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The importance of cross-syndrome comparisons for understanding autism: a developmental approach

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Zaragossa talk, November 2010

Main take-home messages of talk:

Development matters: gene expression, brain, cognition, behaviour
So, adult neuropsychological model of juxtaposition of impaired & intact modules = inappropriate for *developmental* syndromes

Start state can be *domain-relevant*, not necessarily domain-specific but *become* domain-specific over developmental time:
gradual process of *modularization*

Cross-syndrome dissociations *and associations* enable researcher to distinguish similar behavioural outcomes

Scores *"in the normal range"* not necessarily same at neural and cognitive levels

Tracing *full developmental trajectories from infancy* = critical

1st general point:

Development matters

Partial Gene Deletion patients

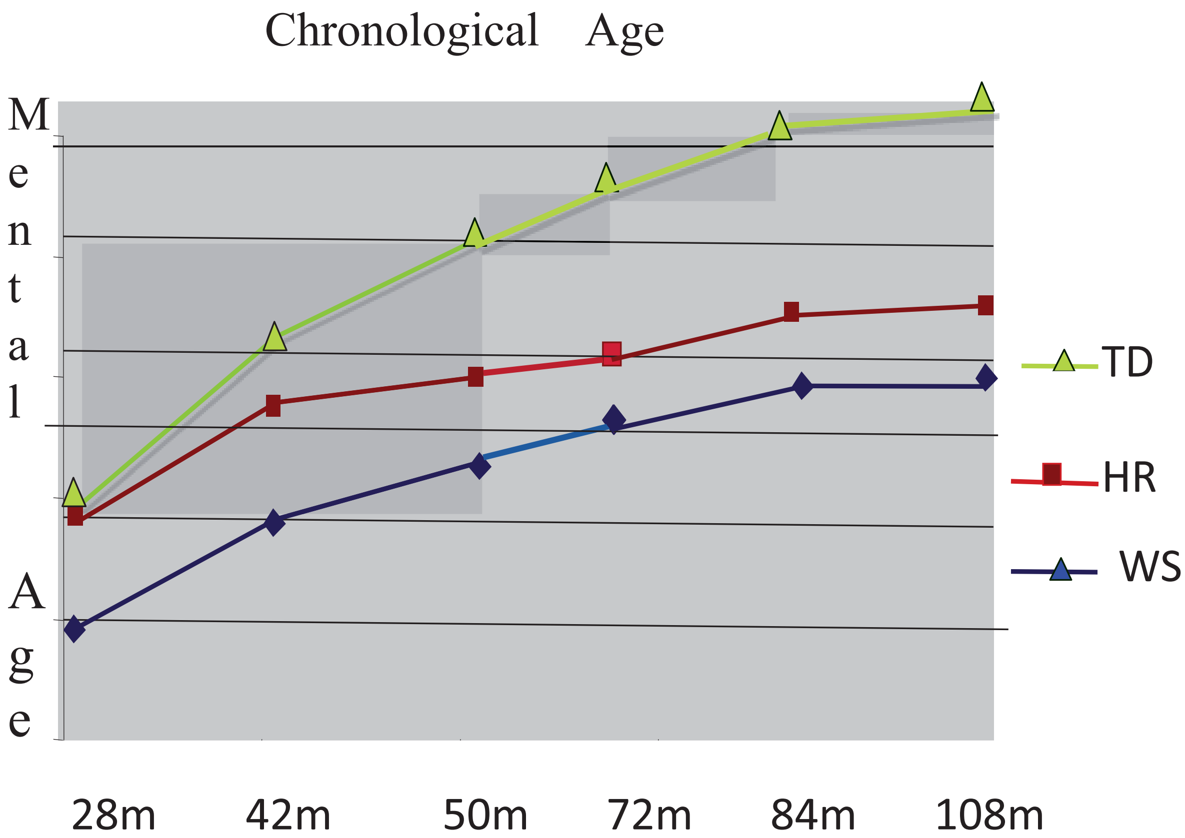
and in-depth phenotyping

PM/TM JS/SS	HD	CS	MM	HR	WS
.....	.....	.....	.....	.....	.....
ELN	ELN	ELN	ELN	ELN	ELN
LIMK1	LIMK1	LIMK1	LIMK1	LIMK1	LIMK1
WBSCR1	WBSCR1	WBSCR1	WBSCR1	WBSCR1	WBSCR1
WBS15	WBS15	WBS15	WBS15	WBS15	WBS15
RFC2	RFC2	RFC2	RFC2	RFC2	RFC2
CYLN2	CYLN2	CYLN2	CYLN2	CYLN2	CYLN2
GTF2IRD1	GTF2IRD1	GTF2IRD1	GTF2IRD1	GTF2IRD1	GTF2IRD1
GTF2I	GTF2I	GTF2I	GTF21	GTF21	GTF21
NCF1	NCF1	NCF1	NCF1	NCF1	NCF1
GTF2IRD2	GTF2IRD2	GTF2IRD2	GTF2IRD2	GTF2IRD2	GTF2IRD2

genotype/phenotype relations: importance of *timing* and tracing *full* developmental trajectories

~ 1 Mb. deletion

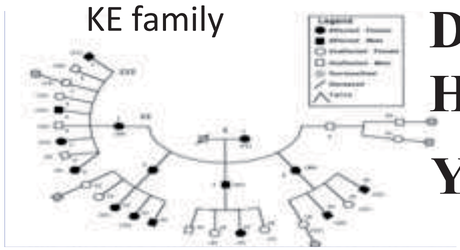
FKBP6
FZD3
WSTF
BCL7B
TBL2
CPETR1
STX1A
CPETR2
ELN
LIMK1
WBSCR1
WBS15
RFC2
CYLN2
GTF2IRD1
GTF2I
NCF1
GTF2IRD2



2nd general point:

Domain-specific vs domain-general?

Domain-relevant approach



Discovery of FOXP2 gene (Simon Fisher & collaborators)

Hype re FOXP: "gene specific to human language" (Pinker, Gopnik)

Yet highly conserved gene across numerous species

BIRD: Foxp2 developmental expression: much greater during song *learning* than subsequent song production (Scharff, Jarvis, Wada et al., 2004)

MOUSE: Foxp2 expression *over developmental time*: transcription increasingly restricted to brain circuits implicated in *motor* control (Lai, Gerrelli, Monaco, Fisher & Copp, 2003)

HUMAN: FOXP2 KE family deficits - *not specific to speech/language*

(Vargha-Khadem,Watkins, Alcock et al. 1999,2000)

- **oro-facial non-linguistic articulation**
- **fine motor control**
- **perception/production of simple rhythms**

skilled coordination & timing of rapid movement sequences

skilled coordination & timing of rapid movement sequences

FOXP2 mutation: impacts most on ->->speech -> -> language:

FOXP2: not domain-specific to language, but most *relevant* to language *over developmental time*

If not domain-specific, but domain-relevant, leads to different questions:

Not only oral communication: piano? Sign language?

Which species-specific repertoires involve rapid movement sequences and their timing?

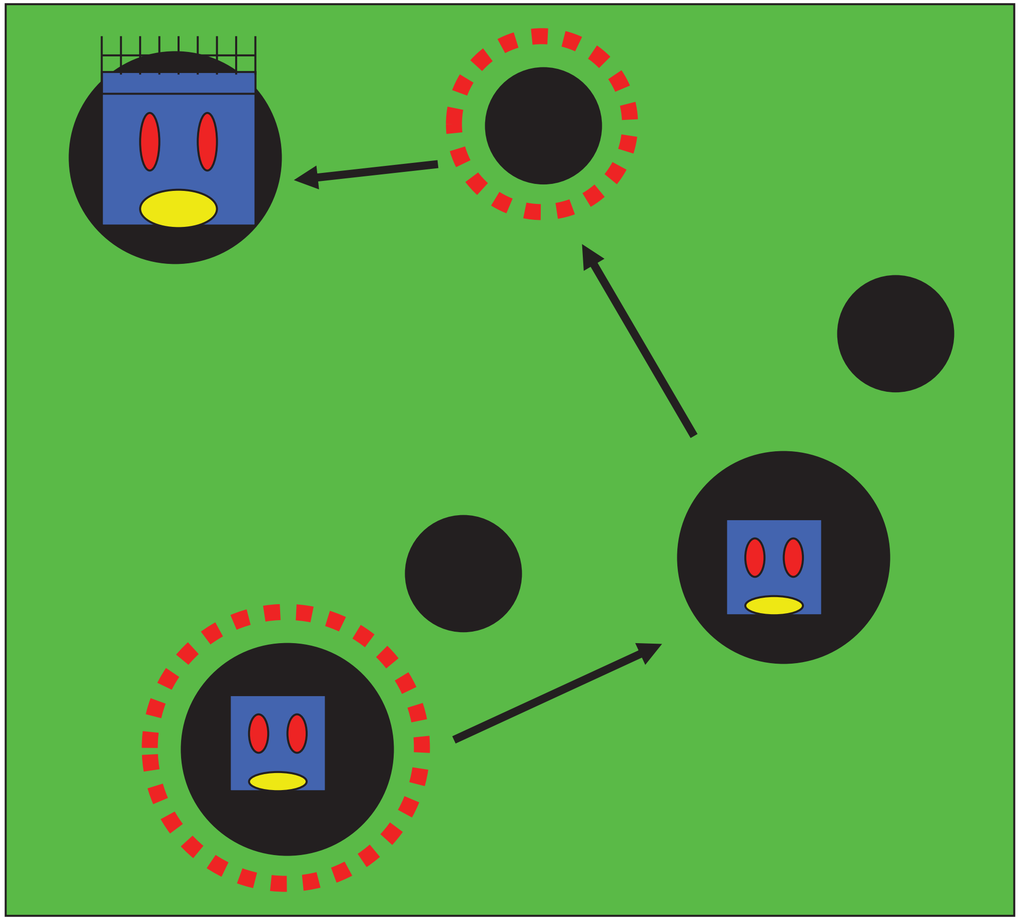
3rd general point:

Importance of cross-syndrome comparisons

1st example: FXS/WS

Selective Attention in toddlers: FXS, WS

CA = 34-50 months MA = 18-36 months



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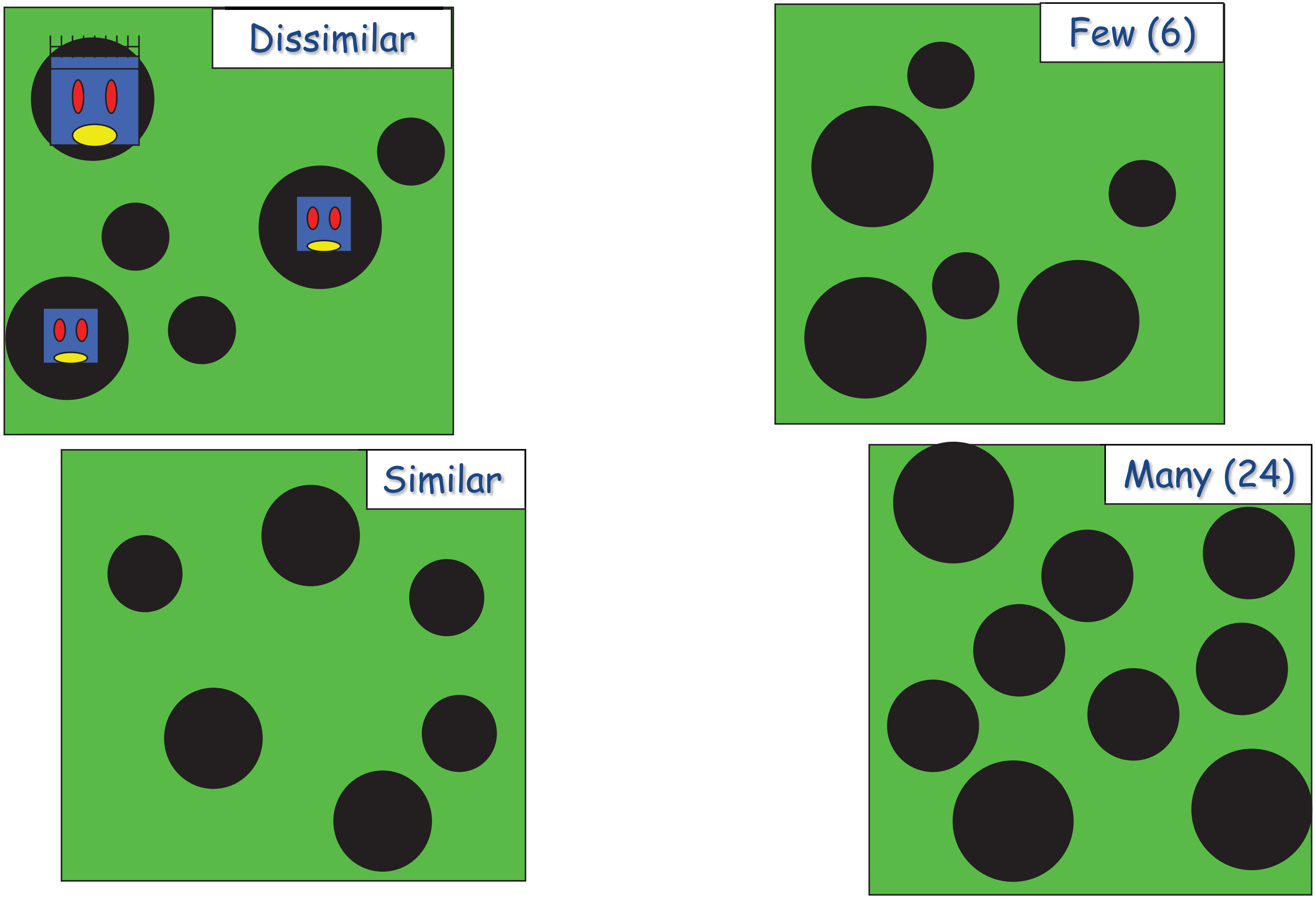
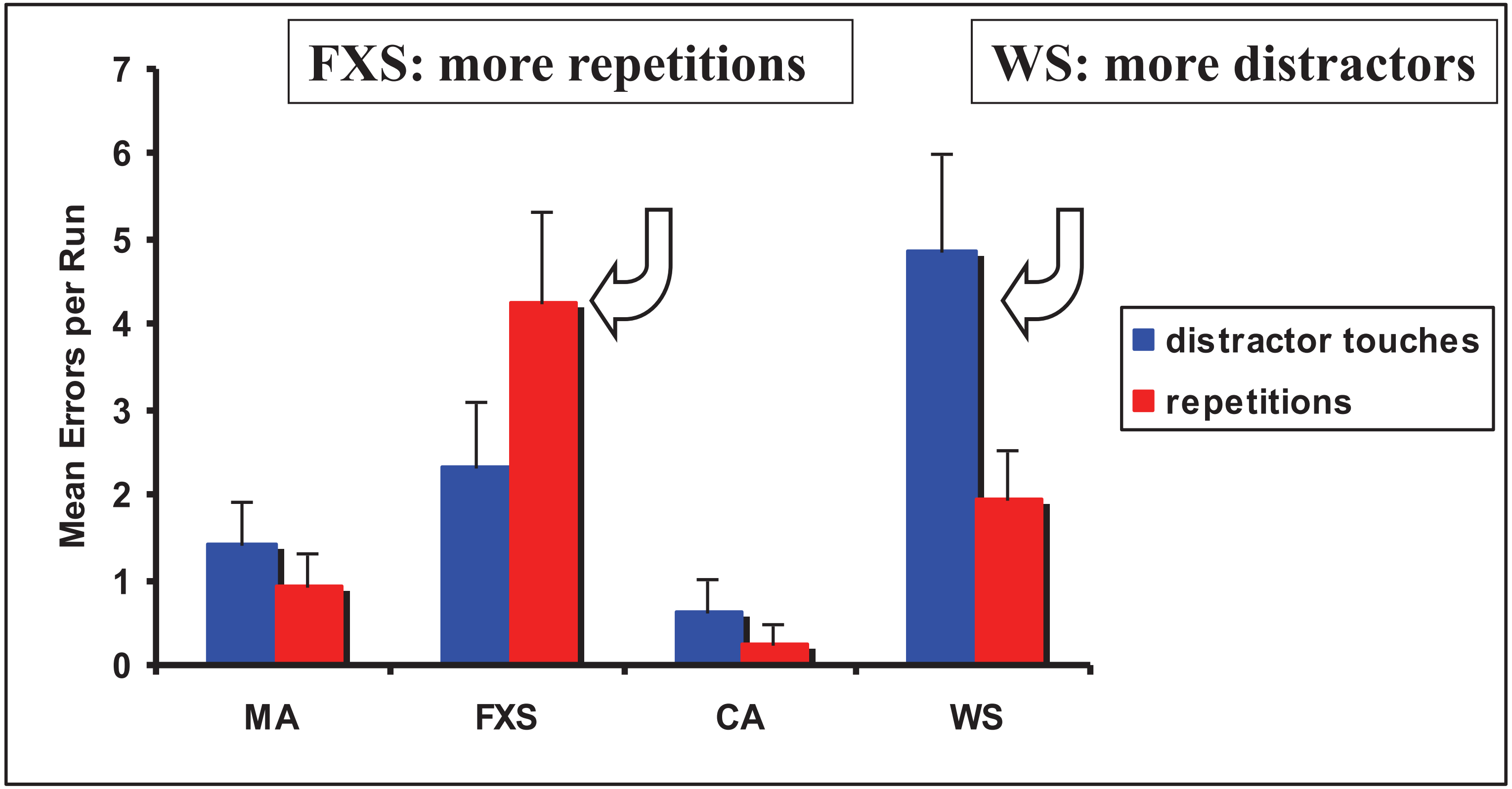

Dissimilar
Few (6)
Similar
Many (24)

Both: attention problems
Search speed/search path: WS=FXS
Error patterns = different
-> different intervention strategies

Search Speed and Path: FXS = WS = TD-MA, but:



Scerif, Cornish, Wilding, Driver & Karmiloff-Smith, 2004, *Developmental Science*; Scerif et al., 2007, *Neuropsychologia*

Importance of cross-syndrome comparisons

2nd example: ASD/WS

Theoretically:

Search for cross-syndrome *dissociations* ->

Innate, independently functioning, domain-specific modules
Can be studied at any age
Mutated genes explain impaired domains

Search for cross-syndrome *associations* ->

Domain-relevant processes
Cross-domain *interactions* early on
Emergent domain-specificity
Must be studied from *infancy*
Different developmental trajectories *over time*

Mutated genes may also explain *'intact'* domains

Autism Spectrum Disorder

Genetically: Multiple genes of small effect

Phenotypically: Aloof
Dislike looking at eyes/faces
Prefer to interact with objects
Good at spatial puzzles

Dissociations

Williams Syndrome

Genetically: 24-28 genes deleted chrom.7

Phenotypically: Very friendly
Fascinated by eyes/faces
Prefer to interact with people
Very poor at spatial tasks

Associations…

Both WS and ASD:

EARLY DEVELOPMENT:

- difficulties with rapid eye movement planning
- atypical eye gaze following; atypical pointing
- atypical triadic attention
- hyperacusis
- obsessions
- atypical sustained and selective attention

LATER DEVELOPMENT:

- better piecemeal learning/poor generalisation
- heightened sensitivities (e.g. to sounds)
- deficits identifying complex emotional expressions
- poor judgment of personal space
- problems with pragmatics of language
- failure on Non-Word Repetition task
- failure on ToM tasks
- same explanation for both? impaired OFC/amygdala connectivity

If true, to differentiate the syndromes, type of question must be asked:

is impaired OFC/amygdala connectivity a *cause*?

or

the *developmental outcome* of atypical attention/atypical processing?

