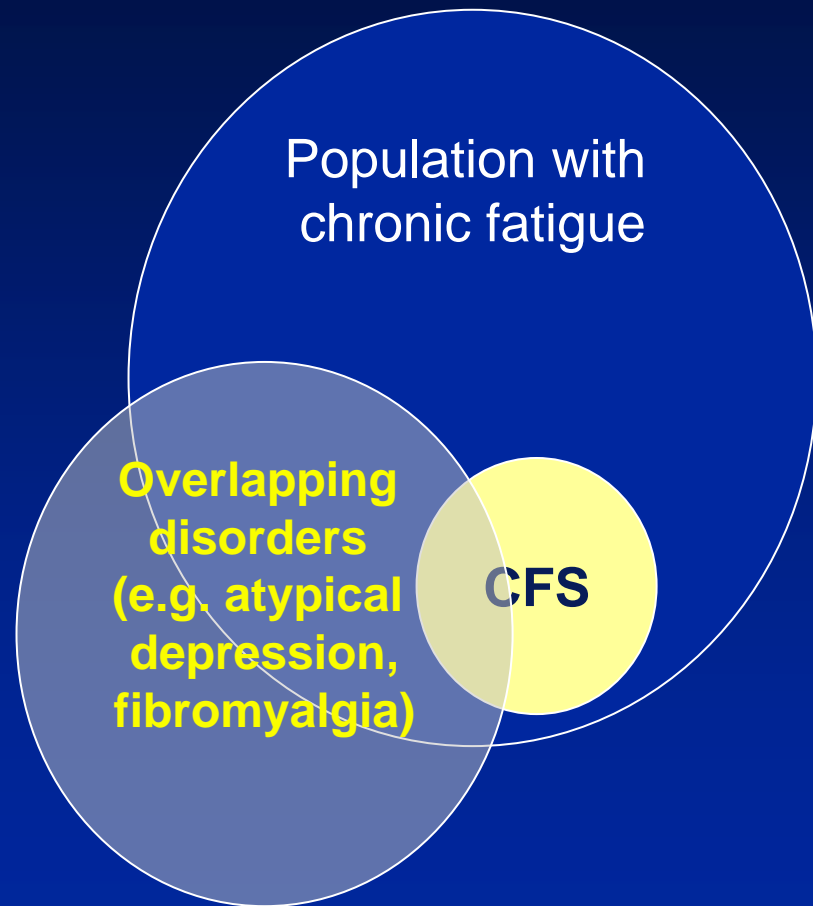


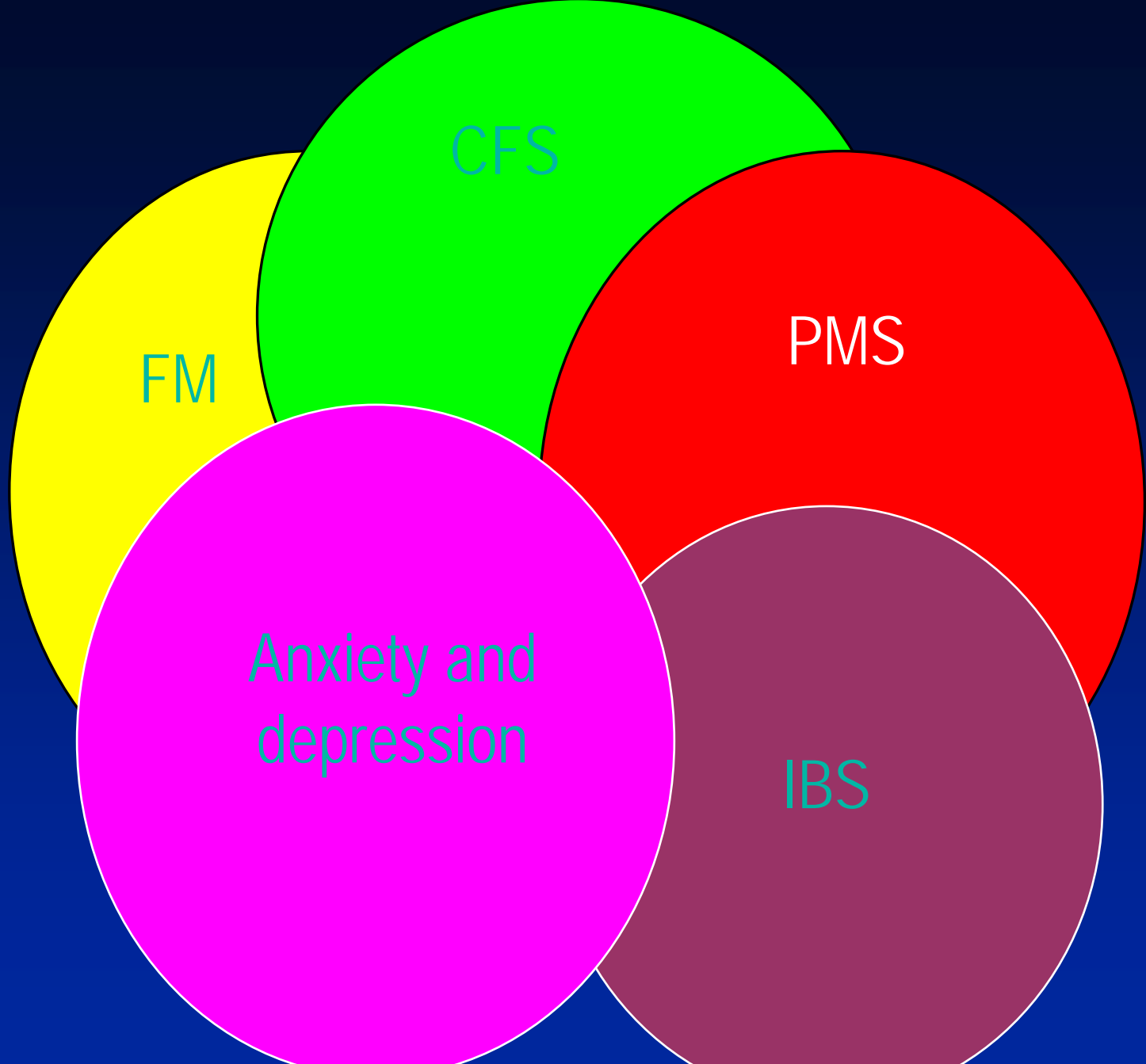
Chronic Fatigue Syndrome Pathophysiology

Dr Anthony Cleare

Reader in Affective Disorders
Head of Section of Neurobiology of Mood Disorders
Institute of Psychiatry

The population





Cluster together – patients often have elements of several

Predisposing factors ('vulnerability')

Precipitating factors ('triggers')

Acute or sub-acute fatigue

Perpetuating factors

Chronic fatigue or CFS

i.e. Multifactorial – all need to be assessed



Predisposing factors in CFS/FM

- Female gender
- Past psychological illness
- Illness in close family members
- History of fatigue/other medically unexplained symptoms
- Genetic
- Childhood Trauma/Abuse

Childhood and Adult Abuse in Fibromyalgia

Walker et al, 1997

	Fibromyalgia (n=36)	Rheumatoid Arthritis (n=33)	P
<i>Childhood abuse</i>			
Physical assault	41.7%	16.7%	<0.05
Penetration	33.3%	13.3%	0.06
<i>Adult assault</i>			
Penetration	66.7%	23.3%	<0.001
Physical assault	47.2%	16.7%	<0.01

Precipitating factors in CFS/FM

- Serious viral illness
- Life events
- Operative stress
- Depression/anxiety
- Medication
- Cancer treatment

Severe Viral Infections

Risk of Chronic Fatigue at 6 months

Viral Meningitis	25%
EBV Glandular Fever	16%
Viral Hepatitis	20%
Common viruses	1% (same as baseline risk)

Risk factors:

Past psychiatric illness (OR 5.5)

Prolonged convalescence (OR 5.4)

Pre-illness fatigue

Perpetuating factors: Psychosocial

Cognitive factors

e.g. loss of control; belief that exercise is harmful;
symptom focussing

Behavioural factors

e.g. use of avoidance

Psychiatric illness

e.g. depression, anxiety

Social Factors

e.g. social support, response of doctors

Perpetuating factors: Biological

- Reduced cortisol levels
- Hypothalamic disturbance
- Circadian rhythm and sleep disruption
- Neurochemical – e.g. Increased central 5-HT
- Autonomic changes
- Physical effects of prolonged or intermittent inactivity

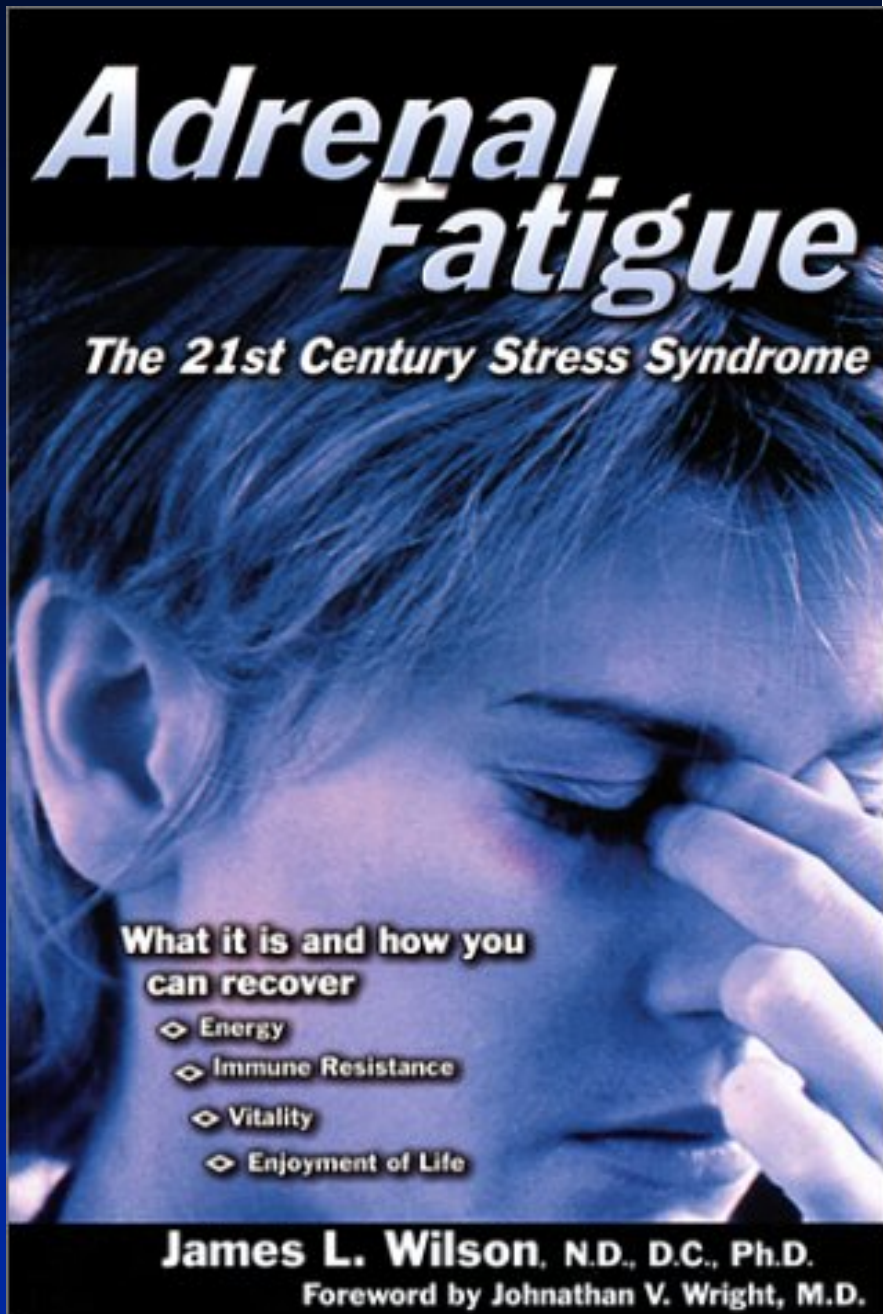
Myths about biology and CFS

- Psychiatrists are not interested in finding biological causes of CFS
- Most of the work in leading journals has come from psychiatrists either directly or via collaborations
- If there are biological factors found, then psychological factors are no longer important and are “trumped”
- Optimal understanding and effective treatment for most biological illnesses needs a psychological approach too
- Trying to understand psychological factors means ignoring biological factors and minimises the illness
- No – although there is still a stigma about psychological factors.

