

Lessons from research in Chronic Fatigue syndrome

Jos WM van der Meer

MD PhD FRCP(Lon) FRCP(Edin) FIDSA MAE

Emeritus Professor of Medicine

Radboud umc Nijmegen



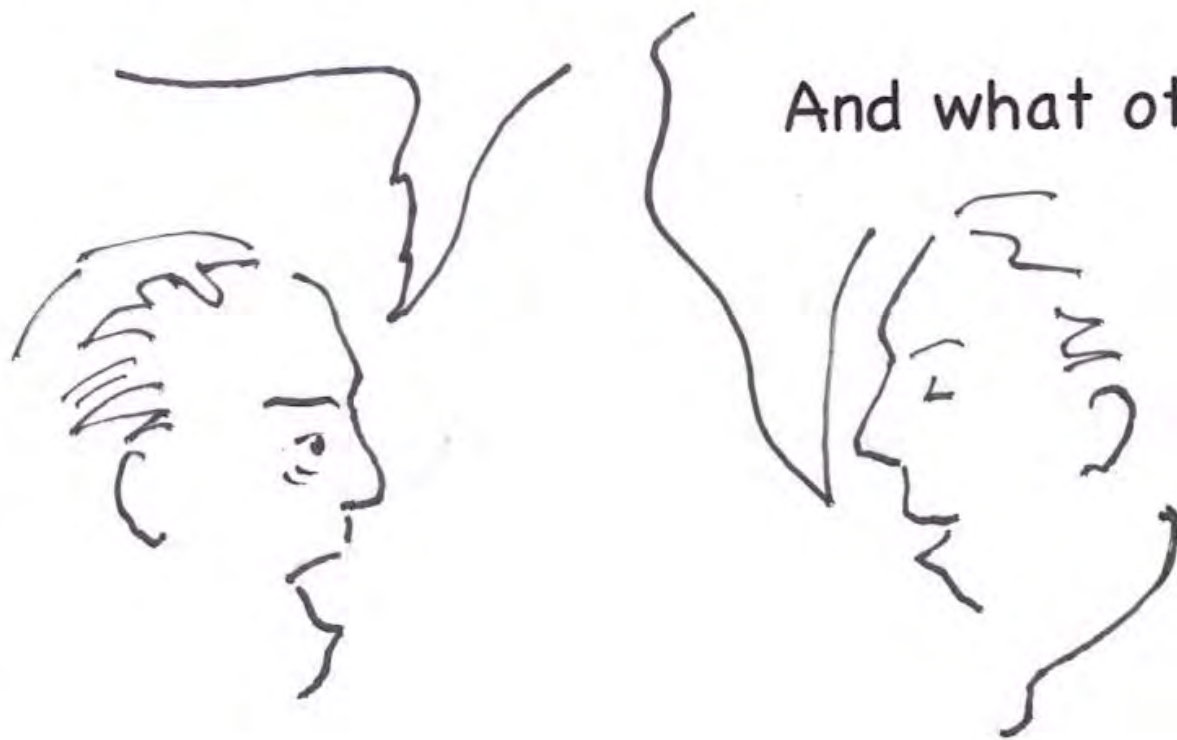
Radboudumc

Incapacitating chronic fatigue

- **Secondary to other disease**
 - a most common complaint
 - commonly ignored by the doctor
- **Chronic fatigue syndrome (CFS)**

Doctor I'm so fatigued....

And what other complaints?



Handwritten signature

CFS

- **Chronic incapacitating fatigue**
- **> 6 months**
- **Medically unexplained**
- **Associated symptoms**
myalgia/ arthralgia/ concentration
disturbances/ memory disturbances/
sleep disturbances/



See also CDC criteria (Fukuda et al)

Reasons for negative medical view on CFS:

- information from outdated psychiatric textbooks
- Inability to diagnose and treat
- irritation about selfdiagnosis
“ME”*
- strong physical attributions

*Myalgic encephalomyelitis

I know what I have got!

It is ME!

Why didn't you make that diagnosis?

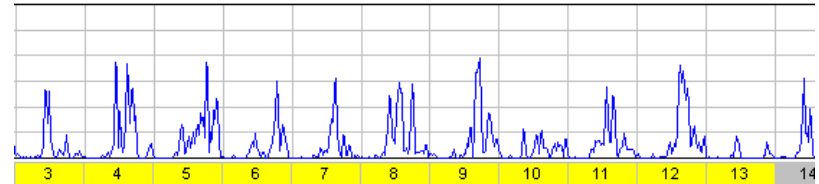


Polarised discussions between

- Doctors who deny the existence of CFS/ME
- Doctors who are convinced it is a psychiatric illness.
- Patients, lay people and doctors who adhere to unscientific and uncritical explanations for CFS.

Can we measure fatigue?

