

# Can the Neurosciences explain Mental Disease and Distress?

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# Mental Health World-wide

- Mental and nervous system disorders constitute 13% of global disease burden (WHO)
- In rich countries, depression, dementia, alcohol, drugs and schizophrenia rank highest

# Mental Health in Europe

- In any year 165 million people – 38% of the population – will develop mental illness
- Wittchen et al Eur. Neuropsychopharmacol 21 655, 2011
- Annual cost €800 billion -24% of health care budget
- European Brain Council, 2011
- Twice as much as cancer yet brain research budgets only a third of cancer
- David Nutt

# WHO 'Grand Challenges' Goal A

- Identify root causes, risk and protective factors:-
  - Modifiable social and biological factors
  - Impact of poverty, violence, war, migration and disaster
  - Identify biomarkers

# Goal A illustrative research questions

(Nature 475, 29, 2011)

- Relationship between early foetal and child development and MNS disorders?
- Phenotypes and endophenotypes across cultural settings?
- Gene-environment interactions?
- What factors promote resilience?
- What role does social context play in persistence of MNS disorder through life?

# How do the questions relate to the challenges?

## Odd:

- Two of the three challenges are in the social domain
- Three and a half of the five research questions are in the biological domain
- Are we looking in the right place?

# What needs to be explained: The epidemiology

- Overall women disproportionately diagnosed  
30.1% of women; 23.4% of men
- Depression and dementia  
Ratio women:men 2:1
- Schizophrenia  
Overall prevalence 0.5-1.0% worldwide  
Ratio working/middle class 2:1  
Afro-Caribbean excess in UK

# What needs to be explained: changes over time?

- Before 1990 estimates for ADHD in children in Britain <1%
- In 2010 estimates for ADHD >5%
  - (in the US 8-10%, disproportionately boys)
- So what has brought about the change?

# Explaining the rise in ADHD

- Not enough time since 1990 for genetic change
- Previous failure to diagnose?
- What's now called ADHD was always there but unrecognised - 'naughty' or behavioural disorder?
- Pharmaceutical enthusiasms?
- Change in social/cultural environment – food, computers or teachers'/parents' expectations?

# The Neuroscientific Hypothesis

1. A disordered molecule leads to a diseased mind
2. The disordered molecule is most likely the result of a disordered gene

# The Neuroscientific Approach 1950s-1990s

- Prior to the rise of genomics:
  - Animal models
    - (depressed marmosets, brain-lesioned rats)
  - Biomarkers (state v trait markers)
    - (CSF, blood, urine)
  - Pharmacology
    - (ex juvantibus logic)

# The Neuroscientific Approach

## 1950s-1990s

- **The molecule of the moment:**
  - Pink spot in schizophrenia etc.
- **Neurotransmitter abnormalities:**
  - Acetylcholine, Glutamate, Dopamine, Serotonin, Gamma-amino butyric acid etc all claimed at one time or another to be 'the' disordered molecule/system

# Neuropharmacological responses

- Target the abnormal neurotransmitter system:
- Eg serotonin in depression
  - Tricyclic antidepressants
    - (amitriptyline)
  - Monoamine oxidase inhibitors
    - (tranylcypromine)
  - Selective serotonin reuptake inhibitors
    - (SSRIs, Prozac, Seroxat)

# Unfortunately:

- Newer antidepressants don't seem to work much better than previous ones
- Even in the most favourable circumstances not much better than placebo
- Resulting in
- Major pharma companies stopping this type of CNS research (eg GSK, Pfizer)

# What do the drugs do?

- At risk of offending both psychiatrists and pharmacologists I suggest that
- In practice most psychotropics seem to target behavioural endpoints rather than root causes  
(if not chemical straightjackets like previous generations then not sufficiently dissimilar)

Need to ask the users

# Neurogenetics before the age of genomics

No Mendelian pattern of inheritance but:-

Claims for substantial heritability of schizophrenia, bipolar affective disorder

Weaker evidence for heritability of depression

However, repeated claims to have identified major genes for any of these conditions fail attempts to replicate them

# Neurogenetics Today

- Animal models through knock-in, knock-out technology – eg ‘Alzheimer’ mice
- Gene-wide association studies drawing on the new genetic biobanks –eg deCode in Iceland

Hypothesis – if not single major genes then  
a small number of genes of major effect

Prospect of personalised medicine?

However:

- GWAS shows anything from 14 to 650 genes (SNP sites) associated with schizophrenia
- Many overlap with bipolar affective disorder
  - (Moskovina et al Mol Psych 2009)
- So maybe these are not distinct diagnostic categories?

# Genes for Depression?

- GWAS shows 328 SNPs highly associated with outcome in genetic studies of depressed patients
  - (Ising et al Arch Gen Psych 2009)

# Conclusion for Pharmacology

Palliative treatments for frank neurological conditions (eg Alzheimer's) optimistic but neuroprotection still a long way off

Neither the hope for personalised medicine nor for single broadly effective drugs for mental distress/disorder seem likely

# Does the problem lie in diagnosis?

- Shifting diagnostic criteria within DSM
- Assumption that mental health disorders can be unequivocally categorised
- Unitary versus spectrum conditions?

# Psychiatry at Stalemate: the problem with DSM

- Psychiatrist Paul McHugh:
- The DSM arbitrarily divides diagnoses based on fashionable distinctions (narcissistic personality disorder versus histrionic personality disorder) whilst lumping together a variety of conditions (schizophrenia spectrum disorders) each of which might have different major genes associated with it.
- *Cerebrum: emerging ideas in brain science*, Dana Foundation, pp93-102, 2010
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# A Modest Proposal for Psychiatry?

- Start with the epidemiology:
  - Why women, why poor people, why ethnic minorities?
  - Why now?
- Pay more attention to some of WHO's research questions:-
  - Modifiable social factors
  - Impact of poverty, violence, war, migration and disaster