



**EORTC  
QUALITY OF LIFE  
GROUP**

25<sup>th</sup> Anniversary  
4<sup>th</sup>–5<sup>th</sup> May, 2006  
Paris, France

# **RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS**

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U776 Biological rhythms and cancer

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EORTC Chronotherapy Group





## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

- **Circadian Timing System;**
- **Circadian Rest/Activity Rhythm;**
- **Circadian Timing System alterations;**
- **Relationship with Quality of Life;**
- **Chronotherapeutic interventions.**

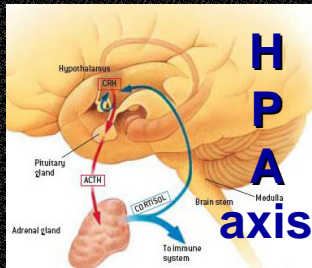


## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

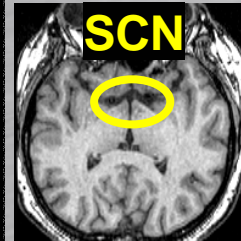
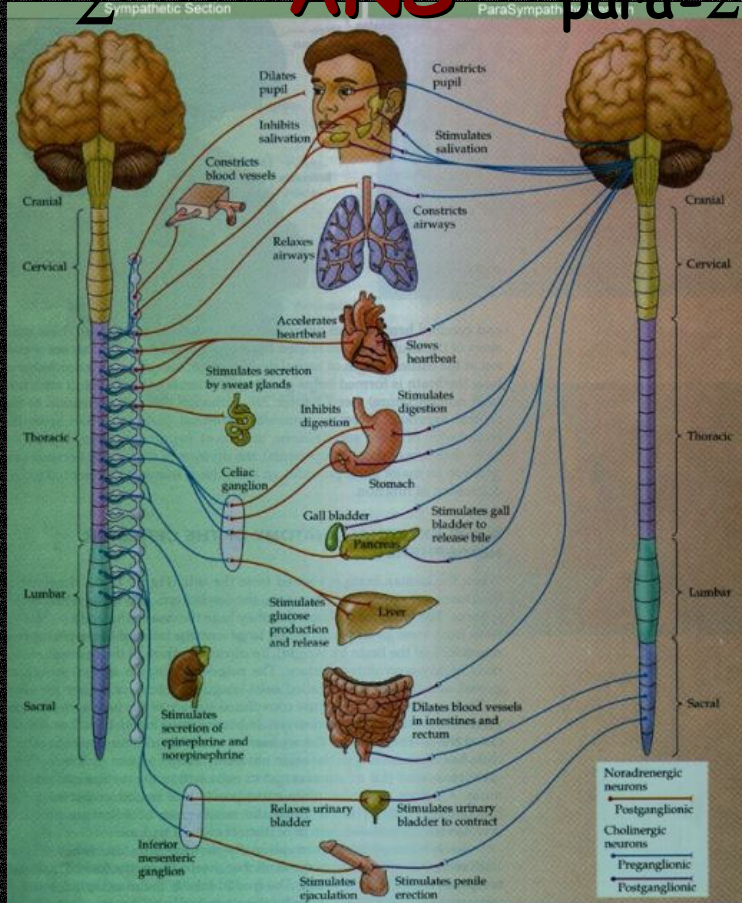
# Circadian Timing System



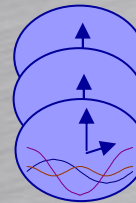
# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN EST/ACTIVITY RHYTHM IN CANCER PATIENTS



**ANS** para-2



**CENTRAL PACEMAKER**



**PERIPHERAL MOLECULAR CLOCKS**

ANS  
HPA  
???

**SCN OUTPUT SIGNALS**

Reppert & Weaver, Nature 2002;  
 Saper, Nature 2005;  
 Hastings, Nature Rev Neurosci 2003;  
 Fu & Lee, Nature Rev Cancer 2003;  
 Schibler & Sassone-Corsi, Curr Opin Mol Biol 2002;  
 Lévi, Lancet Oncol 2001



## **Circadian Timing System**

**Endogenous time-dependent control of several functions, with a period of about 24h**

- **Physiological** Physical Activity, Heart Rate, Blood Pressure, Body Core Temperature, Immune System
- **Endocrine** Cortisol, Melatonin, Growth Factors, Cytokines
- **Behavioural** Food Intake, Sleep/Wake Cycle
- **Psycho-Emotional** Mood, Stress, Cognitive Performance
- **Cellular** Metabolism, Gene Expression, Cell Cycle gating, Apoptosis

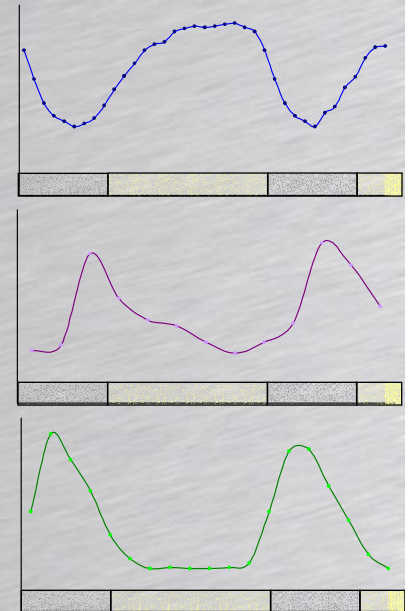
**It can be entrained by environmental cues:**

Light/Darkness, Social Life, Meal Scheduling, etc.

