



Biological and Non-Biological Indices of Disability & Change

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<http://condor.depaul.edu/~lvector/cfs>

Differentiating Level 1 and 2 Indices

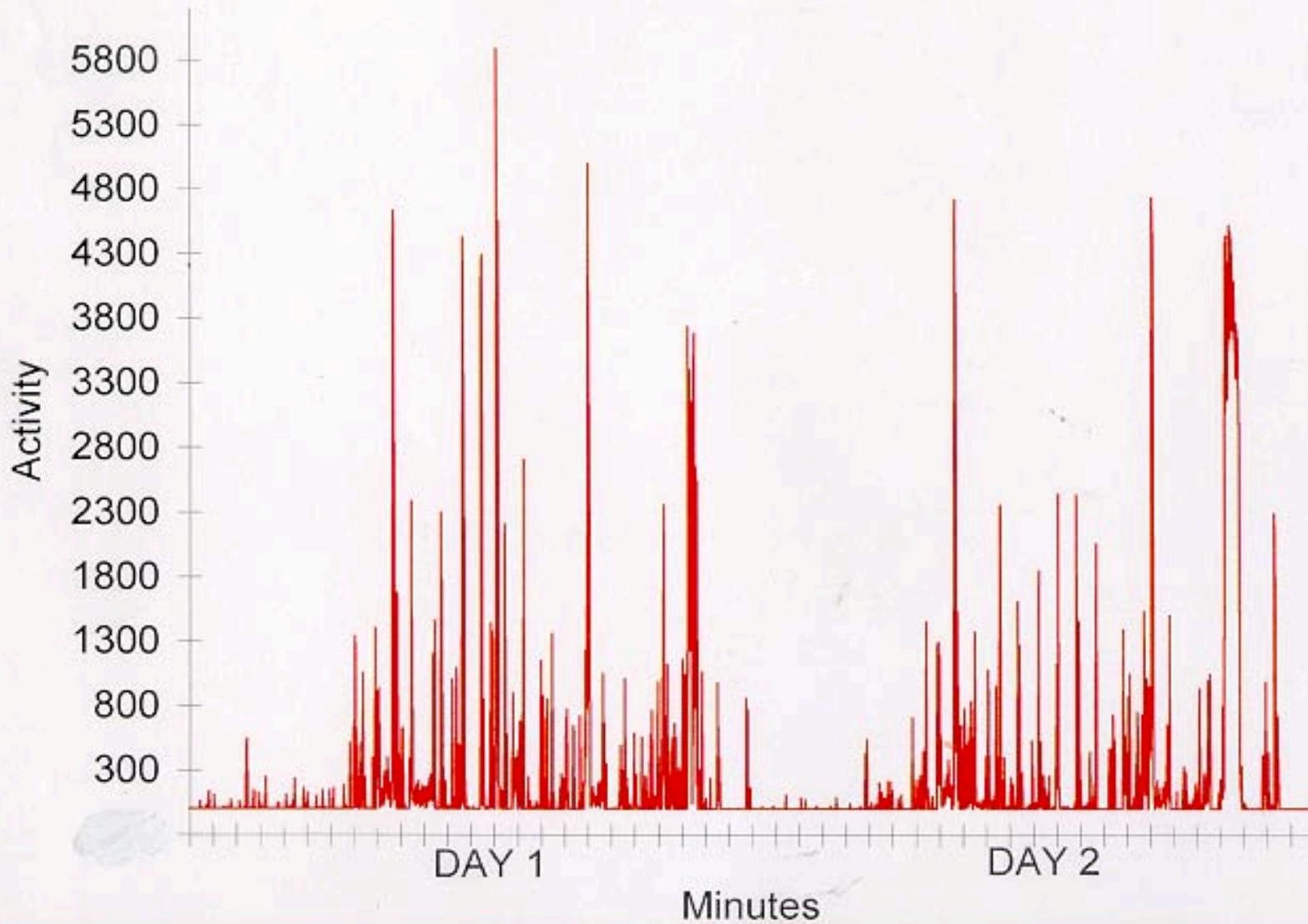
- Level 1
 - Objective biological or behavior
- Level 2
 - Self-report
- Implications for Assessment, Diagnosis and Treatment

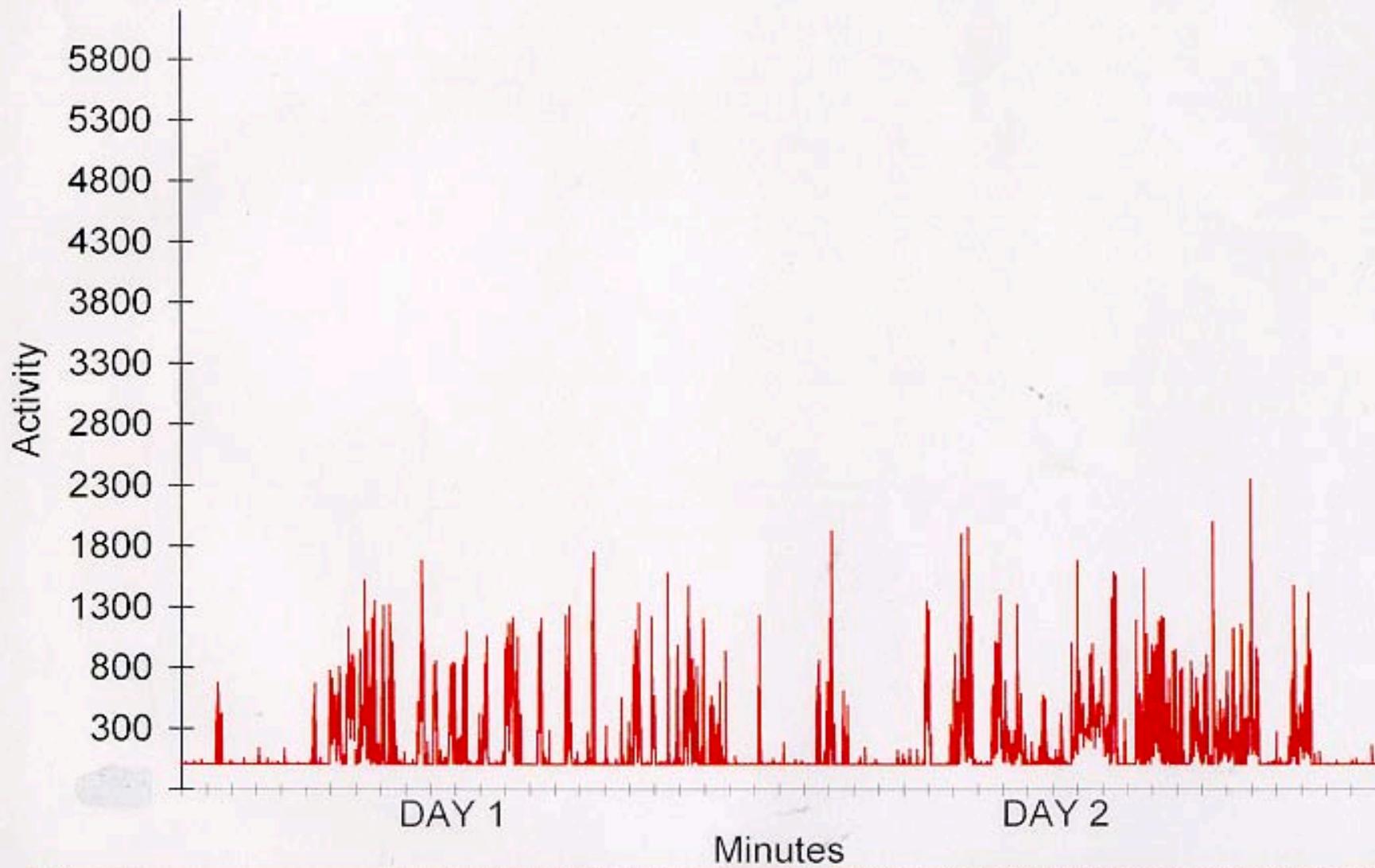
Measuring Fatigue

- Marked degree of new onset of unexplained, persistent or recurrent physical or mental fatigue
 - that substantially reduces activity level (**Canadian Criteria**)
 - that results in substantial reductions in previous levels of occupational, educational, social or personal activities (**Fukuda Criteria**)

Level 1: Behavior Measured by Actigraphy

- Next two slides show two days of activity for a
 - Healthy individual
 - Person with CFS

