Genetic and environmental contributions to callous-unemotional traits and conduct problems

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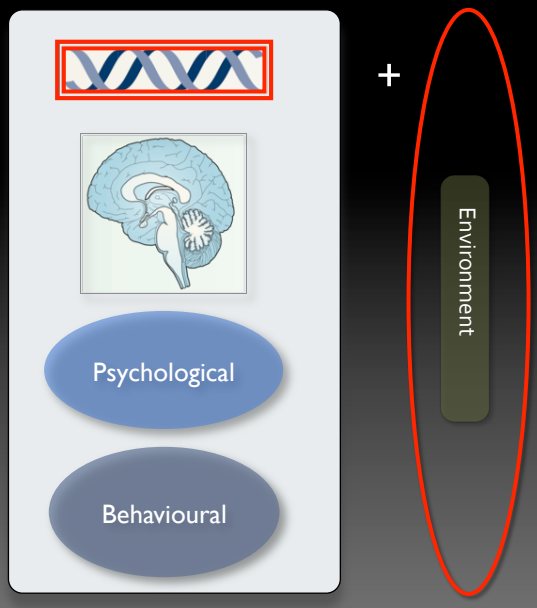
Background

- A growing evidence base indicates that children with high vs. low CU traits:
  - Differ in the severity and variety of antisocial behaviour they display
  - Have different neurocognitive profiles
- What can genetically informative studies tell us about the origin of CU and CP?

Talk 3.



Overview

- Twin Method
- Twin Studies of AB and CU traits
- Molecular Genetic Research
- Environment
- Implications

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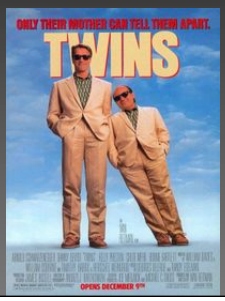
Probing the aetiology: Classical twin design

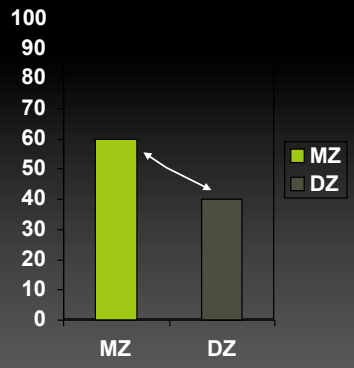
Identical
Monozygotic (produced by the splitting of a single zygote)
MZ



Nonidentical
Fraternal
Dizygotic (produced by two zygotes)
DZ

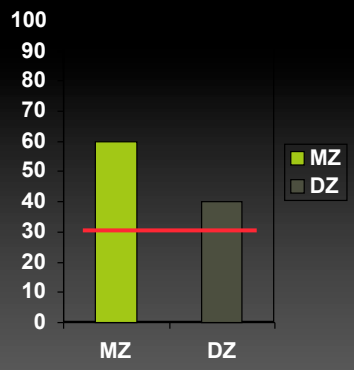
Twin method

- Genetic influence (A) = identical twins > fraternal twins
- The greater resemblance would be expected based on MZ twins sharing all their polymorphic genes



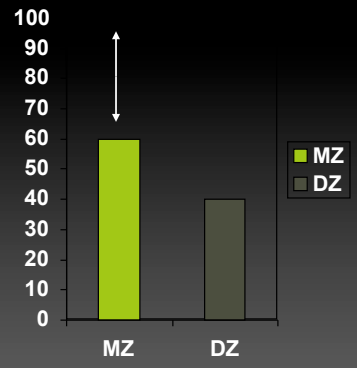
Twin method

- Shared environmental influence (C)= environmental influence that makes family members similar to each other
- Non-identical twins more similar than expected by genetic relatedness



Twin method

- Non-shared environmental influence (E) = environmental influences that make family members different from each other
- Identical twins not 100% identical
  - Measurement error



Heritability and environmental estimates in twin studies

- Apply to a particular population at a particular time
- A, C, and E estimates are likely to partially reflect gene-environment correlation (e.g. rAE) or interaction (e.g. AxE)

A	A AxC rAE
C	C rAC
E	E AxE

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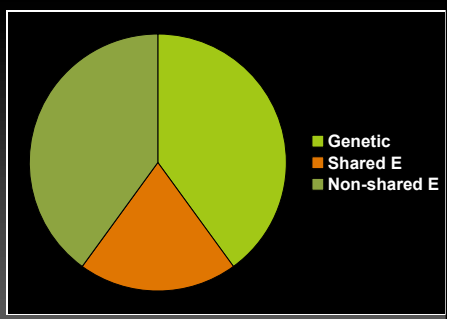
Twin and adoption studies of antisocial behaviour

- Antisocial behavior (AB)
  - Moderate heritability
  - Some shared environmental influence
  - Moderate non-shared environmental influence