## **Circadian Timing System**

### **MARKER RHYTHMS OF CIRCADIAN FUNCTION**

- **BODY CORE TEMPERATURE**
- **CORTISOL (SERUM or SALIVA)**
- **MELATONIN (SERUM or SALIVA or URINE)**



strong endogenous rhythms, multiple samplings (day & night),  
invasive measurement techniques, therapeutic interventions

- **ACTIVITY and REST**



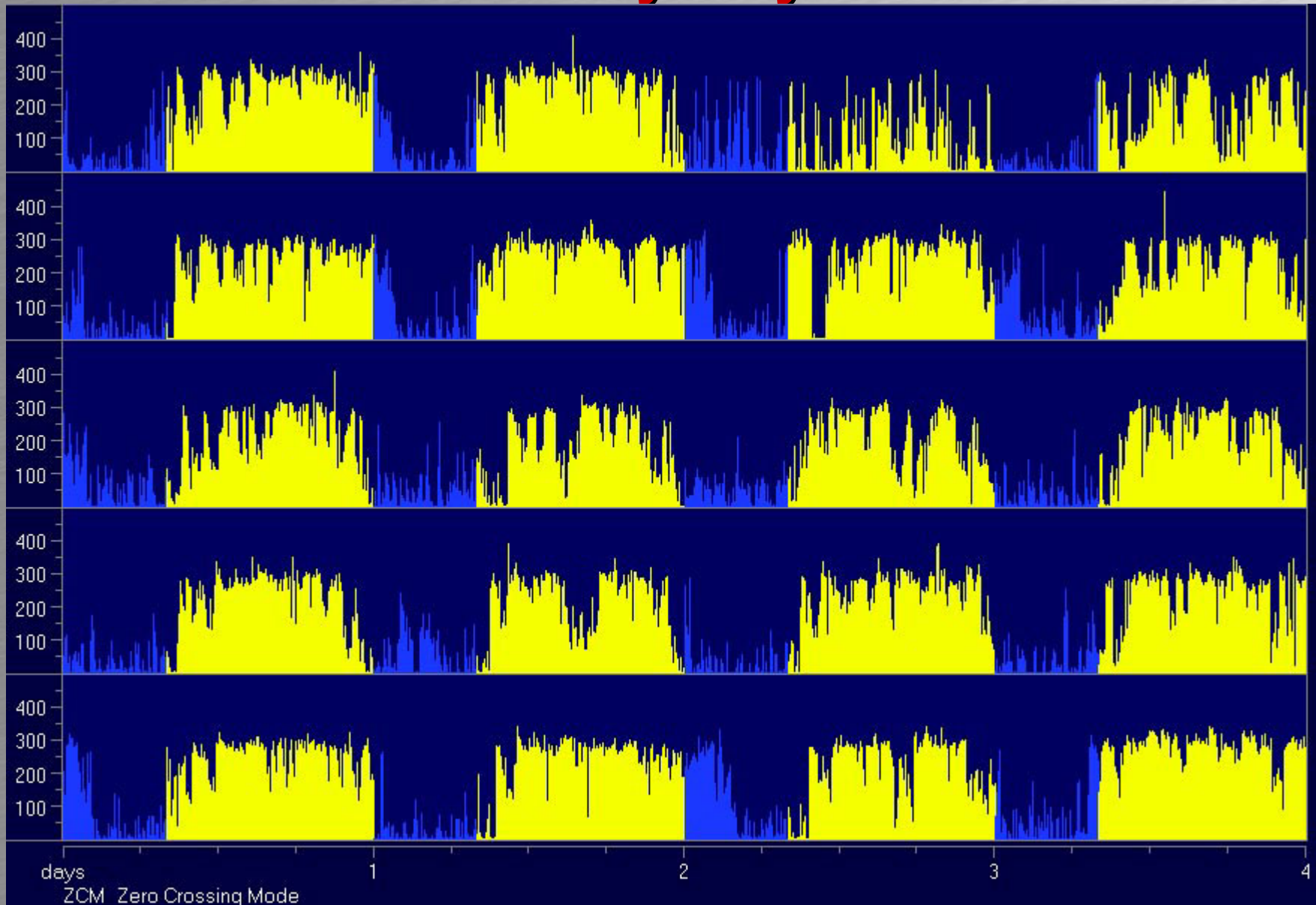
## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

# Circadian Rest/Activity Rhythm



## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

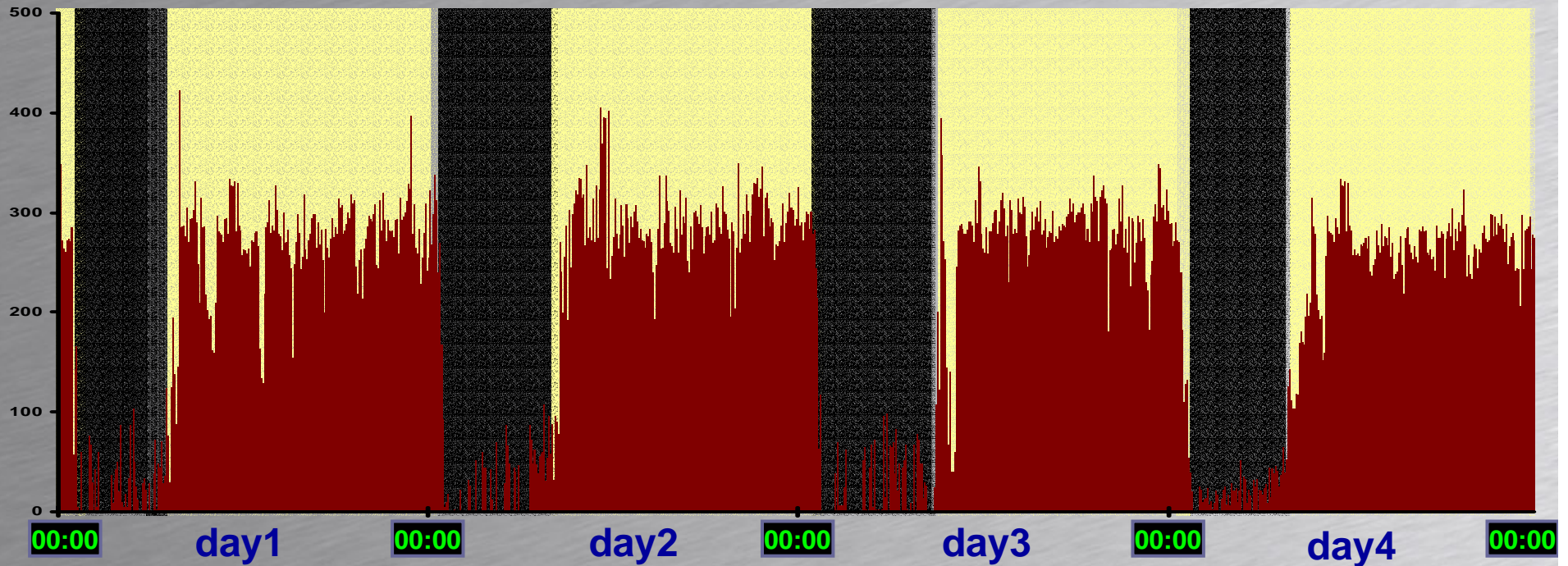
# Circadian Rest/Activity Rhythm: ACTIGRAPH





## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

# Circadian Rest/Activity Rhythm: ACTIGRAPH



AVERAGE ACTIVITY COUNT

sum of movements/minutes

AUTOCORRELATION COEFFICIENT AT 24h ( $r_{24}$ )

$-1 < r_{24} < 1$

robustness and reproducibility along a circadian period (24h)

DICHOTOMY INDEX ( $I < O$ )

$0\% < I < O < 100\%$

difference in activity distribution between wakefulness and rest span



## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

# Circadian Physiology alterations



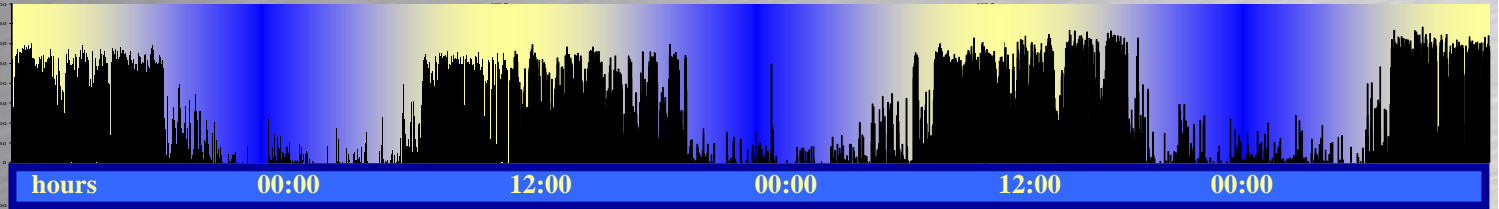
# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

