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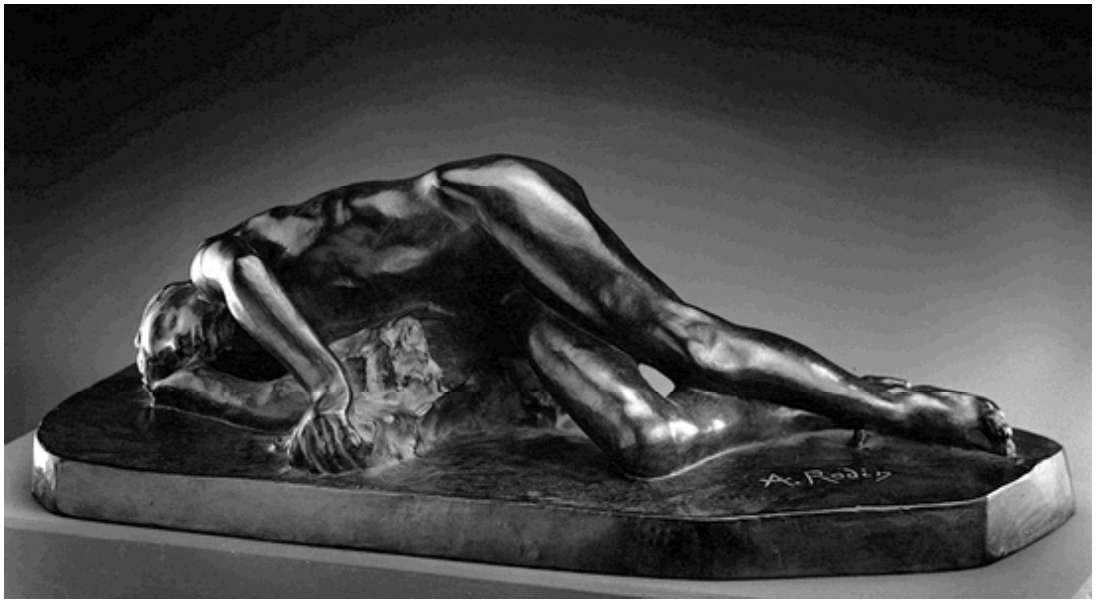
Chronic fatigue syndrome - the state of the art

Andrew Lloyd



Overview

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- What is fatigue?
- Diagnosis of chronic fatigue states
- Epidemiology
- Measurement of fatigue
- Pathophysiology of chronic fatigue syndrome
- Dubbo Infection Outcomes Study
- Treatment of chronic fatigue states

What is fatigue?

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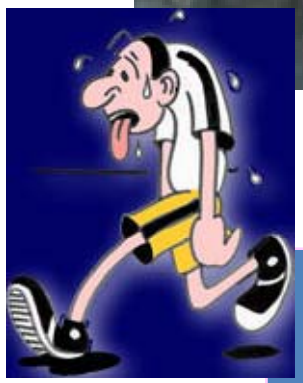
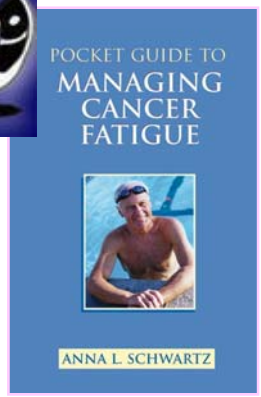
- Fatigue as a ‘sign’ (objective measure):
  - failure of force generation in the muscle
  - physiological or pathological
  - peripheral and central components

- Fatigue as a ‘symptom’:
  - everyday phenomenon
  - disease associated (infective, inflammatory, neurological, mood disorder,…)
  - ‘physical’ and ‘mental’ components





What is fatigue?

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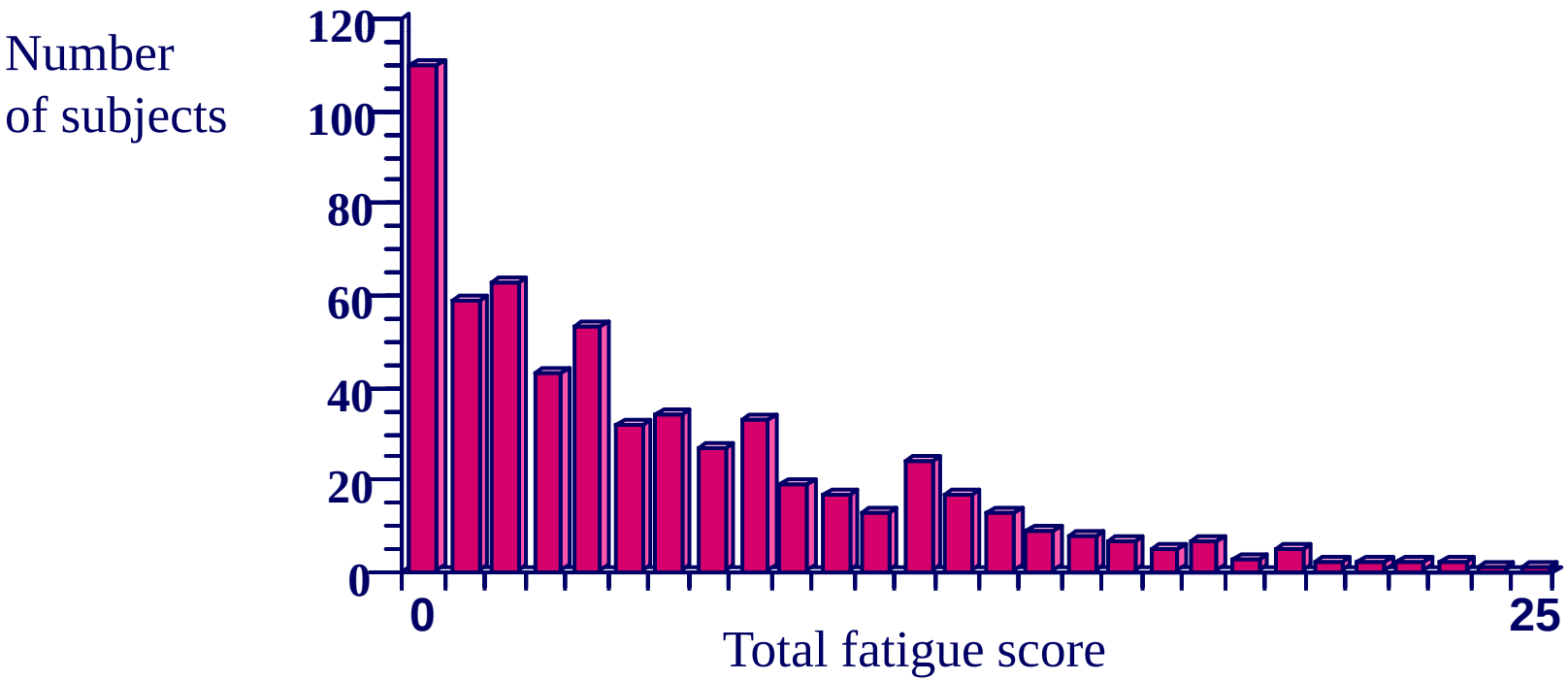
The symptom of fatigue exists as a continuum



What is chronic fatigue syndrome?