- Questionnaires (CIS, SIP)
- Actometer
- Neuropsychologic assessment
- Exercise assessment

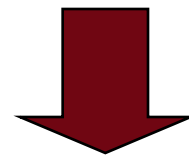


CFS etiology & pathogenesis

Prins et al
Lancet 2006

Predisposing
factors

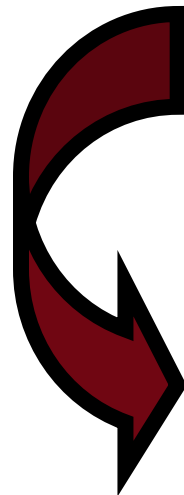
Precipitating
factors



Prognostic
factors

Complaints

Perpetu-
ating
factors



Predisposing factors

Somatic factors

genetic (no convincing candidate genes)

metabolic (no evidence)

Psychological factors

physical inactivity in childhood

trauma in childhood

physical hyperactivity in adulthood

Precipitating factors

Patients attribute CFS to:

- **Infection (e.g., EBV mononucleosis)**
- **Intoxication**
- **Surgery**
- **Anaesthesia**
- **Delivery**
- **Traumatic events**

Precipitating factors

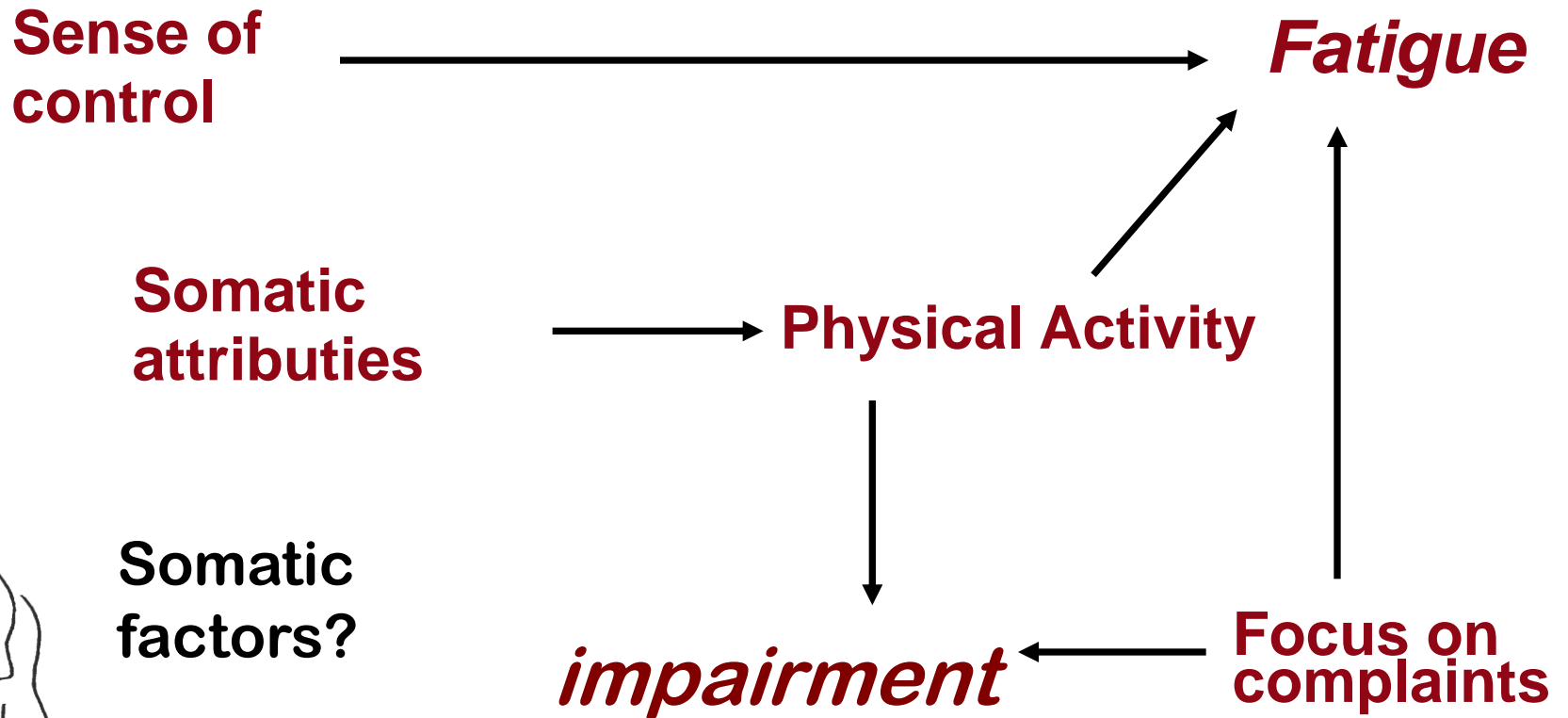
- **Infection**

So far, no unifying cause has been found, hence:

- **either: various causative organisms**
- **or: unknown micro-organism**

Model perpetuating factors in CFS

Vercoulen et al Psychosom Res 1998



Somatic perpetuating factors

Causality? Association?

