Oxford Centre for Developmental Science

Attention, Brain & Cognitive Development

What predicts (good) outcomes in young boys with fragile X syndrome?

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16.11.2012

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Clinical and Cognitive Phenotype

Physical characteristics:

~ 70% fulfill ADHD diagnosis
(Hagerman, 1987; Turk, 1998)

33-67% fulfill ASD diagnosis
(Rogers et al., 2001; Hernandez et al., 2009)

Behaviour and Cognition:

↑ Face Recognition, Long-term memory, Receptive Language — MA

↓ Social cognition, Working Memory, Attention&control

Clinical and Cognitive Phenotype

Physical characteristics:

~ 70% fulfill ADHD diagnosis
(Hagerman, 1987; Turk, 1998)

33-67% fulfill ASD diagnosis
(Rogers et al., 2001; Hernandez et al., 2009)

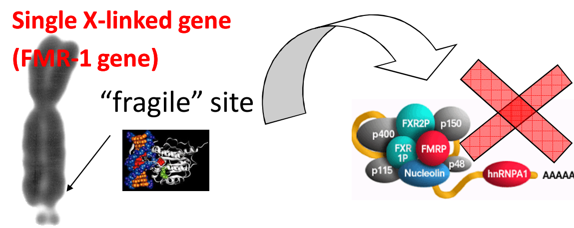
Highly debated, complex clinical presentation:

- **"ADHD" or "ADHD-like"?**
- **"ASD" or "autistic features"?**

Here:

What insights can be gained from studying variable outcomes?

Genetics and Cellular Neuroscience



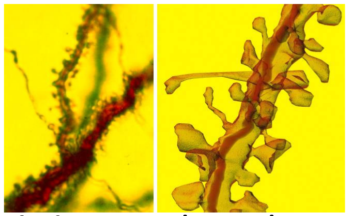
FMRP involved in glutamatergic systems (mGluR), and its silencing has effects on glutamate / GABA balance

A puzzle: How do uneven cognitive profiles and clinical strengths / weaknesses originate?

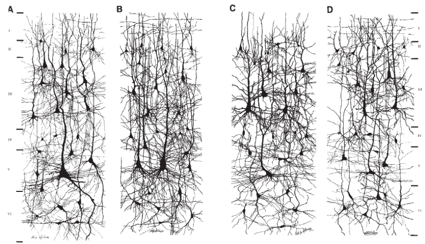
(e.g., D'Hulst & Kooy, 2007, TiNS, Bear et al., 2004, TiNS)

Bridging Cell & System Neuroscience

FXS affects dendritic morphology **[Nimchinsky et al 2002, Ann Rev Physiology]**



Fronto-Parietal Neurones: "All the more spiny to think with" **[Elston, 2003 Cereb Cortex]**



1. **Long-range integration**
2. **Recurrent connections** **[Miller & Cohen, 2001, Ann Rev Neuroscience]**
3. **Neurotransmitter modulation at asymmetric synapses** **[Gao & Goldman-Rakic, 2003, PNAS]**

All rely on mature dendritic spine morphology

Bridging Cell & System Neuroscience

1. Atypical dendritic spine morphology and thus long range integration [e.g., Nimchinsky et al 2002, Ann Rev Physiology]
2. Atypical regulation of extrinsic (e.g., monoaminergic) neurotransmitter systems [e.g., Zhang et al., 2005, Mol Cell Proteomics, Bassell et al., 2009, Neuron]

FMRP highly relevant to cortical and subcortical networks involved in attentional control?

e.g., Scerif and Karmiloff-Smith, 2005 TiCS; Scerif et al., 2005, J of Cog Neuro

"Fragile" Attention Development

Adults

Executive difficulties **[e.g., Cornish et al., 2001, J Cog Neuro]**

Adolescents & school children

Poor response inhibition and sustained attention **[Sullivan et al., 2007, Am J of Med Gen]**

Executive difficulties **[e.g., Munir et al., 2000, Neuropsychologia; Hooper et al., 2008, Neuropsychology]**

Preschoolers & infants

Poor response inhibition **[Scerif et al., 2004, Dev Science; Scerif et al., 2007, Neuropsychologia]**