Associations…

Both WS and ASD:

EARLY DEVELOPMENT:

- difficulties with rapid eye movement planning
- atypical eye gaze following
- atypical pointing
- atypical triadic attention
- hyperacusis – obsessions – ritualisms
- atypical sustained and selective attention

LATER DEVELOPMENT:

- deficits identifying complex emotional expressions
- problems with pragmatics of language
- failure on Non-Word Repetition task
- failure on ToM tasks
- explained in terms of OFC/amygdala connectivity

Another common feature of *both*:

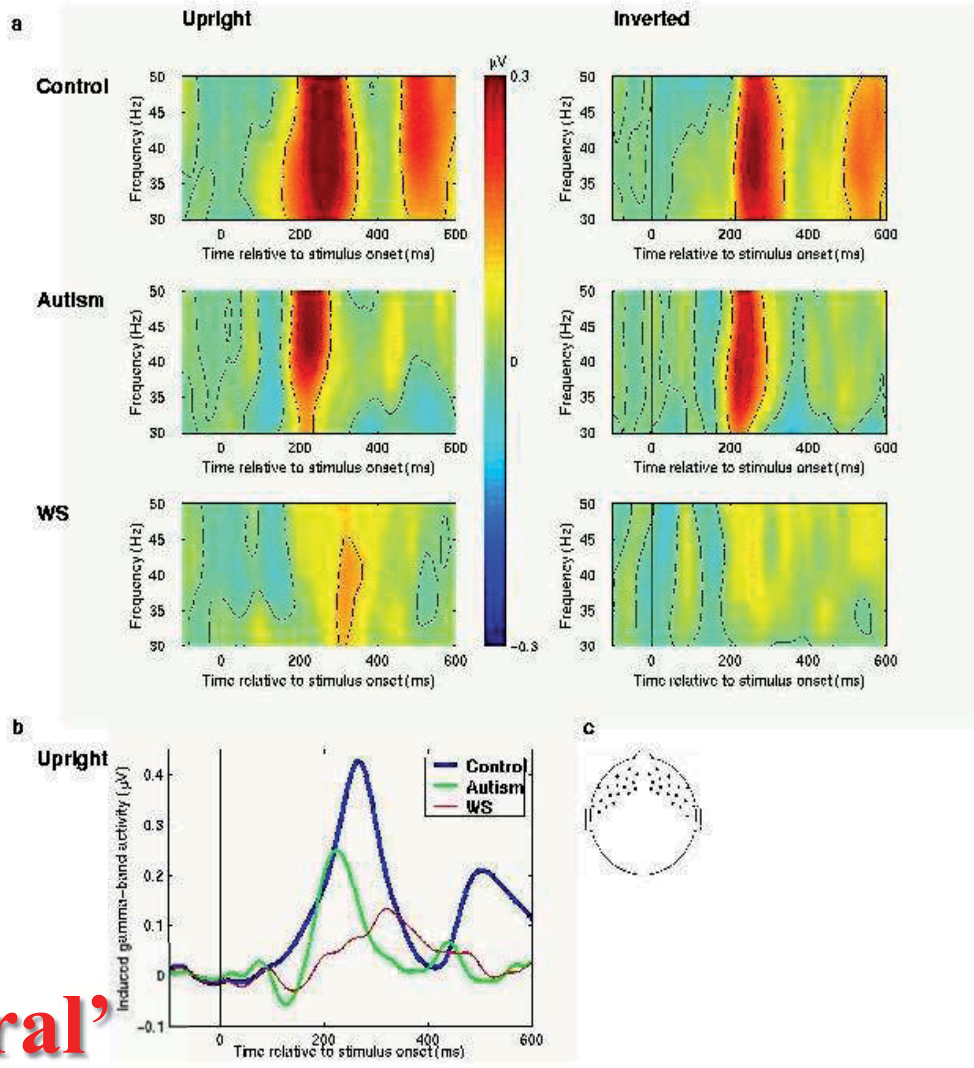
- **focus on features at expense of global configuration**

Comparison of WS and ASD

Both “featural processors” + deficits in integration/binding

yet significant differences in gamma-band oscillations

Need to rethink ‘featural’ at cognitive level



Grice, et al., 2003

Cross-syndrome/cross-modality/cross-domain study

TD/ASD/WS/DS

8 tasks: local/featural vs global/configural processing:

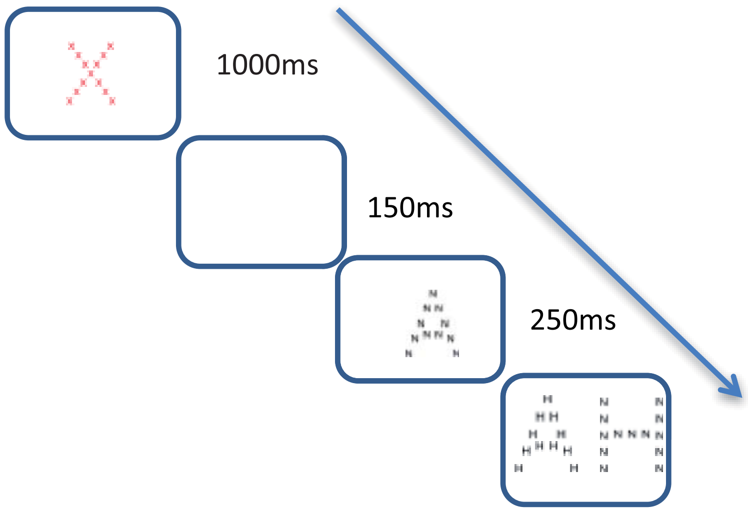
visuo-spatial processing:	**Fragmented Pictures, Navon, Embedded Figures, Picture Memory**
auditory processing:	**Chord Sequence, Phoneme Detection, Sentence Completion, Narrative Gist**

(with undergraduate students, Dean D'Souza and Monica Connolly, in collaboration with Happé & Booth, Inst. of Psychiatry, London)

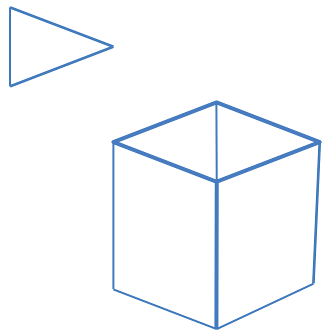
Visuo-spatial Tasks

Fragmented Pictures Task

Navon Task



Embedded Figures Task



Picture Memory Task

Auditory Tasks

Phoneme Detection task

/p/ sound either at beginning (e.g. *protor*) or medial (e.g. *lipod)* or final sound (e.g. *rishap*)

Chord Sequence Task

Sentence Completion Task

Task to complete sentence stems
(e.g. 'Little boys grow up to be men and...')
'In the sea, there's salt and …')

Story Retention Task

Listen to story. Tested on verbatim recall, gist, and on sentence surface form discrimination

Claims in literature: **WS/ASD local bias**
DS global bias

Cross-modality/cross-syndrome comparisons reveal very mixed picture:

WS/ASD/DS = both local and global
(depending on task demands)

ASD = Context least effect **(particularly auditory tasks)**
= Best verbatim recall

WS/ASD 'featural bias' = different when compared directly:

WS *relative weakness* in *global* processing
ASD *relative strength* in *featural* processing

4^{th} general point
Behavioural scores *'in the normal range'*

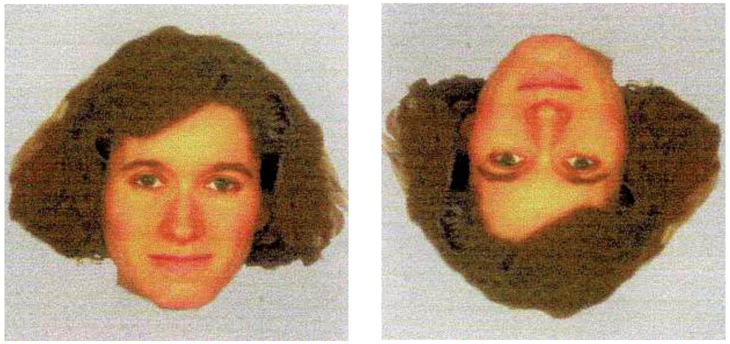
doesn't mean: - same neural processes as TD
- same cognitive processes as TD
- that mutated genes play no role in that domain

Different teams worldwide:

WS face processing: *'in the normal range'*

on standarised tasks (Benton, Rivermead)

"Intact" face processing module in WS?



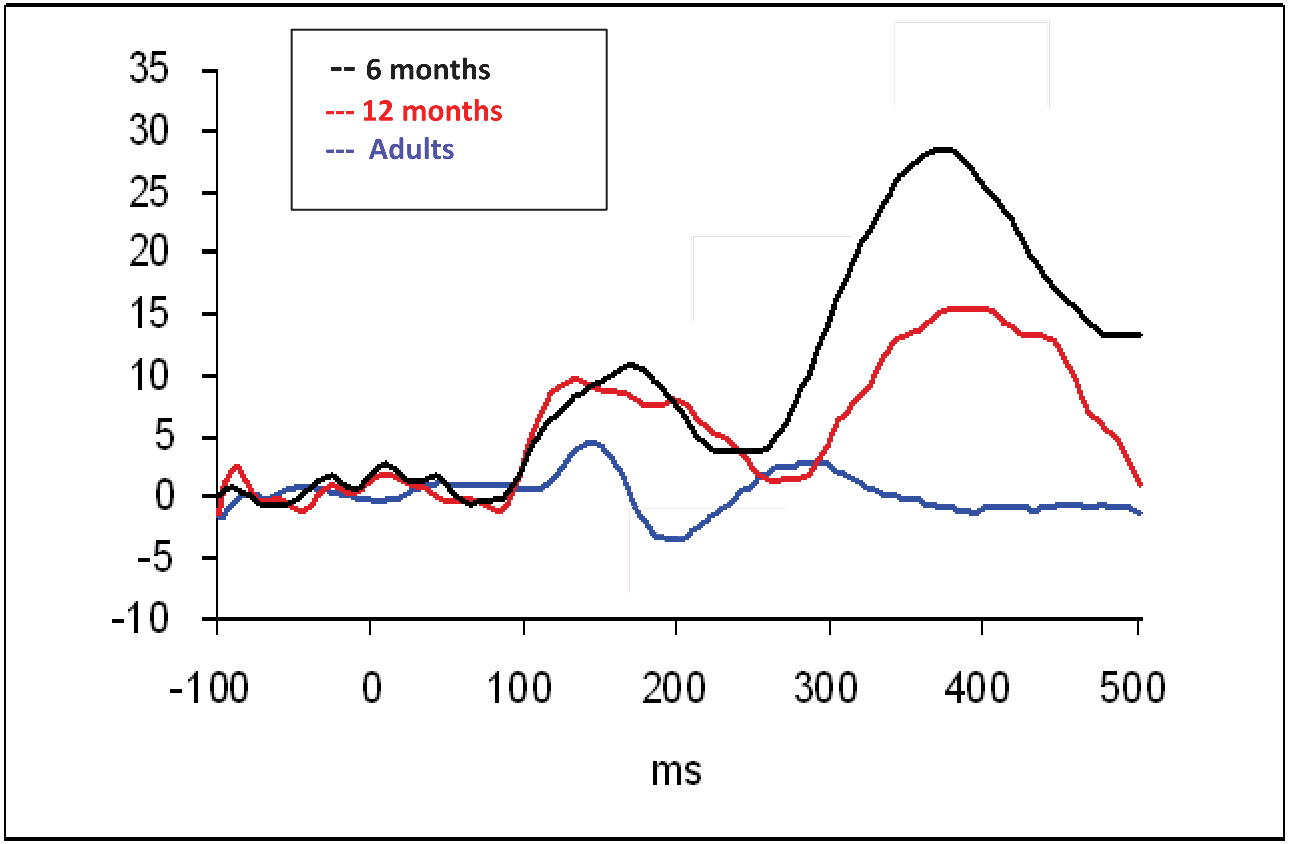
Inversion effect (hallmark of *configural* processing) doesn't emerge developmentally in WS.