Largely irreproducible

Many investigations into the pathophysiology are flawed by the lack of adequate controls

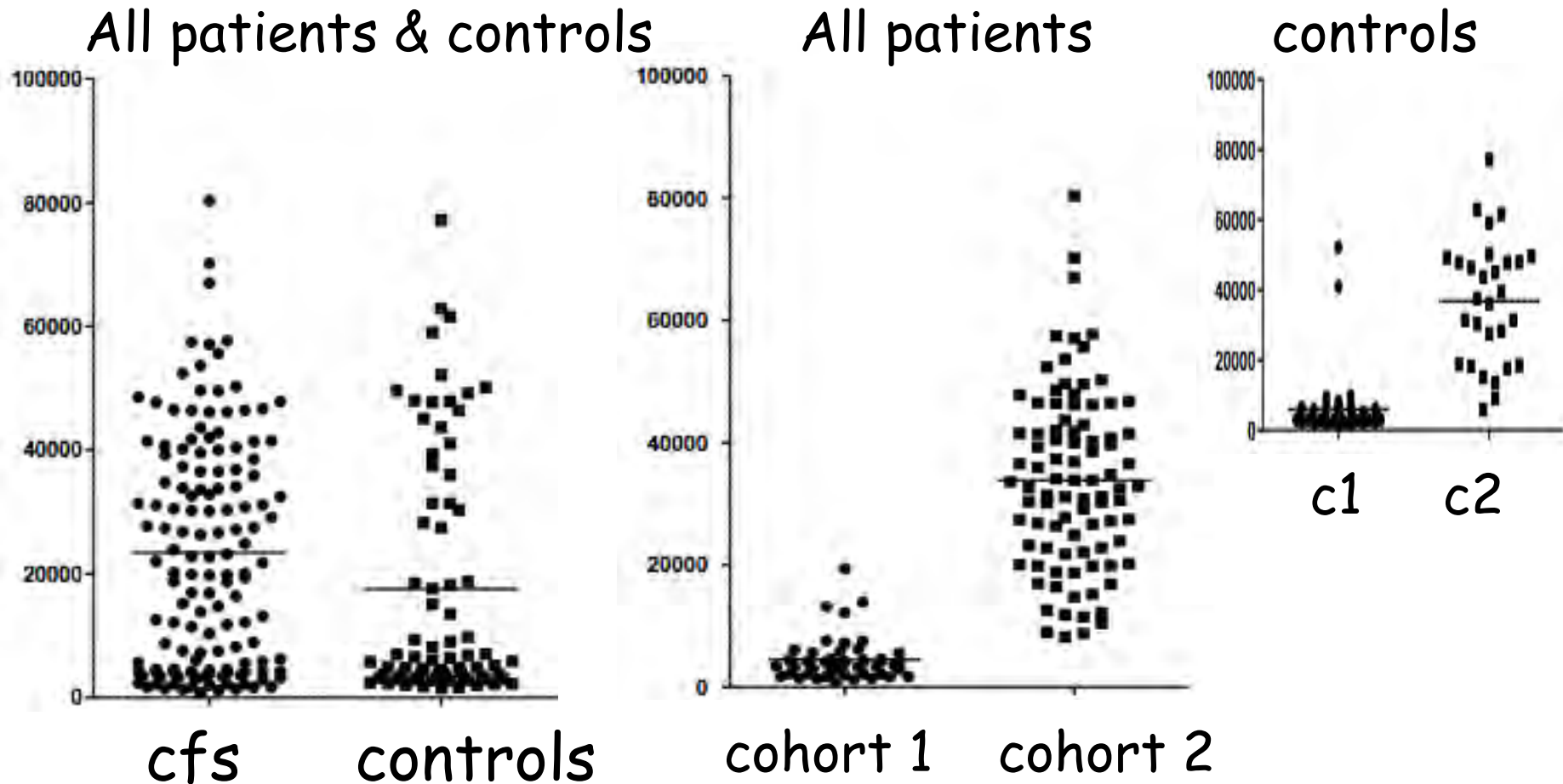
Adequate controls:

- robust matching
- control for actual stress effects
- the same pre-analytical procedures

Neighbourhood controls (Nijmegen); Twins (Seattle)



