Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: An Unsolved Spectrum of Disorders

By: Emily Villar

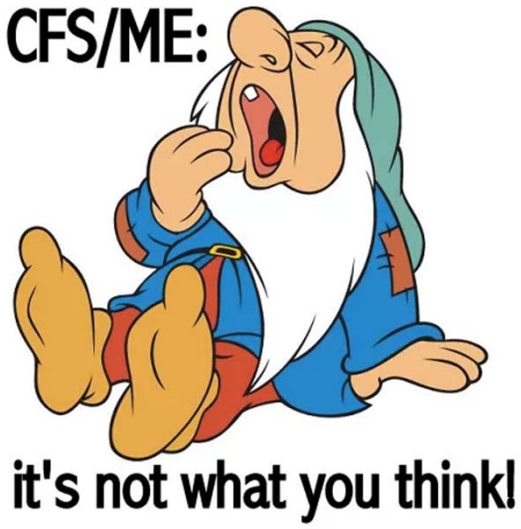
Objectives

- Know the current definitions of CFS / ME
- Recognize differences in pediatrics vs. adults
- Understand emerging evidence about the disease
- Be familiar with the current recommendations & challenges in treating this disease

What is CFS/ME?

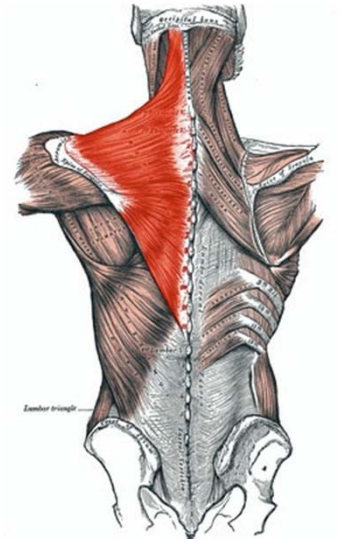
CDC

"Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by intense fatigue that is not improved by bed rest and that may be worsened by physical activity or mental exertion."



Fukuda Criteria

- >6mo fatigue
- Significant impairment with ADL/Work

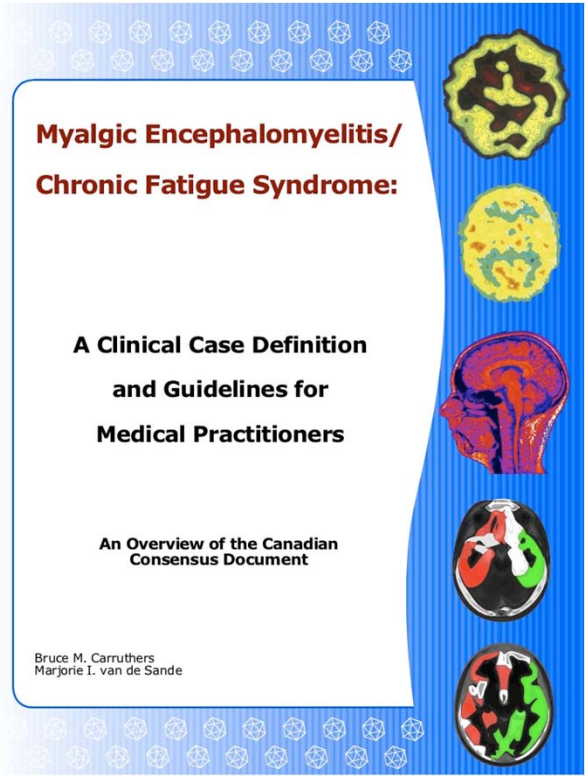


- 4 or more:
  - Post exertion malaise > 24 hrs
  - Un refreshing sleep
  - Significant cognitive impairment
  - Myalgia
  - Arthralgia
  - HA
  - Sore throat
  - Tender LAD

Carruther's Criteria: Intl. Consensus

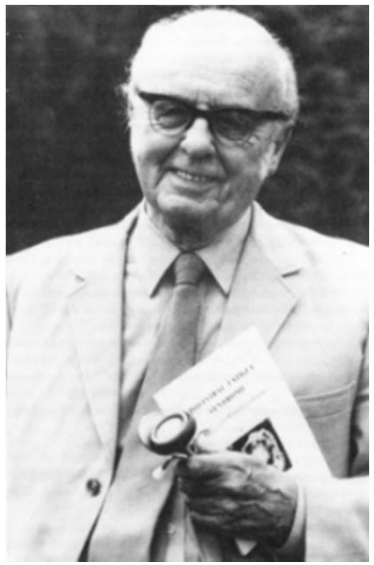
- Myalgic Encephalomyelitis 2011
  - Profound muscle weakness/tenderness
  - Fatigue
  - Neurological abnormalities
  - Circulatory abnormalities
  - Post exertional "malaise"

- Estimated 30-50% of CFS



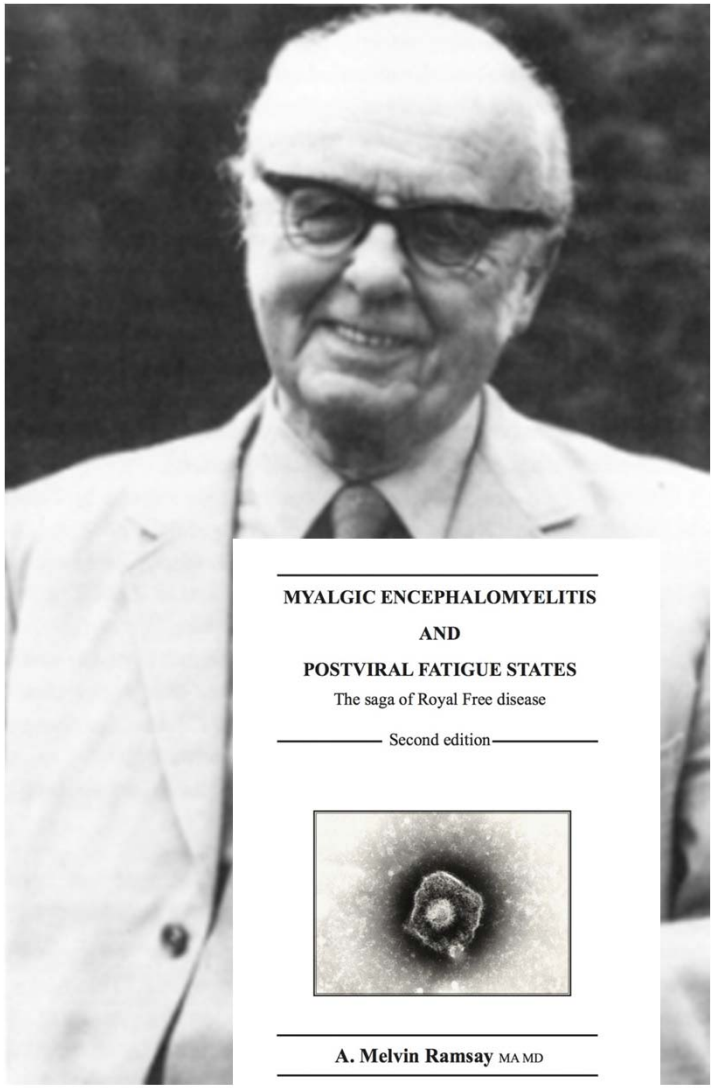
A Timeline

- 1934: "Atypical Poliomyelitis" → "epidemic neuromyasthenia"
  - 100,000 ppl California
- 1940-1980: Various Outbreaks across the World
  - 1948: Iceland "Akureyri Disease" 500 ppl
  - 1955: Royal Free Hospital London "Benign ME" 300 ppl
- 1969: Acknowledged by WHO
  - Benign Myalgic Encephalomyelitis
  - CNS disease entity



A Timeline

- 1970's Theory of Mass Hysteria
  - McEvedy and Beard
- Mid 1980's: Lake Tahoe Epidemic
  - "Raggedy Ann Syndrome"
  - 260 ppl
- 1988: Clinical Picture Defined
  - Ramsay et al: Myalgic Encephalitis
  - Holmes et al: CFS
- 1994: CFS Redefined



ME vs. CFS

- Considered to be interchangeable
- Distinct but overlapping clinical entities
  - Post exertion malaise & cognitive dysfunction not required for dx of CFS
  - Obligatory for dx ME
- Distinction +/- post exertion malaise considered hallmark for diagnosis

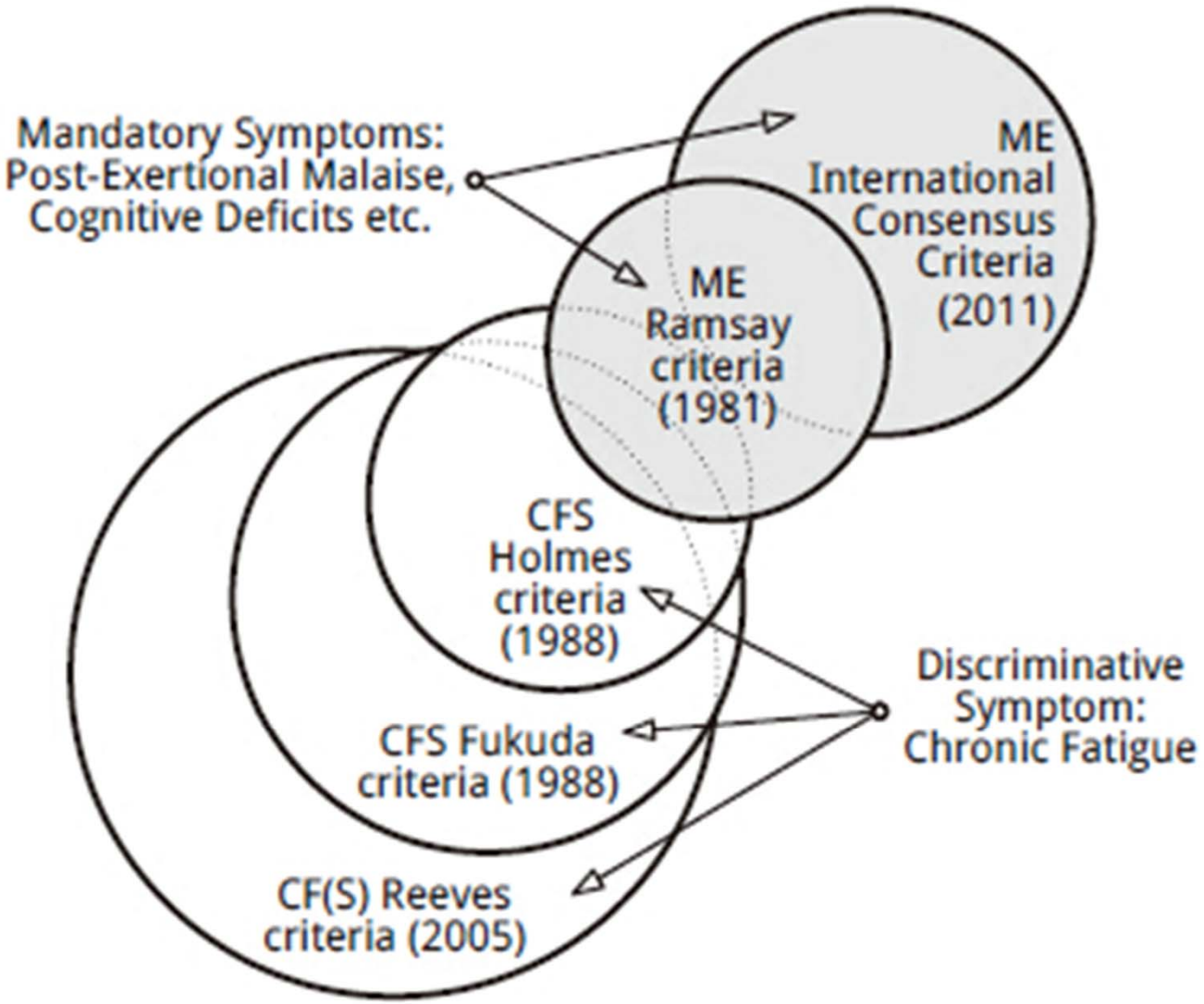
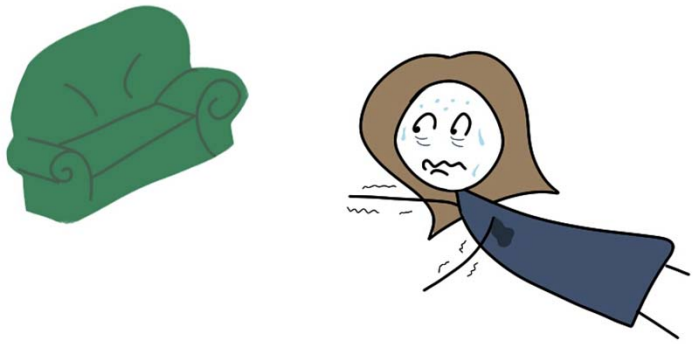
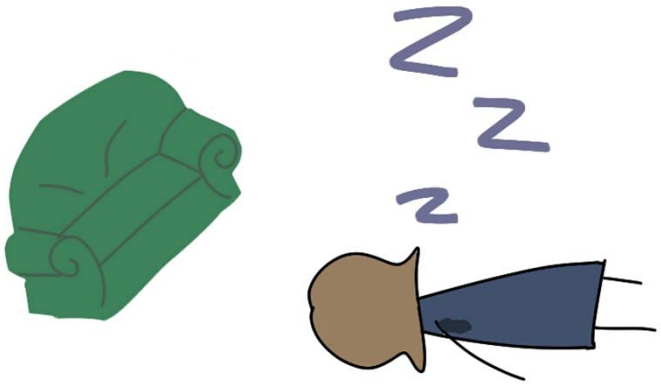


Figure 1 ME and CFS case definitions.

