

# Childhood development in 22q11.2 Deletion Syndrome

Dr Samuel Chawner

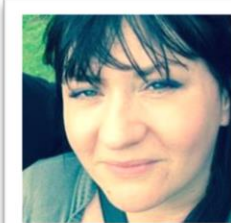
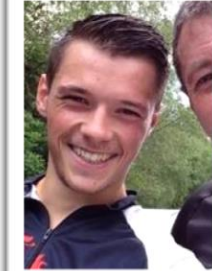
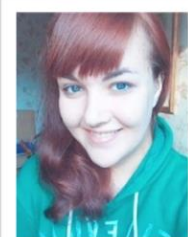
Institute of Psychological Medicine and Clinical Neurosciences

**Cardiff University**



# Cardiff Team

- Psychologists
- Psychiatrists
- Neurologists
- Geneticists and Biologists
- Genetic Counsellors
- Research students





# Who Are We?



San Diego University



Tel Aviv University



Philadelphia University



Cambridge University



Maastricht University



UCLA



Toronto University



Dublin University



Geneva University

Bristol University Oslo University



Lausanne University



Newcastle University



Einstein University



Montreal University



UCL



Leuven University



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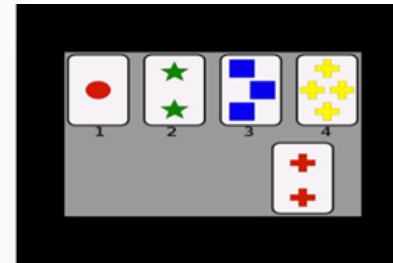
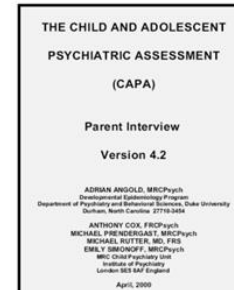


# ECHO STUDY

(Study of Experiences of people with copy number variations)

## Over 200 families! Assessments

- Health, including seizures
- Height, weight, head circumference
- Pregnancy and birth
- Peer relationships
- Development
- Motor skills
- Social skills
- Sleep problems
- IQ
- Learning, reasoning, memory
- Behaviour
- Psychological strengths, weaknesses
- How the brain works



Home School  
and

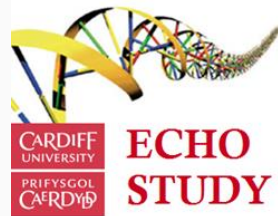


# ECHO STUDY

(Study of Experiences of people with Copy number variations)

- Our aims:
- Make our findings known as widely as possible

- Individuals with 22q
- Their families
- Health care workers
- Support charities
- Wider society



**Mental health in 22q11.2 Deletion Syndrome**

22q11.2 Deletion Syndrome (22q11.2DS) is caused by the deletion of a small amount of DNA on one of a person's two copies of chromosome 22. Babies are often born with life threatening and impairing physical health problems and are delayed in their development. Their parents are usually only told about the condition when they receive the diagnosis. This is often the first time they hear of 22q11.2DS.

**Key Points**

- Individuals with 22q11.2DS have a range of complex needs that impact on their lives.
- Families frequently do not receive the support and information they need.
- Research is crucial to knowledge about the course of individuals with 22q11.2DS.

**Contact**

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**What we have found**

- **Childhood:** High rates of intellectual disability, autism, ADHD, anxiety, depression, sleep disturbances and low mood.
- **Adulthood:** Childhood problems persist into adulthood and there is a high risk of developing schizophrenia and depression.
- **Impairments** in a range of higher mental processes such as attention and planning ability which impact greatly on daily life.
- **Delays** in social, emotional and motor development.
- However many aspects of the life course of individuals with 22q11.2DS are not known yet.

**Partners**

wellcome trust, NIHR, ECHO

16p11.2: rare gene

THE CONVERSATION  
Academic topics, journalists first

16p11.2: rare genetic changes linked to autism now co  
to higher chance of other psychiatric disorders

February 26, 2019 10:14am GMT



Prof MARIANNE VAN DEN BREE  
Cardiff University

BBC BREAKFAST

06:24





# ECHO STUDY

(Study of **E**xperien**C**es of people with **H**c**O**py number variations)



## Our aims:

- Improve genetic counselling and medical and other care/ support
- Learn more about how the deleted/ duplicated genes work
- Work towards prevention in the future



# ECHO STUDY

(Study of ExperiencEs of people with H cOpy number variants)

## IQ/ Learning and Thinking

### • Question 1:

- To what extent do young people with 22q11.2 deletion differ from other young people on:
  - Learning and thinking?

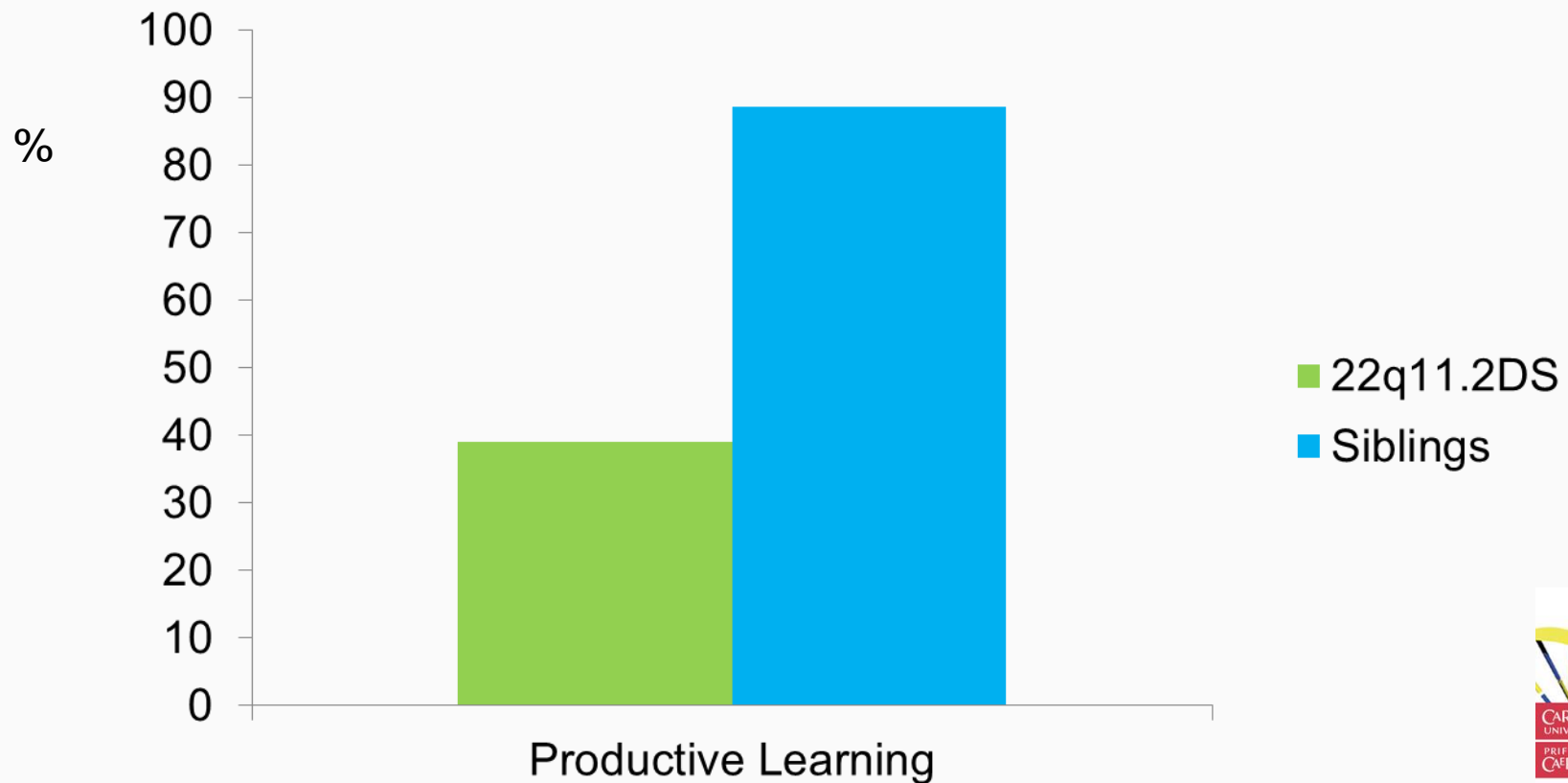




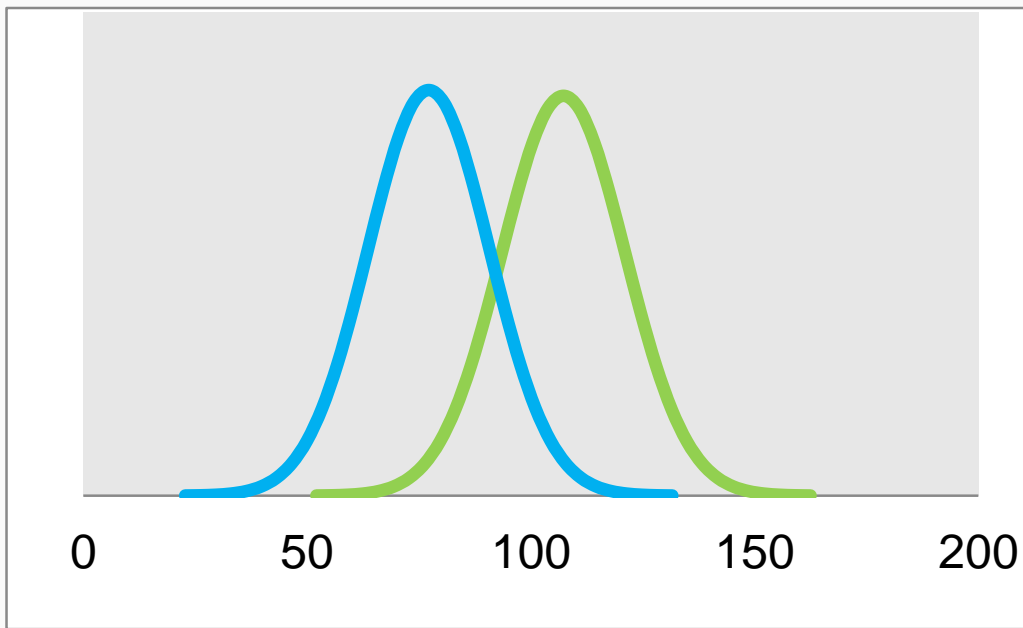
# School



Samuel Chawner







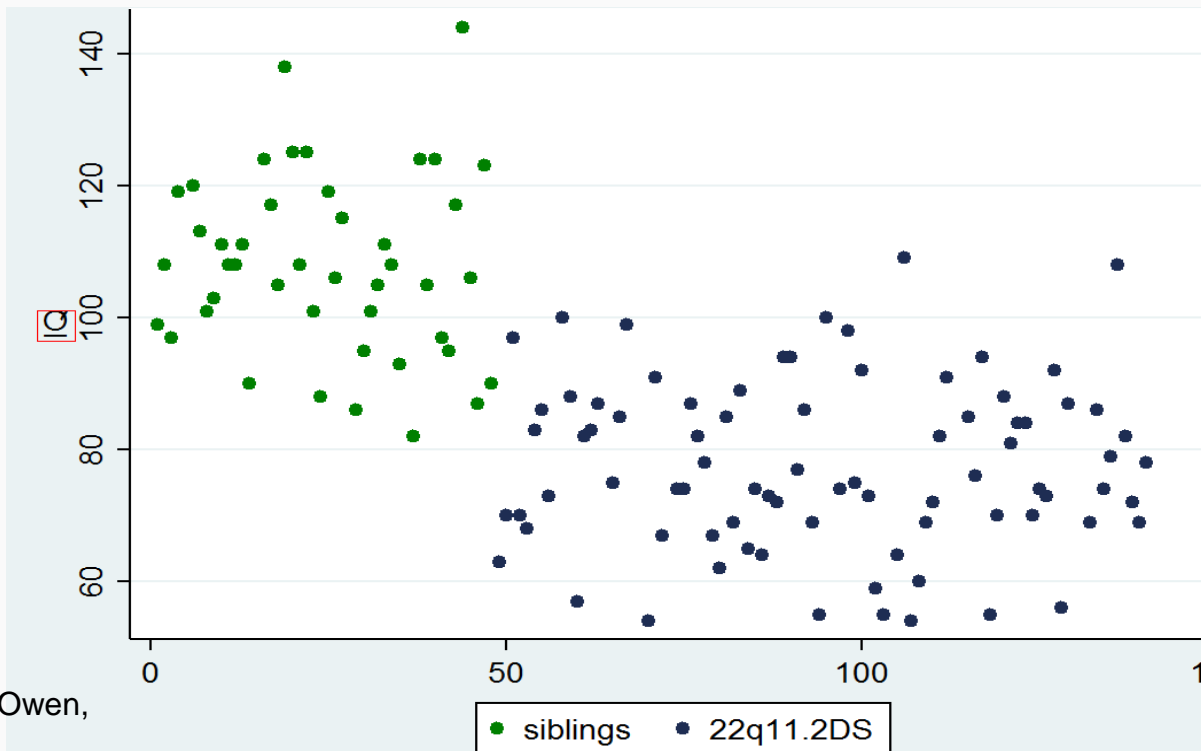
Children with 22q11.2DS: Mean 76.8 (13)

