Assessment and Aetiology of Anxiety Disorders: Biological Aspects

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Nature of psychiatric illnesses

- “The general principles that govern treatment may be simply stated. We may begin with the axiom that a psychological illness demands psychological treatment, and that purely physical remedies can never be more than subsidiary”

  Walshe (1947)
Nature of psychiatric illnesses: Alternative views

- “The boundary between organic diseases and the so-called functional disease or neurosis is entirely imaginary….Disease is inconceivable without some physical underlying basis. The lesion need not be visible microscopically; it may be molecular or bio-chemical.”

  Stewart (1908)
Comorbidity of Depression and Anxiety

- Approximately 95% of patients with depression have at least one symptom of anxiety (Nutt, 1997)
- Patients with Generalised Anxiety Disorder have a 67% lifetime prevalence of comorbid depression (Judd, 1998)
Depression and Anxiety - consequences of comorbidity

- Difficulty with diagnosis
- Difficulty for research
- Implications regarding aetiology
- Inappropriate treatment
Heterogeneity

- Results of biological investigations of anxiety disorders are often inconsistent
- Imply neurobiological heterogeneity within symptom based diagnostic criteria (Charney, 2003)
Facts in Psychiatry

- Genetic factors are involved in psychiatric illnesses
- Drug treatments are effective in psychiatric illness
Genetics of neuroses

- In general poorly studied
  - belief that biology relatively unimportant
  - difficulties of classification and diagnosis

- In general first degree relative risk:
  - 15% - 18% c.f. 2%-8% in controls
  - risk increased by multiple first degree relatives affected
  - risk higher if proband has severe chronic illness

- Twin study (Torgersen, 1983): 32 X MZ, 53 X DZ
  - 34% vs 17% concordance for same diagnosis
  - 53% vs 38% for any neurosis
  - MZ/DZ ratio 2.3 for inpatients, around 1 for out-patients

- No adoption studies for neurosis as a whole
Genetics of Anxiety and Depression

- **Twin studies (Torgersen 1990)**
  - For diagnosis of anxiety MZ > DZ concordance for anxiety but not depression
  - For diagnosis of depression plus anxiety, MZ > DZ for depression plus depression + anxiety
  - Implies anxiety disorders have a different genetic aetiology compared to depression plus anxiety or depression alone

- **Bivariate path analysis of depression and GAD (Kendler et al. 1992)**
  - No role of familial environment in aetiology
  - Similar genetic factors for both (Gorwood, 2004)
  - Non-familial environment determines two syndromes
GAD and Panic disorder

- Relatives of GAD patients
  - 5 X risk of controls (19.5%), but no increase in PD, agoraphobia
- Relatives of PD probands
  - 24.7% probable PD vs 2.3%, with no increased risk of GAD

<table>
<thead>
<tr>
<th>Proband</th>
<th>Number of relatives</th>
<th>PD</th>
<th>Agoraph</th>
<th>GAD</th>
<th>EtOH</th>
<th>Primary Affective Disorder</th>
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<td>PD</td>
<td>241</td>
<td>14.9</td>
<td>1.7</td>
<td>5.4</td>
<td>6.6</td>
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<td>Agoraphobia</td>
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<td>7.0</td>
<td>9.4</td>
<td>3.9</td>
<td>12.9</td>
<td>4.7</td>
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<td>Control</td>
<td>113</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>4.4</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Adapted from Noyes et al. 1986

- Association with polymorphisms of CCK, 5-HT and DA systems (Maron et al. 2005)
OCD and Genetics

- Family studies contradictory: OCD increases risk of psychiatric illness but ? OCD
- Twin study (Carey & Gottesman, 1981)
  - 15 MZ + 15 DZ
  - MZ/DZ = 7 for treatment for OCD, = 2 for ob Sx
- Polymorph of 5-HT$_{1D}$ associated with OCD (Zohar et al. 2004)
PTSD and Genetics

- Difficult doing family studies since exposure to stress necessary (but not sufficient) to produce PTSD (Segman & Shalev, 2003)
- MZ/DZ concordance ratio > 1 (Skre et al. 1993)
- Genetics accounts for approx 30% of variance when adjusted for degree of combat exposure (True et al. 1994)
Evidence for Biological Pathophysiology

- Genetics
- Neuroimaging
- Pharmacological challenges
  - provocation tests
  - monoaminergic systems
- Neuroendocrinology
Neuroimaging and OCD

