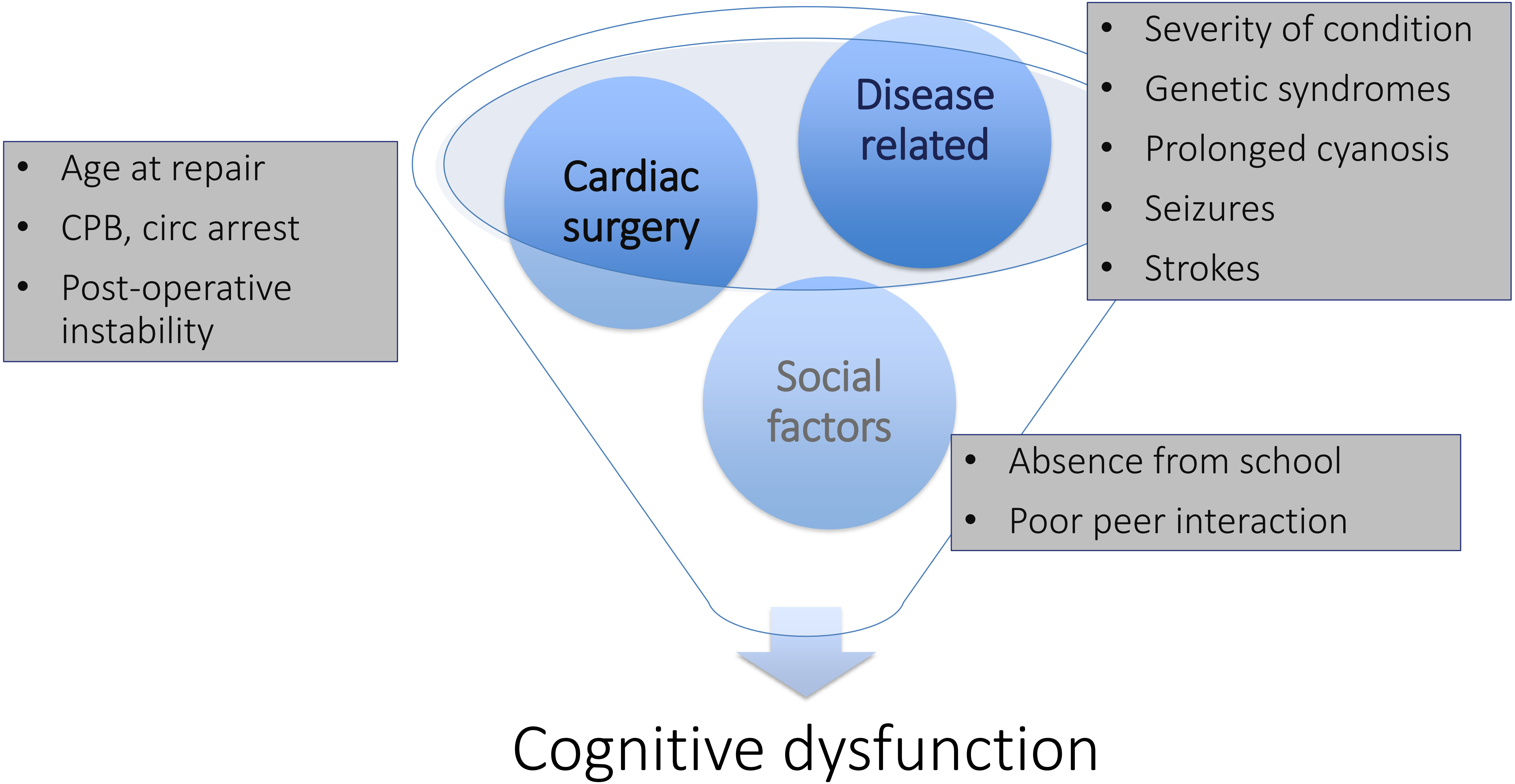
Many were children with developmental problems

These problems do not disappear
when children become adolescents or adults.

Children can 'grow into their deficits'
Defects 'emerge' as demands of life increase

"Among pediatric patients with complex CHD, there is a distinctive pattern of neurodevelopmental and behavioral impairment"

- *Mild cognitive impairment*
- *Impaired social interaction + core communication skillis*
- *Inattention and impulsive behaviour*
- *Impaired executive function*



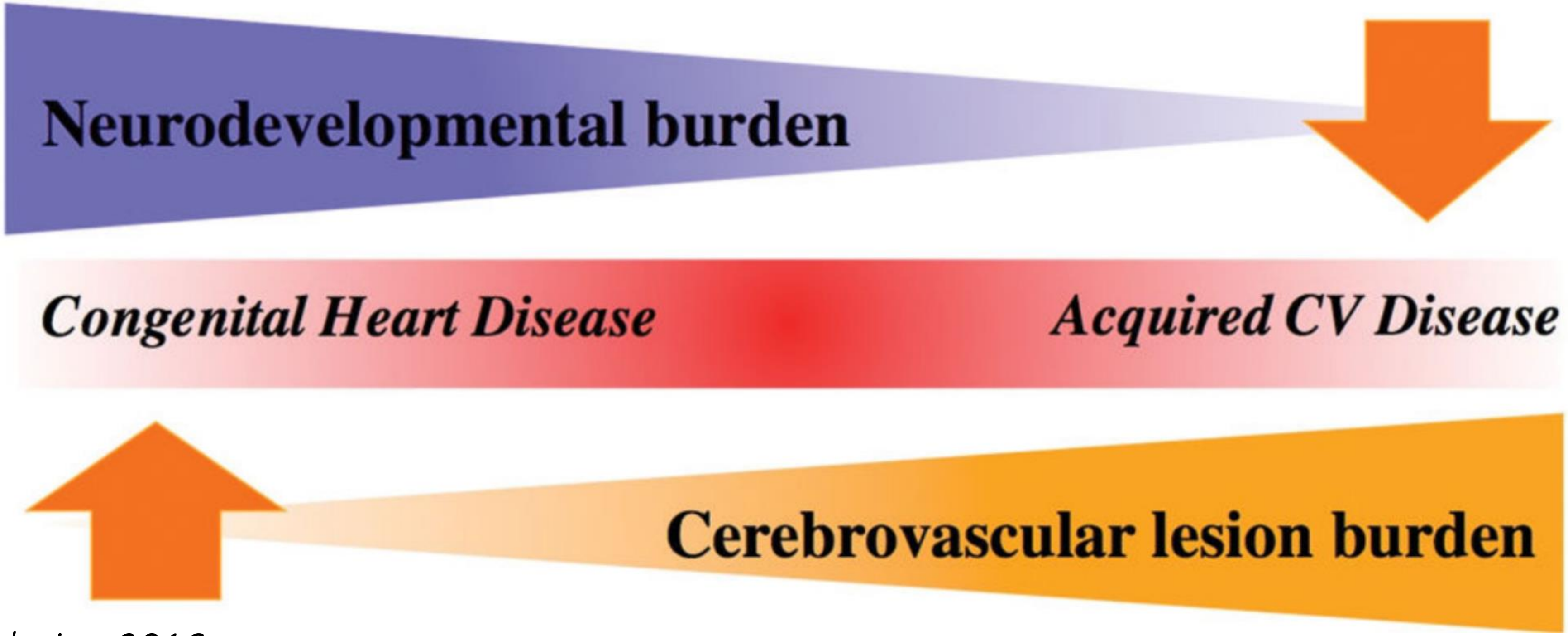
Age at repair
CPB, circ arrest
Post-operative instability
Cardiac surgery
Disease related
Social factors
Severity of condition
Genetic syndromes
Prolonged cyanosis
Seizures
Strokes
Absence from school
Poor peer interaction
Cognitive dysfunction

TERTIARY BRAIN DAMAGE

Brain changes predispose a patient to further injury or prevent repair

ADDING INSULT TO INJURY

As life expectancy increases, so does opportunity for repeated brain injury



Marelli at el. Circulation 2016

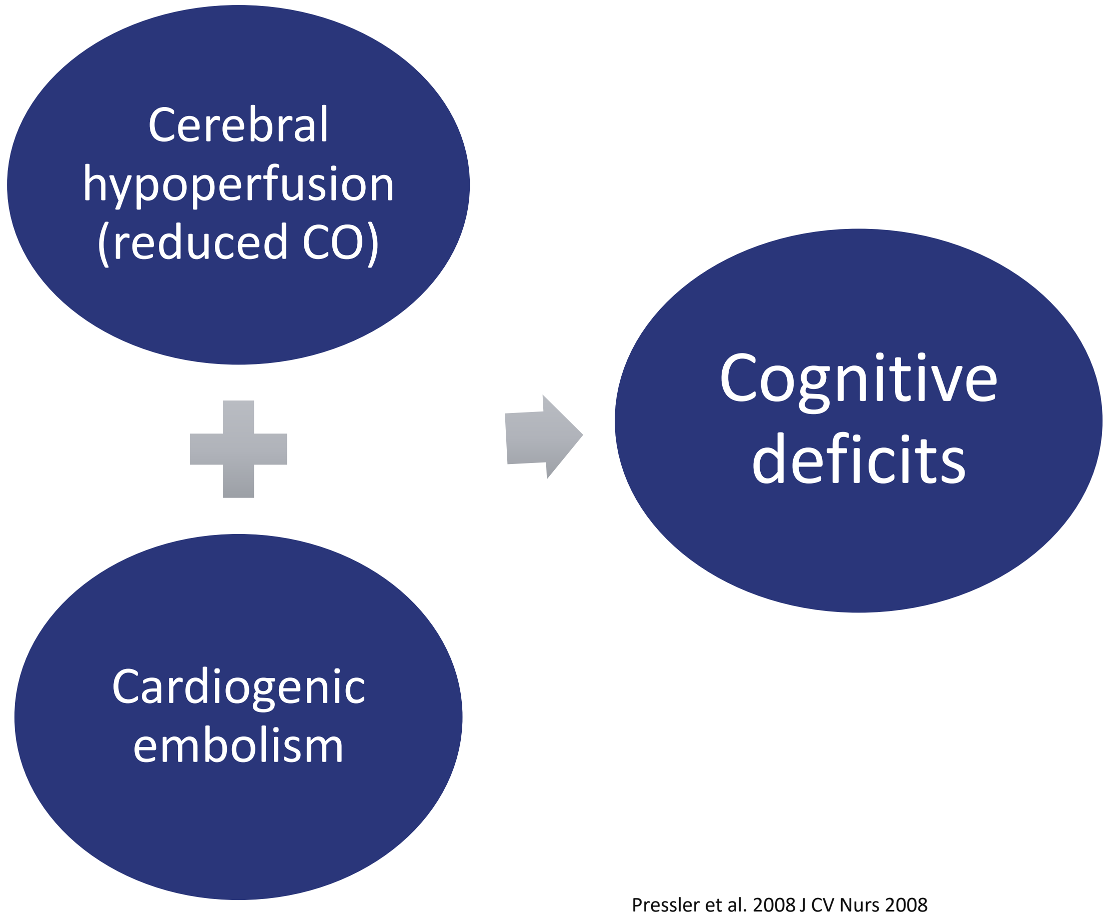
Additional insults in adulthood?

Which of the following have been associated with cognitive dysfunction in adults?

a. Heart failure
b. Atrial fibrillation
c. Critical illness
d. Stroke
e. All of the above

Heart failure

- Impairment in 1 or more cognitive domains (esp. memory and executive function) in 28-58% of patients with HF



Bauer et al. Eur J Card Nurs 2012
Bennett et al. J Cardiovasc Nurs 2003
Cacciatore et al. J Am Geraitr Soc 1998
Pressler et al. 2008 J CV Nurs 2008
Trojano et al. J Neurol 2003
Woo et al. J Cardiac Failure 2005
Vogels et al. Eur J Heart Fail 2007
Zuccala et al, Am J Med 2003
Zuccalas et l. Neurology 2001

REVIEW | Annals of Internal Medicine

Cognitive Impairment Associated With Atrial Fibrillation

A Meta-analysis

#3

Shadi Kalantarian, MD, MPH; Theodore A. Stern, MD; Moussa Mansour, MD; and Jeremy N. Ruskin, MD

Association Between AF and Cognitive Impairment or Cognitive Decline

AF associated with higher risk of cognitive impairment (regardless of stroke) with a RR ~ 1.5