Poor control of eye-movements **[Scerif et al., 2005, J Cog Neuro]**

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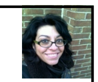
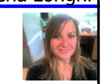
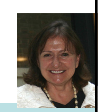
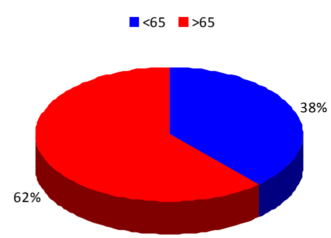
Longitudinal study: attention, outcomes, risk and resilience


Elena Longhi


Vic Cole

* 59 boys with FXS, aged 3-10yrs at Time 1
  - Recruited through the Fragile X Society UK
  - Current analyses following exclusion for ADHD medication
* 129 typically developing (TD) boys, aged 3-10yrs
  - Recruited from local schools
  - Exclusion of elevated Conner's scores


Annette Karmiloff-Smith



	Fragile X syndrome group			
	Mean	SD	Min	Max
Age at Test (yrs)	7.5	2.2	3	[illegible]
Non-verbal IQ Equivalent	63	15.06	40	[illegible]
Mental Age Equivalent (yrs)	4.7	.87	2.8	[illegible]
Conner's ADHD Index	65.6	7.9	48	[illegible]
Conner's T Hyperactivity	63.7	9.2	47	77
Social Comm Questionnaire	19.7	7	5	33


Kim Cornish

Longitudinal study: attention, outcomes, risk and resilience

Time 1: Jan 08 - Oct 08 — Time 2: Jan 09 - Oct 09 — Time 3: Jan 10 - Oct 10

time

Standardised Assessment and Experimental tasks

	Visual	Auditory	Cross-modal
Basic perceptual functioning	Visual Acuity	Audiometry	
Perception of [illegible] stimuli	Spatial contrast	Intensity	
Sustained attention	Visual Oddball	Auditory Oddball	Cross-modal Oddball
Inhibitory control	Visual Go-nogo	Auditory Go-nogo	Cross-modal Go-nogo
Working memory	Dual task		

	Predictors and Outcomes
Non-verbal IQ	Leiter-R
ADHD symptomatology	Conner's CPRS:S and CTRS:S
Environmental meausure	HOME, SES, special needs provisions
Genotyping	Candidate snps
Environmental measures	HOME, SES, special needs provisions
Language abilities	Child Communication Checklist-2
Autistic symptomatology	Social Communication Questionnaire

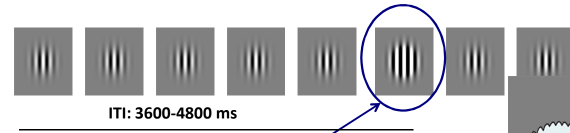
Cornish et al., in press, Dev & Psychopathology; Cornish et al., AJIDD; 2012; Scerif et al., 2012, JCPP; Scerif et al., under review

a. Sustained attention

Sustained attention as the ability to maintain attention over time

3 x
- Practice trials
- Test trial block: 15 oddballs to catch (the 'big wave')

Visual Oddball



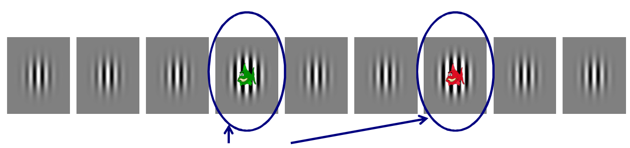
"Catch the fish when you see the big wave in the water"

Measuring Accuracy (% hits), RT, d-prime, log beta

a. Sustained attention & WM Demands

3 x
- Practice trials
- Test trial block: 15 oddballs to catch (the 'big wave')

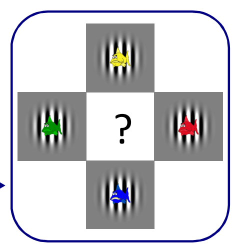
Dual Task



" catch the fish when you see the big wave. This time the fish will be different colours. Try to remember the colours of the fish you catch as you go along – we will test you!"