Rhee & Waldman, 2002

Aetiology of callous-unemotional traits in children and young people

(reviewed in Viding & McCrory, 2012, Development & Psychopathology)

- 15 published twin studies at the time of review
- From U.S., U.K., and Sweden
- Sample sizes moderate (398 pairs) to large (3687 pairs)
- A wide age range across studies (7-24 years)
- A variety of measures

Viding & McCrory (2012)

- CU traits have moderate to strong heritability
- Shared environmental influences do not play a role in driving individual differences in CU traits in adolescents
  - Environmental influences making members of the twin pair similar to each other do not, as a rule, account for individual differences in psychopathic personality in children/adolescent
- Findings in line with adult data on psychopathic and other personality traits
  - Non-shared environmental influences important

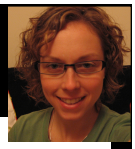
Sex differences?

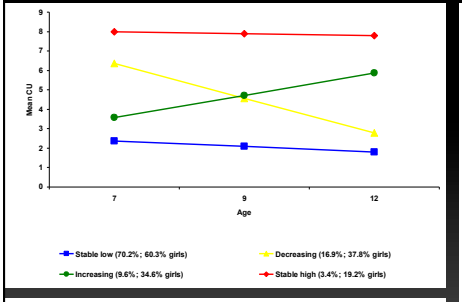
- Qualitative sex differences?
  - Different genes and environments influencing phenotypic variance in males and females
  - Can be tested with twin studies that include opposite sex DZ twins
- Larsson et al., 2006;Viding et al., 2007; Fontaine et al., 2011
  - No support for qualitative sex differences

Sex differences?

- Quantitative sex differences?
  - Do the same genetic and environmental influences affect males and females to a different degree?
  - Can be studied by comparing a model where A, C, E can be different to a model where A, C, E are fixed to be the same between sexes.

Fontaine, Rijsdijk, McCrory & Viding (2010), JAACAP





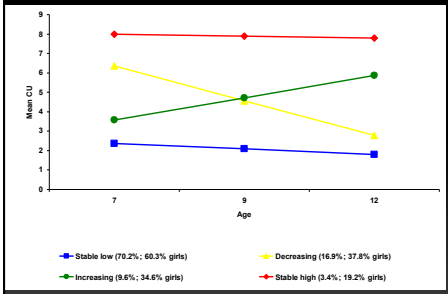
Four trajectories of CU identified through general growth mixture modeling: stable high, increasing, decreasing, and stable low.

Elevated CU associated with:

- increased levels of behavioral difficulties and family risk factors at 4 years old
- higher levels of conduct problems and hyperactivity at 12 years old

These associations were strongest for the stable high group

Fontaine, Rijsdijk, McCrory & Viding (2010), JAACAP



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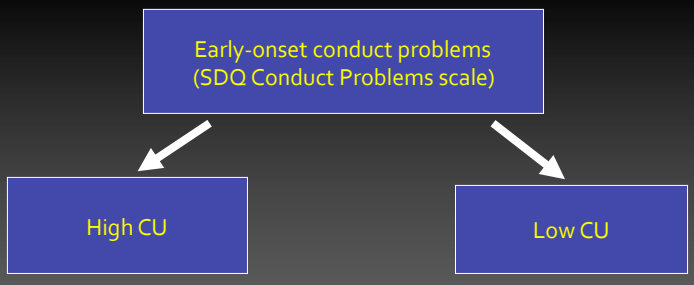
Some evidence for potential quantitative sex differences

	Boys			Girls		
	h^2	c^2	e^2	h^2	c^2	e^2
Stable High CU	**0.78** (0.42 – 0.88)	**0.01** (0.00 – 0.35)	**0.21** (0.12 – 0.34)	**0.00** (0.00 – 0.57)	**0.75** (0.35 – 0.90)	**0.25** (0.07 – 0.48)