Siblings: Mean IQ 108.6 (15.2)

IQ



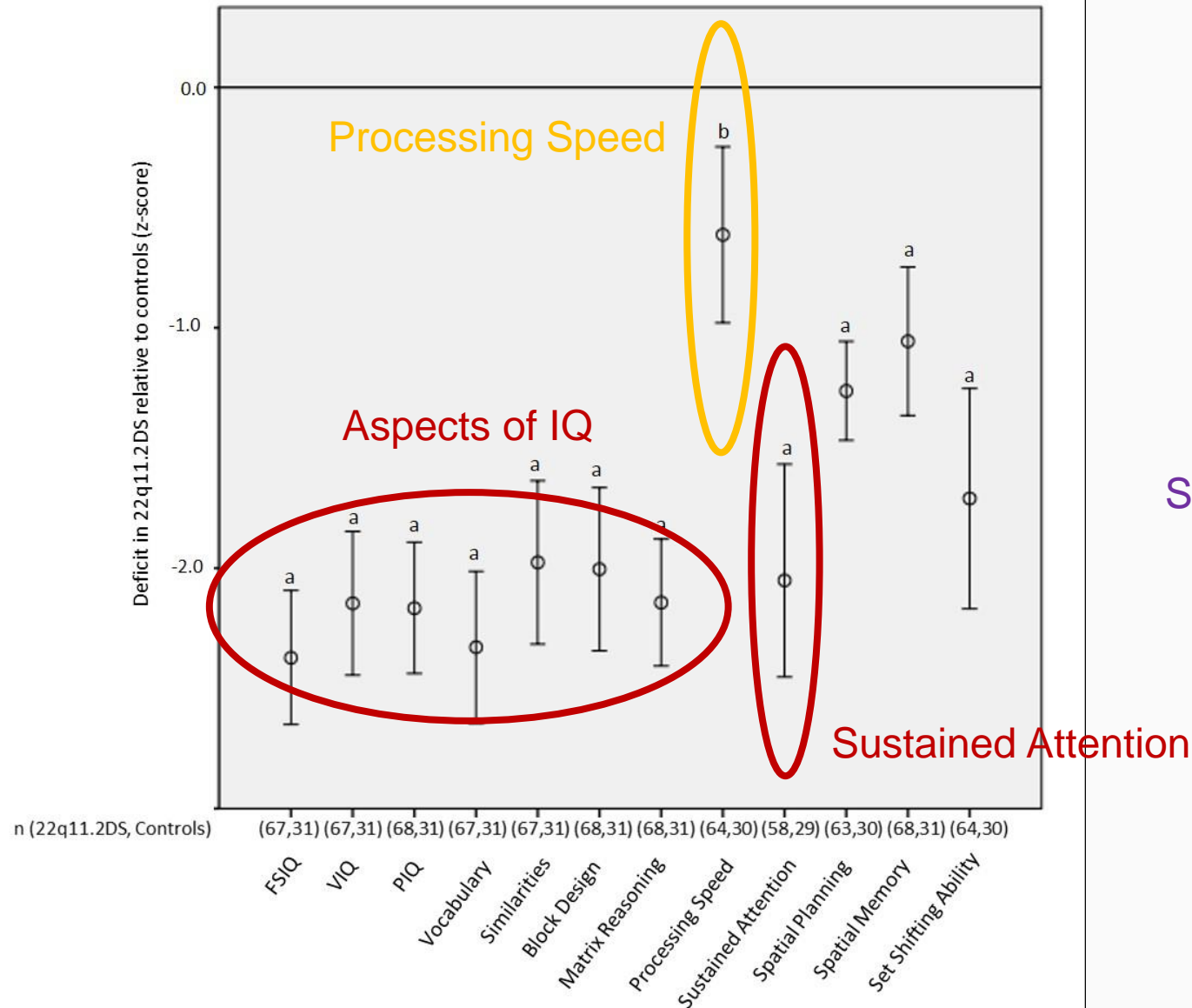
Maria Niarchou



# Other Learning and Thinking



Samuel Chawner



# To Recap

## Question 1:

# IQ/ Learning and Thinking

- Children with 22q11.2 deletion achieve less well in school
- They score lower on IQ tests than their siblings without the deletion
- And also on other tests of learning and thinking  
Indicating more difficulty with attention, reasoning, information processing, planning and remembering





# ECHO STUDY

(Study of ExperiencEs of people with H cOpy number variants)

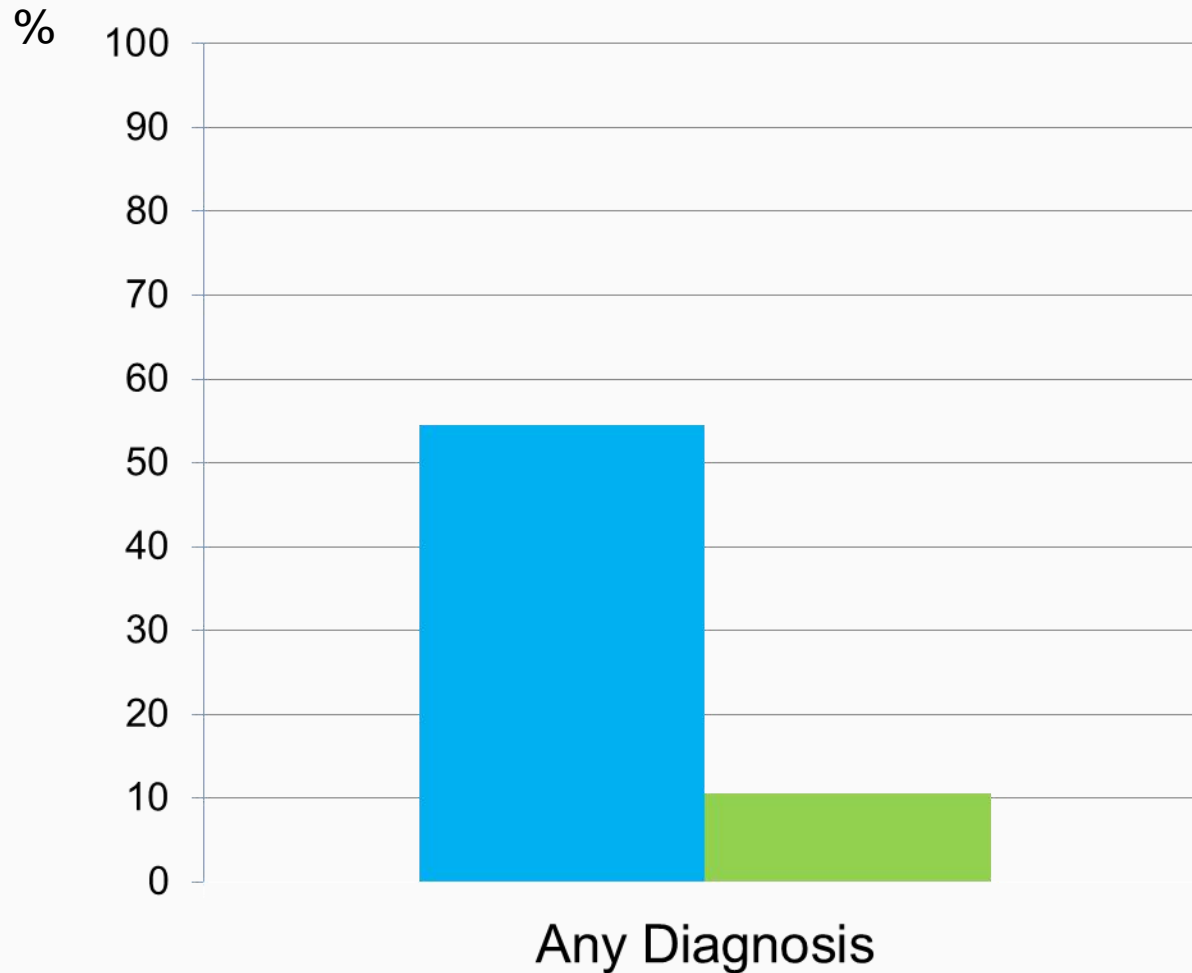
## Psychiatric Strengths and Weaknesses

### • Question 2:

- To what extent do young people with 22q11.2 deletion differ from other young people on:
  - Psychiatric traits?



# Psychological Strengths and Weaknesses



Maria Niarchou

■ 22q11.2 Deletion

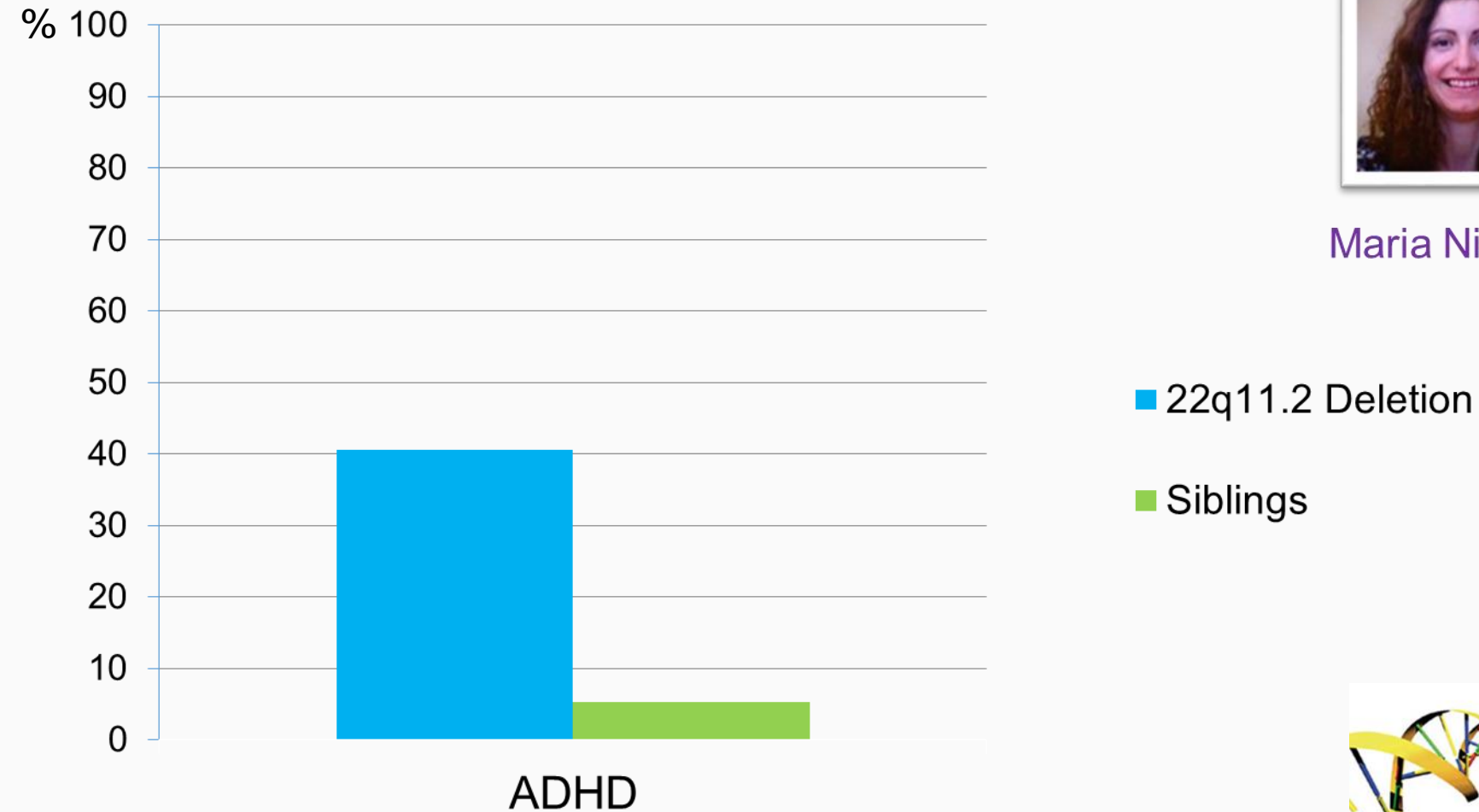
■ Siblings



# Attention Deficit Hyperactivity Disorder (ADHD)



Maria Niarchou





# ADHD

## Hyperactivity/ Impulsivity

- Restless
- Can't remain seated
- Excessive talking
- Blurting out answers
- Constantly interrupting others
- Can't take turns