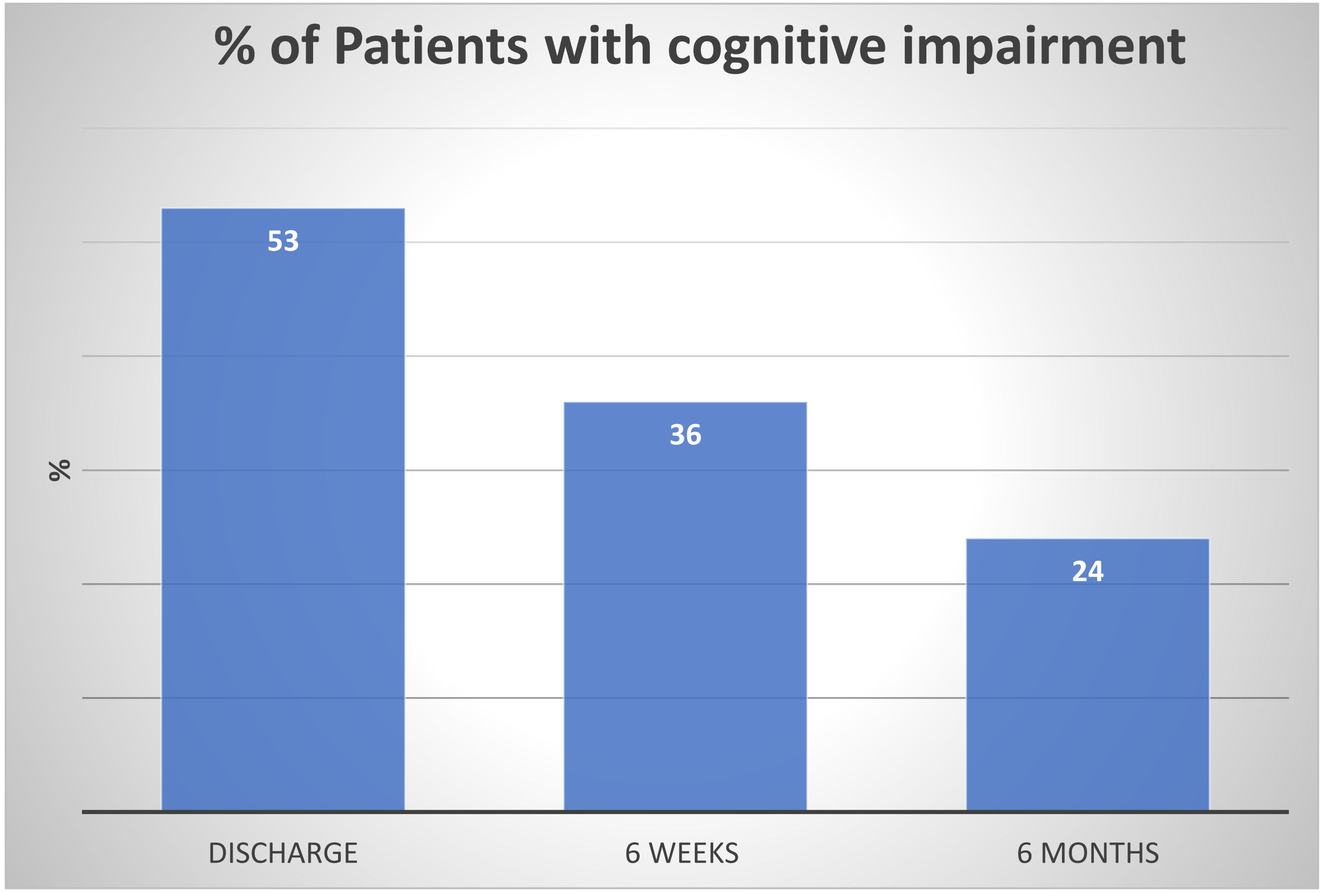
50% patients with severe CHD develop atrial arrhythmias by age 65

(Bouchardi et al Circulation 2009)

LONGITUDINAL ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER CORONARY-ARTERY BYPASS SURGERY

MARK F. NEWMAN, M.D., JERRY L. KIRCHNER, B.S., BARBARA PHILLIPS-BUTE, PH.D., VINCENT GAVER, B.S., HILARY GROCOTT, M.D., ROBERT H. JONES, M.D., DANIEL B. MARK, M.D., JOSEPH G. REVES, M.D., AND JAMES A. BLUMENTHAL, PH.D., FOR THE NEUROLOGICAL OUTCOME RESEARCH GROUP AND THE CARDIOTHORACIC ANESTHESIOLOGY RESEARCH ENDEAVORS INVESTIGATORS*

NEJM 2001

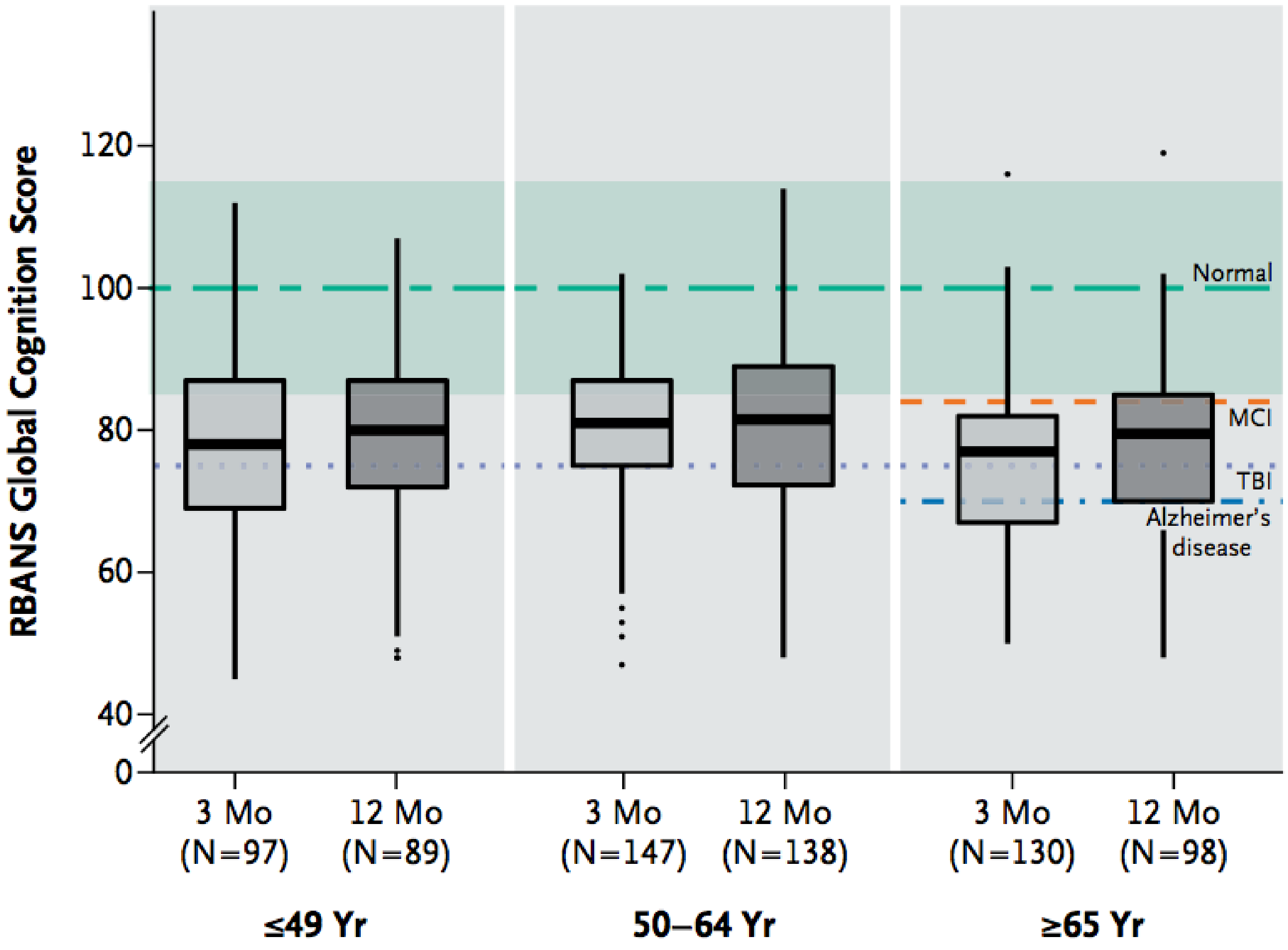


Critical illness

Long-Term Cognitive Impairment after Critical Illness

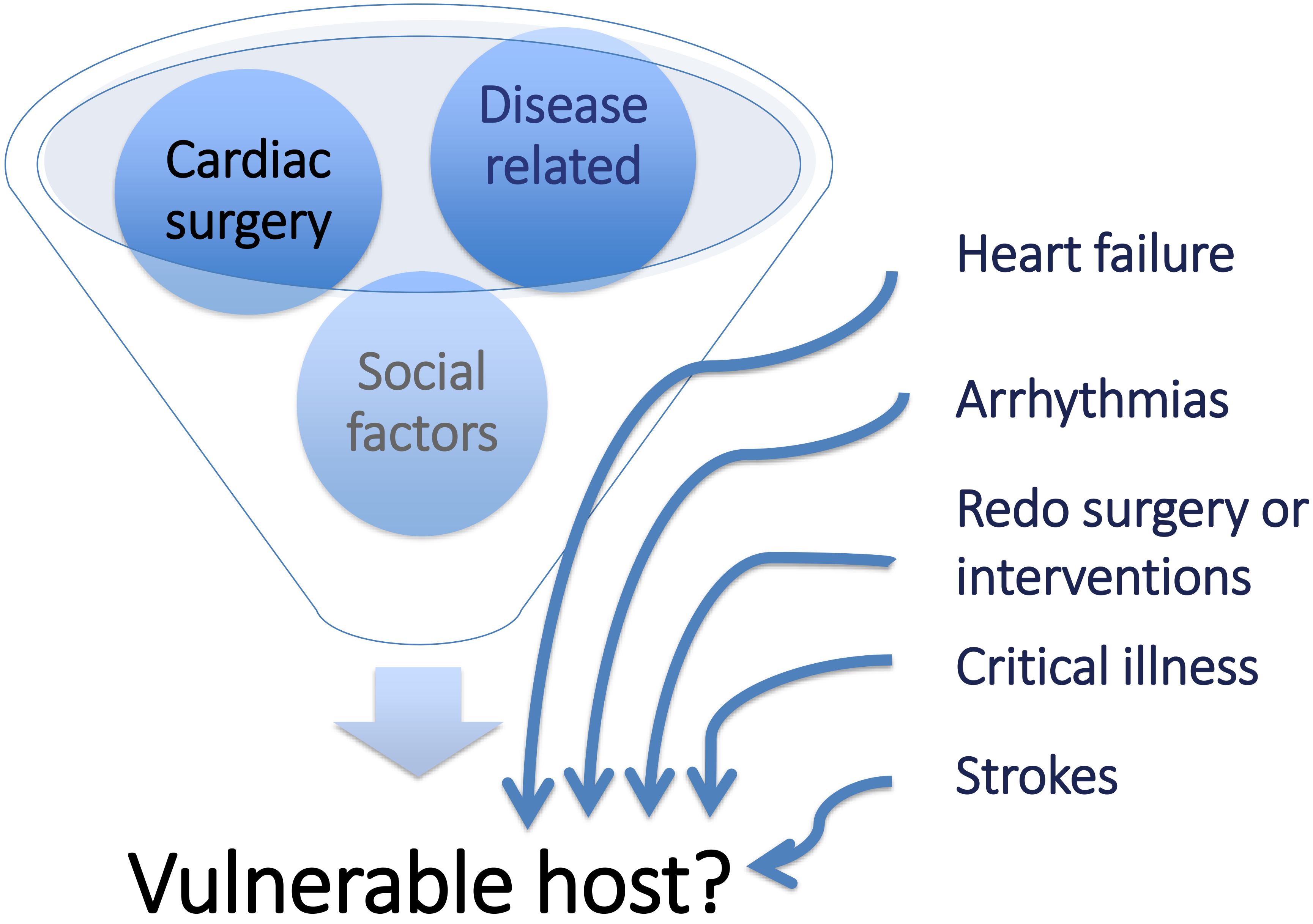
P.P. Pandharipande, T.D. Girard, J.C. Jackson, A. Morandi, J.L. Thompson, B.T. Pun, N.E. Brummel, C.G. Hughes, E.E. Vasilevskis, A.K. Shintani, K.G. Moons, S.K. Geevarghese, A. Canonico, R.O. Hopkins, G.R. Bernard, R.S. Dittus, and E.W. Ely, for the BRAIN-ICU Study Investigators*

NEJM 2013



- 821 patients with respiratory failure or shock
- 90% ventilated, 60% coma
- Similar results in all age groups

RBANS = repeatable battery for assessment of neuropsychological status



Cardiac surgery
Disease related
Social factors
Heart failure
Arrhythmias
Redo surgery or interventions
Critical illness
Strokes
Vulnerable host?

Are there neuropathological changes in ACHD patients?

