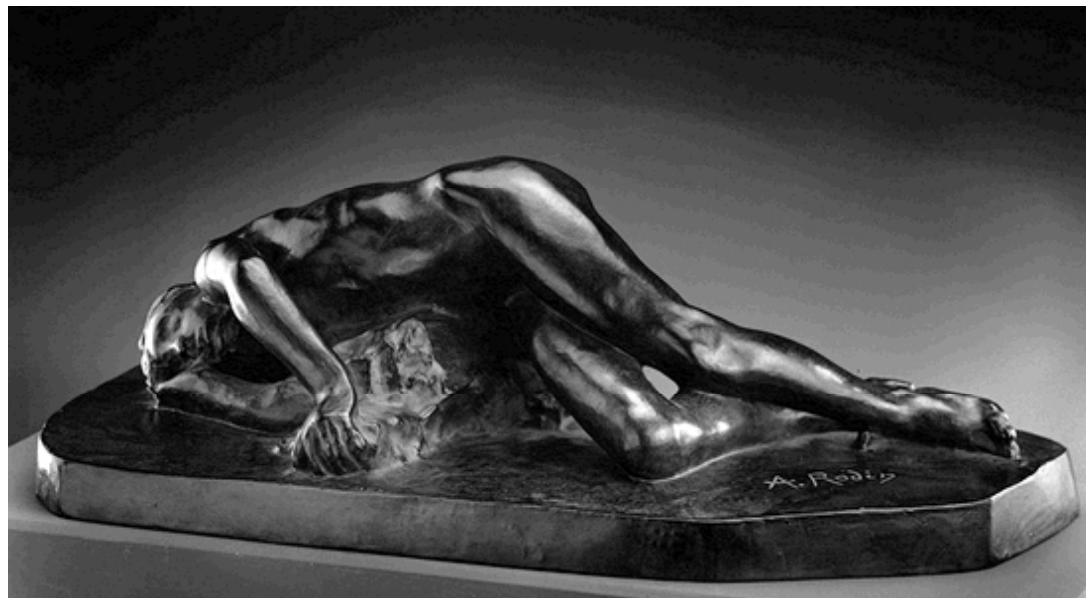




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Chronic fatigue syndrome - the state of the art

Andrew Lloyd





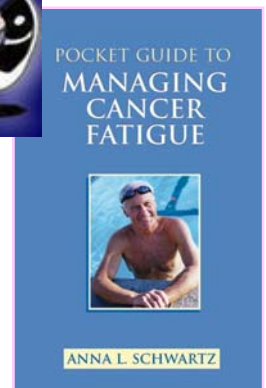
Overview

- 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?

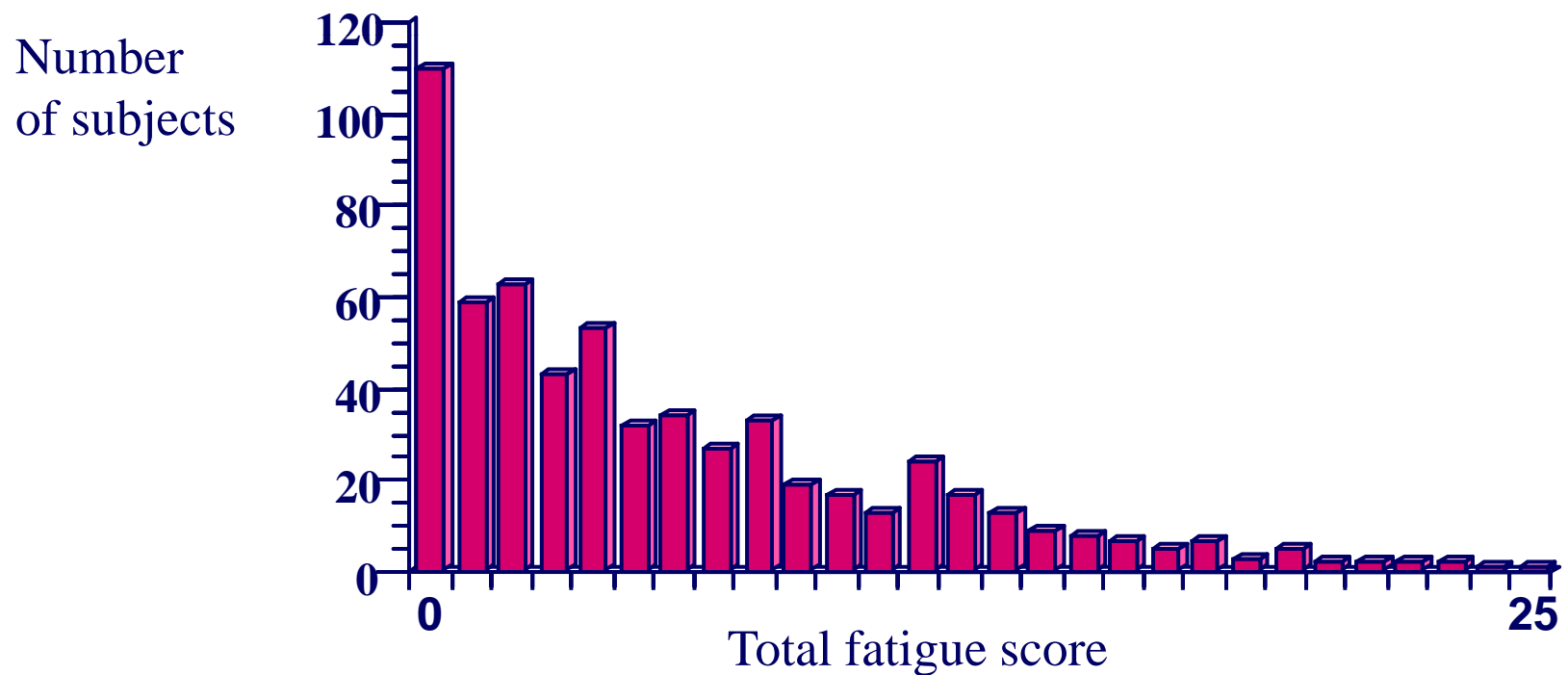
- Fatigue as a 'sign' (objective measure):
 - failure of force generation in the muscle
 - physiological or pathological
 - peripheral and central components
- Fatigue as a 'symptom':
 - everyday phenomenon
 - disease associated (infective, inflammatory, neurological, mood disorder,...)
 - 'physical' and 'mental' components





What is fatigue?