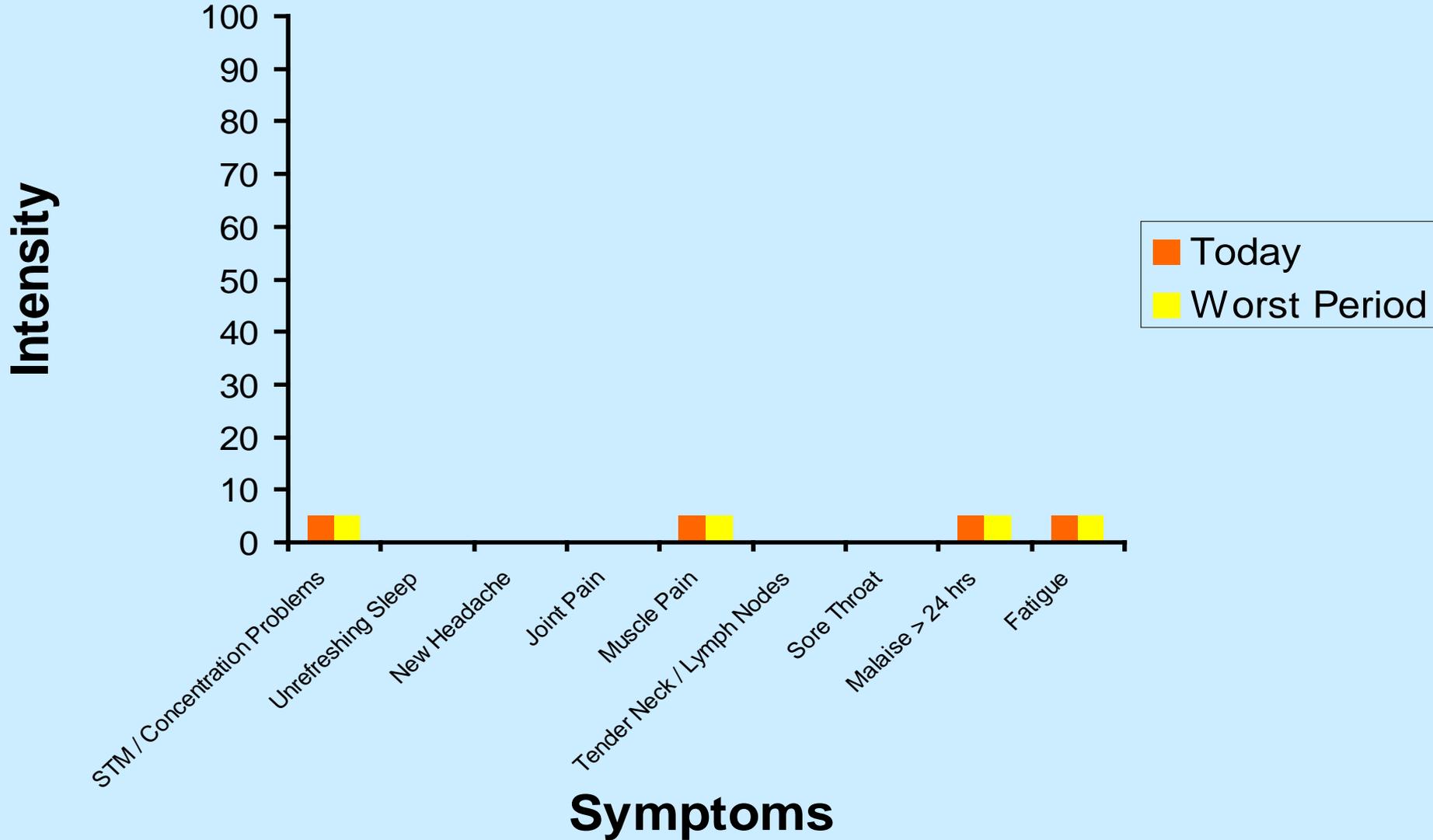




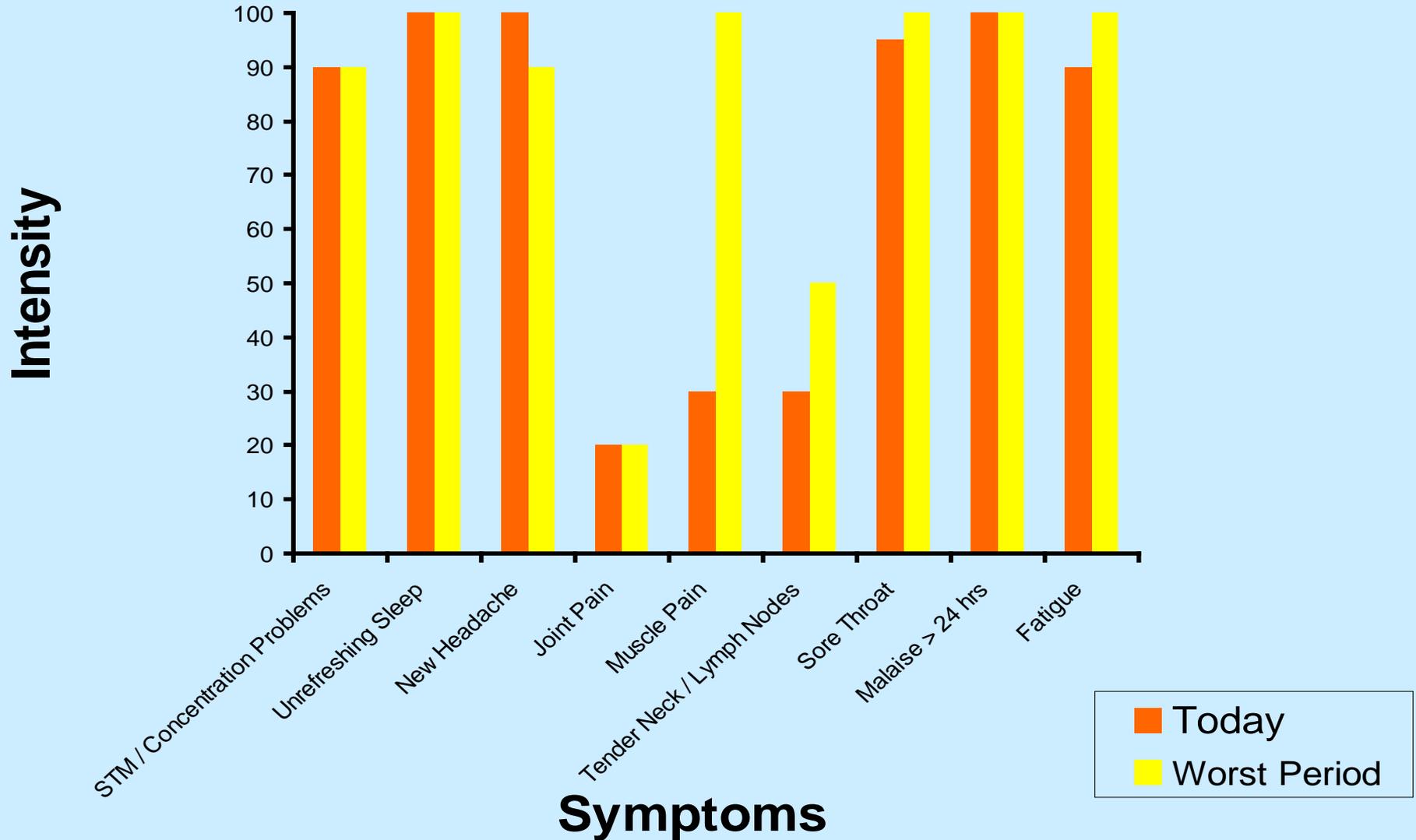
Level 2: Fatigue Scales

- Many fatigue scales do not accurately represent the severe fatigue that is characteristic of CFS
 - (Stouten. 2005)
- Consider issues of intensity and chronicity