- Cognitive processing speed, executive functioning, attention, visual-motor skills rely on white matter integrity

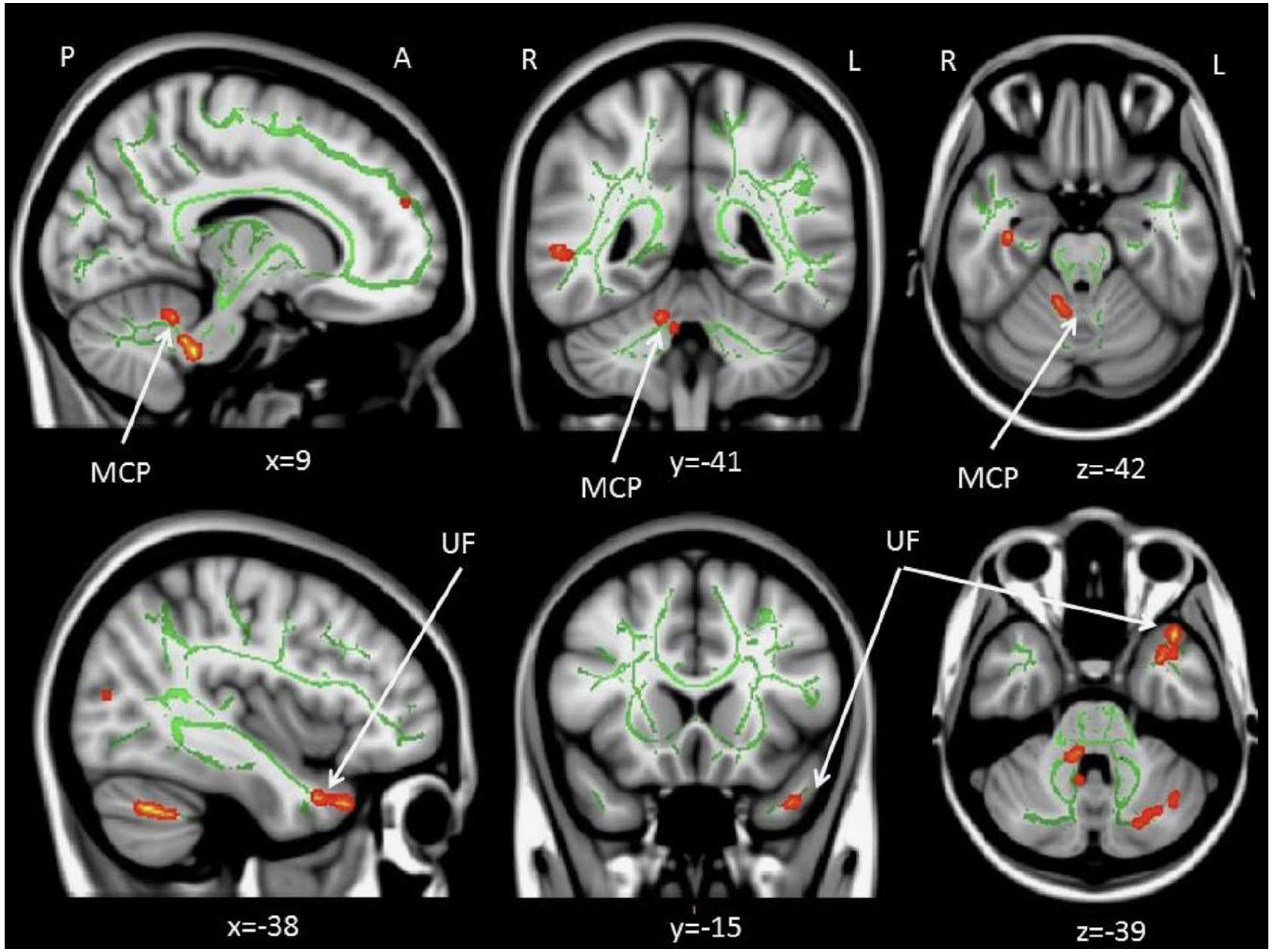
White Matter Integrity Dissociates Verbal Memory and Auditory Attention Span in Emerging Adults with Congenital Heart Disease

Brewster et al. J Int Neuropsych Society 2015

White matter disruption (fractional anisotropy) evident using novel techniques in two areas

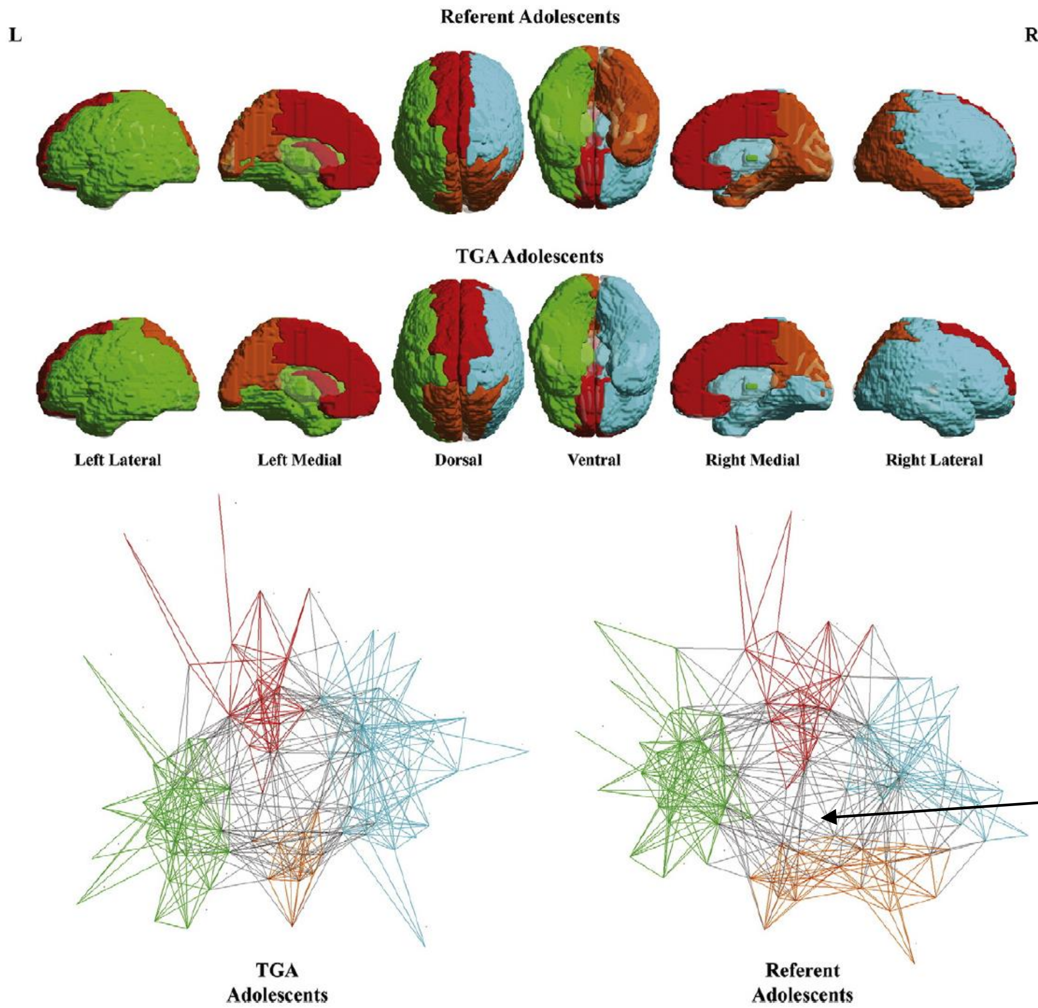
Brain-behaviour relationships established

- Uncinate fasciculus → correlated with verbal memory
- R middle cerebellar peduncle → correlated with attention span



Relationship of white matter network topology and cognitive outcome in adolescents with d-transposition of the great arteries

Ashok Panigrahy[a,b,c,d,1,*], Vincent J. Schmithorst[a,1], Jessica L. Wisnowski[a,c,d], Christopher G. Watson[e,k], David C. Bellinger[e,2], Jane W. Newburger[f,j,2], Michael J. Rivkin[e,g,h,i,2]



N=49 TGA + ASO patients (29 controls)

Graph analysis techniques to diffusion tensor imaging (DTI)

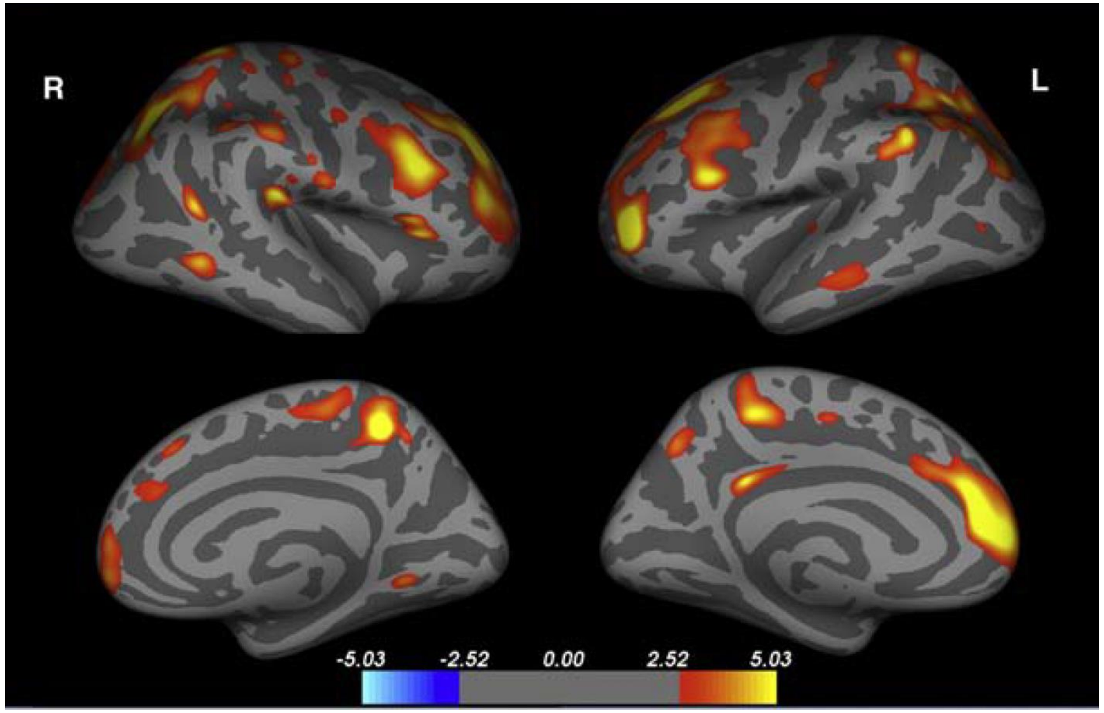
Disruption of organisation of large-scale networks within the brain

Spring-loaded visualisation – fewer connections (gray lines) between intermodular connections in TGA cohort

Neuroimage 2015

Brain Volumetrics, Regional Cortical Thickness and Radiographic Findings in Adults with Cyanotic Congenital Heart Disease☆

Rachael Cordina [a,b], Stuart Grieve [b,c,d], Michael Barnett [e,f], Jim Lagopoulos [e], Nathan Malitz [g], David S. Celermajer [a,b,*]



Cyanotic CHD (n=10)

- Marked macro and microvascular injury
- Extensive gray and white matter loss
- Local cortical (frontal lobe) and subcortical thickness reduction
- Possibly mediated by inflammation and endothelial dysfunction
  - GM volume loss $\underline{\alpha}$ hsCRP, BNP, ADMA

Neuroimage Clinical 2014

Does this translate into cognitive deficits in adults with congenital heart disease?

What do we know about cognitive functioning in adult congenital heart disease?

Manavi Tyagi,[1,5] Katie Austin,[2,*] Jan Stygall,[1] John Deanfield,[3] Shay Cullen,[3] Stanton P. Newman[1,4]

[1]*Centre for Health Services Research, School of Health Sciences, City University London;* [2]*School of Psychology, University of Surrey;* [3]*GUCH Unit, The Heart Hospital, University College of London Hospitals NHS Foundation Trust;* [4]*Division of Cardiovascular Sciences, University College London (UCL);* [5]*Division of Medicine, University College London (UCL), London, United Kingdom*

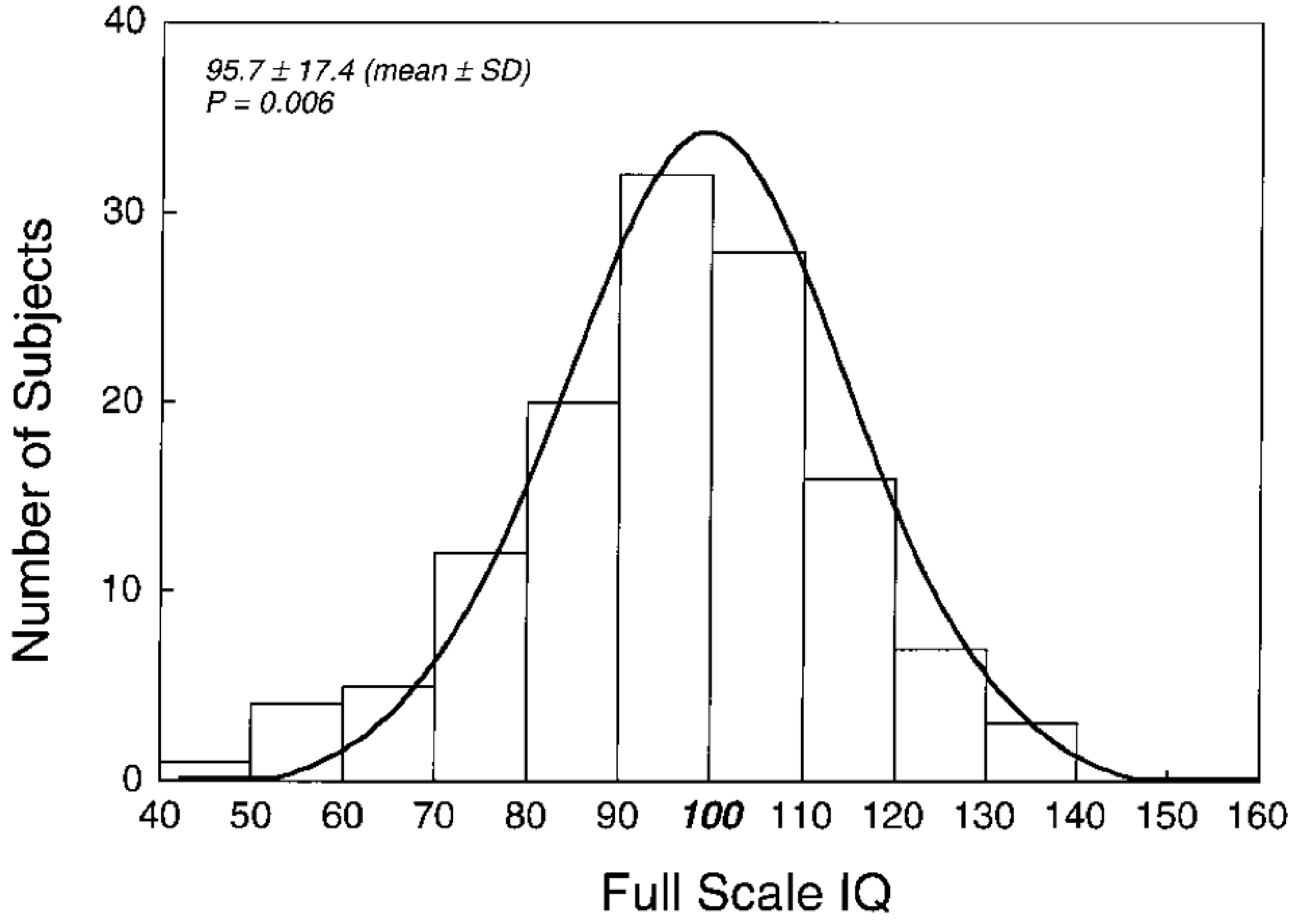
- Search of six databases
  - Inclusion criteria:
    - Adults with CHD + objective cognitive assessment
    - English language, peer-reviewed publications
- 5 articles only identified
  - One was a subset analysis of another