CDC

- Complex and debilitating disease
- Follows Fukuda Criteria
- Complications in Diagnosis:
  - No lab test or biomarker
  - Fatigue common to many illnesses
  - Illness may not be obvious
  - Pattern of remission and relapse
  - Heterogeneous severity



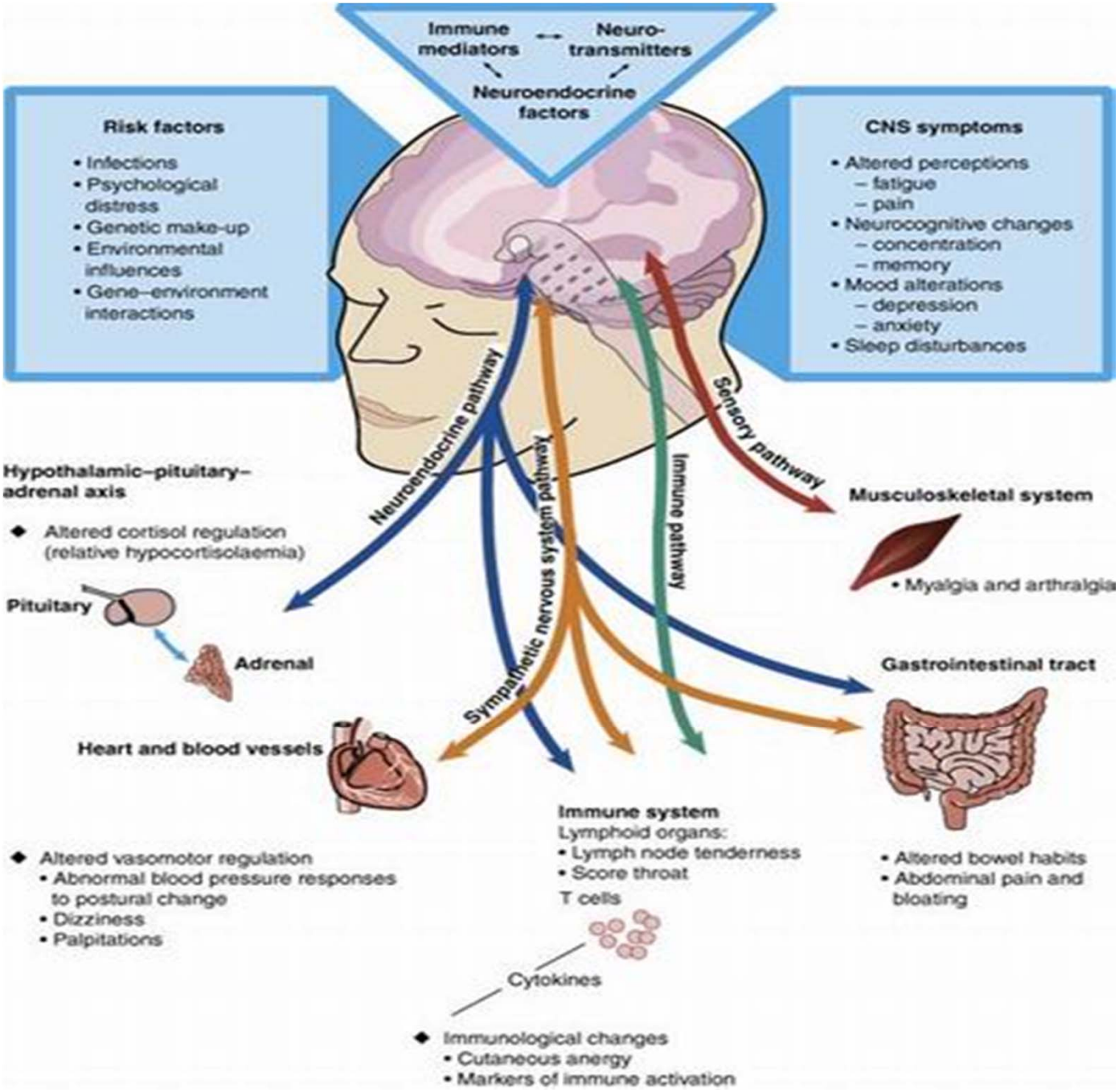


Etiology

- No known etiology

???

- Several etiologic theories
  - Infectious/Post infectious
  - Immune dysfunction
  - Neurotransmitter d/o
  - Metabolism d/o
  - Genetic


Immune mediators
Neuro-transmitters
Neuroendocrine factors
Risk factors
• Infections
• Psychological distress
• Genetic make-up
• Environmental influences
• Gene–environment interactions
CNS symptoms
• Altered perceptions
– fatigue
– pain
• Neurocognitive changes
– concentration
– memory
• Mood alterations
– depression
– anxiety
• Sleep disturbances
Neuroendocrine pathway
Sympathetic nervous system pathway
Immune pathway
Sensory pathway
Hypothalamic–pituitary–adrenal axis
◆ Altered cortisol regulation (relative hypocortisolaemia)
Pituitary
Adrenal
Musculoskeletal system
• Myalgia and arthralgia
Gastrointestinal tract
Heart and blood vessels
◆ Altered vasomotor regulation
• Abnormal blood pressure responses to postural change
• Dizziness
• Palpitations
Immune system
Lymphoid organs:
• Lymph node tenderness
• Score throat
T cells
Cytokines
◆ Immunological changes
• Cutaneous anergy
• Markers of immune activation
• Altered bowel habits
• Abdominal pain and bloating

Epidemiology

- More likely in females
  - 2-4:1
- Most common in young adults and middle aged
- 2 peaks: 10-19 yo & 30-39 yo
- Estimated 0.1-2% of adolescents
  - Largest single cause of long-term school absence in the UK
  - 2.6% Jr High and 5-10% Sr High in Japan

CFS/ME in Children vs. Adults: UK & Dutch cohorts

- UK
  - 210 Kids < 12yo
  - 1568 Adolescents
  - 10,675 Adults
  - CDC Criteria

- The Netherlands
  - 135 12-18yo from FITNET Cohort
  - Severe fatigue
  - <85% school performance & attendance

Results

- Children <12 yo
  - More Gender Balanced
    - 56.7% F : 74-82% FA
  - More likely to present with sore throat
    - 62% vs. 56% Adult
  - Cognitive Symptoms
    - 76.5% : 86.7%/95% A/A
  - Problems with Sleeping
    - 85% vs. 96% Adult
  - Less likely to have post exertion malaise

Results

- Adolescents (12-18 yo)
  - More likely to present w/ HA
    - 81% : 75% & 74 % in young children & adults respectively
  - Less likely to have cognitive dysfunction vs. Adults
  - Less likely to have tender LAD, palpitations, dizziness, malaise

- Adults
  - Lower mean physical function (-8.2 pts)
  - Higher mean fatigue (2.1 pts)

Childhood CFS and Neuro-cognitive impairment

- Problems w/ attention control
  - Previously demonstrated in studies prior to 2008
- ERP in CCFS pts
  - 414 CCFS (9-18 yo)
    - Types 1-3 per ERP findings
  - 190 HC
- Frontal Lobe, Autonomic, & ERP fx

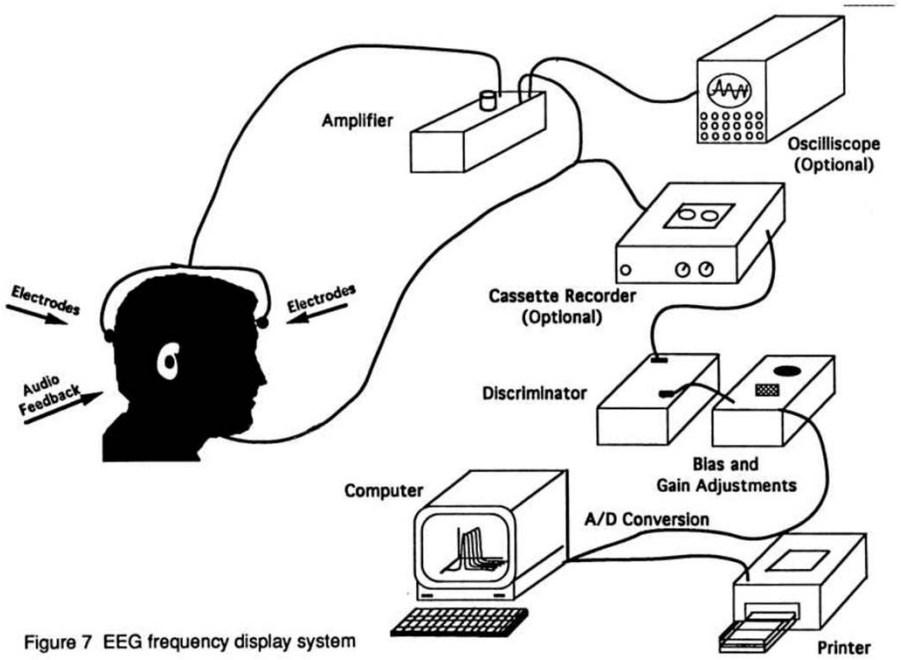
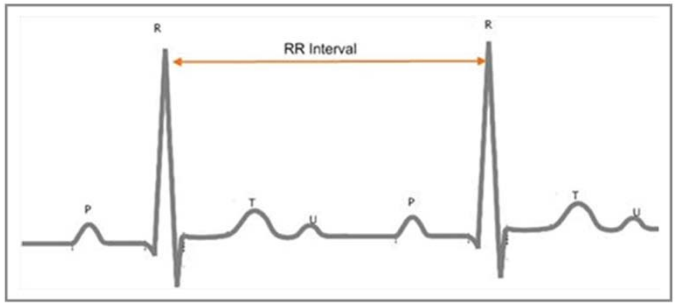


Figure 7 EEG frequency display system



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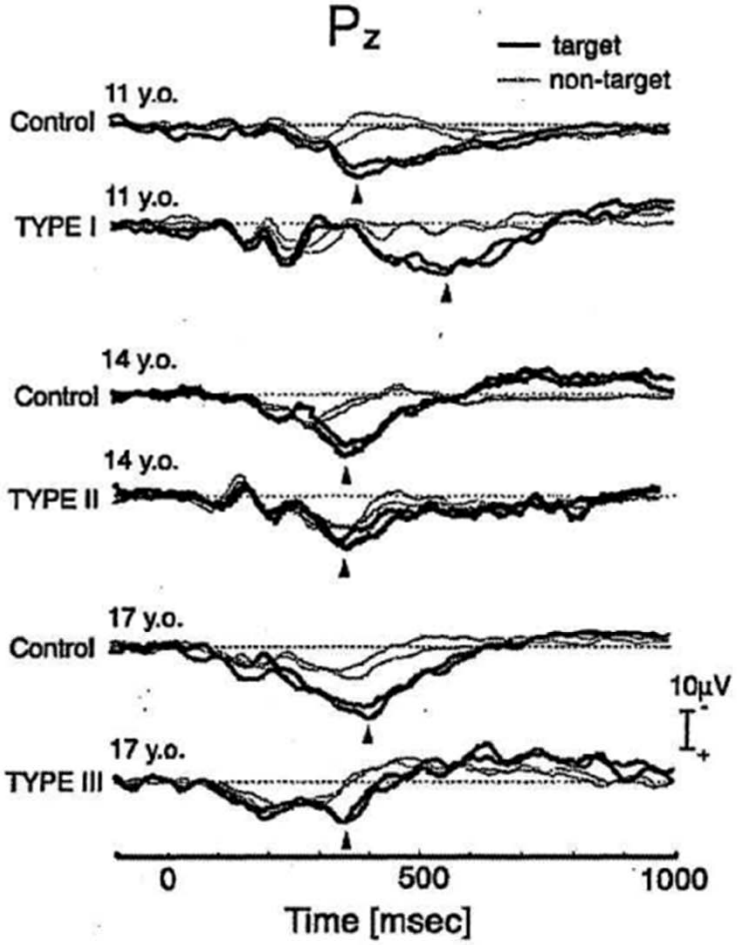
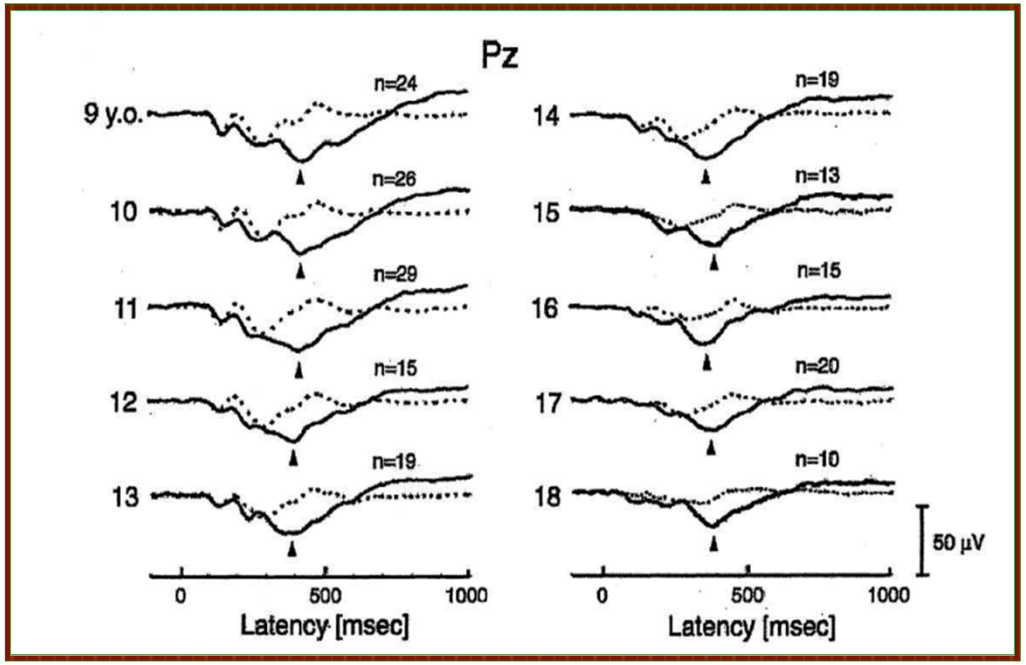
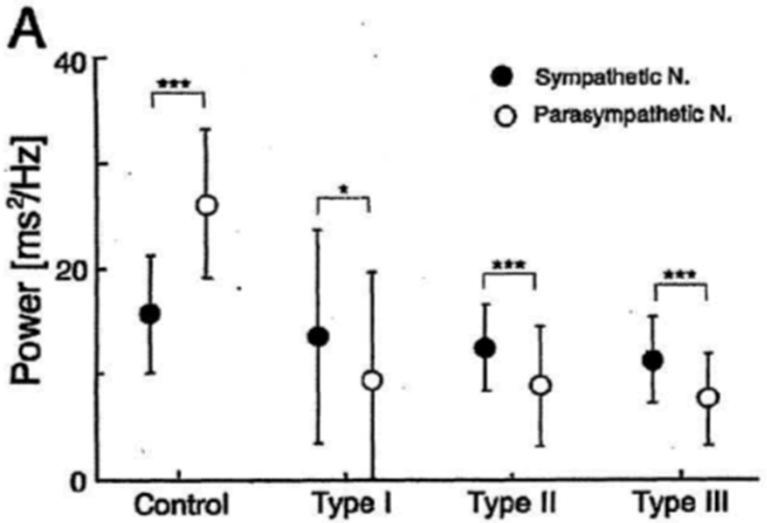
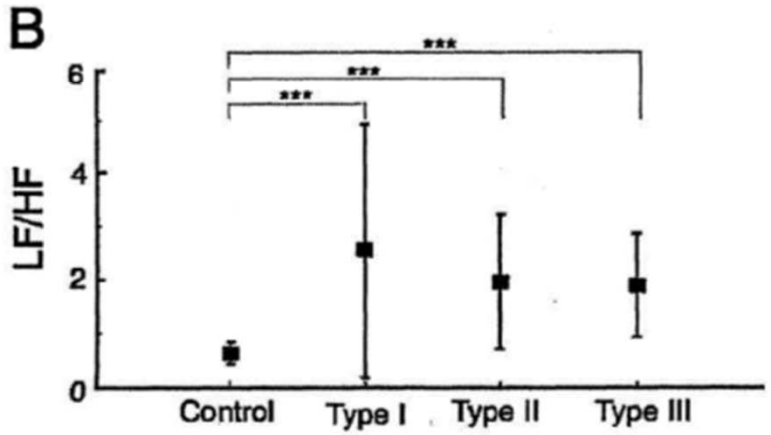
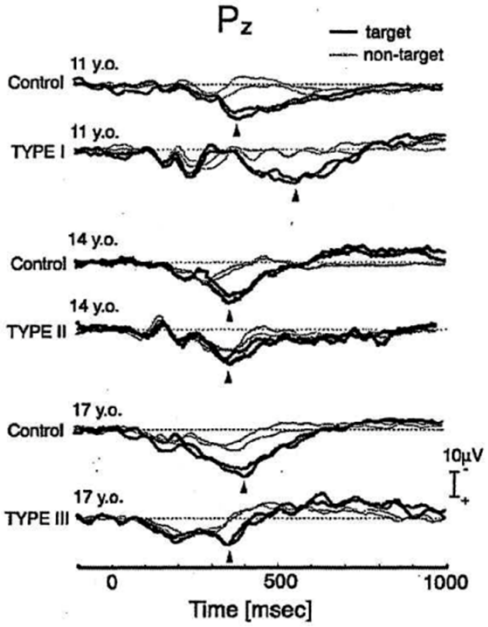
Results