Pat.1

mAct = 136

r24 = 0.68

l<O = 99.7

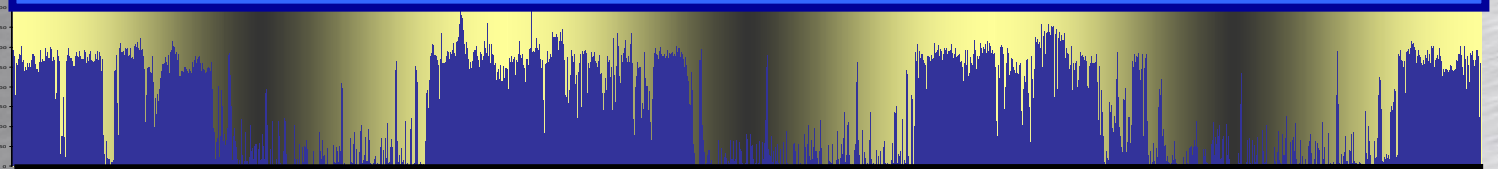


Pat.2

mAct = 114

r24 = 0.69

l<O = 99.9

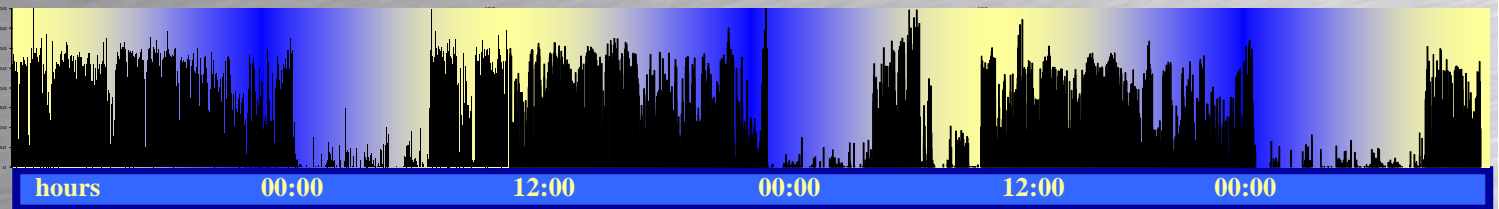


Pat.3

mAct = 134

r24 = 0.41

l<O = 95.7

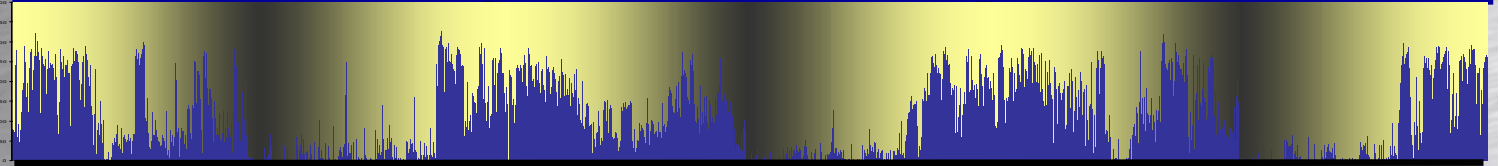


Pat.4

mAct = 87

r24 = 0.41

l<O = 99.2

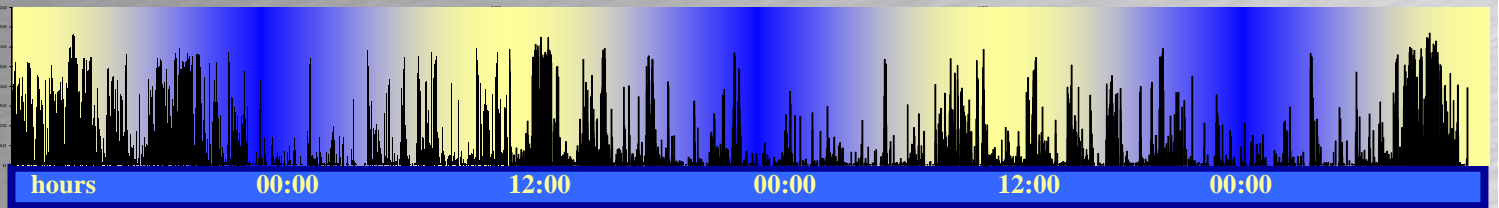


Pat.5

mAct = 73

r24 = 0.01

l<O = 94.4

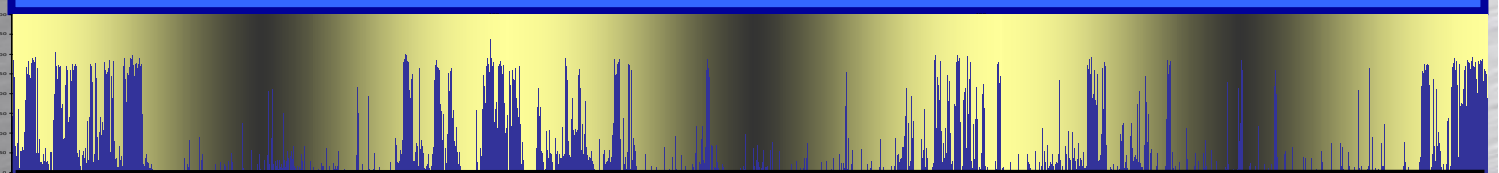


Pat.6

mAct = 49

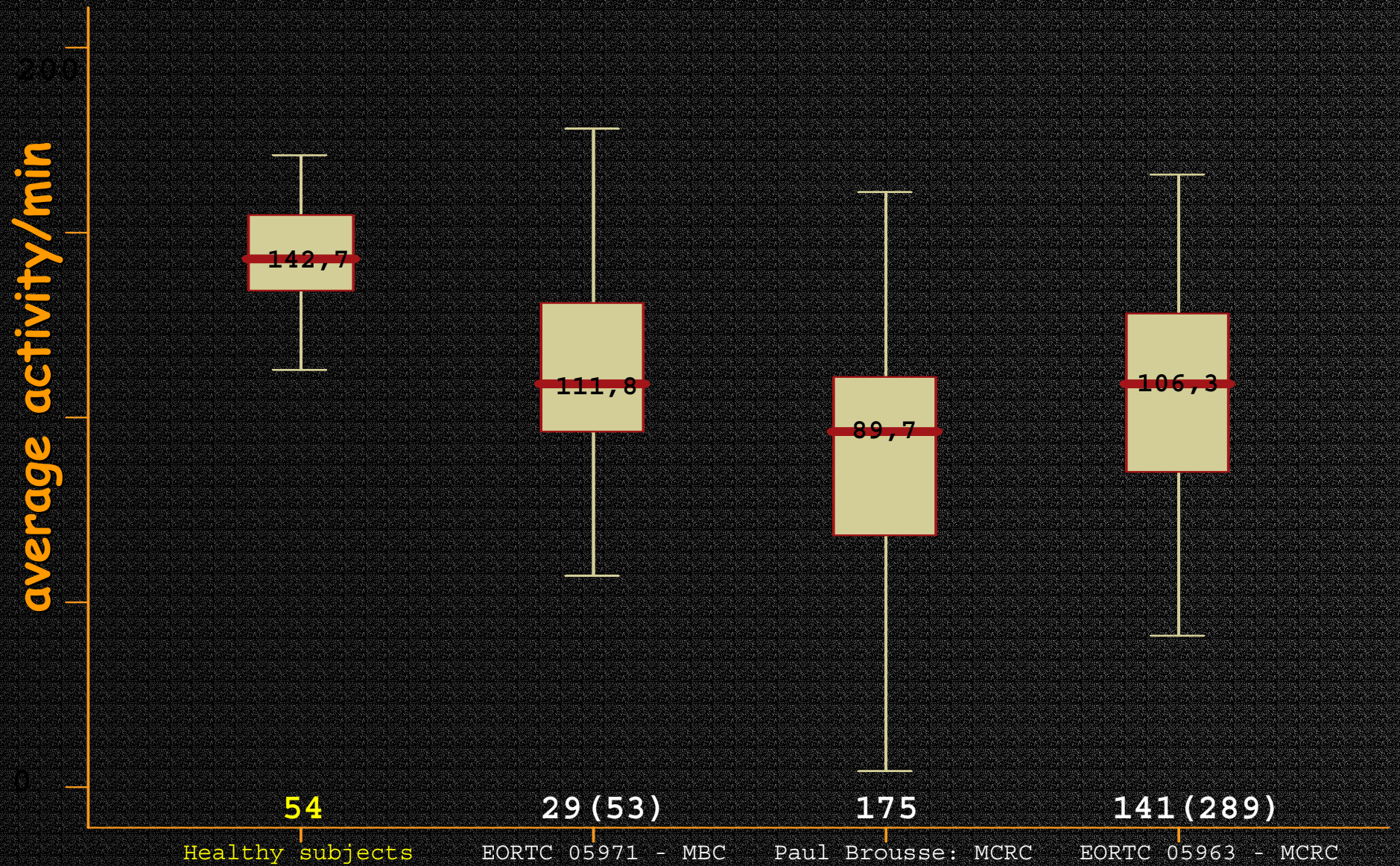
r24 = 0.18

l<O = 90.2



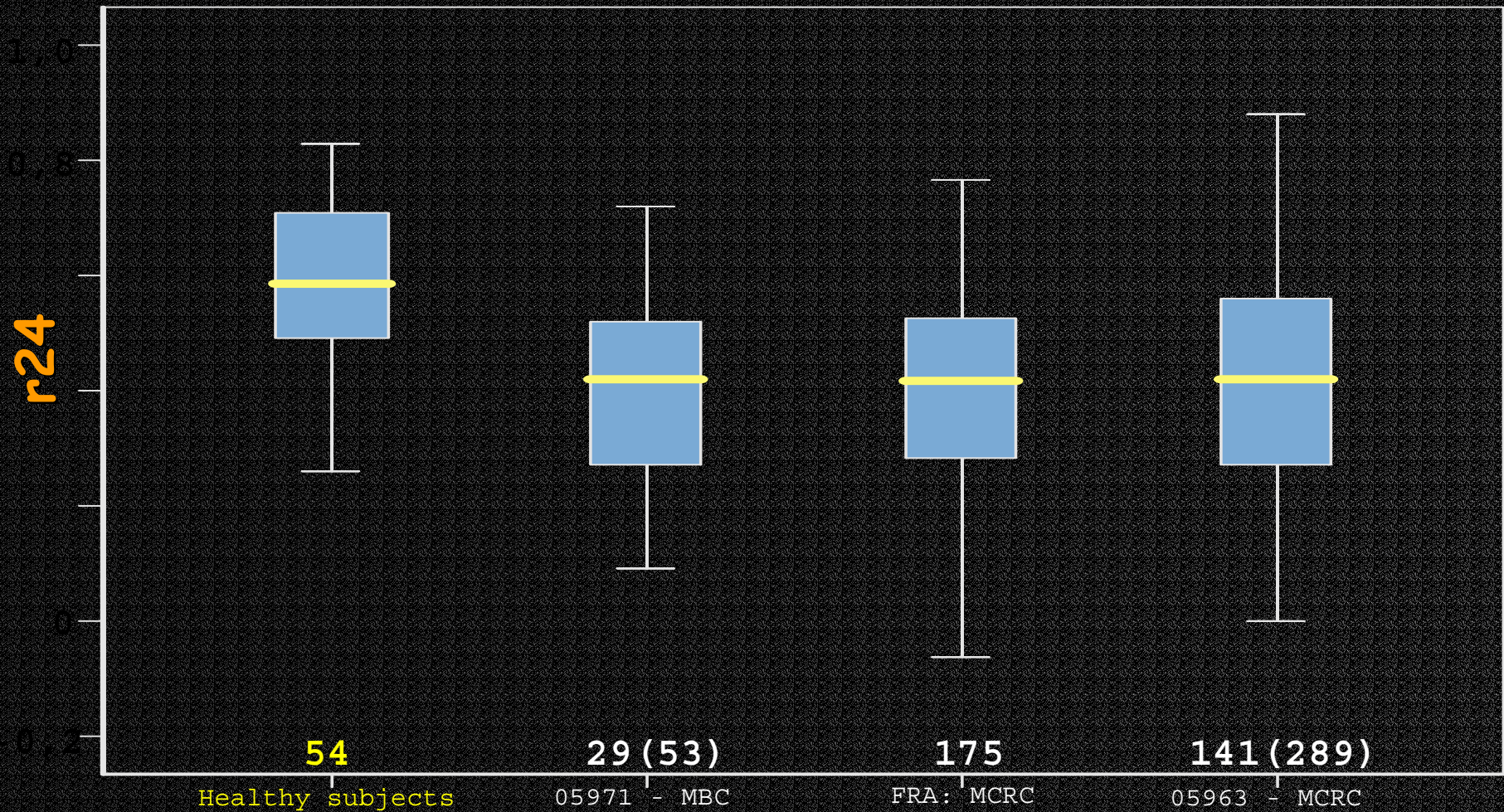


# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS





# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

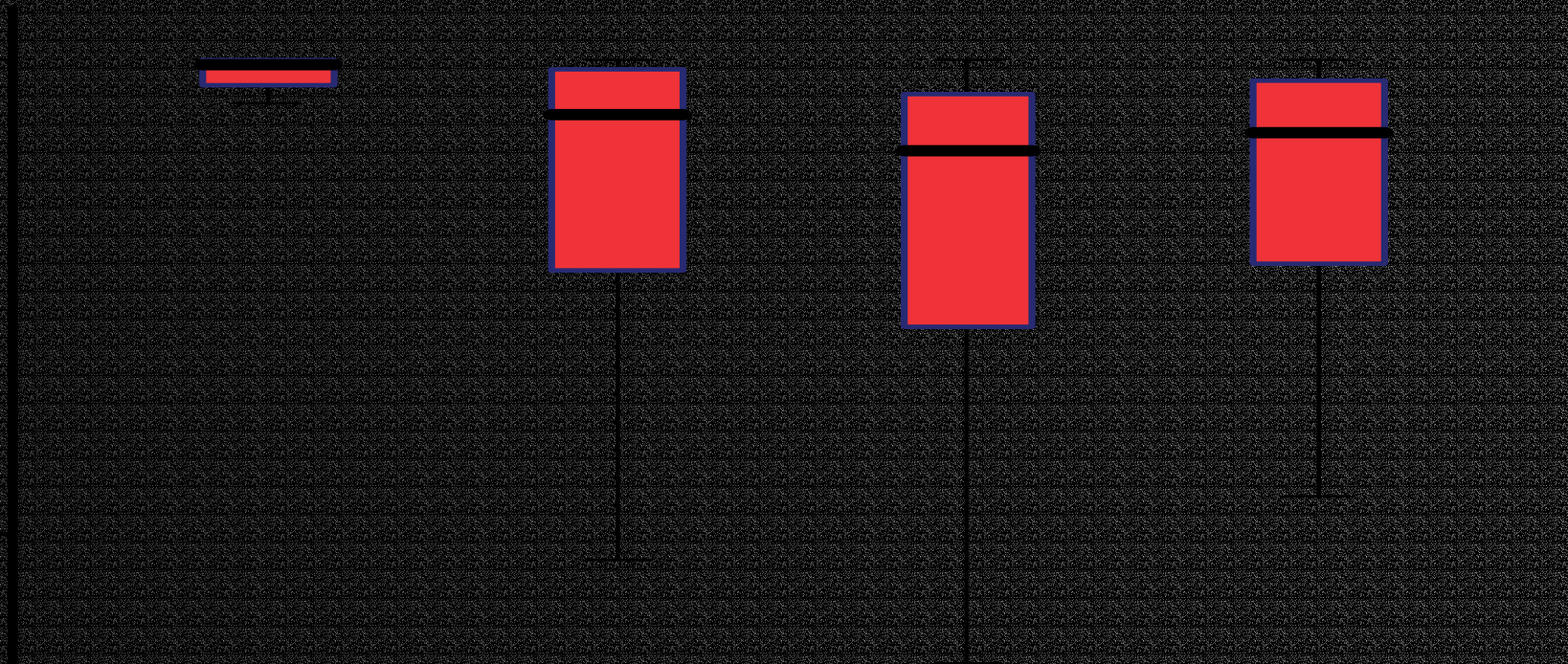


<b>MEDIAN</b>	0,59	0,42	0,42	0,42
<b>1st</b>	0,49	0,27	0,28	0,27
<b>3rd</b>	0,71	0,53	0,53	0,56
<b>MEAN</b>	0,592	0,400	0,396	0,417
<b>SEM</b>	0,021	0,023	0,013	0,011



# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

I<O



**54**  
Healthy subjects

**29 (53)**  
EORTC 05971  
MBC

**175**  
Paul Brousse  
MCRC

**141 (289)**  
EORTC 05963  
MCRC