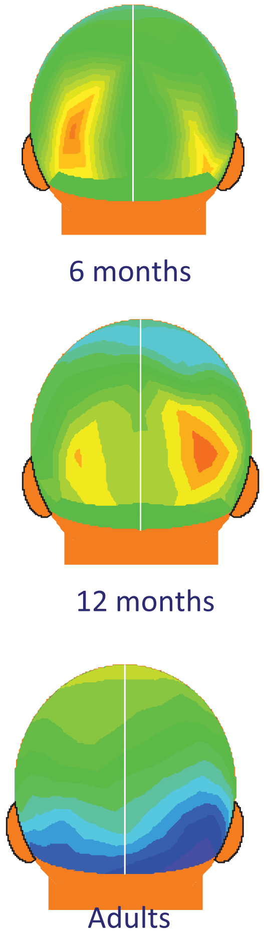
What about WS brain?

Karmiloff-Smith et al., 2004

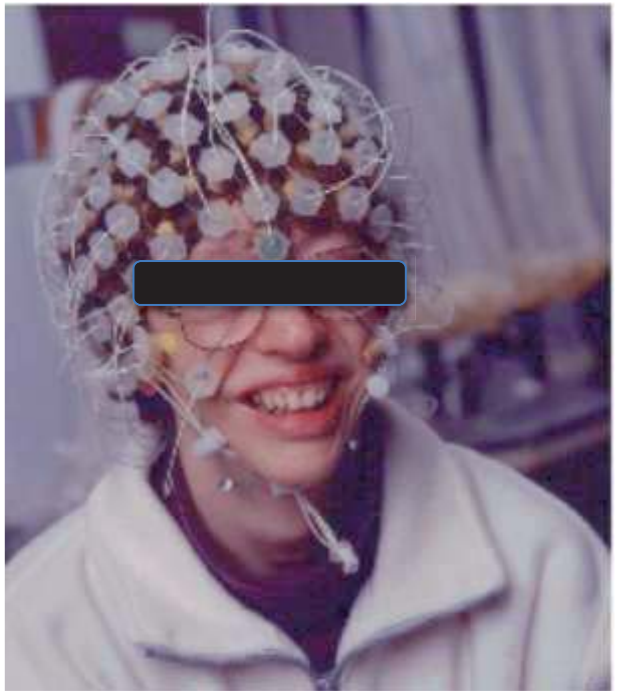
Specialization and localisation (modularization) of brain function are *progressive*

2 decades of face processing research by Johnson, de Haan & collaborators on typically developing infants and children



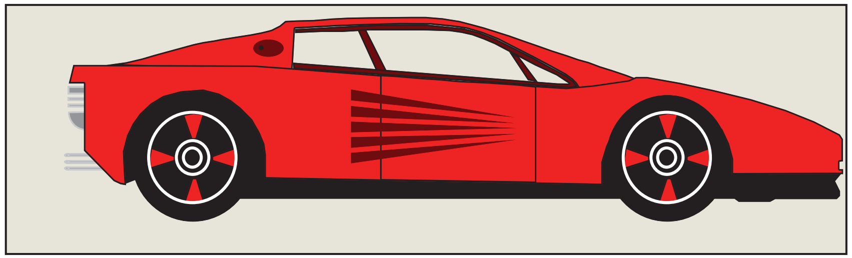


From de Haan, Pascalis & Johnson, 2002; Halit, de Haan & Johnson, 2005



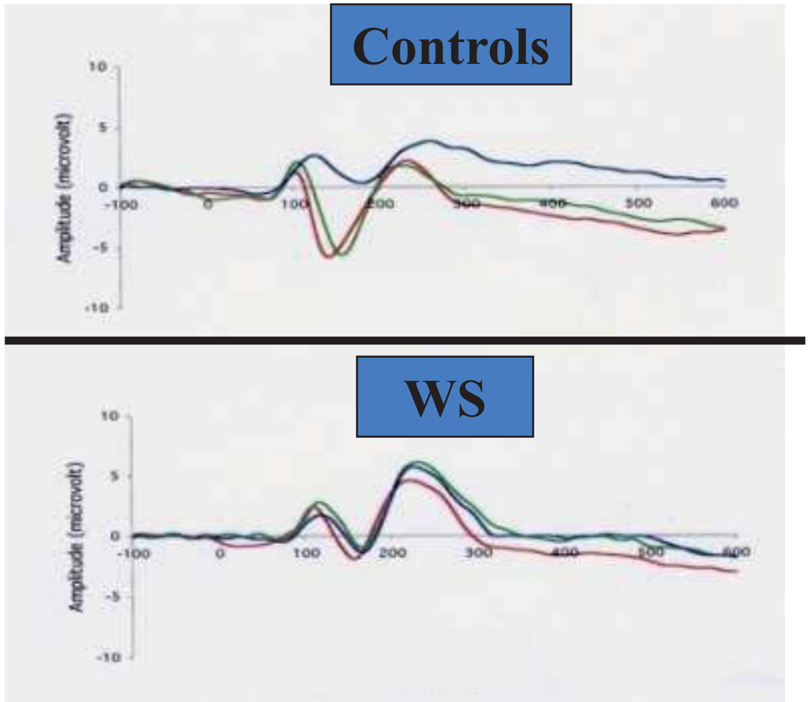
WS *behavioural* scores for face processing = *"in normal range"*

So deleted genes play no role in WS face processing?



Grice, deHaan, Halit, Johnson, Csibra, & Karmiloff-Smith, 2003

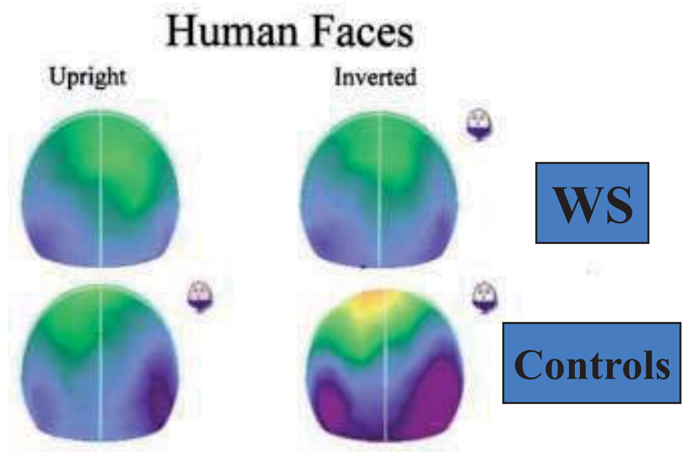
Lack of WS modularization, despite good *behavioural* scores



Healthy controls:
Progressive restriction of input type

WS: failure to specialise

WS: failure to localise



Healthy controls:
Progressive restriction of brain localisation

Behavioural **scores =** ***'in normal range'***
on standardised tasks but underpinned by:

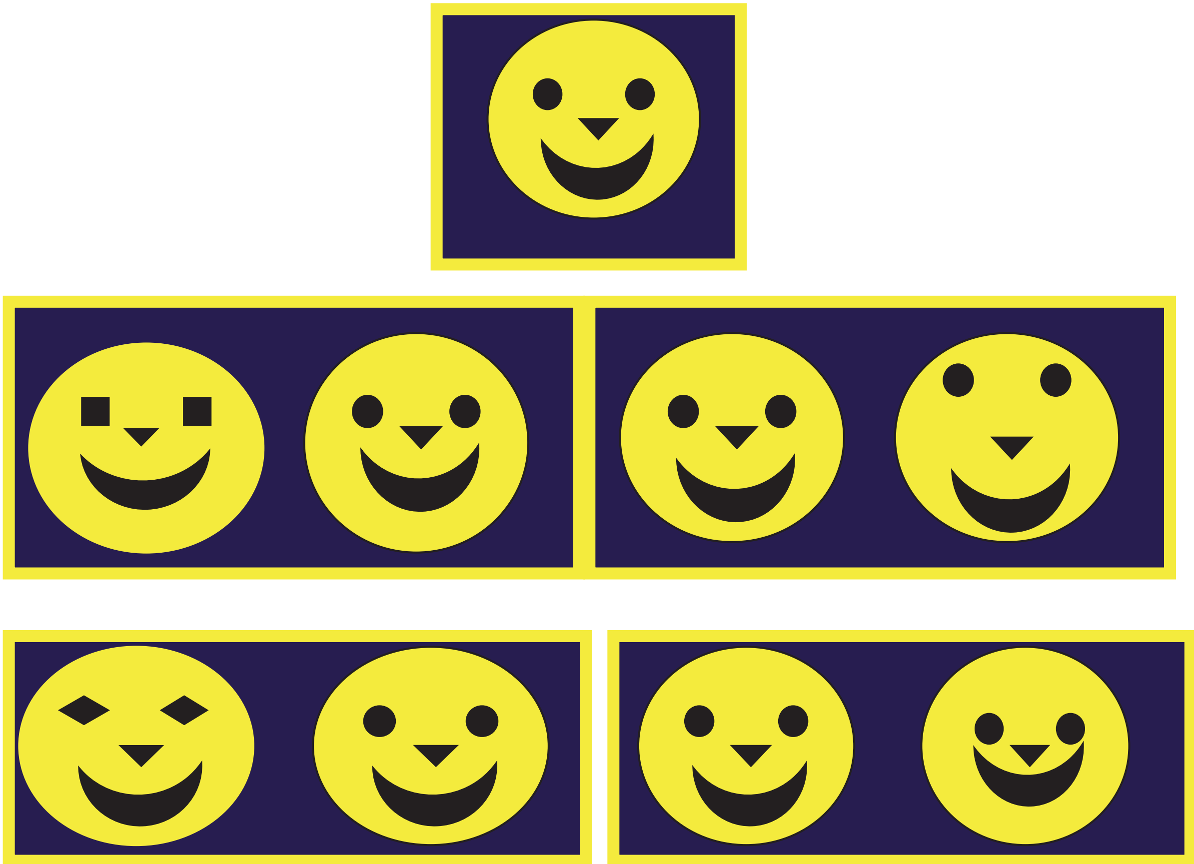
different brain **processes**
different cognitive **processes**