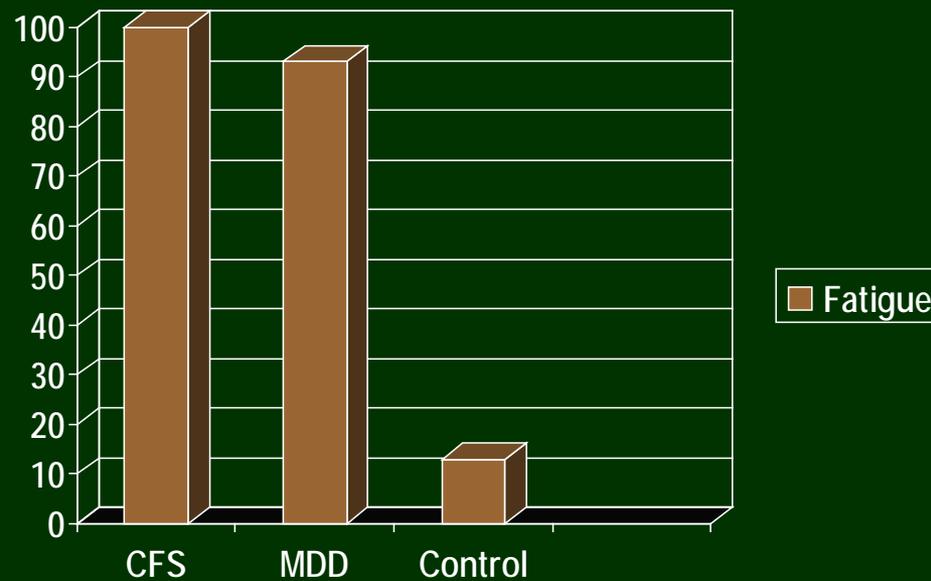
CFS Definitional Symptoms



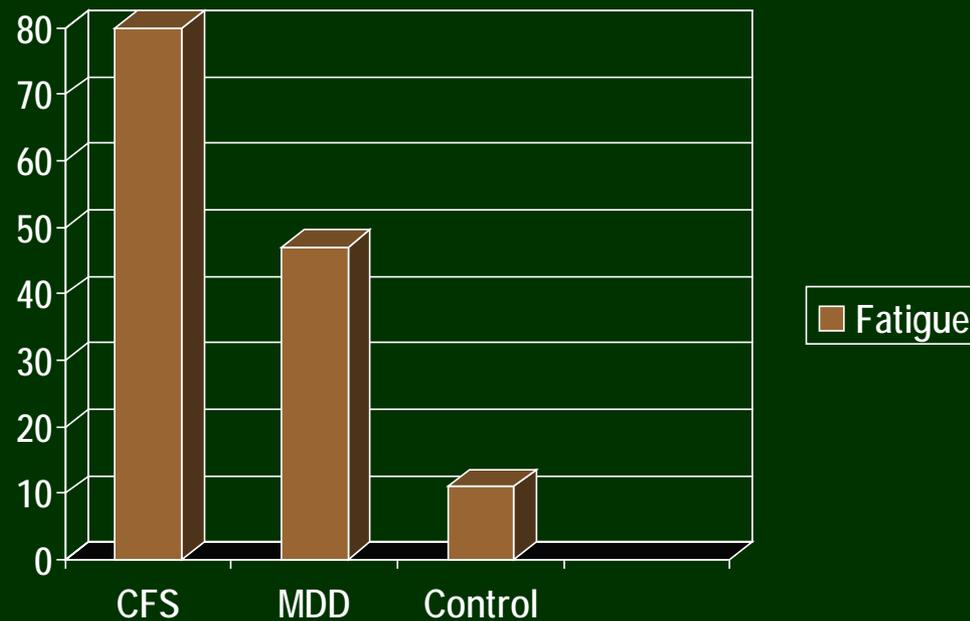
CFS Definitional Symptoms



Percent reporting fatigue for 6 months or longer



Percent reporting severity of fatigue for 6 months or longer



Level 2: ME/CFS Fatigue Types Questionnaire

- Energy Fatigue
- Wired Fatigue
- Brain Fog Fatigue
- Post-exertional Fatigue
- Flu Fatigue

Control	Global
Limbs feel heavy when not moving them	.47
Dead, heavy feeling that occurs quickly after exercise	.57
Muscle weakness even after resting	.56
Next day soreness or fatigue after everyday activities	.53
Physically drained or sick after mild activity	.79
Minimum exercise makes you physically tired	.70
Mind racing when exhausted	.40
Body feels over-stimulated when very tired	.55
Hard to sleep because body and mind feeling tense & agitated	.64
Very hard to relax or reduce muscle tension	.45
Mentally tired after the slightest effort	.64
Thinking is hard work and muddy	.68
Misplace items and cannot remember things	.56
When talking, much difficulty with words	.67
Overwhelming sleepiness	.69
Flu-like symptoms such as nasal congestion, sinus pain, etc.	.58
Muscle ache or pain all over body	.49
Feel like have high temperature of fever	.56
Headaches and nausea	.57
Dizziness	.51
Do not have physical energy to do anything	.65
Lack the energy to talk to anyone	.74

Five Factor Analysis of CFS Types of Fatigue	Post Exertional	Wired	Brain Fog	Flu-Like	Energy
Limbs feel heavy when not moving them	.45	.20	.07	.10	.43
Dead, heavy feeling that occurs quickly after exercise	.76	.17	.29	.14	.09
Muscle weakness even after resting	.53	.18	.16	.30	.41
Next day soreness or fatigue after everyday activities	.70	.13	.18	.34	.22
Physically drained or sick after mild activity	.68	.10	.27	.37	.26
Minimum exercise makes you physically tired	.82	.07	.27	.31	.16
Mind racing when exhausted	.00	.76	.22	.16	.16
Body feels over-stimulated when very tired	.17	.72	.29	.09	.03
Hard to sleep because body and mind feeling tense & agitated	.12	.72	.01	.22	.17
Very hard to relax or reduce muscle tension	.16	.58	.22	.19	.03
Mentally tired after the slightest effort	.49	.15	.58	.12	.25
Thinking is hard work and muddy	.32	.25	.73	.19	.17
Misplace items and cannot remember things	.14	.26	.75	.21	.11
When talking, much difficulty with words	.26	.26	.63	.19	.14
Overwhelming sleepiness	.29	.11	.35	.37	.32
Flu-like symptoms such as nasal congestion, sinus pain, etc.	.18	.20	.14	.76	-.01
Muscle ache or pain all over body	.30	.23	.07	.50	.14
Feel like have high temperature of fever	.13	.24	.16	.63	.05
Headaches and nausea	.20	.17	.13	.68	.21
Dizziness	.20	.00	.18	.59	.25
Do not have physical energy to do anything	.34	.12	.32	.29	.71
Lack the energy to talk to anyone	.32	.31	.22	.17	.50

Level 2: Activity Logs

- The NIH Activity record
 - (ACTRE)
 - daily self-administered log of physical activity over two days
 - obtain a composite of a comprehensive profile of functioning and dysfunction
 - (Gerber & Furst, 1992)

Activity Log: ACTRE Data

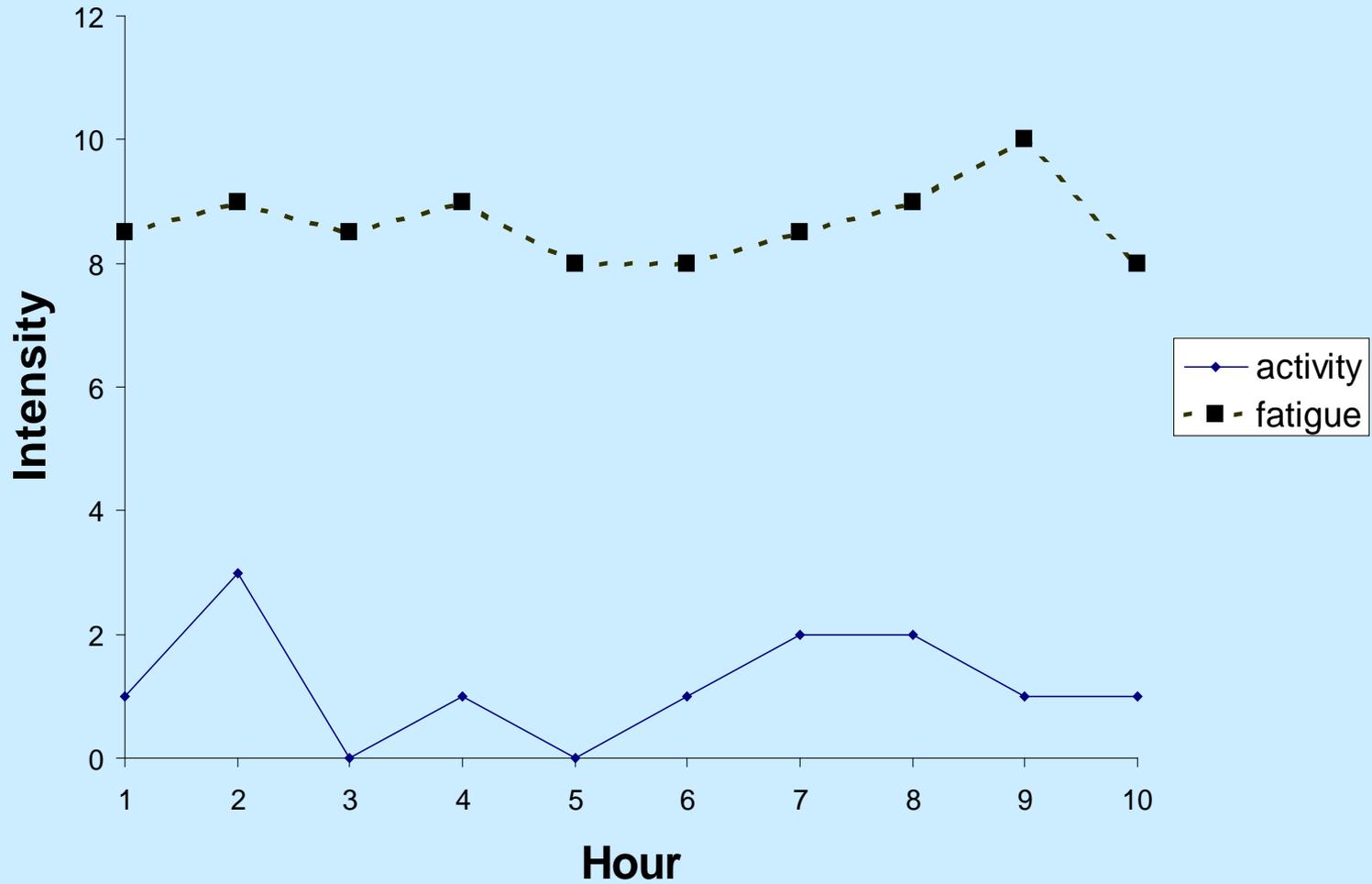
(Hawk & Jason, 2007)