1st	99.5	95.7	95.6	94.4
MEDIAN	99.9	98.5	98.9	98.1
3rd	100	99.6	99.8	99.3



# Circadian Timing System alterations

## DESYNCHRONIZATION (Jet Lag)

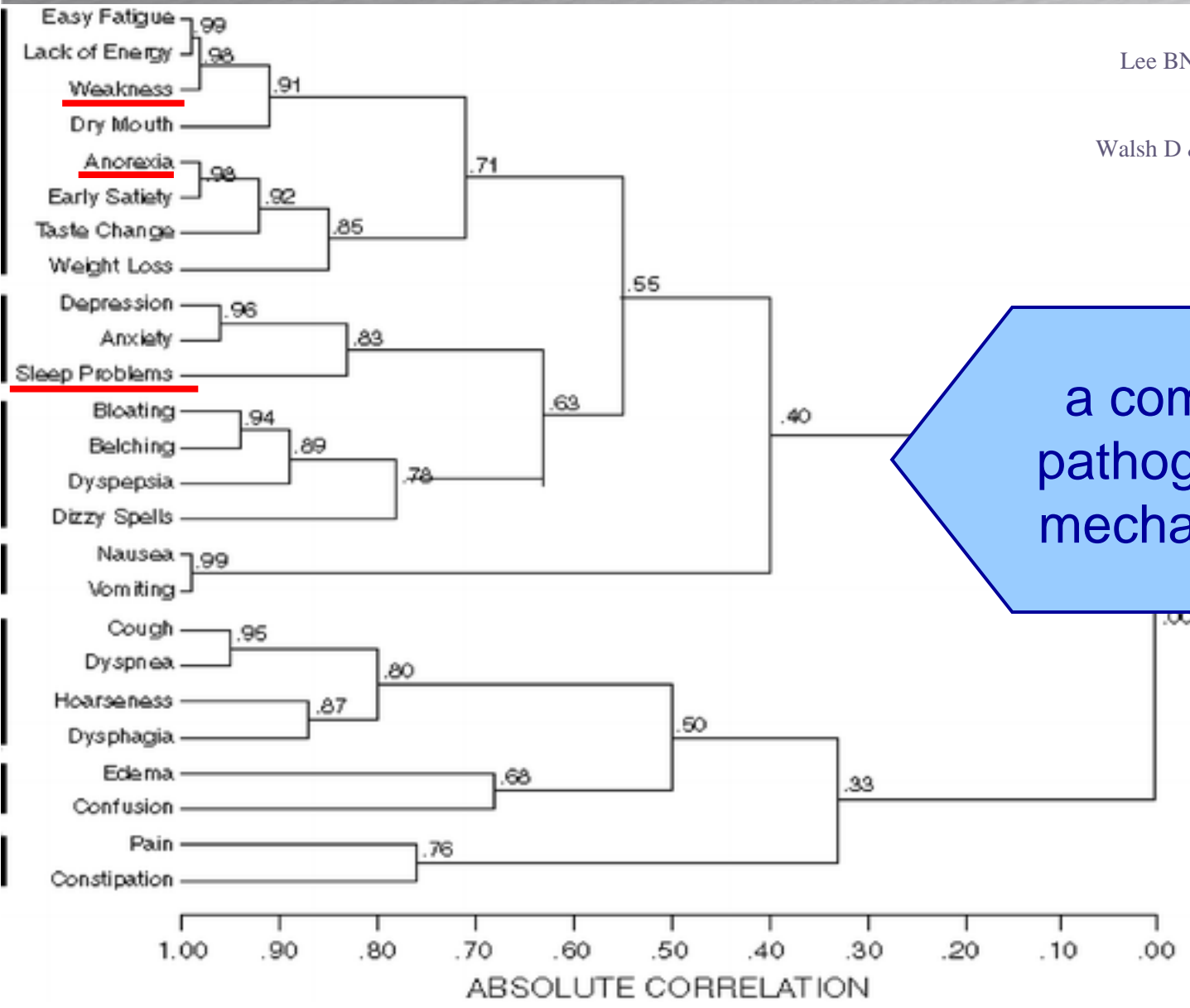
### Rapid long-haul flight over several time zones:

- Poor sleep performance (excessive daytime sleepiness, decreased alertness, irritability, depressed mood);
- Fatigue, weakness, lethargy;
- Decreased efficiency (loss of concentration, difficulty with memory, clumsiness);
- Gastro-Intestinal problems (loss of appetite, indigestion, bowel irregularities).



# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

## Symptom Clusters in cancer patients



JNCI Monograph n° 32, 2004

Lee BN, *et al*, Neuroimmunomodulation, 2004

Cleeland CS, *et al.*, Cancer 2003

Walsh D & Rybiki L, Support Care Cancer, 2006

a common pathogenetic mechanism?



# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

## Cytokine-induced Sickness Behaviour

- Lethargy
- Weakness
- Malaise
- Inability to concentrate
- Fatigue
- Anorexia
- Sleep changes
- Fever

- Acute infection
- Chronic inflammation
- Cancer
- Depression
- ILs/IFNs therapy

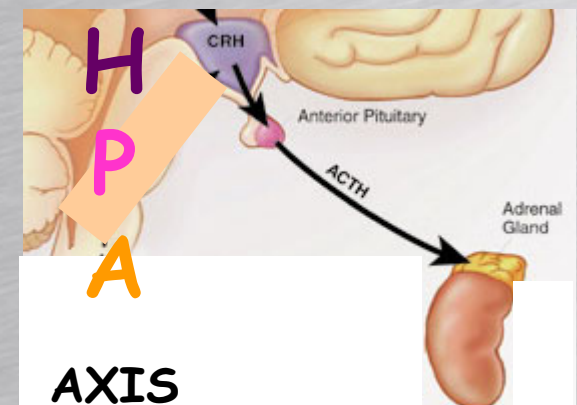
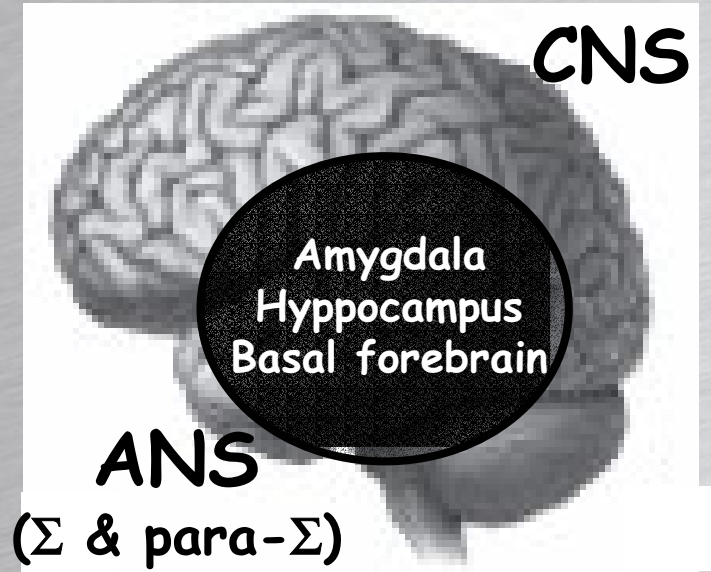
IL-6

IL-1 $\beta$

TGF- $\alpha$

TNF- $\alpha$

VEGF



Raison CL & Miller AH, Biol Psychiatry, 2003  
 Cleeland CS et al., Cancer 2003  
 Lee BN et al., NeuroImmunoModulation 2004  
 Kelley KW et al., Brain Behav Immun 2003



# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

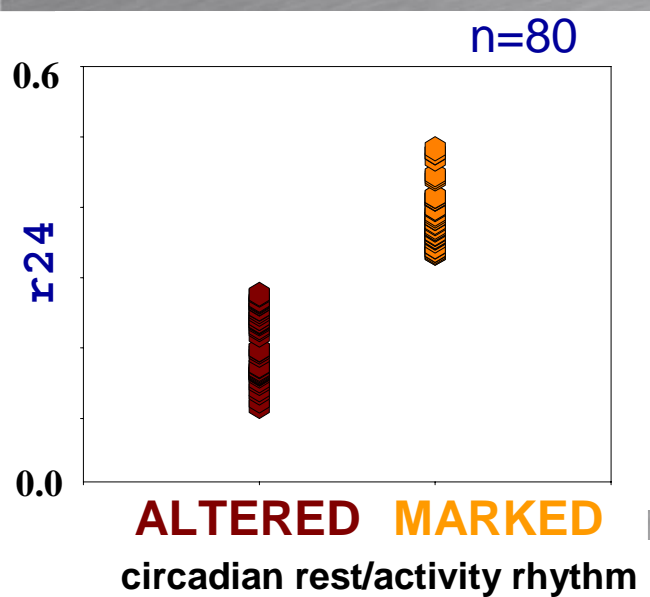
## Cytokine-induced Circadian Rhythms alterations