The symptom of fatigue exists as a continuum





What is chronic fatigue syndrome?

Definition

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



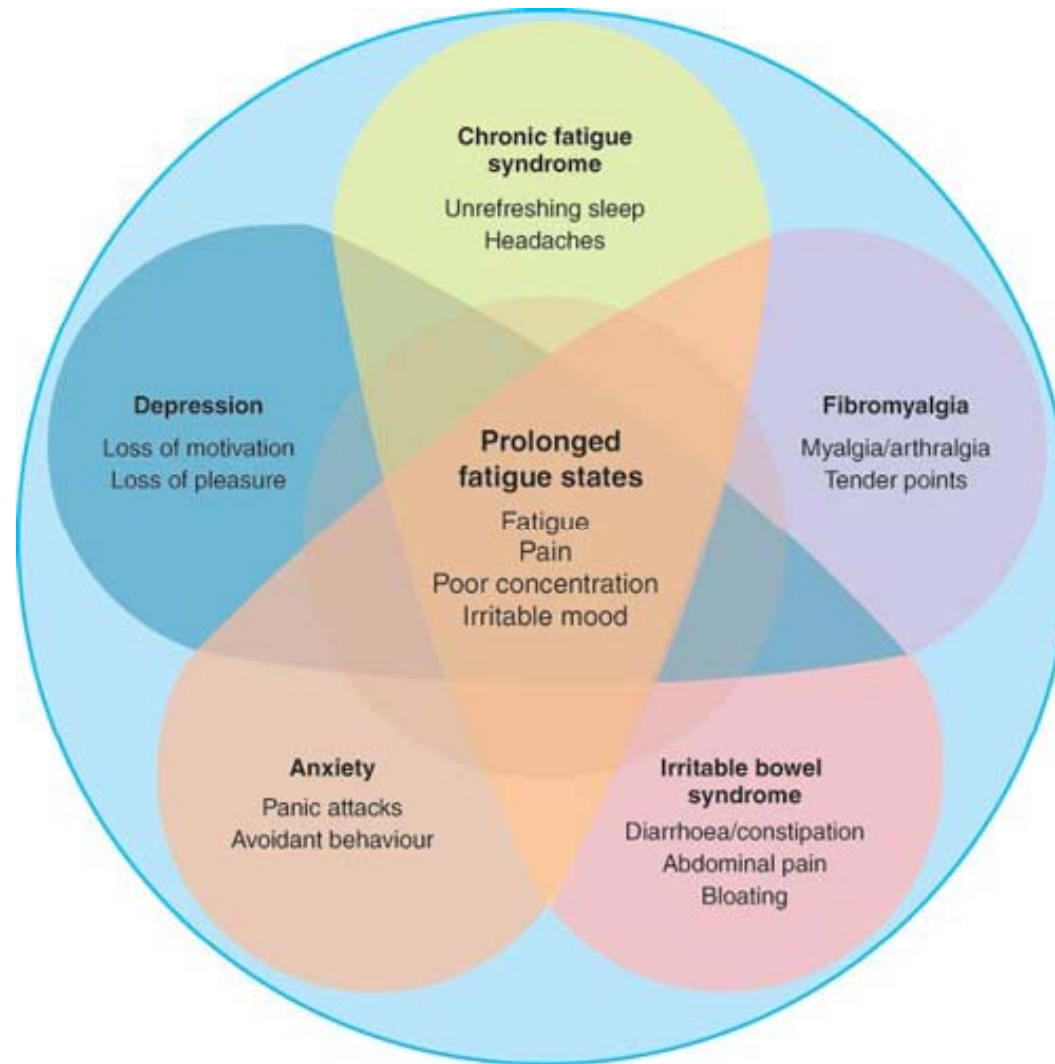
What is major depression?