Multifactorial approach to understanding HPA axis dysfunction in CFS

Adrenal Fatigue

The 21st Century Stress Syndrome




What it is and how you can recover

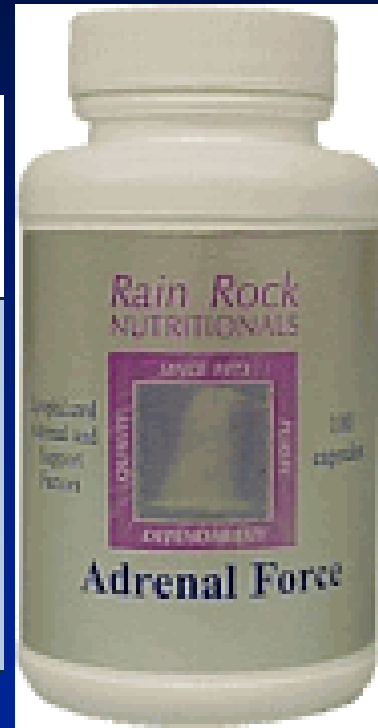
- ◇ Energy
- ◇ Immune Resistance
- ◇ Vitality
- ◇ Enjoyment of Life

James L. Wilson, N.D., D.C., Ph.D.
Foreword by Johnathan V. Wright, M.D.

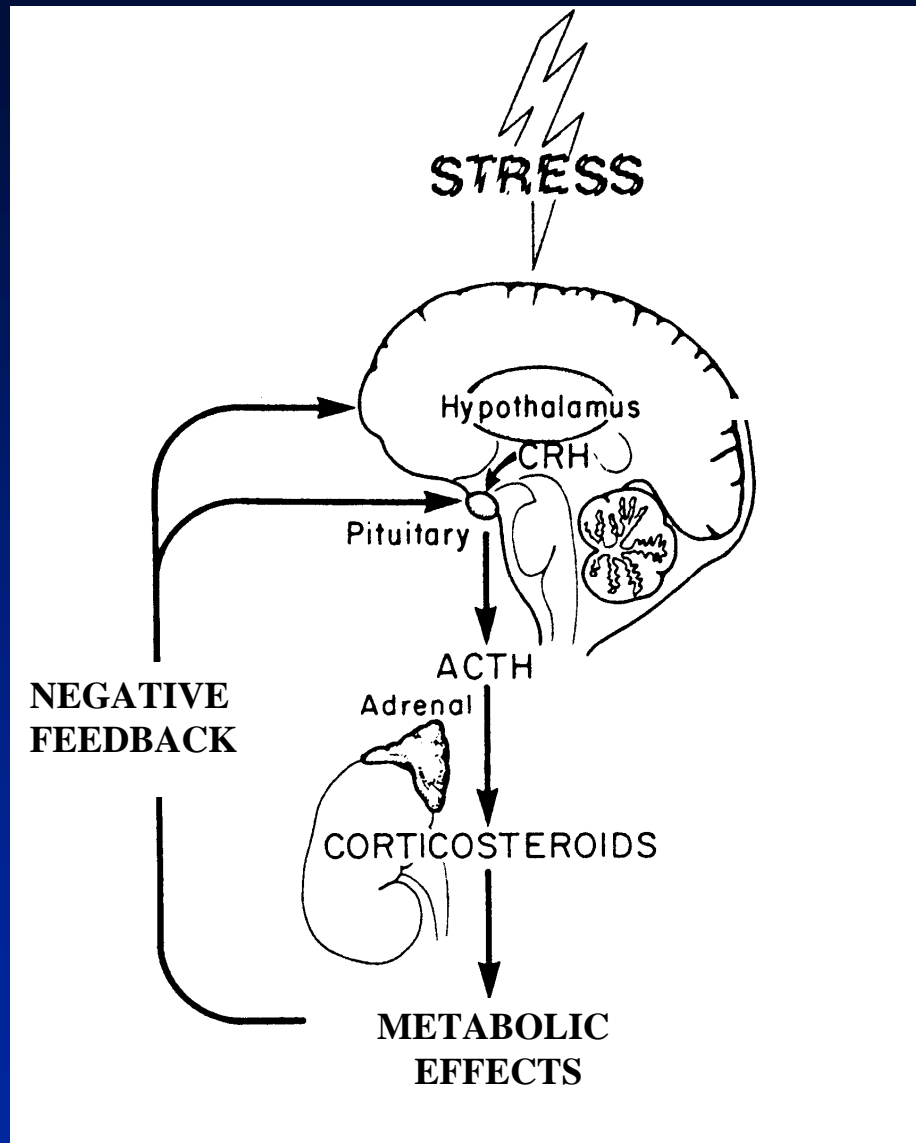
WWW.AdrenalFatigue.org



The 21st Century Stress Syndrome



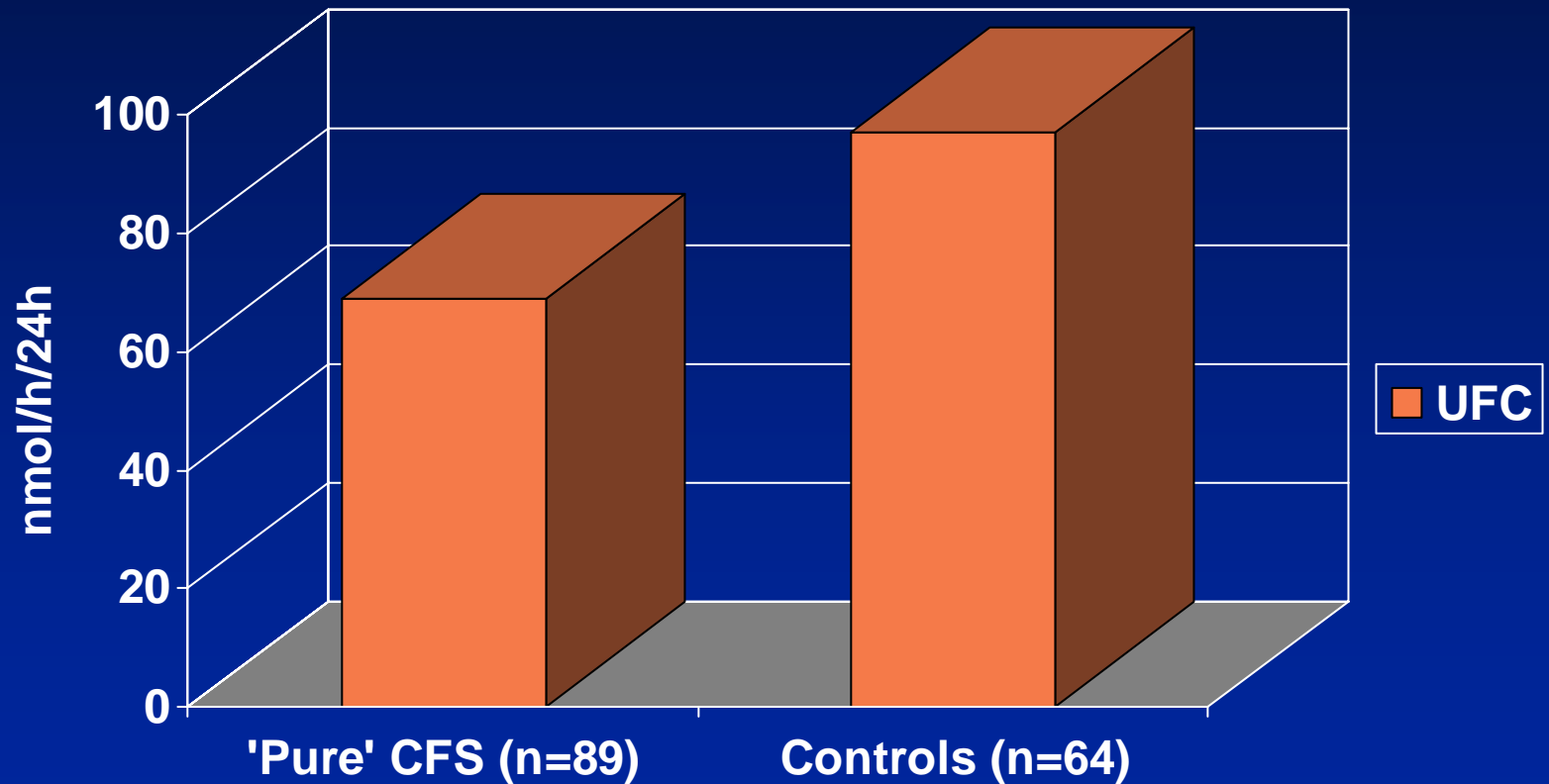
Chronic Fatigue Syndrome
=
Adrenal Fatigue Syndrome?



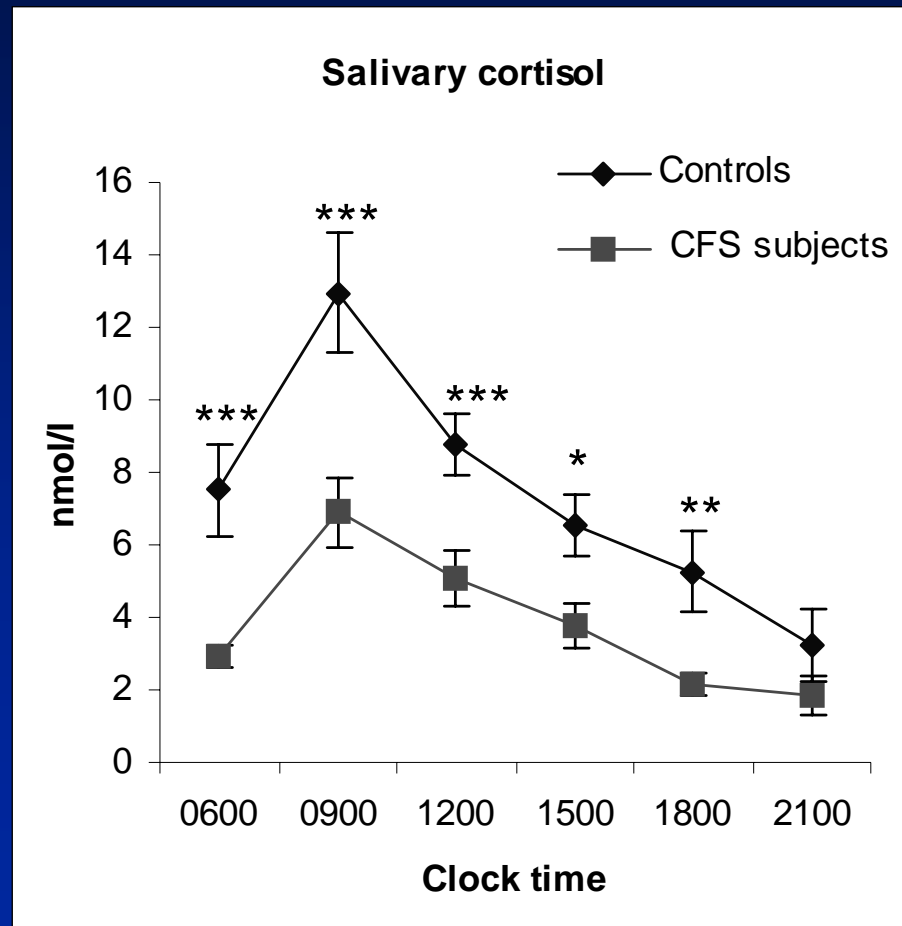
Basal HPA axis function in CFS

Is there low cortisol output in CFS?