Cardiology in the Young 2014

	Sample	Control	Cardiac defect	Assessment tool
Utens[1] *(Netherlands)*	N=242 Mean age 22 Cross-sectional	Reference group	Mixed (ASD, TOF TGA)	Groniger intelligence test (Short form)
Wernovsky[2] *(Boston)*	N=133 Mean age 14	Normed population data	Fontan	Age appropriate IQ test (WAIS)
Eide[3] *(Norway)*	N=166 Mean age 19 Retrospective cohort	384 000 healthy army recruits	Mixed (TGA, VSD/ASD)	Validated Norwegian IQ test
Daliento[4] *(Italy)*	N=54 Mean age 32	Reference group	TOF	Raven's matrices for IQ AND 11 tests to evaluate other domains

[1] J Psychosom Res 1994
[2] Circulation 2000
[3] Pediatr Res 2006
[4] Heart 2005

IQ largely within normal range in these studies

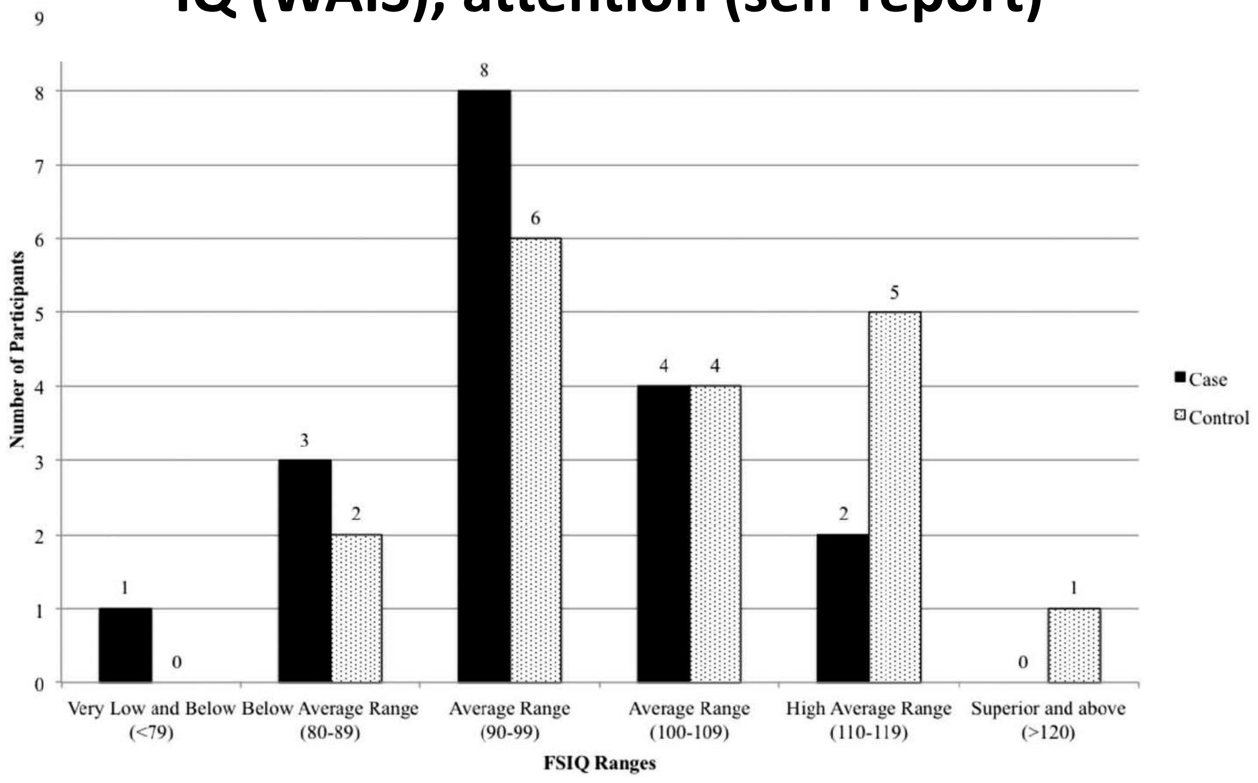


- IQ lower in:
  - More complex disease
  - Cyanosis

Tyagi et al. Cardiol in the Young 2014
Wernovsky et al. Circulation 2000

Cognitive and attentional functioning in adolescents and young adults with Tetralogy of Fallot and d-transposition of the great arteries

N=18 post TOF or TGA surgery
Sibling matched
IQ (WAIS), attention (self-report)



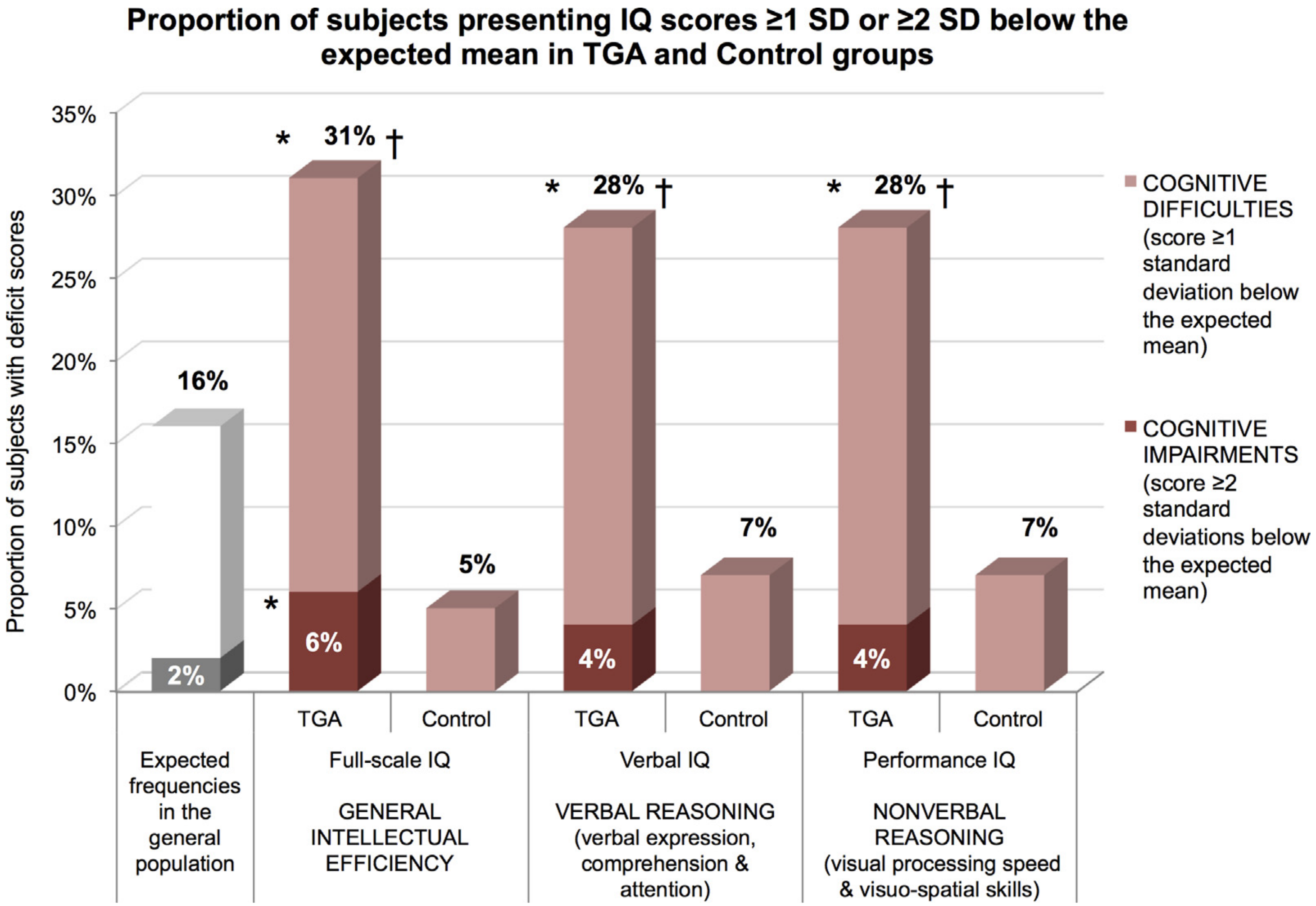
- Lower full scale IQ 96 v 103
  - Relative strength in verbal comprehension
- Attention problems higher in CHD patients (self report and mother report)

Murphy et al. Child Neuropsychology 2017

Cognitive outcomes and health-related quality of life in adults two decades after the arterial switch operation for transposition of the great arteries

Kalfa et al. JCTVS 2017

- N= 67 with TGA + ASO
  (43 matched controls)
- Mean age 23
- IQ (WAIS): Mean IQ 95 v 103*
- Risk factor:
  - Older age at surgery



*P<0.001

Little research on specific areas of cognitive function

- IQ scores are gross measures of overall cognitive functioning
- May mask a variety of subtle impairments

Predictors of Memory Deficits in Adolescents and Young Adults with Congenital Heart Disease Compared to Healthy Controls

Nancy A. Pike[1]*, Mary A. Woo[1], Marie K. Poulsen[2], Wendy Evangelista[1], Dylan Faire[1], Nancy J. Halnon[3], Alan B. Lewis[4] and Rajesh Kumar[5,6,7,8]

UCLA
N=80 (76 controls)
Memory testing (WRAML2)

- **Significant memory deficits** in immediate and delayed tasks in a high proportion of patients
  - 50% v 4% in healthy controls
- Predictor = **number of surgeries**
- **Verbal memory worse than visual memory**
  - visual educational material preferable at transition etc.

Frontiers in Paediatrics 2016

Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes *Heart* 2005

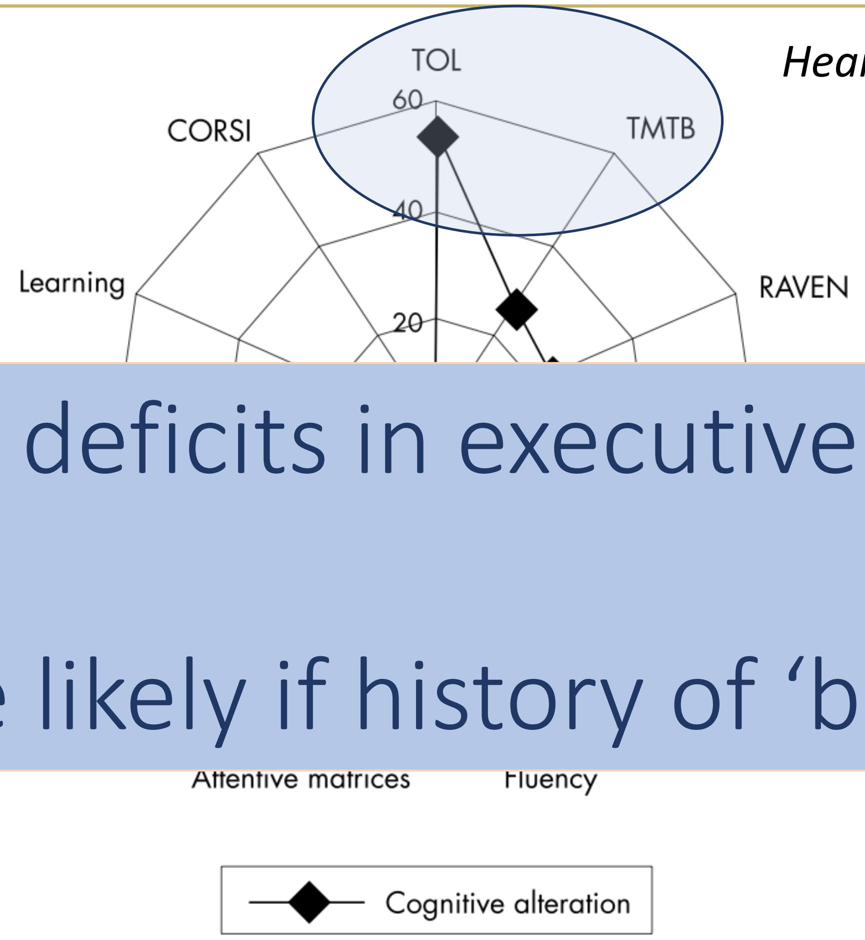
L Daliento, D Mapelli, G Russo, P Scarso, F Limongi, P Iannizzi, A Melendugno, E Mazzotti, B Volpe