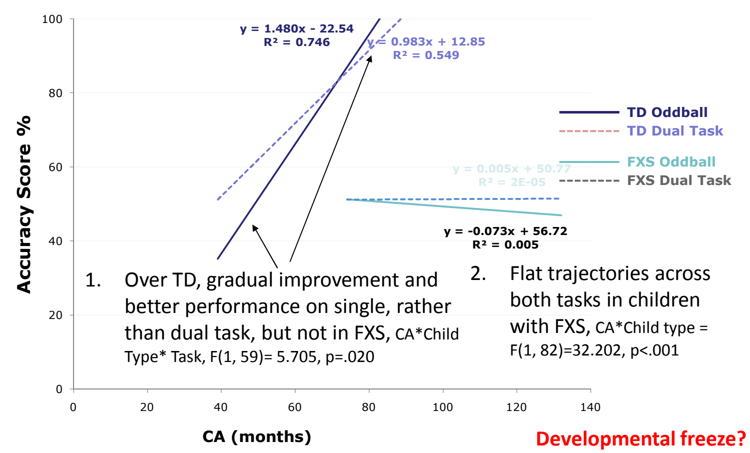
Oddball ask paused after 3, 4 or 5 trials and WM test probe presented:

" What was the colour of the last fish you caught?"



Same dependent measures + Memory Acc.

a.Trajectories over chronological age

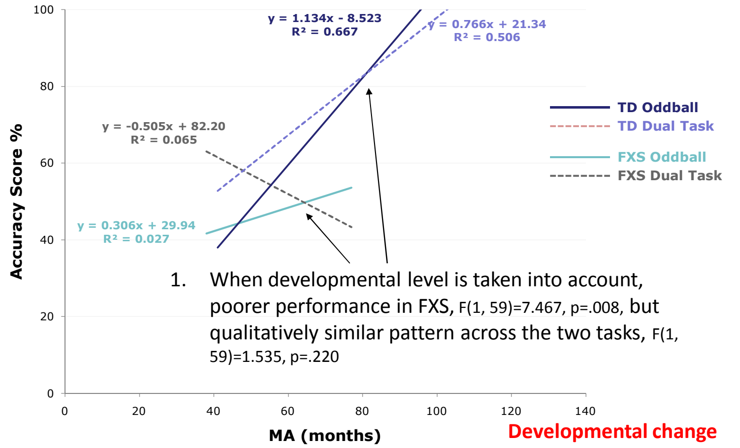


1. Over TD, gradual improvement and better performance on single, rather than dual task, but not in FXS, CA*Child Type* Task, F(1, 59)= 5.705, p=.020
2. Flat trajectories across both tasks in children with FXS, CA*Child type = F(1, 82)=32.202, p<.001

Developmental freeze?

Cornish et al., in press, Dev & Psychopathology

a. Traject. over developmental level

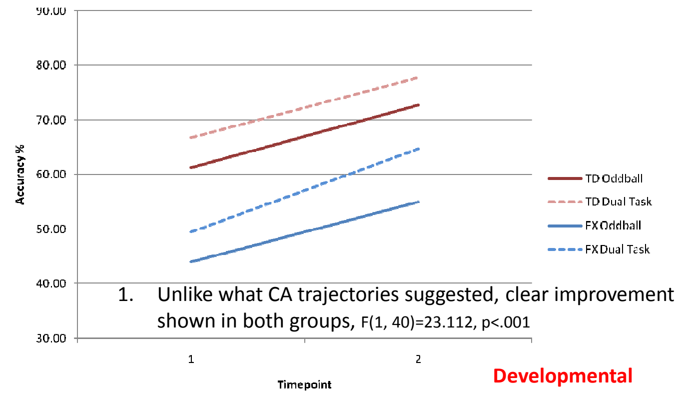


1. When developmental level is taken into account, poorer performance in FXS, F(1, 59)=7.467, p=.008, but qualitatively similar pattern across the two tasks, F(1, 59)=1.535, p=.220