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



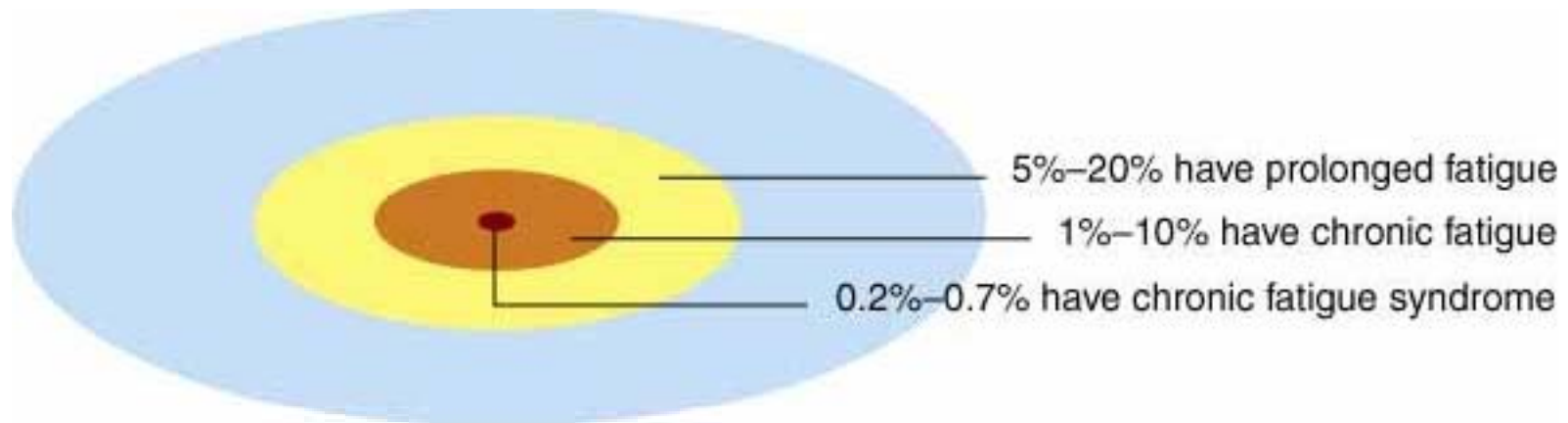
Fatigue-related disorders








How common is chronic fatigue?

Prevalence estimates



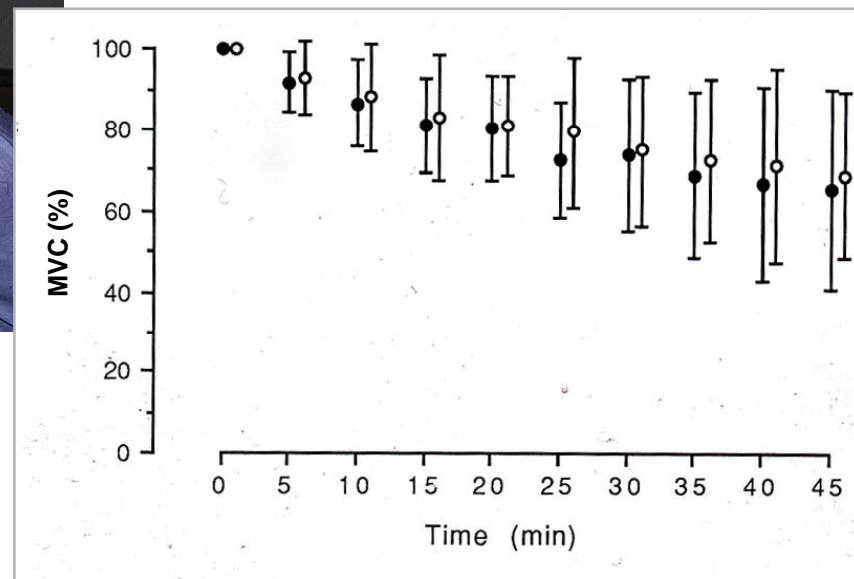
Definitions:

-  **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.



How can chronic fatigue be measured?

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



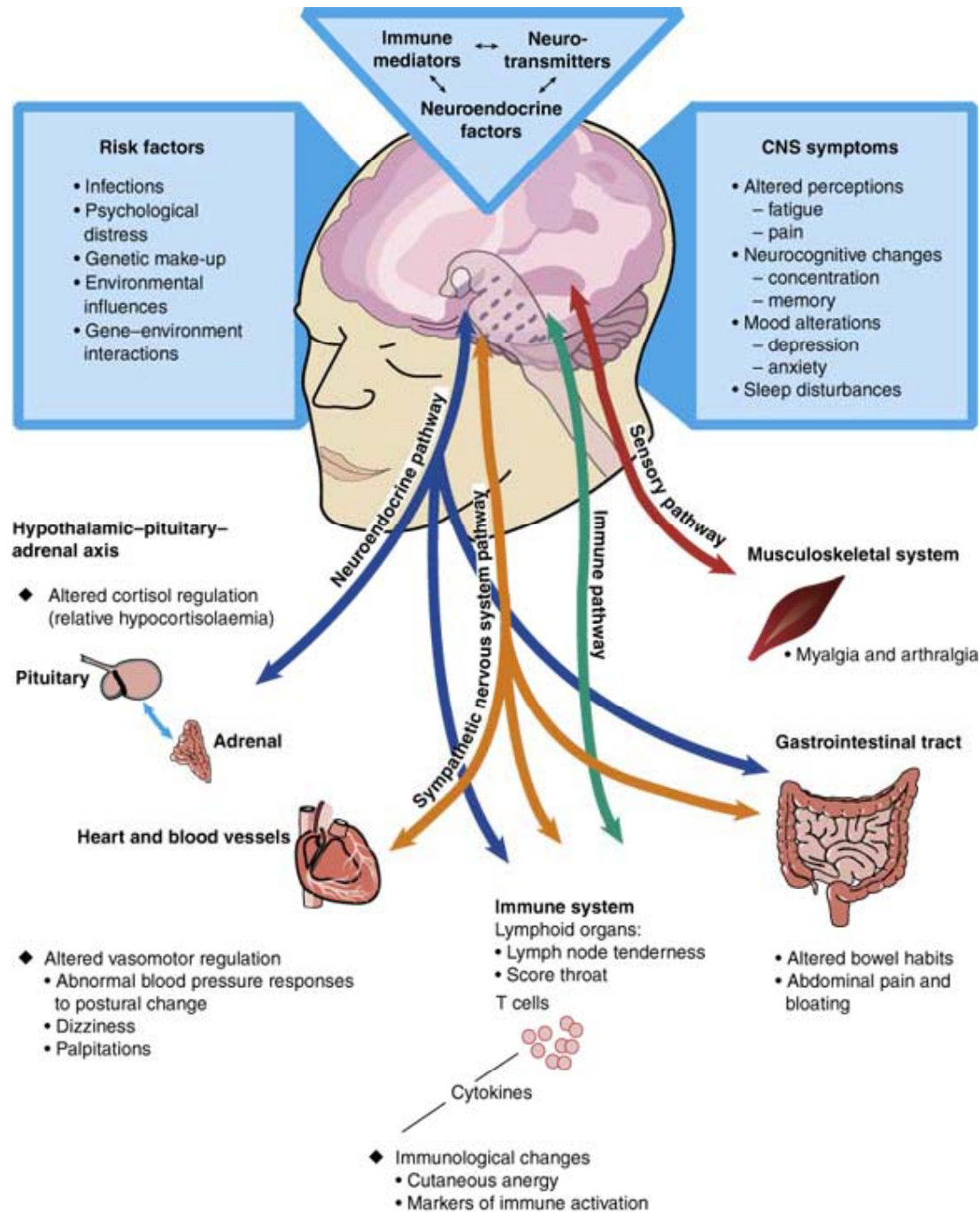
Lloyd A et al. Muscle strength, twitch properties, voluntary activation and perceived exertion in normal subjects and patients with chronic fatigue syndrome *Brain* 1991; 114: 85-98.