- 54 patients with TOF (Italy)
  - Mean age 32y
  - Mean age 8y at operation. All CPB + deep hypothermia
- Battery of 11 tests
  - IQ largely within normal range

Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes

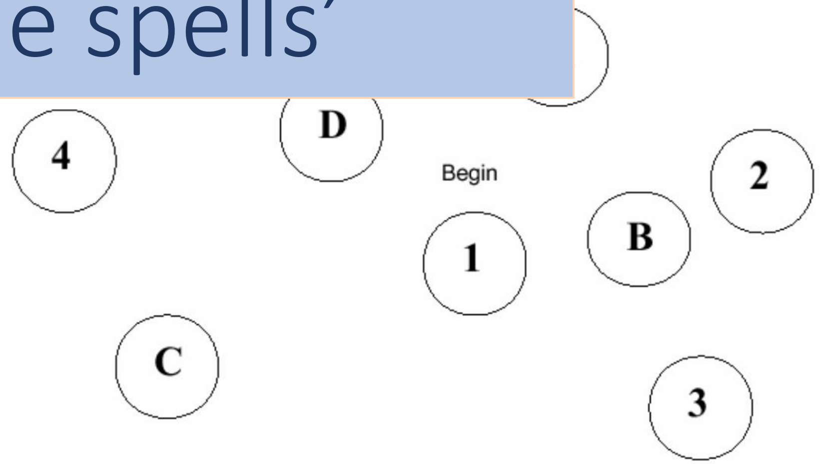
L Daliento, D Mapelli, G Russo, P Scarso, F Limongi, P Iannizzi, A Melendugno, E Mazzotti, B Volpe

Heart 2005



Clear deficits in executive functioning

More likely if history of 'blue spells'



Neurocognitive and executive functioning in adult survivors of congenital heart disease

NICHE study, Texas

– Cohort study (n=48)
  - Adults 18-49y
  - Moderate or severe CHD*
  - Cardiac surgery for CHD <5y age

Moderate
- AVSD, Coa, Ebstein, TOF, VSD

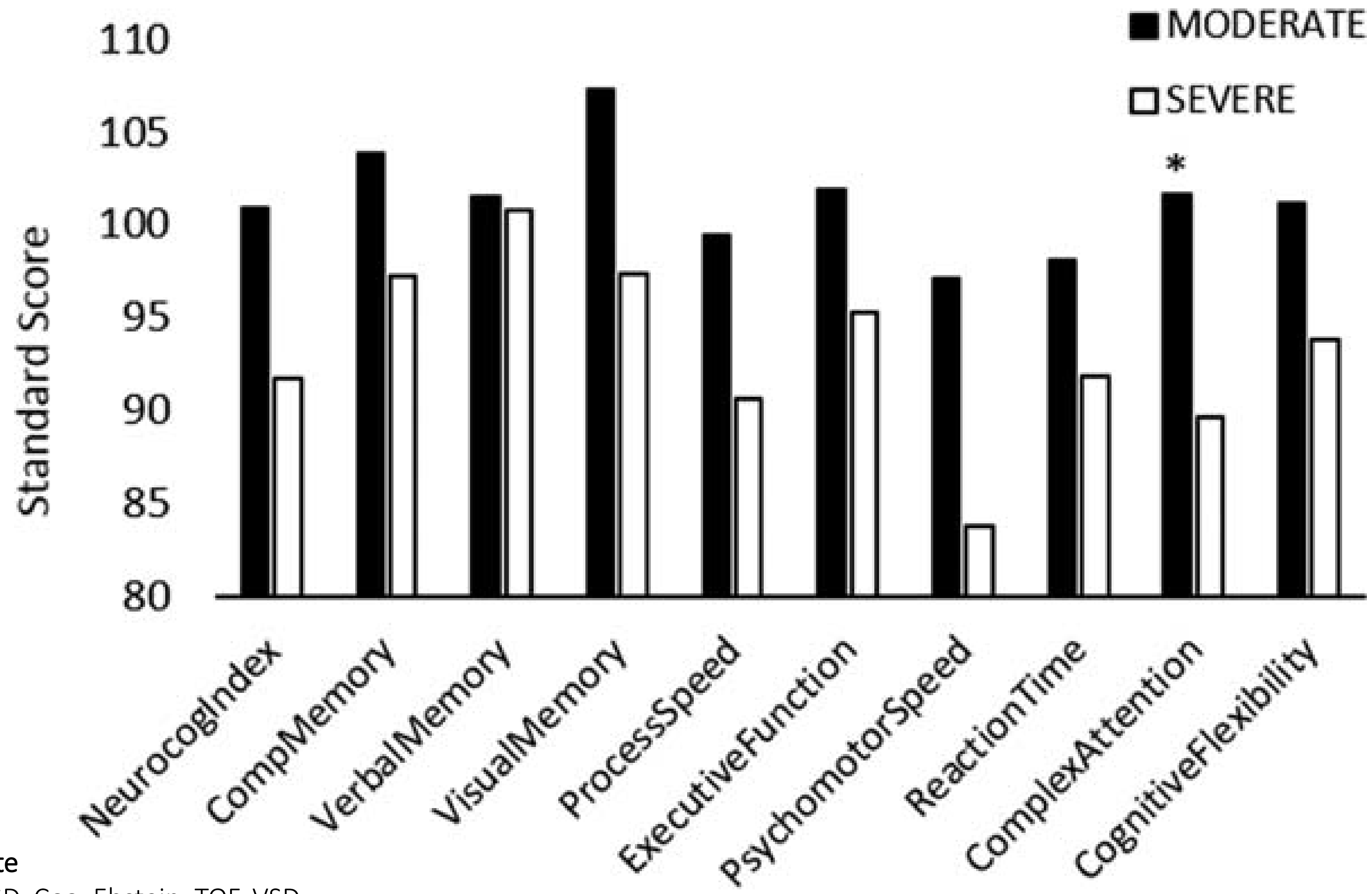
Severe
- Cyanotic, Fontan, TGA

– Neurocognitive tests
  - Computer based test assessing a variety of domains
  - BRIEF self-report form to assess executive function

**32nd Bethesda Guidelines*

Klouda et al. Congenital Heart Disease 2017

NICHE Study: deficits worse with complex disease



Severe vs. moderate

- Worse in all domains
- 6 fold increase in 'moderate neurocognitive impairment'

