Newcastle University

Psychobiology Research Group

Assessment and Aetiology of Anxiety Disorders: Biological Aspects

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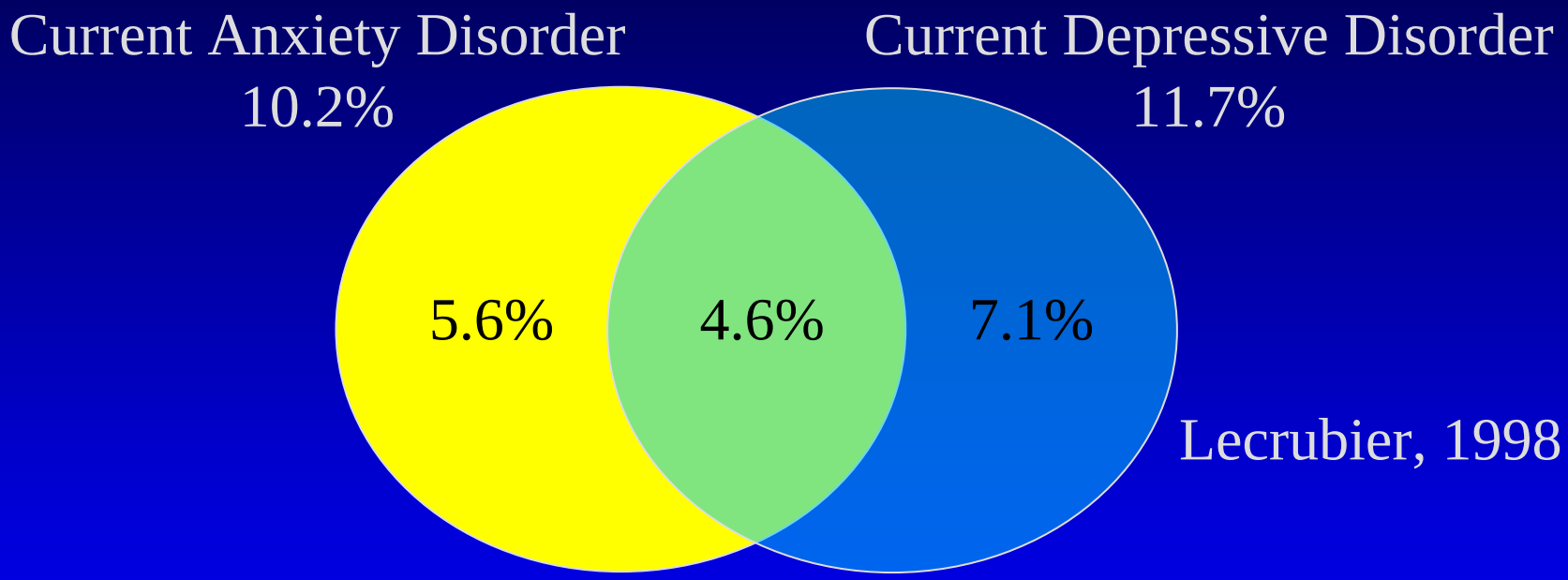
Nature of psychiatric illnesses

- “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 that 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% life time 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

Proband	Number of relatives	Morbid risk (%)				
		PD	Agoraph	GAD	EtOH	Primary Affective Disorder
PD	241	14.9	1.7	5.4	6.6	4.1
Agoraphobia	256	7.0	9.4	3.9	12.9	4.7
Control	113	3.5	3.5	3.5	4.4	7.1

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: ↓ n-acetylaspartate in corpus striatum (Bartha et al. 1998)
- SPECT/fMRI hyperperfusion (Adler et al. 2000; Alptekin et al. 2001; Busatto et al. 2001; Neel et al. 2002):
  - 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 L 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)
  - Esp. 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)

