Causes of common mental health problems in adults

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Sir Francis Galton (1822-1911)

‘…Nature prevails enormously over nurture’ (1883)

The history of twins as a criterion of the relative powers of nature and nurture (1876)
‘..a born devil, on who’s *nature, nurture cannot stick.*’ Prospero of Caliban in Shakespeare’s ‘The Tempest’ Act iv scene i

(Michael Horton as Caliban)
Psychiatrists’ opening gambits 1

Have you suffered vexation, grief or reverse of fortune?

Phillipe Pinel

(quoted by Sir Michael Rutter)
ELIOT SLATER
Psychiatrists’ opening gambits 2

Are you a twin?

Eliot Slater
(quoted by Sir Denis Hill)
<table>
<thead>
<tr>
<th>Remarkable Symptoms: whether mischievous.</th>
<th>Dangerous to others.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whether hereditary.</td>
<td>Brother.</td>
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</table>
Cardiff Study of Depression in Siblings (Farmer et al 2000)

<table>
<thead>
<tr>
<th></th>
<th>% reported current</th>
<th>% reported past</th>
<th>% CATEGOr cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-siblings</td>
<td>7.4</td>
<td>17.6</td>
<td>18.5</td>
</tr>
<tr>
<td>C-siblings</td>
<td>0</td>
<td>4.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>
Behaviours that run in families

- Huntington’s disease
- Alzheimer’s disease
- Depression
- Schizophrenia
- Personality
- Intelligence
- Religious involvement
- Attending medical school
Why might a disorder run in families?

- Shared genes
- Shared environment
- A combination of the two
Sources of family resemblance and differences

resemblance

genes

shared environment

behaviour

differences

non-shared environment
Natural experiments teasing apart genes and environment

Twin studies: is there more similarity monozygotic (one egg) than dizygotic (two egg) pairs?

Adoption studies: do individuals resemble their biological relatives more than adopting relatives?
The Cholmondeley Ladies c.1600-10
MZ TWINS

- MZ (monozygotic) twins have 100% of their genes in common (they’re ‘natural clones’)
- Shared environment also makes them similar
DZ TWINS

- DZ (dizygotic) twins have 50% shared genes
- They also share environment to roughly the same extent as MZ twins
Common behavioural disorders

Twin probandwise concordance

MZ  DZ

Alcoholism (females)  Alcoholism (males)  Schizophrenia  Alzheimer’s disease  Autism  Major affective disorder  Reading disability

Plomin, Owen and McGuffin (1994) Science
Structural Equation Modelling: a Simple Univariate Model

\[ r_{12} = \beta h^2 + c^2 \]
Variance components for liability to clinical depression

- Genetic: 70%
- Shared E: 10%
- Residual: 20%

Data from McGuffin et al 1996
Archives General Psychiatry
53(2):129-36
Coaction

- Phenotype = Genes (G) + Environment (E)
  - Shared
  - Non-shared
Additive Genes (A), Common Environment (C) and Non-Shared Environment (E)

Data from McGuffin, Riley and Plomin, Science 2001; 5507, 1232-1233
Types of Gene Environment Interplay

- Coaction
- Interaction
- Covariation

- Additive
- Multiplicativc
- G & E correlated
G-E covariance (correlation)

- Passive (receive G & E from parents)
- Active (inheriting G influences seeking of E)
- Evocative (G elicits E)
G-E covariance (correlation)

- Passive eg, alcohol misuse
- Active eg, a talent for football
- Evocative eg, signed up and coached at Man U. (and people want to buy him drinks)
GE Correlation Vs Interaction

- Correlation: genetic influence on *exposure* to different environments

- Interaction: genetic control of *sensitivity* to different environments
Statistical Interaction
Biological Interaction: specific molecules
Additivity
Interaction

- Environ 1
- Environ 2
- Genotype 1
- Genotype 2

Graph showing interaction between different environments and genotypes.
G-E interaction: antisocial behaviour and adversity (Cadoret et al. 1995)

![Graph showing antisocial behaviour percentage for low and high adversity levels for parent ASP and no ASP parents.](image-url)
The Causes of Depression

- Onsets of depression have a more than chance association with adversity (‘life events’)
- Depression is familial
- Life events are also familial
Life events in Camberwell (McGuffin et al 1988)
Life events are familial

- Family studies:

- Twin studies:
Why are life events familial?

- Some events affect multiple members
- Hazard prone behaviour (risk taking or bad planning)
- Threat perception (neuroticism or ‘dysfunctional attitudes’)
Life Events, Genes and Depression: both GxE and rGE?

- GxE:
  - Genetic influence on sensitivity to events in twins (Kendler et al 1995)
  - Familial personality traits affect response to events in sib pairs (Farmer et al 2003)
Life Events, Genes and Depression: both GxE and rGE?