Developmental change

Cornish et al., in press, Dev & Psychopathology

a. Longitudinal trajectories

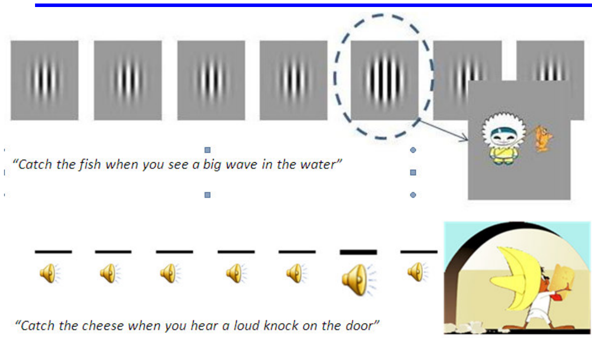


1. Unlike what CA trajectories suggested, clear improvement are shown in both groups, F(1, 40)=23.112, p<.001

Developmental improvements

Cornish et al., in press, Dev & Psychopathology

b. Attention as predictor of outcomes



→ clinically-related outcomes? ADHD and ASD symptomatology

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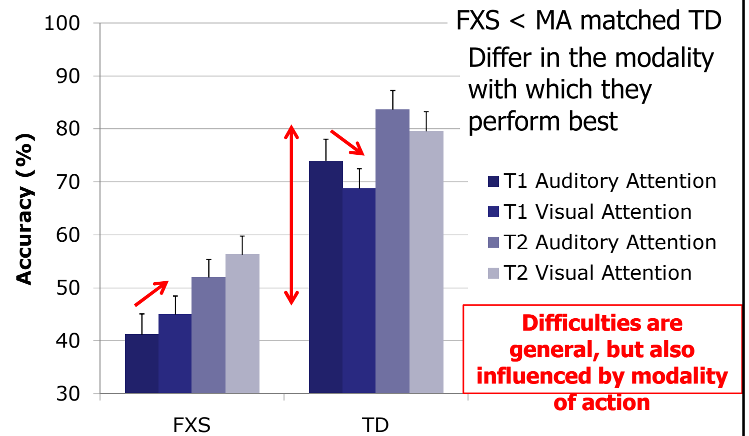
b. Attention as predictor of outcomes



FXS < MA matched TD

Differ in the modality with which they perform best

Difficulties are general, but also influenced by modality of action

Scerif et al., 2012, JCPP

b. Differential longitudinal predictors of ADHD and ASD symptoms in FXS

	T1 Aud	T1 Visual
T2 IQ	.051	.241
T2 Conner's Oppositional	-.034	-.058
T2 Conner's Cognitive / Inatt	-.258	-.010
T2 Conner's Hyperactive	-.256	**-.382* 13.9%***
T2 Conner's ADHD Index	-.266	**-.498** 19%****

FXS < MA matched TD

Differ in modality with which they perform best

Reversal for predictors of later autistic spectrum symptoms:

T1 Aud (false alarms) correlates with T2 SCQ scores (.422, 17%)

Attentional control relates to later ADHD/ASD and in ways that depend on modality

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Scerif et al., 2012, JCPP; Cornish et al., 2012; AJIDD

c. Mechanisms for Variability?

Dianne Newbury

Differences in cognitive outcome across boys with FXS

1. Differences in environmental input over developmental time [Hessl et al., 2002, 2003]

2. Genes beyond FMR1

FXS specific: e.g., downstream molecular pathways - mGluR and GABA [D'Hulst & Kooy, 2007, Trends in Neurosci]

ADHD/ASD related candidates

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2. Common risk and unique pathways to outcomes

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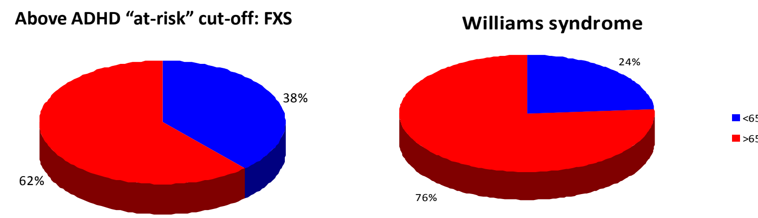
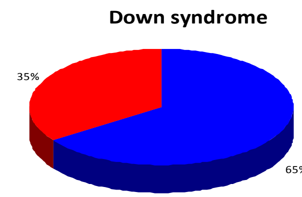
Cross-syndrome comparisons: Distinct pathways to common risk?



Mechanisms underpinning similarities and differences?