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Definition

- Unexplained, persistent or relapsing fatigue, that is:
  - of new, definite onset
  - not due to exertion
  - not relieved by rest
  - associated with a substantial reduction in daily activities

and

- Four or more of:
  - impaired short term memory or concentration
  - sore throat
  - tender lymph nodes
  - muscle pain
  - joint pain
  - headaches
  - unrefreshing sleep
  - post-exertional malaise

and

- Exclusion of medical and psychiatric disorders

Fukuda K et al. *Ann Intern Med* 1994; 121: 953-9.

What is major depression?

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Definition

- Depressed mood
- Loss of interest and pleasure in usual daily activities

and

- Five or more of:
  - appetite or weight change
  - sleep disturbance
  - activity disturbance
  - fatigue
  - self-reproach or guilt
  - poor concentration
  - morbid thoughts

- Exclusion of medical disorders

Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV

Fatigue-related disorders

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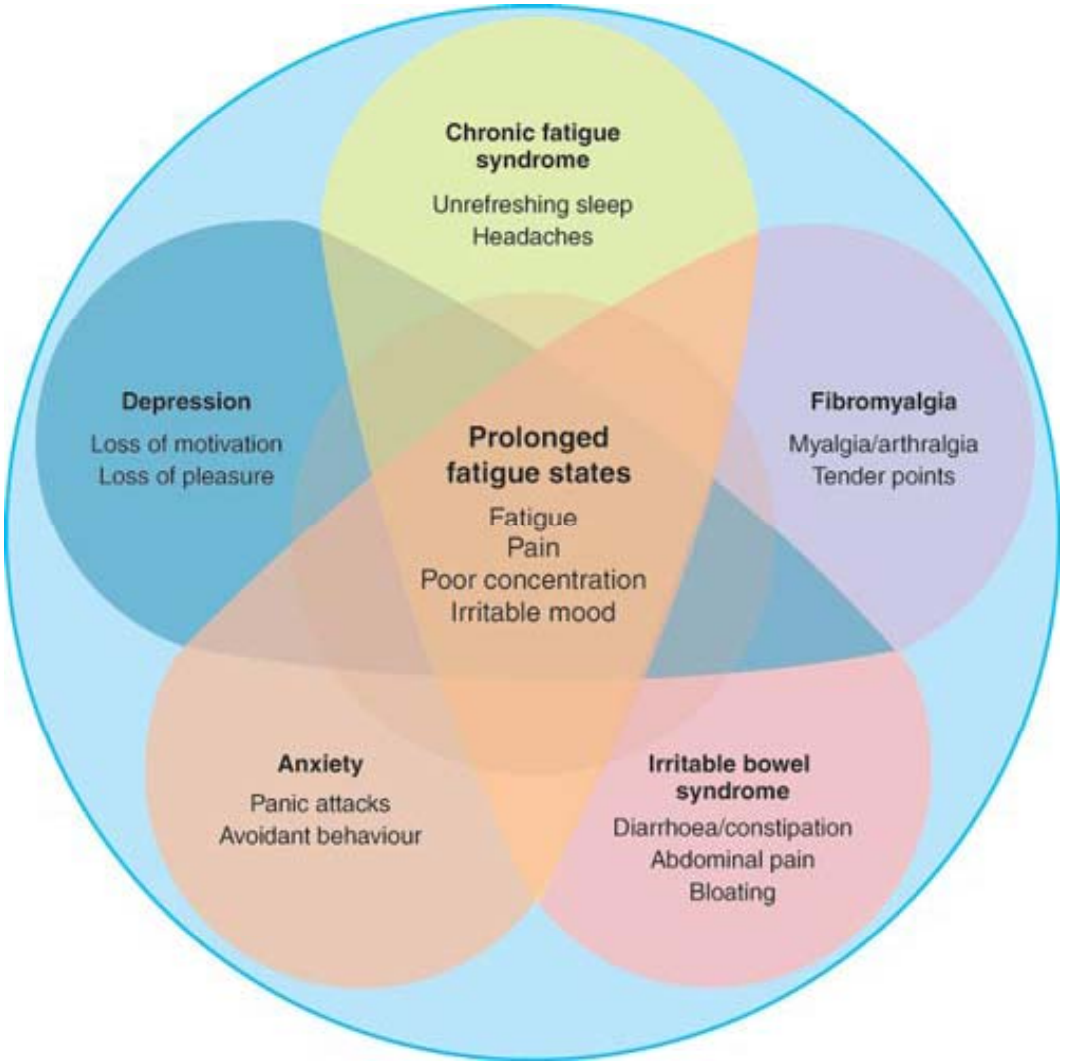

How common is chronic fatigue?