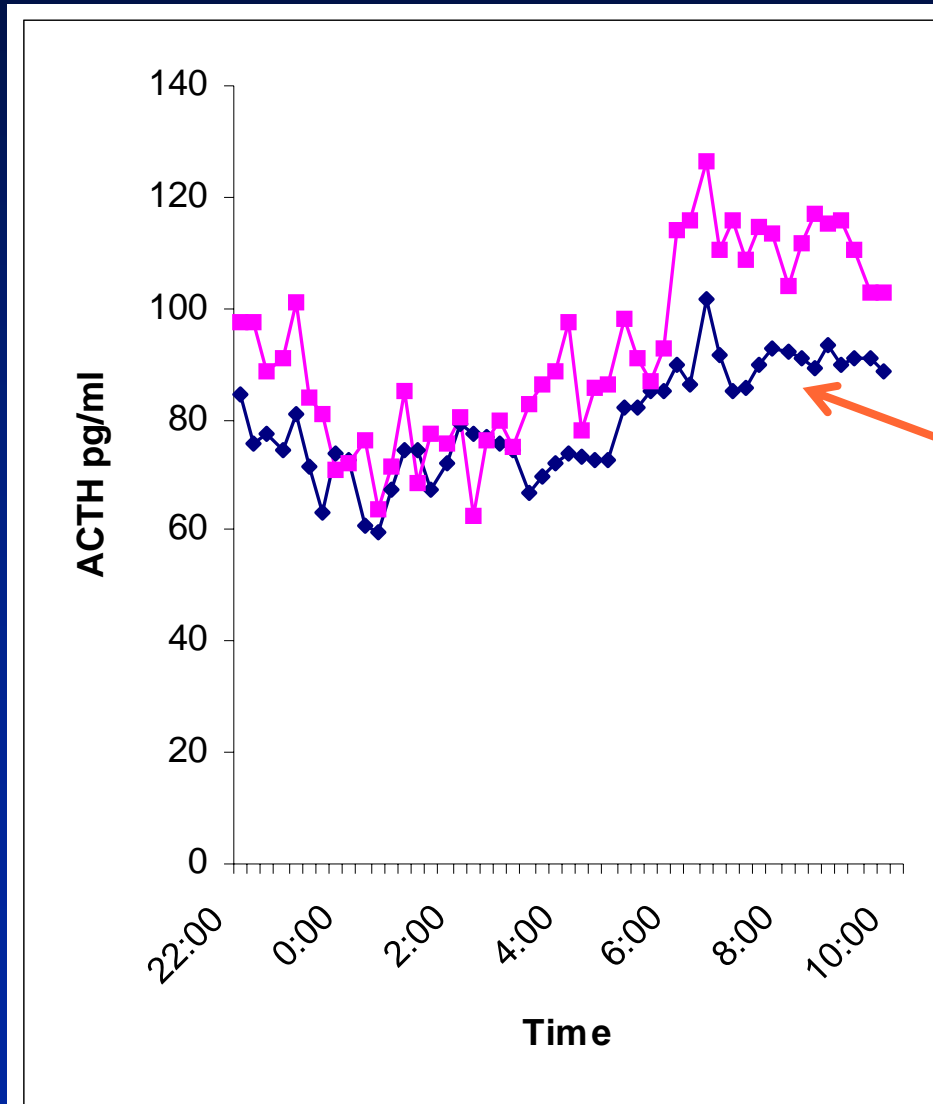
24 h Urinary Free Cortisol Output



Salivary Cortisol in CFS



Overnight ACTH in CFS and healthy controls – 15 minute blood sampling



Controls
CFS

CFS patients
have lower
morning surge
in ACTH

Summary of literature

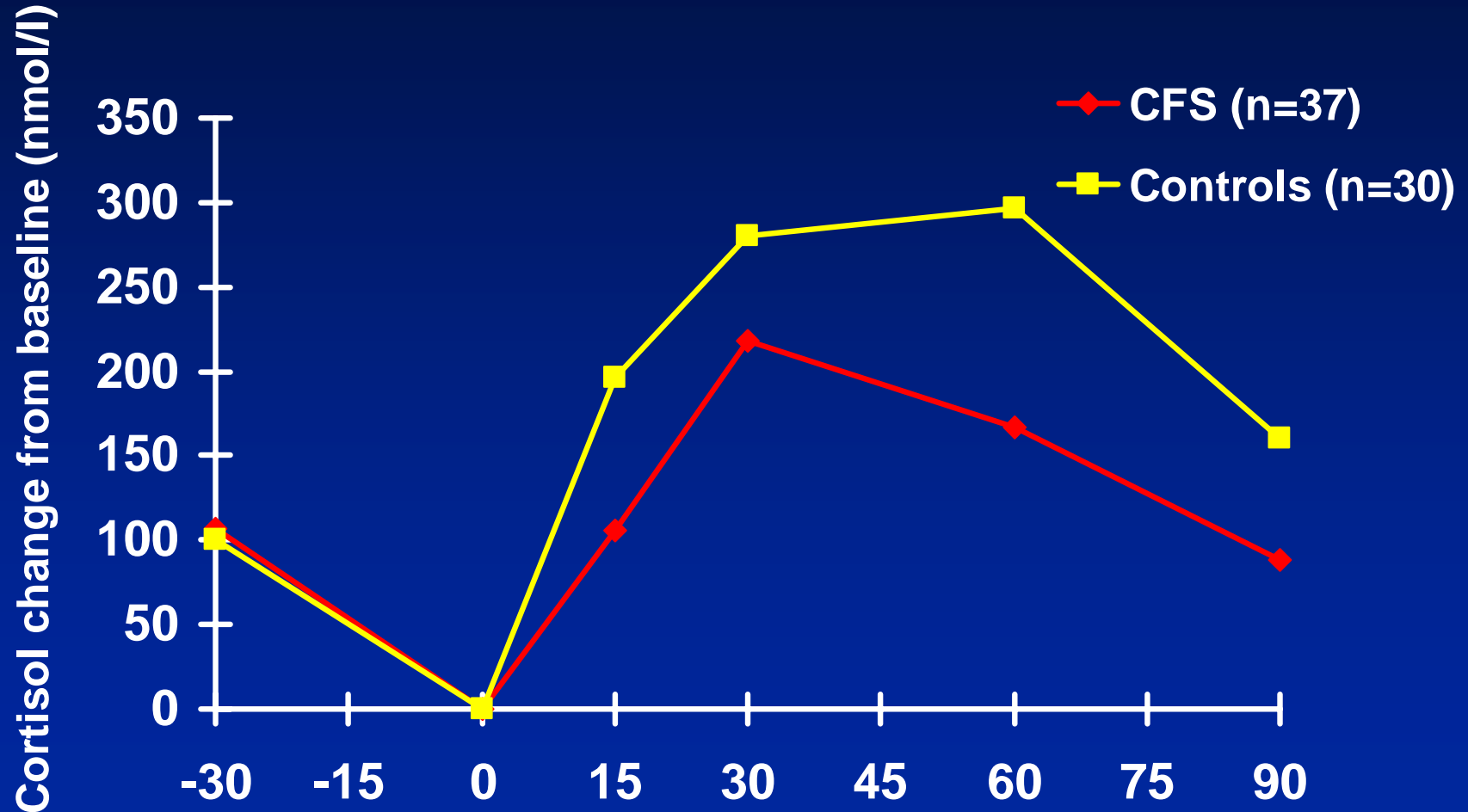
- Basal Studies
 - UFC – 4/6 low cortisol
 - Serial blood samples – 3/6 low cortisol
 - Serial saliva samples – 2/5 low cortisol
- Overall 9/17 studies found low cortisol
- Different samples, different results?
- *Note that studies using single blood samples unreliable (and very inconsistent)*

Dynamic Endocrine Testing

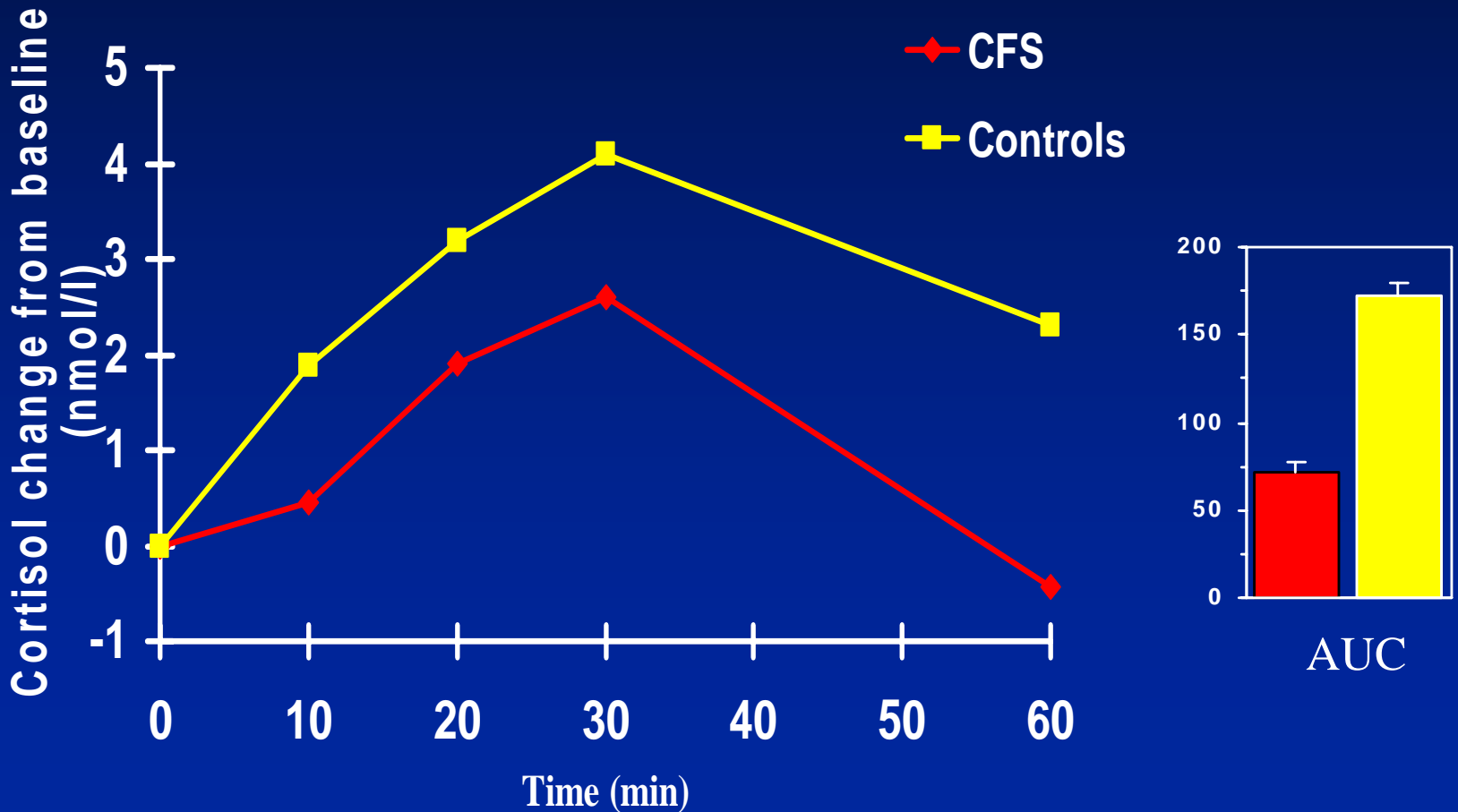
Is there an abnormal HPA axis
response to challenge/stress?

