Detection of sleep disturbancies as a tool for early intervention in DS persons

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Introduction (I)

- In addition to the routine health maintenance needs of all persons, those with DS have specialized needs failure to adress.
- These specific health maintenance concerns may lead to misdiagnosis and failure to reach the highest level of function possible.
- Studying sleep abnormalities in DS, and in animal models for DS, may help to better understand some specific neural features for them but also for the general population. This research will lead to new therapeutical strategies

Introduction(II)

- Sleep affects learning and development in human and in other animals, but the role of the sleep in developmental learning has been examinedonly recently in a few studies. Many recent studies performed in birds, drosophyla, mice and rats have bring new highlights on the physiological and biochemical knowledge of circadian rythms.
- Moreover some pathologies are either directly or indirectly related to altered circadian rythms: (Smith-Magenis and restless legs syndromes, depression, mental retardation, Alzheimer disease etc…)

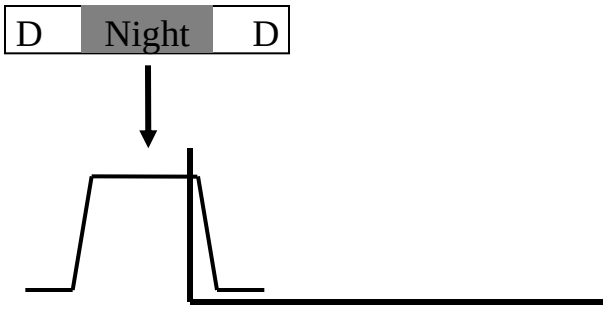
BAD SLEEP CAN INDUCE

A) POOR EFFICIENCY at school or work

B) ATYPICAL SYMPTOMS :

- bad mood and depression??
- diverses manifestations about food
- Decrease of vigilancy
- gastro-intestinal manifestations
- migraines

⇒ Need of sleep-wake **re-synchronisation** by a chronobiotic compound :



The stuff of the sleep in humans

First hour: ***Slow wave sleep (SWS) or non-rapid eye movement sleep (NREM)***

- Relaxation of the muscles and the eyes
- Decrease of heart rate, blood pressure and body temperature

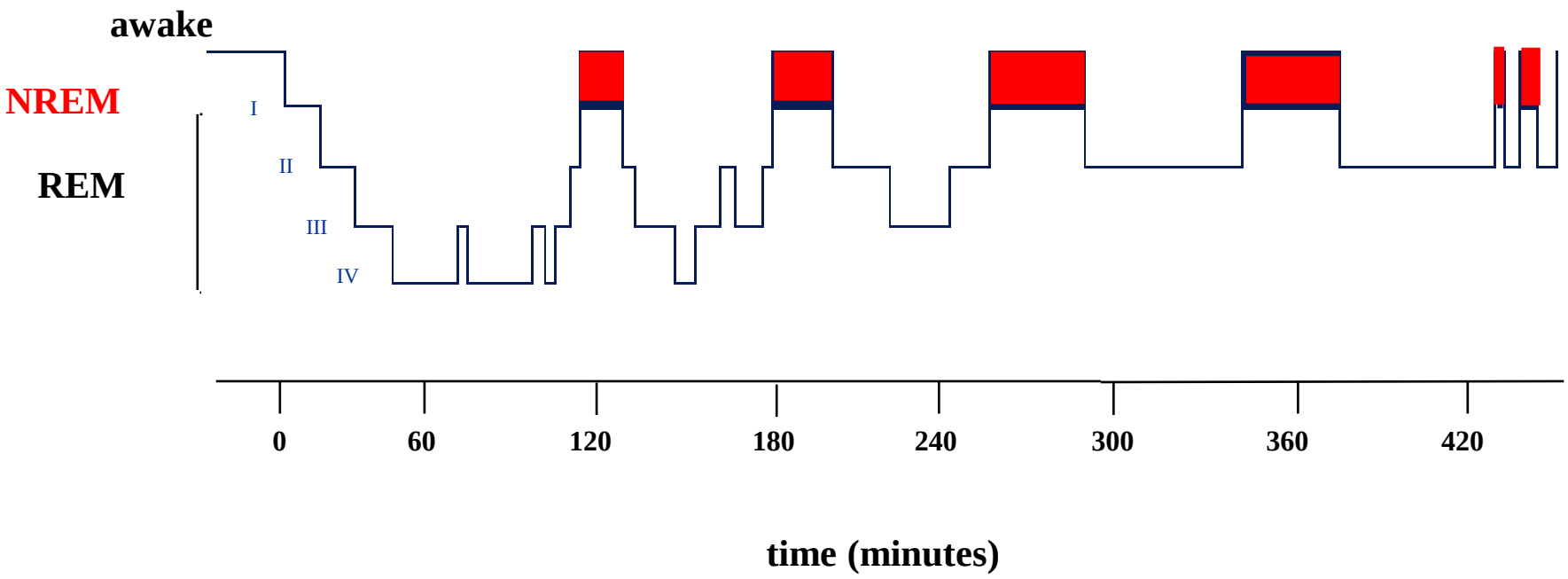
Second hour: ***Rapid eye movement (REM) sleep also called Paradoxal Sleep (PS)***