	CFS	MDD	Cs
Time fatigue	75%	36%	4%
Time rest	25%	5%	1%

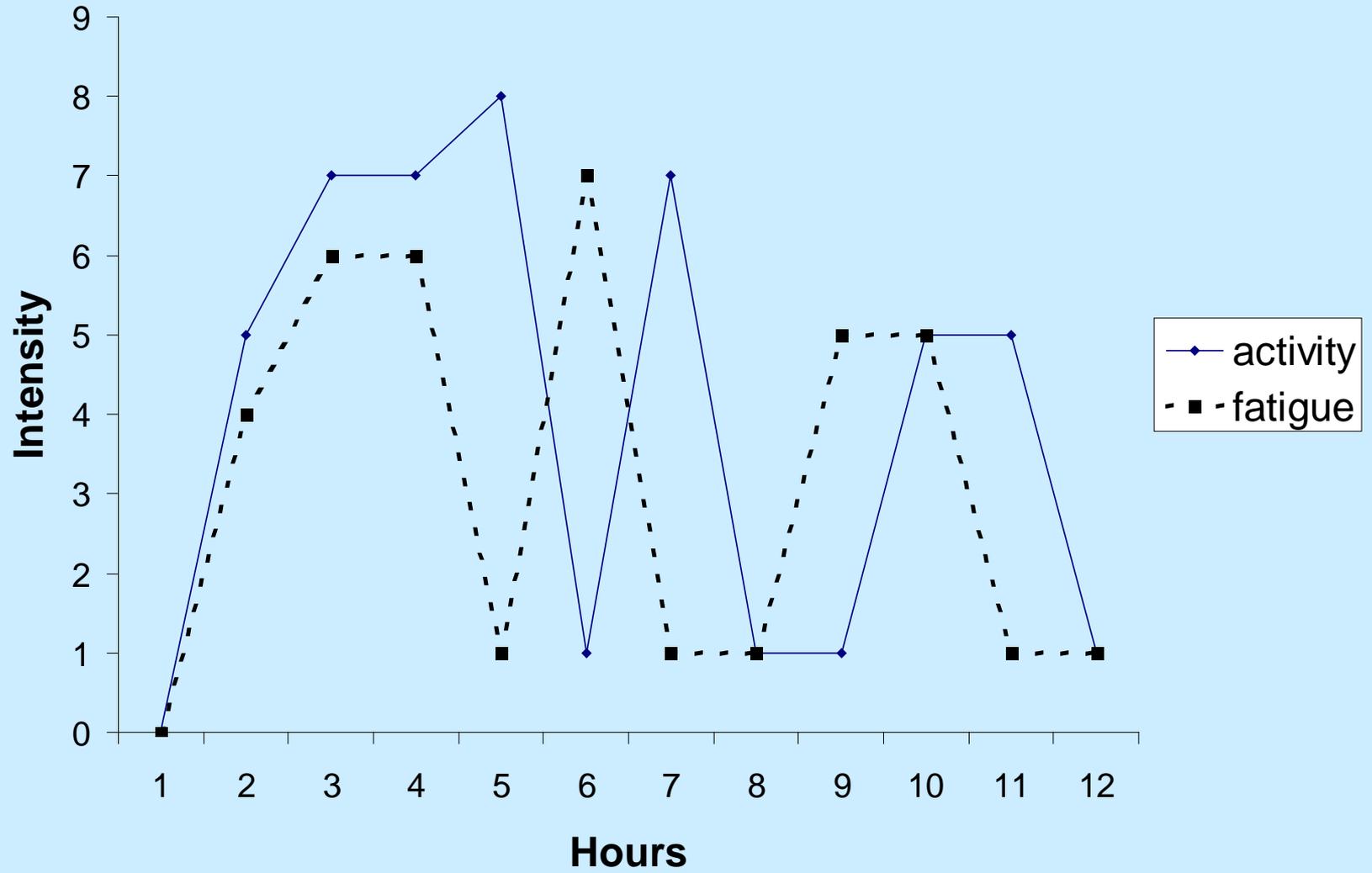
Level 2: Time Series Data

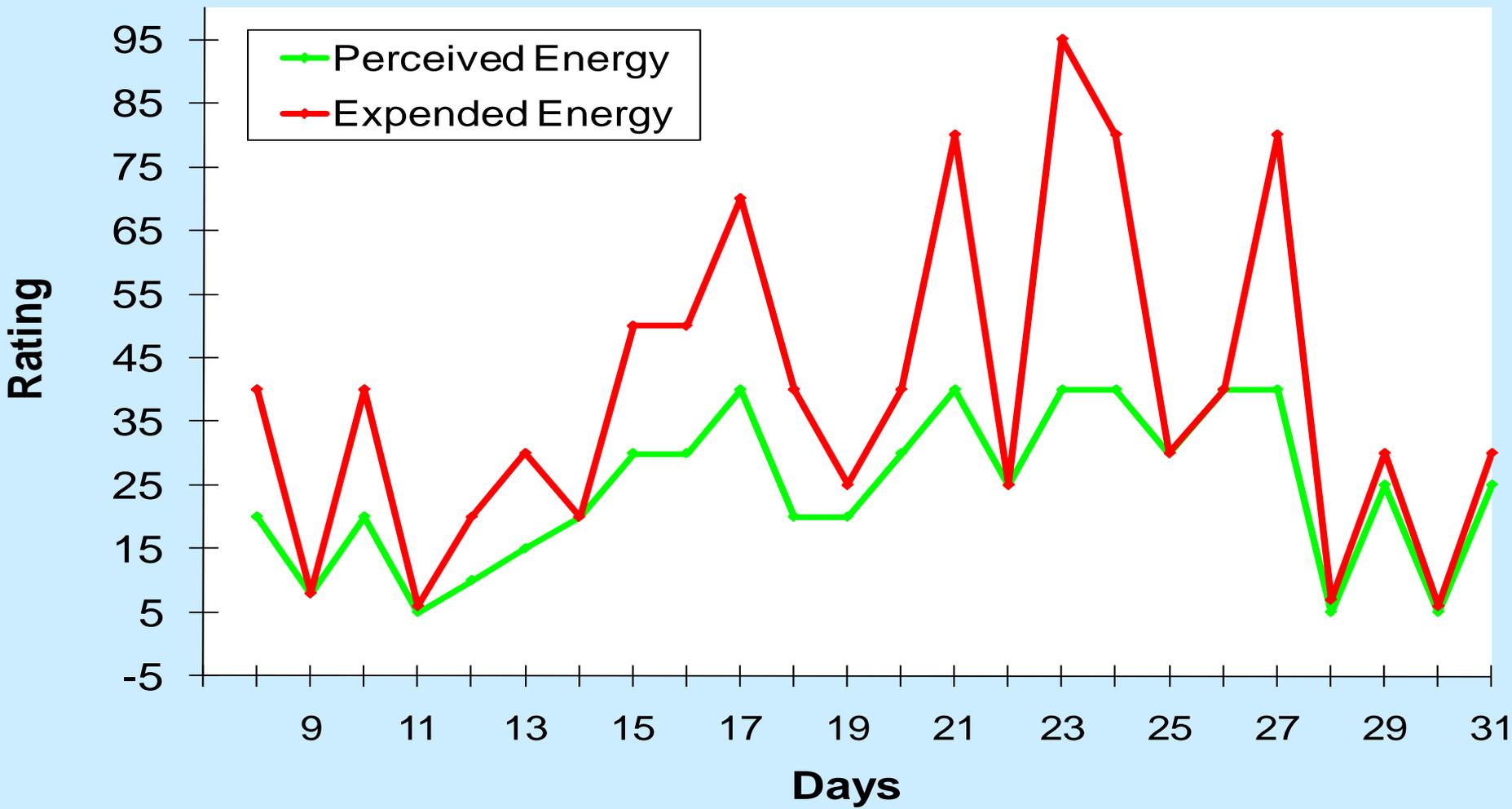
- Can show the relationship between activity and fatigue
 - Intensity, chronicity, slope
- Case studies