### Intracerebral infusion of $TGF-\alpha$ altered:

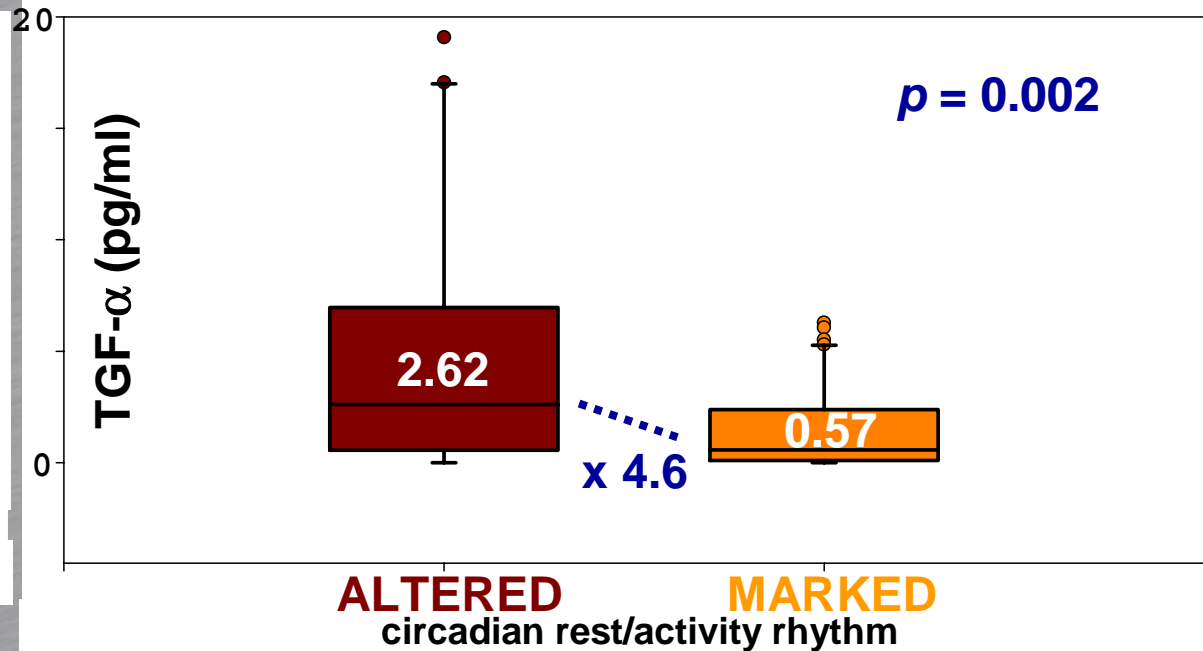
- Sleep/wake cycles & Core Body Temperature;
- Activity ( $\uparrow$  resting and inactivity;  $\downarrow$  wheel running and grooming);
- Eating habits ( $\downarrow$  eating;  $\equiv$  drinking:  $\rightarrow$  weight loss)

Kramer A, *et al.*, Science 2001  
Snodgrass-Belt *et al.*, Brain Res 2005

Rich TA *et al.*, Clin Cancer Res 2005



$\uparrow TGF-\alpha$  **fatigued pts** (median x5.3;  $p=0.006$ )  
**anorexic pts** (median x4.4;  $p=0.012$ )





## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

A common (and potentially targetable) pathogenetic mechanism may underlie both Circadian Timing System alterations and the occurrence of some clustered systemic symptoms (fatigue, anorexia) .



**Circadian Rest/Activity Rhythm  
&  
Health Related Quality of Life**



## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

### FATIGUE ↔ CIRCADIAN REST/ACTIVITY RHYTHM

<u>nbr of pts</u>	<u>disease setting</u>	<u>questionnaire</u>	<u>refs</u>
72	Early & Metastatic Breast Cancer	Piper Fatigue Scale	Berger AM Oncol Nurs Forum, 1998 & 1999
85		MFSI-SF & FACT-B	Roscoe JA Support Care Cancer, 2002
78		MAF & FSCL	Ancoli-Israel S Support Care Cancer, 2006
24	radiotherapy for bone metastases	Lee Fatigue Scale	Miaskowski C J Pain Symptom Manage, 1999
33	Advanced NSCLC	EORTC QLQ-C30	Levin RD Br J Cancer, 2005
200	Metastatic Colorectal Cancer	EORTC QLQ-C30	Mormont MC Clin Cancer Res, 2000
108		EORTC QLQ-C30	Innominato PF Proc. ASCO Meeting 2005



## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

### ◀ CORRELATIONS ( $I < 0$ ) ▶

Spearman  $\rho$  ;  $p < 0.001$

<b>QoL scale</b>	<b>Paul Brousse study n=200 MCC pts</b>	<b>EORTC 05963 study n=108 MCC pts</b>	<b>WHO - PS</b>
FATIGUE	- 0,33	- 0,40	0,48
APPETITE LOSS	- 0,29	- 0,30	0,41
PHYSICAL FUNCTIONING	0,43	0,37	- 0,39
<b>GLOBAL QOL</b>	<b>0,34</b>	<b>0,40</b>	- 0,37

# Chronotherapeutic interventions

## BEHAVIOURAL

- ❖ Timed physical activity;
- ❖ Timed meal schedule;
- ❖ Timed sleep routine;
- ❖ Timed light exposure.

## PHARMACOLOGICAL

- ❖ Awakening hydrocortisone;
- ❖ Evening melatonin;
- ❖ Small EGFR-TK inhibitors;
- ❖ Psychostimulants.



## RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

**The Circadian Timing System can be considered as a biological and therapeutically targetable determinant of symptoms (fatigue, anorexia), functioning domains (physical) and Health-Related Quality of Life.**

**Circadian Timing System functioning can be objectively, continuously and non-invasively monitored (wrist-actigraphy).**

**Further (collaborative) studies are needed:**

**longitudinal evaluation of circadian rest/activity rhythm (during treatment; after treatment);  
co-variation of Quality of Life scales and circadian rest/activity rhythm along time;  
development of a circadian module, with actigraphy as an anchor.**



# RELATIONSHIP BETWEEN QUALITY OF LIFE AND CIRCADIAN REST/ACTIVITY RHYTHM IN CANCER PATIENTS

## ACKNOWLEDGEMENTS



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Toronto (CAN)

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EORTC QoL Group



EORTC Data Centre

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