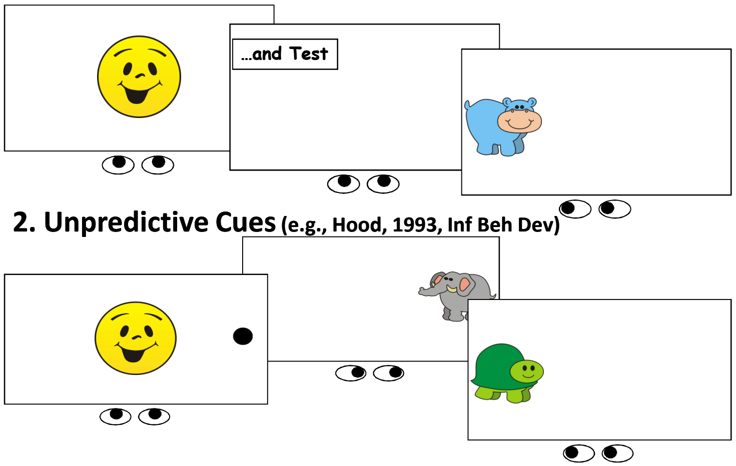


Scerif & Steele (2011) Prog Brain Res; Fung et al. (2012) Ann Rev Neurology

Comparisons from Infancy

1. Predictive Cues (e.g., Johnson, 1995, Dev Psychobio)

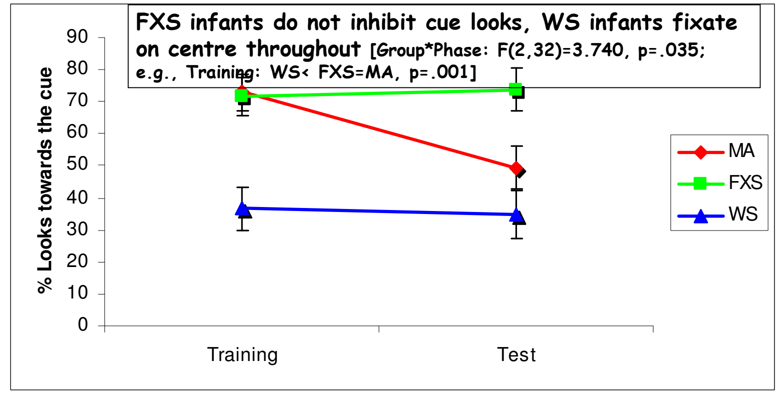
2. Unpredictive Cues (e.g., Hood, 1993, Inf Beh Dev)



Predictive Cues

(Scerif et al., J o Cog Neurom 2005; Cornish, Scerif, & Karmiloff-Smith, 2007, Cortex)

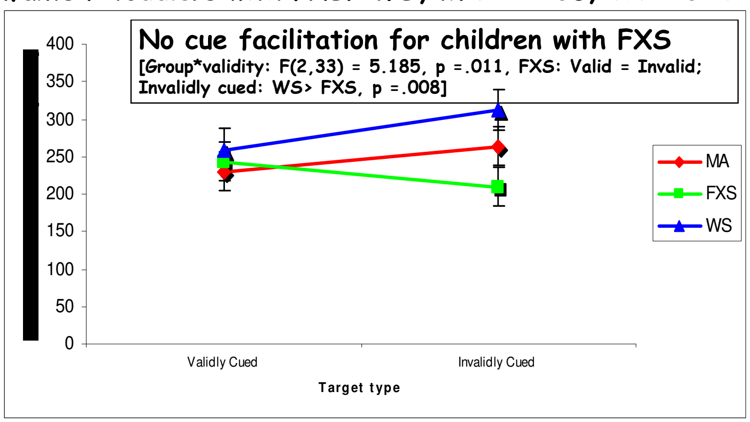
infants / toddlers with FXS/ WS, MA = 2-36, CA = 3-41



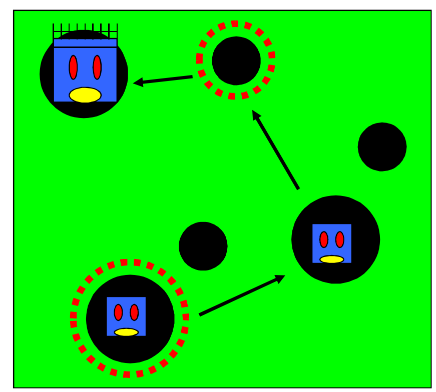
Unpredictive Cues

(Cornish, Scerif, & Karmiloff-Smith, 2007, Cortex)