Moderate

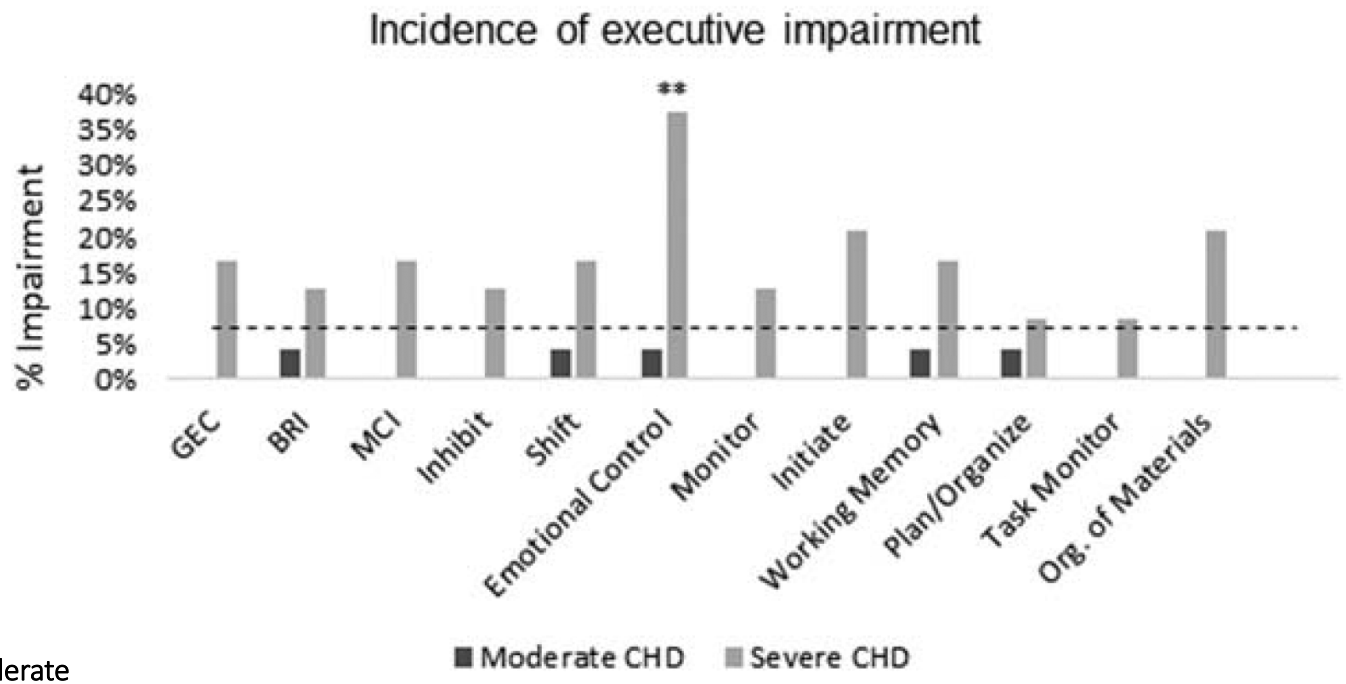
- AVSD, Coa, Ebstein, TOF, VSD

Severe

- Cyanotic, Fontan, TGA

NICHE study : Executive impairment in severe CHD

Problems with emotional regulation in particular



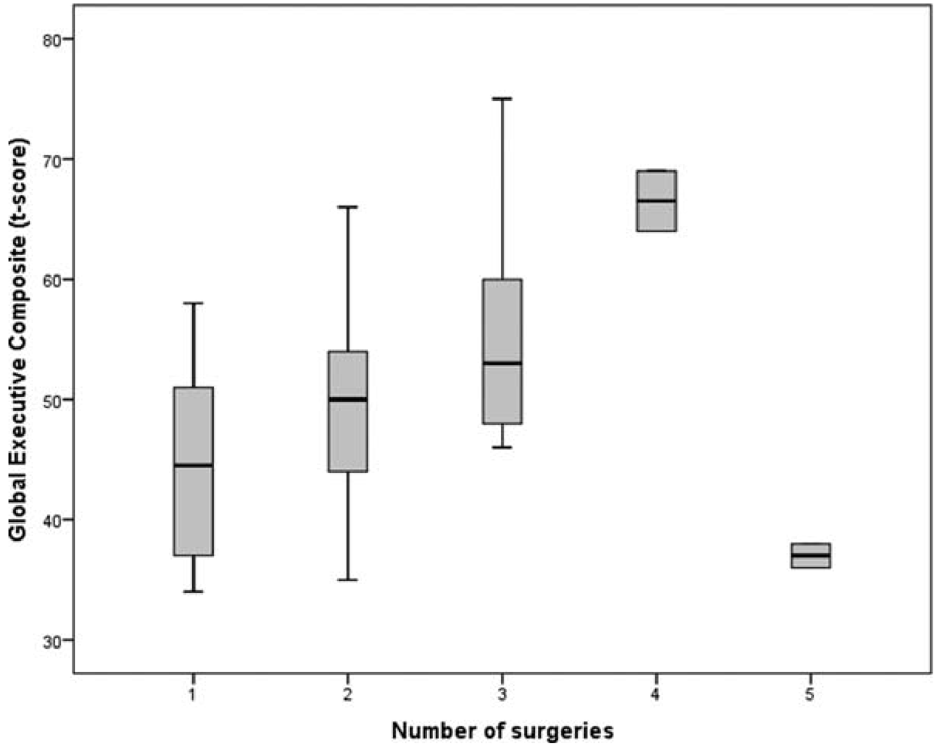
Moderate

- AVSD, Coa, Ebstein, TOF, VSD

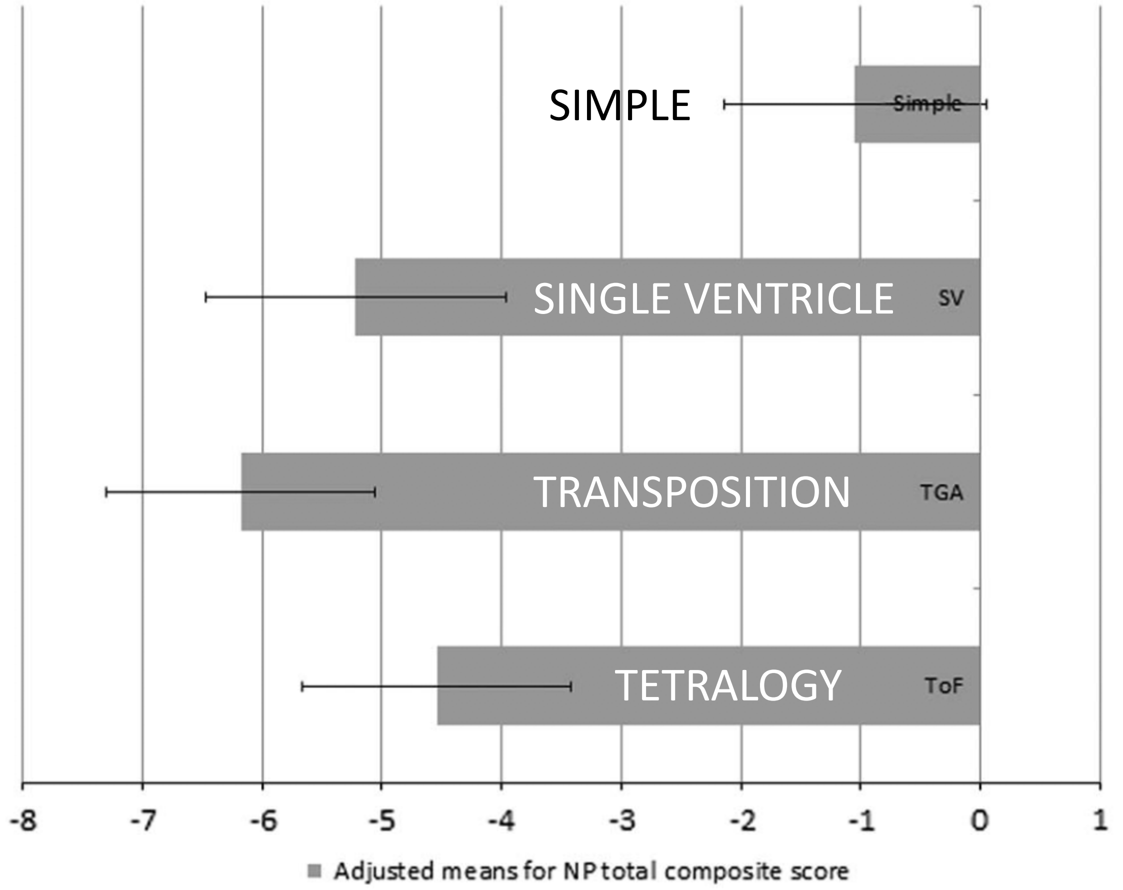
Severe

- Cyanotic, Fontan, TGA, pulmonary atresia

Executive functioning strongly correlated to number of cardiac operations



Cognitive dysfunction in adult CHD with different structural complexity



- Cross-sectional study at Heart Hospital, London (N=310)
- Battery of 15 tests
- IQ within normal range
- 41% showed impaired function on at least 3 tests
- **Significant executive dysfunction**
  - Stroop, WCST, TMTB

Tyagi et al. Cardiology in the Young 2017

Implications of cognitive impairment in ACHD patients

- Adherence
  - Ability to manage complex treatment regimens
  - Ability to assess and self-manage symptoms
- Ability to understand patient education
- Loss to follow-up
- Medical consent

Implications of cognitive impairment in ACHD patients

- Association with social functioning[1]
  - Specific impairments in **theory of mind** (esp. 'third person')[2]
    - Eg. Pragmatic language impairment, difficulty reading social cues
  - May limit ability to form healthy relationships
- Association with psychiatric disorders[3]
  - 3 x general population
- Association with ADHD[4 5]
  - Up to 1/3

[1]Marino et al, Circulation 2012
[2]Chiavarino et al. J Health Psych 2013
[3]Kovacs et al, Int J Card 2009
[4]Hansen et al. Pediatr Int 2012
[5]Yamada et al. Can J Card 2013

Identification: *may be subtle*

May manifest as:

- Workplace or Education issues
  - Poor grades or ‘Learning disability’ at school
  - Struggling with higher education
  - Difficulty holding a job
- Behavioural issues
  - Crime, addiction, risk-taking
- Psychological issues
- Difficulties with social / intimate relationships

Royall et al. J Am Geriatr Soc 1992
Schillerstrom et al. Psychosomatics 2005

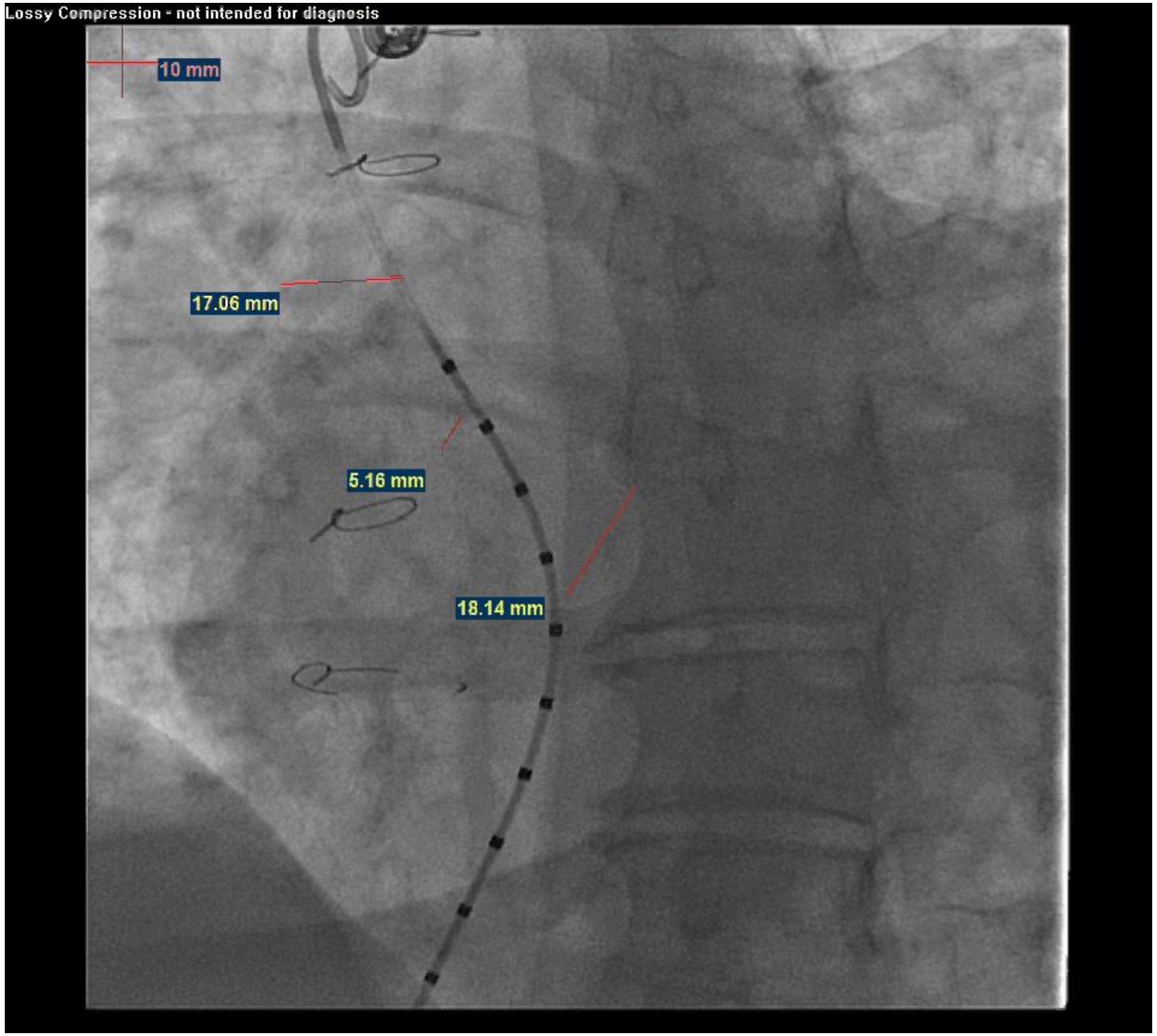
What to do once suspect cognitive dysfunction?

- No good screening tests
  - Clinical history and collaborative history
  - MMSE not useful
- Formal assessment?
  - Neuropsychologist

  +- vocational/educational counselling

  +- community living assessment (OT)
- Assess for associated psychological issues

(How) can we intervene?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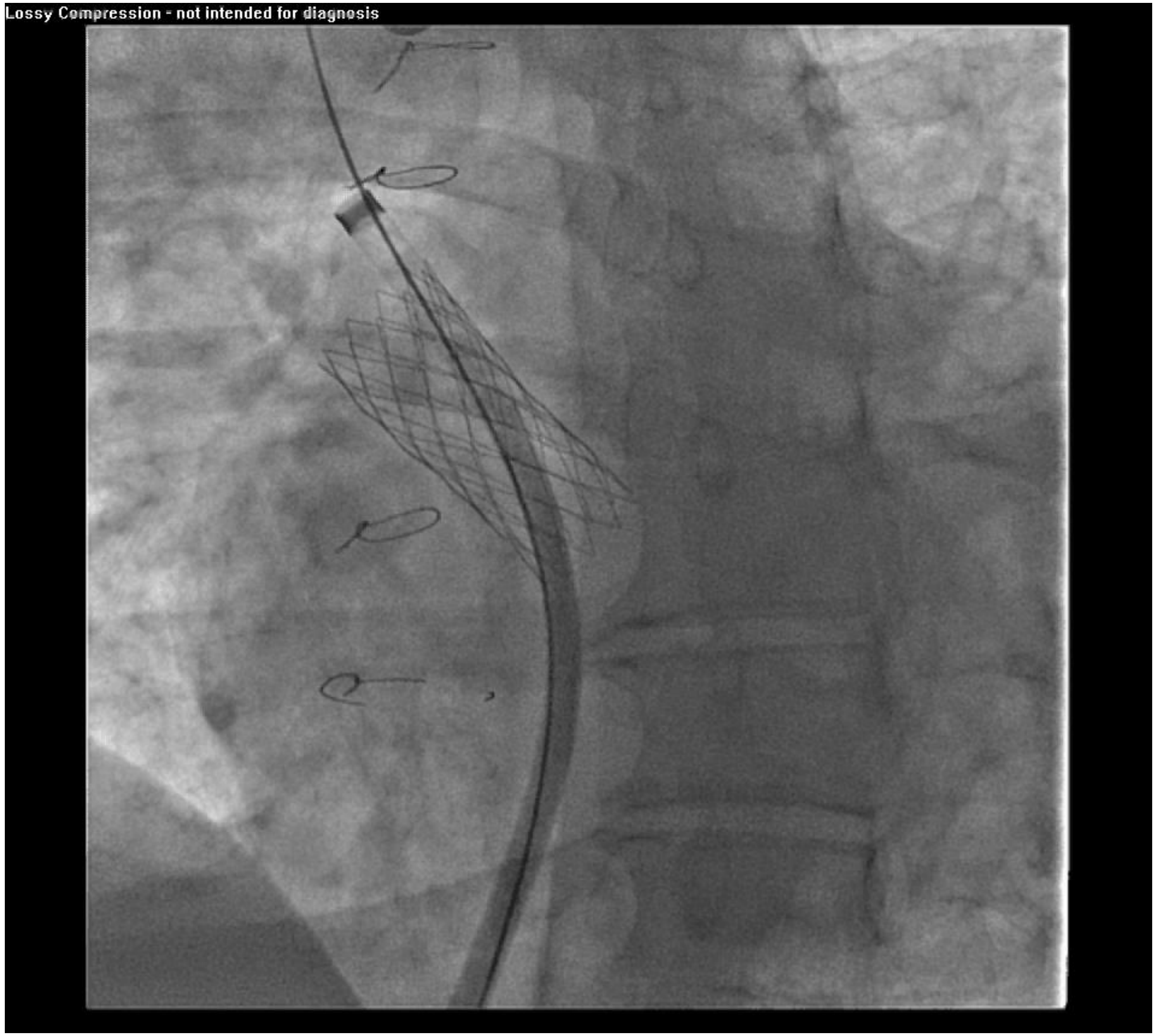

Lossy Compression - not intended for diagnosis

Interventions:
Compliance, self-management

- No specific interventions documented in literature for ACHD patients

- Compensatory mechanisms
  - Modify communication re medical condition
    - Repetition, multiple modalities (verbal, written)
    - Educational materials
    - "Internet-delivered health behaviour change interventions"
  - Frequent medical contact
    - Role of nurse practitioner

Interventions for executive dysfunction

- Metacognitive approaches[1 2]
  - Goal management training (GMT)
    - Rehabilitation technique (Acquired brain injury)
    - Complex tasks divided into smaller tasks
- Working memory training[3 4]
  - Structured computer based programs (eg Cogmed)

[1]*Levine et al. J Int Neuropsychol Soc 2000*
[2]*Krasny-Pacini et al. Disabil Rehabil 2014*
[3]*Soderqvist et al. Dev Psychol 2012*
[4]*Rueda et al. Dev Coogn Neurosci 2012*

Interventions
Pharmacological therapy?