- MRI: no volume changes
  - WMH in orbitofrontal cortex (Kim et al. 2001)
- MRS: $\downarrow$ n-acetylaspartate in corpus striatum (Bartha et al. 1998)
  - Basal ganglia and orbitofrontal cortex
  - Correlation of activity in orbitofrontal cortex and symptoms (Adler et al. 2000; Busatto et al. 2001; Evans et al. 2004)
- Hypothesised cortex-striatum-thalamus-cortex circuit involvement (Saxena & Rauch 2000)
- DTI: lower fractional anisotropy in ant. cingulate and parietal region (corr with YBOCS) (Szeszko et al. 2005)
Neuroimaging and PTSD

- SPECT demonstrates left amygdala activation in PTSD patients on exposure to combat sounds (Liberzon et al. 1999)
  - ? Relates to arousal and comorbid depression
- 5-25% atrophy in PTSD (3 studies; Sapolsky, 2000)
  - Especially hippocampus (Brambilla et al. 2002)
  - Associated with explicit memory impairment in two studies showing greatest atrophy (Bremner et al. 1995; Gurvits et al. 1996)
  - Small hippocampus may increase susceptibility to PTSD (Gross & Hen, 2004)
Neuroimaging and Panic Disorder

- ↓ Temporal lobe MRI vol (Brambilla et al. 2002)
  - greatest with early onset and severity of illness (Ontiveros et al. 1989)
- High rate of septo-hippocampal abnormalities (correlates with EEG abnormalities: Dantendorfer et al. 1996)
- ? Hippocampal functional change
  - ↑ PET glucose metabolism (Bisaga et al. 1998)
  - ↓ SPECT rCBF (De Cristofaro et al. 1993)
Provocation of Panic

- Acid-base balance / $pCO_2$
  - Lactate, bicarbonate, hypercapnia, hyperventilation
- Benzodiazepine receptors
  - Flumazenil, inverse agonists
- Noradrenergic system
  - Yohimbine, TCA’s
- Serotonergic system
  - Buspirone, SSRI’s
- Others
  - Caffeine, CCK, hypoglycaemia, cognitive challenges
  - N.B. CCK less effective in women with short 5-HTTLPR allele (Maron et al. 2004)
Acid-base balance

- Anxious patients produce more lactate on exercise than controls (Jones & Mellersh, 46).
- IV lactate produces panic (Pitts & McClure, 67).
  - specific for panic
  - treatment with imipramine blocks effect
  - arouses PD patients from sleep
- Mechanisms
  - hypocalcaemia (Pitts & McClure, 67) – NO!
  - chemoreceptors more sensitive to pH and hypoxia (Carr & Sheehan, 1984)
  - induced metabolic alkalosis and hyperventilation (Gorman et al. 1989)
Respiratory Alterations

- Hyperventilation
  - produces similar somatic symptoms but rarely full panic
  - does produce panic if 5% CO₂ co-administered
- 35% CO₂ rapidly provokes panic
- During panic
  - low CO₂ levels - probably secondary
- Administration of CO₂ relieves attack
HPA axis

CRH mRNA in the PVN

STRESS

CRH

Metabolism / energy balance

Pituitary
ACTH
Adrenal Glands

CORTISOL

Immunosuppression

Cognitive function

Brain neurochemistry
HPA axis and depression

- 50% + of depressives have elevated cortisol levels
- Depressed patients also have:
  - Raised CRH levels in CSF
  - Enlarged pituitary glands
  - Enlarged adrenal glands
- ? Abnormality in depression is impaired feedback
- Foetal/infant stress in animals produces long lasting effects on HPA axis responsivity
  - ? Mechanism for social adversity predisposing to depression
HPA axis

Hypothalamus

-ve

GRs

CRH

AVP

Pituitary

-ve

GRs

ACTH

Adrenal Cortex

Circulating Cortisol
HPA axis and PTSD

- Increased CRH in CSF but normal or low cortisol levels (Baker et al. 1999; Sautter et al. 2003)
- DST normal (Kosten et al. 1990) or enhanced (Stein et al. 1997), irrespective of co-morbid depression
- Increased lymphocyte GRs (Yehuda et al. 1995) &implies enhanced feedback?
HPA axis and Panic Disorder

- Basal HPA activity results equivocal
  - probably increased in severe illness (Wedekind et al. 2000)
- During spontaneous attacks cortisol increased
  - no correlation with severity of attack
- During induced attacks
  - lactate: No (Seier et al. 1997)
  - CO2: No (Sinha et al. 1999)
  - yohimbine: Yes (Gurguis et al. 1997)
- DST & DEX-CRH midway between depressed and controls (Schreiber et al. 1996)
Conclusions

- While “neurotic” disorders are often viewed as being the very antithesis of organisity:
  - Genetic factors are important
  - Neuroimaging often reveals abnormalities
  - Neurochemical and neuroendocrine abnormalities are found

- However the research in this area is hampered by diagnostic problems and the high rates of comorbidity