- rGE:

  - Self reported events heritable, parent reported not (Thapar and McGuffin 1996)

- Genetic overlap between self reports of life events and depressive symptoms (Thapar et al 1998)
Biological Interaction: specific molecules
Toward Behavioral Genomics

Peter McGuffin, Brien Riley, Robert Plomin

The genetics of behavior offers more opportunity for media sensationalism than any other branch of current science. Frequent news reports claim that researchers have discovered the “gene for” such traits as aggression, intelligence, criminality, homosexuality, feminine intuition, and even bad luck. Such reports tend to suggest, usually incorrectly, that there is a direct correspondence between carrying a mutation in the gene and manifesting the trait or disorder. Rarely is it mentioned that traits involving behavior are likely to have a more complex genetic basis. This is probably because most journalists—in common with most educated laypeople (and some biologists)—tend to

How much heritability? Estimates of genetic and environmental effects from recent twin studies (11). A, additive genetic variance, or heritability; C, variance explained by shared environment; E, variance due to unique environmental factors.
Karyotype@ensembl
Finding genes

- One of the major benefits of the Human Genome Project is a dense map of markers (“signposts” for genome searching)

- Linkage studies use genetic markers to track genes in families

- Association studies can pinpoint genes in populations
Positional cloning

- Linkage (or LD)
- location
- gene identification
- structure and sequence
- gene product

prediction
diagnosis
treatment
Allelic association

- Cases

- Controls
Serotonin genes

MAOA = Monoamine oxidase A

5-HTT/SERT = Serotonin transporter
The serotonin transporter gene

From Lesch and Mössner *Biol. Psychiatry*, 1998
The association between SLEs and self-reports of depression symptoms at age 26, as a function of 5-HTTLPR genotype

Caspi et al, Science 2003
SERT promoter polymorphism, life events and depression

- 17/34 studies replicate (8/34 partial)

- All non-replications based on brief self report questionnaire measures of life events

- Negative studies tend to be in adolescent or older subjects

G-E interaction and SERT promoter polymorphism

- Maternal separation stress effects (ACTH) in macaque monkeys (Barr et al 2004)
- Amygdala activation and fearful stimuli (Hariri et al 2002, Surguladze et al 2008)
- Short allele tryptophan depletion → depressive symptoms (e.g., Neumeister et al 2002)
- Response to antidepressants (SSRIs) (e.g., Huezo-Diaz Uher et al 2009)
Genome wide association studies

- Made possible by micro-array technology
- Interrogate the entire genome using 500K-1M single nucleotide polymorphisms (SNPs)
- Require huge samples
Illustrating results from GWA studies

Manhattan plot

Genome-wide significance: p=5 x 10^{-8}

Suggestive significance: p=5 x 10^{-6}
The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia

EK Green¹, D Grozeva¹, I Jones¹, L Jones², G Kirov¹, S Caesar², K Gordon-Smith¹,², C Fraser¹, L Forty¹, E Russell¹, ML Hamshere¹,³, V Moskvina¹,³, I Nikolov¹,³, A Farmer⁴, P McGuffin⁴, Wellcome Trust Case Control Consortium⁵, PA Holmans¹,³, MJ Owen¹, MC O’Donovan¹ and N Craddock¹
Copy Number Variants (CNVs)

- Gains or losses of DNA from 10 Kb to 5 Mb (~12% of genome)
- Detected by variety of methods including comparative genome hybridisation, cytogenetics, bioinformatics
- Can be inherited or occur de novo
Copy Number Variants (CNVs)

- Bonus or ‘by product’ of GWAS
- CNVs targeted by new generation GWAS arrays (e.g., Illumina 610 Quad)
- Implicated in autism
- Even more convincing recent evidence in schizophrenia
- Rare variants account for more of the risk than previously assumed?
Depression associated with deletions

Rucker et al, in preparation
Epigenetic regulation of gene expression

Overly simplistic!
Two common fears of environmentalists

• Geneticists are out to prove that genes determine behaviour

• They might be right!
G and E: Let’s get this straight

- It’s not Nature *versus* Nurture
- The effects of genes on behaviour are pervasive
- Genetic studies provide the best evidence in favour of environmental effects
- GE interplay is complex
- Finding genes, G, and discovering how they work in combination with E ( & that includes Rx!) can potentially revolutionize psychiatry
Psychiatrists’ opening gambits 3

I understand that life has not been kind to you. Tell me....

Anonymous wise old psychiatrist
(quoted by Prof Kenneth Rawnsley)
Psychiatrists’ opening gambits 3

... is there any other insanity in the family?

Anonymous wise old psychiatrist
(quoted by Prof Kenneth Rawnsely)