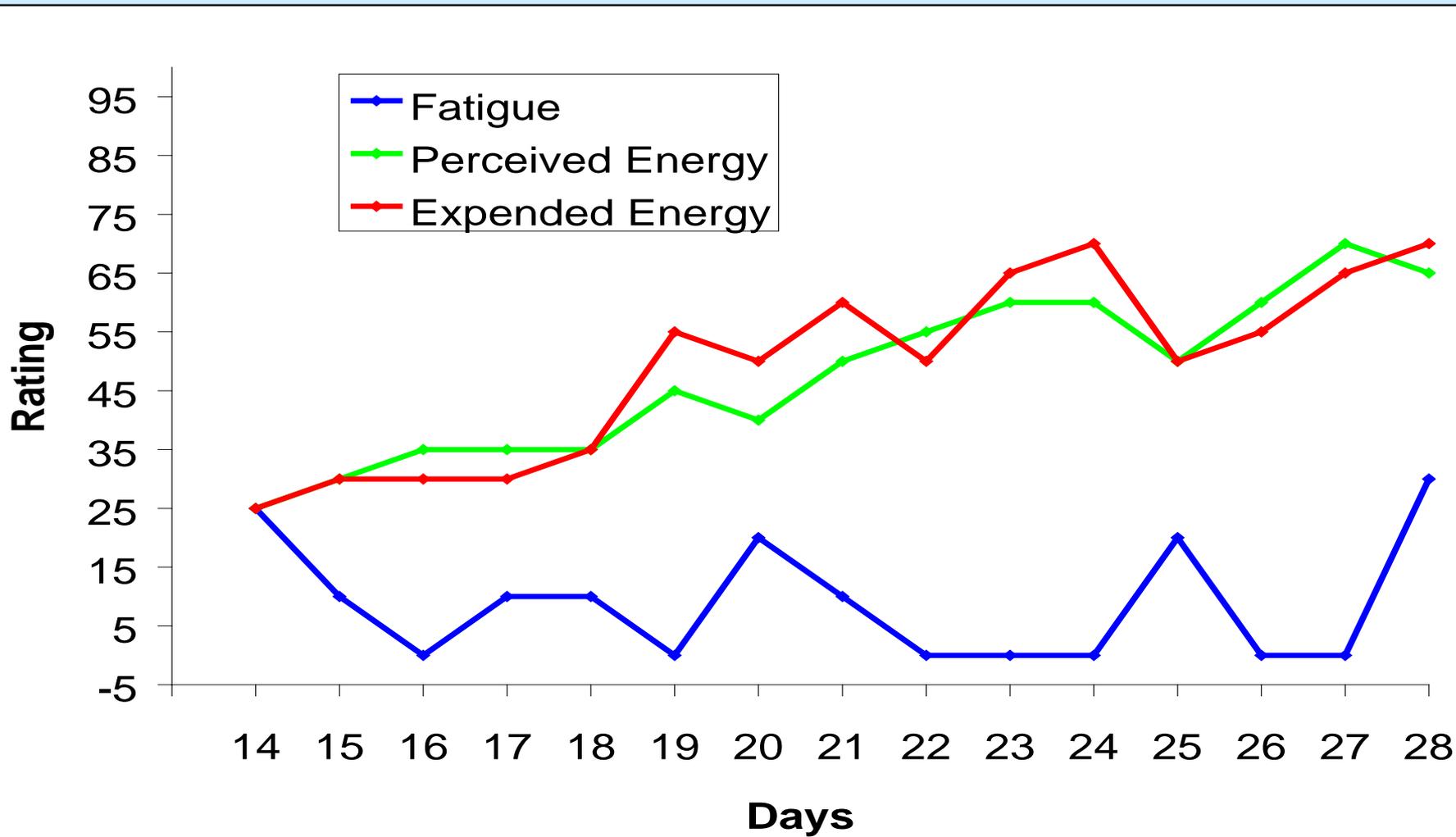
Fatigue as a function of Activity

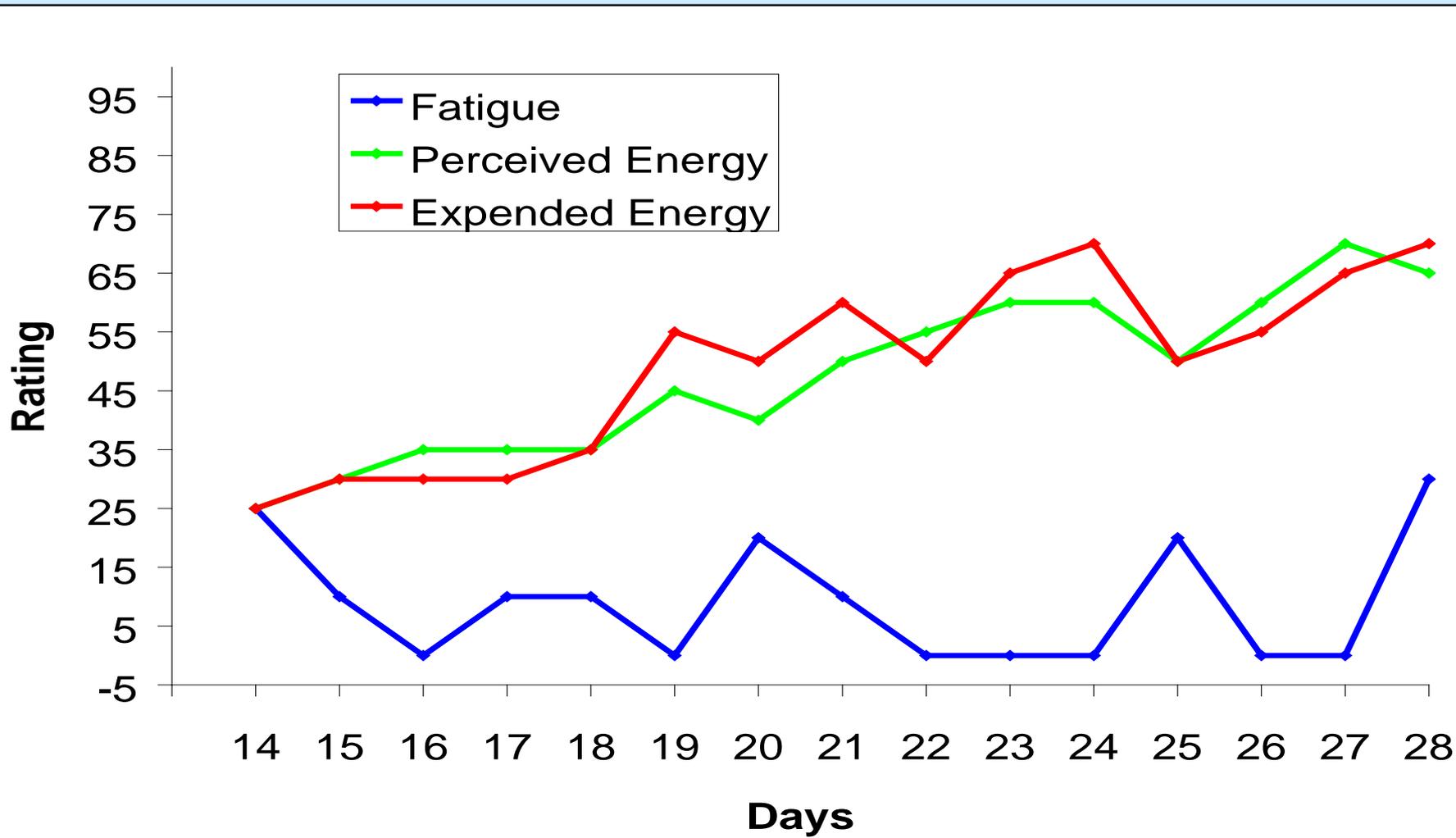


Fatigue as a function of Activity



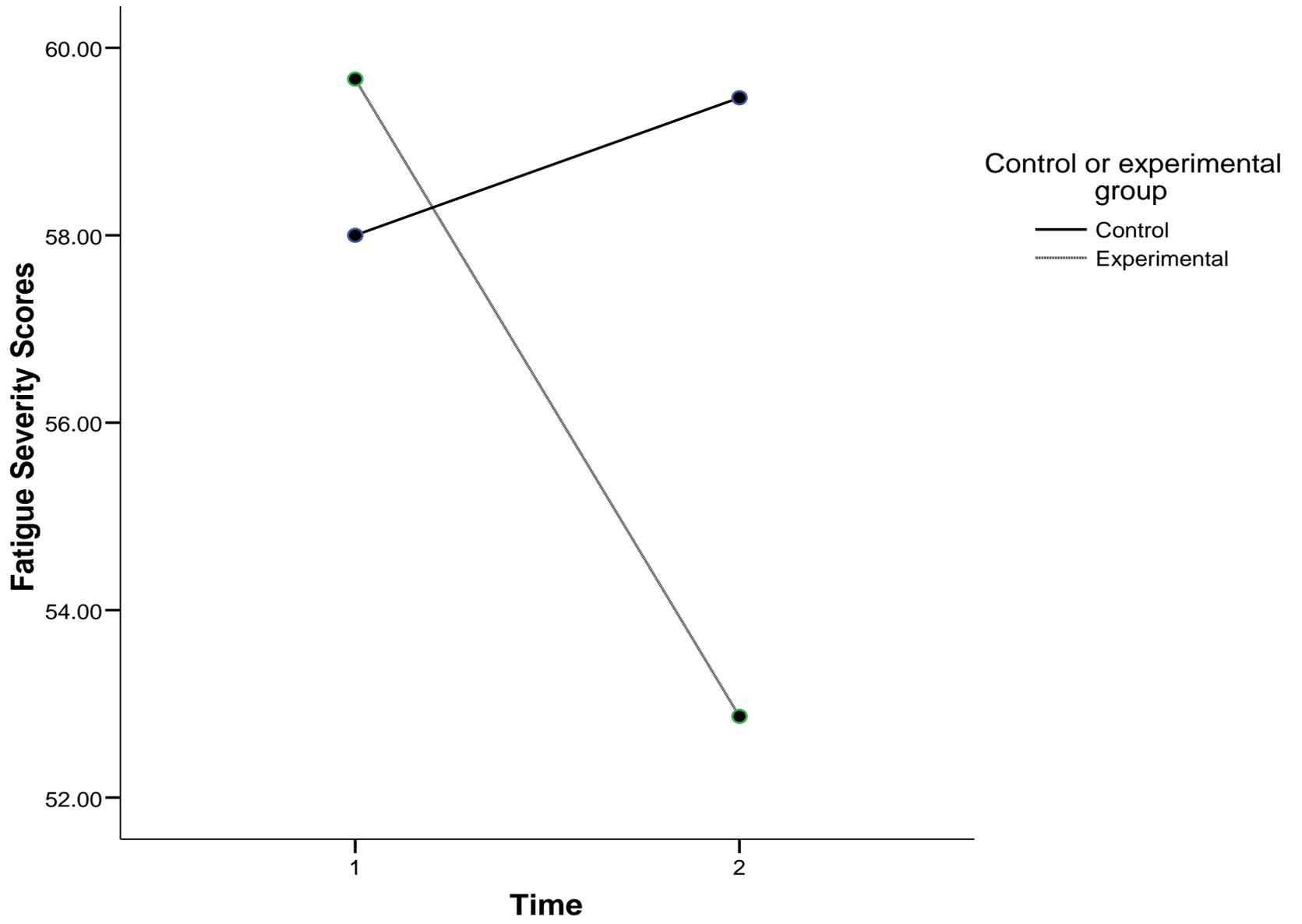






Intervention Study with Level 2 Data

- Participants with CFS were randomly assigned to either a 4-month buddy intervention or a control condition
 - Those received a student buddy intervention had significantly greater reductions in fatigue severity and increases in vitality
 - 📄 (Jason, Roesner, et al., 2010)