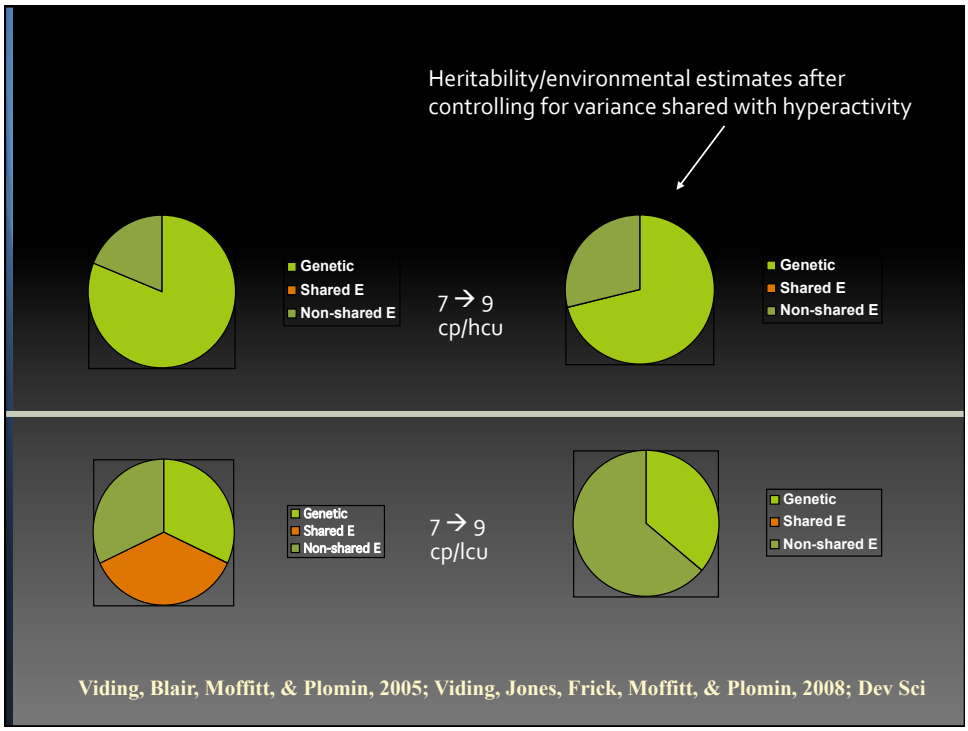
Origins of stability of CU traits across development

- Blonigen et al. (2006); Forsman et al. (2008)
  - Heritability estimates remain similar across time-points
  - CU: phenotypic stability mostly due to genetic influences; change environmentally influenced

Is there a difference in the origin of conduct problems between children with high vs. low CU traits?



DeFries-Fulker analysis: Top 10% CP, Top 10% +/- CU



Summary

- CU traits are heritable; possibly more heritable for boys than for girls
- Stability of CU traits in childhood/adolescence largely driven by genetic influences
  - Change environmental?
- CP more heritable in children with CU traits than in their non-CU counterparts

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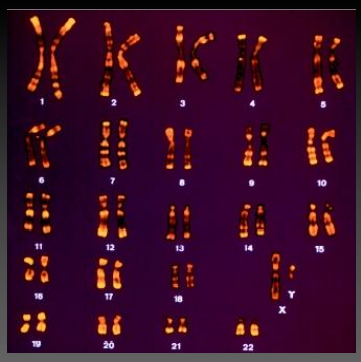
Molecular genetics

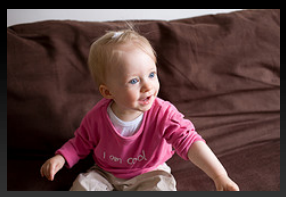
- Twin and adoption studies do not tell us about actual genes
  - However important in establishing, e.g.:
    - whether a trait/disorder is heritable
    - whether the genetic effects are stable throughout development
    - whether there is heterogeneity in aetiology between different subtypes
    - help focus molecular genetic investigations
- Molecular genetic studies of behaviour and psychiatric illness attempt to understand the specific genetic influences on a trait/disorder

Genes

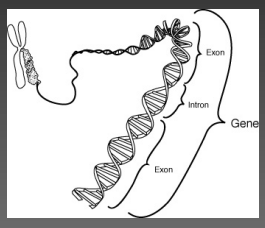
- The genome comprises the entire set of chromosomes for the organism
- Every chromosome is made up of DNA, each strand of which contains many genes

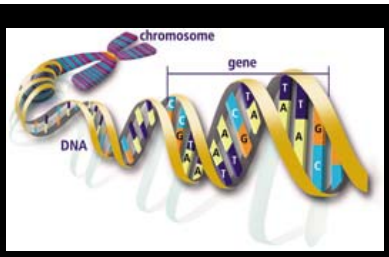


Genes



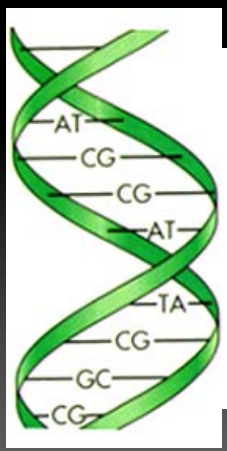
- Genes are the particles on chromosomes that carry the genetic information that is passed from parents to their offspring

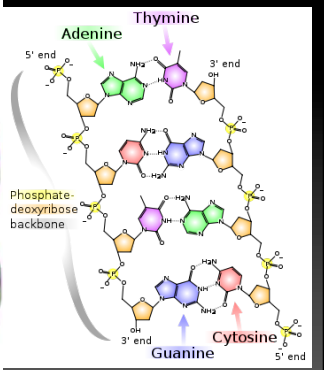




- A gene is a unit of DNA that codes for a protein.
- The genome has start and stop signals to define a gene.
- The genome has also got regions that regulate whether gene is expressed or not (or how much it is expressed) – the expression can be responsive to environmental conditions (epigenetics)

- GATC nucleobase (guanine, adenine, thymine, cytosine) code can vary between individuals – a gene that has more than one variant is called a polymorphism
- Variants are called *alleles* (many in each gene). We have two copies of every gene (which may be different alleles)
  - Exceptions, e.g. X-linked genes, males have only one copy
- Alleles can cause:
  - Different shaped proteins
  - Different amounts of protein





'Allelic variation' in mini coopers

Better for sunny days -
Miserable on rainy days.