How can chronic fatigue be measured?

Initials: [] [] [] []			Subject ID: [] [] [] [] [] []				
First name Surname			Interviewer to complete				
Date of birth: [] / [] / [] [] [] []			Time of day: [] : [] []				
Day Month Year			Please use 24hr time				
Today's date: [] / [] / [] [] [] []			Sex: male female				
Day Month Year			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		Never or some of the time	A good part of the time	Most of the time
1. Headaches?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	18. Feeling nervous or tense?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Feeling irritable or cranky?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	19. Feeling unhappy & depressed?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Poor memory?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	20. Feeling constantly under strain?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Pains in your arms or legs?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	21. Everything getting on top of you?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Joint pain?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	22. Being unable to overcome difficulties?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Waking up tired?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	23. Losing confidence?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Rapidly changing moods?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	24. Getting annoyed easily?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Fainting spells?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	25. Dizziness?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Nausea?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	26. Feeling tired after rest or relaxation?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Arms or legs feeling heavy?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	27. Feeling lost for the word?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Weak muscles?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	28. Diarrhoea or constipation?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Muscle pain after activity?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	29. Gas or bloating?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Needing to sleep longer?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	30. Fevers?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. Prolonged tiredness after activity?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	31. Back pain?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. Poor sleep?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	32. Sore throat?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. Poor concentration?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	33. Numb or tingling sensations?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17. Tired muscles after activity?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	34. Feeling frustrated?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

The pathophysiology of unexplained fatigue



XMRV????



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QuickTime™ and a
decompressor
are needed to see this picture.

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XMRV????



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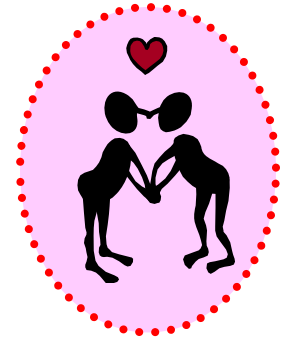
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Dubbo Infection Outcomes Study - DIOS



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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