Measuring Fatigue Causing Disability

- Medical Outcome Study
 - (MOS or SF 36)
 - ▣ (Ware & Sherbourne, 1992)
 - Distinguishes CFS from other fatiguing illnesses
 - ▣ (Buchwald et al., 1996)

How Measure Substantial Reductions

- SF-36 Role-Emotional has the lowest threshold for both identifying individuals with CFS and identifying others who did not have this illness
 - (Jason, Brown, et al., 2010)
- Vitality, Social Functioning, and Role-Physical have the highest threshold
 - These subscales capture significant limitations in ability to accomplish activities in life

Post-Exertional Malaise:

- Canadian and Fukuda criteria
- Post-exertional malaise occurs usually with twenty-four hours or longer to recover
 - with loss of physical or mental stamina
 - rapid muscle or cognitive fatigability

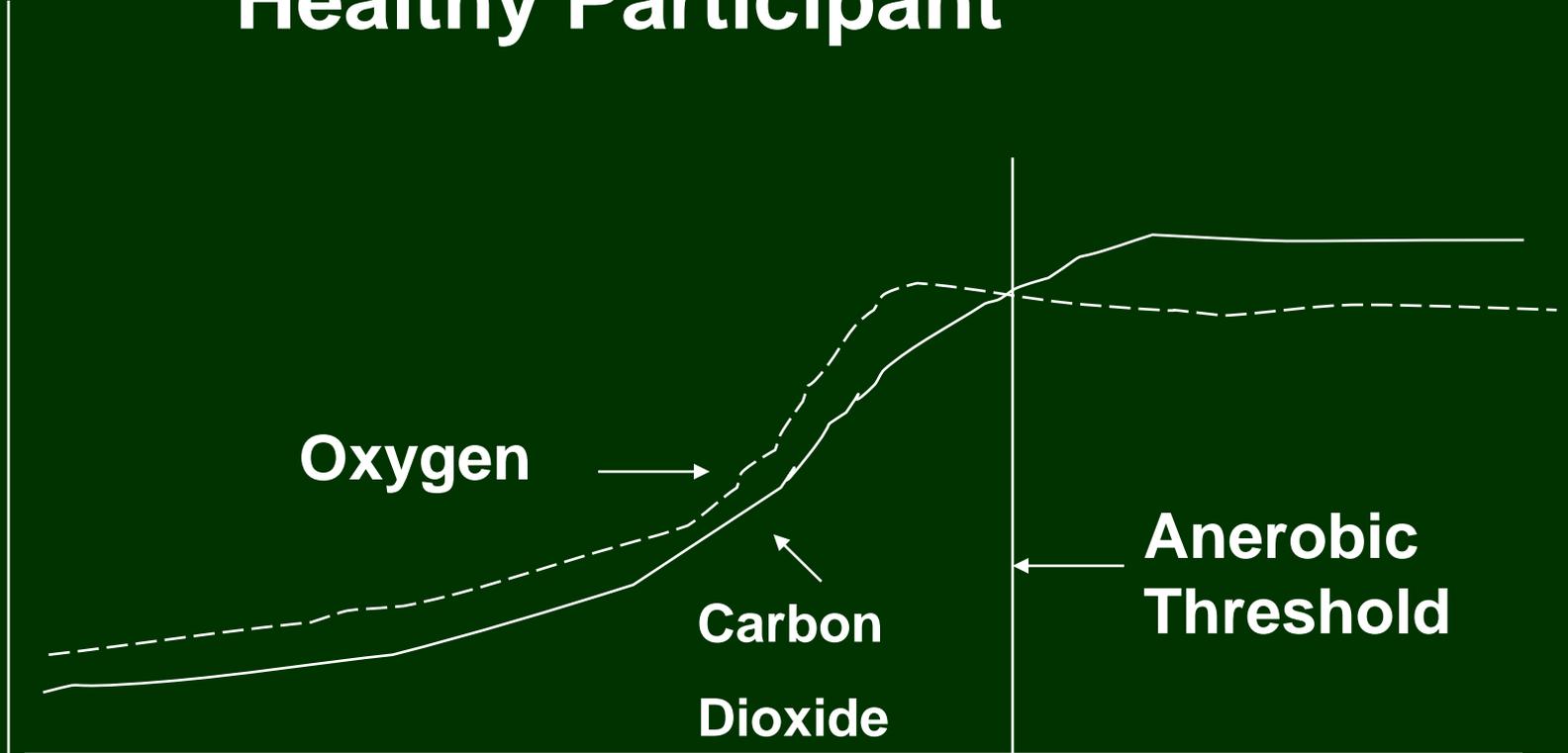
Level 1: Measuring Post-Exertional Malaise

- Increases in the expression for sensory, adrenergic, and immune genes following moderate exercise
 - (Light, White, Hughen, & Light, 2009)

Level 1: Functional Capacity testing

- Cardio-Pulmonary Exercise Testing
 - Bike or treadmill and expired gas analysis
 - Confirms impairment & accepted by Social Security
 - Accurate, reproducible

Healthy Participant



Oxygen



Carbon
Dioxide

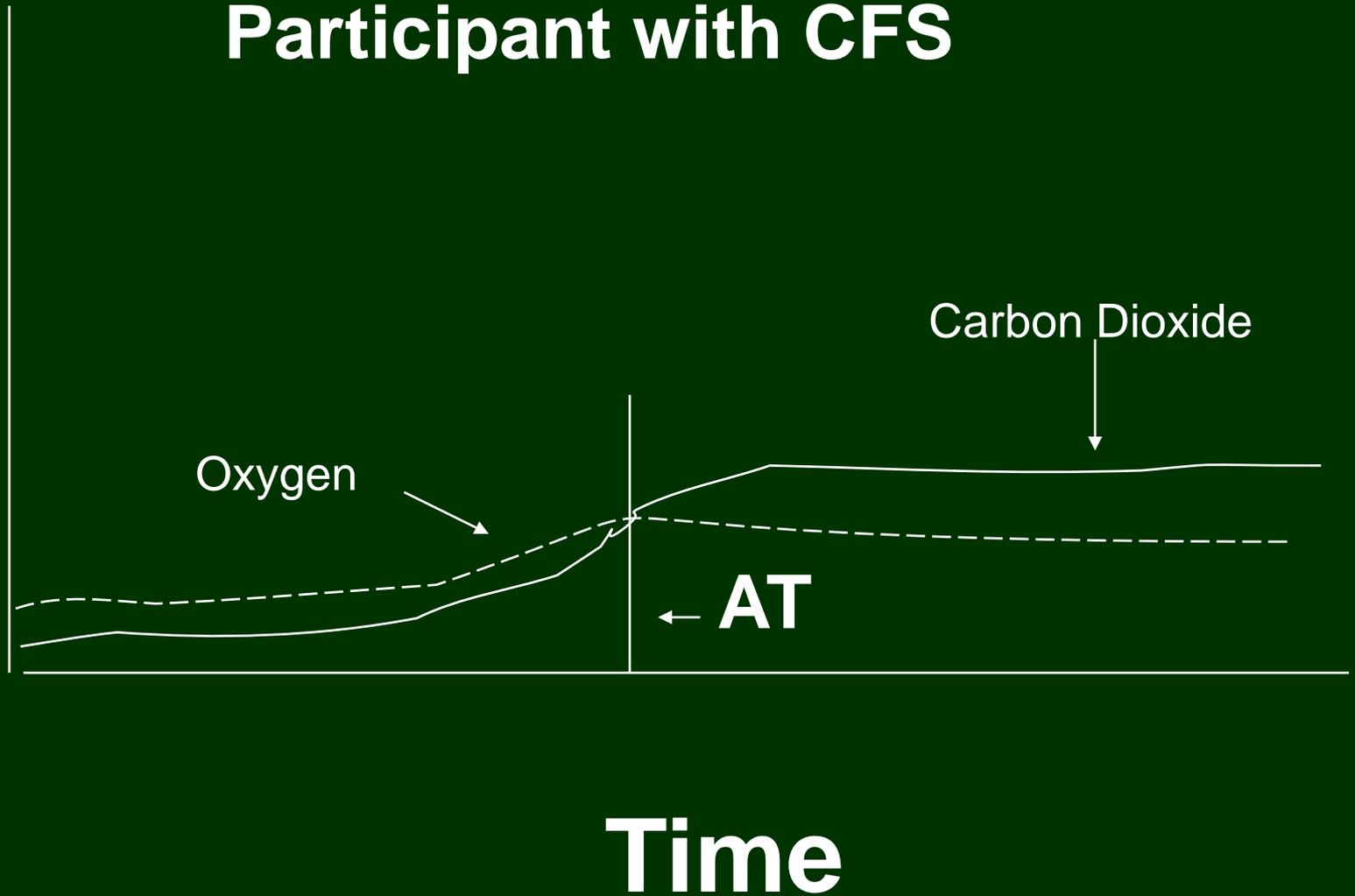


Aneerobic
Threshold



Time

Participant with CFS



	Class 1	Class 2	Class 3	Class 4
Impairment	0%	10-25%	30-45%	50-100%
Description	OK	Mild	Moderate	Severe
Max VO2	>25	20-25	15-20	<15