Haploinsufficiency of WSCR genes plays role
not just in impaired domains,
but also in ***proficient*** **domains**

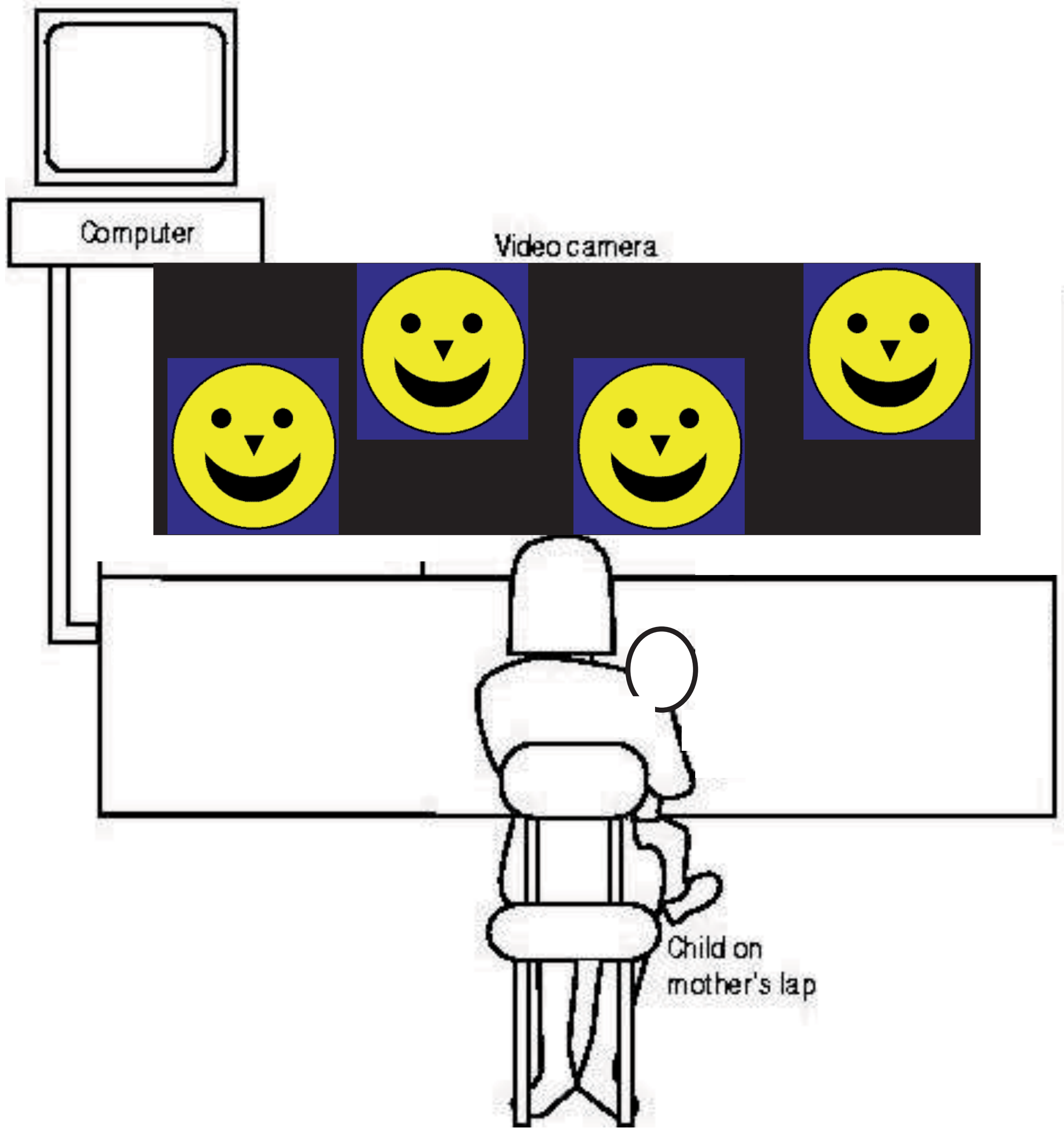
5^{th} general point:

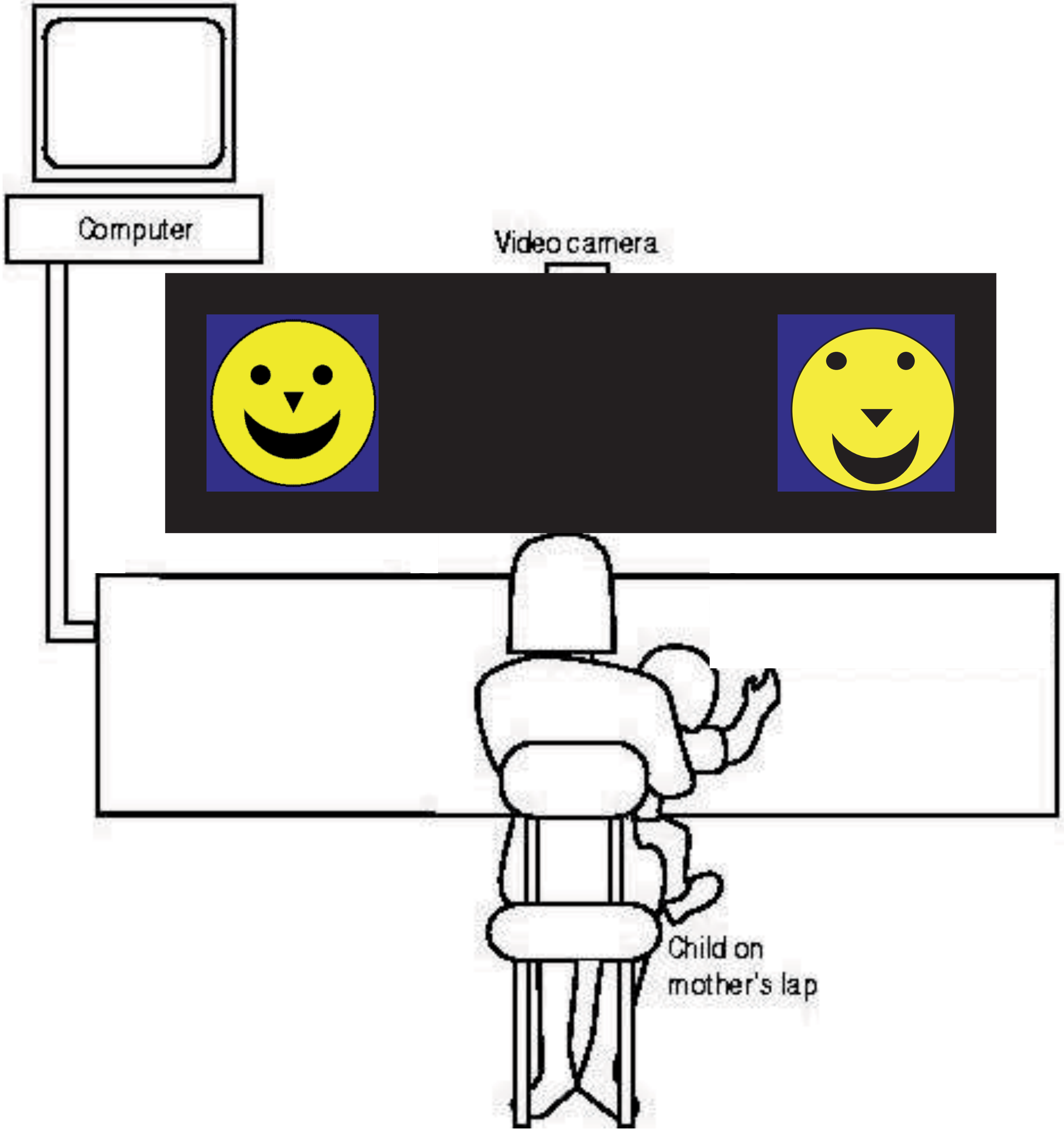
Phenotypic outcomes must be traced back to roots in infancy