HPA axis in CFS

CRH Test - cortisol response



Salivary cortisol response to awakening

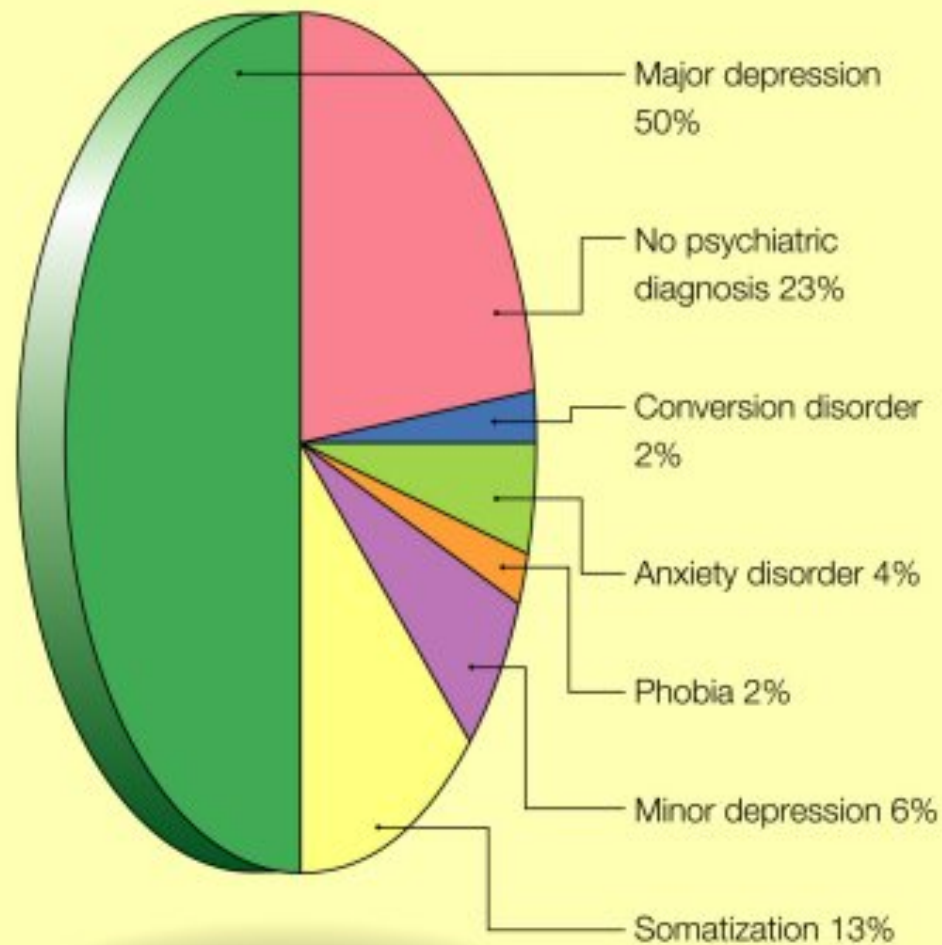


Summary of Literature

- Challenge Studies (ACTH and/or cortisol response)
 - CRH – 3/3 blunted
 - AVP – 1/1 blunted
 - ACTH (synacthen) – 1/1 (high dose); 1/3 (low dose)
 - IST – 1/4 blunted
 - Naloxone – 1/1 blunted
 - Exercise – 2/2 blunted
 - Social stress – 1/1 blunted
 - **Overall - 11/16 blunted, none enhanced**

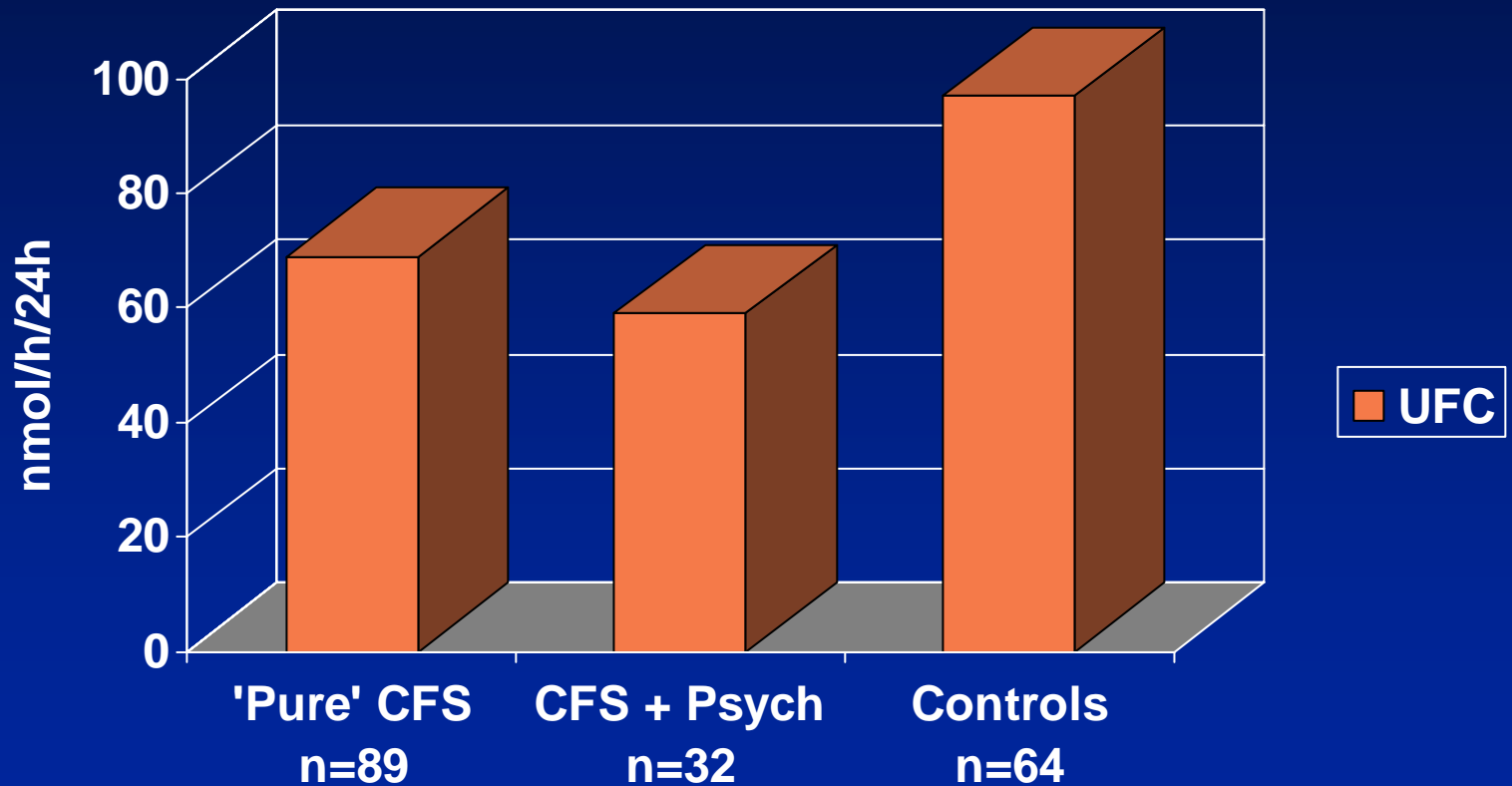
Controlling for confounders

Psychiatric diagnoses in a hospital sample of patients with chronic fatigue syndrome



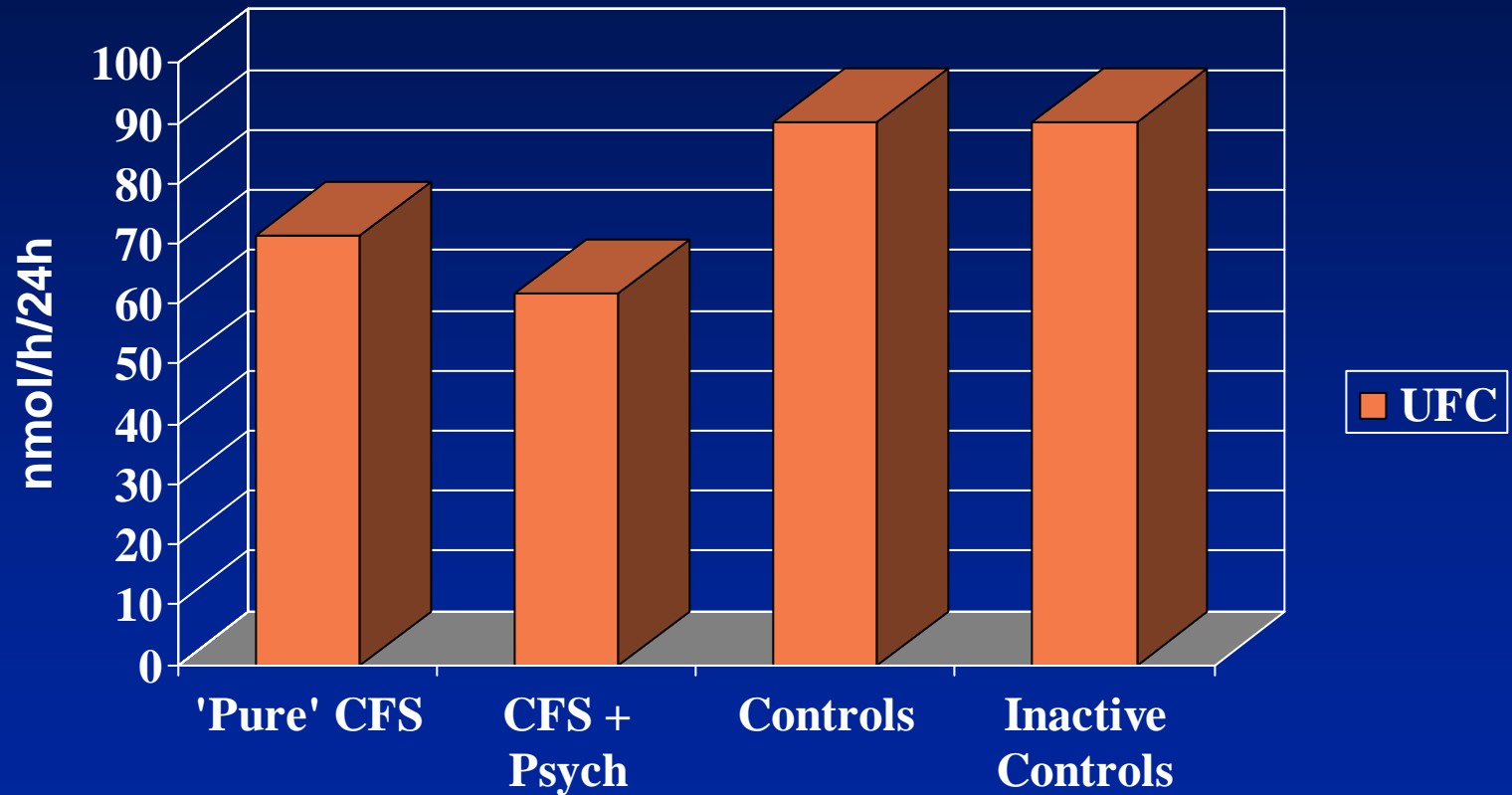
Source: Wessely S, Powell R. *J Neurosurg Psychiatry* 1989; **52**: 940-8.