- Muscles are almost paralysed (except those for breathing)
- Heart rate, Blood pressure, body temperature are variable
- Active dreaming and high level of brain activity

The course of the night

- Alternative cycles of SWS and REM
- The whole cycle lasts for 90 mn over the night course and is repeated several times during the night

Sleep organisation du sommeil in control person



The waking and sleeping in brain(I)

- Brain is **active during sleep as it is during awakeness!!**

- Sleep is characterized by the frequency, amplitude and morphology of:
  - EEG (ElectroEncephograph) waves
  - EMG (Electro-Muscular activity Graph)
  - EOG (Electro-Ocular activity Graph)

- The frequency of EEG is labeled by the number of cycles per second :

  alpha (α): 8-13 Hz; beta (β): ≥13 Hz;

  Delta (δ): ≤ 4Hz; Theta (τ): 4-7Hz

The waking and sleeping in brain(II): *Neurotransmitter pathways*

- Cholinergic: acetylcholine neurones are essential during REM and wakefulness
- GABAnergic: ↑ during REM
- Histaminergic: active during wakefulness and involved in arousal
- Serotoninergic: reduced in NREM and minimal in REM. Decreased in depression; it can be measured by 5HydroxyTryptophane release.
- And many others specific for certain types of neurons

Sleep disorders in the general population

- **Insomnia**
- **Obstructive sleep apnea: OSA**:
  - 20-40 % more or less mostly in aged persons
  - -Tendency to fall asleep during the day,
  - -During sleep: as sleep deepens, the airway muscles in the throat deepens, preventing breathing and entering in the deeper stages of SWS and causing more frequent arousals (>2 per hour)
  - Risk of high blood pressure and heart attack.
  - **Consequences in devellopment and growth, when present in young**
- **REM disorder**
  - Failure of the muscles to be paralysed during REM sleep.
  - Affects day-time activities
- **Sleep fragmentation:** frequent arousals without apnea
- **Restless legs syndrome**
- **Narcolepsia**

OSA in DS population (I)

- **More than ten apneas per sleep hour**
- **Hypoventilation**
- **Arterial oxygen desaturation**
- **Significant increase in the low and very low frequencies components of the heart rate variability** (Ferri et al.1998)
- **Risk factors for OSA in DS**
  - **small upper aiways**
  - **increased incidence of lower respiratory tract anomalie**
  - **recurrent enlargement of the adenoid tonsils**
  - **macroglossia and glossptosis**

OSA studies in the DS population (II)

1) Spanish Study by J.Miguel –Diez (**2003**, Madrid)

108 patients aged 1-18 years.

