Modules, genes and evolution
Lessons from developmental disorders

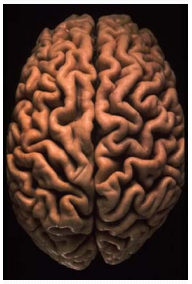
Dr. Michael Thomas
Developmental Neurocognition Lab
Centre for Brain & Cognitive Development
Birkbeck College, University of London, UK

Modularity

- Modules first invoked to explain perceptual processes
- Later extended to higher cognitive abilities
- Properties:
  - Domain-specific / specialized to particular tasks
  - Encapsulated
  - Fast
  - Automatic
  - Often innate
  - Perhaps localized in the brain

Evidence for modularity

- Adult deficits
- Evolutionary claims
- Early competencies
- Genetic disorders with uneven cognitive profiles

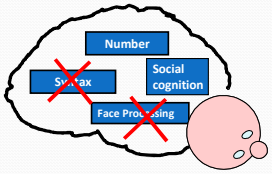


Acquired Deficits

Acquired Deficits

Acquired deficits in adulthood

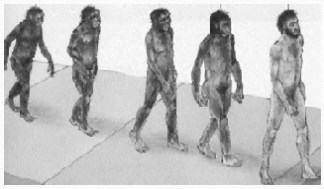
- Specific cognitive deficits viewed as evidence of impaired module



Agrammatism

Prosopagnosia

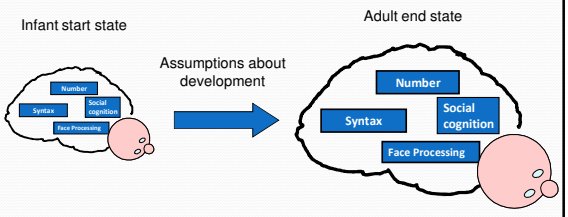
Evolution



Evolution

Early competencies

- How do early infant abilities relate to adulthood?

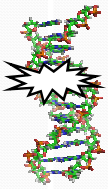


Modularity and genetic disorders

- Some genetic disorders seem to show similar modular deficits to those found in adult neuropsychological patients
- Uneven cognitive profile
- Behaviour in the normal range (e.g., on standardized test) = intact module
- Behaviour below the normal range = impaired module

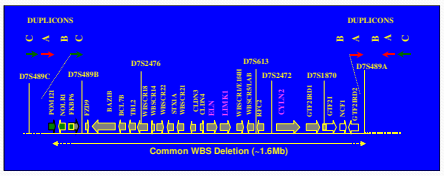
Genome specifies cognitive components?

Developmental disorders



Examples (1) Williams syndrome

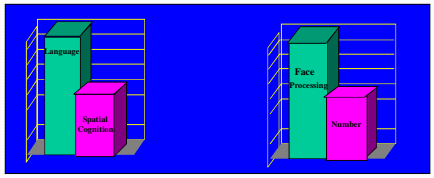
- WS genotype



- WS Critical Region: hemizygotic deletion of ~ 28 genes on chromosome 7 @ q11.23

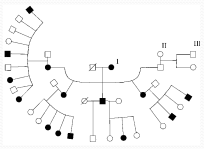
(1) Williams syndrome (WS)

- Claimed phenotype
  - Intact: Language, face processing
  - Impaired: Visuospatial processing, number



(2) Specific Language Impairment (SLI)

- Delay in language development
- Particular impact on syntax and morphology
- No obvious brain damage or environmental cause
- Non-verbal ability in normal range
- Heritable
- British KE family: impaired and unimpaired members
- Traced to mutation of single gene, FOXP2 on chromosome 7