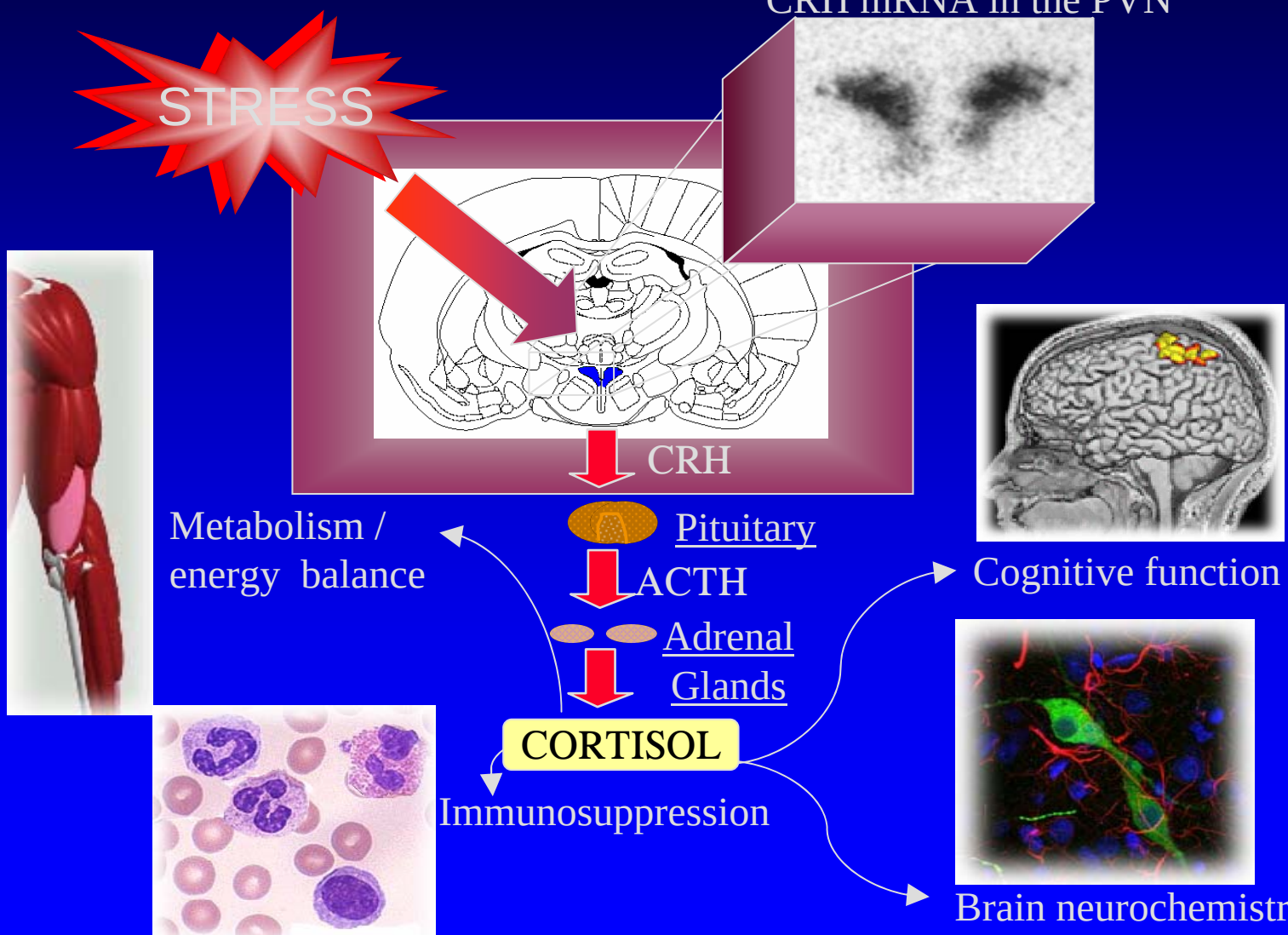
Acid - base balance

- 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% CO_2 co-administered
- 35% CO_2 rapidly provokes panic
- During panic
  - low CO_2 levels - probably secondary
- Administration of CO_2 relieves attack

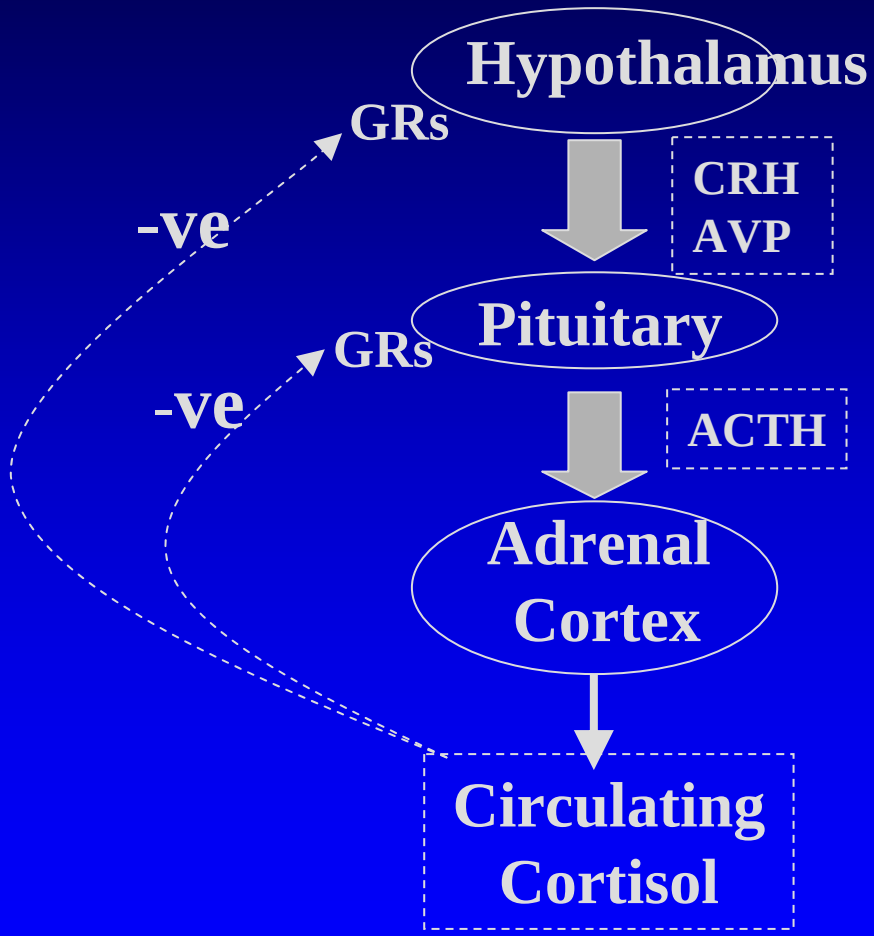
HPA axis


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
GRs
-ve
CRH
AVP
Pituitary
GRs
-ve
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 (Badelow et al. 2000)
  - 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