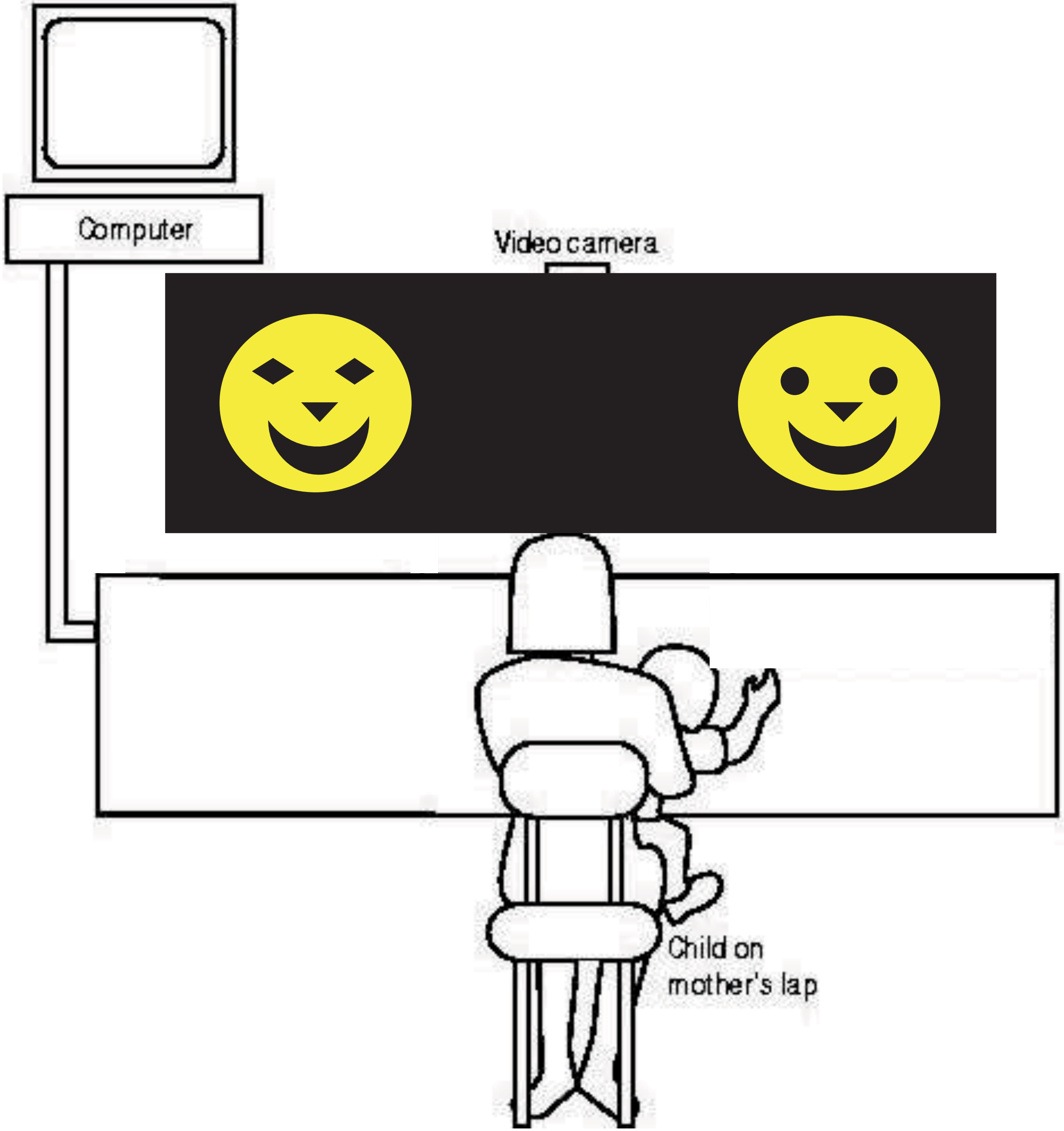
Example 1: Face processing



Karmiloff-Smith, et al., 2004


Computer
Video camera
Child on
mother's lap


Computer
Video camera
Child on
mother's lap


Computer
Video camera
Child on
mother's lap

TD infants: notice both featural/configural

Williams infants: featural (Karmiloff-Smith et al., 2004)

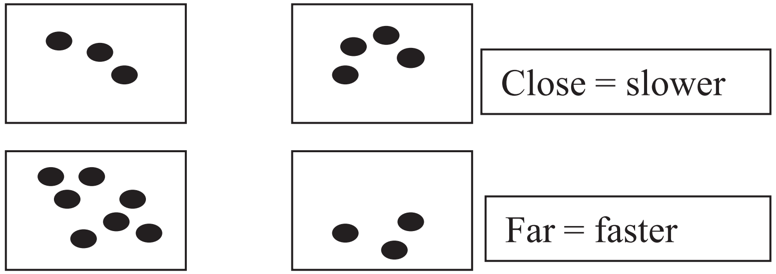
New studies: Dynamic faces + eye tracker
Eye gaze following
Face Pop-Out

Compare infants with WS, DS and infants at risk of ASD

Tracing phenotypic outcomes from adults, adolescents, children, back to infancy

Example 2: Numerical processing

Adolescents and adults:



Butterworth Battery: TD > DS > WS

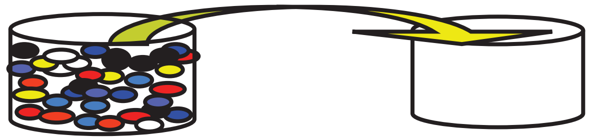
SDE, addition/subtraction, number facts etc.

Children:

Counting: WS = DS = TD

but 1,2,3……4….5,6,7,8,9,10

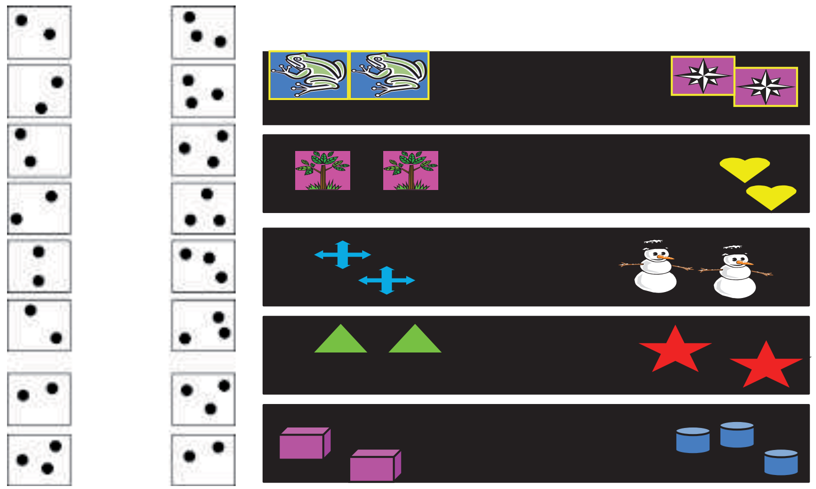
Understanding cardinality:
TD > WS (very poor)
DS = study in progress



Spatial MA predicts cardinality in TD
Verbal MA predicts cardinality in WS - different developmental trajectories

Ansari & K-S, 2002; Paterson Girelli, Butterworth & K-S, 2003

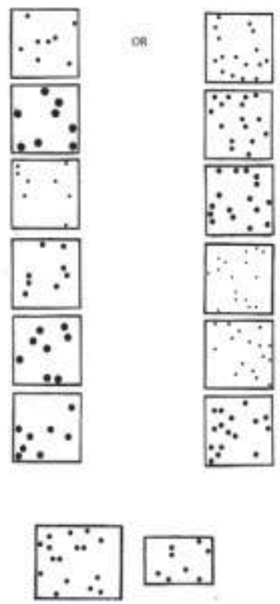
Infants:



Exact small number (2 vs 3):

TD infants OK @ 3-4 months
WS/DS tested @ 10-39 months
WS=CA; DS<MA
Replicated in second set of infants with dot arrays

WS=TD>DS



Approximate large number (magnitude)

TD OK ratio 1:2 @ 7 months
WS/DS tested @ 10-39 months
DS=CA; WS=MA

DS=TD>WS

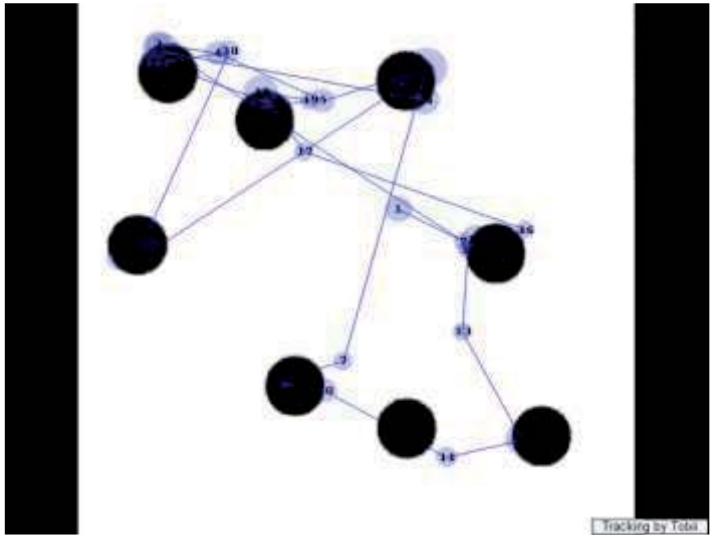
Paterson, Brown,Johnson & K-S, 1998; Van Herwegen, Ansari, Xu & K-S,2008;
d'Souza, Dekker, van |Herwegen, Radic , Ansari, Xu & K-S, subm.

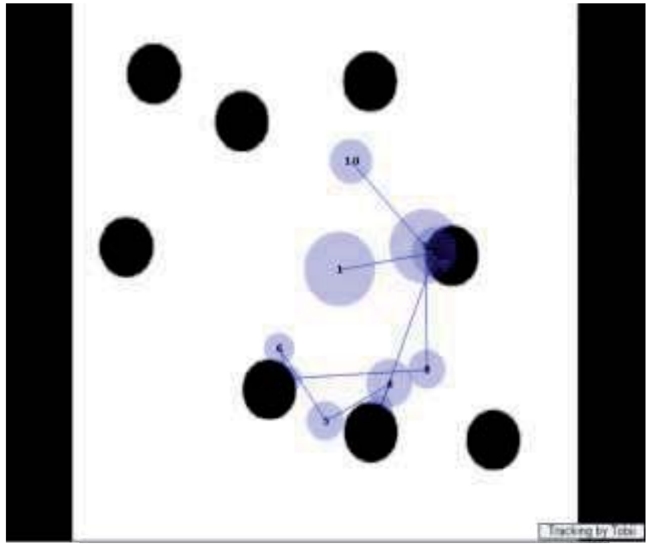
Cross-syndrome *developmental* studies of number suggest:

approximate **large-number discrimination (magnitude) = more predictive of later number abilities than**
exact **small-number discrimination**