24 h Urinary Free Cortisol Output



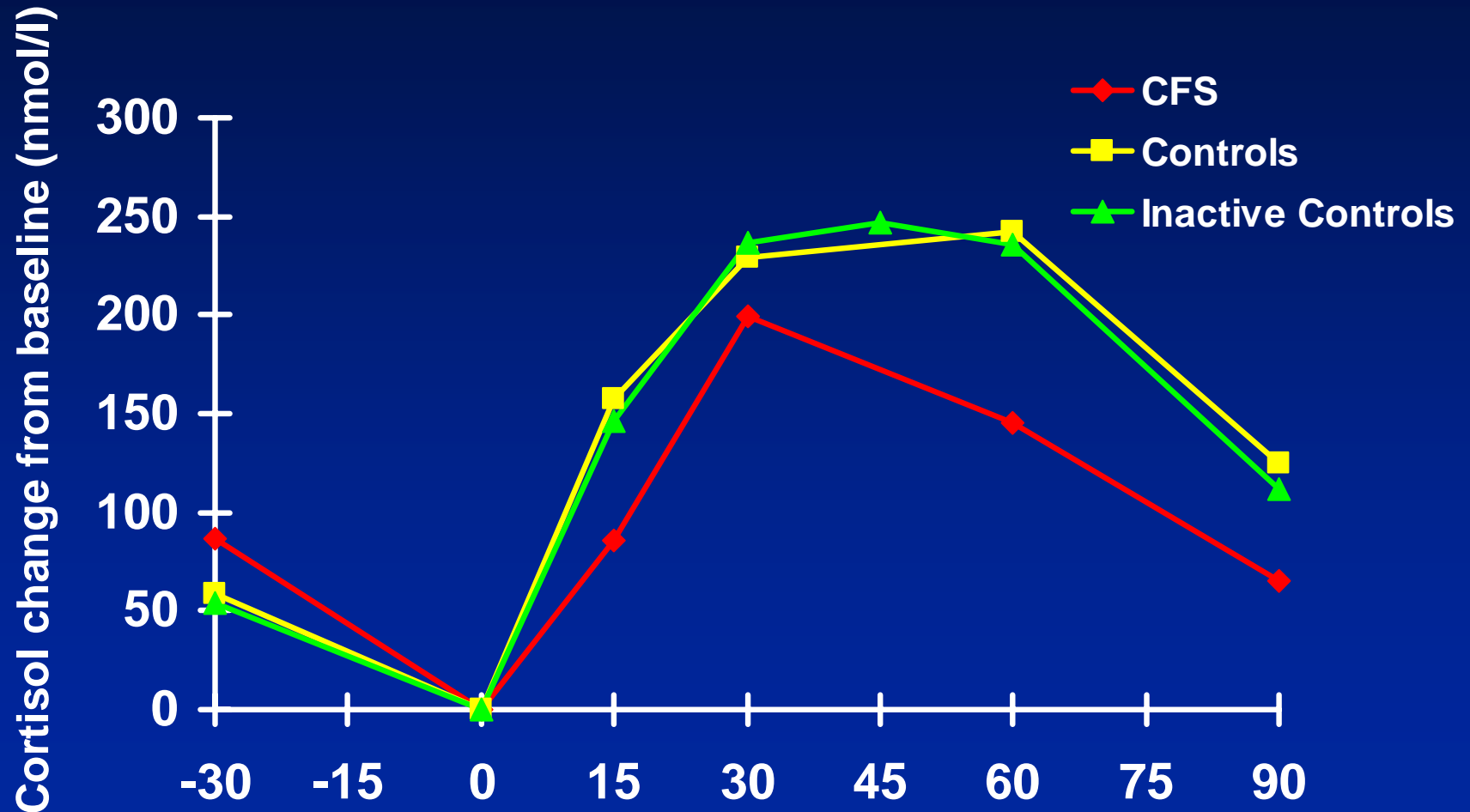
Cleare et al, Am J Psychiatry, 2001

24 h Urinary Free Cortisol Output



HPA axis in CFS

CRH Test - effect of inactivity



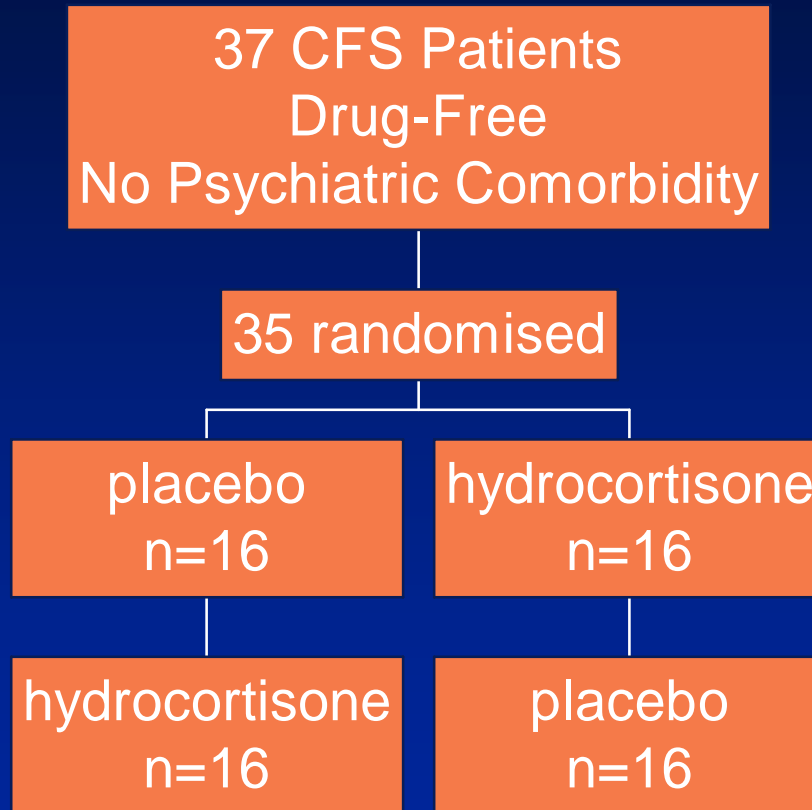
Effects of Sleep Disturbance in CFS

- Strong HPA axis effects
- Leese et al (1996) studied the effect of 5 days of night shift working v day shift working:
 - lowered basal cortisol levels
 - blunted ACTH response to CRH
 - similar to the pattern seen in CFS

Clinical Significance

Does low cortisol matter?