## Inattention

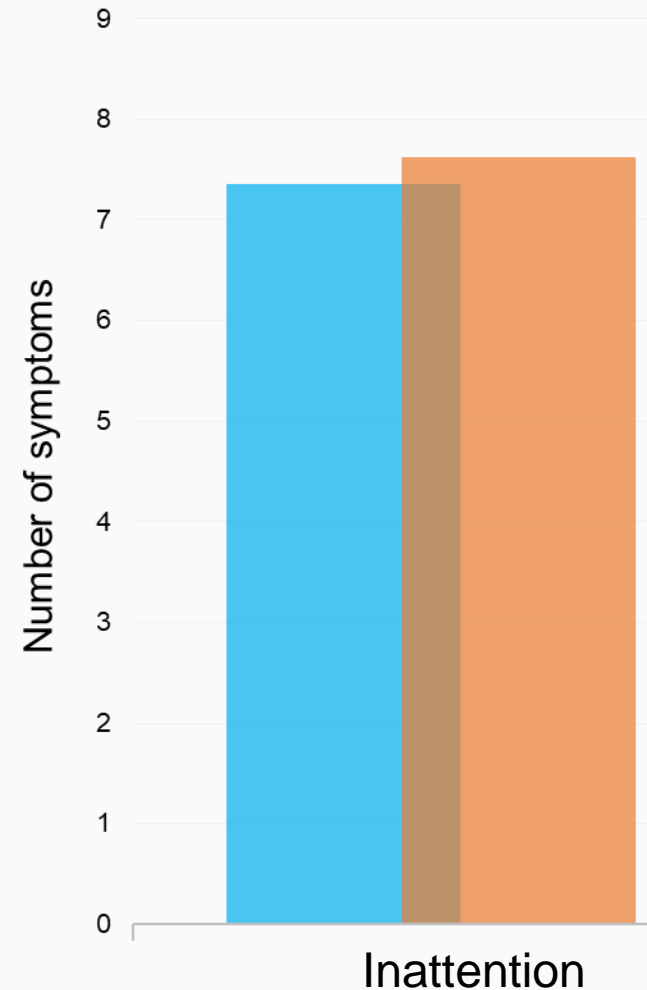
- Careless mistakes
- Not listening
- Not following instructions
- Easily distracted
- Loses things
- Forgetful



# ADHD



Maria Niarchou



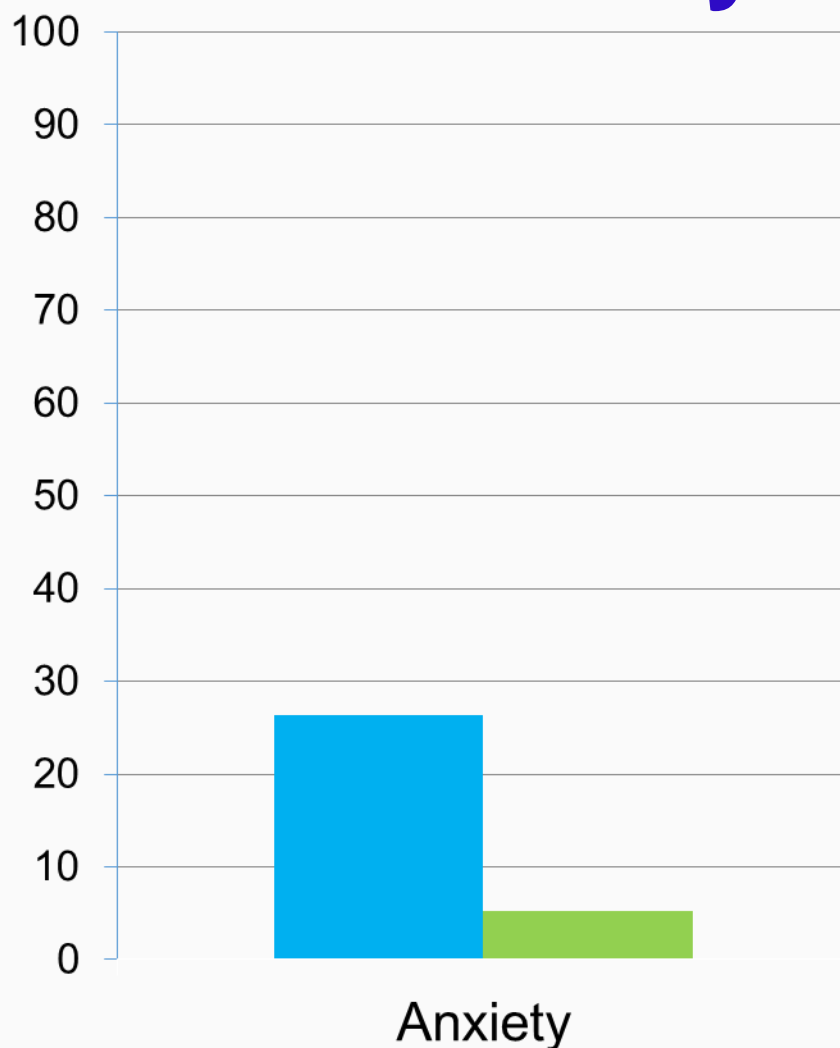
- Children with 22q11.2DS
- Children seen in ADHD clinic

Important information for clinicians to help with recognizing ADHD  
in children with 22q11.2DS

# Anxiety Disorder



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■ 22q11.2 Deletion  
■ Siblings

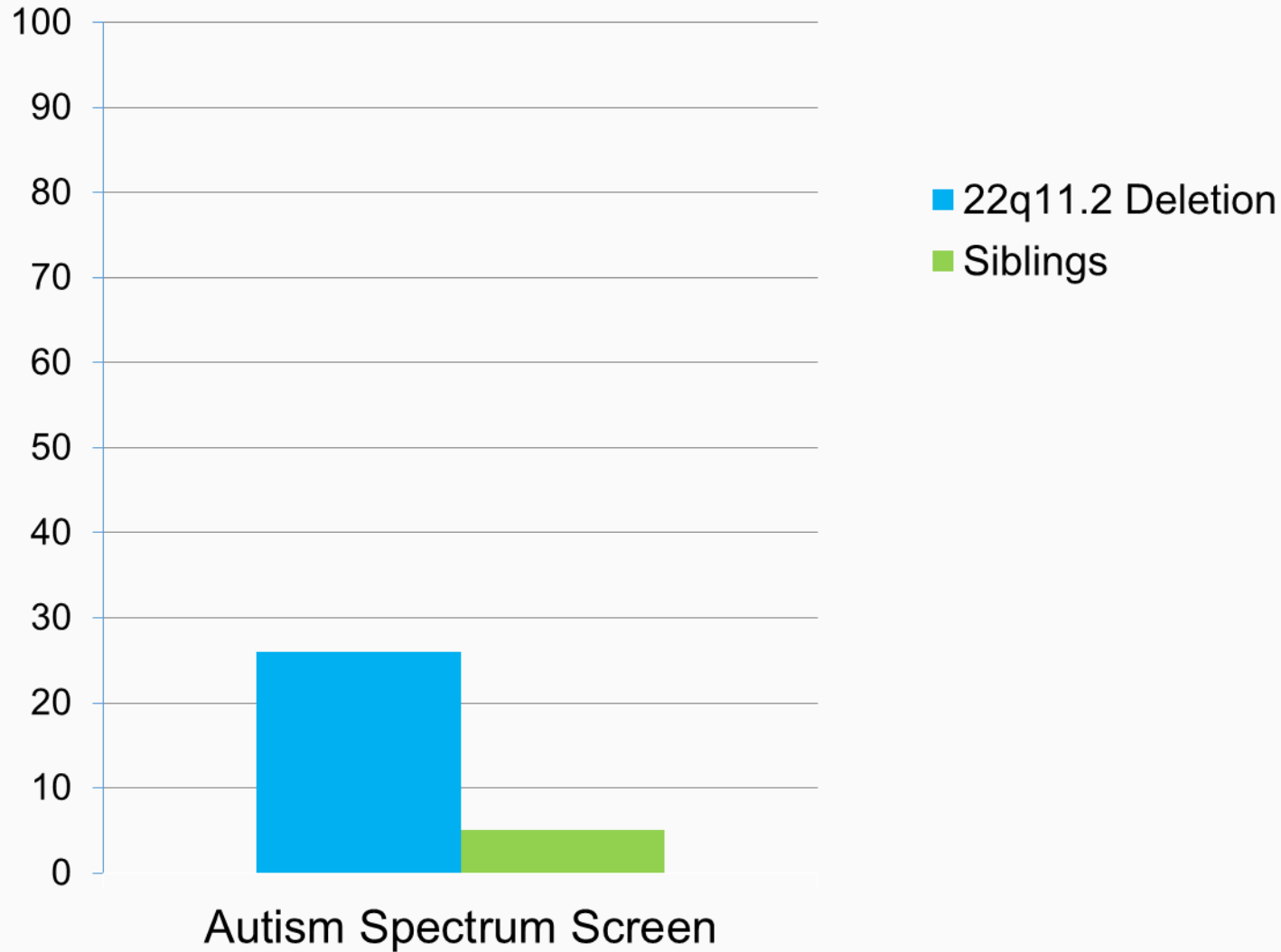
- Uneasiness
- Worry
- Fear
- On edge, restless
- Muscle tension
- Irritability