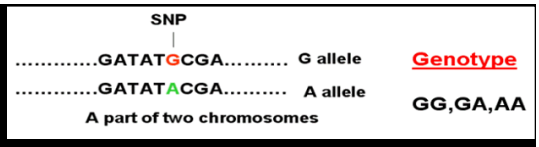
Better for rainy days -
Too hot on sunny days.

Two alternative forms of the same gene are good for different purposes.

May increase likelihood of one behaviour/disorder, but decrease likelihood of another.

- There are several types of DNA variation , e.g.:
  - **variable number of tandem repeats** of a particular stretch of DNA
    - ATTCGATTCGATTCGC
    - ATTCGATTCGC
  - **single nucleotide polymorphisms**
    - GTGTTGT
    - GTTTTGT

SNPs



– 90% of DNA sequence variability is single-nucleotide polymorphisms (SNPs): single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist.

C

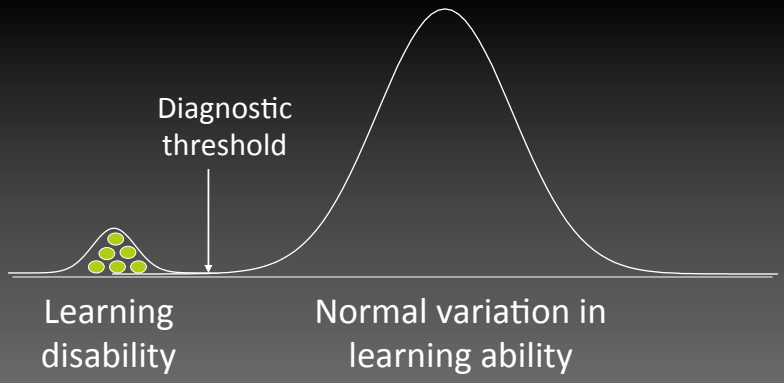
...CCGTGTGATTAT ATGCCTACTATA ...

T

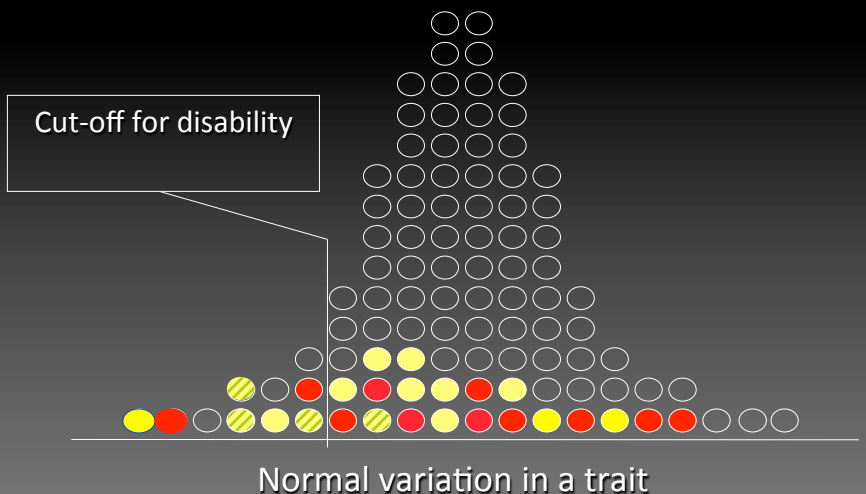
– Abundant (millions in the human genome)

- More than 99% of human DNA sequences are the same across the population
  - the 1% accounts for individual differences
- Variations in the genome (such as a single nucleotide polymorphism – SNP) are found about every 1000th bp
- These polymorphisms account for much of individual differences in the risk for psychiatric disorders

The one-gene one-disability (OGOD) model does not seem to apply to most psychiatric disorders/behaviours; there have been very few 'big hits' in psychiatric genetics