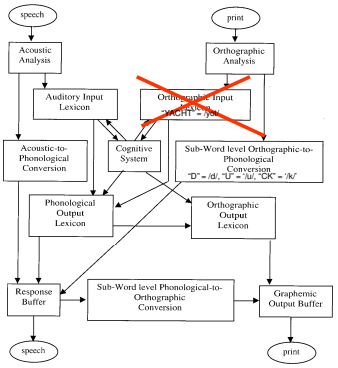
Modular interpretation

- '.....overall, the genetic double dissociation is striking.....The genes of one group of children [SLI] **impair** their grammar while **sparing** their intelligence; the genes of another group of children [WS] **impair** their intelligence while **sparing** their grammar.'
  (Steven Pinker, 1999, p. 262, italics added)

Problems with this view of disorders

- Take the example of **developmental dyslexia**
  - DUCK (regular)
  - GOOB (novel)
  - YACHT (exceptions)
- Deficit specific to reading
- Runs in families (genetic component)

Model of reading

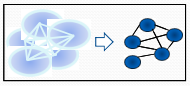


Developmental 'Surface' Dyslexia

- How do the components know what to do in the first place?
- What stops the components compensating for each other when one is failing to develop?
- How can a specific deficit for reading be inherited when reading is a recent cultural invention?

Some facts about development

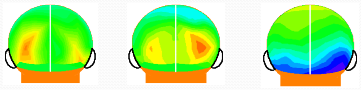
- The infant cognitive system is less differentiated and less modular
- Modularity is emergent across development
  - Specialization
  - Localization
- Development is characterized by interactivity



Example: face processing localization

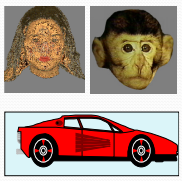
Typically developing infants

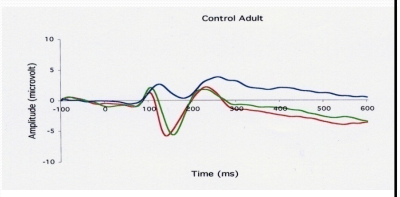
- Progressive modularization of face processing in normal infants over developmental time (first 12 months and beyond)
  - 2 decades of research by Johnson, de Haan, de Schonen, Simion and others



6 months | 12 months | adult

Example: face processing specialization





Grice et al., 2001, 2003

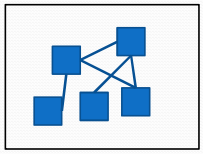
Modularity and developmental disorders

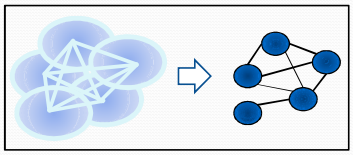
- Cannot assume adult modular structure present in the start state
- Scores in normal range ('intact') don't necessary imply normal underlying processes
- Deficits must be characterized in terms of atypically constrained developmental trajectory
- Include the developmental process in the explanation!

Karmiloff-Smith, 1997; Bishop, 1997

Specify the developmental process

- Plasticity
- Interactivity
- Redundancy
- Compensation
- Environment

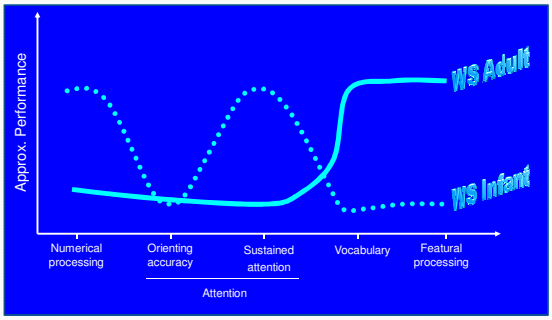




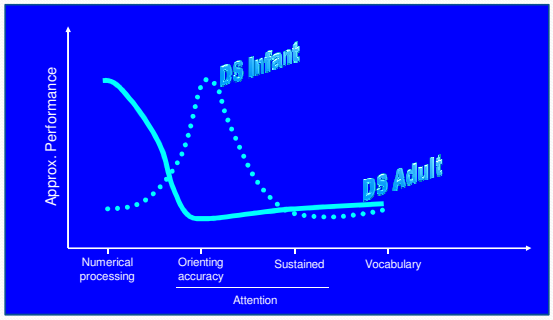
Williams syndrome revisited

- Comparison of cognitive profile of Williams syndrome and Down syndrome (Paterson et al., 1999)
  - Adults
  - Toddlers
- Language vs. Number
- Adulthood
  - Language: WS > DS Number: DS > WS
- Toddlers
  - Language: WS = DS Number: WS > DS