TGFbeta-1 in CFS

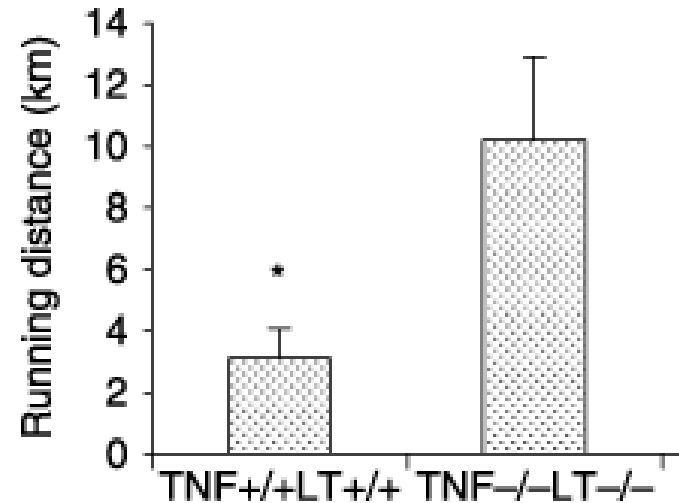


Roerink et al unpublished

Substrate

Central fatigue, hence in the CNS

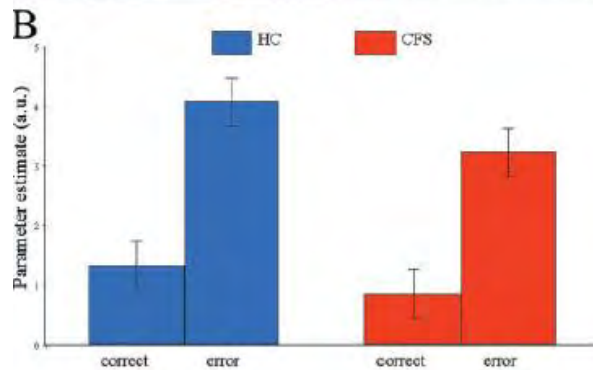
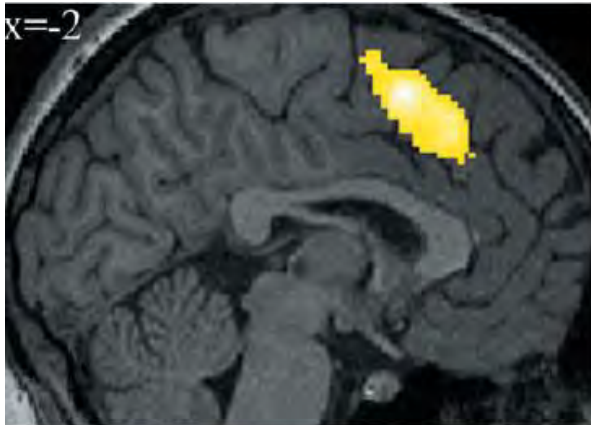
- Functional studies
- Blood (not where the action is)
- CSF
- Neuro-imaging
- Animal experiments
- Interventions



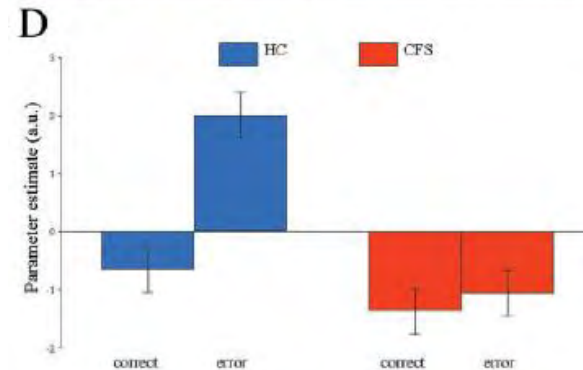
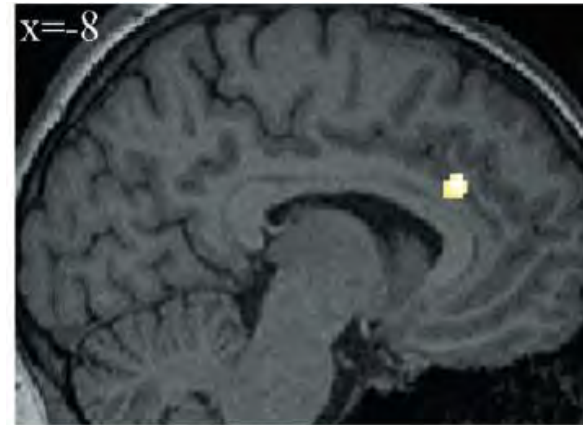
Netea et al 2007