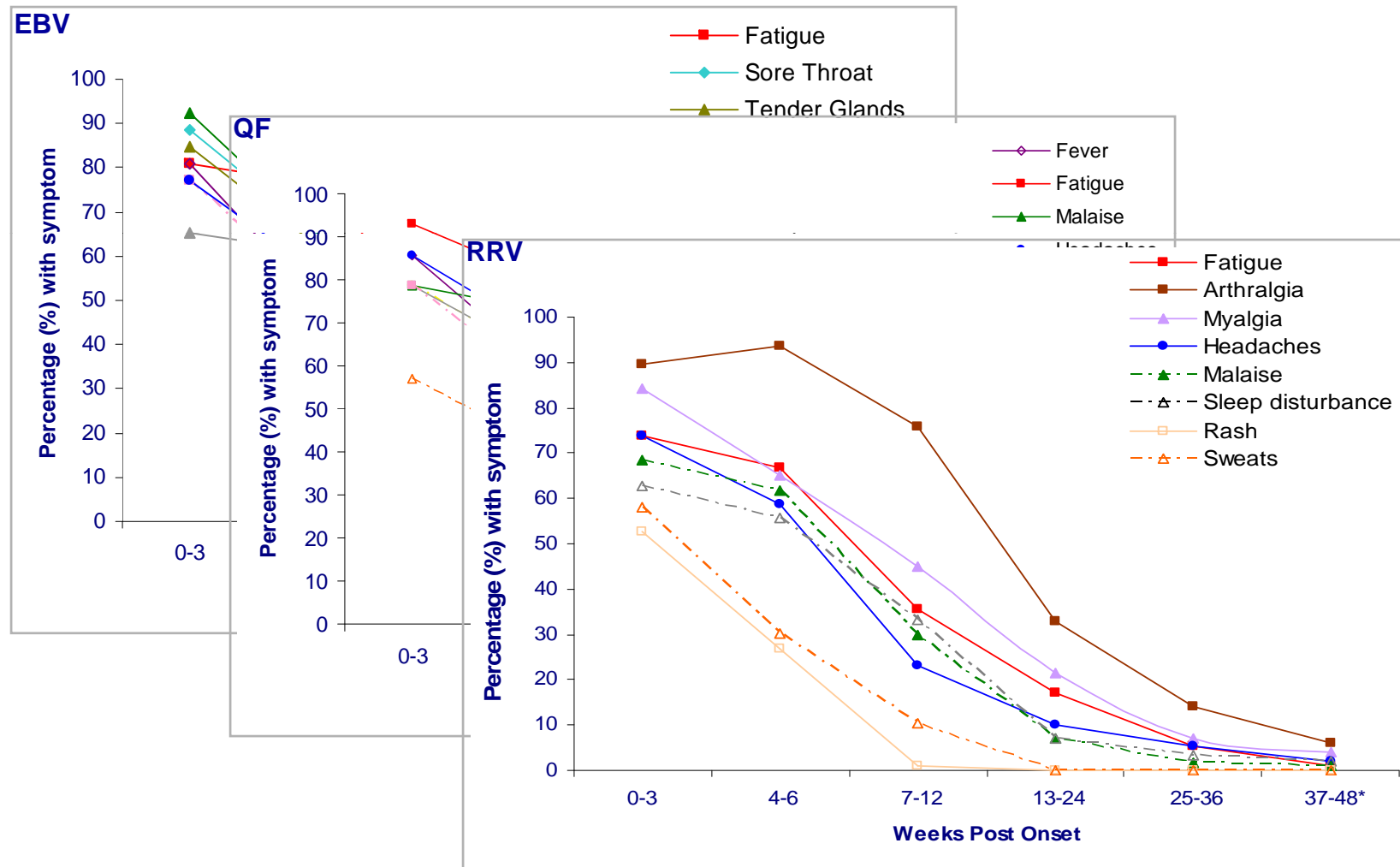


Characteristics of the DIOS cohort

	<u>EBV</u>	<u>RRV</u>	<u>QF</u>	<u>Unconf.</u>
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



DIOS - Natural history of illness





Post-infective fatigue (PIFS) outcomes

PIFS (% of subjects who are cases)

Cohort	<i>Baseline</i>	<i>3 months</i>	<i>6 months*</i>	<i>12 months</i>
<i>EBV (n=68)</i>	59	19	10	6
<i>RRV (n=60)</i>	58	23	15	5
<i>QF (n=43)</i>	78	16	13	5
<i>Unconfirmed (n=82)</i>	62	16	10	6

*Also met diagnostic criteria for CFS



Illness severity index - DIOS

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



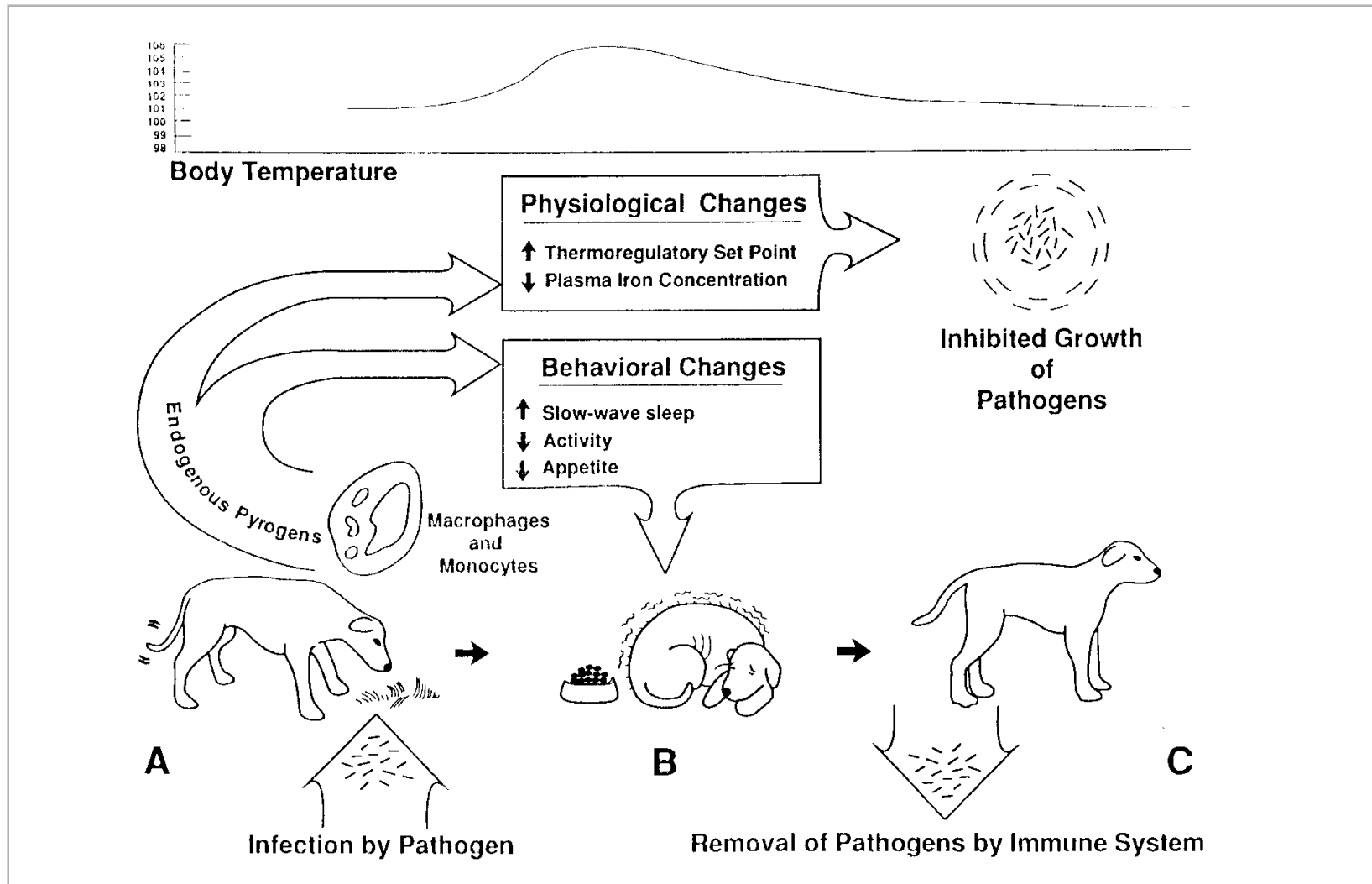
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The biological basis of the behaviour of sick animals (Hart 1988)