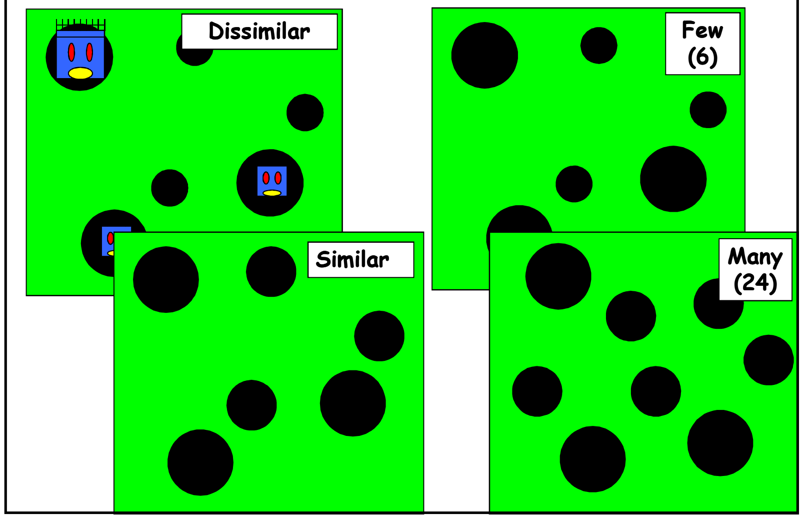
infants / toddlers with FXS/ WS, MA = 2-36, CA = 3-41



Comparisons in toddlerhood



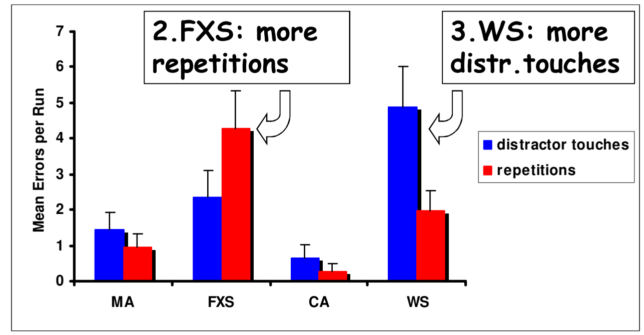
(Scerif, Cornish, Wilding, Driver & Karmiloff-Smith, 2004, Dev Science)



(Scerif, Cornish, Wilding, Driver & Karmiloff-Smith, 2004, Dev Science)

Toddlers with FXS / WS; MA = 18-36 months, CA = 34-50

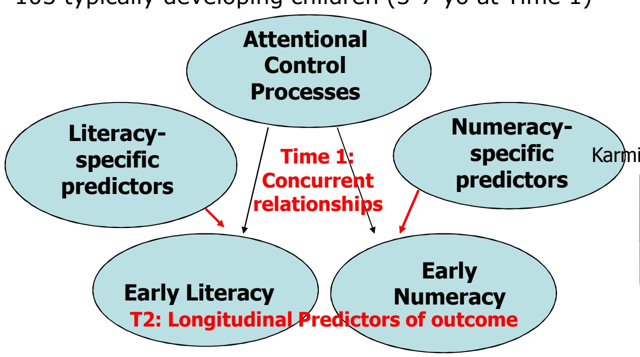
1.Search Speed and Path: FXS = MA, CA, WS



Attention difficulties across syndromes: longitudinal outcomes

Ann Steele

27 children with Williams syndrome
27 children with Down syndrome
103 typically developing children (3-7 yo at Time 1)



Annette Karmiloff-Smith

Kim Cornish

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Steele et al., 2012, Child Dev; under review, JCPP; Cornish et al., 2012, Front Psychol