Level 2: Post-Exertional Malaise

- The ME/CFS Fatigue Types Questionnaire could be used to confirm symptoms of post-exertional malaise
 - feeling dead heavy feeling after exercise
 - feeling drained or sick after exercise

Sleep:

- Canadian and Fukuda Criteria
- There should be unrefreshing sleep or sleep quantity or rhythm disturbance

Sleep Disturbance

- High frequency of sleep disorders in CFS and FM
 - (Hickie & Davenport , 2000)
- Alpha intrusion in deep sleep
 - Not specific
 - seen in other chronic pain conditions

Level 1: Sleep Problems

- Un-refreshing sleep, disturbance of sleep quantity, or rhythm disturbance
 - documented by polysomnography
 - (Shaver, 2003)

Level 2: Sleep Problems

- The Pittsburgh Sleep Questionnaire
 - developed to measure sleep quality in psychiatric research

Canadian Criteria

- A significant degree of arthralgia and/or myalgia

Fukuda Criteria

- Pain is within following CFS-defining symptoms
 - headaches of a new type, pattern, or severity
 - muscle pain
 - multi-joint pain without swelling or redness
 - sore throat
 - tender cervical/axillary lymph nodes

Level 1: Pain

- Pain can be measured by increases in the expression for sensory, adrenergic, and immune genes following moderate exercise
 - (Light, White, Hughen, & Light, 2009)

Level 2: The McGill Pain Questionnaire (MPQ)

- A human figure drawing on which patients are asked to mark the location of their pain
- 78 adjectives and patients identify their experience by circling word descriptors
- A pain intensity index
 - well validated
 - inexpensive

Neurocognitive manifestations

- Canadian and Fukuda criteria
- Neurocognitive manifestations
 - Confusion
 - impairment of concentration and short term-memory

Level 1: Neurocognitive

- fMRI, SPECT, or PET scans indicating brain injury
 - (Lange et al., 2005; Hyde, 2007)
- Significant reductions in brain grey matter volume in patients with CFS
- Declines were linked to reductions in physical activity
 - de Lange et al. (2005)

Level 2: Cognitive Function

- Measurement of cognitive function is complex and time consuming
 - The Cambridge Neuropsychological Test Automated Battery (CANTAB)
 - ☒ administered via a touch-sensitive computer screen
 - ☒ the most practical single tool to assess cognition in CFS research studies, includes
 - tests of memory
 - attention
 - executive function

Canadian Criteria

- At least one symptom from two of the following categories
- Autonomic manifestations
 - (neurally mediated hypotension)
- Neuroendocrine manifestations
 - (e.g., recurrent feelings of feverishness and cold extremities)
- Immune manifestations
 - (e.g., recurrent sore throats)

Level 1: Autonomic Manifestations

- Tilt table test showing decreased blood pressure and increased heart rate
 - (Hyde, 2007)

Level 1: Dysfunction in the heart

- 81% of patients with CFS and none of controls experienced ejection fraction decreases
 - suggesting left ventricular dysfunction in the heart
- Those having more severe symptoms experiencing greater decreases
 - Natleson's group (Peckerman, Chemitiganti et al., 2003).

Dysautonomia

- Plasma volume and total body water are usually low
 - about 20% down from normal levels
- Tilt table testing can be used to demonstrate abnormalities

Tilt Table Testing Outcomes

Diagnosis	Symptoms	Heart Rate	Blood pressure
Normal	0	↑ 10-15	
Orthostatic Intolerance	0	↑ 30	
NMH	Within 15 min	↑ then ↓	↑ then ↓



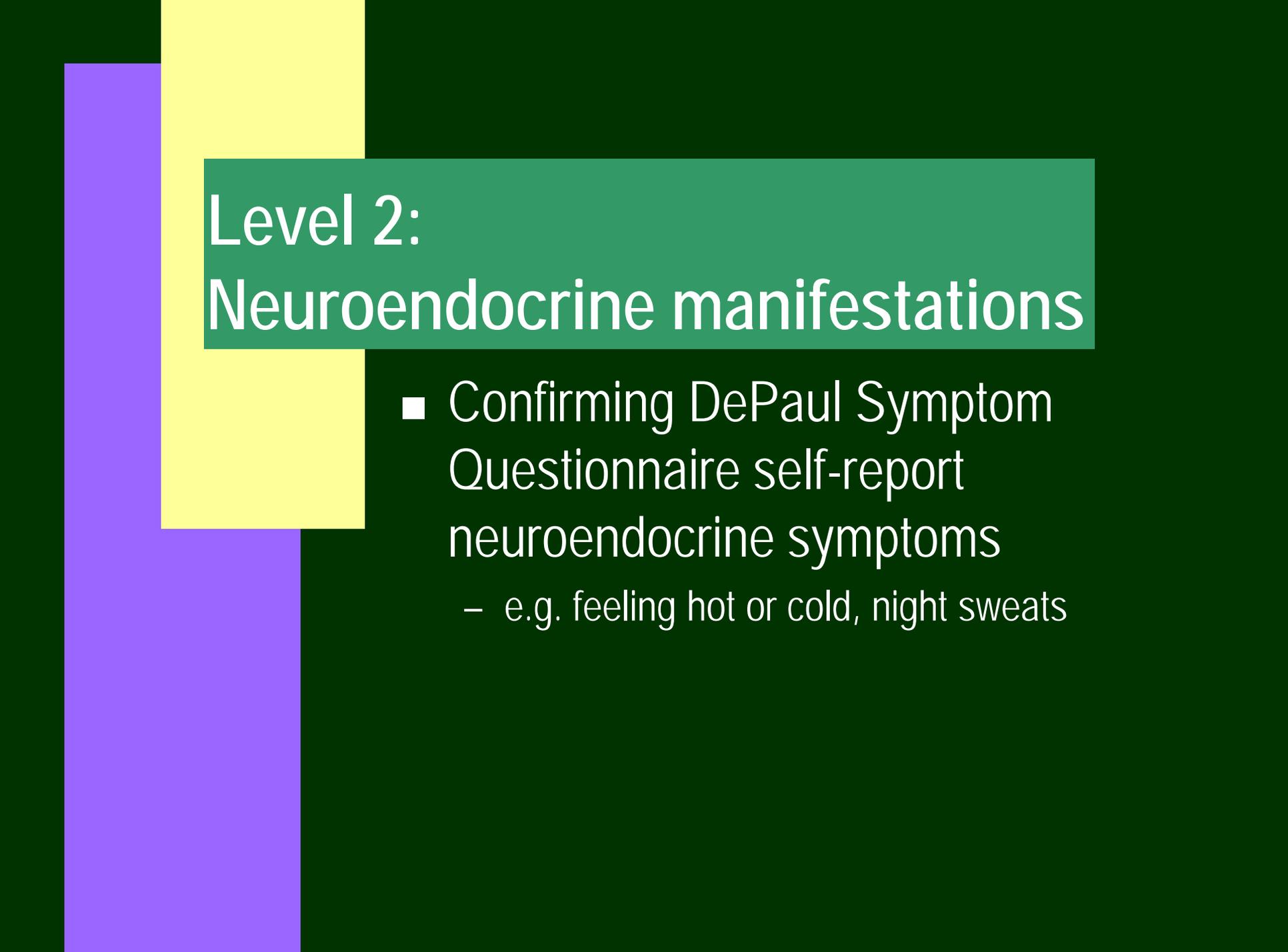
Level 2:

Autonomic Manifestation

- Autonomic manifestations can be assessed by the DePaul Symptom Questionnaire
 - feeling unsteady on feet, fainting

Level 1: Neuroendocrine Manifestations

- Neuroendocrine manifestations can be measured by abnormal levels of circulating cortisol
 - (Torres-Harding et al., 2008)



Level 2:

Neuroendocrine manifestations

- Confirming DePaul Symptom Questionnaire self-report neuroendocrine symptoms
 - e.g. feeling hot or cold, night sweats

Level 1: Immune manifestations Infectious Agents

- Virus
 - Herpesviruses (EBV, CMV, HHV6)
 - Enteroviruses (polio)
 - “Stealth Viruses”
- Retroviruses (or retroviral factions)
- Bacteria
 - Chlamydia, Mycoplasma, Borrelia (Lyme)

Level 1: Immunology

- Over-activation in the immune system
- Th1 to Th2 shift
- Elevations in CD5+CD19+ subset and decreased natural killer cell cytotoxicity
 - (Maher, Klimas, & Fletcher, 2003)

Level 2: Immune Manifestation

- DePaul Symptom Questionnaire to confirm immune dysfunction
 - e.g., feeling feverish, having a sore throat

Intervention with Immune and Neuroendocrine Biomarkers

- About 100 Patients with ME/CFS were provided biweekly meetings with a trained nurse therapist for 13 sessions
 - There were baseline, post and six and twelve month follow-ups
 - Jason et al. (2007)

Improvers vs Non-Improvers on SF-36 Physical Functioning

- Half were Improvers and other half were Non-improvers over time
 - Two groups had no significant **baseline** differences on Physical Functioning

▣ Jason et al. (2008)

