Neurocognitive outcomes and interventions in ACHD survivors

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EXPANDED FOCUS:
Mortality → patient centred outcomes

- Functional status
- QOL
- Psychosocial wellbeing
- Cognitive function

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?
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

<table>
<thead>
<tr>
<th>IQ Score</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>0.1%</td>
</tr>
<tr>
<td>70</td>
<td>2.1%</td>
</tr>
<tr>
<td>85</td>
<td>13.6%</td>
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<tr>
<td>100</td>
<td>34.1%</td>
</tr>
<tr>
<td>115</td>
<td>13.6%</td>
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<tr>
<td>130</td>
<td>2.1%</td>
</tr>
<tr>
<td>145</td>
<td>0.1%</td>
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</tbody>
</table>

Borderline 70-79
‘Average’ 90-110
Subscales of IQ score

- Perception reasoning
- Processing speed
- Verbal comprehension
- Working memory
Additional testing components?

- Memory
- Academic achievement
- Visual motor integration
- Attention
- Executive function
**Executive function:**
Group of processes that control & regulate other cognitive processes

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**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*

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

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

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

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

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

Children can ‘grow into their deficits’
Defects ‘emerge’ as demands of life increase
Cognitive dysfunction

- Age at repair
- CPB, circ arrest
- Post-operative instability

Cardiac surgery

- Disease related
  - Severity of condition
  - Genetic syndromes
  - Prolonged cyanosis
  - Seizures
  - Strokes

Social factors

- Absence from school
- Poor peer interaction
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
Cognitive Impairment Associated With Atrial Fibrillation
A Meta-analysis
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)
% of Patients with cognitive impairment

<table>
<thead>
<tr>
<th>Time</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>53</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>36</td>
</tr>
<tr>
<td>6 Months</td>
<td>24</td>
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</table>
Critical illness

Long-Term Cognitive Impairment after Critical Illness


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
Vulnerable host?

Cardiac surgery

Social factors

Disease related

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


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
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 \( \Delta \) hsCRP, BNP, ADMA
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. Newman1,4

1Centre for Health Services Research, School of Health Sciences, City University London; 2School of Psychology, University of Surrey; 3GUCH Unit, The Heart Hospital, University College of London Hospitals NHS Foundation Trust; 4Division of Cardiovascular Sciences, University College London (UCL); 5Division 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
<table>
<thead>
<tr>
<th>Sample</th>
<th>Control</th>
<th>Cardiac defect</th>
<th>Assessment tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utens¹ <em>(Netherlands)</em></td>
<td>N=242 Mean age 22 Cross-sectional</td>
<td>Reference group</td>
<td>Mixed (ASD, TOF TGA)</td>
</tr>
<tr>
<td>Wernovsky² <em>(Boston)</em></td>
<td>N=133 Mean age 14</td>
<td>Normed population data</td>
<td>Fontan</td>
</tr>
<tr>
<td>Eide³ <em>(Norway)</em></td>
<td>N=166 Mean age 19 Retrospective cohort</td>
<td>384,000 healthy army recruits</td>
<td>Mixed (TGA, VSD/ASD)</td>
</tr>
<tr>
<td>Daliento⁴ <em>(Italy)</em></td>
<td>N=54 Mean age 32</td>
<td>Reference group</td>
<td>TOF</td>
</tr>
</tbody>
</table>

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)
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. Pike¹*, Mary A. Woo¹, Marie K. Poulsen², Wendy Evangelista¹, Dylan Faire¹, Nancy J. Halhon³, Alan B. Lewis⁴ and Rajesh Kumar⁵,⁶,⁷,⁸

• 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.
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
Clear deficits in executive functioning
More likely if history of ‘blue spells’
Neurocognitive and executive functioning in adult survivors of congenital heart disease

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

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

*Moderate
  • AVSD, Coa, Ebstein, TOF, VSD

*Severe
  • Cyanotic, Fontan, TGA

NICHE study, Texas

*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

![Incidence of executive impairment](image)

Executive functioning strongly correlated to number of cardiac operations

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**Moderate**
- AVSD, Coa, Ebstein, TOF, VSD

**Severe**
- Cyanotic, Fontan, TGA, pulmonary atresia
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
  • Specific impairments in theory of mind (esp. ‘third person’)
    • Eg. Pragmatic language impairment, difficulty reading social cues
    • May limit ability to form healthy relationships
• Association with psychiatric disorders
  • 3 x general population
• Association with ADHD
  • Up to 1/3

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

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?
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\textsuperscript{1,2}
  • Goal management training (GMT)
    • Rehabilitation technique (Acquired brain injury)
    • Complex tasks divided into smaller tasks

• Working memory training\textsuperscript{3,4}
  • Structured computer based programs (eg Cogmed)

\textsuperscript{1}Levine et al. J Int Neuropsychol Soc 2000
\textsuperscript{2}Krasny-Pacini et al. Disabil Rehabil 2014
\textsuperscript{3}Soderqvist et al. Dev Psychol 2012
\textsuperscript{4}Rueda et al. Dev Coogn Neurosci 2012
Interventions
Pharmacological therapy?

• Methylphenidate
  • Improved executive function in ADHD patients\textsuperscript{1,2}
  • Arrhythmia / MI risk in ACHD patients?\textsuperscript{3,4}

• Sertaline
  • Improved executive function in depressed patients with mild TBI\textsuperscript{5}

\textsuperscript{1}Kuperman et al. Ann Clin Psych 2001
\textsuperscript{2}Meyers et al. J Clin Oncol 1998
\textsuperscript{3}Shin et al. BMJ 2016
\textsuperscript{4}Sinha et al. Case Rep Cardiol 2016
\textsuperscript{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**

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\(^1\) Andreas et al. J Am Coll Card 1996
\(^2\) 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 resynchronisation 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
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
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 (e.g., Apathy)

Schillerstrom et al. Psychosomatics 2005
Neurocognitive Index (NCI)

- Composite Memory
- Psychomotor Speed
- Reaction Time
- Cognitive Flexibility
- Complex Attention

- Verbal Memory
- Visual Memory
- Motor Speed
- Processing Speed

- Executive Function
- Simple Attention

Brief-Core Battery

- 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 Test (CPT) Approx. 5 Minutes
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)

<table>
<thead>
<tr>
<th>Moderate CHD</th>
<th>Severe CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No significant difference vs. normative samples</td>
<td>• Significant differences in</td>
</tr>
<tr>
<td></td>
<td>- Neurocognitive index</td>
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<tr>
<td></td>
<td>- Processing speed</td>
</tr>
<tr>
<td></td>
<td>- Psychomotor speed</td>
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<tr>
<td></td>
<td>- Reaction time</td>
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<tr>
<td></td>
<td>- Complex attention</td>
</tr>
</tbody>
</table>
Future challenges for studies

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

Benefits

Generalisability of findings

Specific conditions may bias findings

Heterogeneity may dilute specific effects

Disadvantages
Future directions

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

- IQ test v broader Ax
- Single diagnosis v combined population
- Generational effect
Manifestations of executive dysfunction

- Remove?

May explain some of common occurrence of:
- disorganised,
- hyperactive,
- impulsive and
- sometimes aggressive behaviour
Define impact of a condition

Related treatments

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
Kalantarian et al Ann Int Med 2013
Interventions

• Vocational or educational counselling

• Community living skills