- Prevalence: **54.6 %** (boys : 64.7 %; girls : 38.5 %)
- more important in younger.
- In this study : only tonsillar hyperplasia may play a role

2) American study by S. Shott (2007, Cincinatti, USA) :

56 patients aged 4-63 months

- Prevalence : **57%**
- carbon dioxide > 45mm Hg for 65%of them and >50mm for 10%. Showing brain oxygene desaturation!!
- In this study 65% were reported by their parents with no sleep problems!

OSA studies in DS population (III)

3) C. Richmond (**2007**, Sydney, Australia) : of a

- 33 persons aged 0.2 to 19 years old who snored
- Prevalence: **97%** with 15% having moderate (5-10) and 46% with more than 10.

4) ST. Leung (**2007**, Hong-Kong):

- 22 persons aged 10+/- 6 years
- Prevalence: **59%** have OSA
- among them 40% did not snore.

Frequency: 30- 40%

Recording of sleep

Patients from Grenoble Cohort (22 males aged 22)

	Controls	DS
Index of Apnea	**0.2 ± 0.1**	**7.0 ± 2.5** ★★
Incomplete Index of Apnea	**9.9 ± 0.1**	**40.9 ± 8.0** ★★★
SaO_2	**97.5 ± 0.2**	**94.3 ± 0.4** ★★★
Time of $SaO_2 < 90\%$	**0.0 ± 0.0**	**2.5 ± 1.1** ★★

★★★ P< 0.05;
★★★ P<0.001

Conclusions on OSA in the DS population

- The four studies (and some others before) agree on the **40%** patients suffering from OSA and
- highlight **recommendation of polysomnography for all children with DS at age 3-4 years or even earlier even if they do not snore or had adenotonsillectomy**
  - **No european studies! (may be coming from Fondation Lejeune and Trisomie 21 France within 2 years)**

The biochemical and pharmacological aspects of OSA should me more investigated at the gene level because it is a real new phenotype as CHD

Consequences of OSA

A) On *physiological level*

- **Hipoxia**: decrease of the oxygen level which can induces **damage to the brain and the heart!!**

- **Hipercarbemia**: increase of the carbon dioxyde (very toxic compound)

- Cardiac problems: **rythm variability**

- **Hypertension**

B) *On cognitive level*

- **Somnolencia , decrease in attention, concentration, and memory abilities**

- **Moto deficits especially for fine motor skills**

C) *On behavior level*

- **Difficulty to rest, Hyperactivity, Agressivity**

Specific treatments for DS persons

- Without for the moment specific treatement, ther are some hallmarks:
- It is necessary to investigate sleep in children befor they are adults even if you think that they sleep well!!
- But most countries do not have the medical facilities to investigate sleep even for the general population!

Which treatments for OSA??

- Medical
- Mecanical
- Surgical

In order to decide for a treatment there is an absolute need for appropriate diagnosis of the level and the strentgh of the obstruction

Medical Treatments

- **A) For nasal obstruction**

  - spray of a saline solucion
  - anti-alergic
  - spray of steroids or antihistaminics

  Pay attention:Avoid risk factors like tobacco!!

B**) Body health**

  - Neccessity to loose weight if necessary
  - walking, swimming and all kinds of sports
  - Nutrition and sleep??
  - Necessity for a good relation before sleeping (relaxation??)

Mecanical treaments

Apparatus with positive pressor (**PAP**)

- This apparatus should be adapted to any kind of mouth: but not yet for the moment!!! a european claim??!!!

Surgery treatments

- **Amigdalis and vegetations removal**

  100% success in the general population

  but only 40-50% dans la population DS

- **Dentition**

  it is very important to maintain the best postion of mandibullars

- **Lingual resertion:** it is not anymore done except in exceptional cases!! early oropraxis is much much efficient!!