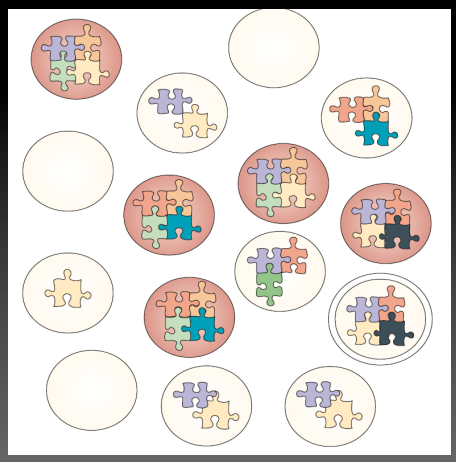


The quantitative trait locus (QTL) model for common complex disorders



The puzzle of complex psychiatric genetics

- **Polygenic, heterogeneous disorders**
- **Generally weak risk effects**
- **Gene-gene and gene-environment interactions?**



Goldman et al *Nat Rev Gen* 2005

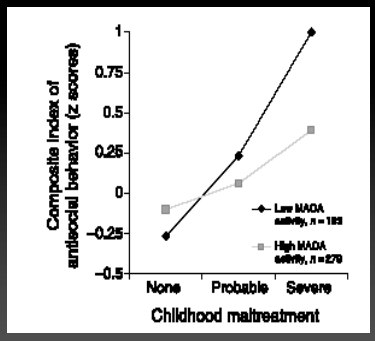
Keep in mind!

Molecular genetic studies of psychiatric disorders and traits have produced very few 'big hits'

- Genetic effects small and probabilistic, most studies lack sufficient power to detect such effects
- Genetic effects may be conditional on environmental risk exposure or the presence of other risk genes

What genes for antisocial behaviour?

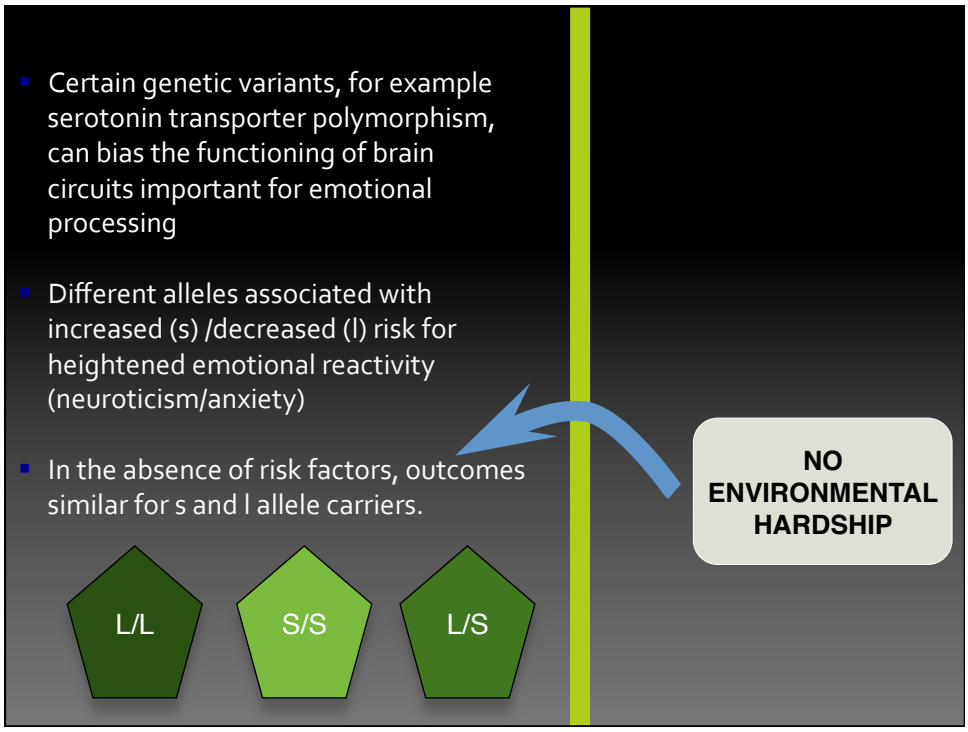
- Most molecular genetic research into antisocial behaviour has not differentiated between CU subtypes
  - Several serotonin and dopamine system genes implicated (+ some other 'hits') – variable success in replication
- 'MAOA-antisocial behaviour' association, especially when GxE accounted for
  - But does this relate to threat reactive, low CU aggression?