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Acute sickness response

- Stereotyped symptom set associated with infection or inflammation:
 - fevers, sweats, musculo-skeletal pain,
 - neurocognitive difficulties, anorexia, hyperalgesia
 - social withdrawal, 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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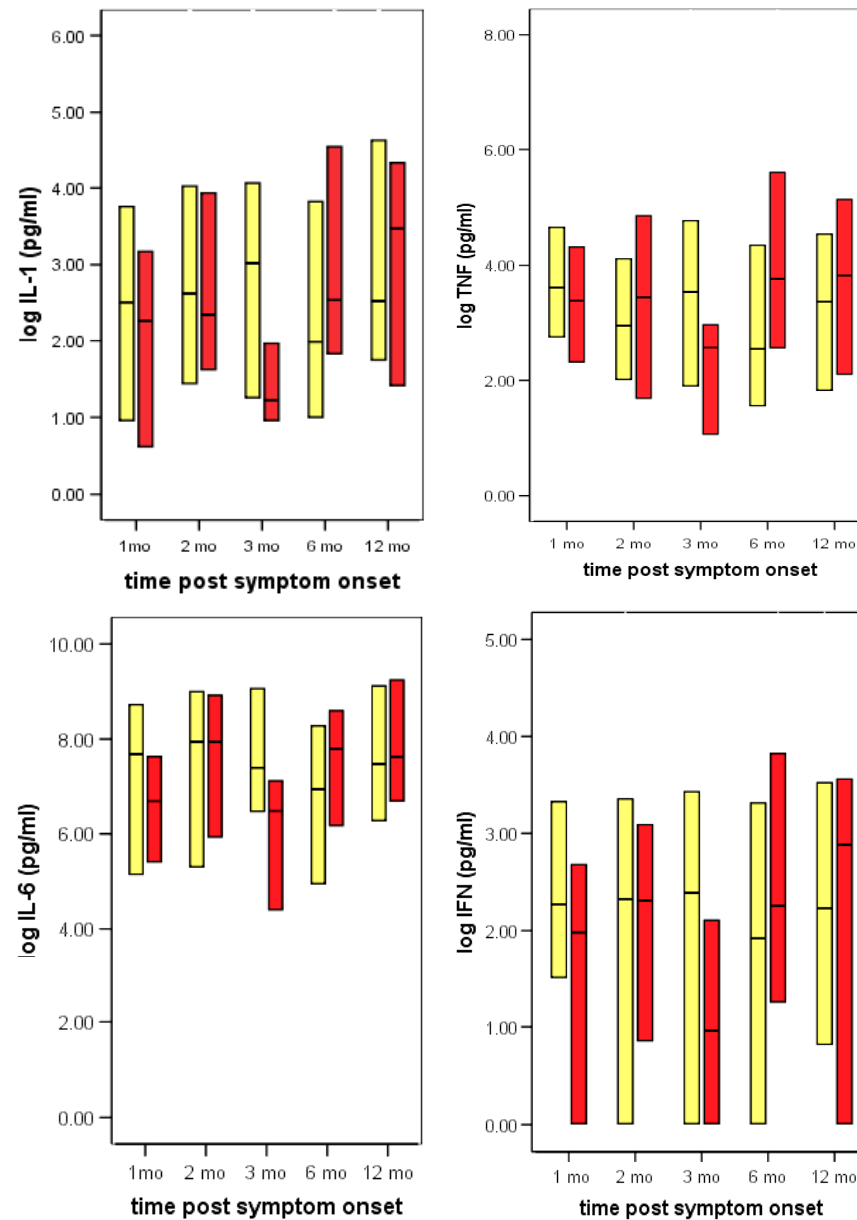
Correlations between cytokine production and symptoms of the acute sickness response in acute Q fever (n=22) (Spearman's r values)				
Reported Symptoms	IL-1 β		IL-6	
	Serum	Medium	Serum	Medium
Fever	.30	.44	.30	.20
Malaise	.22	.53	.04	.43
Anorexia	.35	.38	.20	.18
Arthralgia	.21	.56	.02	.42
Myalgia	.08	.56	.01	.47
Excessive fatigue	.18	.47	-.07	.45
Tired/heavy muscles	.14	.52	-.13	.60
Head ache	.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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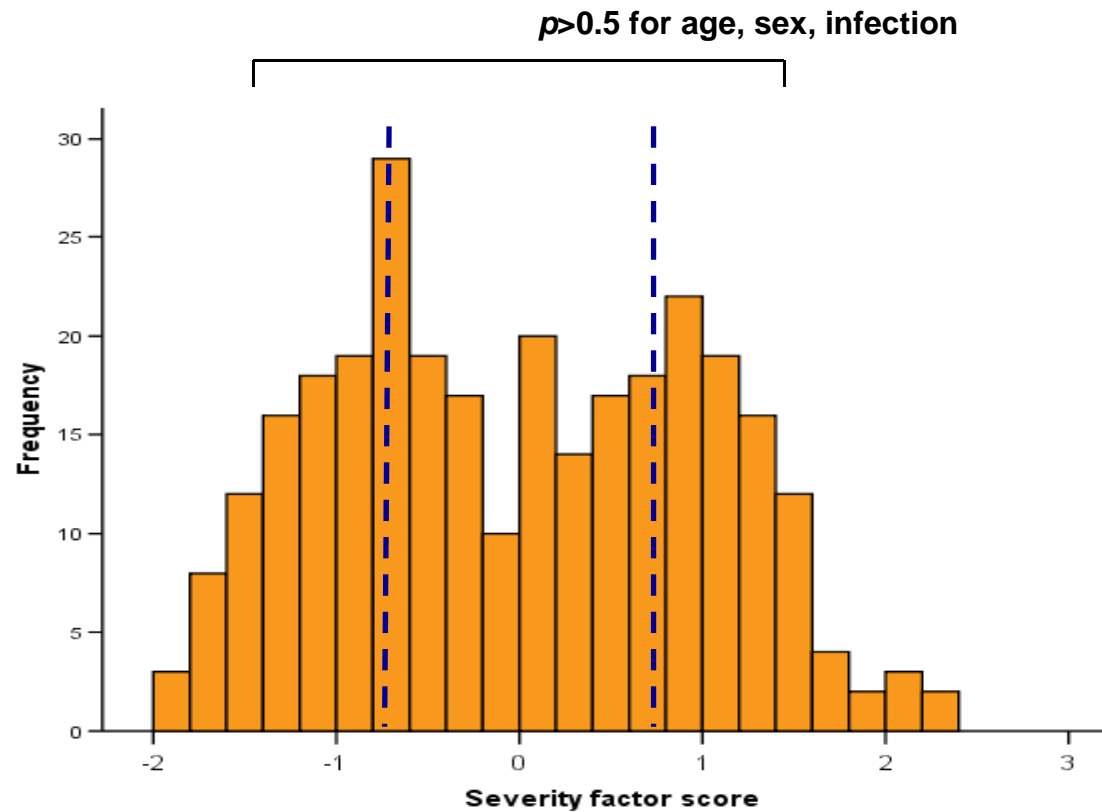