Scanning large arrays-> focus on *quantities*

Scanning small arrays-> focus on *individual objects*



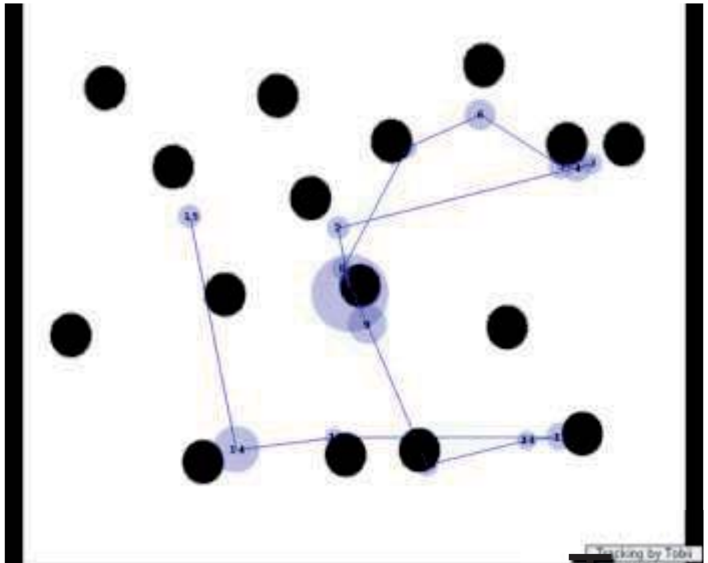


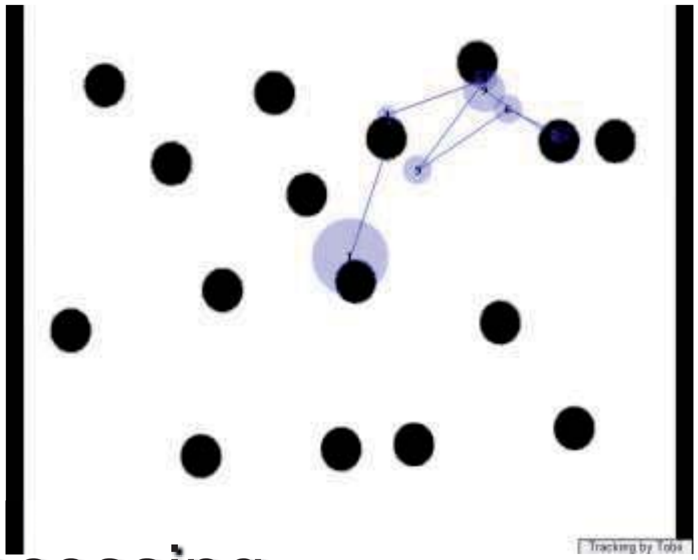
DS infant:

focus on quantities

WS infant:

focus on individual objects





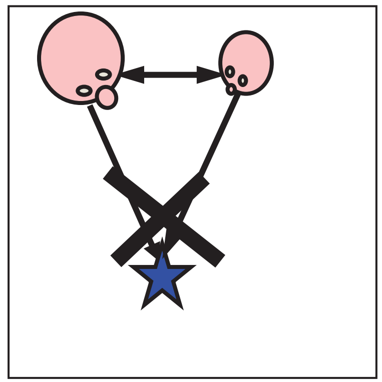
Top-down processing

Why different patterns in WS and DS?

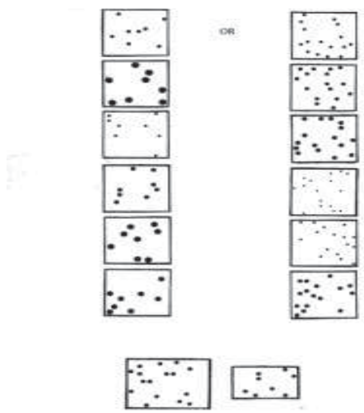
REMINDER:

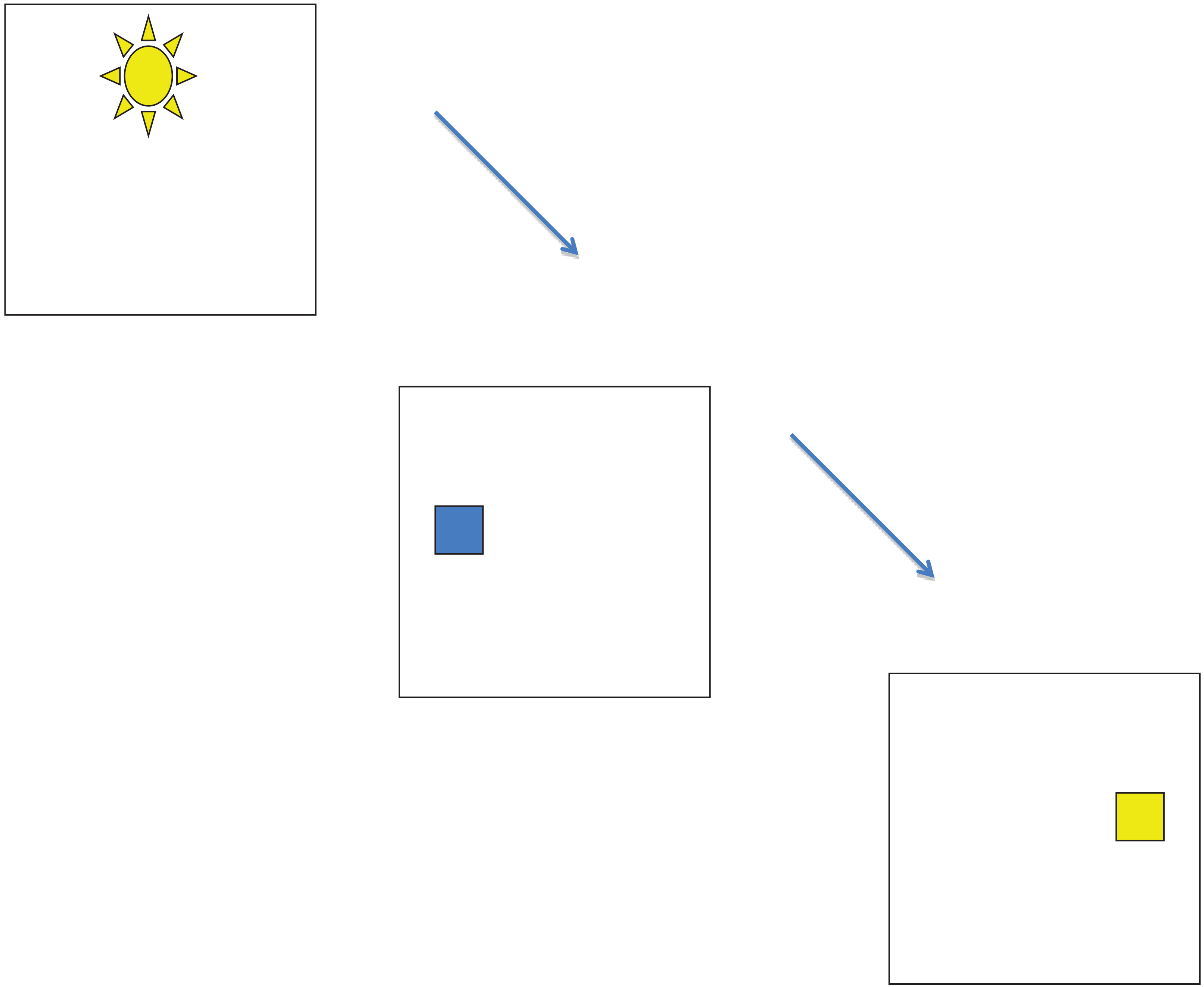
-Face processing: WS more featural

-Language: WS poor triadic interaction

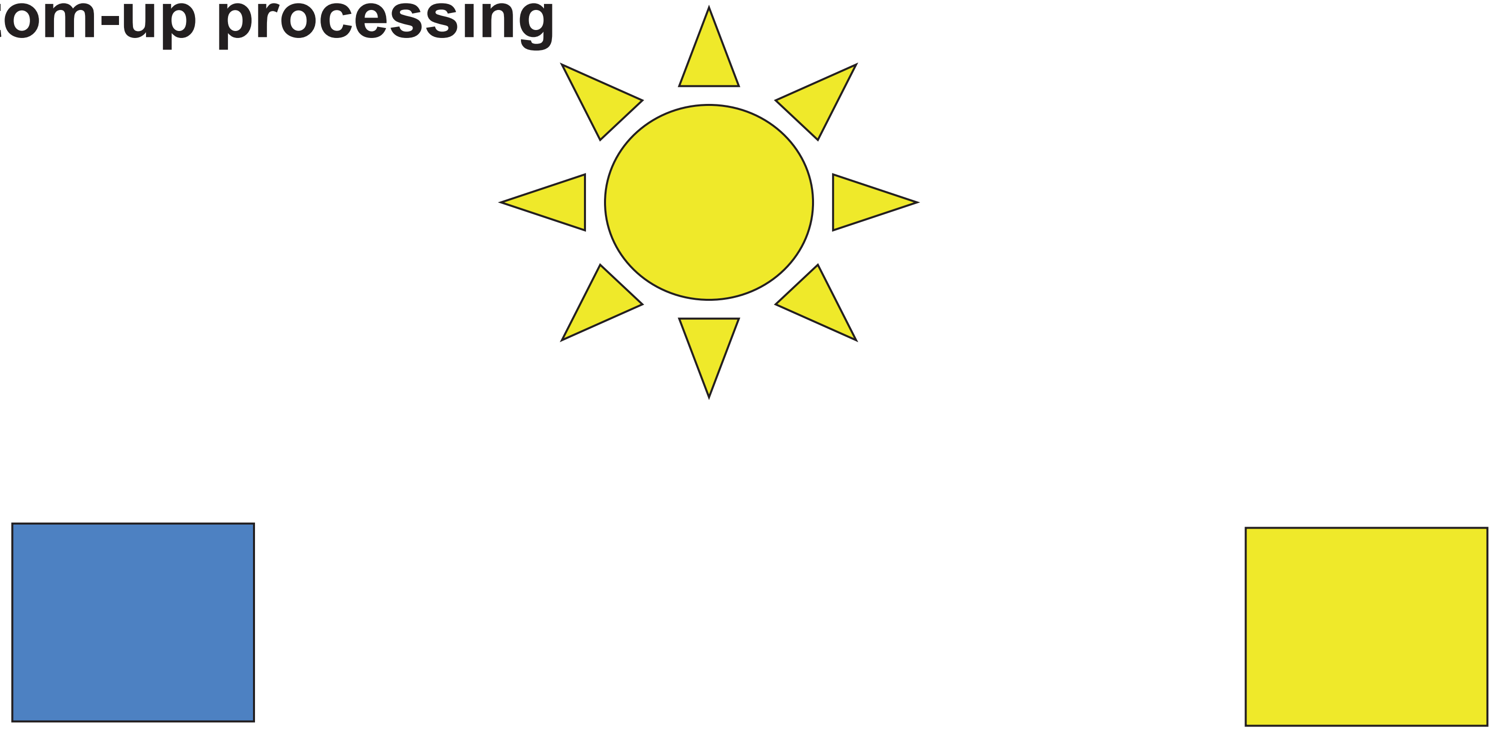


-Number: WS poor on large number displays

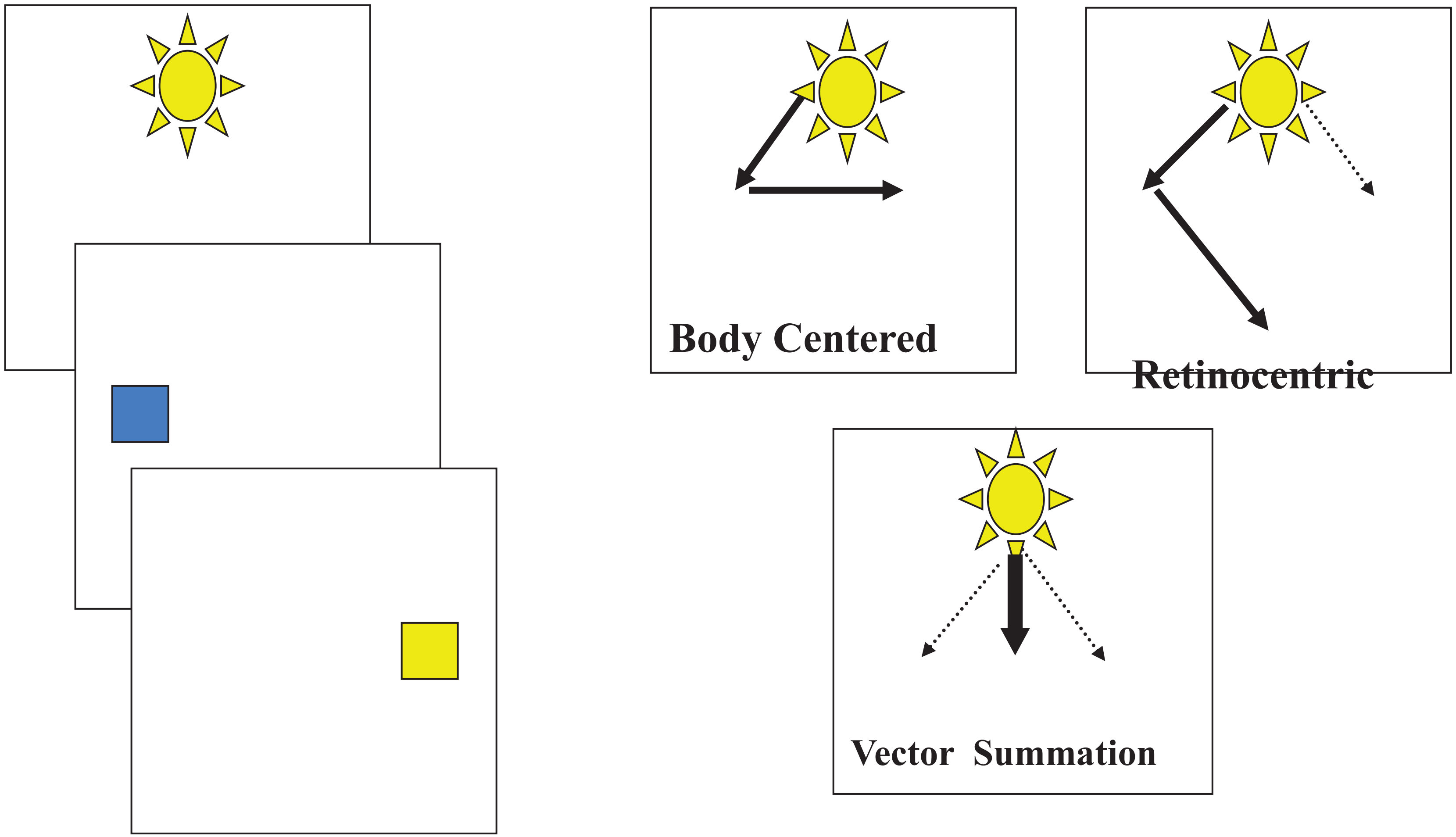




Bottom-up processing



Visuo-spatial precursors
DS=TD infants/toddlers, WS=very impaired



Brown, Paterson, Johnson, Gilmore & Kamiloff_Smith, 2003

Basic-level deficits in *visual* saccade planning early in WS developmental trajectory

- sticky fixation (DS not)
- focus on features (DS on global)
- featural processing of faces
- reduced triadic interaction (true of DS)
- smaller vocabulary (true of DS)
- delay in critical mass for onset of grammar (true of DS)
- poor large approximate number, good small exact number (DS opposite)

Cascading developmental effects over time **across several *emerging* higher-level, linguistic/cognitive systems**

DS different reason for similar early language delays

Importance of cross-syndrome comparisons
-> increasingly detailed syndrome-specific developmental trajectories

+ *early, syndrome-specific* remediation strategies
(even in cases where behavioural scores = identical)

Implications for intervention

- **Must be *syndrome-specific* from basic research**

- **Must start in *early infancy***

(*before* e.g. language, face processing or number deficits emerge)

e.g. for WS number deficit, don’t train number, but

rapid saccadic eye movements

-> possible cascading effects *over developmental time* on triadic interaction, vocabulary, grammar, face processing and number

Domain-relevant, Neuroconstructivist approach causes researcher to:

- predict less obvious deficits elsewhere in system
- think more dynamically /developmentally
- ask different kinds of questions

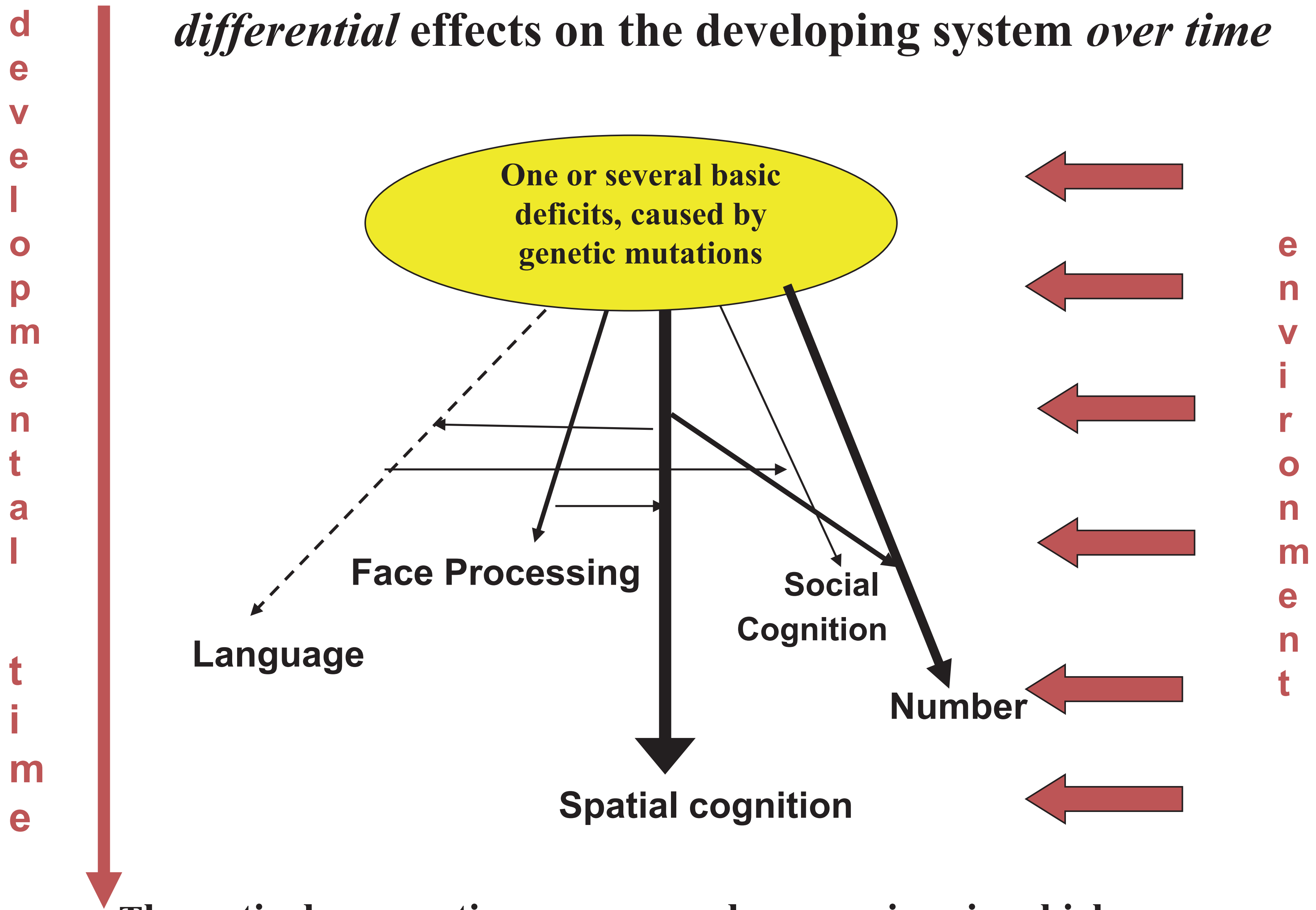
Static questions

Which modules are impaired and which are intact?
How are syndromes dissociated?
Where is domain X processed in the brain?

Dynamic questions

Is there a *developmental* explanation?
Are changes the same over developmental time?
How are syndromes dissociated *and* associated?
How do neural circuits *change* with development?

differential effects on the developing system *over time*



Theoretical assumption: very complex mappings in which *ontogenetic development* plays *major* role

Main take-home messages of talk:

Adult neuropsychological model of juxtaposition of impaired & intact modules = inappropriate for *developmental* syndromes

***Development matters*: gene expression, brain, cognition, behaviour**
Nothing is static across developmental time

Start state can be *domain-relevant*, not necessarily domain-specific but *become* domain-specific over developmental time:
Gradual process of *modularization*

Cross-syndrome dissociations *and associations* enable researcher to seek subtly different causes for similar behavioural outcomes
‘*Normal range*’ behaviour = not always normal neural/cognitive processes

Tracing *full developmental trajectories from infancy* = critical

One sole principle for developmental science

Developmental studies must be

truly developmental!

A paradox?   No!

Developmental approach is NOT the study of children

but study of developmental change at the level of gene expression/brain/cognition/behaviour/environment

Thank you!

Joint work mentioned in talk with past and current Collaborators/Postdocs/Students

Funding

wellcome trust

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