3. Neurocognitive risk mechanisms within syndrome

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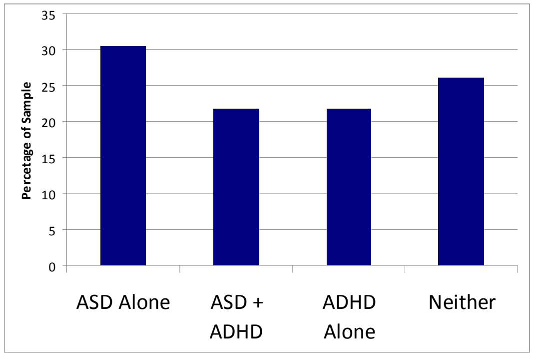
Complexity within syndrome groups

Dianne Newbury

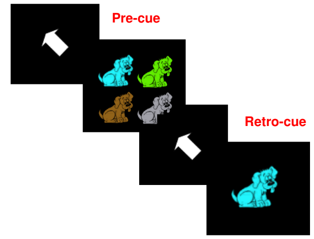


Could risk for complex phenotype be accounted for by genetic and environmental factors beyond the causative mutation?

Mechanisms of difficulties: Temporal dynamics?

Andria Shimi

Participants:
7-year-olds
11-year-olds
adults



Was the probe one of the initial four stimuli?

Neural dynamics: EEG

Shimi, Nobre, Astle & Scerif, under review

Shimi, Kuo, Astle, Nobre, & Scerif, in prep

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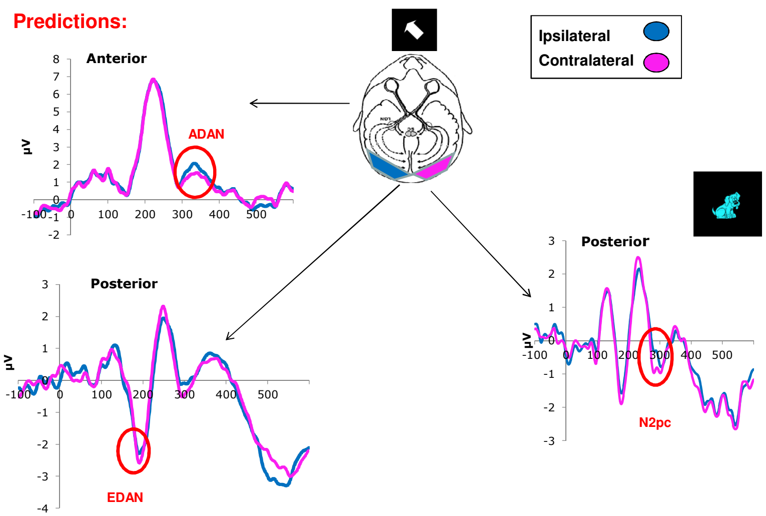
Temporal dynamics of attention orienting

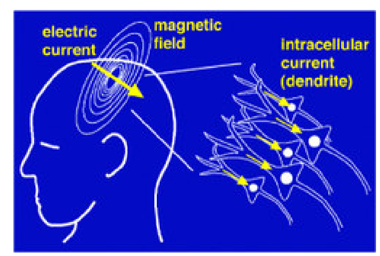
Predictions:



Mechanisms of difficulties: Recruitment of sources and networks?

MEG Methods: going from sensors to sources and their networks

Duncan Astle



MEG data, for now TD children (aged 9-11) and adults.
Which sources and networks distinguish adults and children performance → Ask similar questions of boys with FXS

Astle, Kuo, Luckhoo, Woolrich, Nobre, & Scerif, in prep

Taking Stock & Discussion Points

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Predicting and understanding good outcomes at multiple levels

1. Exploring individual differences over time is key at all levels
2. Developmental trajectories to be tested empirically:
   * Longitudinal designs open the road to studying predictors of good outcomes: Mechanisms?
   * Comparisons with children with different syndromes may provide insights into common and unique mechanisms
3. Mechanisms of variability:
   * Within-group differences provide insights into environmental and genetic predictors
   * Neural underpinnings of differences?

Many thanks to

ALL CHILDREN AND FAMILIES WHO PARTICIPATED…

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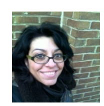
…to you and…

…Collaborators and funders supporting this work

JAMES S. MCDONNELL FOUNDATION

wellcome trust

Ann Steele



Elena Longhi

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