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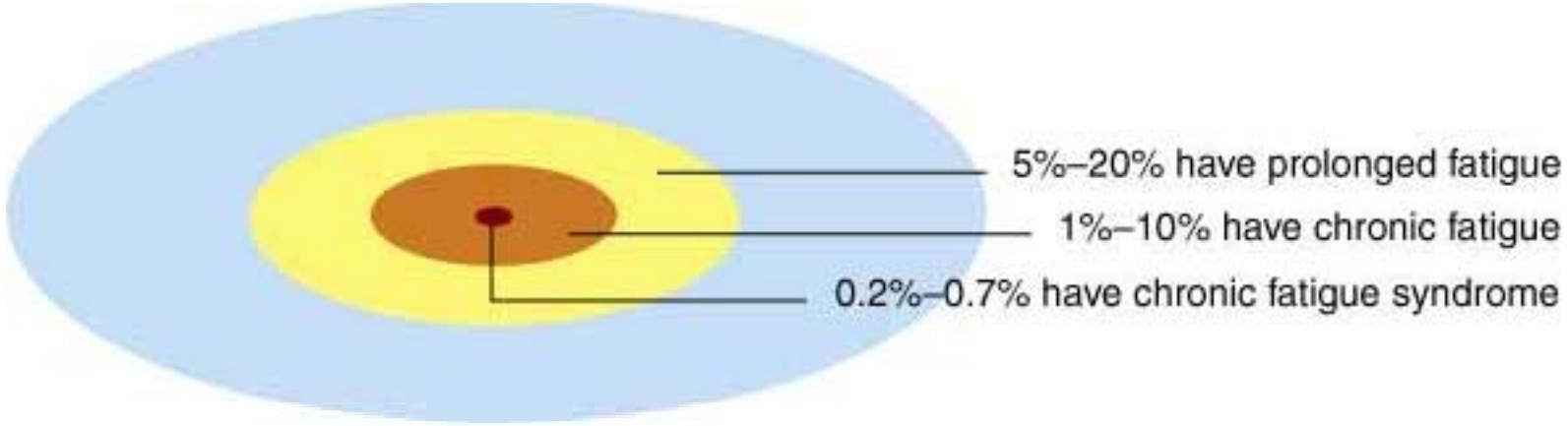
Prevalence estimates



Definitions:

- ***Prolonged fatigue*** — prolonged and disabling fatigue lasting at least one month.
- ***Chronic fatigue*** — prolonged and disabling fatigue lasting at least six months.
- ***Chronic fatigue syndrome*** — prolonged and disabling fatigue lasting at least six months, unexplained by other medical or psychological conditions.

Working Group Royal Australasian College of Physicians, including Lloyd A. Chronic fatigue syndrome - Clinical practice guidelines 2002. *Medical Journal of Australia* 2002;176:S17-55.

How can chronic fatigue be measured?

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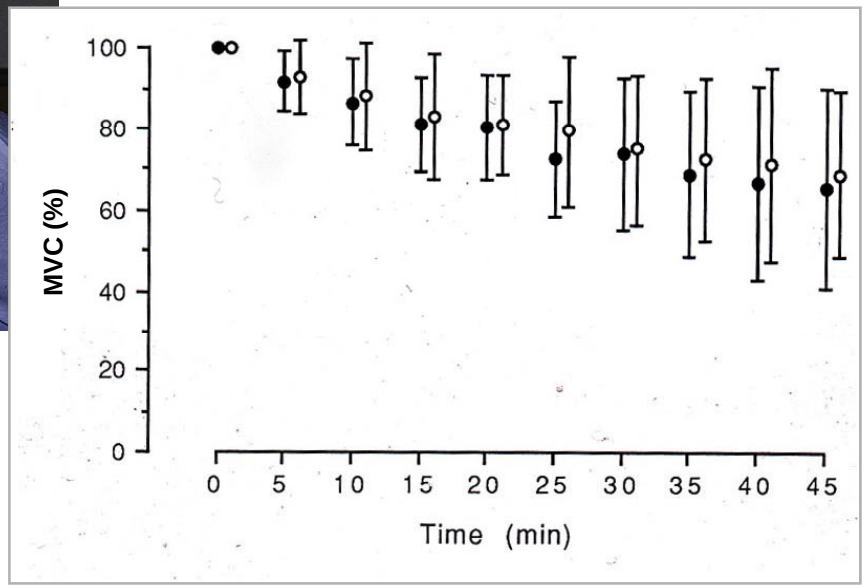
‘Neurophysiological’ fatigue: - a failure of force generation in the muscle



Lloyd A et al. Muscle strength, twitch properties, voluntary activation and perceived exertion in normal subjects and patients with chronic fatigue syndrome *Brain* 1991; 114: 85-98.

How can chronic fatigue be measured?

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Initials: ____ (First name, Surname) **Subject ID:** ____ (Interviewer to complete)

Date of birth: __ / __ / ____ (Day / Month / Year) **Time of day:** __ : __ (Please use 24hr time)

Today's date: __ / __ / ____ (Day / Month / Year) **Sex:** male female (Circle one)