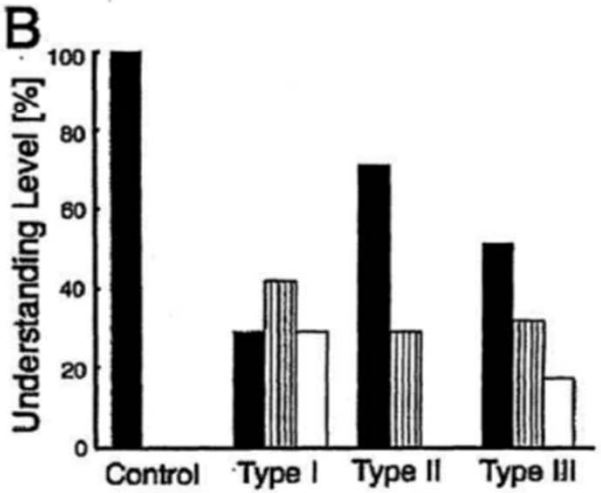

Pz
target
non-target
11 y.o.
Control
11 y.o.
TYPE I
14 y.o.
Control
14 y.o.
TYPE II
17 y.o.
Control
17 y.o.
TYPE III
10μV
0
500
1000
Time [msec]


Pz
9 y.o.
n=24
10
n=26
11
n=29
12
n=15
13
n=19
14
n=19
15
n=13
16
n=15
17
n=20
18
n=10
50 μV
0
500
1000
Latency [msec]
0
500
1000
Latency [msec]


A
Power [ms²/Hz]
40
20
0
Sympathetic N.
Parasympathetic N.
***
*
***
***
Control
Type I
Type II
Type III


B
LF/HF
6
4
2
0
***
***
***
Control
Type I
Type II
Type III


Pz
target
non-target
11 y.o.
Control
11 y.o.
TYPE I
14 y.o.
Control
14 y.o.
TYPE II
17 y.o.
Control
17 y.o.
TYPE III
10μV
0
500
1000
Time [msec]


B
Understanding Level [%]
100
80
60
40
20
0
Control
Type I
Type II
Type III

Impact of CFS on Cognitive Fx in Adolescents

- Cross sectional & retrospective studies
  - Change in cognitive fx w/ poor performance in school
- IQ correlation pre & post CFS symptoms
- Current IQ data : retrospective CITO data
  - 59 pts recruited from FITNET Trial
  - 40 HC

Results

Eur J Pediatr

Table 2 Intelligence assessment scores of adolescents with CFS and healthy adolescents

	CFS (SD)[a] n=59	Healthy (SD)[a] n=40	Mean difference (95 % CI)	p value	Adjusted difference (95 % CI)[b]	p value
CITO score[c] (501–550)	540.4 (7.0)	541.0 (6.6)	−0.6 (−3.6; 2.4)	0.705	−1.0 (−3.1; 1.1)	0.329
Initial secondary school level[d]						
Level 1—%	28.8	22.5				
Level 2—%	28.8	35.0		0.721		
Level 3—%	42.4	42.5				
Current secondary school level						
Level 1—%	32.2	22.5				
Level 2—%	37.3	30.0		0.223		
Level 3—%	30.5	47.5				
Intelligence level						
Measured IQ score[e]	103.3 (11.4)	111.2 (11.0)	−8.0 (12.6; −3.3)	0.001	−6.5 (−10.9; −2.1)	0.004
Performance IQ						
Block design (1–18)	10.3 (2.5)	11.8 (2.2)	1.5 (0.6; 2.5)	0.002	−1.4 (−2.4; −0.4)	0.006
Picture completion (1–18)	9.1 (2.9)	10.7 (2.1)	1.6 (0.5; 2.7)	0.005	−1.3 (−2.5; −0.1)	0.036
Verbal IQ						
Information (1–19)	11.0 (2.8)	11.7 (3.0)	0.7 (−0.6; 2.0)	0.268	−0.3 (−1.5; 1.0)	0.663
Vocabulary (1–19)	11.1 (2.2)	11.3 (2.2)	0.2 (−0.8; 1.1)	0.728	−0.3 (−1.2; 0.7)	0.572

Table 3 Mean IQ score by school level of adolescents with CFS compared with healthy peers

	Educational level 1 (VMBO)[c]	*n*	Educational level 2 (HAVO)[c]	*n*	Educational level 3 (VWO)[c]	*n*
Intelligence quotient (IQ)[a]						
CFS	96.8 (8.6)	19	104.8 (9.2)	22	108.2 (13.5)	18
Controls[b]	104.1 (14.0)	8	110.5 (6.9)	12	114.7 (10.8)	19

There are significant differences between groups at all school levels, $p=0.005$

VMBO Voorbereidend Middelbaar Beroeps Onderwijs, *HAVO* Hoger Algemeen Voortgezet Onderwijs, *VWO* Voorbereidend Wetenschappelijk Onderwijs, *CFS* chronic fatigue syndrome

[a] Values are means (SD)

[b] CFS $n=59$, Controls $n=39$ (1 participant incomplete due to illness)

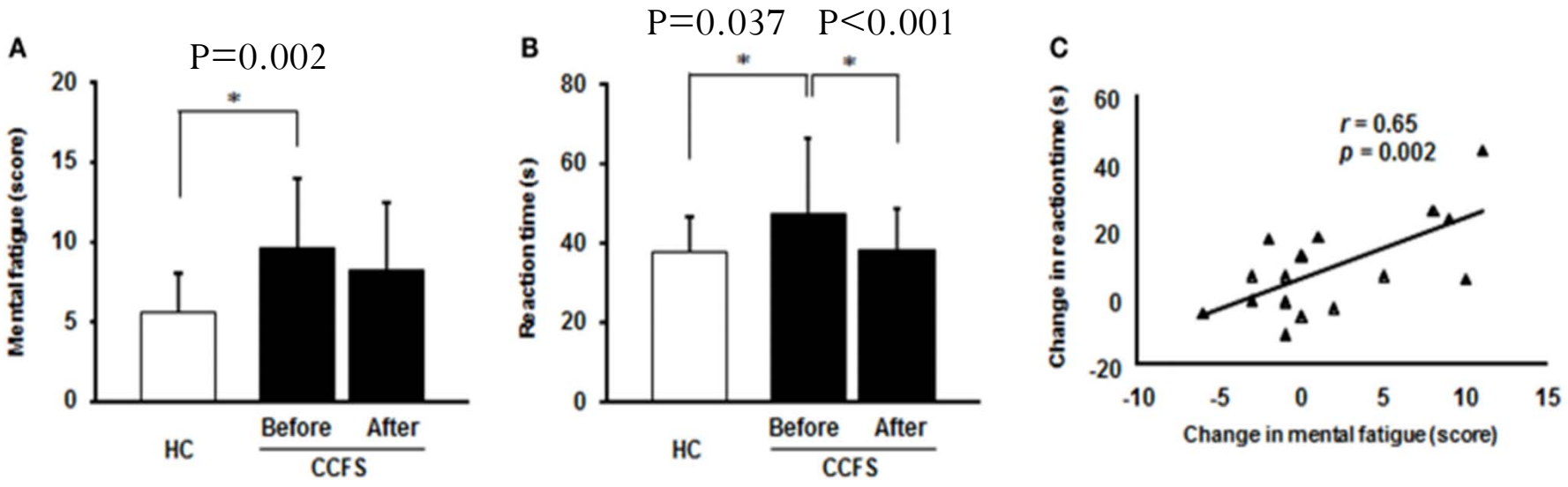
[c] VMBO, HAVO and VWO correspond, respectively, to 'average', 'above average' and 'high' levels of attainment

Treatment for Attention Control

- Data from 2004 suggesting CBT potentially beneficial
- 2009 CBT described as ineffective & potentially harmful
- Recent randomized control studies → SSRI + CBT effective for teen depression

Combination Therapy in CCFS

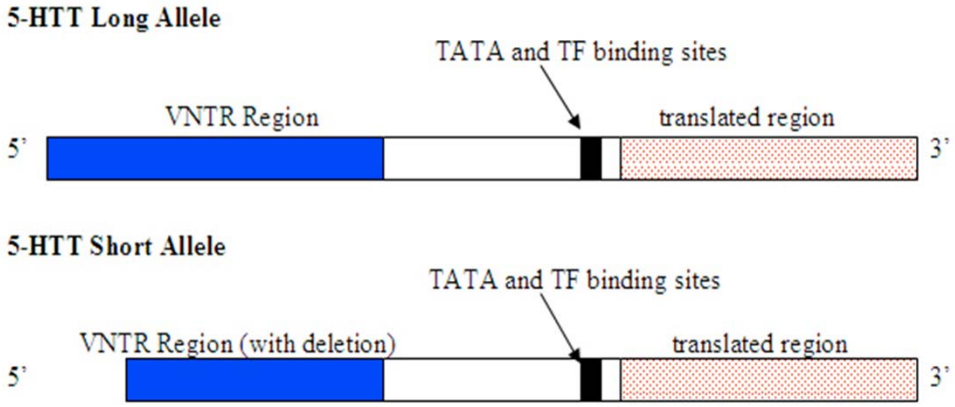
- 19 CCFS and 25 HC
  - mATMT
- Improved
  - Motor Skill
  - Attention
  - Spatial working memory