# Autism

%



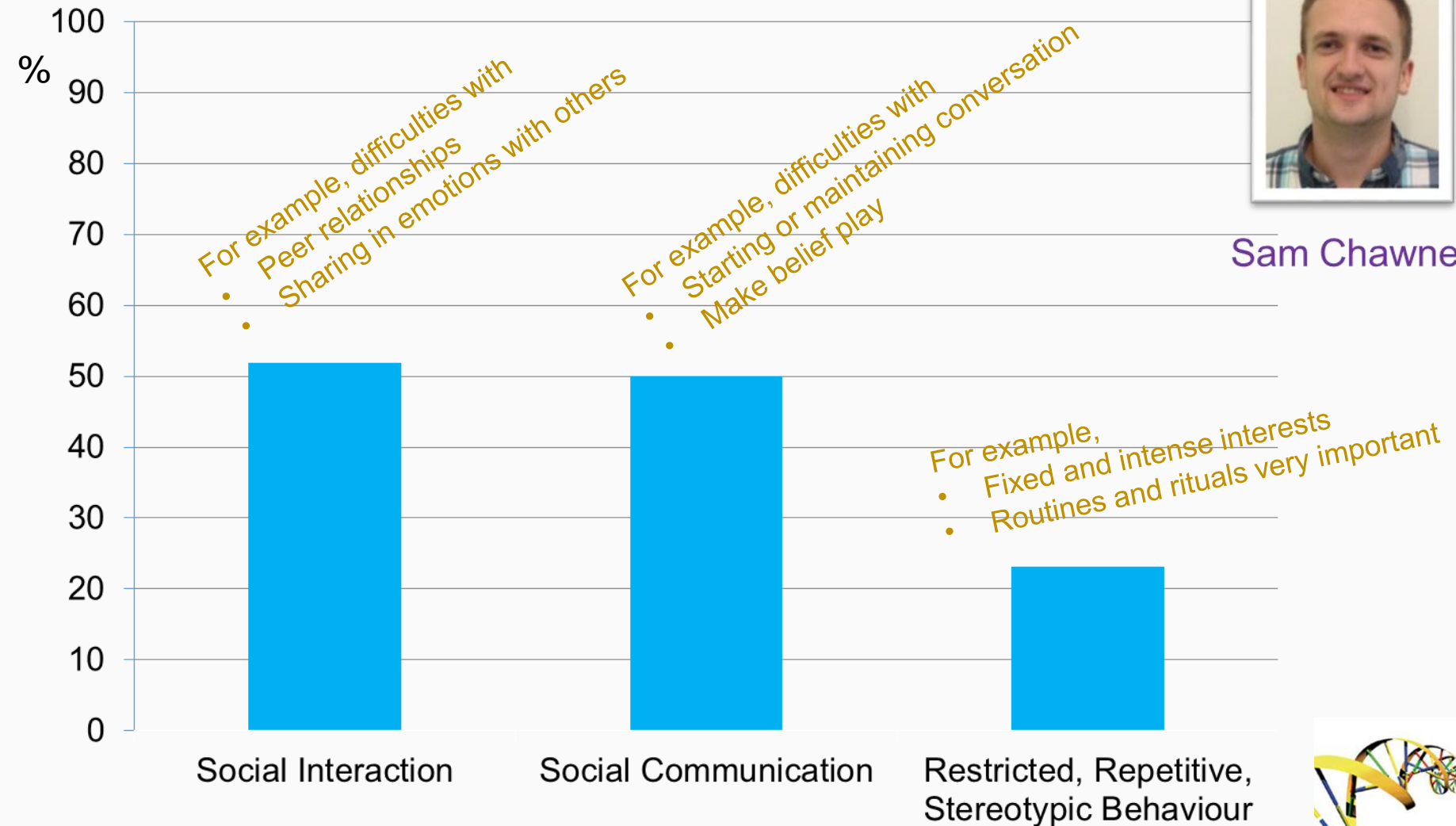
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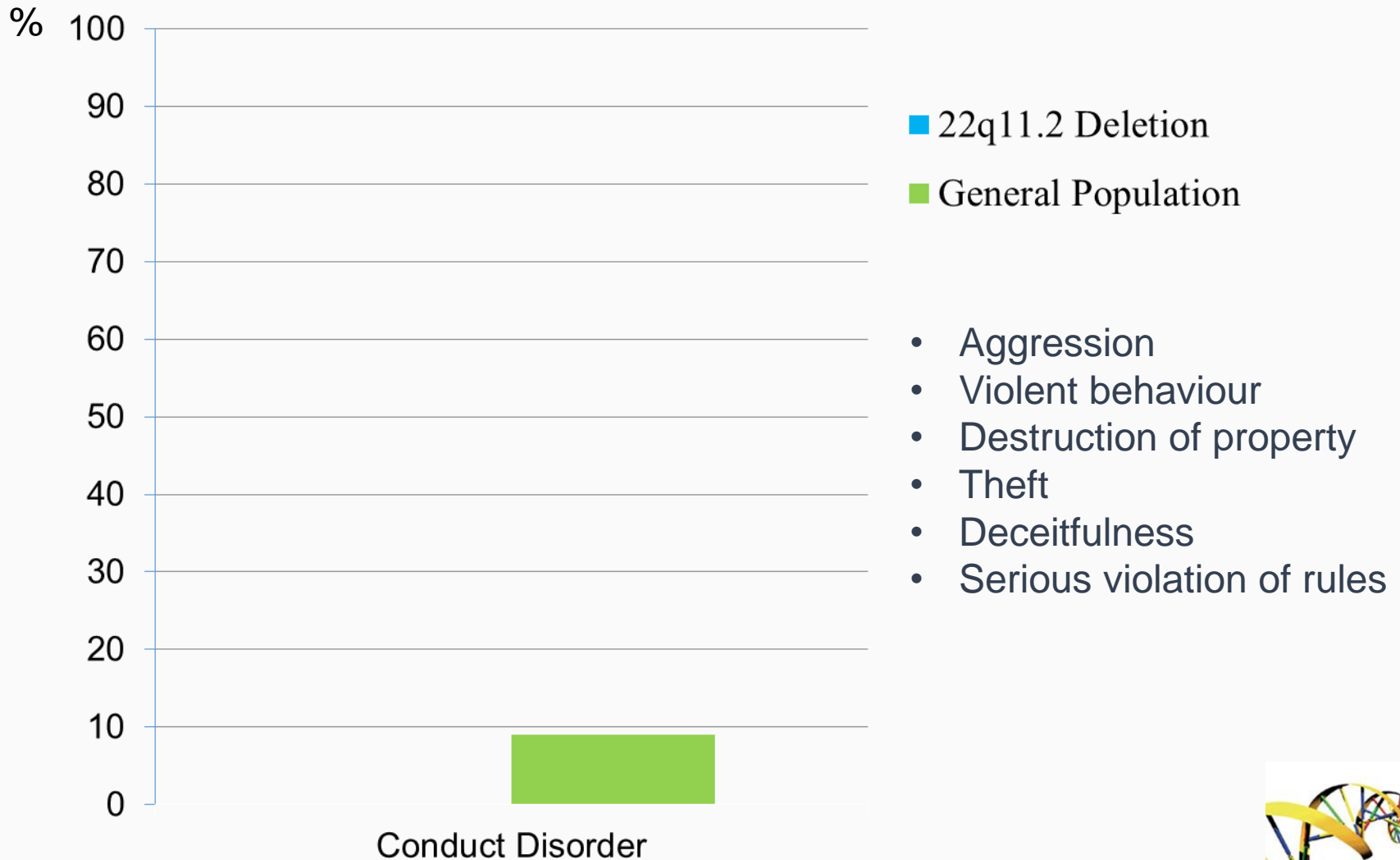
# Autism



Sam Chawner



# Conduct Disorder





# To Recap

## Question 2:

### Psychiatric Strengths and Weaknesses

- Children with 22q11.2 deletion are more likely to have ADHD, anxiety and autism than their siblings without the deletion
- But less likely to have conduct problems
- It is important clinicians are aware that psychiatric problems such as ADHD or autism may look different in 22q11.2DS

# Links between Learning/ Thinking and Psychological Traits

## •Question 3:

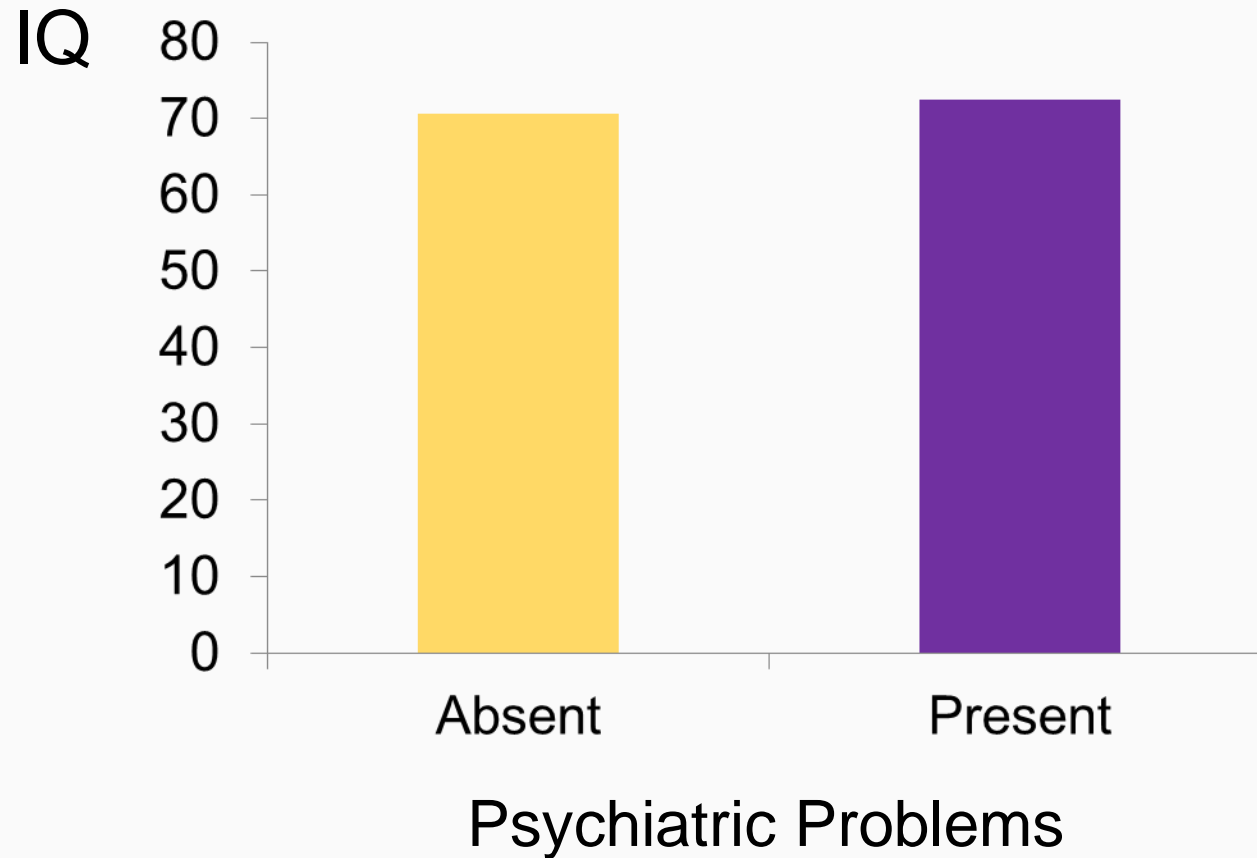
- Do young people with 22q11.2 deletion who have more problems with learning and thinking have more psychiatric problems?



# IQ and Psychological Traits

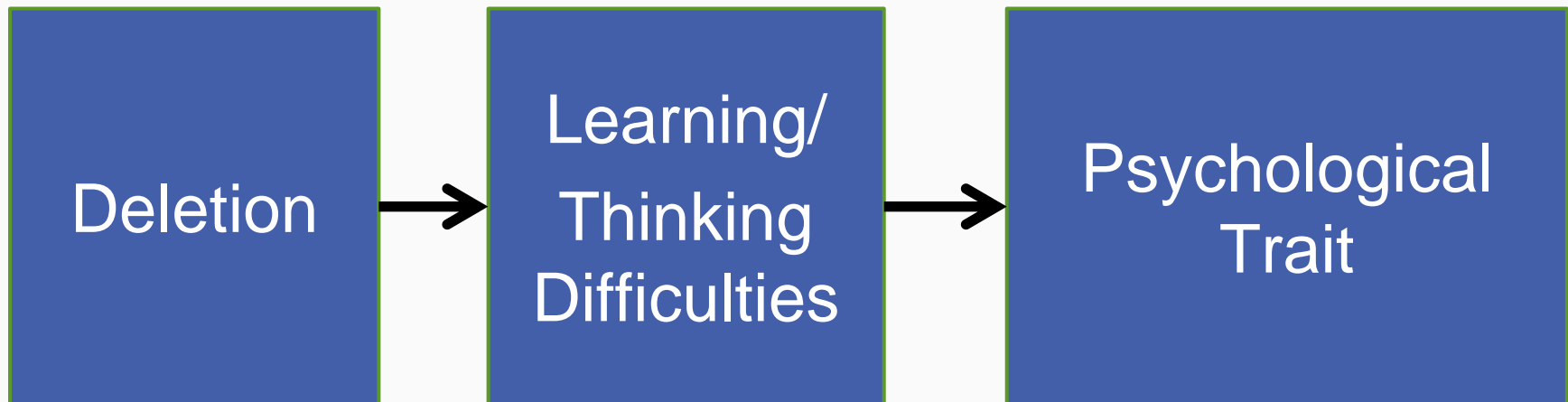
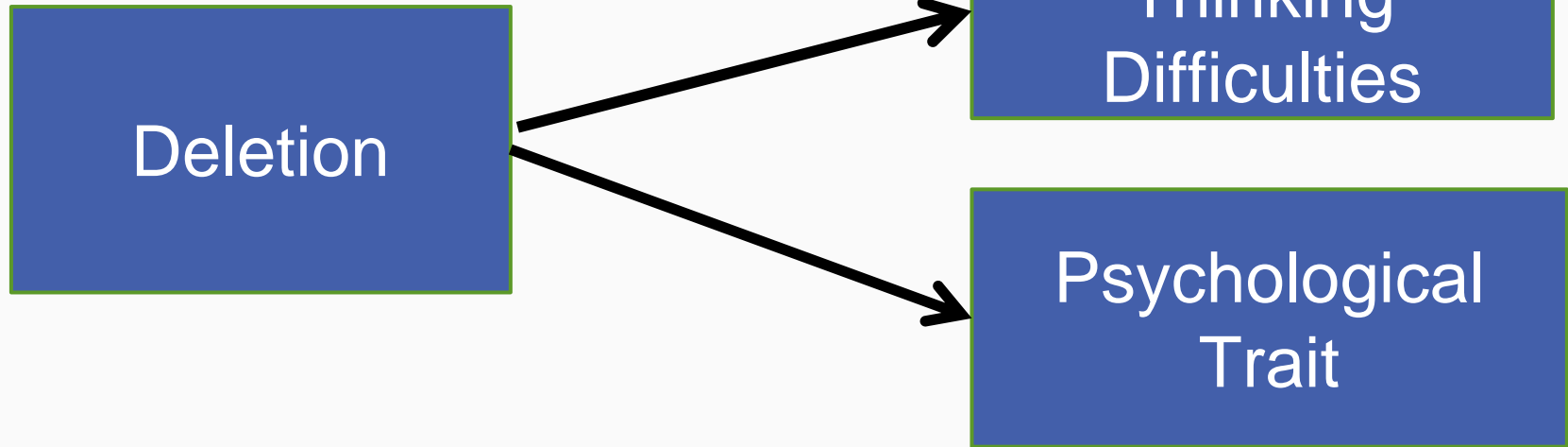