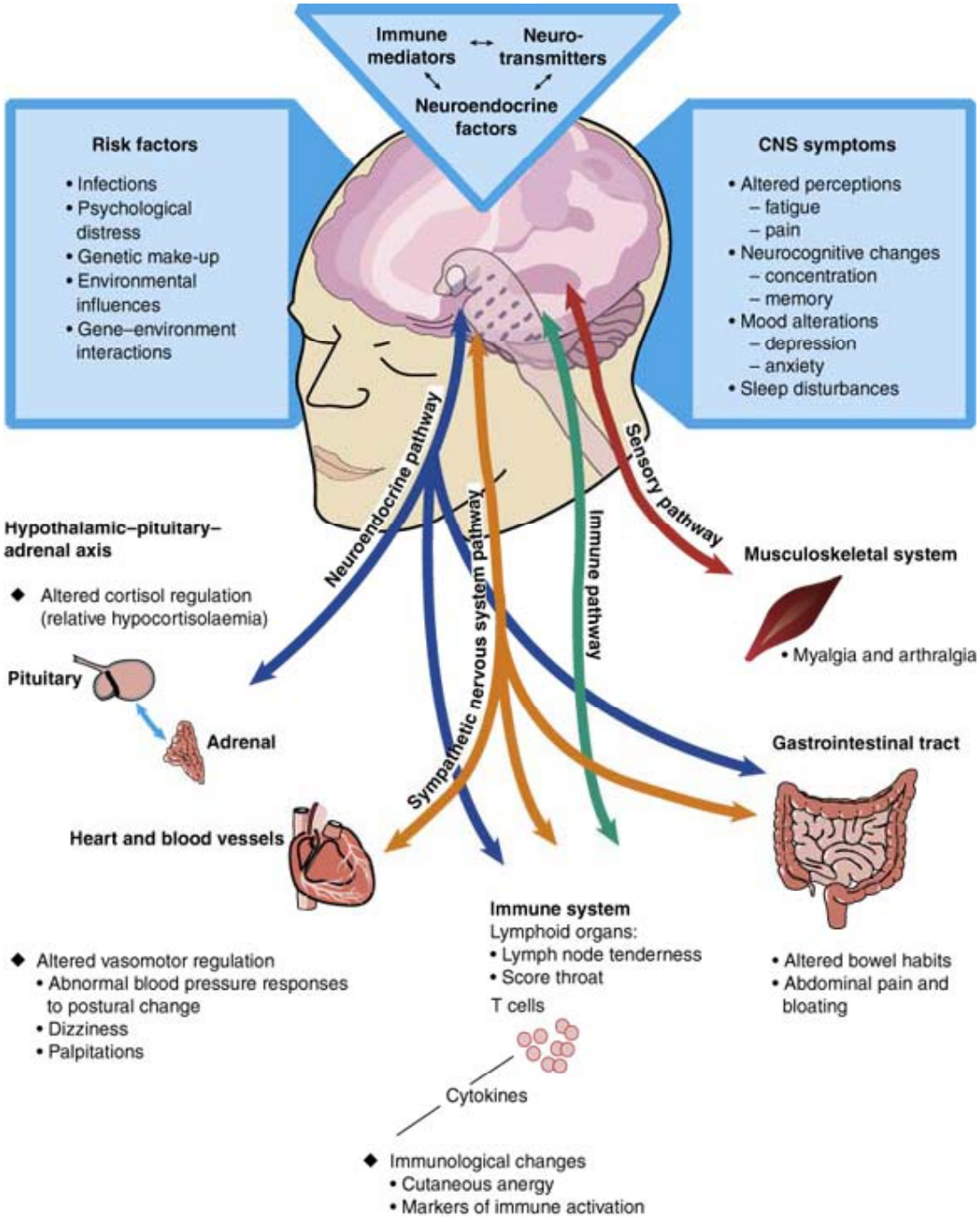
SPHERE Questionnaire

We would like to know about your general health. For ALL questions, please tick, cross or colour the circle that most closely matches your response. There are no right or wrong answers. Please answer ALL questions.

Over **the past few weeks** have you been troubled by:

	Never or some of the time	A good part of the time	Most of the time
1. Headaches?	○	○	○
2. Feeling irritable or cranky?	○	○	○
3. Poor memory?	○	○	○
4. Pains in your arms or legs?	○	○	○
5. Joint pain?	○	○	○
6. Waking up tired?	○	○	○
7. Rapidly changing moods?	○	○	○
8. Fainting spells?	○	○	○
9. Nausea?	○	○	○
10. Arms or legs feeling heavy?	○	○	○
11. Weak muscles?	○	○	○
12. Muscle pain after activity?	○	○	○
13. Needing to sleep longer?	○	○	○
14. Prolonged tiredness after activity?	○	○	○
15. Poor sleep?	○	○	○
16. Poor concentration?	○	○	○
17. Tired muscles after activity?	○	○	○
18. Feeling nervous or tense?	○	○	○
19. Feeling unhappy & depressed?	○	○	○
20. Feeling constantly under strain?	○	○	○
21. Everything getting on top of you?	○	○	○
22. Being unable to overcome difficulties?	○	○	○
23. Losing confidence?	○	○	○
24. Getting annoyed easily?	○	○	○
25. Dizziness?	○	○	○
26. Feeling tired after rest or relaxation?	○	○	○
27. Feeling lost for the word?	○	○	○
28. Diarrhoea or constipation?	○	○	○
29. Gas or bloating?	○	○	○
30. Fevers?	○	○	○
31. Back pain?	○	○	○
32. Sore throat?	○	○	○
33. Numb or tingling sensations?	○	○	○
34. Feeling frustrated?	○	○	○

The pathophysiology of unexplained fatigue



XMRV????

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Dubbo Infection Outcomes Study - DIOS

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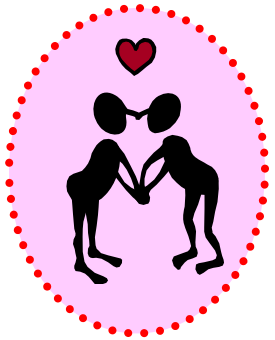
- Epstein-Barr virus:
  - DNA virus
  - infectious mononucleosis in young adults
  - fever, pharyngitis, lymphadenopathy
- Ross River virus:
  - RNA virus
  - mosquito-borne seasonal infection
  - rash and arthritis
- Q fever:
  - Intracellular bacterium *Coxiella burnetii*
  - zoonotic infection
  - severe acute illness with hepatitis and pneumonia



Characteristics of the DIOS cohort

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	EBV	RRV	QF	Unconf.
Sample size (n)	68	60	43	82
Age (mean; yrs)	22	40	40	38
Sex (% female)	57	45	14	44
Education (%<10 yrs)	23	43	51	44
Employed (%)	45	81	95	76
Student (%)	49	2	3	10

Hickie I et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *British Medical Journal* 2006; 33:575-80