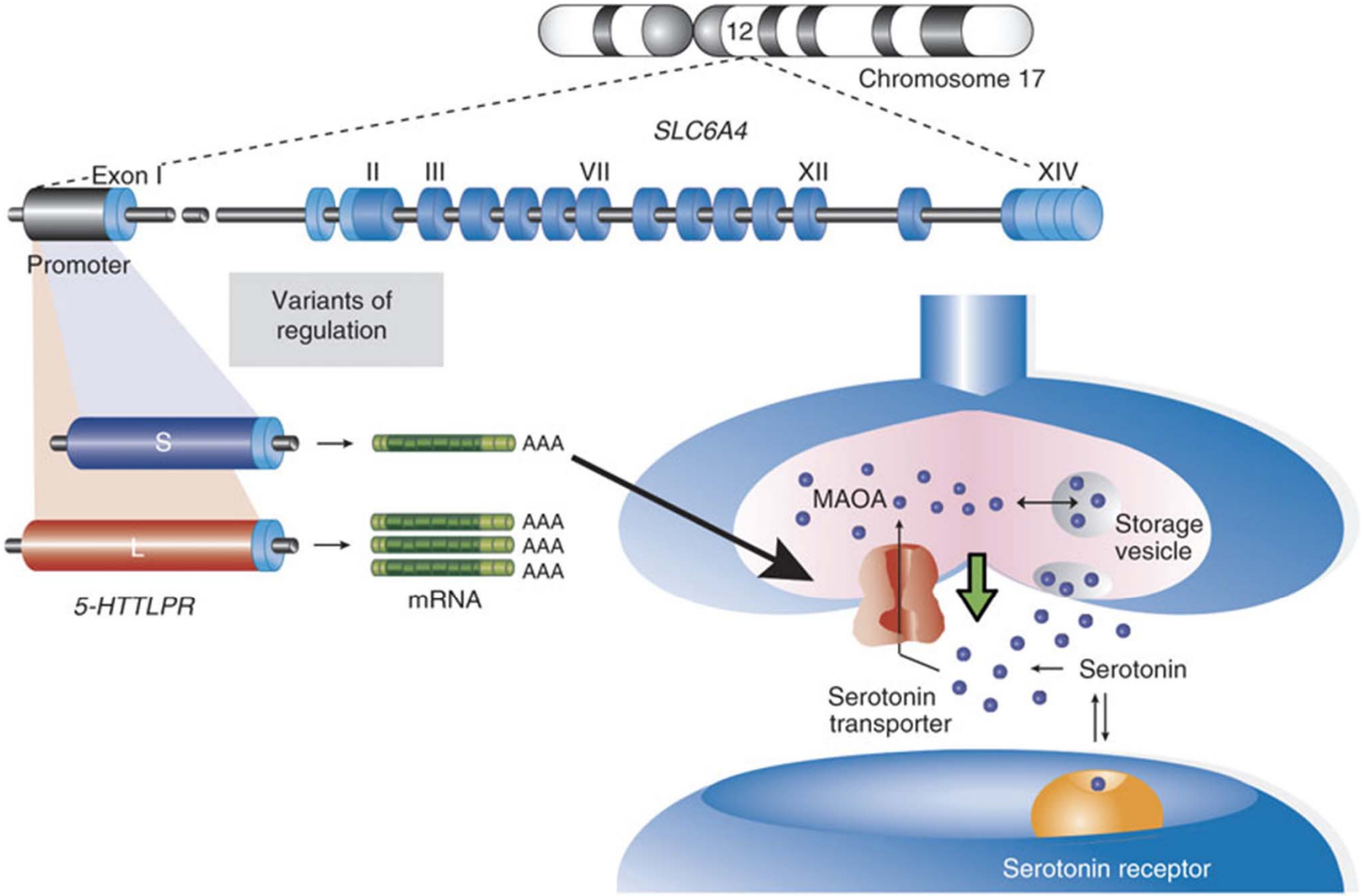


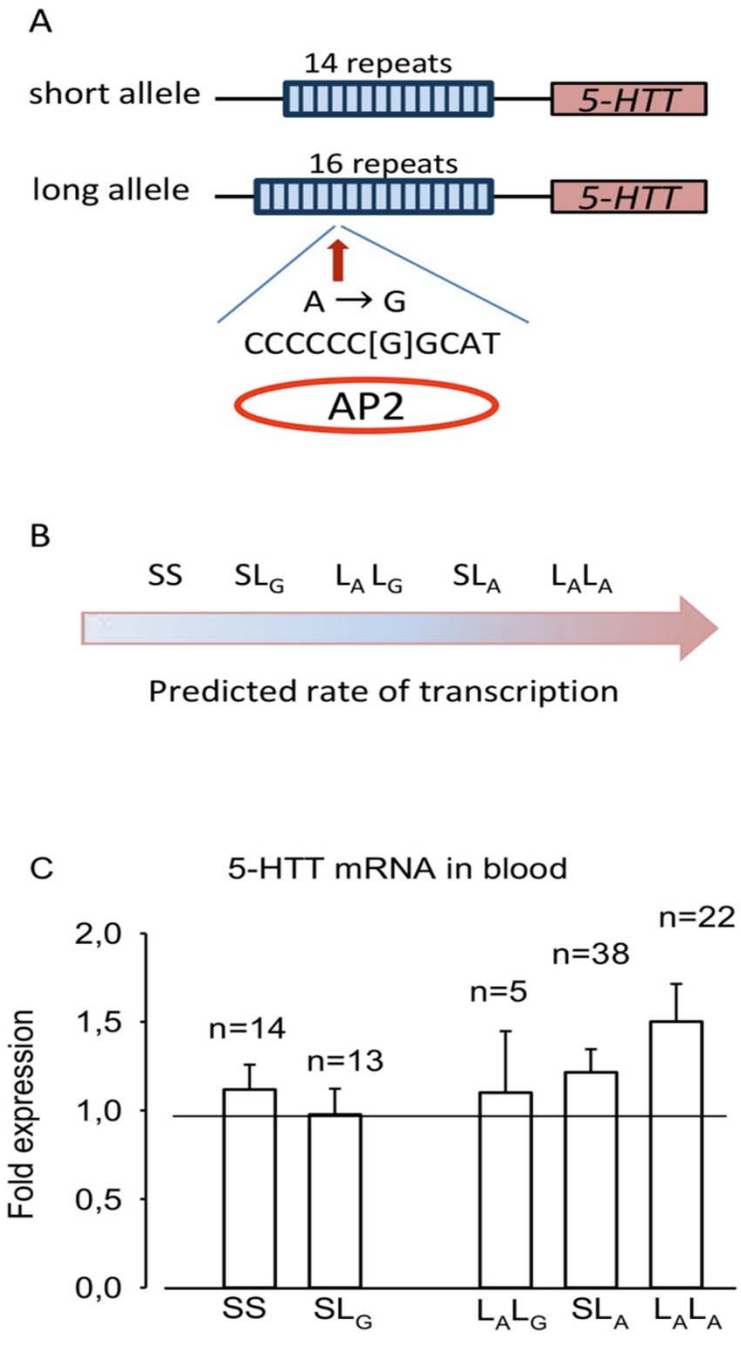
5-HTTLPR & SNP rs25531 A>G genotype in young CFS pts

- Serotonin transporter 5-HTT important for CNS re-uptake

- 5-HTT genotype affects transcription rate
  - Short: SS or SLg
  - Long: LaLg, SLa, LaLa




12
Chromosome 17
SLC6A4
Exon I
II
III
VII
XII
XIV
Promoter
Variants of regulation
S
L
5-HTTLPR
AAA
AAA
AAA
AAA
mRNA
MAOA
Storage vesicle
Serotonin
Serotonin transporter
Serotonin receptor

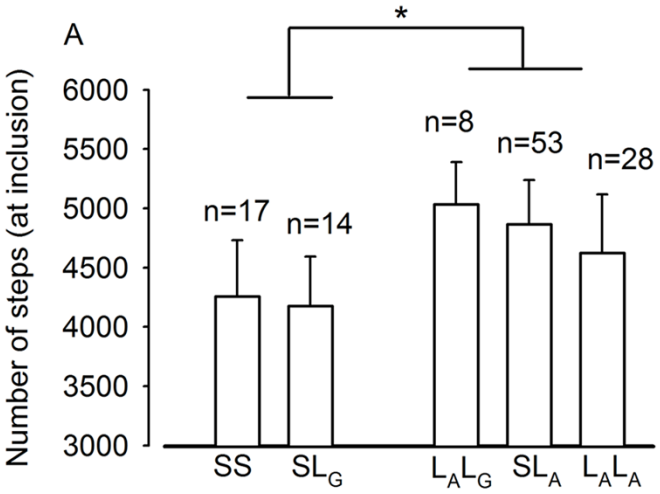

A
14 repeats
short allele
5-HTT
16 repeats
long allele
5-HTT
A → G
CCCCCC[G]GCAT
AP2
B
SS
SL_G
L_A L_G
SL_A
L_A L_A
Predicted rate of transcription
C
5-HTT mRNA in blood
Fold expression
2,0
1,5
1,0
0,5
0,0
n=14
n=13
n=5
n=38
n=22
SS
SL_G
L_A L_G
SL_A
L_A L_A

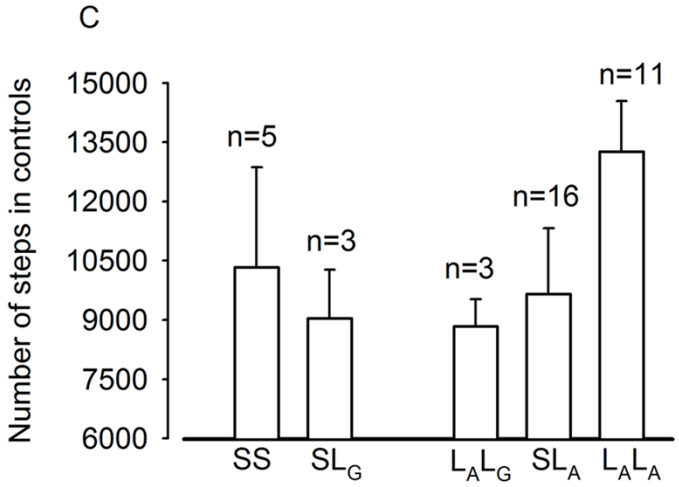
Methods

- 120 pediatric patients
  - Dept of Peds: Oslo University Hospital, Norway
  - National Referral Center for CFS pts 12-18 yo
- 38 age/gender matched HC
- Main Outcomes
  - Steps/Day
  - Functional Disability Inventory
    - Range 0-60
    - Subcategories 0-4: No Trouble – Impossible

Results

P= 0.008





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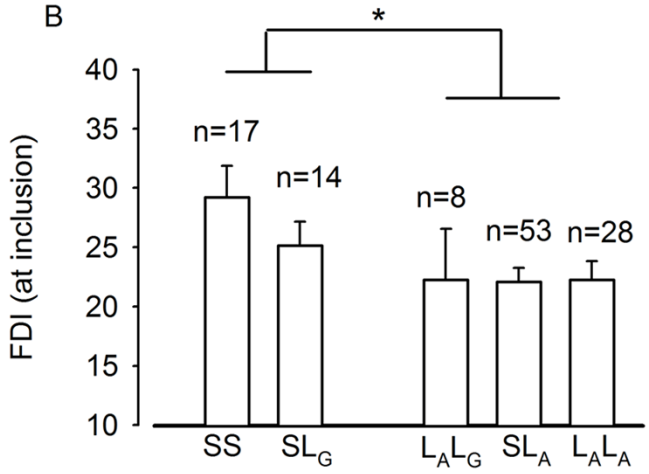
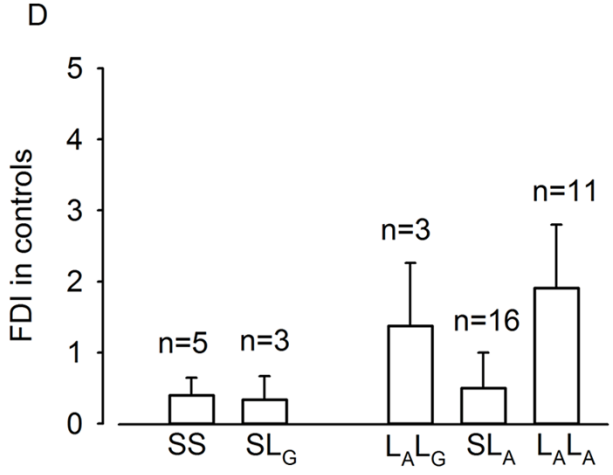
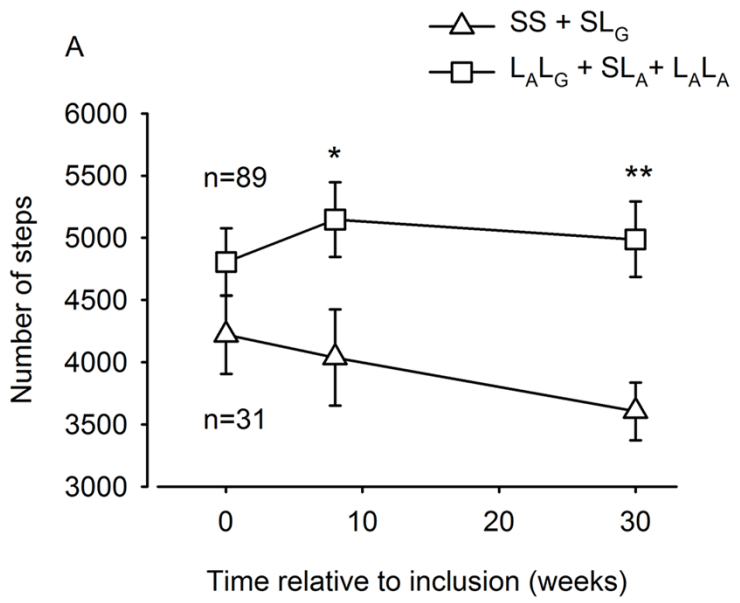


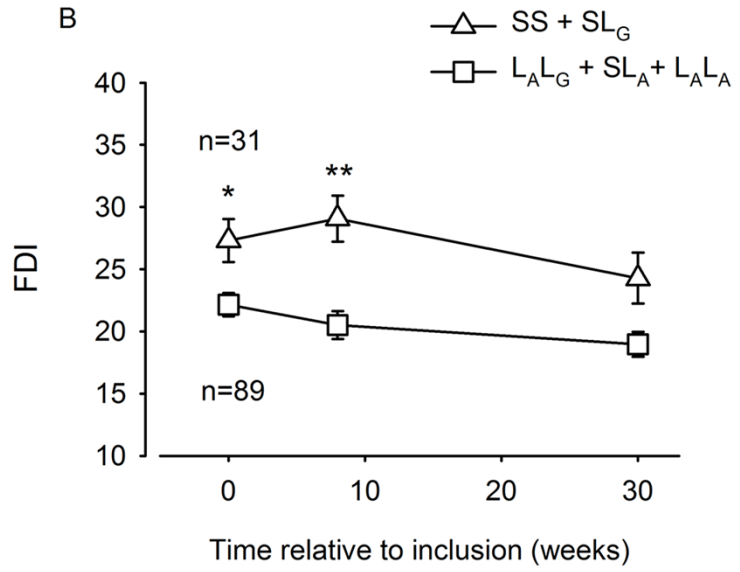


Results

- SS & SLg
  - Sig lower steps/day
  - Sig higher FDI score
  - Worse 30 week outcomes

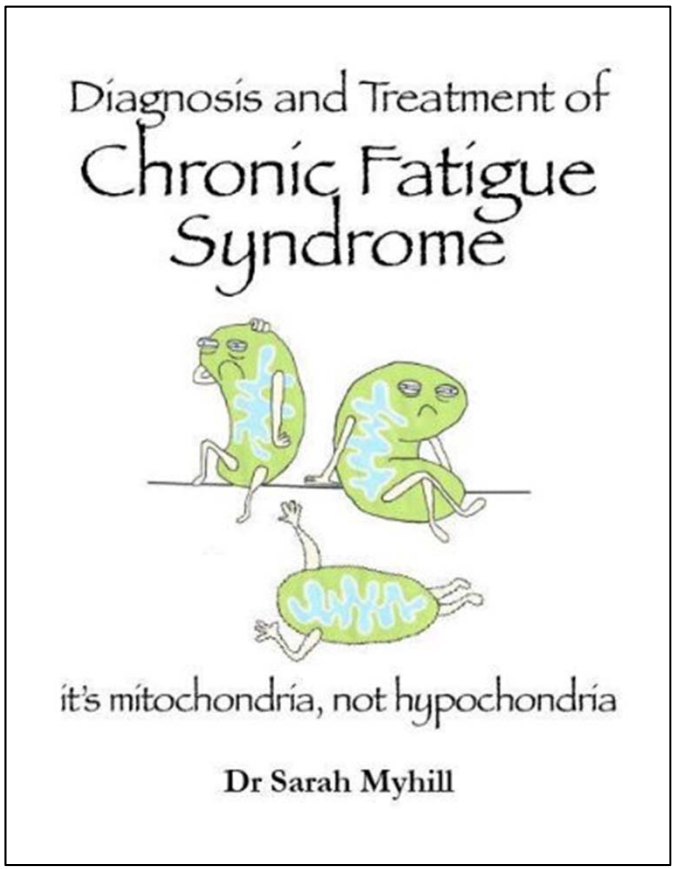
- 5-HTT genotype maybe a factor in maintenance of CFS