Hydrocortisone therapy in CFS



Hydrocortisone Dose

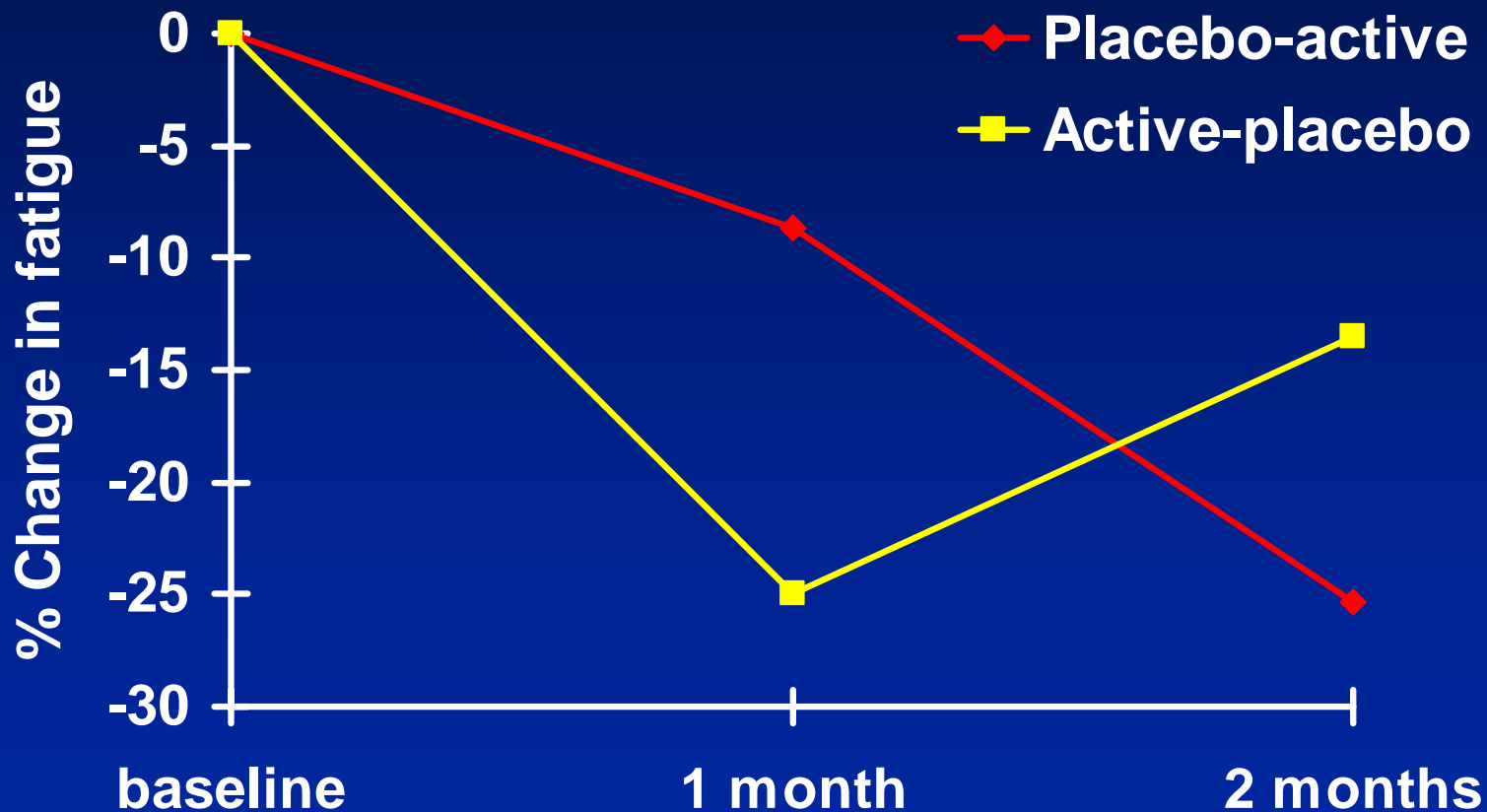
5mg - 14 patients

10mg - 18 patients

32 completed both hydrocortisone and placebo phases

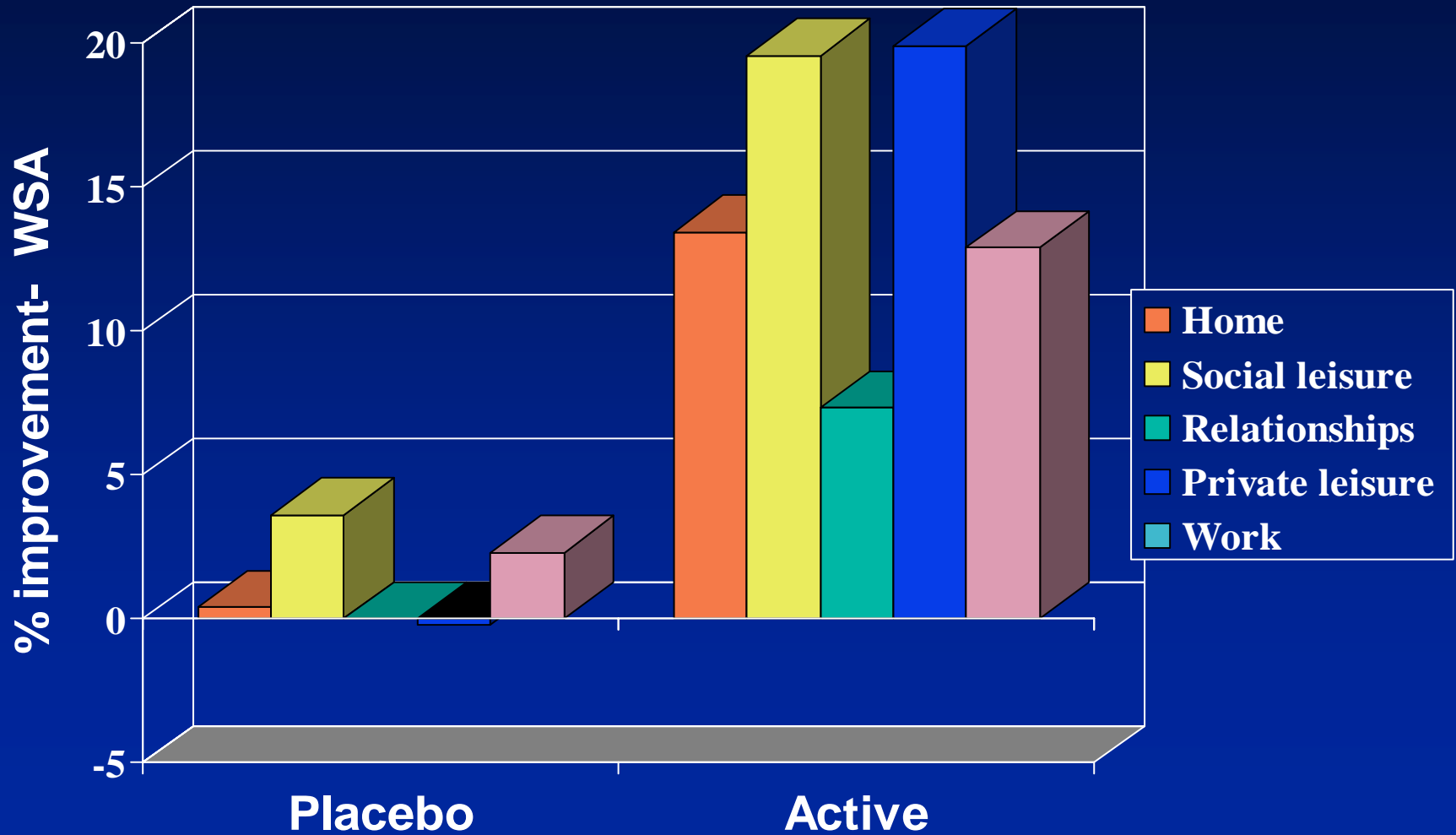
Hydrocortisone therapy in CFS

Effect on fatigue



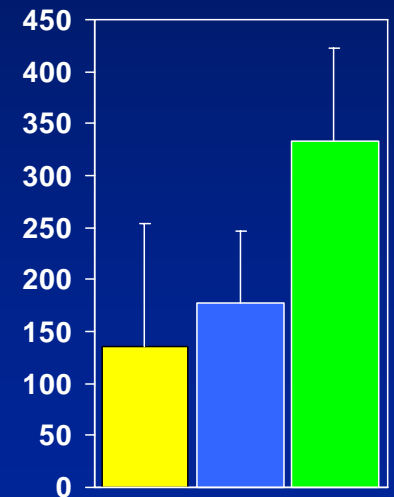
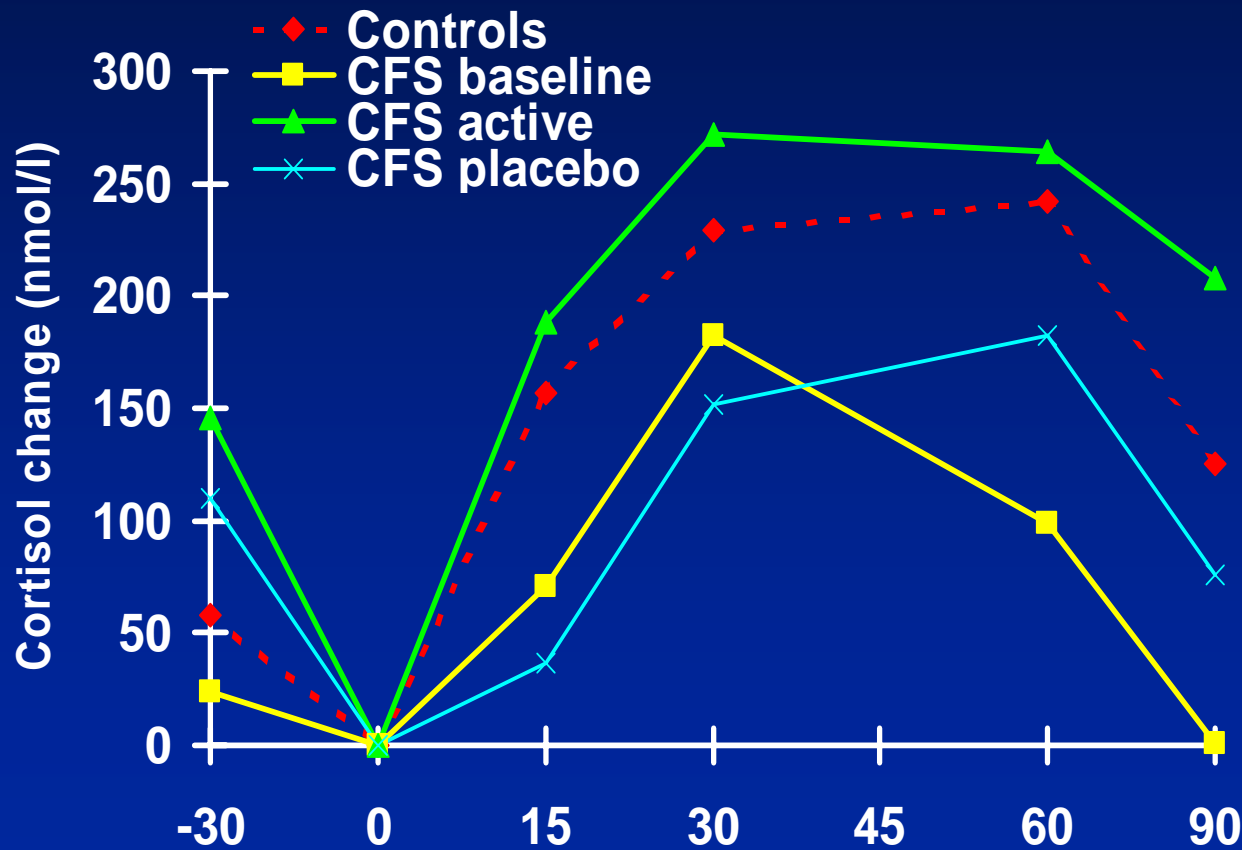
Hydrocortisone therapy in CFS

Disability



Hydrocortisone therapy in CFS

CRH Test in responders to hydrocortisone



AUC

Phase of illness and cortisol

When do cortisol changes occur?

Prospective cohort studies

Predisposing factors (*'risk factors'*)

**Precipitating factors
(*'triggers'*)**

Acute or sub-acute fatigue

Perpetuating factors

Chronic fatigue or CFS



EBV Study

- 71 subjects with clinically and immunologically defined EBV
- Followed up for 6 months
- Rate of fatigue 40% at 6 months (11% continuously for 6 months)
- Salivary cortisol profiles (0800, 1200, 1600, 2000) at time of diagnosis, 3 months and 6 months later

EBV Study – cross sectional results

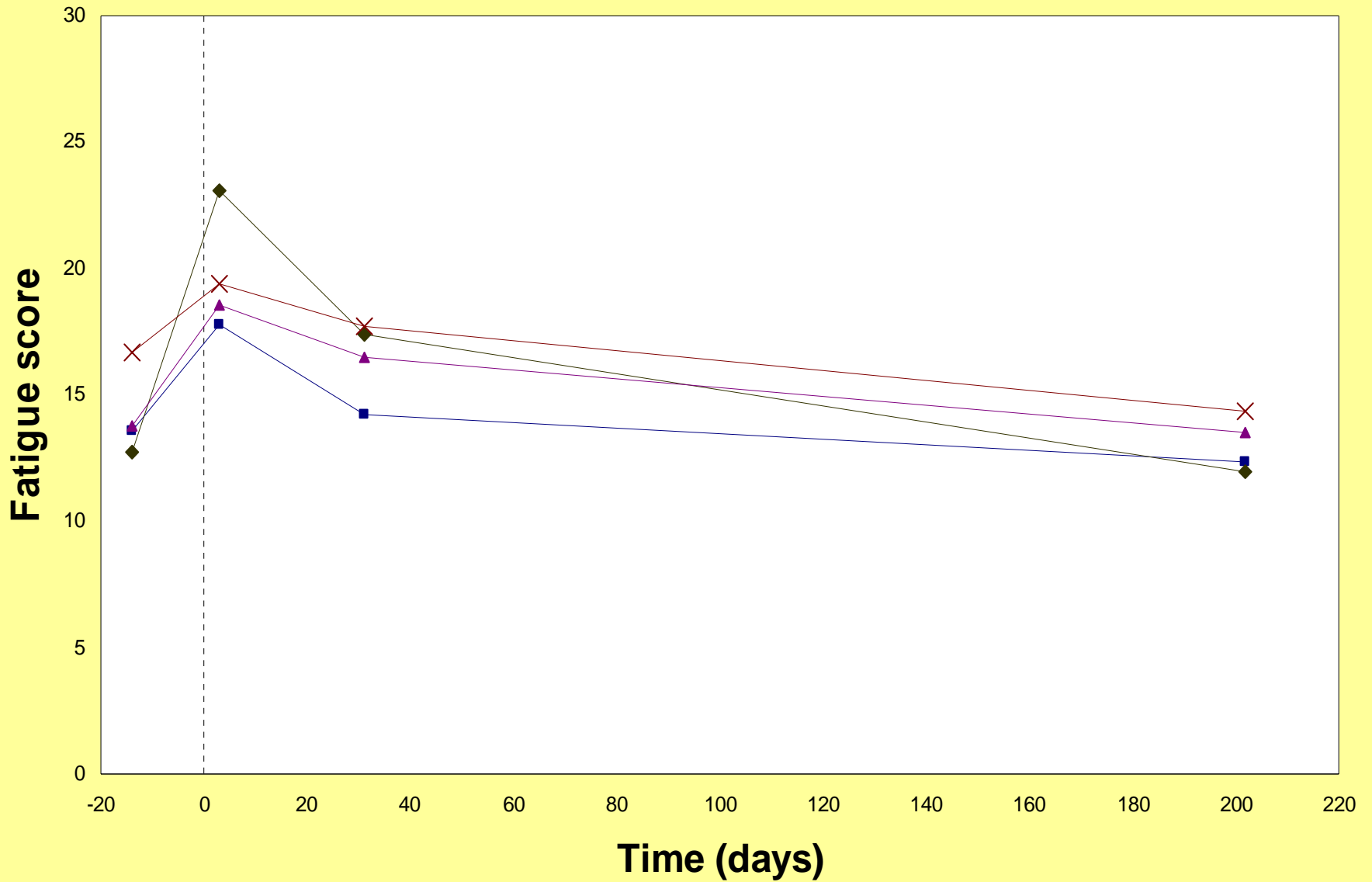
Cortisol output (AUC – nmol/l.h)