Sleep characteristics other than OSA in Down syndrome

- **Sleep fragmentation :**frequent awakenings and arousals only partially related to obstructive sleep apnea

- **Sleep patterns abnormalities (Levanon, 1999, Polish study 2007):**
  paradoxical sleep :**PS ↓= REM↓**
  undifferential sleep ↑
  oculomotor frequencies ↓

  might be relevant for their cognitive poor efficiency

- **Morover during apnea-free periods,**
  - the low frequency (sympathic function) ↑
  - the high frequency (vagal activity) ↓

Suggesting a brainstem dysfunction

thus should be related to what we know for brainstem dysfunction in DS and animal models

Metabolism and sleep and chromosome 21 genes

- Brain relies almost **exclusively** on **glucose** as its energy substrate. Glucose is transported from blood to neurons and glia by transporters (***glut1 is on chromosome 21!***). It has been shown that hippocampal extra cellular glucose concentration was decreased during a difficult spatial task
- Some key regulators of **Calcium** metabolism have been shown (in rats) to be altered during sleep (***many genes on chromosome 21 are connected to Ca+ regulation: Dyrk1a, PCP4***)
- **Adenosine** metabolism: adenosine is involved as building block of nucleic acids and energy storage molecules, a modulator at the synaptic level, neuroprotective against hypoxia, control of sleepness etc
- Metabolism of **cholesterol** (The ***connected to Ts21***)

Sleep comparison between DS, and autism

- The two groups show a relation between the level of mental retardation and REM sleep
- **Sleep apnea only in DS** (*may be related to plama homocysteine and 1-C metabolism, March 2005 paper*)
- Autism have frequent nocturnal awakings, lower sleep efficiency, decrease SWS , decrease NREM *(Brain Feb2005)*
- Sleep anomalies in autism are more important than in DS (except for the apnea) suggesting a more severe brain defect in autism than in DS

Sleep Characteristics in Alzheimer disease

- In early AD: disruption of nighttime sleep patterns
- In late AD: increment in the propensy to sleep during daytime

At the biochemical level

- May be related to loss of **AcetylCholine** containing cells in the basal forebrain
- May be related to **A beta peptides** (from APP metabolism)

How to study sleep in the general population and in DS(I)

1) **Polysomnography including**:

- ElectroEncephograph with waves determination
- Electro-Muscular Graph
- Electro-Ocular Graph

2) **Use of medication** may help to better understand the abnormalities (specific neurotransmiiters agonits or antagonists)

3) Positron emission tomography (PET) and the use of specific tracers for neurotransmitters, ligands for receptors,

It is feasible to study specifically the activity of small group of cells in a specific area of the brain!!

How to study sleep in the general population and in DS(II)

- 2 studies by the group of Heisss WD in Cologne showing with ***PET technique***

- the involvment of cerebral acetyl esterase activity in mild impairment (Herholz K.,2005) already known but showing the feasibility of the technique

- imaging the acetylcholine esterase activity in brainstem nuclei in the regulation of sleep and wakefulness in two patients with AD (Eggers C., 2007)

- *A **genetic study*** on AD patients being recorded for sleep abnormalities have shown a polymorphism in the promoter of MAOA (monoamine oxidase A) involved in the synthesis of melatonine through serotonine (Craig D. 2006)

To understand the molecular basis of the sleep abnormalities it is possible to study animal models such as mice and even drosophila

Animal models to study sleep (I)

Advantages:

- a lot of slightly different models can be used (overexpressing a specific gene or invalidated for that gene through ES cells « the Nobel price of this year ») and the strains used are well controlled

- a lot of biological assays can be performed from proteomics to electrophysiology

- these animals can be used in different laboratory thus reproducible results are obtained

Examples of scientific work (II)