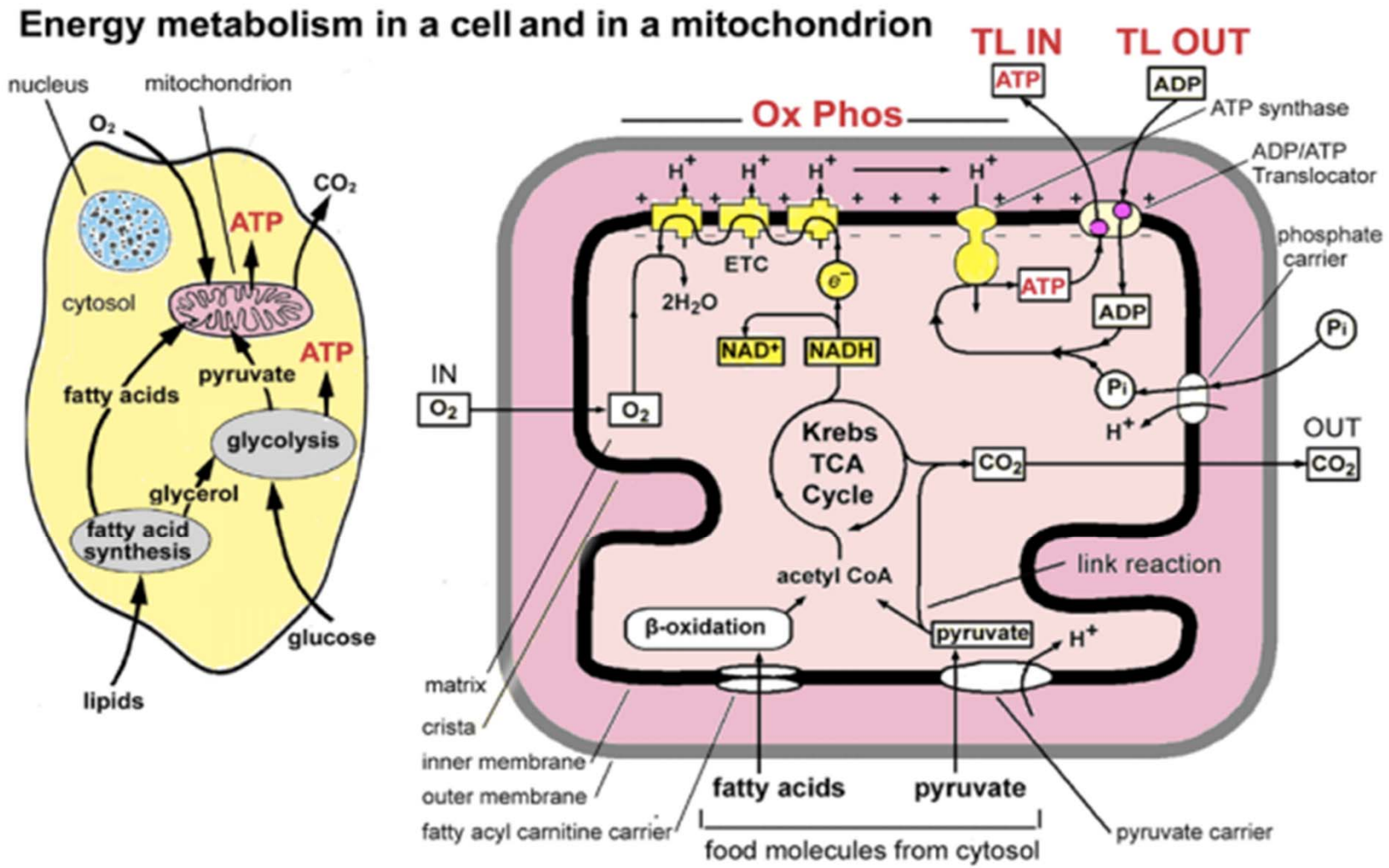


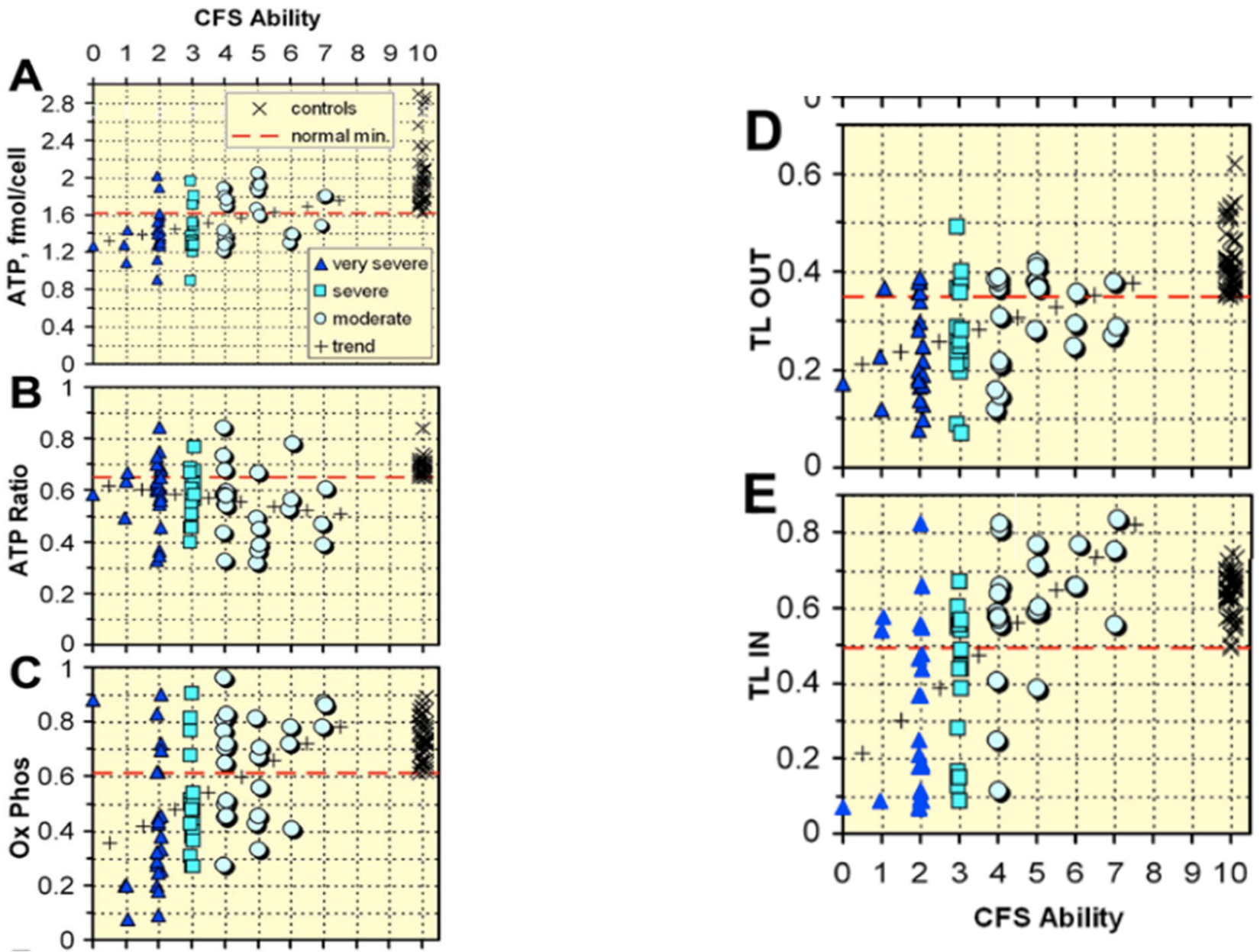
CFS & Mitochondrial Dysfunction

- Mounting evidence of dysfunctions on cellular level
- ATP Profiles
  - Very Severe – Severe – Moderate
- 71 CFS Patients
  - Ages 14-75 (mean 47 yo)
  - 54 female
  - 17 male
- 50 Healthy Controls



Chronic fatigue syndrome and mitochondrial dysfunction




CFS Ability
A
ATP, fmol/cell
controls
normal min.
very severe
severe
moderate
trend
B
ATP Ratio
C
Ox Phos
D
TL OUT
E
TL IN
CFS Ability

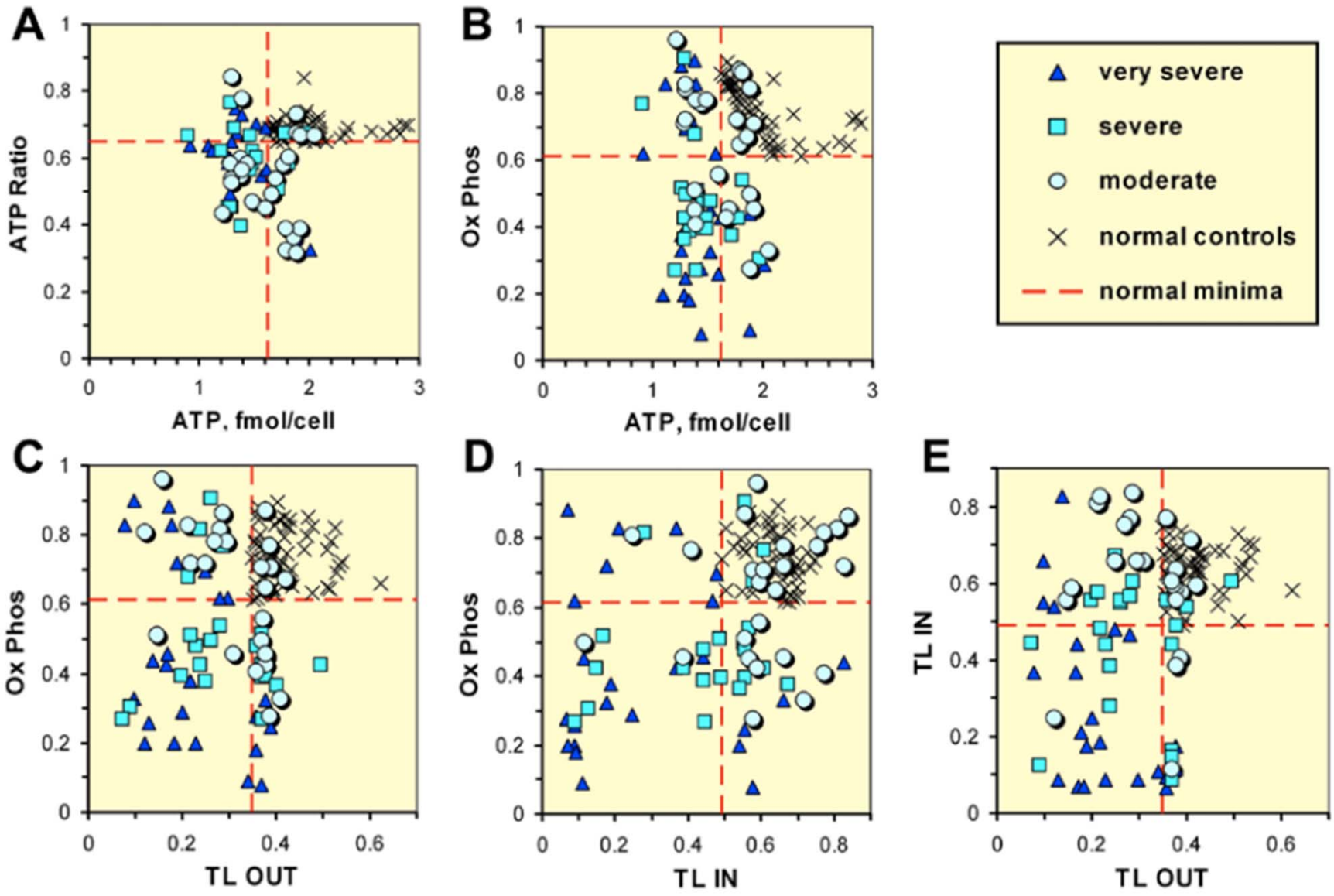
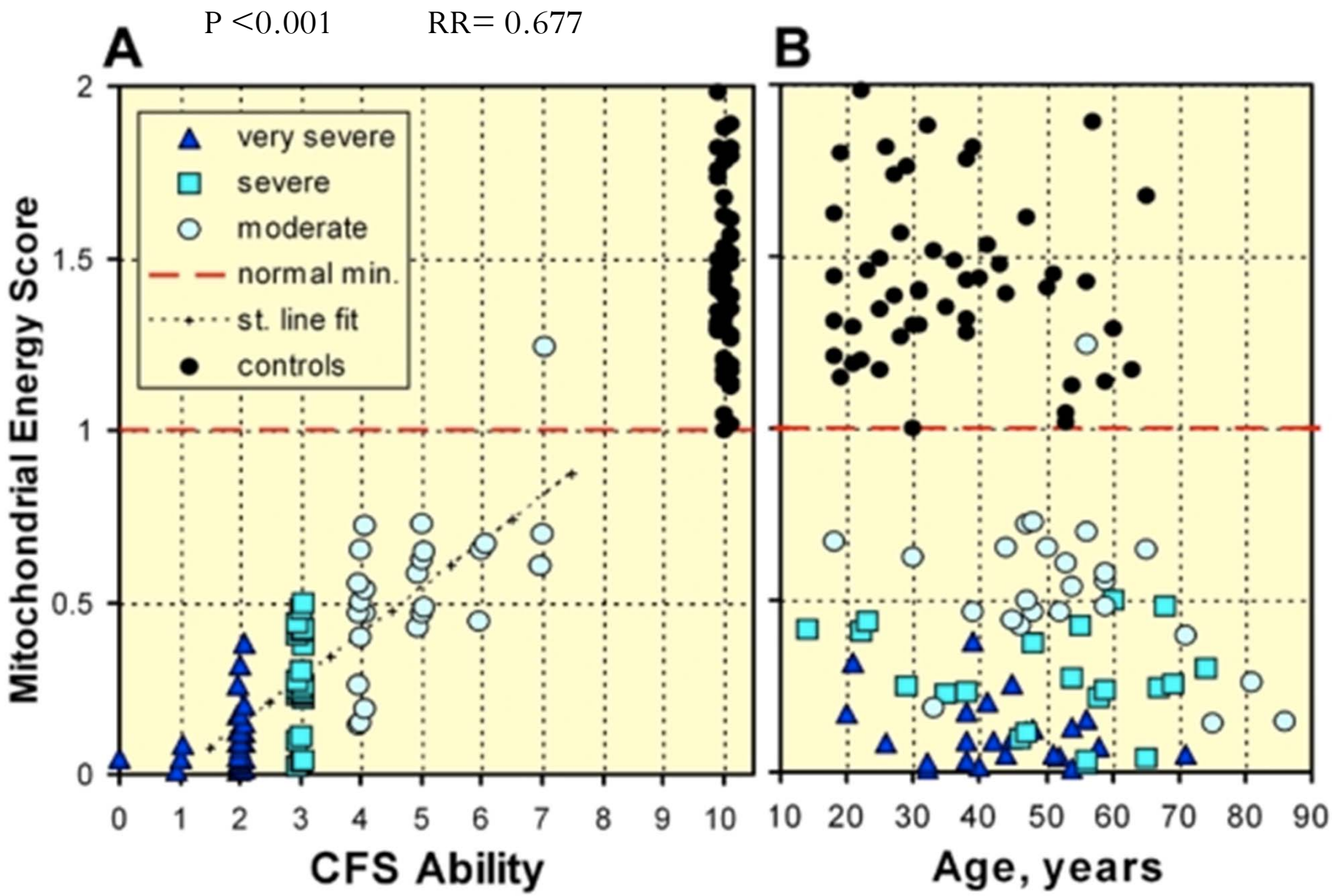
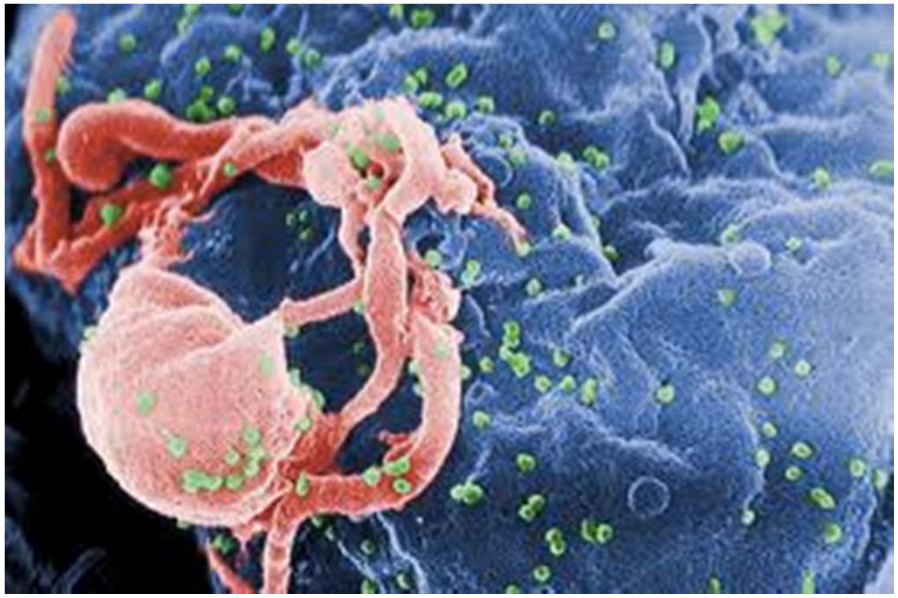


Figure 3. Scatter plots of correlations between pairs of factors measured in the "ATP profile".