Radboudumc

brain *function*

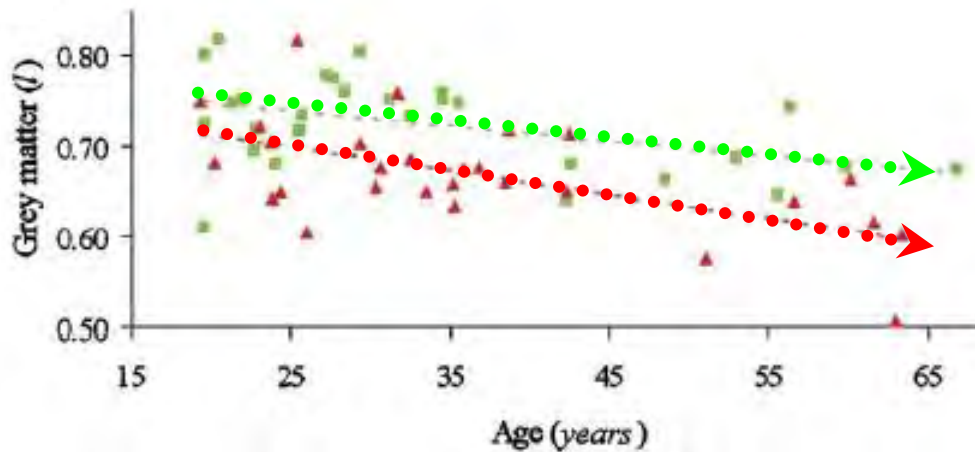
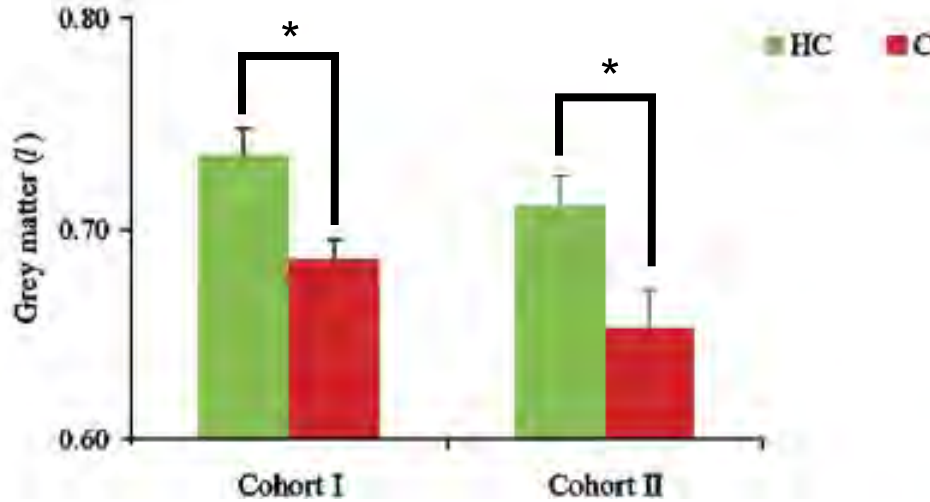
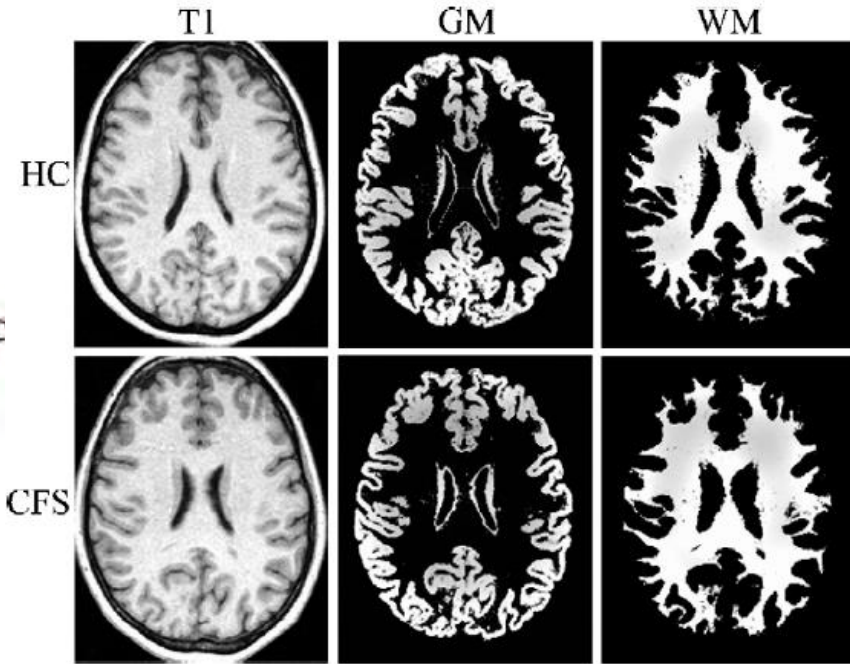


Cognitive error-related responses are not disturbed



Affective/Motivational error-related response is disturbed

Brain structure

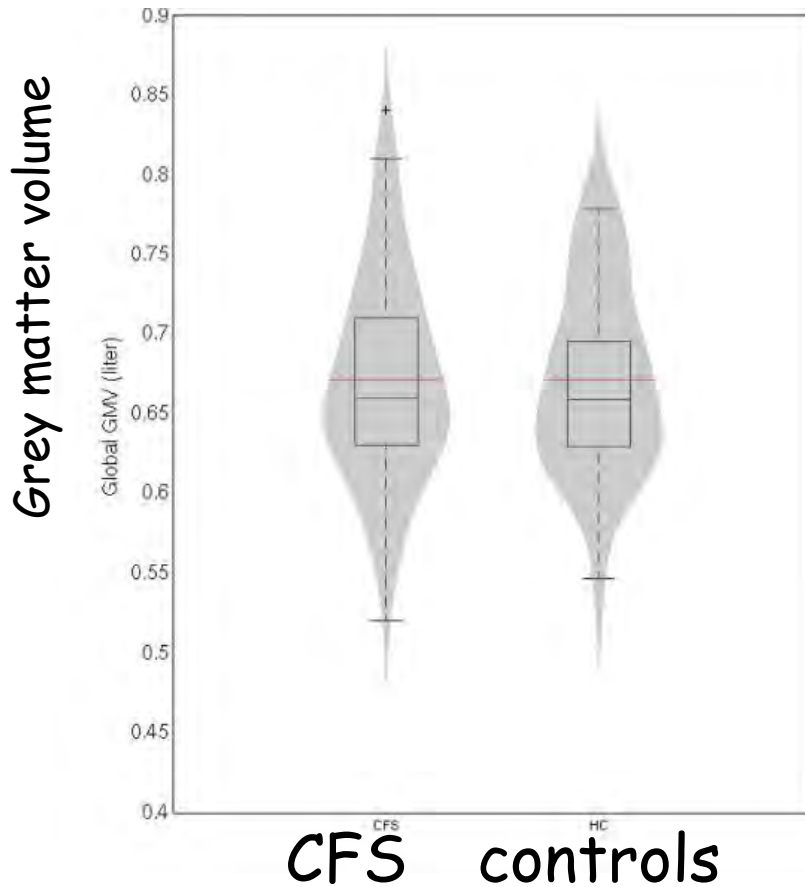


Independent confirmation in 2 other papers, but:

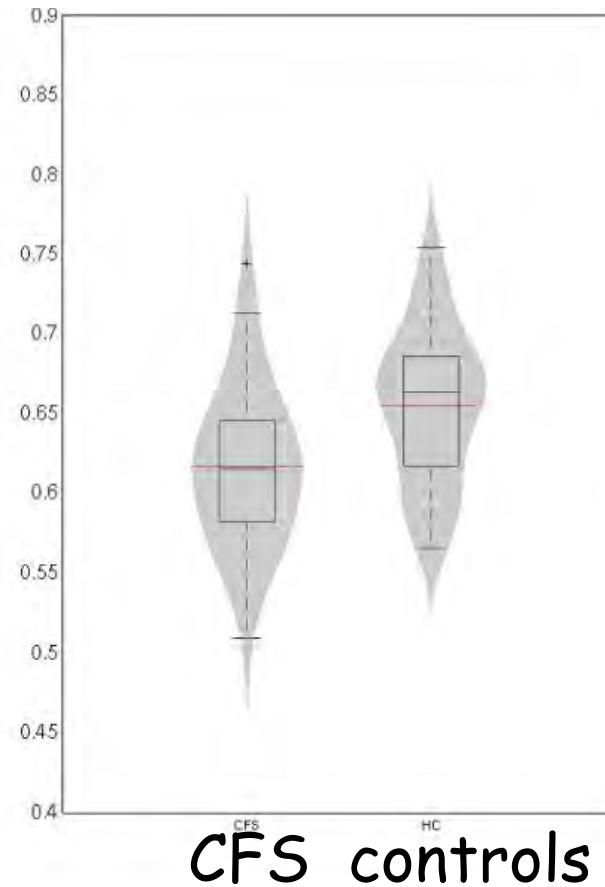
Recent large study

(Van der Schaaf et al Biol Psychiatry 2015)

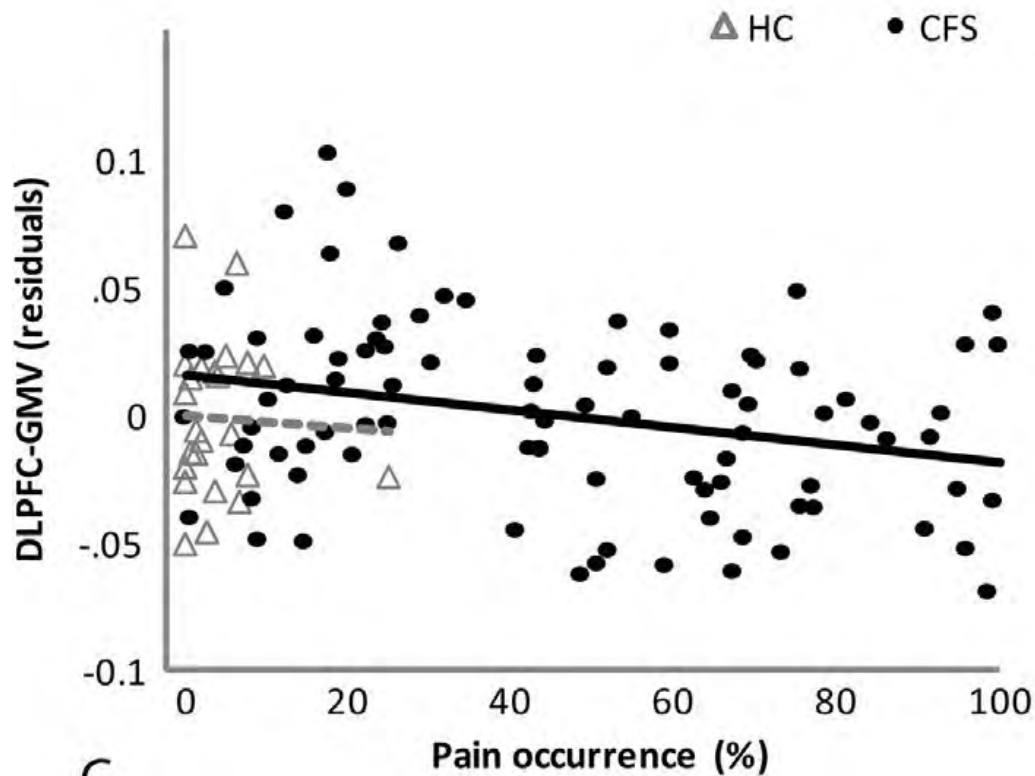
2016 cohort



2006 cohort revisited



Pain is related to decreased grey matter



C.