- Methylphenidate
  - Improved executive function in ADHD patients[1 2]
  - Arrhythmia / MI risk in ACHD patients?[3 4]

- Sertaline
  - Improved executive function in depressed patients with mild TBI[5]

[1]Kuperman et al. Ann Clin Psych 2001
[2]Meyers et al. J Clin Oncol 1998
[3]Shin et al. BMJ 2016
[4]Sinha et al. Case Rep Cardiol 2016
[5]Fann et al. Psychosomatics 2001

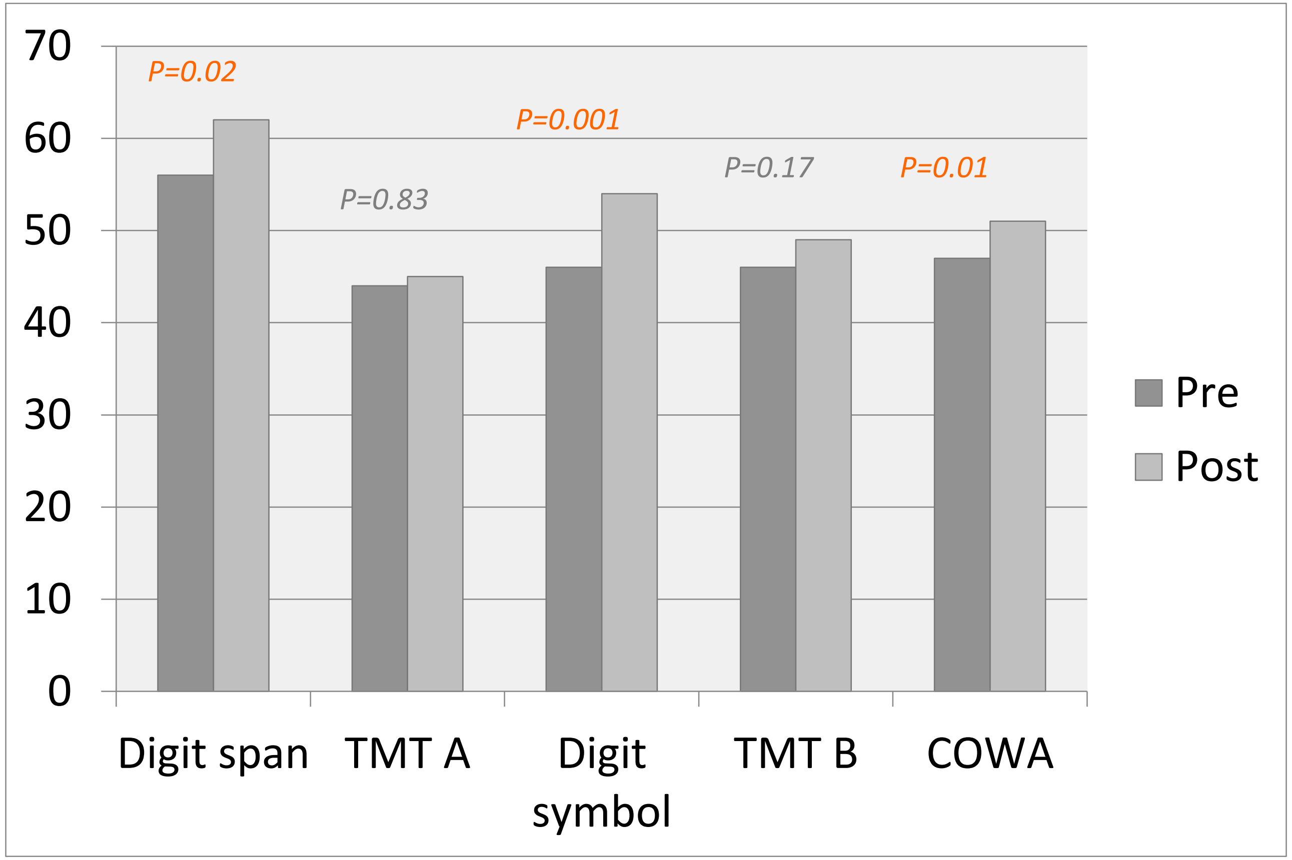
Interventions
Improve oxidative or perfusion deficits?

- Oxygen
  - Improved executive function seen in patients with OSA or CHF with O2 therapy[1 2]
- Exercise?
  - RCT in CHD (TOF, Fontan)
    - Improved self-reported cognitive functioning and parent-reported social functioning [3 4]
- Cardiac resynchronisation therapy in HF

[1]Andreas et al. J Am Coll Card 1996
[23]Richards et al. J Neurol Neurosurg Psych 1997
[3]Hillman et al. Nat Rev Neurosci 2008
[4]Dulfer et al. J Adolesc Health 2014

Interventions

Cardiac resynchonisation therapy: A pilot study examining cognitive change in patients before and after treatment



Dixit et al. Clin Cardiol 2010

Conclusions

- Vulnerable host to ongoing insults
- Intelligence (IQ) often within normal range
- Specific (and subtle) deficits may exist
  - Executive dysfunction common
- May affect other domains
  - Work, education, social functioning
- Heightened awareness important but no ideal screening test
- Interventions are predominantly compensatory

Neurodevelopmental Outcomes in Children With Congenital Heart Disease: Evaluation and Management: A Scientific Statement From the American Heart Association

Bradley S. Marino, Paul H. Lipkin, Jane W. Newburger, Georgina Peacock, Marsha Gerdes, J. William Gaynor, Kathleen A. Mussatto, Karen Uzark, Caren S. Goldberg, Walter H. Johnson, Jr, Jennifer Li, Sabrina E. Smith, David C. Bellinger and William T. Mahle

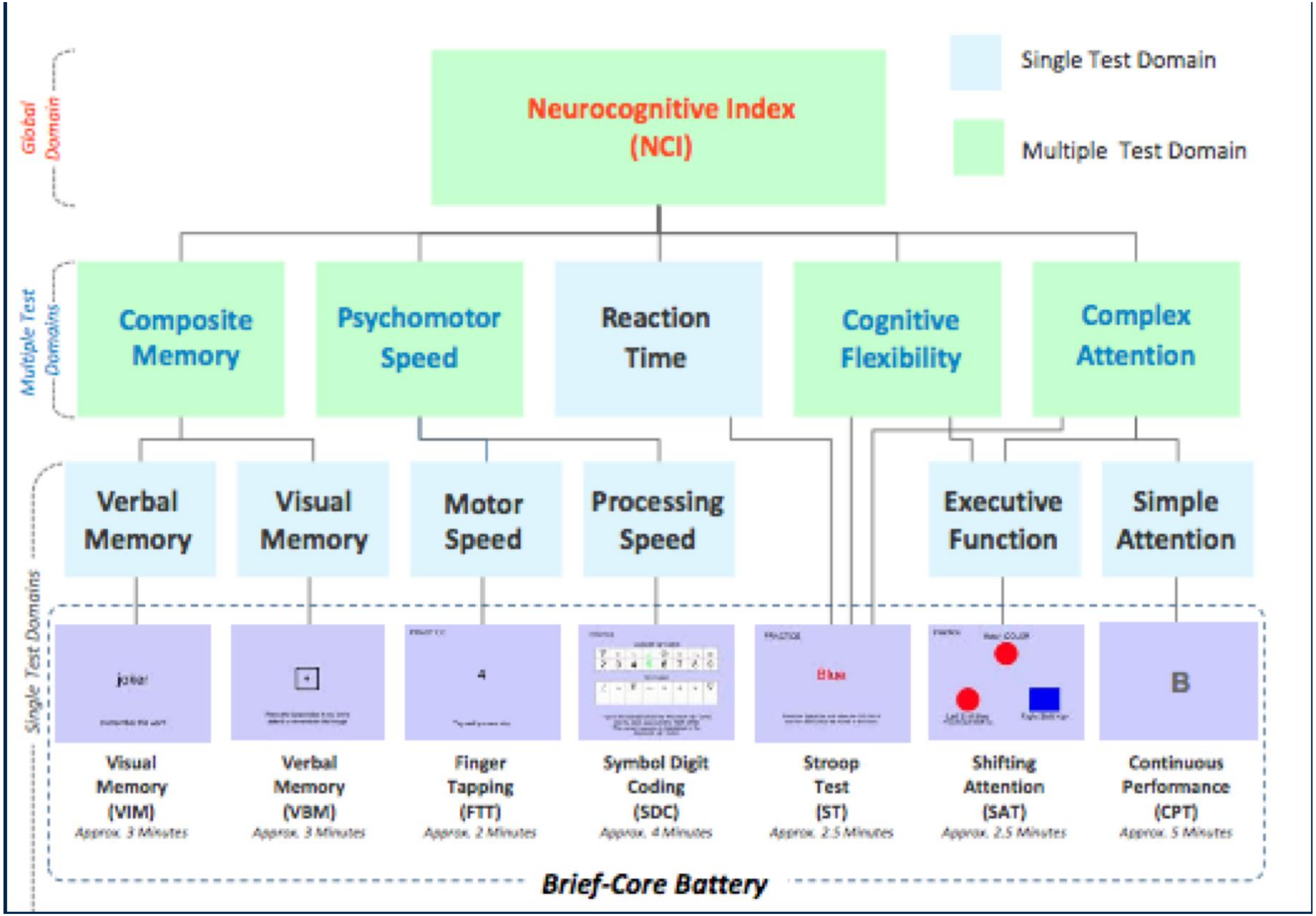
1. Neonates or infants requiring open heart surgery
2. Other cyanotic lesions not requiring early surgery
3. Any CHD and a co-morbidity below
    - Prematurity
    - Genetic abnormality or syndrome
    - CPR at any point, history of mechanical support (ECMO)
    - Prolonged hospitalisation (post op LOS > 2 weeks)
    - Perioperative seizures

Marino et al. Circulation 2012

Functional impact of executive dysfunction

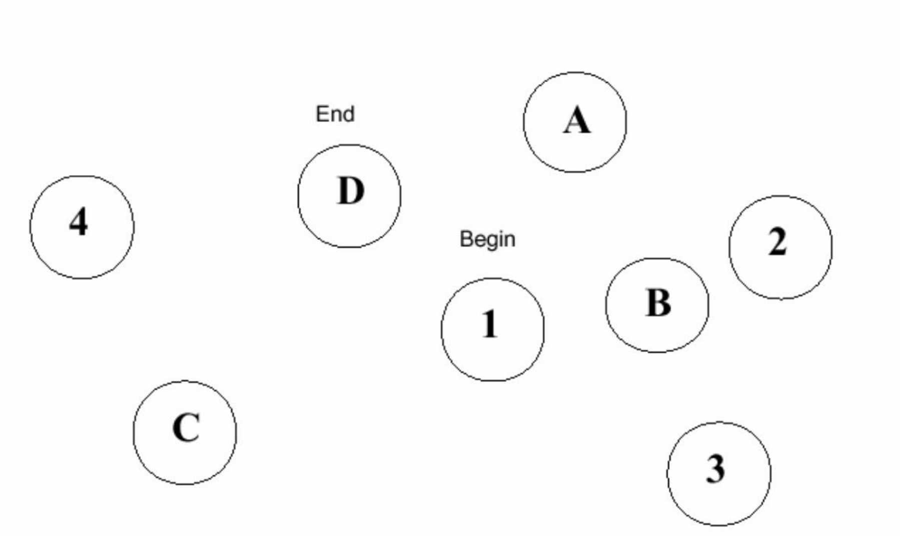
- Self-management
- Compliance and resistance to care
- Level of care, ability to live alone
- Medical decision-making capacity, informed consent
- Mood disorder (eg Apathy)

Schillerstrom et al. Psychosomatics 2005

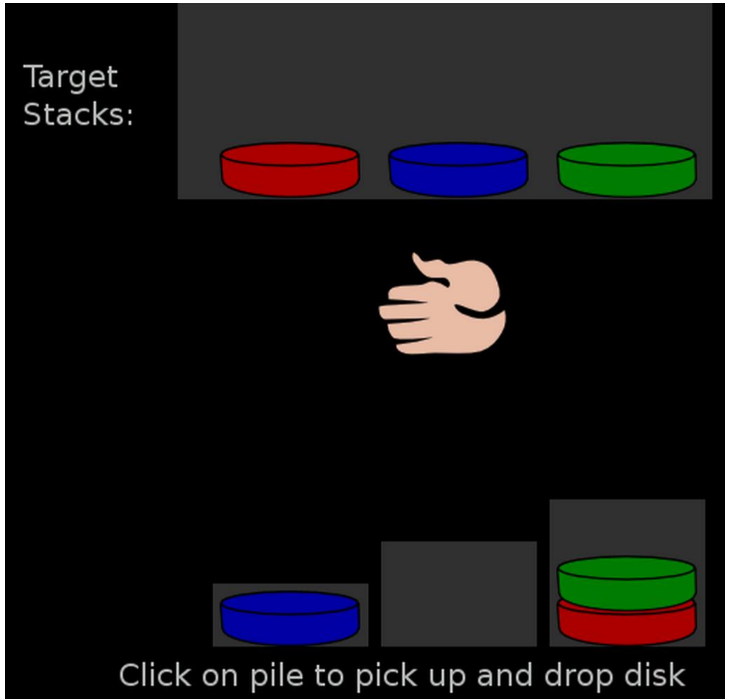

Single Test Domain
Multiple Test Domain
Global Domain
Neurocognitive Index (NCI)
Multiple Test Domains
Composite Memory
Psychomotor Speed
Reaction Time
Cognitive Flexibility
Complex Attention
Single Test Domains
Verbal Memory
Visual Memory
Motor Speed
Processing Speed
Executive Function
Simple Attention
Visual Memory (VIM)
Approx. 3 Minutes
Verbal Memory (VBM)
Approx. 3 Minutes
Finger Tapping (FTT)
Approx. 2 Minutes
Symbol Digit Coding (SDC)
Approx. 4 Minutes
Stroop Test (ST)
Approx. 2.5 Minutes
Shifting Attention (SAT)
Approx. 2.5 Minutes
Continuous Performance (CPT)
Approx. 5 Minutes
Brief-Core Battery