P <0.001
RR= 0.677
A
B
very severe
severe
moderate
normal min.
st. line fit
controls
Mitochondrial Energy Score
CFS Ability
Age, years
0
0.5
1
1.5
2
0 1 2 3 4 5 6 7 8 9 10
10 20 30 40 50 60 70 80 90

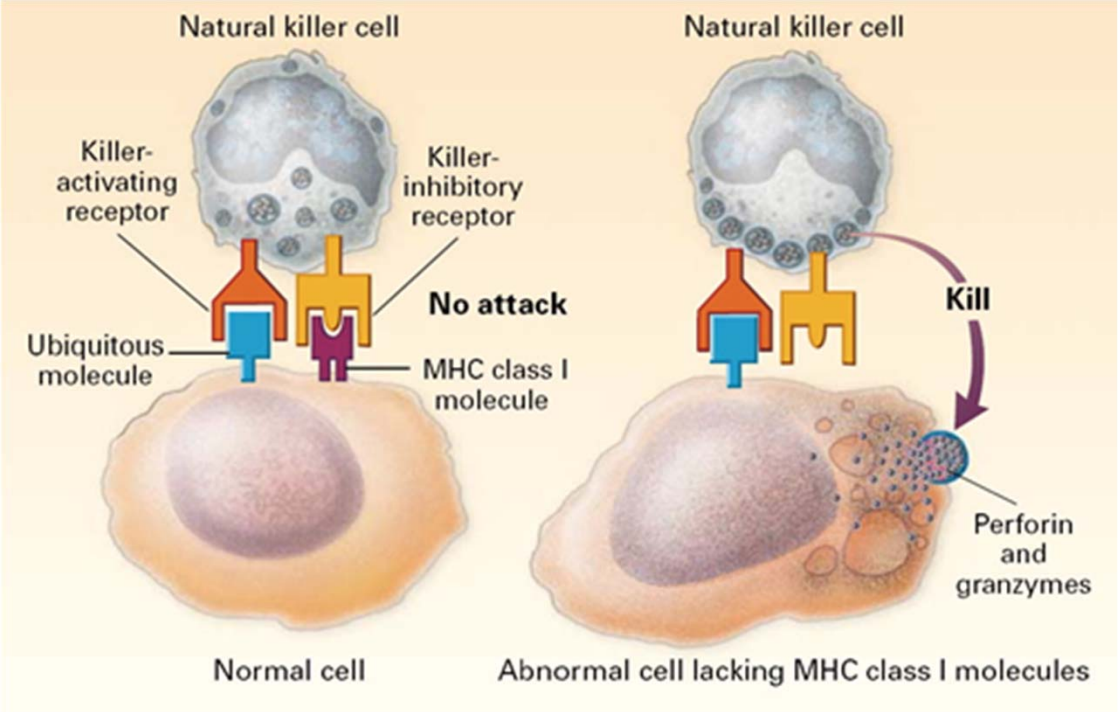
Post Viral/Infectious Etiologies

- EBV – HHV6 – Coxsackie B – HTLV – XMRV – Lyme
- Mostly ruled out as directly causative
- Post Viral Immune Dysfunction



Reduced NK cell activity in CFS

- CFS w/ known reduced NK cytotoxic & lytic activity
  - Demonstrated in numerous studies
  - Maintained throughout course of disease



Longitudinal investigation of NK cells in CFS

- Investigating NK cell cytotoxic activity
- 65 CFS vs 21 HC
- Flow cytometry protocols
  - K652 cells: erythroleukemia
  - Baseline → 6mo → 12mo

    T1 → T2 → T3

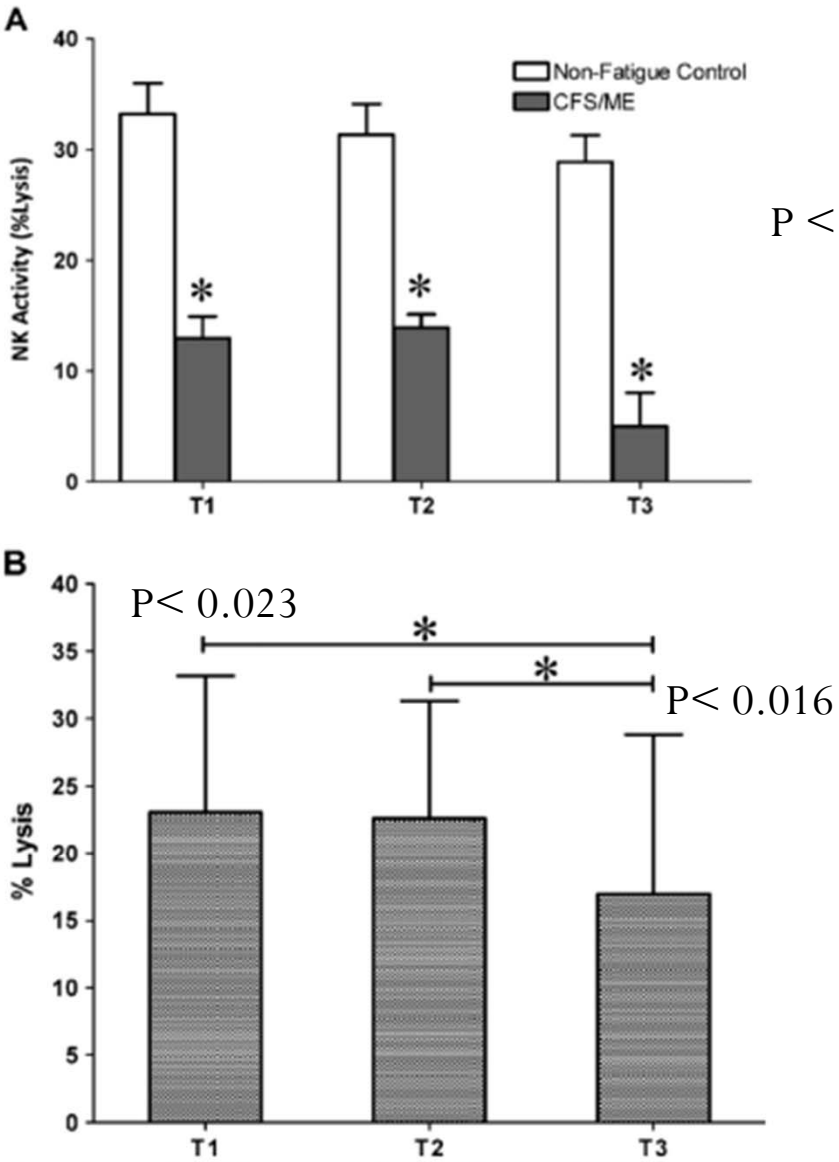
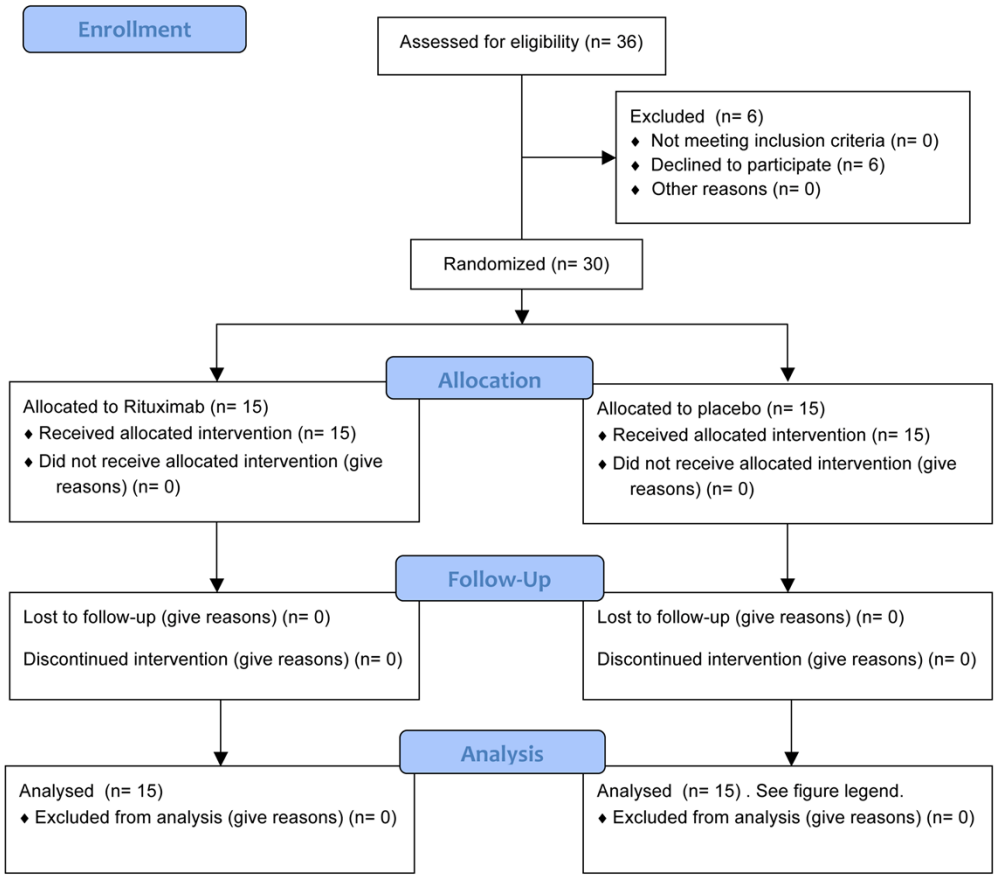
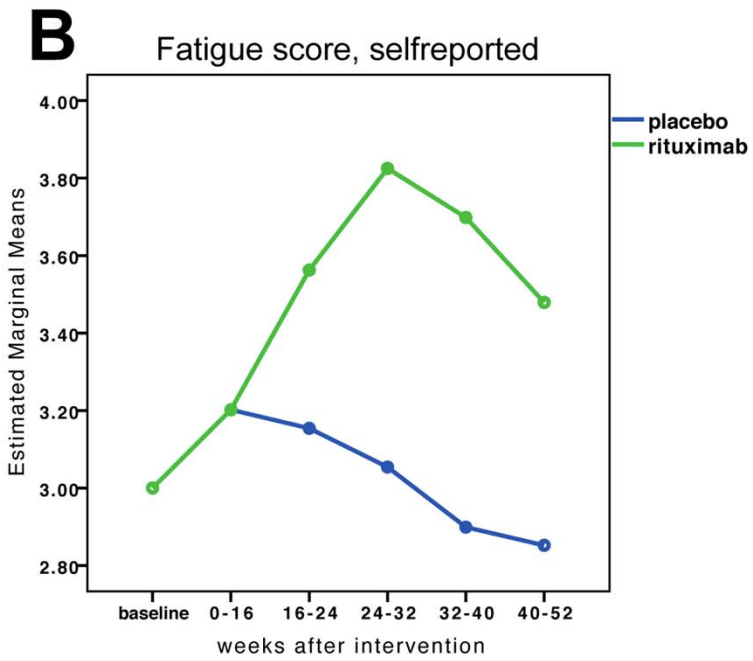


Figure 1 NK Cytotoxic activity was decreased at all time points in the CFS/ME patients. (A) Cytotoxic activity presented as % lysis of K562 cells by NK cells assessed overtime at T1, T2 and T3 in the CFS/ME patients (black bars) and control (white bars) participants. **(B)** Cluster analysis showing the overall cytotoxic activity in the whole participant group. *Indicates statistical significant results relative to controls. Statistics are presented as mean ± SEM.

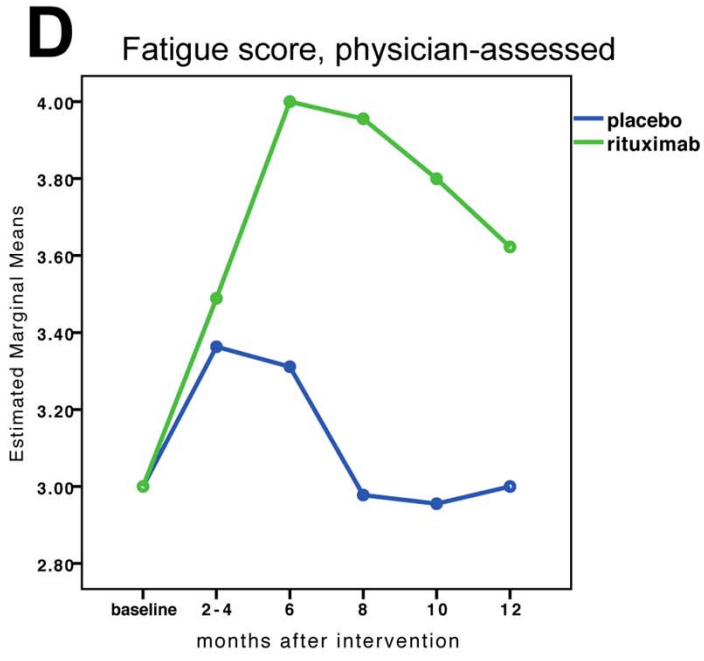
Benefit from B-Lymphocyte Depletion Using Rituximab in CFS pts

- Double blind Placebo-controlled
- 30 CFS patients
  - 15 Rituximab
  - 15 Saline
- f/u 12 mo





Rituximab - Placebo						
difference:	0.00	0.00	0.41	0.77	0.80	0.63
95% CI, lower:		-0.31	-0.28	0.16	0.16	-0.09
95% CI, upper:		0.31	1.10	1.38	1.44	1.34
p-values:		1.00	0.23	0.016	0.016	0.083



Rituximab - Placebo						
difference:	0.00	0.13	0.69	0.98	0.84	0.62
95% CI, lower:		-0.35	-0.09	0.33	0.11	-0.09
95% CI, upper:		0.61	1.47	1.62	1.58	1.34
p-values:		0.060	0.081	0.004	0.025	0.086