DIOS - Natural history of illness

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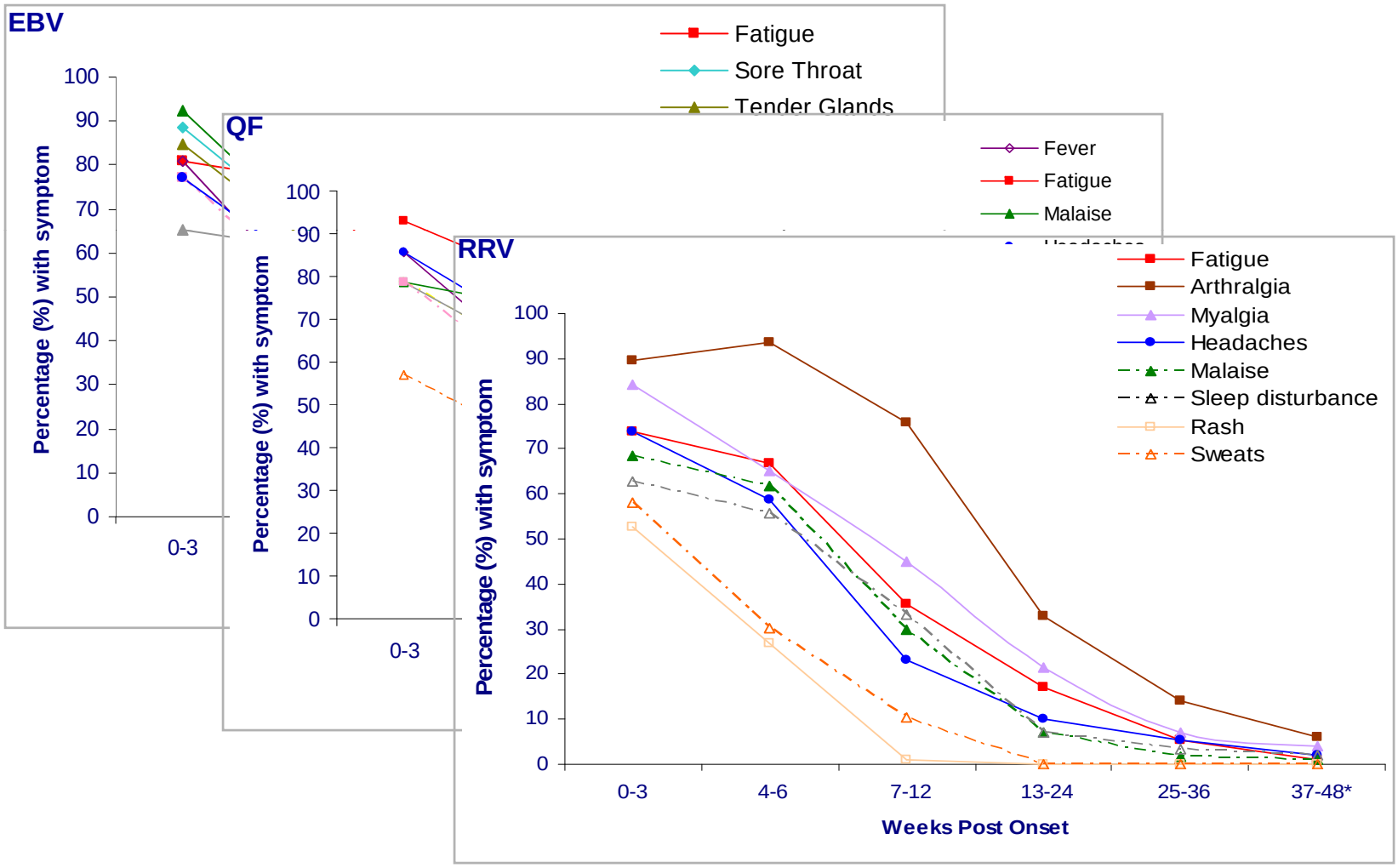

Post-infective fatigue (PIFS) outcomes

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	PIFS (% of subjects who are cases)			
Cohort	*Baseline*	*3 months*	*6 months**	*12 months*
EBV (n=68)	59	19	10	6
RRV (n=60)	58	23	15	5
QF (n=43)	78	16	13	5
Unconfirmed (n=82)	62	16	10	6

*Also met diagnostic criteria for CFS

Illness severity index - DIOS

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Symptom	loading
Tired after rest	0.743
Waking up tired	0.737
Arms or legs heavy	0.735
Weak muscles	0.733
Tiredness after activity	0.720
Frustrated	0.685
Needing more sleep	0.671
Irritable or cranky	0.652
Muscle pain after activity	0.649
Pains in your arms/legs	0.636
Easily annoyed	0.610
Joint pain	0.584
Poor sleep	0.544
Poor concentration	0.541
Fevers	0.513
Myalgia	0.496
Excessively exhausted	0.421
Constantly under strain	0.415
Headaches	0.397
'Chills' or shivers	0.340
No appetite	0.312
Malaise	0.293

- Principal components analysis (PCA):
  - n=321 Caucasian subjects
- Correlation with disability:
  - days out of role (p=0.001)
  - days in bed (p=0.001)
- Age, sex, infection type did not predict severity scores (p>0.4)

Predictors of prolonged illness

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The biological basis of the behaviour of sick animals (Hart 1988)

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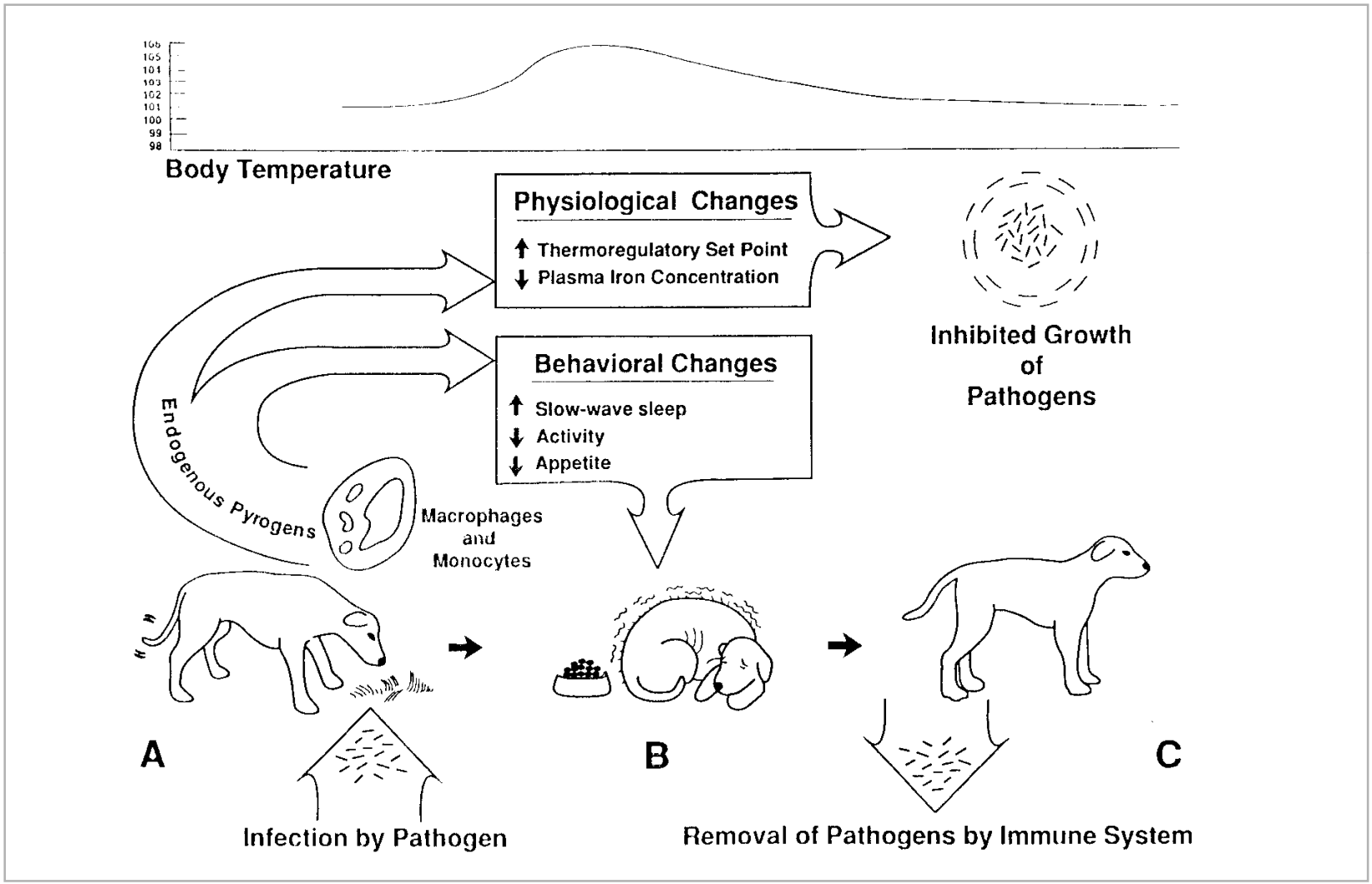