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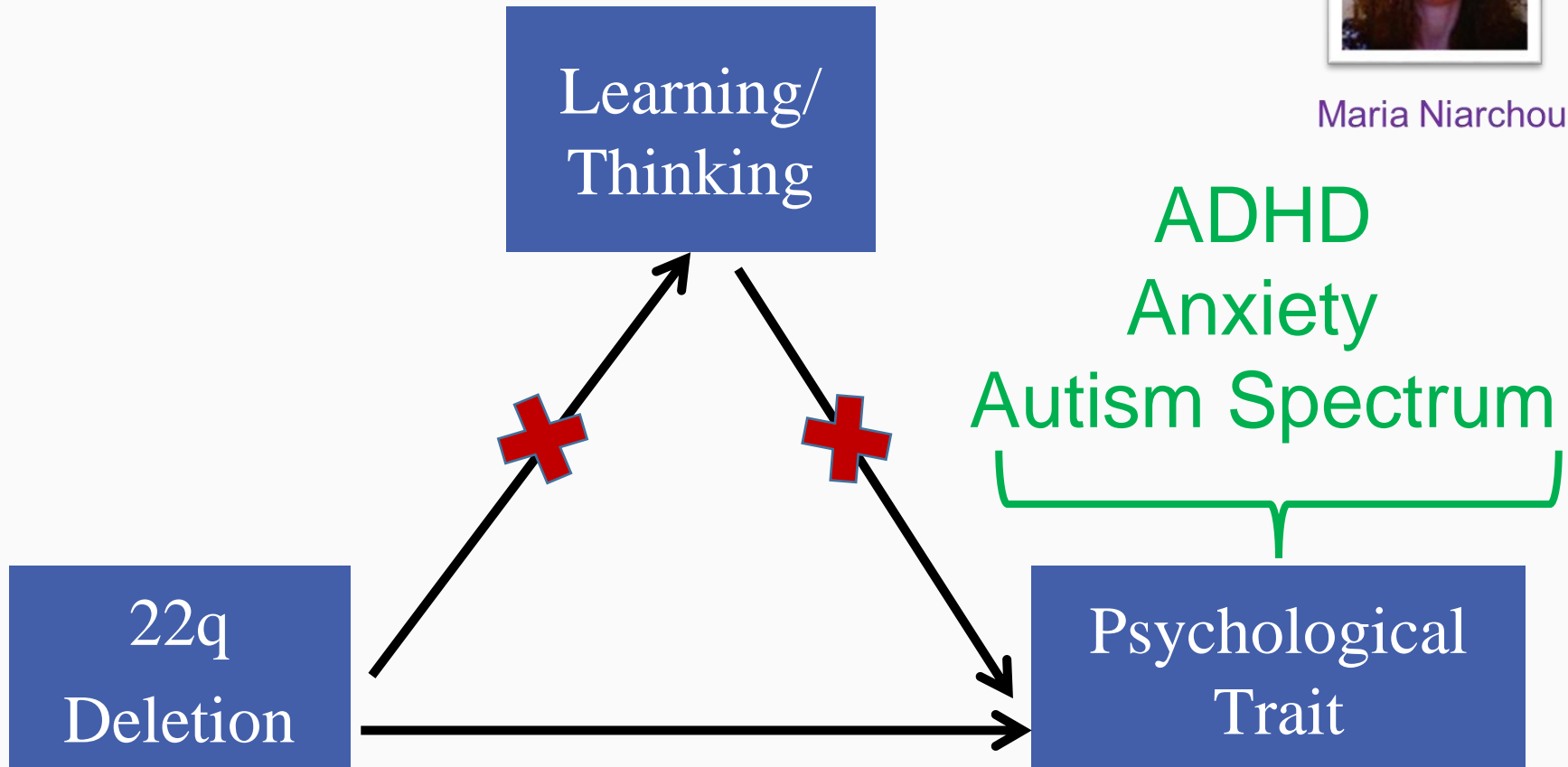




# Learning/ Thinking and Psychological Traits



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# To Recap

## Question 3:

### Links between Learning/ Thinking and Psychological Traits

- We find no evidence that children with 22q11.2DS with lower IQ are more likely to have psychological problems
- Also, we find no link between other problems with learning and thinking and psychological problems

# ECHO STUDY

(Study of Experiences of people with Copy number variants)

## Changes from Childhood to Adolescence

### • Question 4:

- Are there changes over time in:
  - Learning and thinking?
  - Psychological traits?

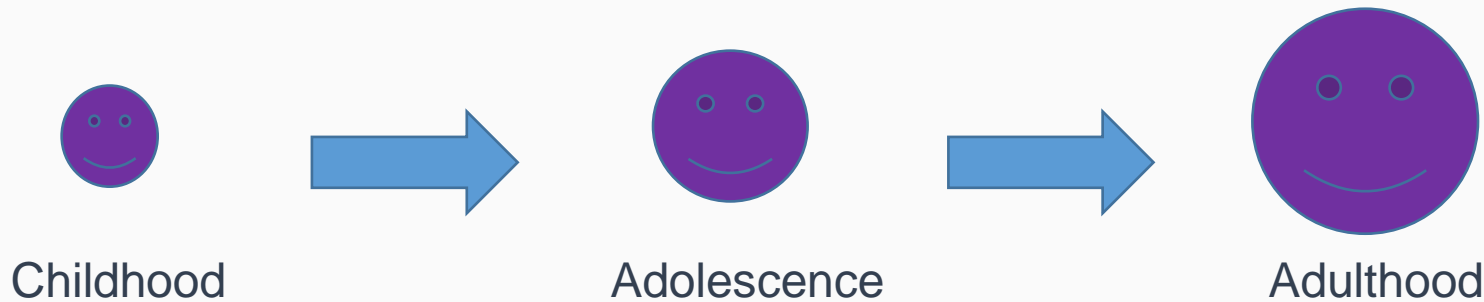


# ECHO STUDY

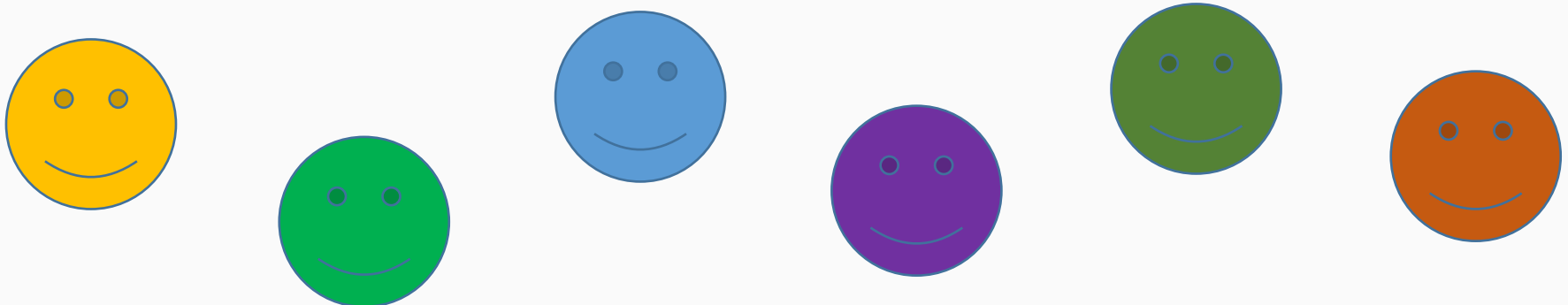
(Study of Experiences of people with copy number variations)



## Follow-up visits

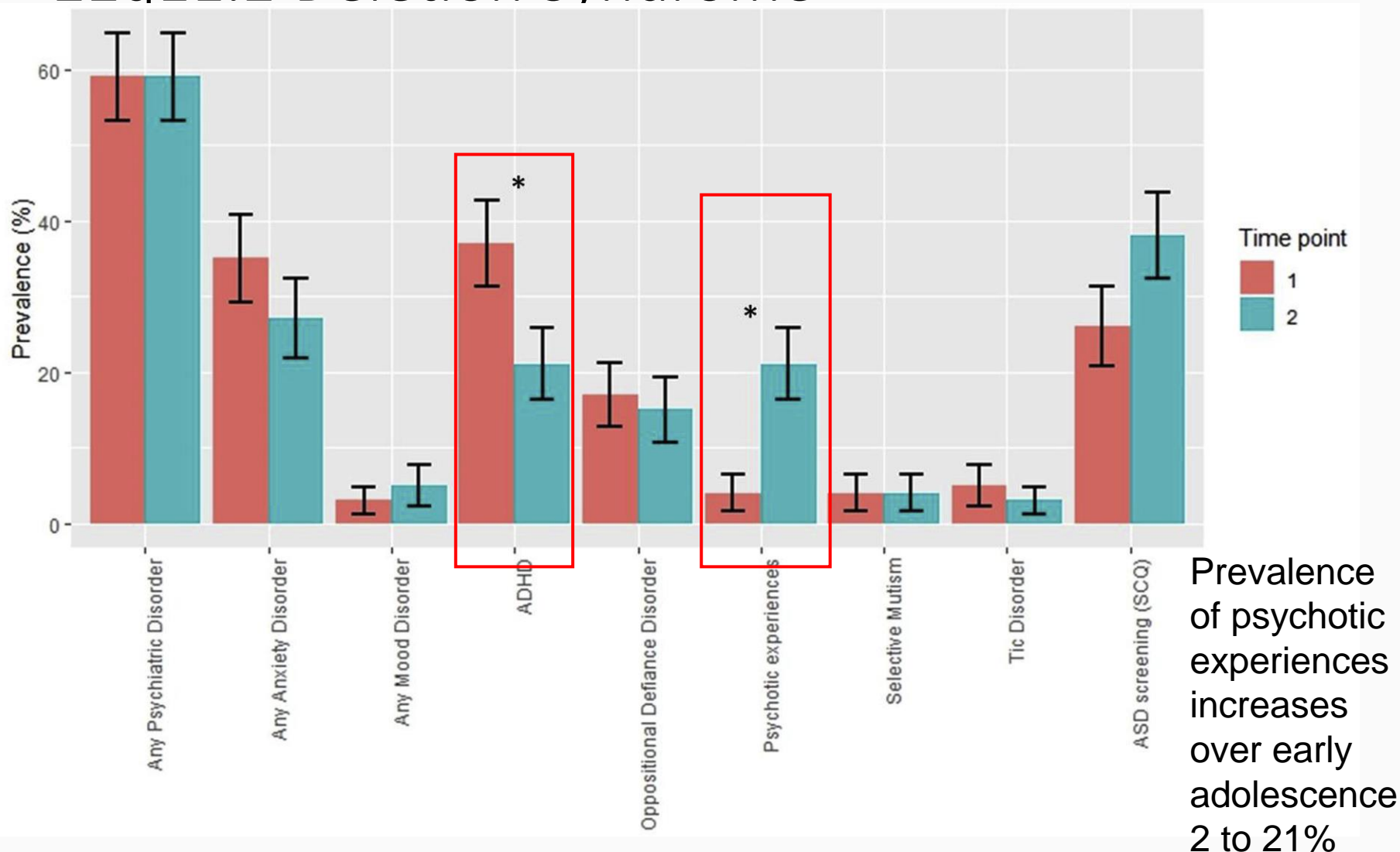


- ~120 families have taken part at least 2 times
- How stable are traits over time?
- What can families expect in the future?