- **Sleep/ fragmentation** is shown in mice with a dysruption of the hypocretin system (Zhang S. et al 2007) a model for narcolepsia and a mutation in a gene of the GABA system has also been proposed in another study (Hamet P. 2006)
- Rats exposed prenatally to valproic acid are a model of **autism**; sleep abnormalities have been shown in these animals and brain serotonin was higher suggesting a defect in serotonergicsystem responsible for irregular sleep/awake in autism (Tsujino N. et al. 2007)
- Numerous studies on mice or rat with **chronic sleep deprivation** have been performed and have shown a memory impairment, suppression of hippocampal plasticity and related genes along with a depletion of glycogen and increase of oxidative stress (McEwen BS 2006; Guzman-Marin R. 2006)

Examples of scientific work (III)

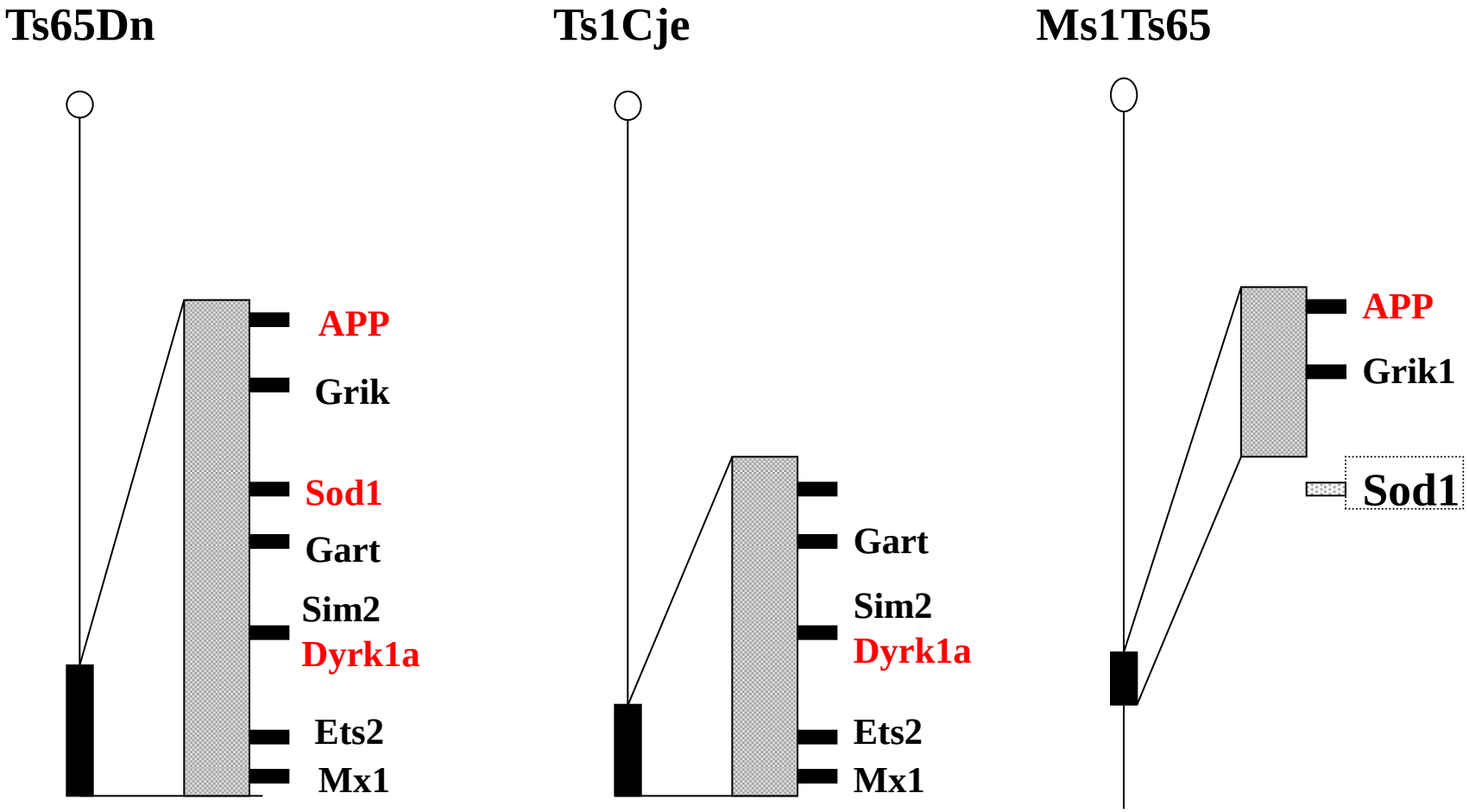
- In a model of **depression** in mice a sleep fragmentation has been shown with an abnormal responses to HT receptors (Popa D. and J. Adrien, 2006)