Acute sickness response

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- Stereotyped symptom set associated with infection or inflammation:
  - fevers, sweats, musculo-skeletal pain,
  - neurocognitive difficulties, anorexia, hyperalgesia
  - social withdrawl, mood disturbance
- Immunologically (cytokine)-triggered
  - animal studies
  - cytokine administration in humans
  - correlative studies in natural infection
- Neurologically-mediated

Cytokine production and acute sickness response

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Correlations between cytokine production and symptoms of the acute sickness response in acute Q fever (n=22) (Spearman's r values)				
	IL-1β		IL-6	
Reported Symptoms	Serum	Medium	Serum	Medium
Fever	.30	**.44**	.30	.20
Malaise	.22	**.53**	.04	.43
Anorexia	.35	.38	.20	.18
Arthralgia	.21	**.56**	.02	.42
Myalgia	.08	**.56**	.01	**.47**
Excessive fatigue	.18	**.47**	-.07	**.45**
Tired/heavy muscles	.14	**.52**	-.13	**.60**
Headache	.09	.38	.03	**.57**
Poor concentration	-.14	.32	.07	**.54**
Depression	.00	.38	.02	**.51**
Anhedonia	.30	**.62**	.25	**.48**

Vollmer-Conna et al. Production of pro-inflammatory cytokines correlates with symptoms of acute sickness behaviour in humans. *Psychological Medicine* 2004: 34: 1289-1297.

Cytokine production in PIFS

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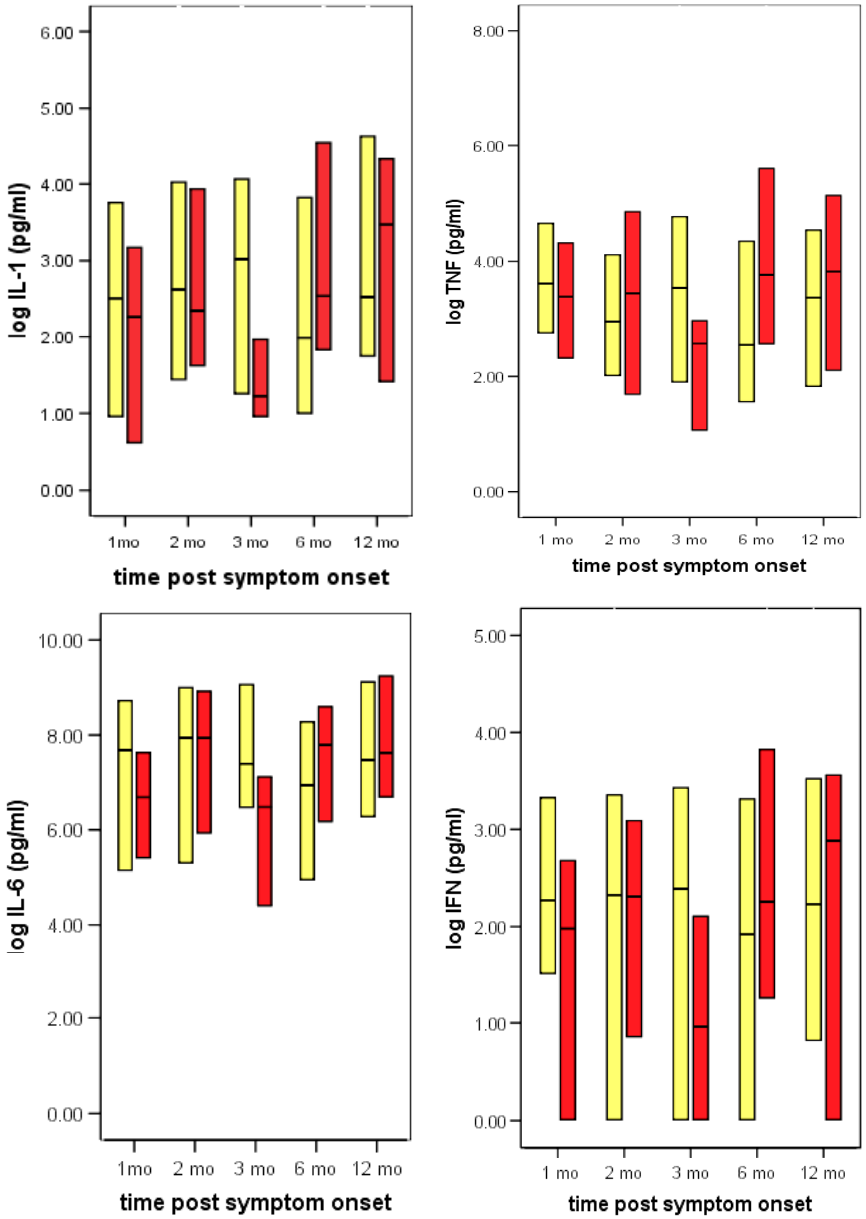

Vollmer-Conna U, et al. Post-infective fatigue syndrome is not associated with altered cytokine production. *Clinical Infectious Diseases* 2007; 45:732-735.