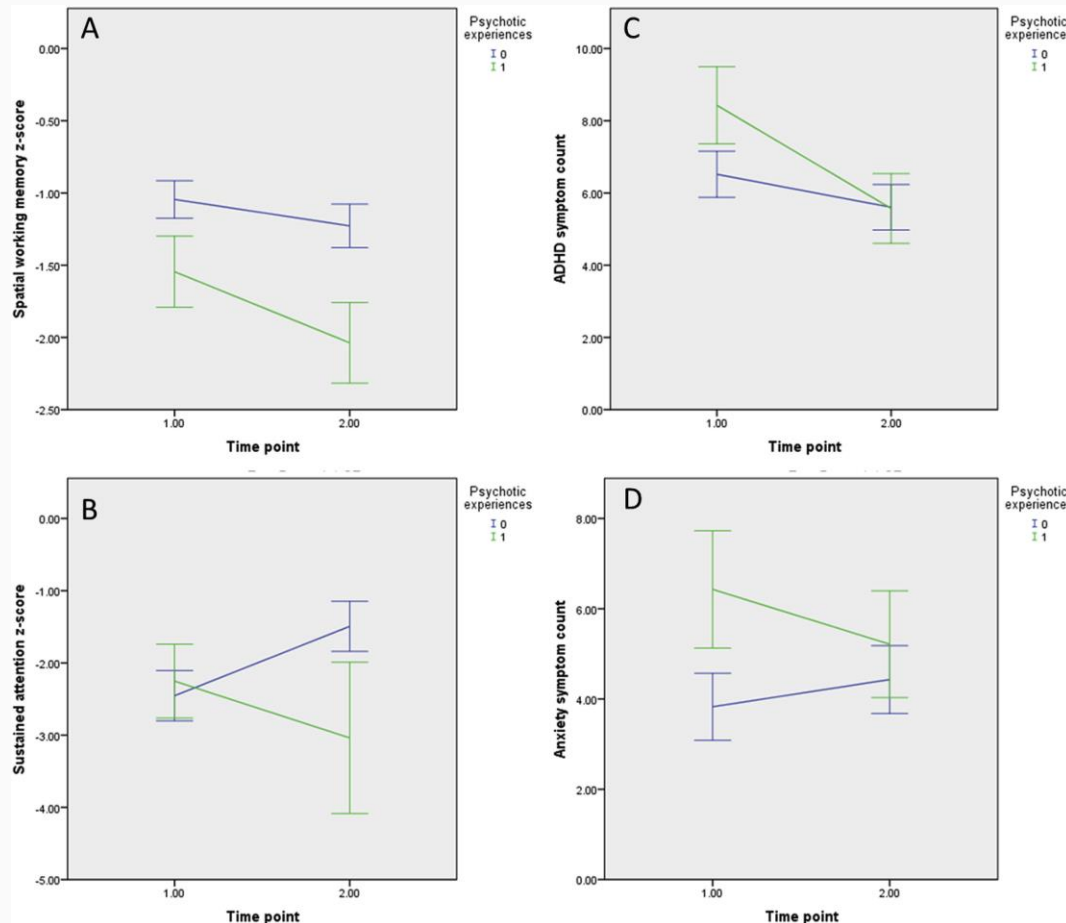


# Longitudinal psychiatric development in 22q11.2 Deletion Syndrome



# Emergence of psychotic experiences predicted by psychopathology and cognition

Spatial working memory deficits



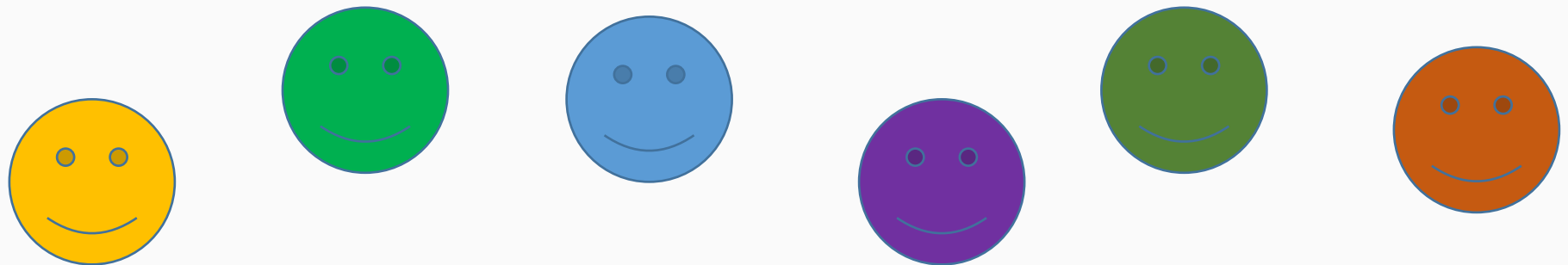
Change in ADHD symptoms

Sustained attention decline

Baseline anxiety symptoms

## Conclusions Thus Far

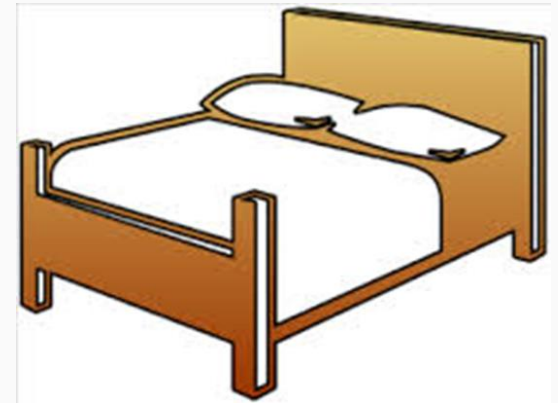
- All children with 22q11.2DS have more or less the same deletion
- Yet, their outcomes are very variable
- They show more variation in their IQ than their siblings
- Although they have a higher risk of psychological problems, almost half do not have any psychiatric disorder
- Risk for some psychological problems is lower than in other children (e.g., conduct disorder)
- Each child has their own strengths and weaknesses
- This is particularly the case for children with the 22q11.2 deletion



# ECHO STUDY

(Study of Experiences of people with copy number variants)

## What have we found so far?





# ECHO STUDY

(Study of ExperiencEs of people with H cOpy number variants)

## Sleep Disturbances

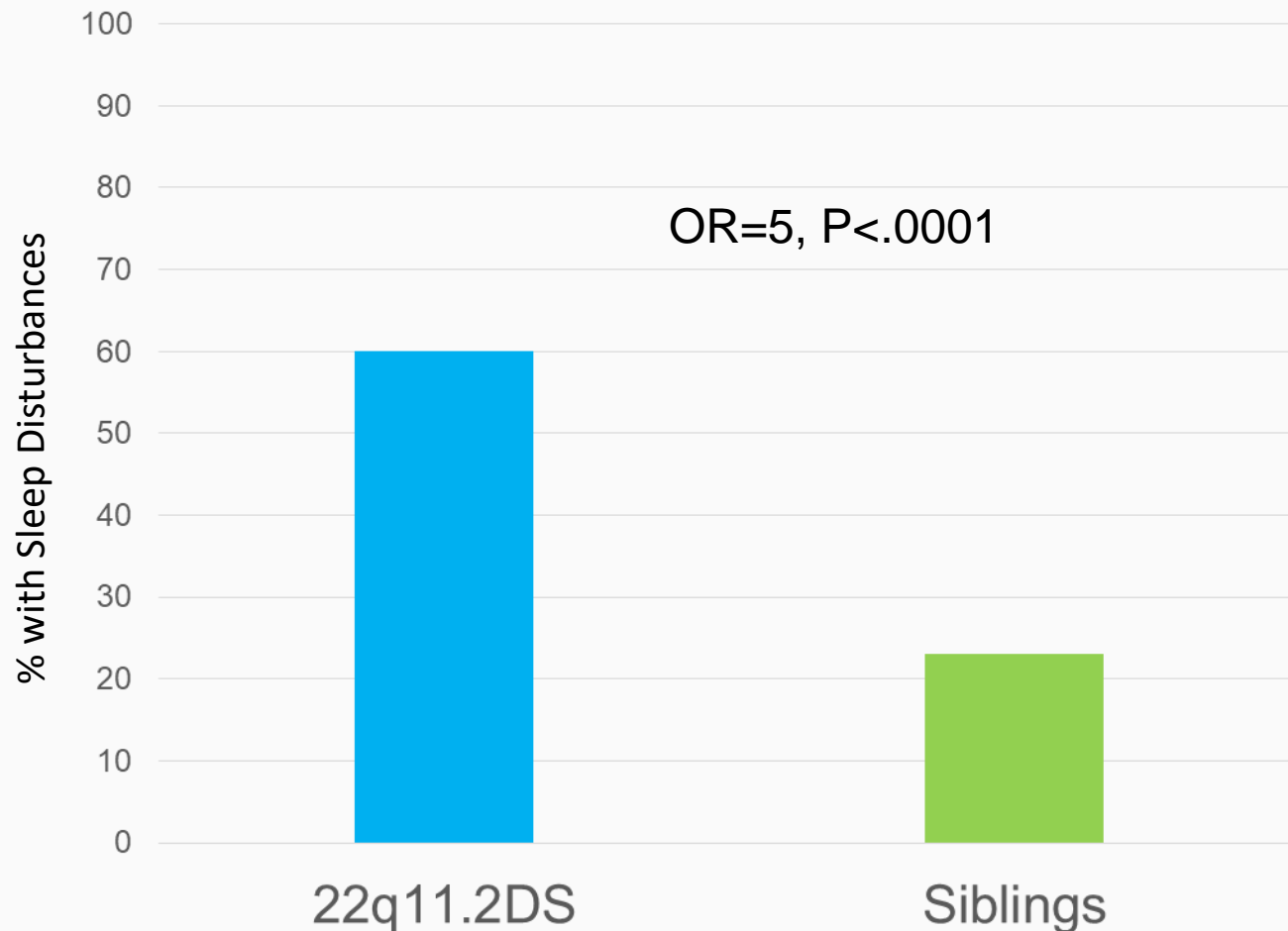
### •Question 5:

- Do young people with 22q11.2 deletion have more difficulties with sleep than other young people?
- Are the children with poor sleep more likely to have other problems?

# Sleep Disturbances in Children with 22q11.2DS



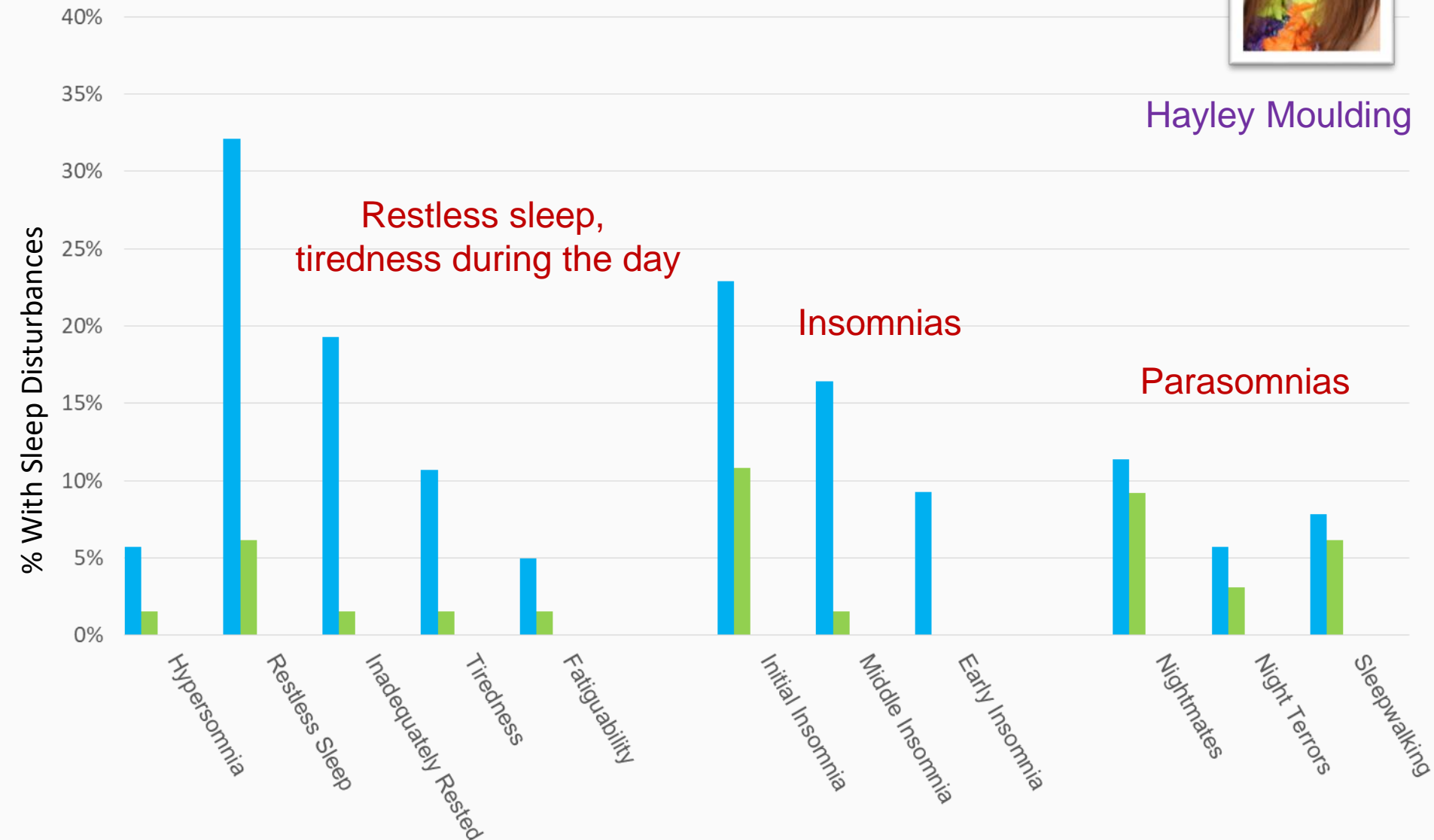
Hayley Moulding



# Sleep Disturbances in Children with 22q11.2DS



Hayley Moulding



# Disturbed Sleep in Children with 22q11.2DS



21%

## Insomnia

- Trouble falling asleep
- Trouble staying asleep
- Early morning waking

34%

## Restless Sleep

- Hypersomnia (daytime sleepiness, extended sleep duration)
- Restless sleep
- Inadequately rested sleep
- Tired, worn out
- Fatigued