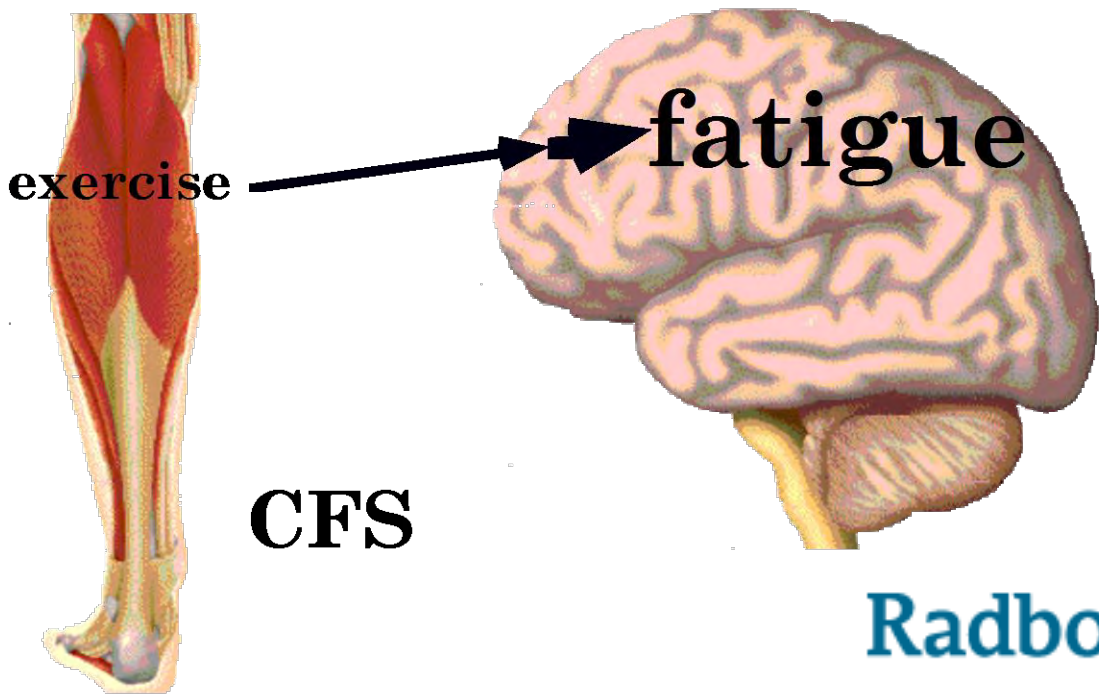
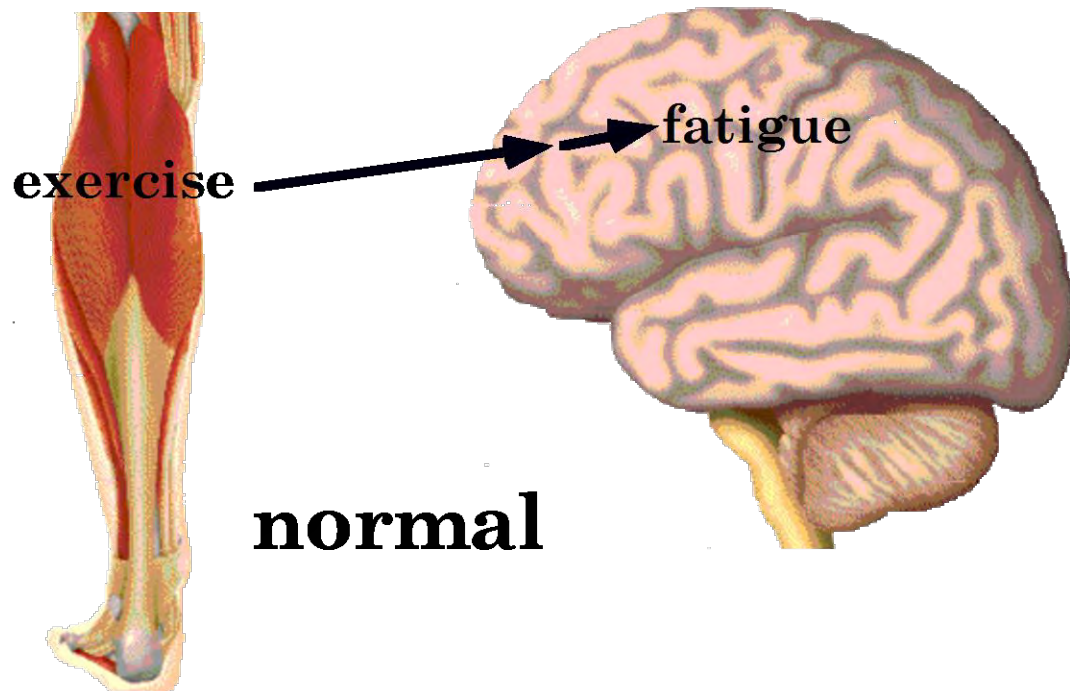


CFS, a perceptual disorder

- **Sleep**
- **Exercise tolerance**
- **Concentration**
- **Memory**
- **Movement registration**