Vollmer-Conna U, et al. Post-infective fatigue syndrome is not associated with altered cytokine production. *Clinical Infectious Diseases* 2007; 45:732-735.



Genetic determinants of illness severity

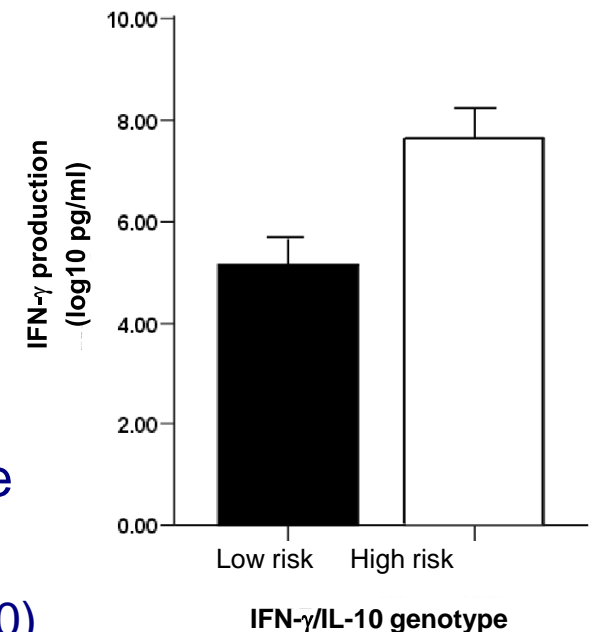
- Candidate gene studies - functional SNPs:
 - Immunological: IL-6, TNF- α , IL-10, IFN- γ
 - Neurobehavioural: COMT, 5HTT, MAO-A, NPY





Candidate gene study - results

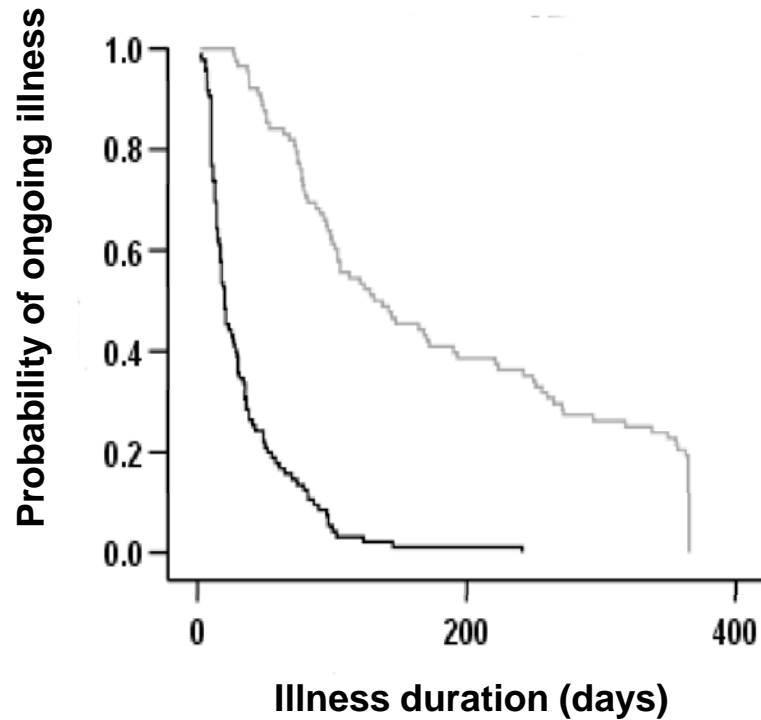
- Hardy Weinberg equilibrium
- *High illness severity:*
 - IFN- γ +874: TT ($p=0.04$; OR 1.9)
 - NPY -399 TT ($p=0.07$; OR 1.9)
 - NPY +1201 GG ($p=0.04$; OR 2.1)
 - NPY +5325 CC ($p=0.05$; OR 1.9)
- *Low illness severity:*
 - IL-10 -592 CC ($p=0.03$; OR 1.9)
- *High illness severity and combined genotype*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