Differential Outcomes

- Those with most severe immune baseline characteristics tended to be non-improvers
- CFS is associated with a shift toward a Type 2 immune response
 - Those with this pattern at baseline tended not to improve over the course of the trial

Baseline Cortisol Levels

- Patients categorized into Abnormal vs Normal **Baseline** cortisol levels
 - Abnormal if cortisol over 5 testings during one day
 - ☐ continued rise
 - ☐ flat
 - ☐ abnormally low over time
 - Jason et al. (2008)

Differential Outcomes

- Patients baseline Normal cortisol had most improvement over time for
 - activity levels
 - fatigue severity
 - depression
 - anxiety

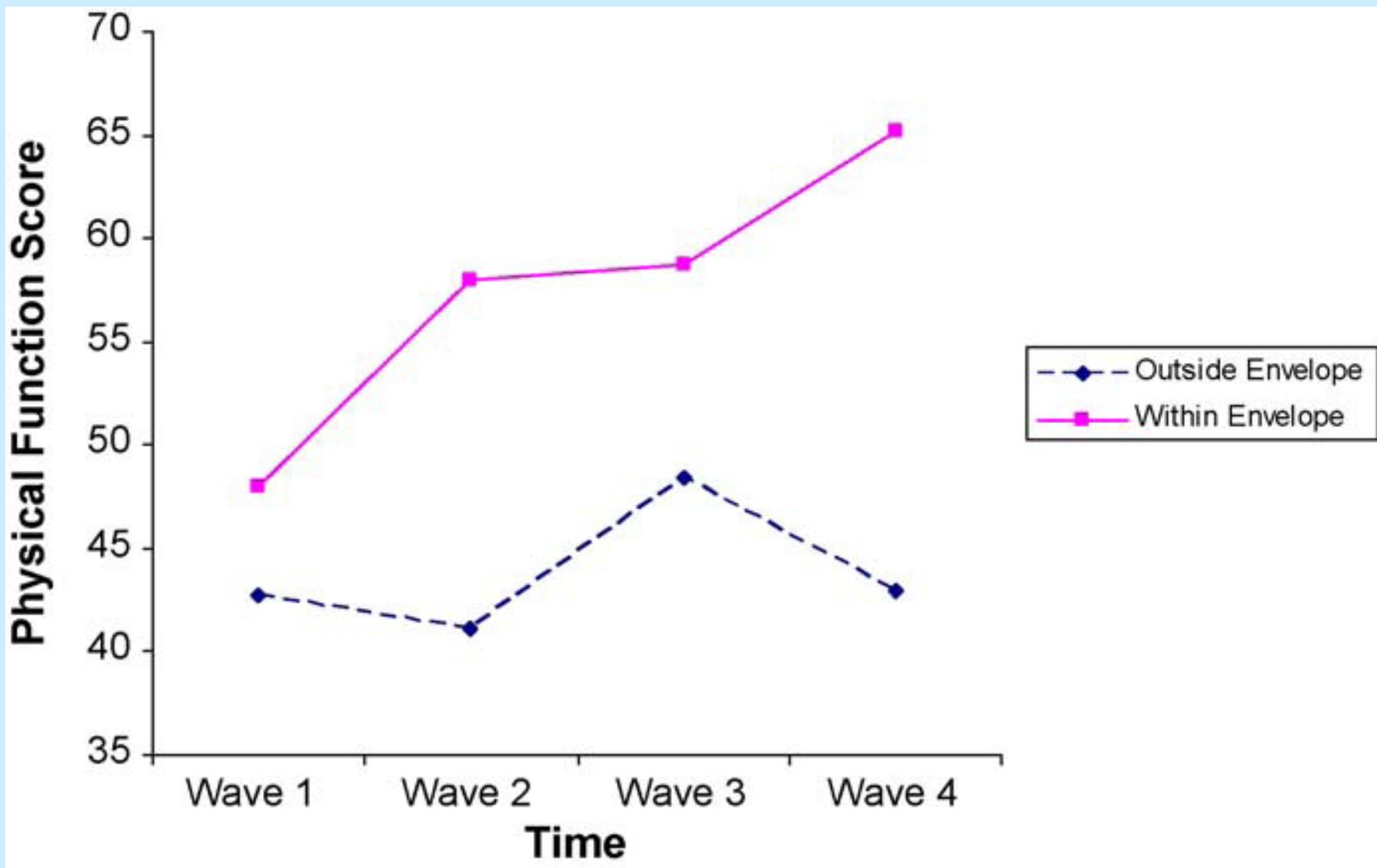
Differential Outcomes

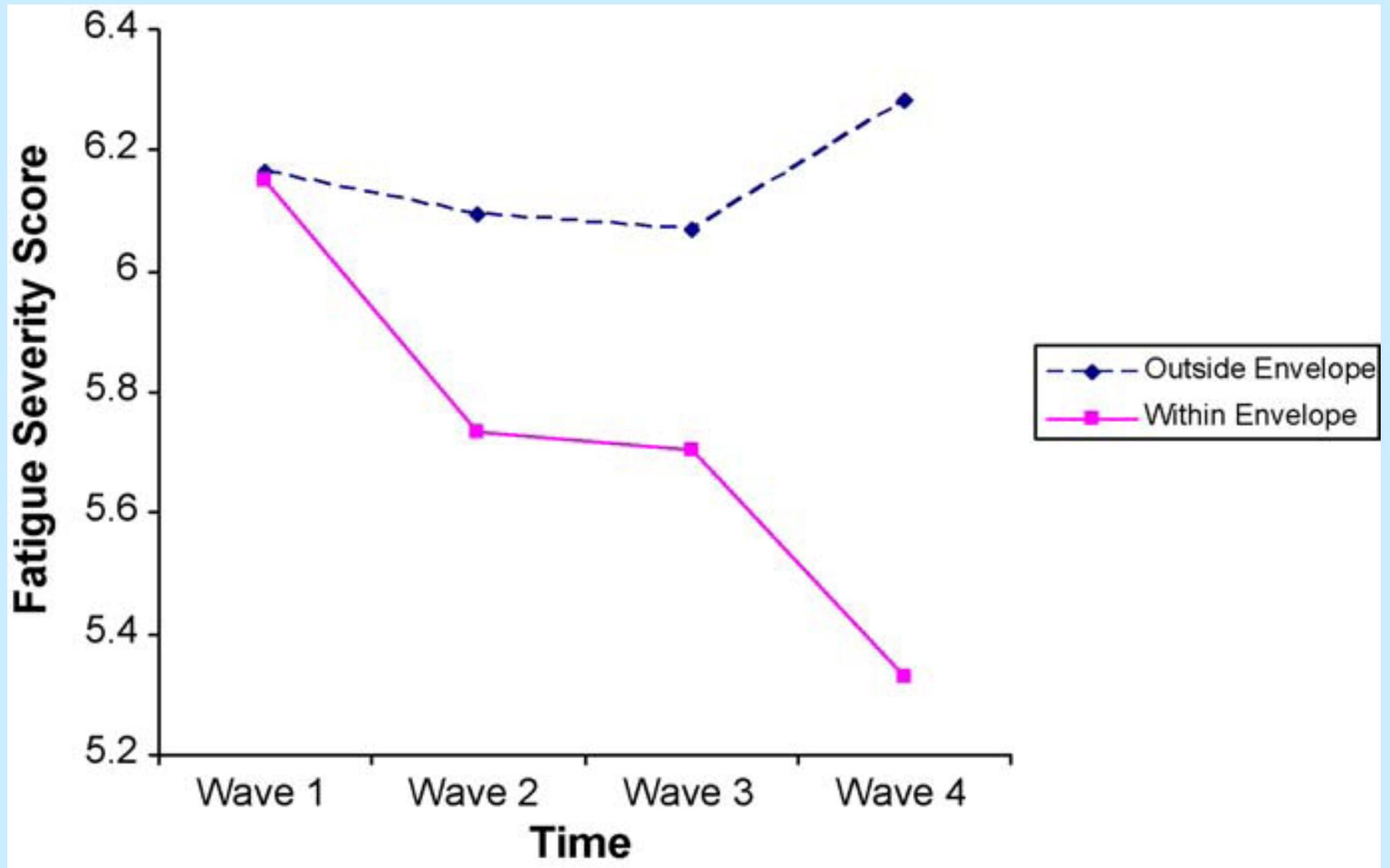
- Patients with normal baseline cortisol evidenced improvements on a number of immunologic and self-report measures
 - Patients most impaired on HPA functioning at baseline were least able to improve when provided non-pharmacologic interventions

Energy Envelope Findings

- Two groups of patients were identified following participation in non-pharmacologic intervention
- Some were able to keep expended energy close to available energy and others were not successful at this task
 - Estimated weekly energy quotients
 - Divided expended energy level by perceived energy level and multiplying by 100

📄 (Jason, Benton et al. 2009)





Conclusion

- Those who were able to stay within their energy envelope had significant improvements in physical functioning and fatigue severity
 - Findings suggest that helping patients with CFS maintain appropriate energy expenditures in coordination with available energy reserves can help improve functioning over time

Implications

- Advantages to using both Level 1 and 2 indices
- Level 1 has clear advantages
 - Level 2 has recall bias problems

Variability within Level 2 Measures

- Trying differentiate CFS from Major Depressive Disorder
 - Activity Log Data on percentage of time fatigue reported better predictor than single measure of Fatigue
 - 📄 King, Jason, Torres-Harding (2006)