Infant vs. Adult Cognitive Profiles: WS



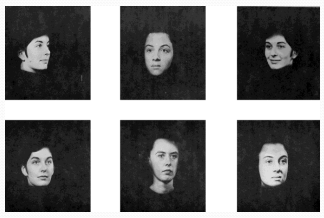
Infant vs. Adult Cognitive Profiles: DS



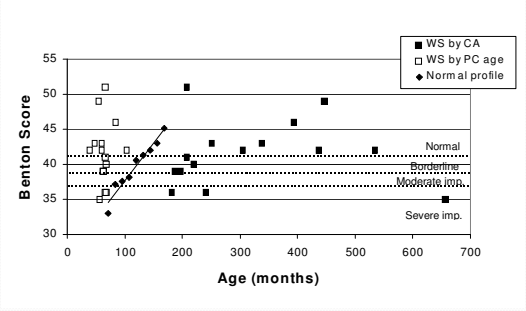
Williams syndrome revisited

- Consider areas of relative strength
  - Face recognition
  - Language

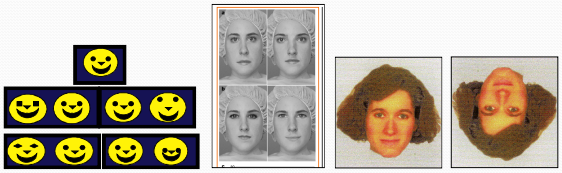
"Normal looking" performance?



WS performance on face recognition



Cognitive processes underlying good behavioral scores: same as normal?

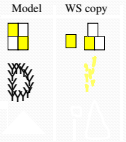


- Reduced sensitivity to faces differing in configurations
- Reduced sensitivity to inversion

Karmiloff-Smith, Thomas, et al., 2004

Atypicality does not simply affect faces

Face processing:)
Space processing:) all processed more featurally
Sound processing:) than configurally

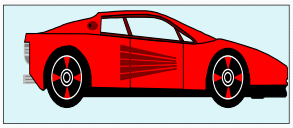


WS=featural; Autism also=featural: same??

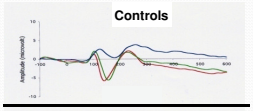
Williams syndrome revisited

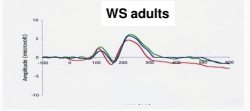
- Brain level

WS adolescent in Geodesic HD-ERP net



Grice et al., 2001, 2003



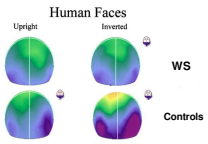


Healthy controls:
Progressive restriction of input type

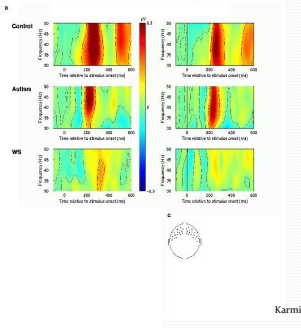
WS: failure to specialize

WS: failure to localize

Healthy controls:
Progressive restriction of brain localization



Gamma-band bursts: integration/binding of features



Atypical brain function in both syndromes, but cross-syndrome difference at brain level

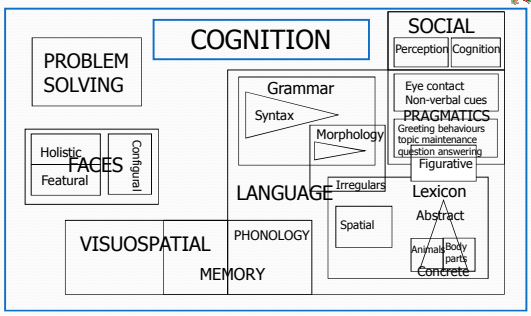
Rethink notion of "featural" at cognitive level.....