Genetic determinants of illness severity

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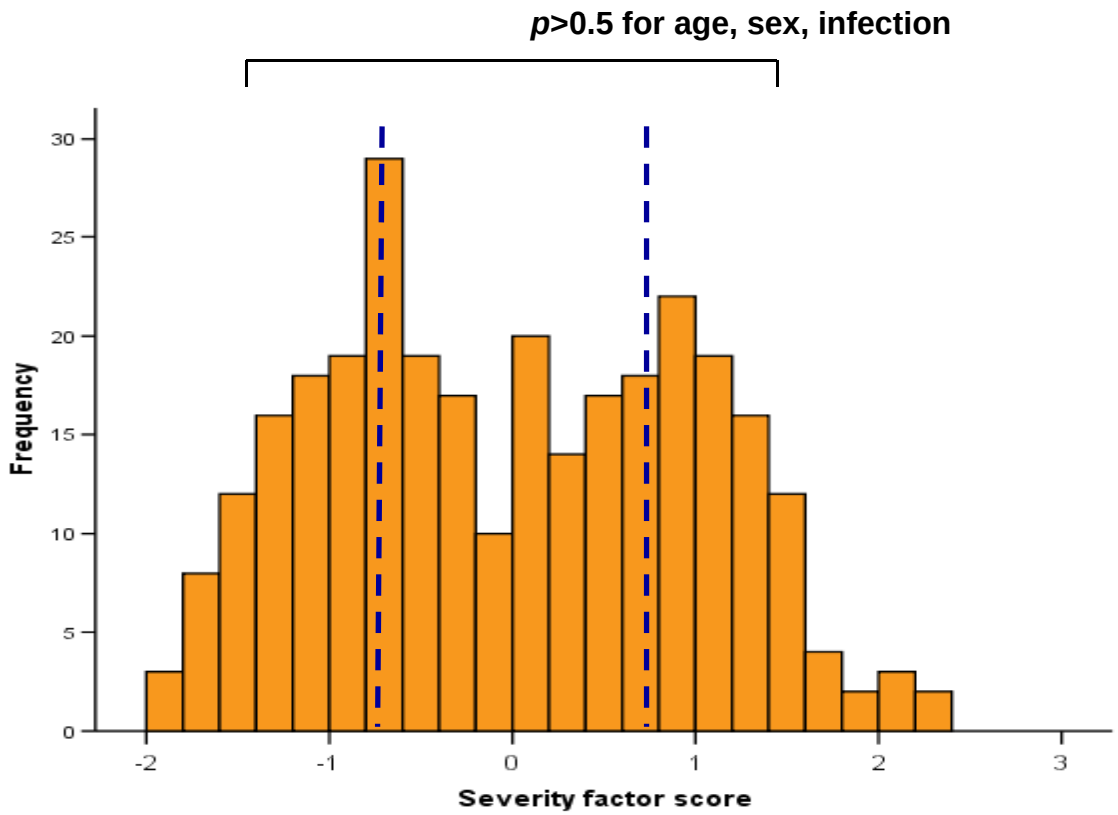
- Candidate gene studies - functional SNPs:
  - Immunological: IL-6, TNF-α, IL-10, IFN-γ
  - Neurobehavioural: COMT, 5HTT, MAO-A, NPY



Candidate gene study - results

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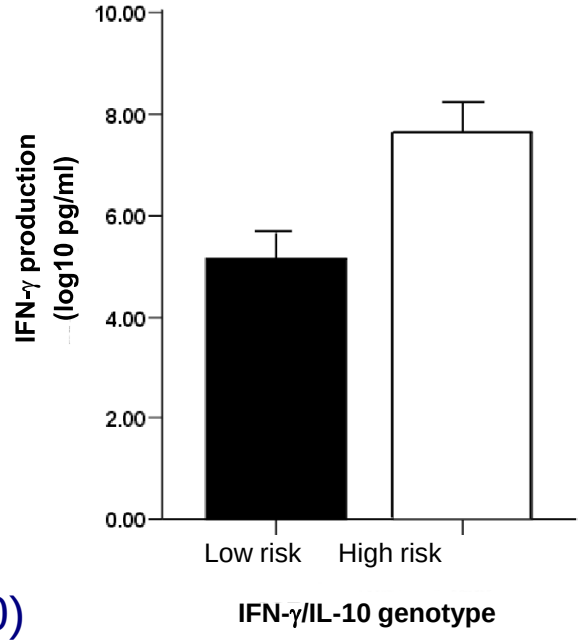
- Hardy Weinberg equilibrium
- *High* illness severity:
  - IFN-γ +874: TT (*p*=0.04; OR 1.9)
  - NPY -399 TT (*p*=0.07; OR 1.9)
  - NPY +1201 GG (*p*=0.04; OR 2.1)
  - NPY +5325 CC (*p*=0.05; OR 1.9)
- *Low* illness severity:
  - IL-10 -592 CC (*p*=0.03; OR 1.9)
- High illness severity and combined genotype
  - IFN-γ TT / IL-10 CC (*p*=0.01; OR 3.2)
  - IFN-γ TT / NPY +1201 GG (p=0.001; OR 11.0)



Genetic determinants of illness duration

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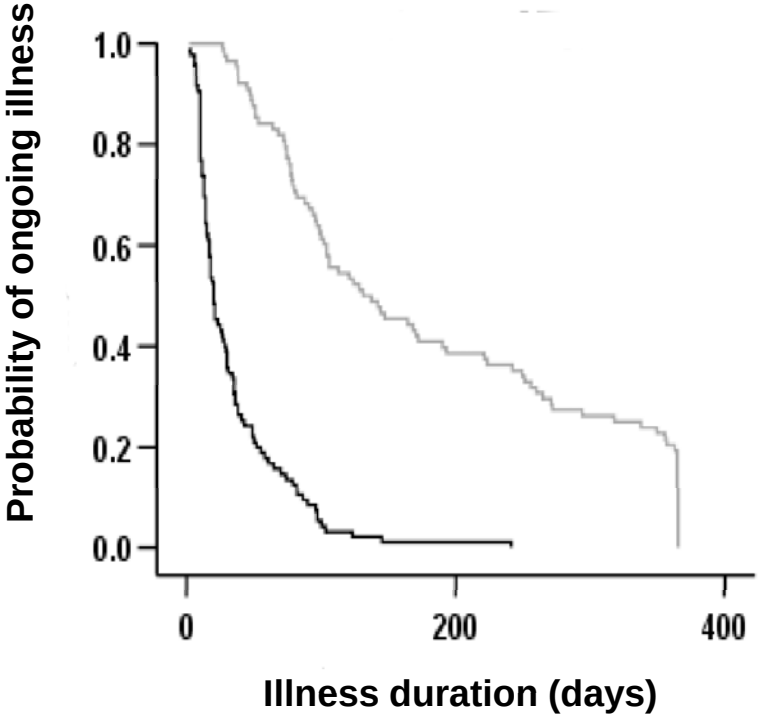
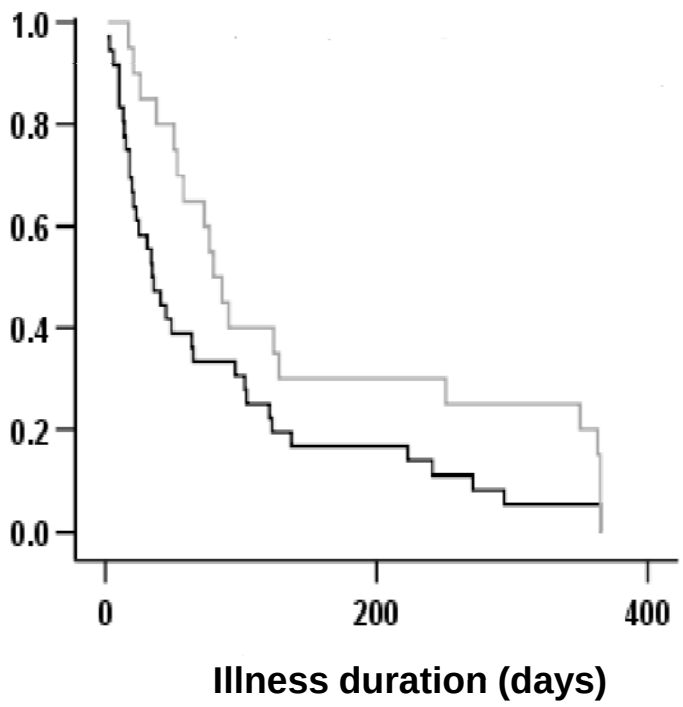
Acute illness severity