	Fatigue Cases	Non-cases
Baseline	95.4 (31.8)	90.1 (14.6)
3 months	99.4 (37.8)	84.5 (20.7)
6 months	94.5 (33.0)	93.9 (26.8)

- Non-significant differences
- Also no effect of *change* in AUC cortisol between baseline and 6 months and fatigue status at 6 months

Post Operative Fatigue Study

- Prospective model of a fatigue syndrome
- Assessments
 - Pre-operatively
 - Day 2-3
 - 1 month
 - 6 months post operatively
- 4 groups of surgery – minor, gynaecological, major abdominal, cardiac
- 184 participants
- Salivary cortisol profiles at 0800, 1200, 1600 and 2000 h



■ Minor surgery ◆ Major abdominal surgery ▲ Gynaecological surgery ✕ Cardiac surgery

Mean Differences (95% CI) in Cortisol Values (AUC: nmol/l.h) Between Fatigue Cases and Non-Cases

Cortisol value	Fatigue pre-op	Fatigue day 2-3	Fatigue 1 month	Fatigue 6 months
Pre-op	4.2 (-5.8, 14.3)	7.6 (-6.9, 22.0)	-6.5 (-18.2, 5.2)	12.9 (1.3, 24.5)*
Day 2-3	18.3 (-4.3, 40.8)	26.1 (-3.6, 55.8)	14.6 (-9.8, 38.9)	41.2 (17.7, 64.6)**
1 month	-9.0 (-19.7, 1.6)	-0.2 (-16.6, 16.1)	9.7 (-1.5, 20.9)	5.9 (-3.9, 15.7)
6 months	3.1 (-5.7, 11.9)	3.3 (-10.0, 16.5)	4.0 (-5.8, 13.8)	9.5 (0.5, 18.5)*

Phase of Illness

Conclusions

- Acute/sub acute fatigue – **No link to low cortisol**
- Early chronic fatigue (6 months) – **No link to low cortisol**
- Late chronic fatigue – **Low cortisol**

Higher cortisol may also act as a risk factor – stress, depression, neurotoxicity, early experiences

Multidimensional model of HPA axis in CFS

Illness phase
Sleep
Psychiatric Illness
Past Abuse
Medication
Psychosocial Stress
Physical Activity
Diet
Genetics



HPA axis change
(heterogeneous)



Contributes to
fatigue maintenance

Cognitive Behavioural Therapy in CFS

- If some HPA axis disturbance is related to inactivity, sleep disturbance etc., then therapy targeting these should reverse the HPA axis changes
- CBT involves elements of:
 - Balancing rest and activity
 - Graded return to activity
 - Sleep hygiene
 - Cognitive restructuring (e.g. attitudes to symptoms, attitudes to exercise)
 - Problem solving
- Strong evidence of efficacy in CFS

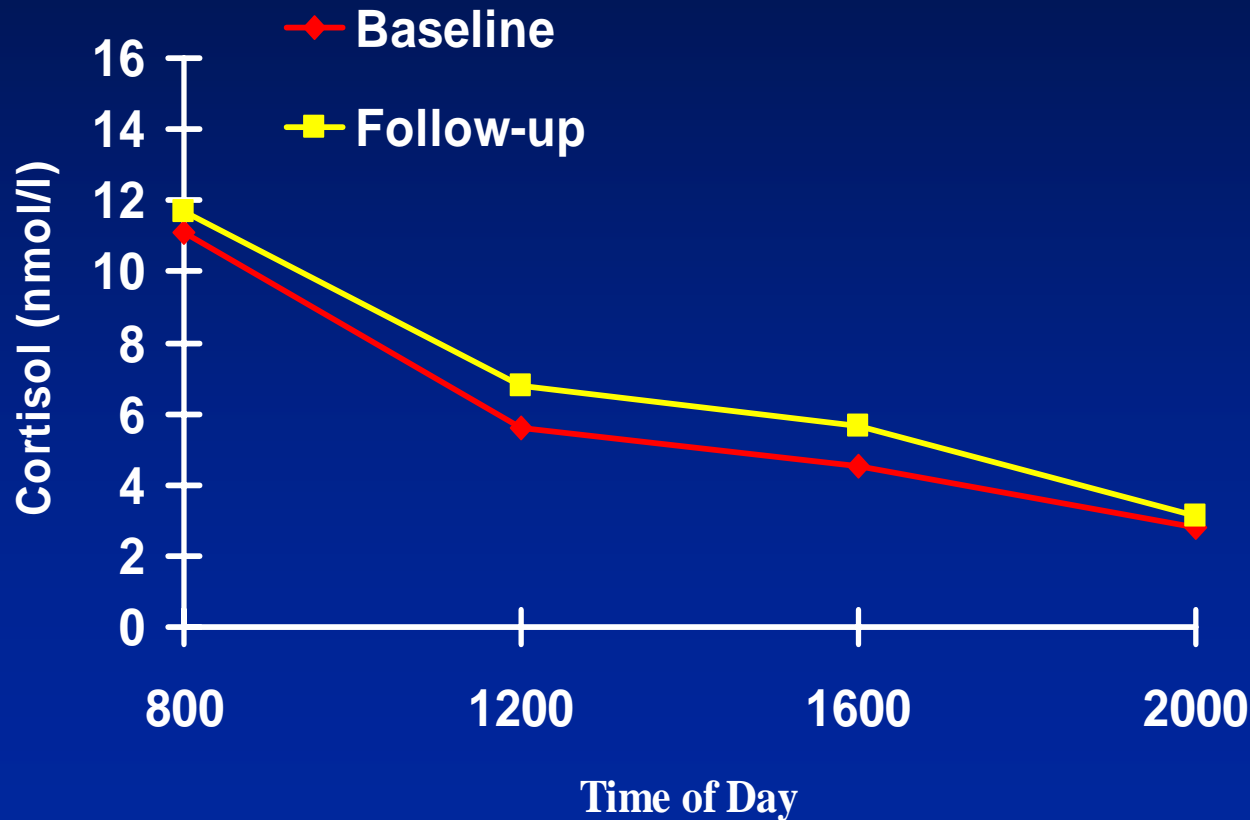
Cognitive Behavioural Therapy in CFS

Effects on Adrenal Function

- Neuroendocrine testing at baseline and after 6 months of cognitive behavioural therapy
- N = 107 subjects
- UFC
- Salivary cortisol profile
- CRH test

CBT in CFS

Salivary cortisol profile

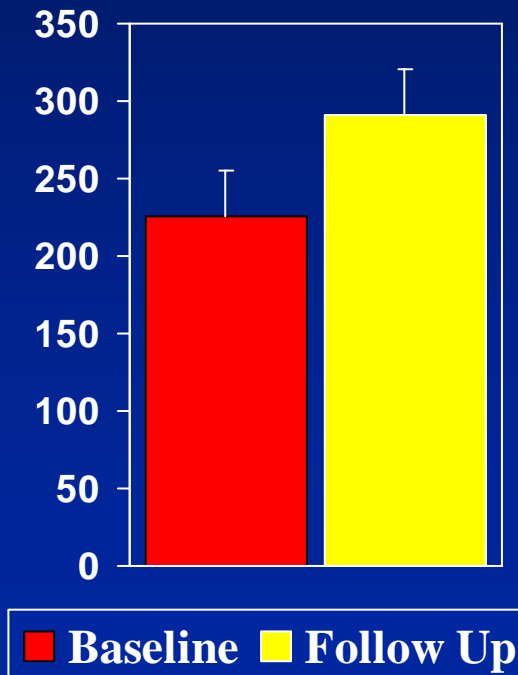


Significant at $P < 0.05$

CBT in CFS

CRH test

AUC cortisol



Significant at $P < 0.05$

Response rate and pre-CBT endocrine status

- 43% responders (CGI much improved or very much improved)
- Low basal cortisol output (UFC) predicted poor treatment response
 - Responders 100 (70) nmol/day
 - Non-responders 70 (44) nmol/day ($P < 0.05$)