Karmiloff-Smith, Grice, Csibra, Johnson, & Spratling

Language

- WS infants, toddlers and children:
  - extremely delayed in onset of babbling
  - extremely delayed in segmenting speech stream
  - rely more on perceptual cues than linguistic labels
  - production precedes pointing
  - comprehension doesn't show normal advance over production
  - comprehension in WS infants/toddlers as delayed as in DS
  - don't use or follow eye gaze for referential communication,
  - despite fascination with faces (dyadic vs triadic joint attention)
  - don't understand referential function of pointing
  - auditory perception follows atypical developmental pathway
- No single explanation: all contribute, in complex interactions, to late onset and atypical trajectory of WS language

Fractionation in Williams syndrome?



KE family revisited

- Cognitive level
- Closer investigation revealed deficits not specific to language nor to speech output (Alcock, 1995; Watkins, Dronkers, & Vargha-Khadem, 2002)
  - oral-facial movements
  - aspects of the perception of rhythm
  - production of rhythmic movements of the hands
  - IQ lower in affected than unaffected

KE family revisited

- Brain level
- Detailed research on KE family revealed widespread structural and functional brain differences in affected family members outside of normal adult language areas (e.g., Watkins et al., 2002)
- Most children with Specific Language Impairment do not have FOXP2 mutation

A case study of compensation in SLI

- Disorder within a developmental perspective
- Brain level

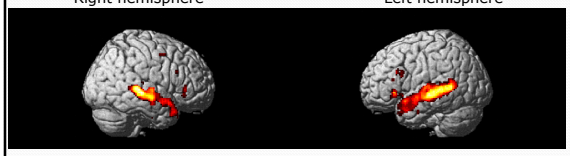
Case study: CK

- Adult male, 42 years old
- School records from 1971, on joining (6;1) and leaving (9;3) specialist language school
  - Reduced babbling as baby
  - 3 words at 2-years (girl, pig, stop) did not speak again until 5;3 SLT from 4;11
  - 6;7: difficulties with auditory memory and morphological inflections (<4yo)
  - NVIQ: 110 (113), VIQ: 69 (111)
- As adult:
  - **Receptive vocab: 99%ile**
  - WAIS vocab definitions: 16%ile
  - WAIS verbal comp: 25%ile
  - **Naming test: z-score=0.16**
  - CELF recall of sentences=1%ile
  - NW-Rep: z-score -1.94
  - **Auditory discrim: ceiling**
  - Verbal fluency SS=80
  - Reading: 19%-ile
  - Spelling: 16%ile
  - **WAIS picture comp: 63%ile**
  - **WAIS block design: 50%ile**

Price, Thomas, Donlan & Richardson (unpublished)

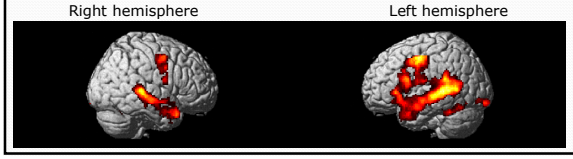
Controls: activation for auditory sentences

Right hemisphere Left hemisphere



Controls: activation for visual sentences

Right hemisphere Left hemisphere

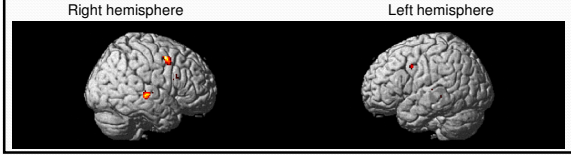


CK: **less activation** relative to controls (auditory and visual)