Results

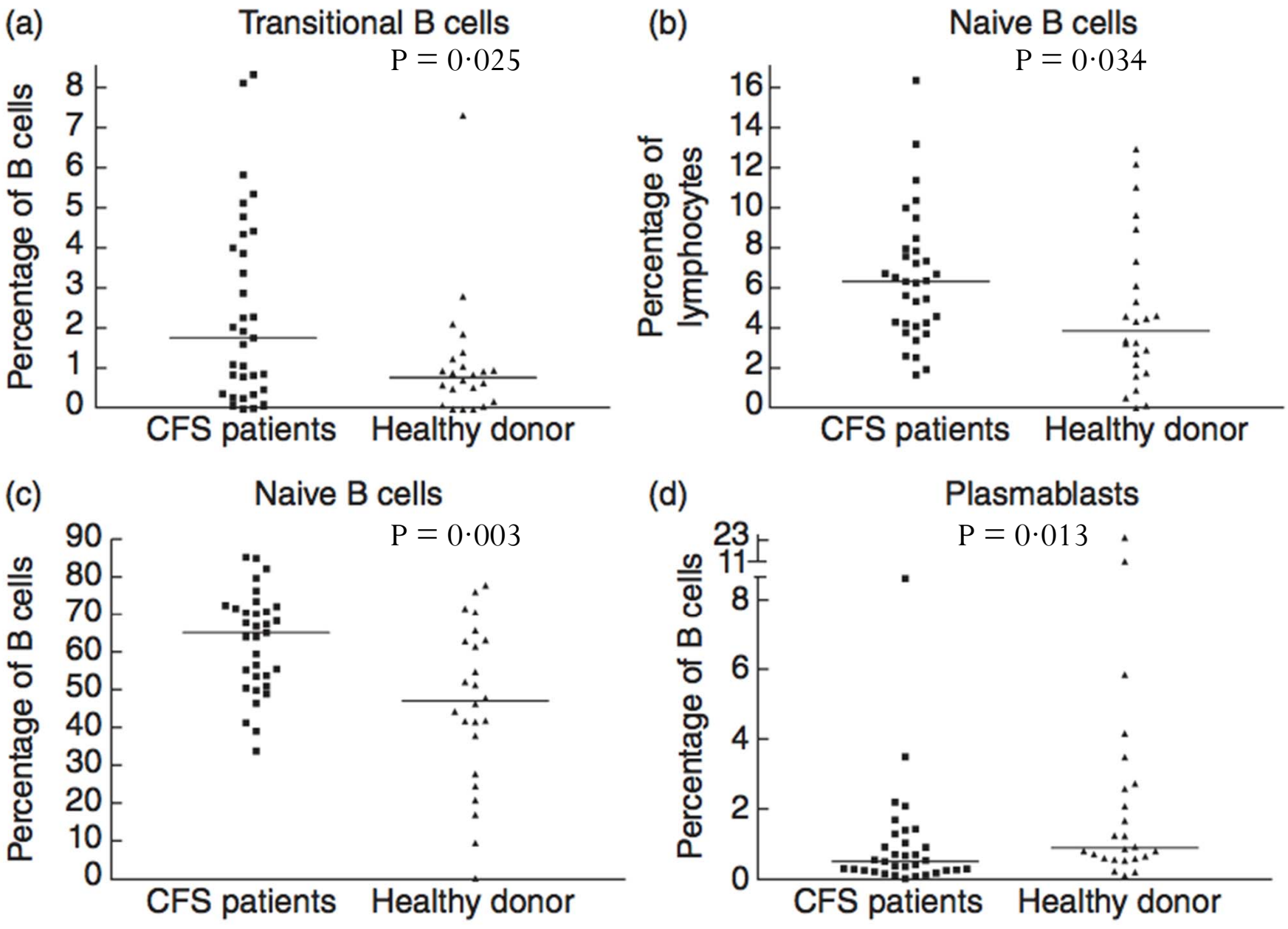
67% improvement w/Rituximab

13% w/placebo

P = 0.003

Altered functional B cell subset populations in CFS

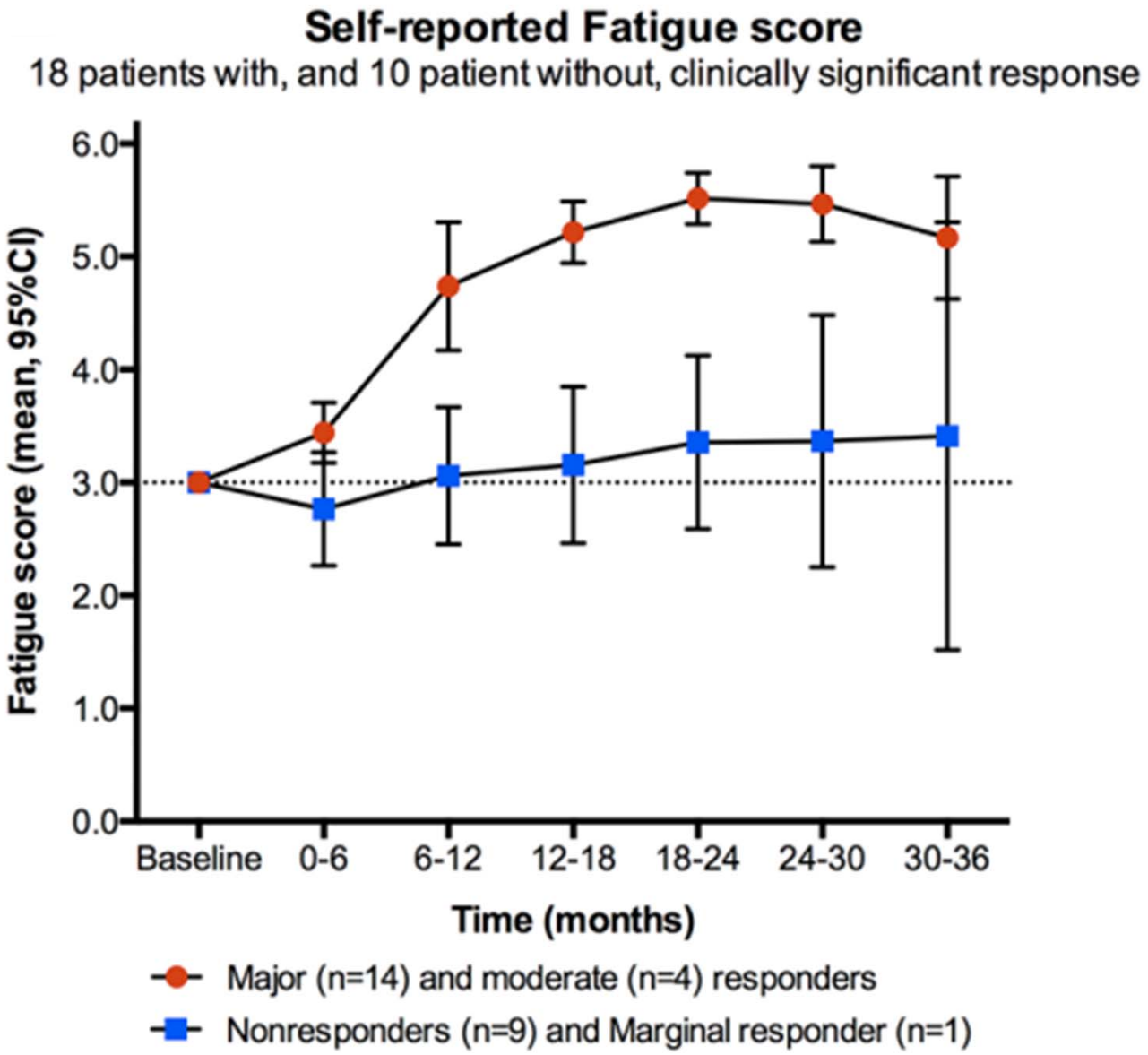
- Response to Rituximab suggests B-cell pathology
- 33 CFS vs. 24 HC
- Differences noted in transitional and naïve B-cell expression

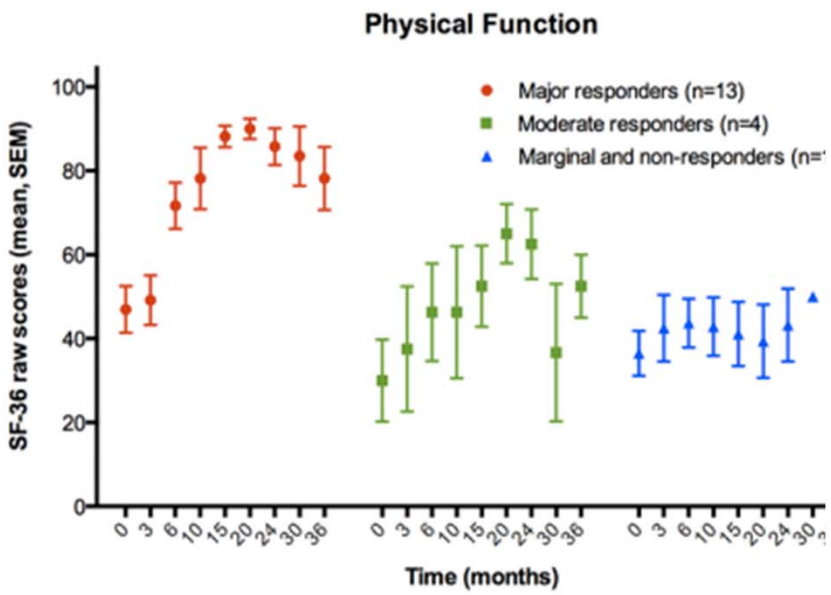

(a)
Transitional B cells
P = 0·025
Percentage of B cells
0
1
2
3
4
5
6
7
8
CFS patients
Healthy donor
(b)
Naive B cells
P = 0·034
Percentage of lymphocytes
0
2
4
6
8
10
12
14
16
CFS patients
Healthy donor
(c)
Naive B cells
P = 0·003
Percentage of B cells
0
10
20
30
40
50
60
70
80
90
CFS patients
Healthy donor
(d)
Plasmablasts
P = 0·013
Percentage of B cells
0
2
4
6
8
11
23
CFS patients
Healthy donor

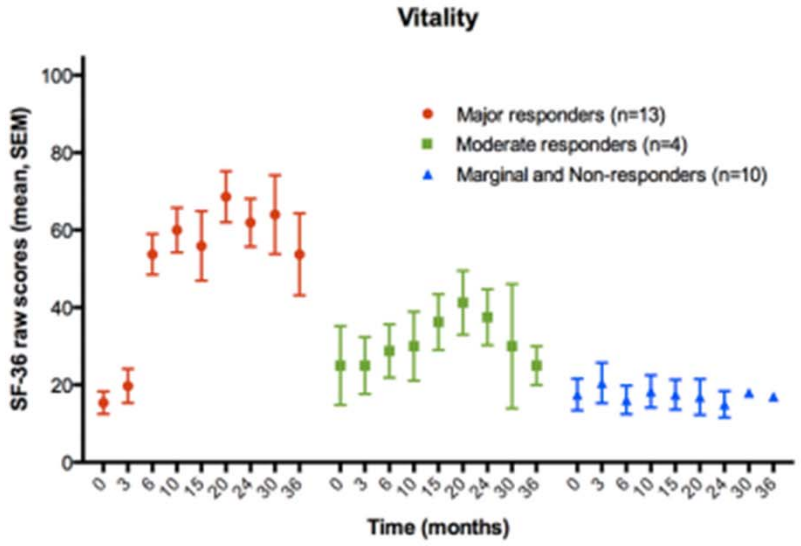
B-Cell Depletion in CFS: Open Label Phase II w/Rituximab Maintenance Tx

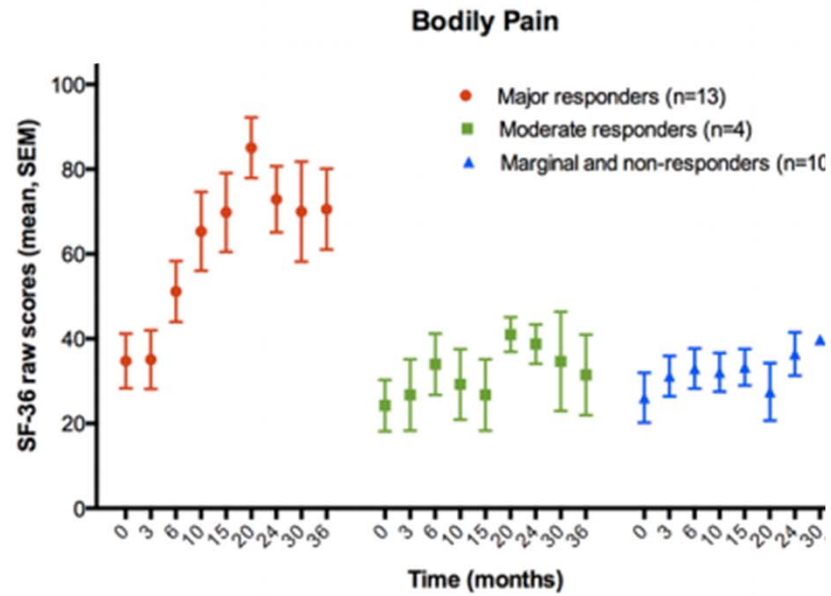
- 29 CFS pts
  - Rituximab x2 – 2wks apart
  - Maintenance @ 3, 6, 10, 15 mo
  - f/u 36 mo

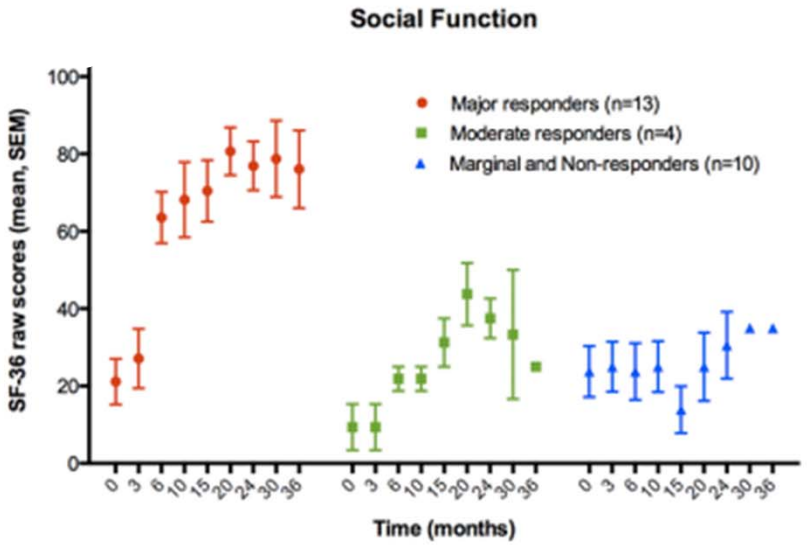
- 18 or 64% w/clinically significant responses
  - 14 major
  - 4 moderate
  - Mean response 26 mo