Cognitive Behavioural Therapy in CFS

Conclusions

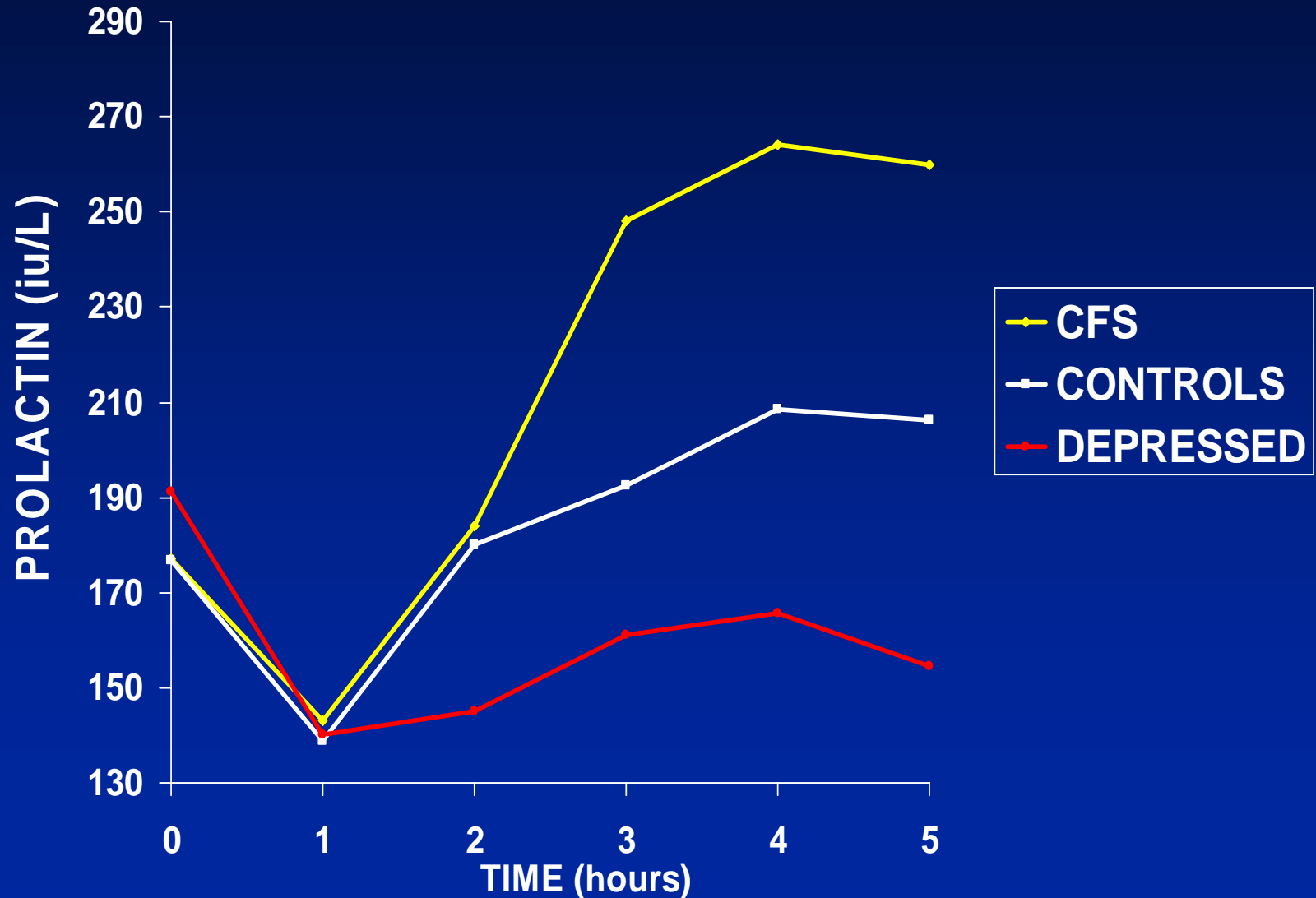
- CBT has biological effects, even in the presence of modest clinical effects in this sample
- CBT leads to normalisation of the HPA axis
- Most likely exerts HPA axis effects via normalisation of factors mediating HPA axis disturbance such as sleep, deconditioning, etc.

Conclusions re HPA axis

- HPA axis is changed in direction of
 - Low cortisol output
 - Blunted response to challenge
- Not a uniform change
 - Related to several factors
 - Occurs later in illness course
- Does have symptomatic significance
 - Maintaining factor
- Reversible by CBT

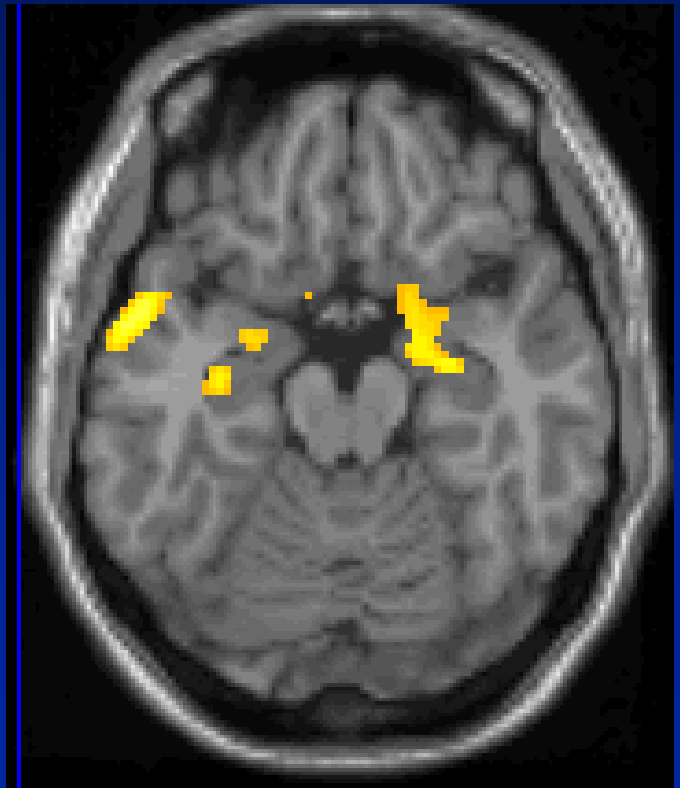
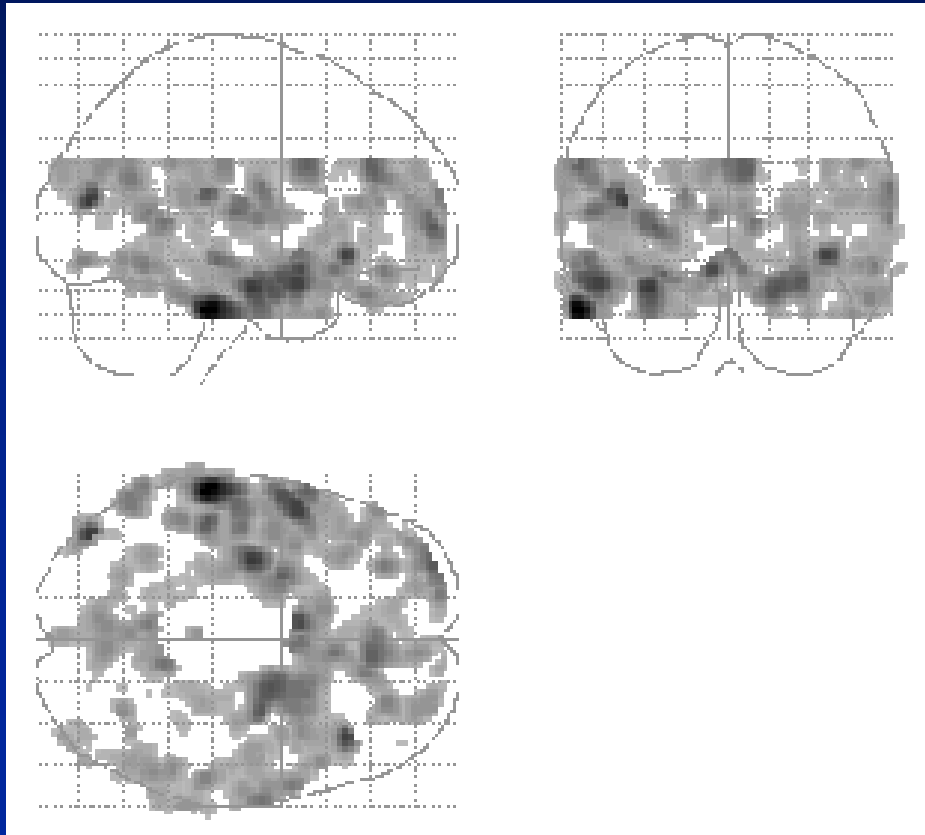
Serotonergic Function

Prolactin responses after 30mg D-fenfluramine



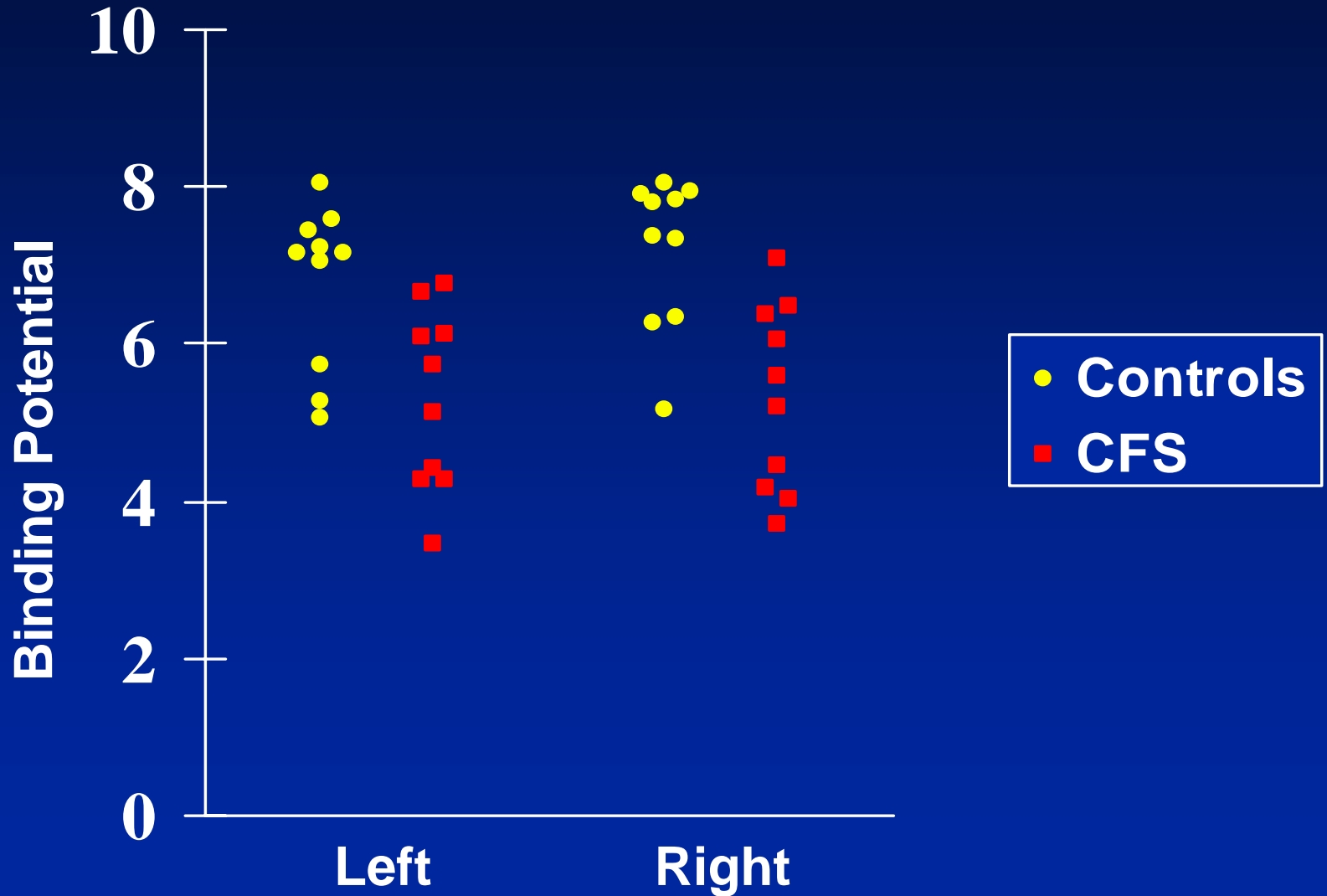
[11C]WAY-100635 in CFS

Areas of decreases in 5-HT_{1A}
binding in CFS v controls



SPM Analysis

Hippocampal 5-HT_{1A} Receptor Binding



In Summary

- Several emerging areas of interest that may be relevant in pathophysiology of CFS
- Understanding must be part of a multifactorial model including predisposing, precipitating and perpetuating factors: biological factors may operate at each of these levels
- Biological models of CFS are complementary to psychosocial models (as in all biopsychosocial medicine)
- Unlikely to be one biological process, and unclear where the boundary will lay between CFS and other fatigue states