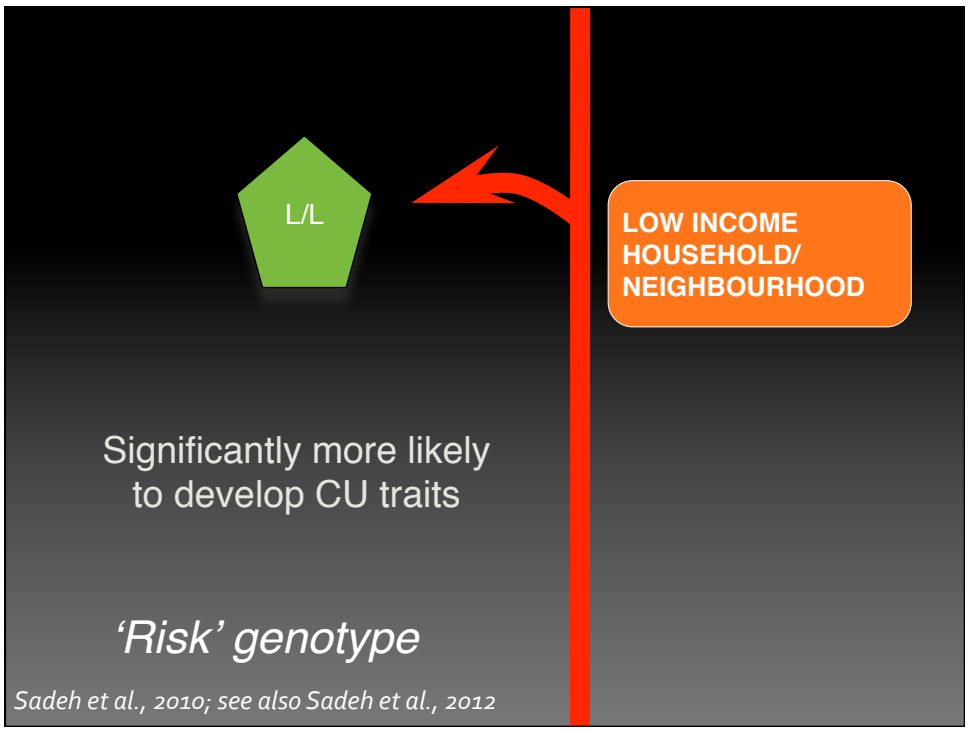


Caspi et al., 2002
Byrd et al., 2013

What genes for CU?

- Those conferring low emotional reactivity/ arousal? (Viding & Jones, 2008; Glenn, 2010)


Certain genetic variants, for example serotonin transporter polymorphism, can bias the functioning of brain circuits important for emotional processing
Different alleles associated with increased (s) /decreased (l) risk for heightened emotional reactivity (neuroticism/anxiety)
In the absence of risk factors, outcomes similar for s and l allele carriers.
L/L
S/S
L/S
NO ENVIRONMENTAL HARDSHIP


L/L
LOW INCOME HOUSEHOLD/ NEIGHBOURHOOD
Significantly more likely to develop CU traits
'Risk' genotype
Sadeh et al., 2010; see also Sadeh et al., 2012

What genes for CU?

- Neurodevelopmental genes?

BRAIN
A JOURNAL OF NEUROLOGY

Size matters: Increased grey matter in boys with conduct problems and callous–unemotional traits

Stéphane A. De Brito,[1] Andrea Mechelli,[2] Marko Wilke,[3] Kristin R. Laurens,[1] Alice P. Jones,[4] Gareth J. Barker,[5] Sheilagh Hodgins[1] and Essi Viding[4,6]

Small, but not perfectly formed: decreased white matter concentration in boys with psychopathic tendencies

Molecular Psychiatry (2011) **16,** 476–477; doi:10.1038/mp.2010.74; published online 15 June 2010

SA De Brito[1,2], EJ McCrory[1,2], A Mechelli[3], M Wilke[4], AP Jones[2,5], S Hodgins[6] and E Viding[1,7]

ORIGINAL ARTICLE

Heritable Variations in Gray Matter Concentration as a Potential Endophenotype for Psychopathic Traits

Fruhling V. Rijsdijsk, PhD; Essi Viding, PhD; Stéphane De Brito, PhD; Matteo Forgiarini, BSc; Andrea Mechelli, PhD; Alice P. Jones, PhD; Eamon McCrory, DClinPsych, PhD

(REPRINTED) ARCH GEN PSYCHIATRY/VOL 67 (NO. 4), APR 2010 WWW.ARCHGENPSYCHIATRY.COM
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THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
Journal of Child Psychology and Psychiatry **:* (2010), pp **–** doi:10.1111/j.1469-7610.2010.02236.x

In search of genes associated with risk for psychopathic tendencies in children: a two-stage genome-wide association study of pooled DNA

Essi Viding,[1,2], Ken B. Hanscombe,[2] Charles J.C. Curtis,[2] Oliver S.P. Davis,[2] Emma L. Meaburn,[2] and Robert Plomin[2]
[1]Division of Psychology and Language Sciences, University College London, UK; [2]Institute of Psychiatry, King's College London, UK