Self-reported Fatigue score
18 patients with, and 10 patient without, clinically significant response
Fatigue score (mean, 95%CI)
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Baseline
0-6
6-12
12-18
18-24
24-30
30-36
Time (months)
Major (n=14) and moderate (n=4) responders
Nonresponders (n=9) and Marginal responder (n=1)

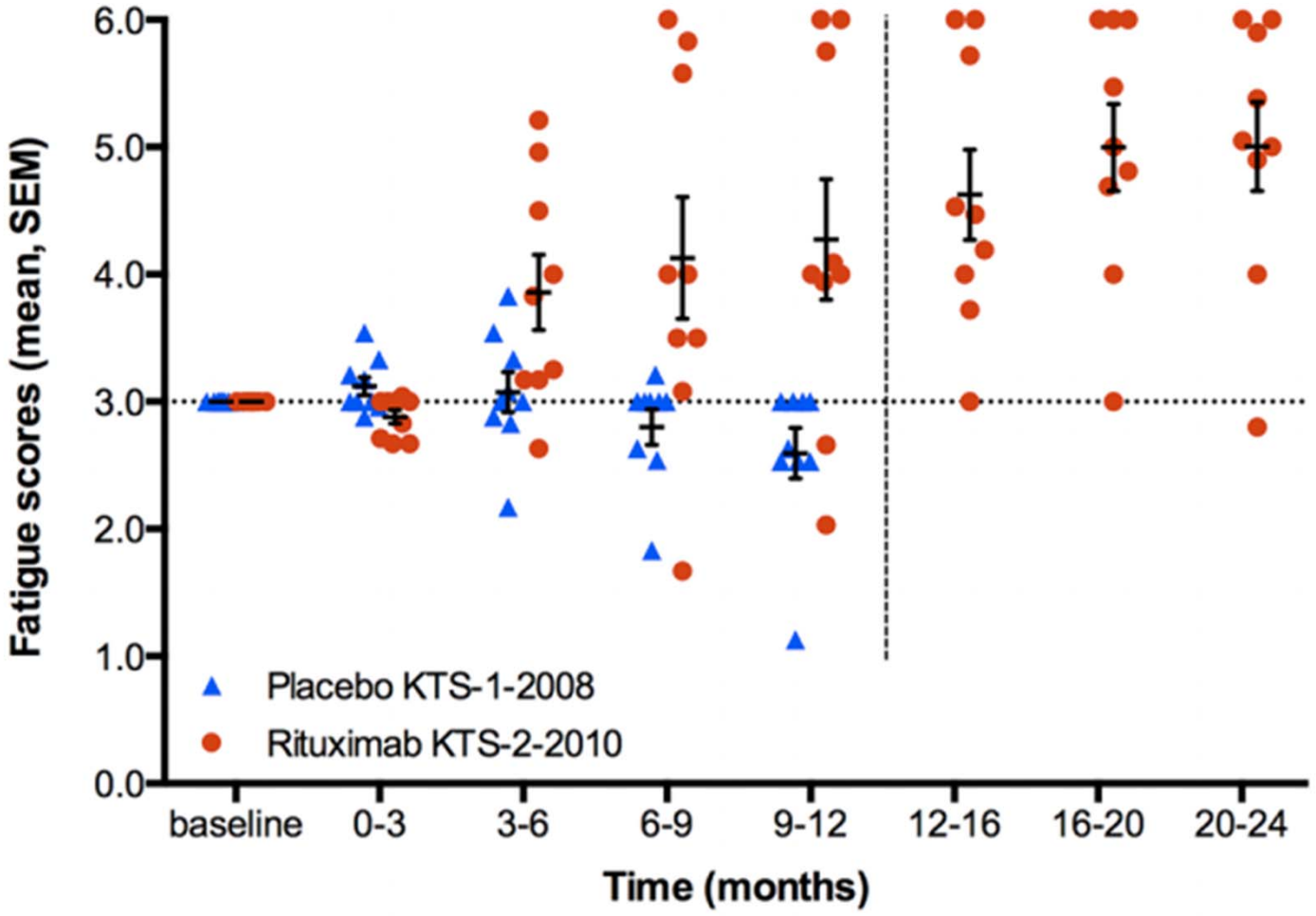

Physical Function
Major responders (n=13)
Moderate responders (n=4)
Marginal and non-responders (n=
SF-36 raw scores (mean, SEM)
Time (months)


Vitality
Major responders (n=13)
Moderate responders (n=4)
Marginal and Non-responders (n=10)
SF-36 raw scores (mean, SEM)
Time (months)

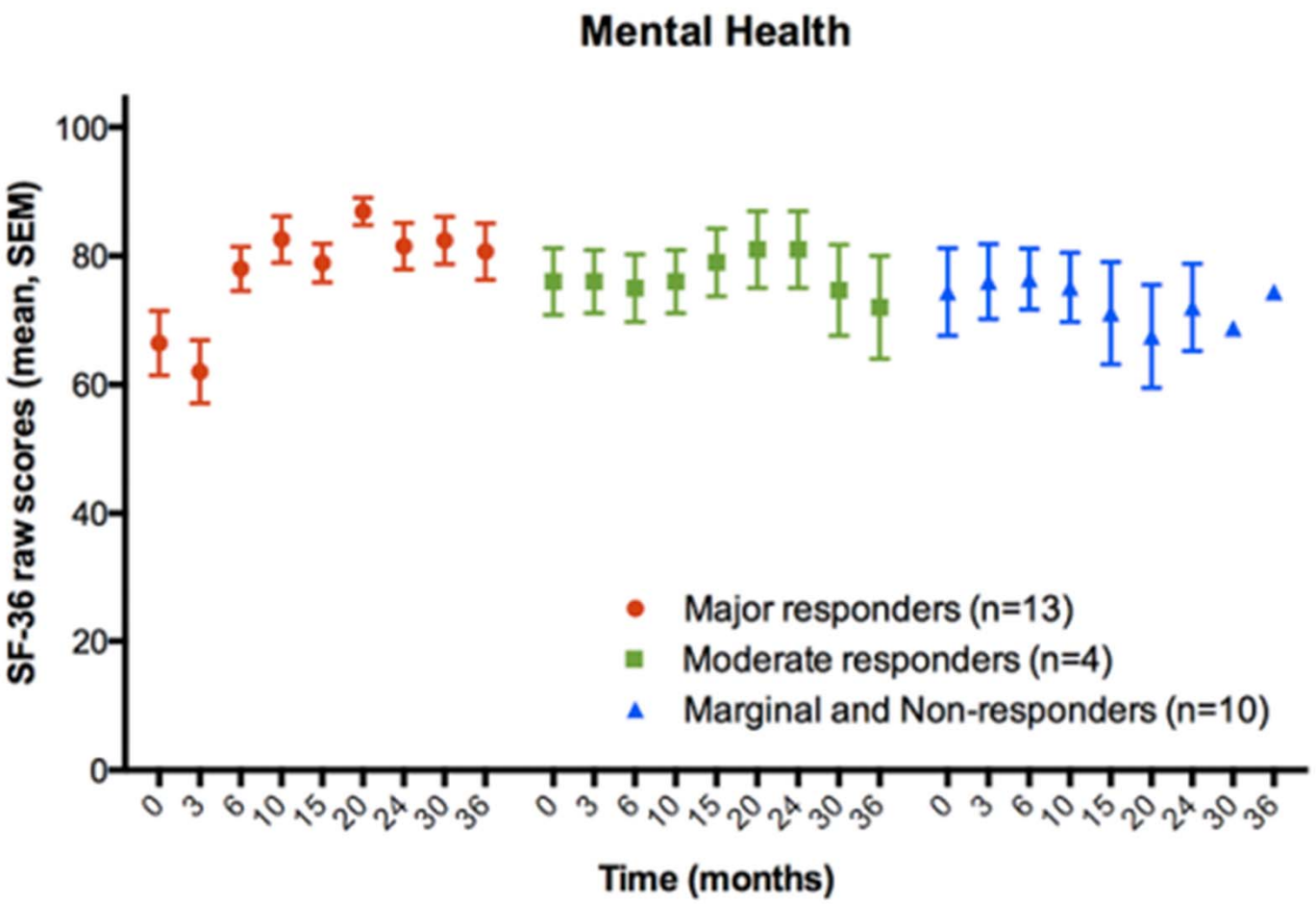

Bodily Pain
Major responders (n=13)
Moderate responders (n=4)
Marginal and non-responders (n=10
SF-36 raw scores (mean, SEM)
Time (months)


Social Function
Major responders (n=13)
Moderate responders (n=4)
Marginal and Non-responders (n=10)
SF-36 raw scores (mean, SEM)
Time (months)

Nine patients with Placebo in KTS-1-2008, given Rituximab in KTS-2-2010



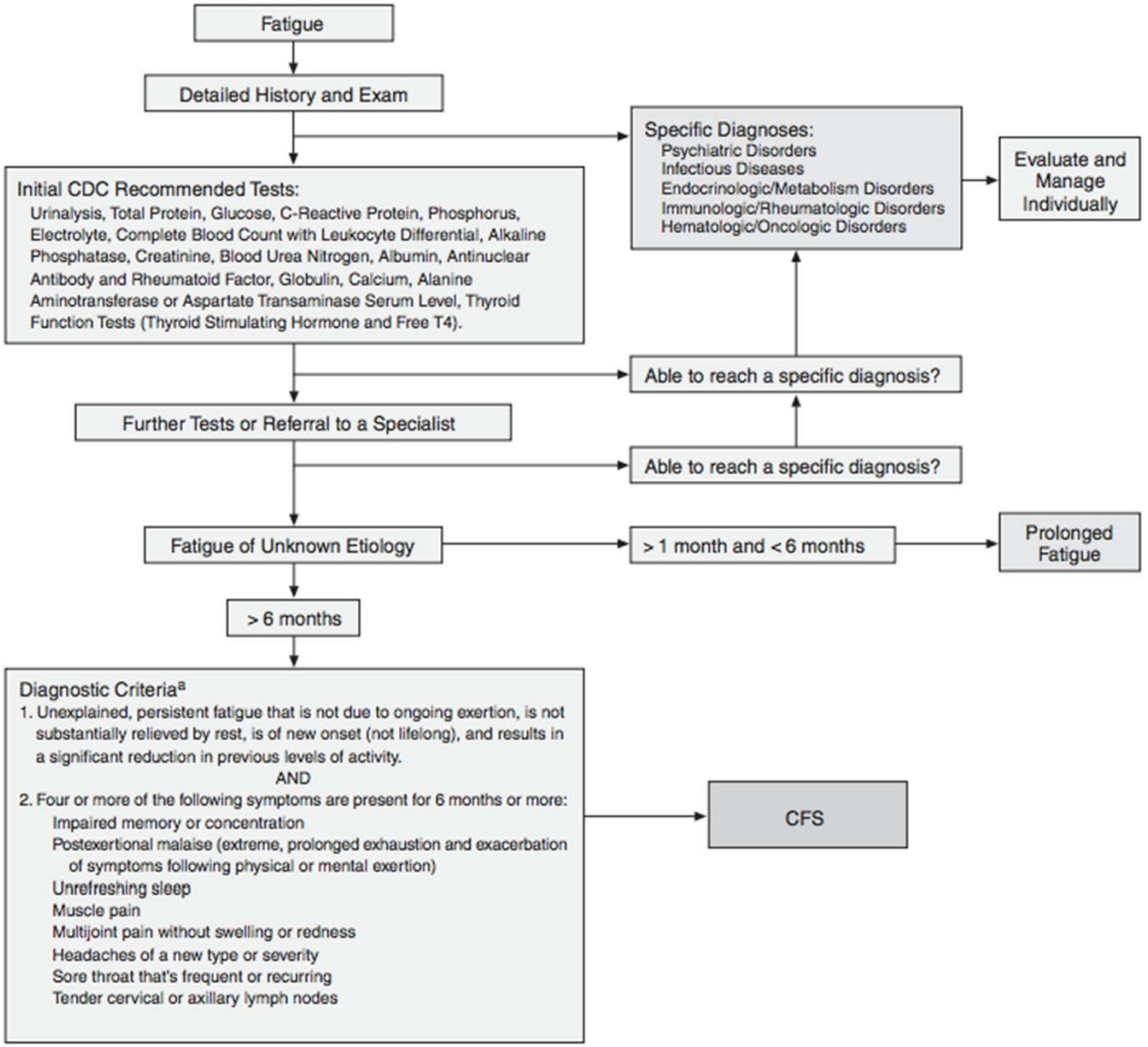
p=0.003 for interaction Time*Group (until 12 months)


Mental Health
SF-36 raw scores (mean, SEM)
100
80
60
40
20
0
0 3 6 10 15 20 24 30 36
0 3 6 10 15 20 24 30 36
0 3 6 10 15 20 24 30 36
Time (months)
Major responders (n=13)
Moderate responders (n=4)
Marginal and Non-responders (n=10)

NIH Funding per FY 2011-2016

Bioengineering	$3,303	$3,498	$3,234	$3,329	$3,353	$3,432
Biotechnology	$5,823	$6,089	$5,698	$5,889	$5,925	$6,046
Brain Cancer	$280	$281	$280	$289	$290	$299
Brain Disorders	$3,864	$3,968	$3,708	$3,894	$3,920	$4,014
Breast Cancer	$715	$800	$657	$682	$685	$704
Burden of Illness	$40	$84	$72	$73	$74	$76
Cancer	$5,448	$5,621	$5,274	$5,392	$5,414	$5,568
Cardiovascular	$2,049	$2,040	$1,964	$1,950	$1,957	$2,004
Cerebral Palsy	$23	$42	$18	$21	$21	$21
Cervical Cancer	$119	$112	$98	$116	$116	$119
Charcot-Marie-Tooth Disease	$13	$13	$11	$14	$14	$14
Child Abuse and Neglect Research	$30	$32	$30	$30	$30	$31
Childhood Leukemia	$59	$77	$67	$105	$105	$108
Chronic Fatigue Syndrome (ME/CFS)	$6	$5	$5	$5	$5	$6
Chronic Liver Disease and Cirrhosis	$303	$288	$282	$293	$294	$300
Chronic Obstructive Pulmonary Disease	$108	$101	$102	$107	$108	$110
Climate Change	$6	$8	$8	$6	$6	$6
Climate-Related Exposures and Conditions 10/	$155	$157	$137	$131	$131	$134
Clinical Research	$10,503	$10,951	$10,604	$11,087	$11,132	$11,376
Clinical Trials	$3,093	$3,208	$3,155	$3,221	$3,233	$3,298
Colo-Rectal Cancer	$313	$302	$281	$271	$272	$280

Figure 1. Algorithm for Evaluating Chronic Fatigue Syndrome (CFS)



Conclusions

- Heterogeneous severity of disorders
- Lacking clear diagnostic criteria
- Concrete reproducible evidence and research lacking and underfunded
- No specific treatment guidelines
- Treatment based on symptom relief

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