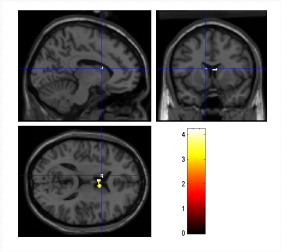
Right hemisphere Left hemisphere

CK: **extra activations** relative to controls (auditory and visual)

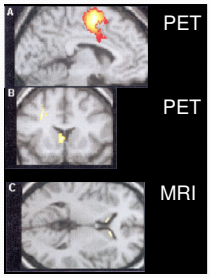
Right hemisphere Left hemisphere



CK: extra activations relative to controls – visual (*shows bilateral activation of the Caudate)



PET data from KE family (FOXP2 mutation)
[Vargha-Khadem et al., 1998]



(nb, unlike CK, affected KE family members showed increased Broca's area activation)

Results

- Reduced activation in normal temporal regions
- Increased activation in dorsal premotor and superior temporal
- Increased activations in caudate nucleus

- Extra activation is in motor areas
- Consistent with sub-articulation during comprehension
- Attempts to support semantic retrieval?

Interpretation

- Competing explanations
  - Compensation (adaptive)
  - System cannot prevent activation of task-irrelevant circuits (neutral)
  - Task-irrelevant activations cause interference (adaptive for some other task?)
- Conclusions
  - Functional imaging useful to explore the types of compensation that the brain attempts
  - But are atypical activations always adaptive?

Genotype-phenotype relations

- Plomin and colleagues (e.g., Kovacs & Plomin, 2006)
- Genes are generalists, environments are specialists

'multivariate genetic research on learning abilities and disabilities in areas such as reading, language, and mathematics consistently shows that genetic influences on diverse abilities and disabilities largely overlap'

- Pleiotropy = each gene affects many traits
- Polygenicity = many genes affect a trait
- Genes likely to have widespread effect on brain and alter general processing properties
  - COMT
  - BDNF

Kovacs & Plomin (2006)

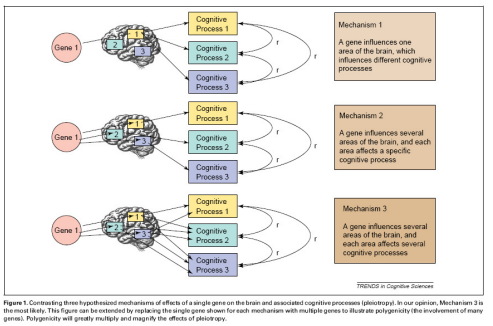


Figure 1. Contrasting three hypothesized mechanisms of effects of a single gene on the brain and associated cognitive processes (pleiotropy). In our opinion, Mechanism 3 is the most likely. This figure can be extended by replacing the single gene shown for each mechanism with multiple genes to illustrate polygenicity (the involvement of many genes). Polygenicity will greatly multiply and magnify the effects of pleiotropy.

Implications for diagnosis

- For developmental disorders, scores outside normal range may trigger intervention
- Scores inside normal range must be interpreted more carefully
  - Sensitivity of test?
  - Normal underlying process?
  - Background IQ of family?
- Status of modules can only be discovered by looking beneath behaviour "in the normal range" at the underlying cognitive and brain processes

Conclusion

- Modules are the product of a dynamic developmental process in which domain-specific systems emerge over developmental time
- Disorders must be viewed within this developmental framework rather than as broken pieces of a static normal cognitive system

Acknowledgements

- Annette Karmiloff-Smith
- Medical Research Council, UK
- British Academy
- Chris Donlan
- Cathy Price
- Fiona Richardson
- Dagmara Annaz
- Members of the DNL
- Julia Grant
- Sarah Paterson
- Emma Laing
- Thierry Nazzi
- Gaia Scerif
- Kate Humphreys
- Sarah Grice
- Mayada Elsabbagh

- m.thomas@bbk.ac.uk
- http://www.psyc.bbk.ac.uk/research/DNL/