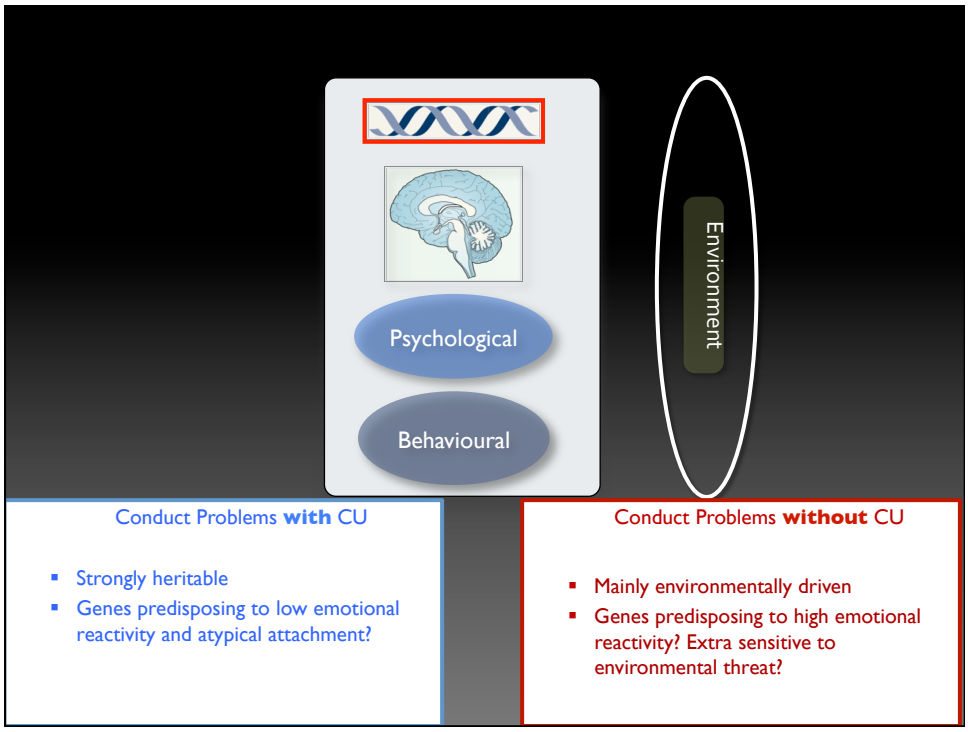
- Some tentative hits near neurodevelopmental genes for CP/HCU (Viding et al., 2010)
  - Not replicated in our own genome-wide association study of CU traits (Viding et al., 2013)
  - One of the 'tentative hits', a SNP near ROBO2, replicated by an Australian group – but associated with CP (rather than CU; Dadds et al., 2013)

What genes for CU?

- Those promoting affiliation/attachment?
- Oxytocin is thought to have a role in promoting empathic and affiliative behaviors, which children with CU lack.
- Beitman et al. (2012) found an association between OXTR rs237885 single nucleotide polymorphism (SNP) of the oxytocin receptor gene and CU in a sample of aggressive children
- Malik et al. (2012 - the same research group), on an overlapping sample, failed to find any association between CU and a different set of oxytocin receptor SNPs.

Summary

- Molecular genetic work in its infancy
  - Different risk genes for HCU and LCU?
  - Rare variants?
- Genes act in a probabilistic manner and in concert with environmental factors
- No genes FOR CP or CU!
  - Genetic factors may 'bias' information processing, which can predispose individuals to be at risk for developing antisocial behaviour and psychopathic personality



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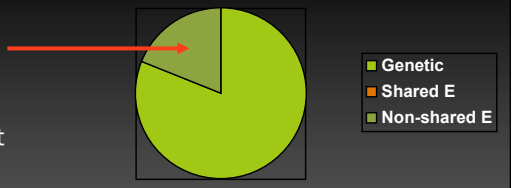
All this behavioural genetic talk seems to ignore the environment…

- High heritability and atypical neural activity do not equal immutability
- Both twin and molecular genetic studies demonstrate that environment matters
- Longitudinal data suggest that CU traits can both increase or decrease across development
- We also know that brain development is not fixed



HCU - Environments

- We need to understand gene-environment interplay, in particular gene-environment correlation
  - Do associations between parenting and child outcome reflect an environmental process or genetic vulnerability?
  - What does the child bring into the parenting dynamic?
- We need to distinguish between *'what is'* and *'what can be'*
  - Not untreatable

Wootton et al., 1997; Viding et al., 2009; Waller et al., 2013; Dadds et al., in press

- Waller, Gardner, & Hyde (2013) - Parenting focused interventions can be effective for children with high levels of CU
- 'Warm' parenting associated with reduced CP in children with CU

Psychiatry Research 199 (2012) 201–207

Contents lists available at SciVerse ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Outcomes, moderators, and mediators of empathic-emotion recognition training for complex conduct problems in childhood

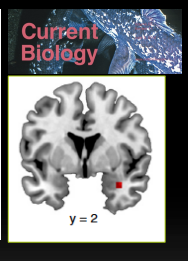
Mark Richard Dadds [a,*], Avril Jessica Cauchi [a], Subodha Wimalaweera [a], David John Hawes [b],