Cyanosis

- Often used as a proxy for disease complexity
- Utens:
  - **Lower Mean IQ if cyanotic condition**



- Daliente :
  - **TOF + blue spells**
  - Attention/concentration
    (Trail Making A & B)
  - Executive function (planning)
    (Tower of London tasks)



NICHE results (48 patients)

Moderate CHD

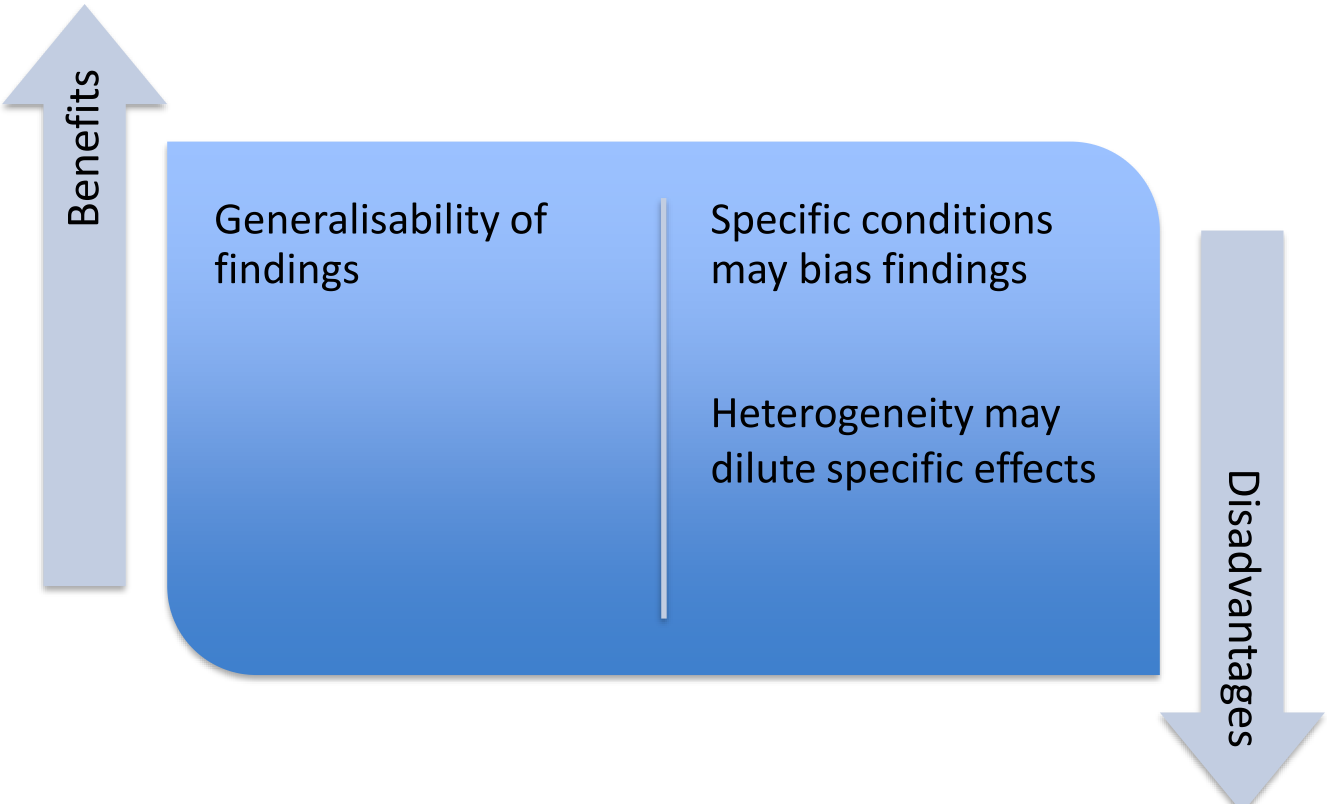
- No significant difference vs. normative samples

Severe CHD

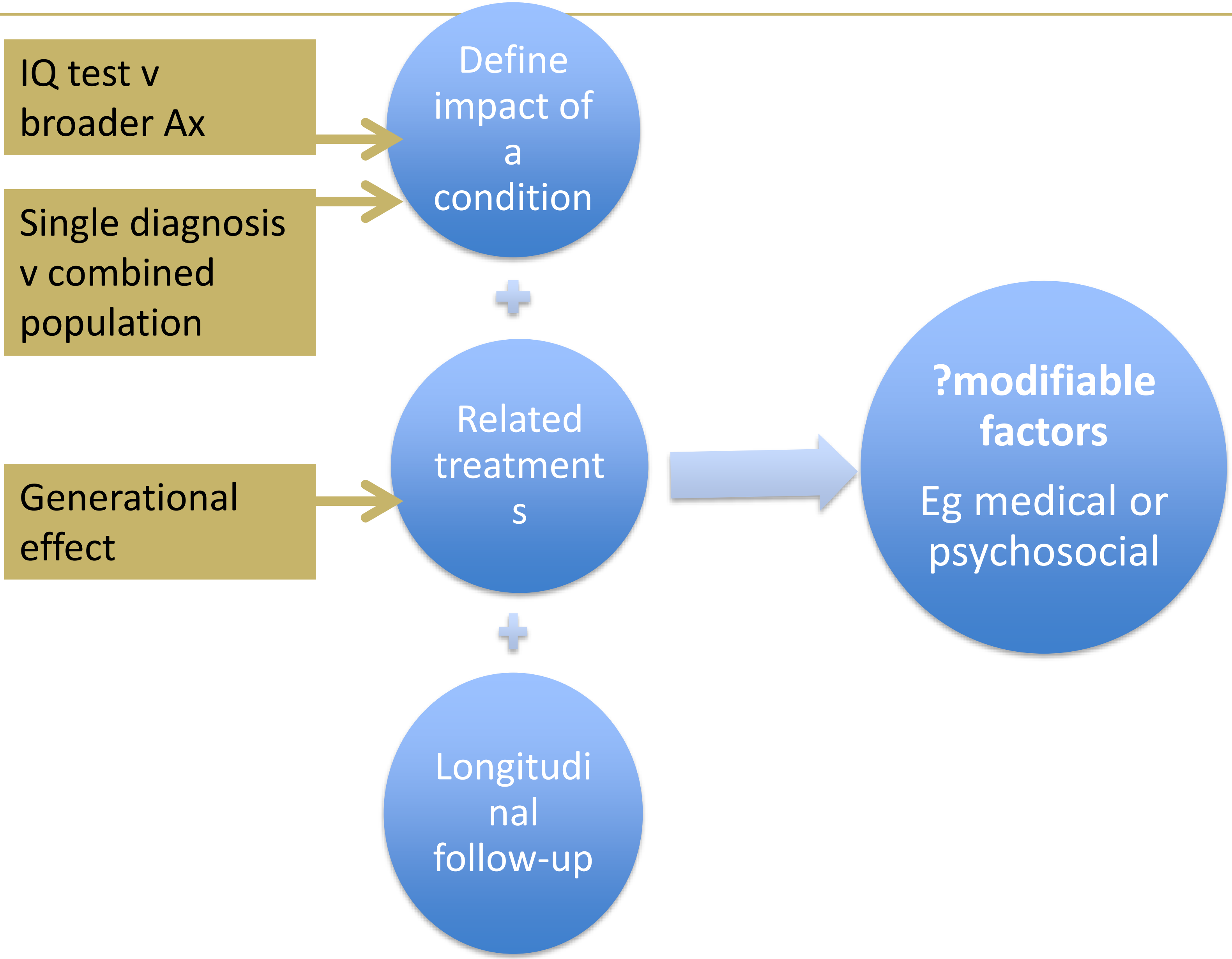
- Significant differences in
  - Neurocognitive index
  - Processing speed
  - Psychomotor speed
  - Reaction time
  - Complex attention

Future challenges for studies

- IQ testing vs. broader cognitive assessment
- Study total population
  - ? Combined population (vs. single diagnosis)

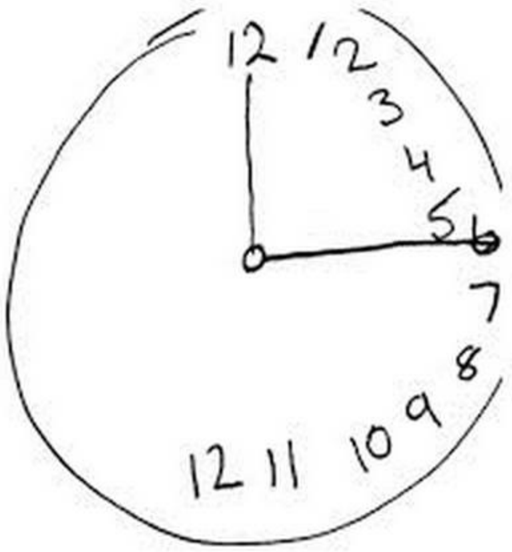


Future directions



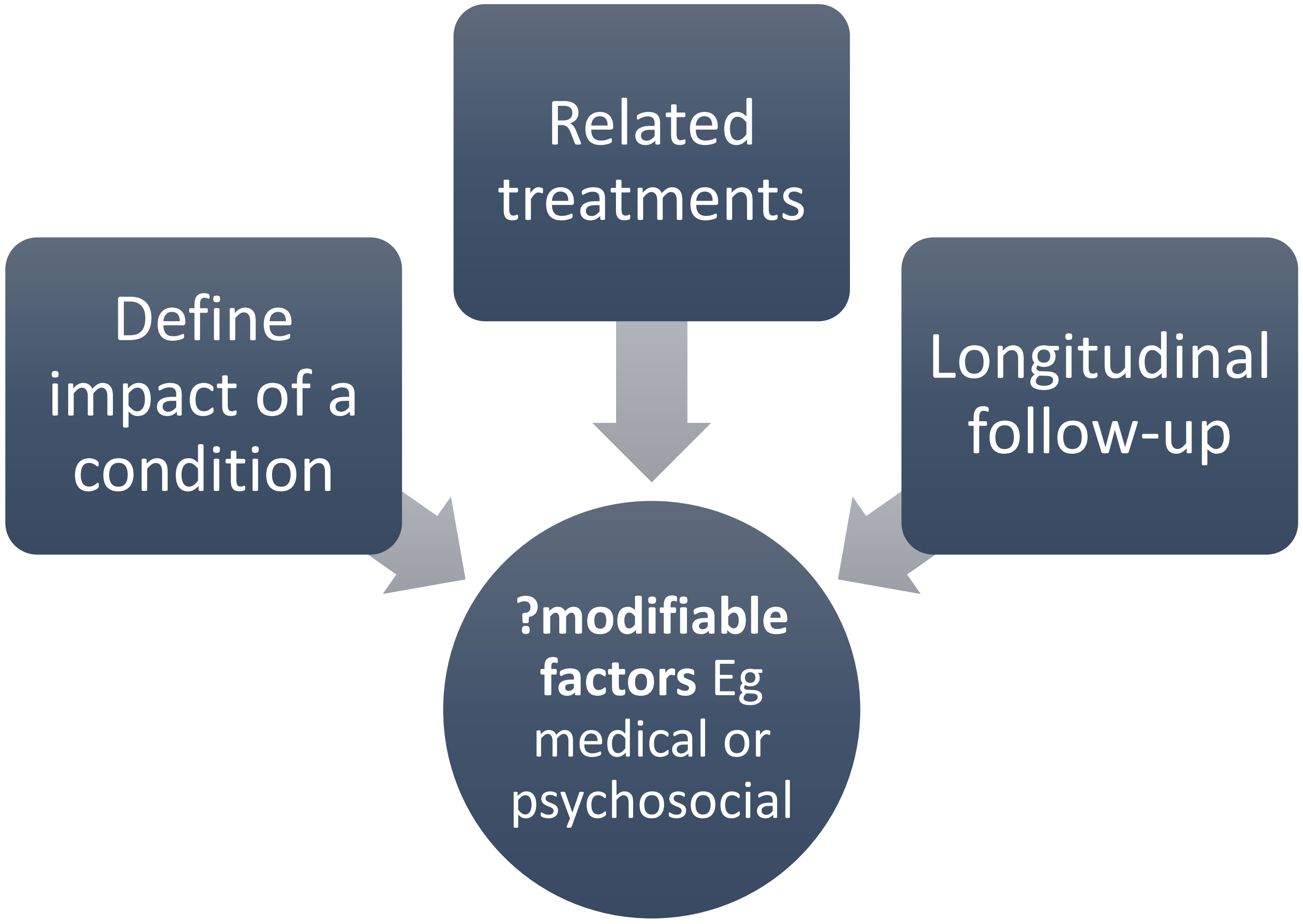
Manifestations of executive dysfunction

- Remove?



May explain some of common occurrence of:

- disorganised,
- hyperactive,
- impulsive and
- sometimes aggressive behaviour



Related treatments
Define impact of a condition
Longitudinal follow-up
?modifiable factors Eg medical or psychosocial

Atrial fibrillation

Mechanisms?

- Shared risk factors
  - DM, HT, CHF
- Cardioembolism
- Cerebral hypoperfusion – low CO
  - Beat to beat variability in cardiac cycle length
  - Loss atrial contraction
- Periventricular white matter lesions

Bunch et al Heart Rhythm 2010
Elias et al. J Stroke Cerevrovasc Dis 2006
Kalantarian et al Ann Int Med 2013

Interventions

- Vocational or educational counselling
- Community living skills

Kamphuis et al. Arch pediatr adolesc med 2002