High risk IFN-γ / IL-10 genotype



Summary

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- PIFS is not mediated by ongoing cytokine production in the periphery
- Severity of the acute infection is the major predictor of prolonged fatigue
- Genetically-determined variations in immune response & neurobehavioural genes predict illness severity and duration
- *Hypothesis:* Persistent microglial cell activation and local mediator production mediate PIFS in genetically predisposed individuals

CFS - how should it be treated?

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Double-blinded placebo controlled trials (n~80)

Antivirals:

- Acyclovir
- Valganciclovir

Immunological agents:

- transfer factor
- intravenous immunoglobulin
- corticosteroids

Anti-depressants:

- moclobemide
- fluoxetine
- phenelzine
- segeline

Metabolic agents:

- fludrocortisone
- magnesium sulphate

Centrally-active agents:

- galantamine
- modafinil
- L-carnitine

Vitamins:

- Vitamin B12
- Co-enzyme Q10

CFS - how should it be treated?

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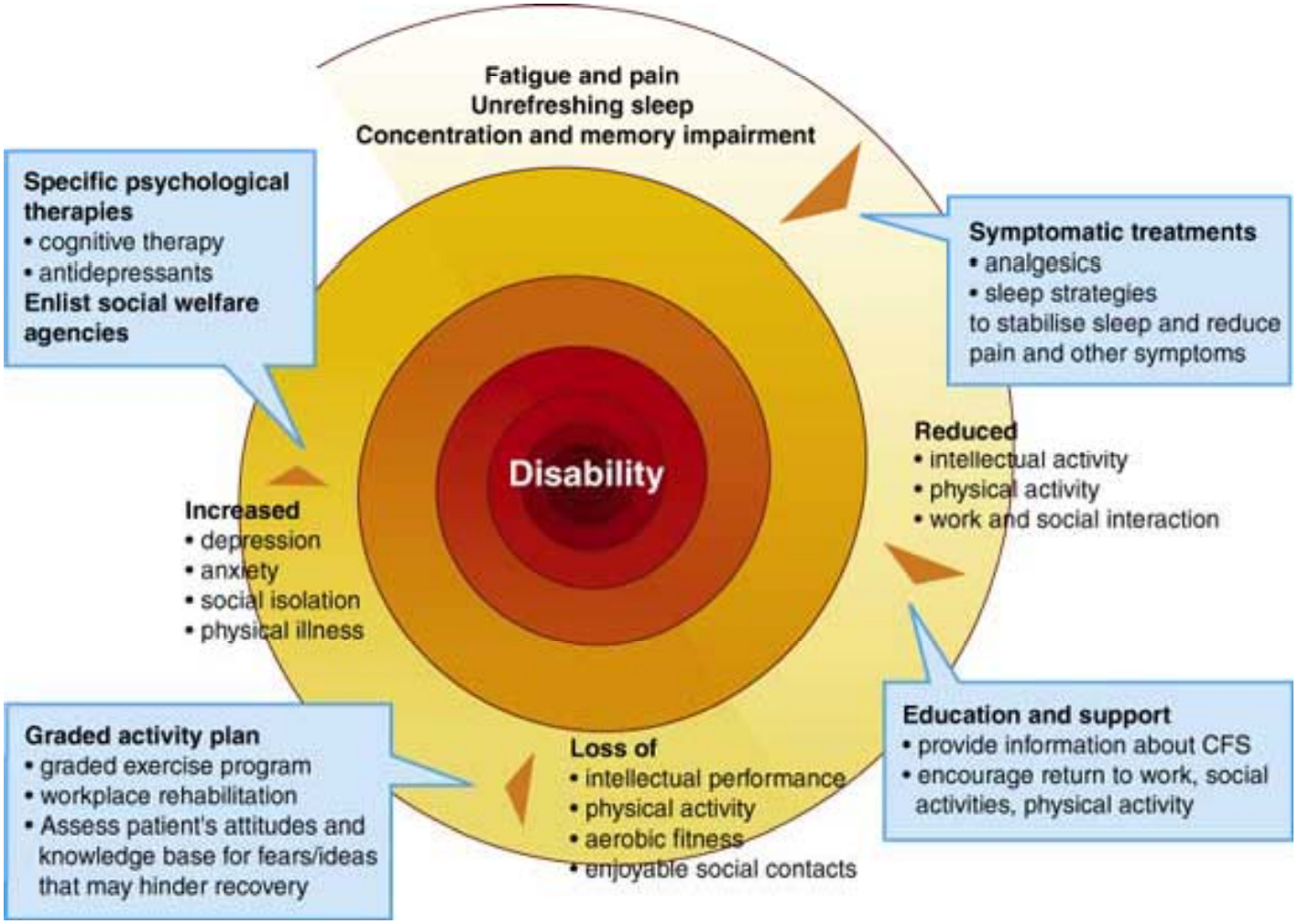

Acknowledgements

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