45%



Hayley Moulding



# Restless Sleep and Other Problems

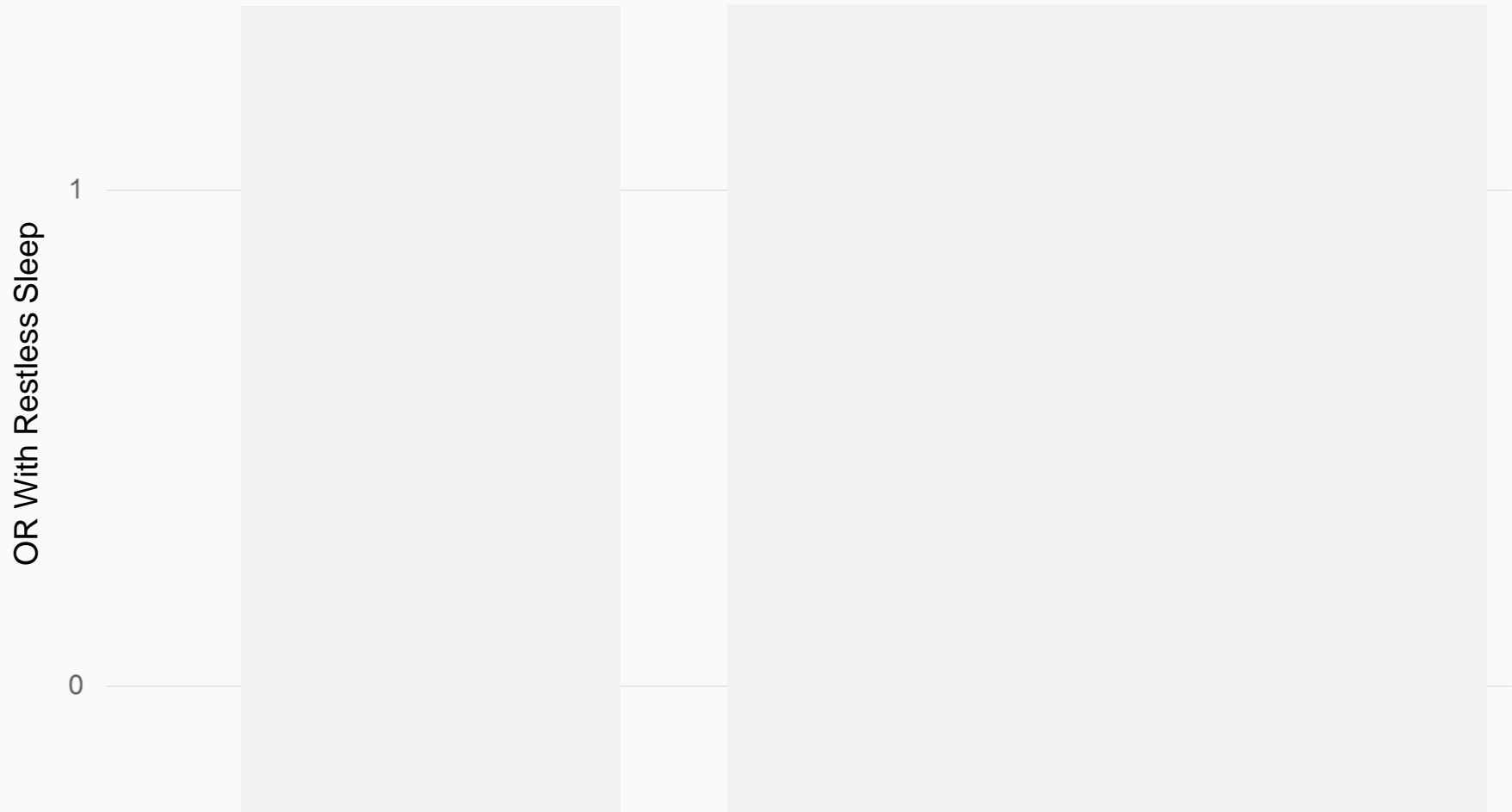


Hayley Moulding

Psychological Problems

Motor Problems

Learning/ thinking





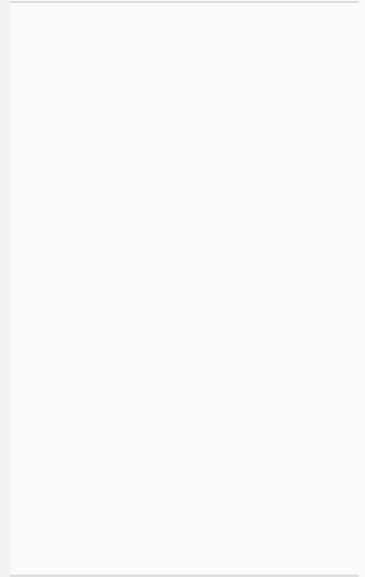
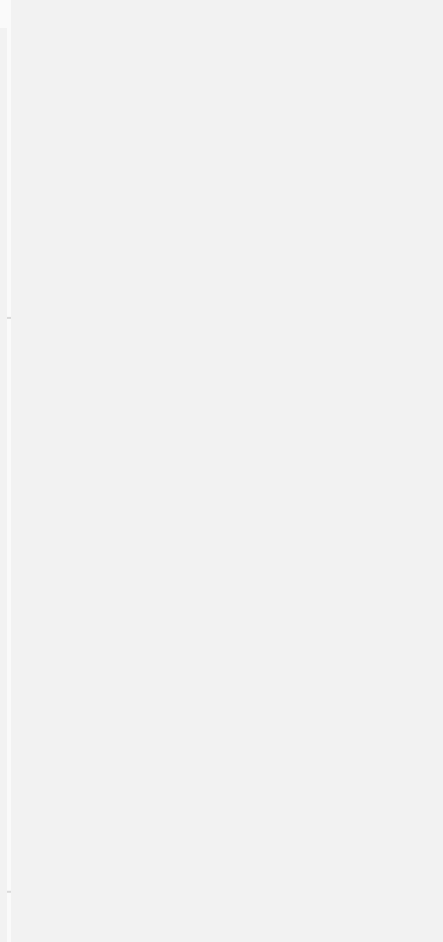
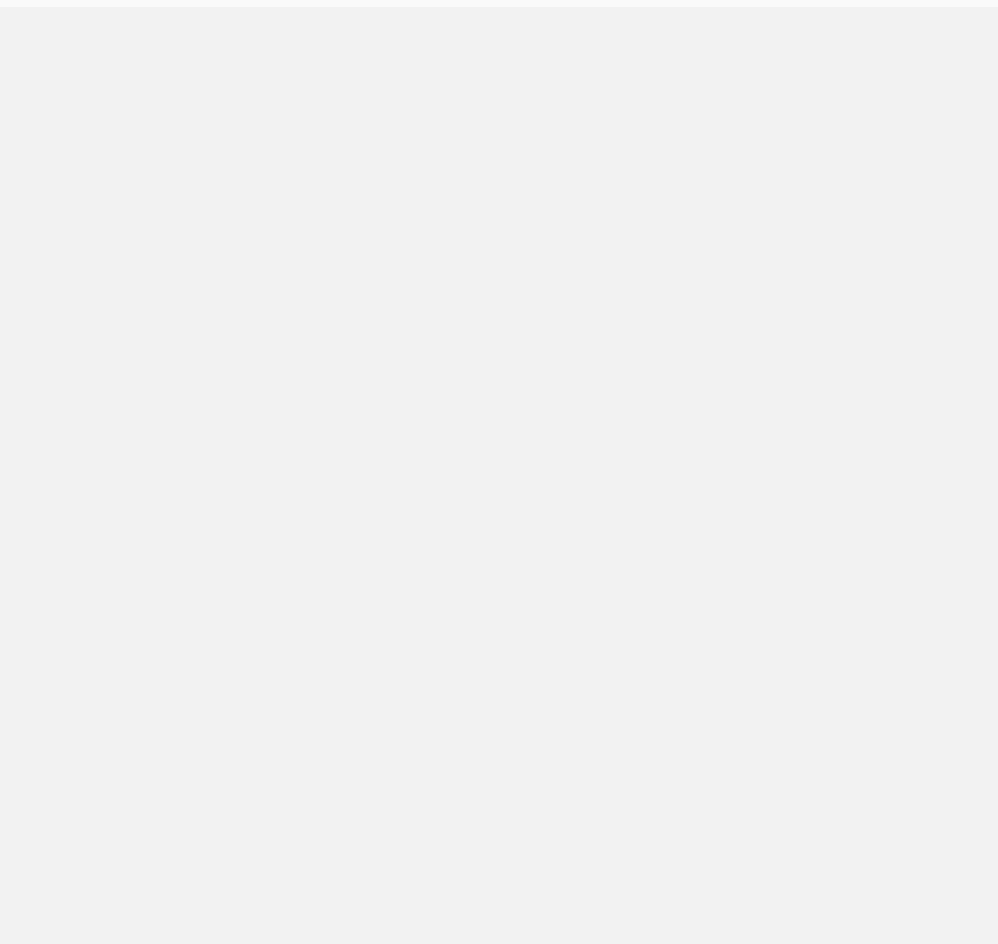
# Insomnia and Other Problems

Psychological Problems

Motor Problems



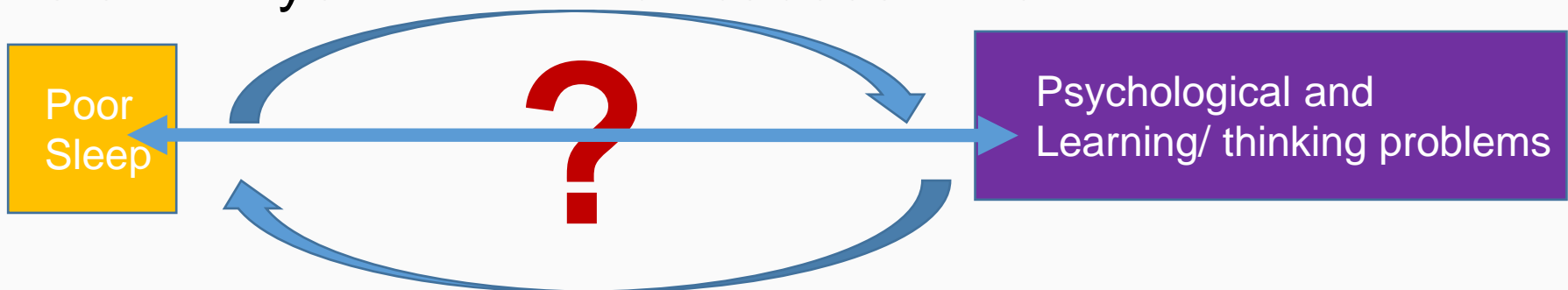
Hayley Moulding



# To Recap

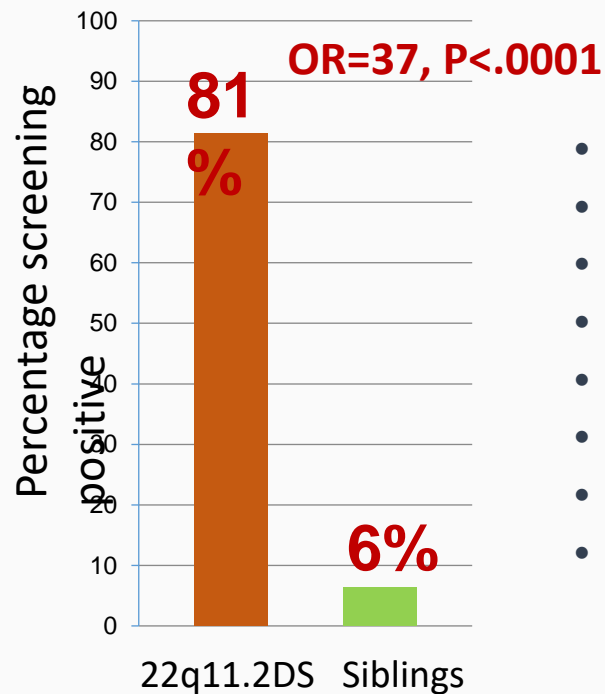
## Question 5: Sleep Disturbances

- Children with 22q11.2DS sleep less well
- They can have trouble falling or staying asleep (insomnia) or sleep doesn't bring enough rest (restless sleep)
- Poor sleep is more likely in children who experience:
  - Certain psychological problems (ADHD, anxiety)
  - Motor problems
  - Thinking/ planning (set shifting)
- We do not yet know which causes which



## Question 6: Motor & Neurological findings

# Development Coordination In 22q11.2DS



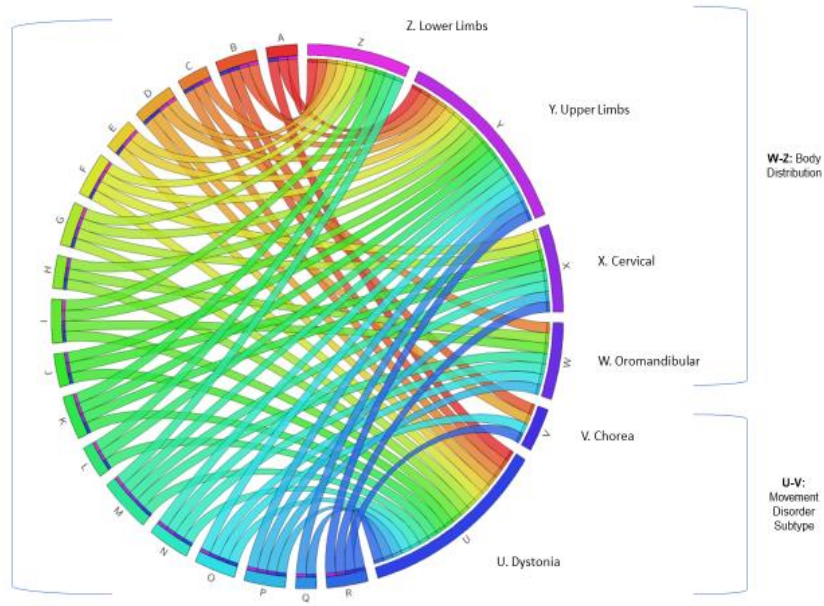
- Throwing
- Hitting
- Catching
- Running
- Jumping
- Writing
- Cutting
- Sports



Cunningham, Delpont, Cumines, Busse, Linden, Hall, Owen and van den Bree. British Journal of Psychiatry (2018).