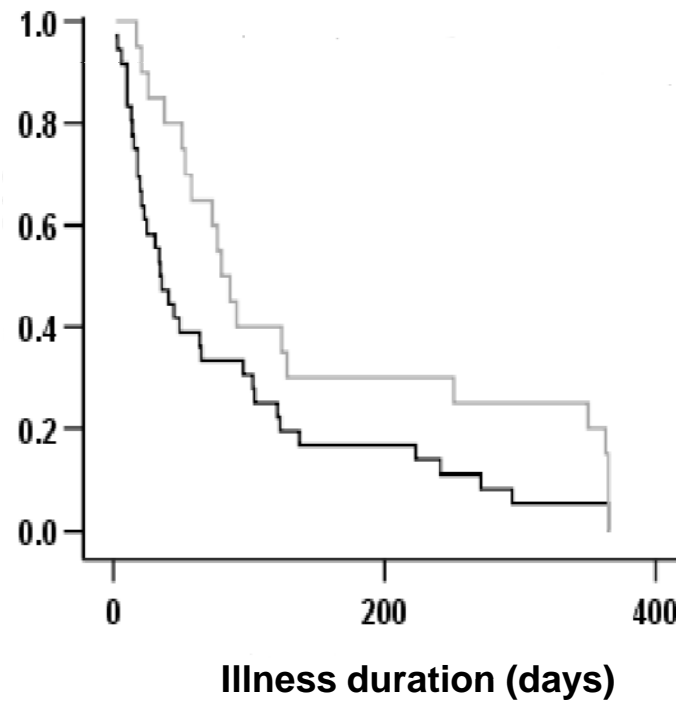


Genetic determinants of illness duration

Acute illness severity



High risk IFN- γ / IL-10 genotype





Summary

- 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?

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:

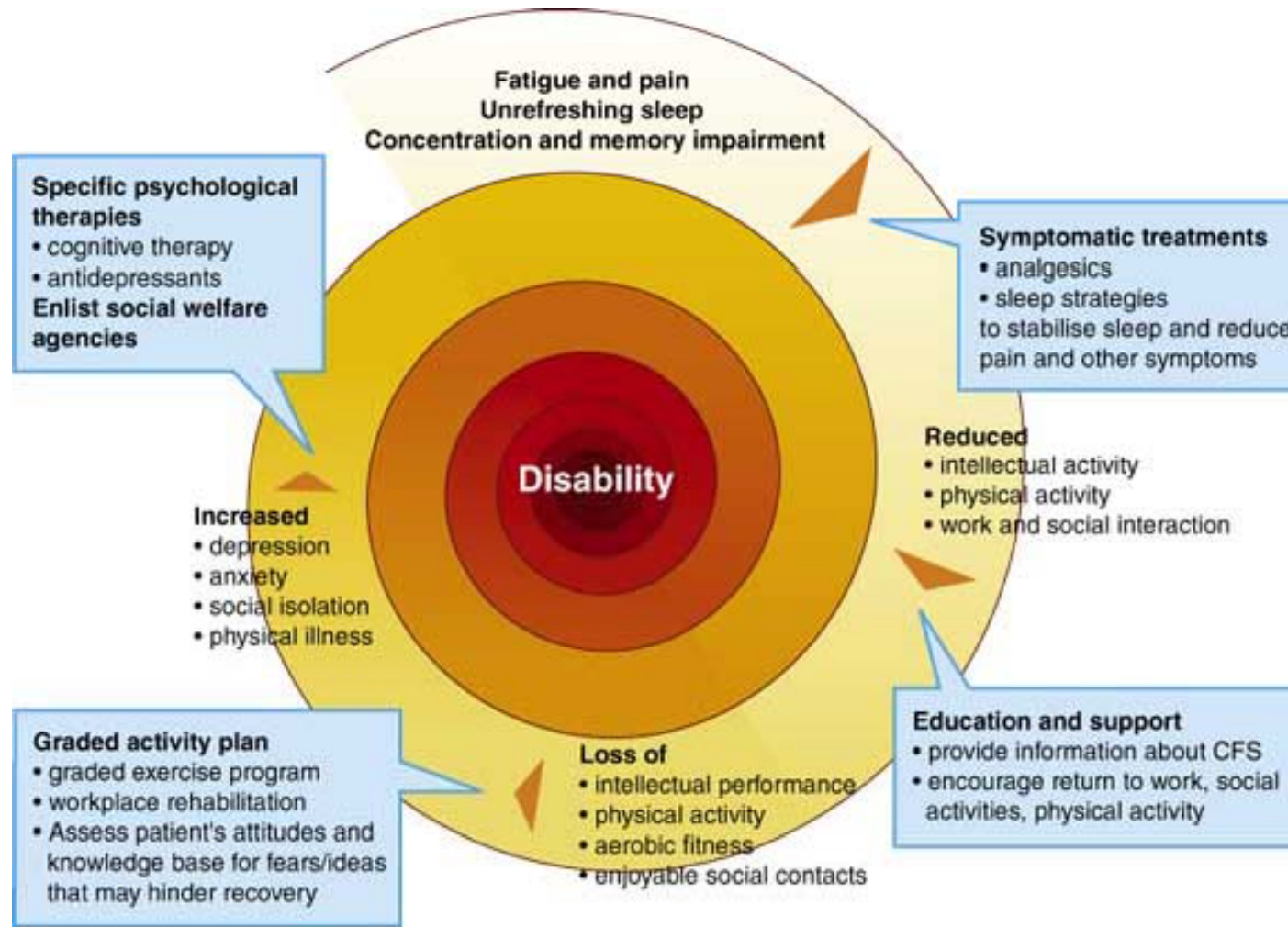
- galantamine
- modafinil
- L-carnitine

Vitamins:

- Vitamin B12
- Co-enzyme Q10



CFS - how should it be treated?





Acknowledgements

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