- Reduced behavioural problems, increased parent reported empathy following treatment – most pronounced for children with high CU

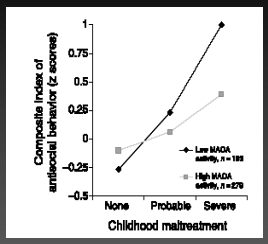
LCU - Environments

Heightened neural reactivity to threat in child victims of family violence

Eamon J. McCrory[1,2,*], Stéphane A. De Brito[1,2,*], Catherine L. Sebastian[1], Andrea Mechelli[3], Geoffrey Bird[4,5], Phillip A. Kelly[1,2], and Essi Viding[1]

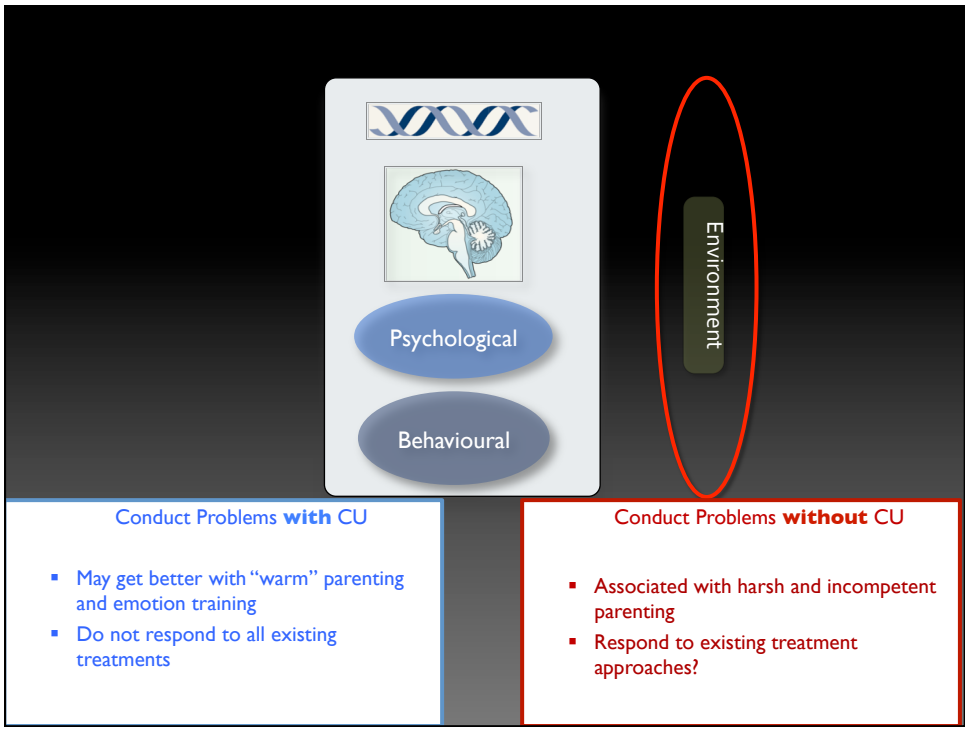


- Environmental main effects and gene-environment interplay
- Dose – response relationship between harsh/ inconsistent parenting and conduct problems
- Parenting interventions work well



Caspi et al., 2002

Wootton et al., 1997; Viding et al., 2009; Waller et al., 2013



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SUMMARY

- Conduct Problems:
  - Similar outward behaviour by different mechanisms (equifinality)
- CU traits designate a subgroup of children who:
  - are genetically vulnerable to CP
  - have low amygdala response to other people's distress
  - lack ability to resonate with other people's emotions

Implications?

- Pro-sociality, but by slightly different means depending on the child's level of CU traits?
- High CU:
  - Support for positive parenting.
  - Emphasise what is in it for the child? How may his/her good behaviour guarantee access to rewards and privileges?
  - Attention to other people's emotions? Anchoring to own emotional experience?
- Low CU:
  - Existing CP interventions work well:
    - Sanctions and rewards
    - Empathy induction

Future research targets to broaden evidence base

- More gene-environment interplay studies
- Neuroimaging studies using a wider array of tasks
- Behavioural studies investigating different types of rewards
- More treatment studies
  - Different settings: clinic, school, community
- Longitudinal studies combining multiple levels of analyses

UCL

Acknowledgements

TEDS, Schools, families and children

Developmental Risk & Resilience Unit

Eamon McCrory, Caroline Bradley, Marine Buon, Charlotte Cecil, Laura Finlayson, Lucy Foulkes, Philip Kelly, Patricia Lockwood, Amy Palmer, Elena Rusconi, Sophie Samuel, Ana Seara-Cardoso, Chloe Thompson-Booth

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