Buchwald et al, Vercoulen et al, Bazelmans et al



Natural course of CFS over 18 months

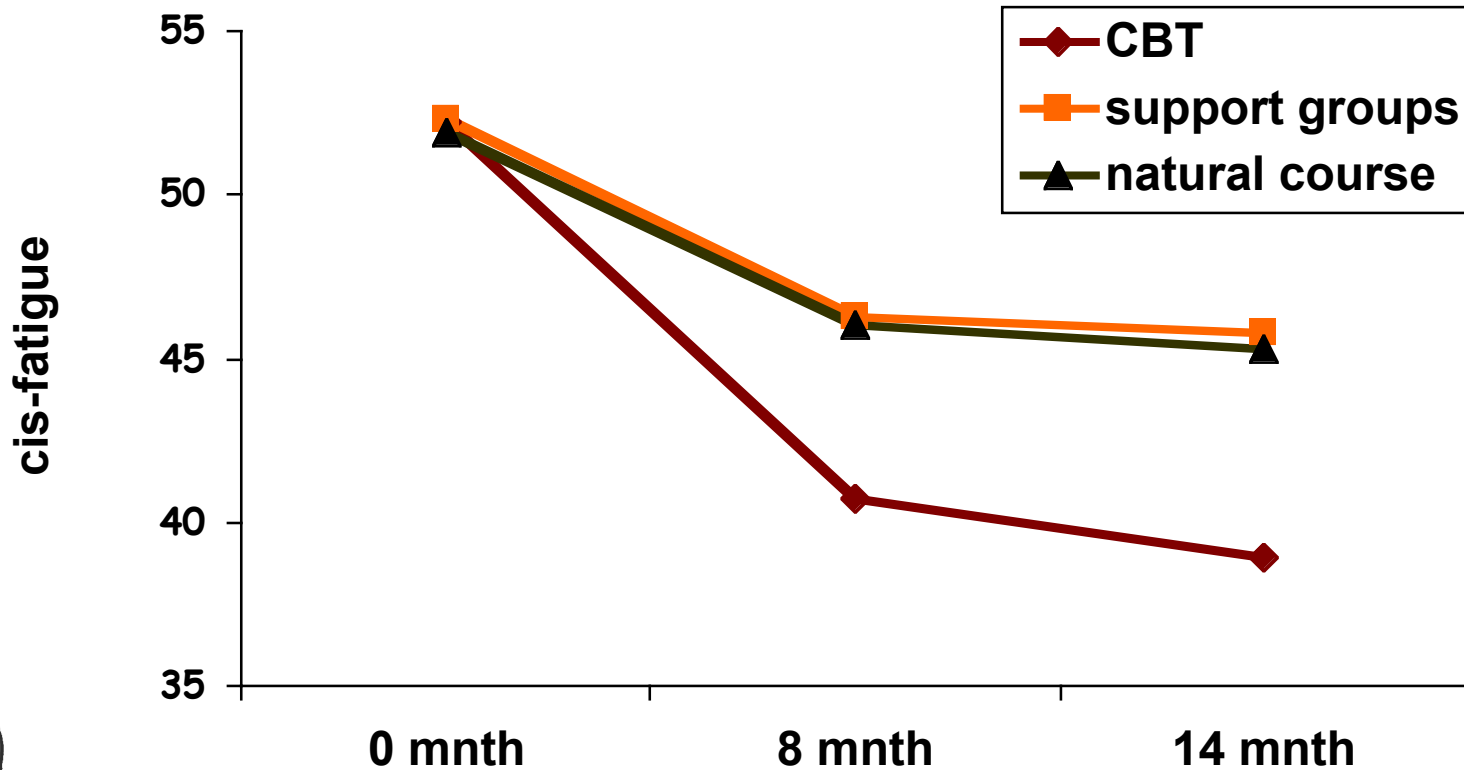
recovery	3%
improved	17%
unchanged	60%
worse	20%

INTERVENTIONS

- **Fluoxetine (Prozac®) - no effect***
- **Galantamine - no effect**
- **Food supplement - no effect**
- **Low dose steroids - effect?**
- **Cognitive behavioural therapy - effect**
- **Acetyldine: no effect**
- **Ondansetron: no effect***
- **Tryptophane depletion: no effect***
- **Anakinra → results pending**

CBT for CFS

effect on fatigue severity



CBT-SG p = .0001

CBT-SG p = .0015

CBT-NC p = .0001

CBT-NC p = .0016



Prins et al Lancet 2004

Radboudumc

Recovery after CBT

- | | |
|--|-----|
| 1. Fewer or no symptoms | 73% |
| 2. No physical impairment | 64% |
| 3. No social impairment | 57% |
| 4. No substantial impairment | 58% |
| 5. No serious fatigue | 58% |
| 6. No serious fatigue and not impaired | 51% |
| 7. Positive attitude to fatigue | 45% |



Knoop, Bleijenberg, et al 2007

Institute of Medicine Consensus: Systemic exertion intolerance disease

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

Prevalence of Postural Orthostatic tachycardia syndrome (POTS)

Adult

CFS (n=331)	5.7%
non-CFS (n=318)	6.9%

Adolescent

CFS (n= 88)	18.2%
non CFS (NM=23)	17.4%



Roerink et al J Int Med 2016

Acknowledgement

Gijs Bleijenberg
Hans Knoop
Jan Vercoulen
Ellen Bazelmans
Judith Prins
Maaïke de Vries
Petra Servaes
Syberen van der Werf
Maurice Albers
Eufride Klein Rouweler
Lieke de Jong
Ria te Winkel
Berna de Vree
Megan Roerink
Marieke van der Schaaf

Joep Galama
Caroline Swanink

Jan Fennis
Patricia Soetekouw
Frederique Brouwers
Lammy Elving
Jacques Lenders

Floris de Lange
Ivan Toni
Peter Hagoort