# Question 6: Motor & Neurological findings

## Neurological Findings



19 Children with 22q11.2DS (letters A – R)

18 (95%) had a movement disorder

Mostly dystonia

X Upper limbs, Y lower limbs, Z craniofacial

Dystonia causes involuntary contractions of your muscles, which lead to twisting and repetitive movements.

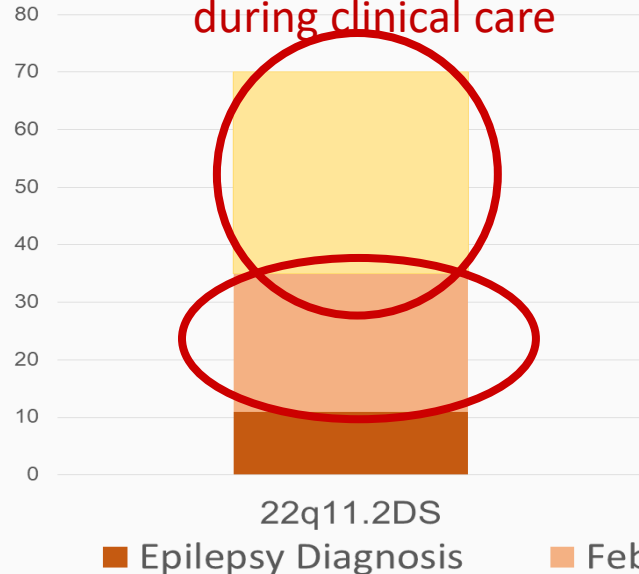
Cunningham AC, Fung W, Massey TH, Hall J, Owen MJ, van den Bree MBM, Peall KJ. Mov Disord. 2020

## Question 6: Motor & Neurological findings

# Epilepsy and Seizures

Seizure risk may not always be detected during clinical care

OR=12,  $P<.0001$



### Febrile Seizures

#### Definition:

Febrile seizure is a seizure accompanied by fever ( $> 38^{\circ}\text{C}$ ) without CNS infection of defined cause in infants and children 3 months to 6 years of age [Avg. 18 - 22 months]

Does not include seizures occurring during fever in children with past H/o. afebrile seizure.

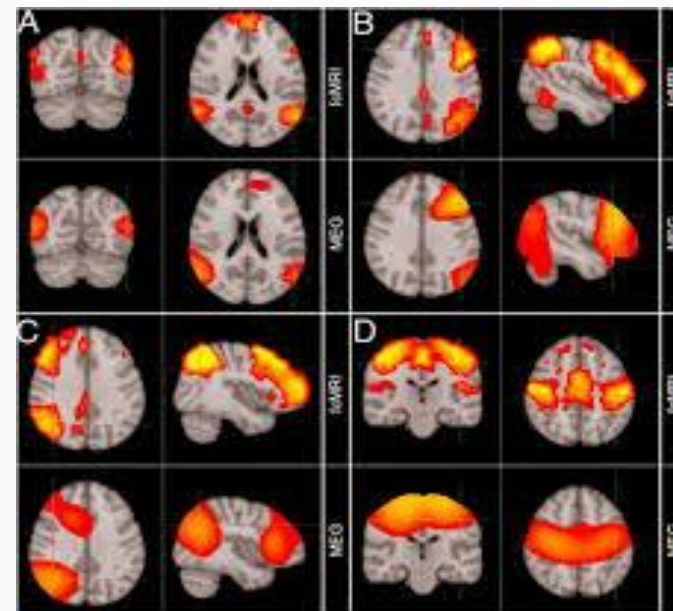
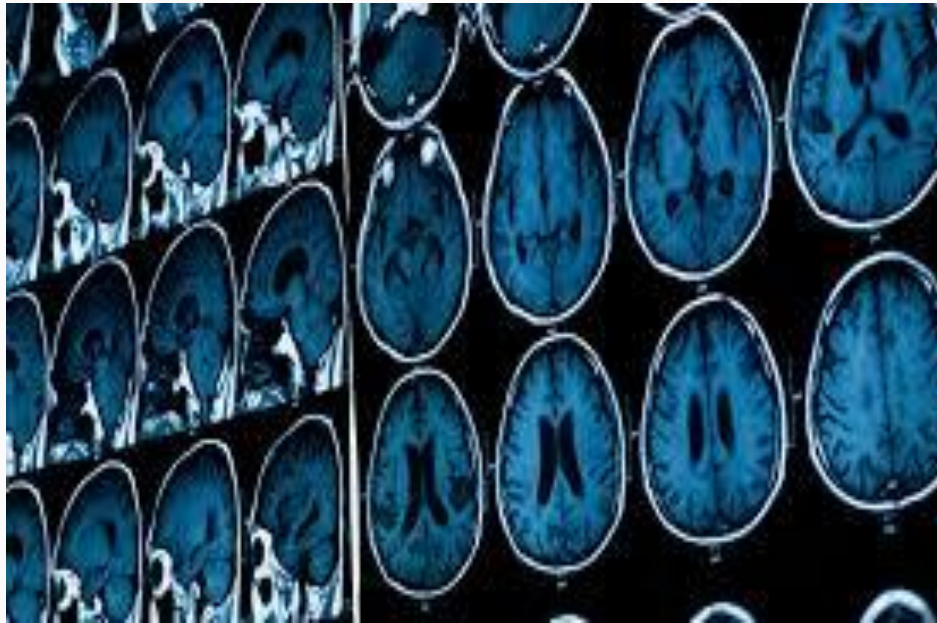


Febrile seizures may be associated with immunological problems in 22q11.2DS

# Question 7: Brain Structure and Function



Jo Doherty





# Brain Structure and Function

Magnetic  
Resonance  
Imaging (MRI)

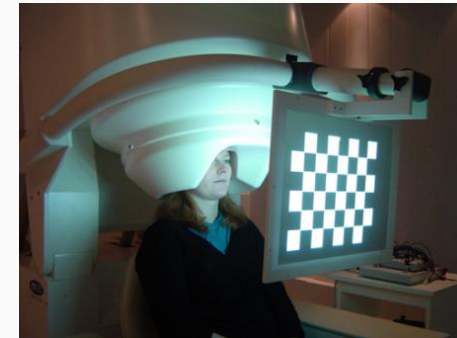


Jo Doherty

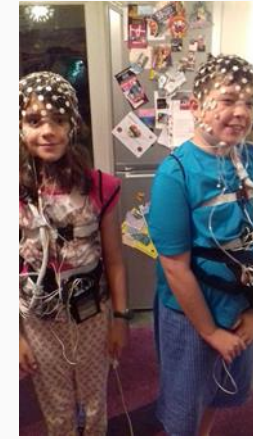
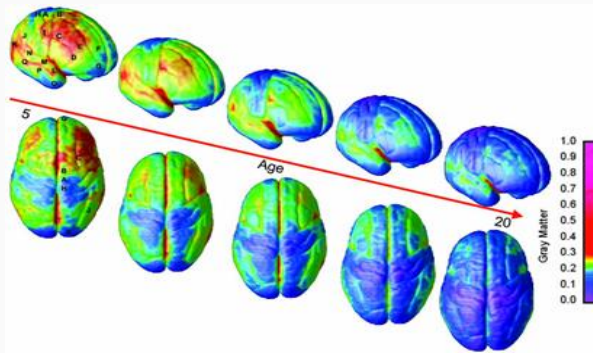
## • What do we measure?

- What do brain connections look like?
- How does the brain work during different activities
- Brain activity at rest/sleep
- Concentrations of important chemicals in the brain

Magnetoencephalo  
graphy (MEG)



Electroencephalography (EEG)

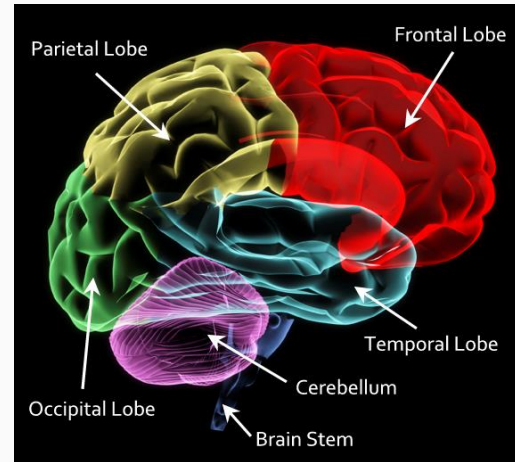


# Brain Structure and Function



Jo Doherty

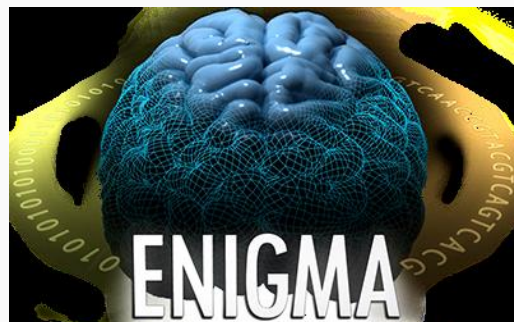
- Effective communication between brain areas is important for optimal learning, thinking, memory
- Little is known about how well different parts of the brain work together in 22q11.2 deletion
- Better insight can increase our understanding of learning and behaviour



# Brain structure and function

## • What have we found?

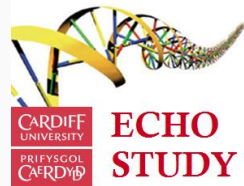
- Generally, parts of the brain are less well-developed
- Brain is wired differently
- Reductions in mean, axial and radial diffusivity of major cortico-cortical and cortico-thalamic tracts in the 22q11.2 group.
- Posterior limb of internal capsule had higher axial diffusivity, and there was higher fractional anisotropy in callosal and projection fibres in the 22q11.2 group.
- Psychiatric illness associated with diffusivity reductions in multiple regions.



Carrie Bearden

Large sample of ~475 people with 22q11,2DS and 315 without from many countries

Sun et al., Molecular Psychiatry, 2018  
Villalón-Reina et al, submitted  
Ching et al., in preparation  
Doherty et al., in preparation



# Conclusions



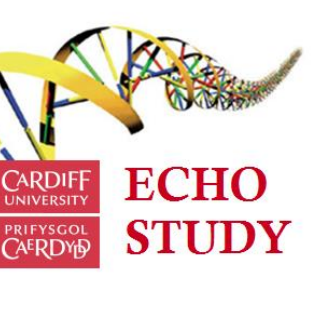
- Children with 22q11.2DS are more likely to experience problems across a range of developmental, physical, sleep and psychiatric problems
- Psychiatric problems may present differently from other children (e.g., ADHD and autism), and the mental health profile is different in adults
- Presence of certain problems can indicate increased risk of others (e.g., sleep)
- There are brain connectivity differences in individuals with 22q11.2
- Our findings should help families and clinicians with planning care, considering for example:
  - Psychiatric assessment
  - Occupational therapy
  - Sleep hygiene training



# Conclusions



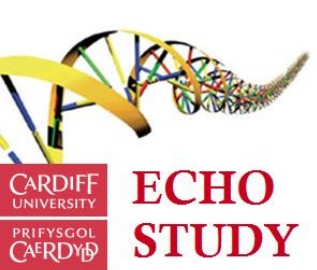
- We are starting to understand 22q11.2DS better
- But there is still a lot we do not know
- There is still a great lack of awareness of 22q11.2DS amongst the public and clinicians
- Families still often struggle to get recognition and optimal care for their child



# BIG THANK-YOU TO FAMILIES, CLINICIANS and CHARITIES for supporting our Studies







# Funding Acknowledgments

**The Baily Thomas**  
Charitable Fund

**Knowledge Transfer  
Partnerships**

**Innovate UK**  
Technology Strategy Board

**W**  
**wellcome**

thewaterloofoundation\*

hefcw

**NCMH**  
National Centre for Mental Health

**cost**  
EUROPEAN COOPERATION  
IN SCIENCE & TECHNOLOGY

**NIH** National Institute  
of Mental Health

**MRC** Medical  
Research  
Council

**MRC** Medical  
Research  
Foundation

**iMAGiNE iD**

**MINDDS**  
Maximising Impact of research in  
NeuroDevelopmental Disorders

**22q** **IBBC**  
International 22q11.2 Brain Behavior Consortium

**DEFINE**  
Defining Endophenotypes from Integrated Neurosciences