- Sleep and circadian abnormalities has been observed in « **Alzheimer transgenic mice** » and shown to be related to abnormal cholinergic transmission. They also showed the efficacity of donepezil (AChesterase inhibitor) in awakeness promoting as well as passive immunization with an antibody against Aβ (Wisor JP 2005)

Examples of scientific work (III) for studying DS

Many different animals for modelling DS

- Transgenic mice for one gene: SOD1, DyrK1A, S100beta, APP
- partial trisomic mice : Ts65Dn (138 genes in 3 sets); Ts1Cje (85 genes)


Ts65Dn
APP
Grik
Sod1
Gart
Sim2
Dyrk1a
Ets2
Mx1
Ts1Cje
Gart
Sim2
Dyrk1a
Ets2
Mx1
Ms1Ts65
APP
Grik1
Sod1

Our own work

EA3508, University Paris-Diderot

- We started in 2004 to study sleep patterns in collaboration with Dr.N. Sarda in Lyon for the mice that we had in our group in Paris
- 1) **Transgenic mice for the hSOD1 gene** (Colas D. 2004)

  2) **Transgenic mice for the hAPP gene** (Colas D. 2005)

  3) **Transgenic mice for the hSOD1 gene and TsCJe:** collaboration with the team of Dr. J. Adrien (Inserm U288, CHU Salpétrière, Paris)

Sleep alterations in homozygous hSOD1 mice

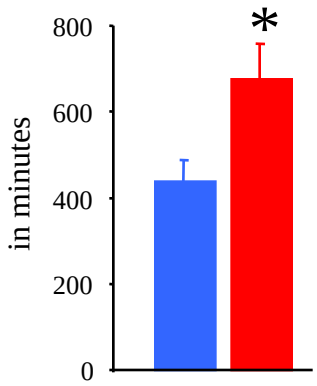
Work done in the team of Dr.J. Adrien, Inserm U288, Paris

controls

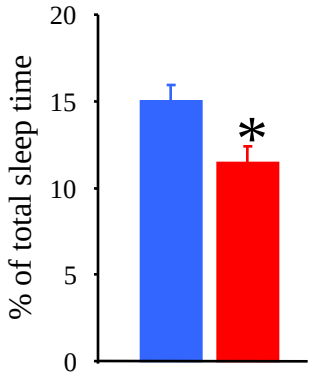
hSOD1

REM sleep

Spontaneous REM sleep latency



REM sleep amounts



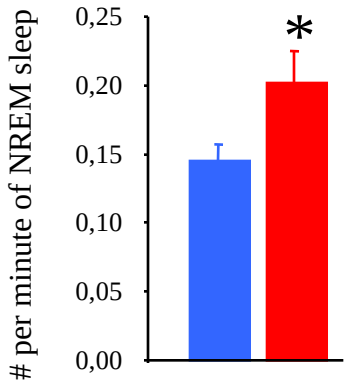
➢ **lengthened spontaneous REM sleep latency**

➢ **decreased REM sleep amounts**

Non-REM sleep

Brief awakenings within non-REM sleep

as an index of sleep fragmentation



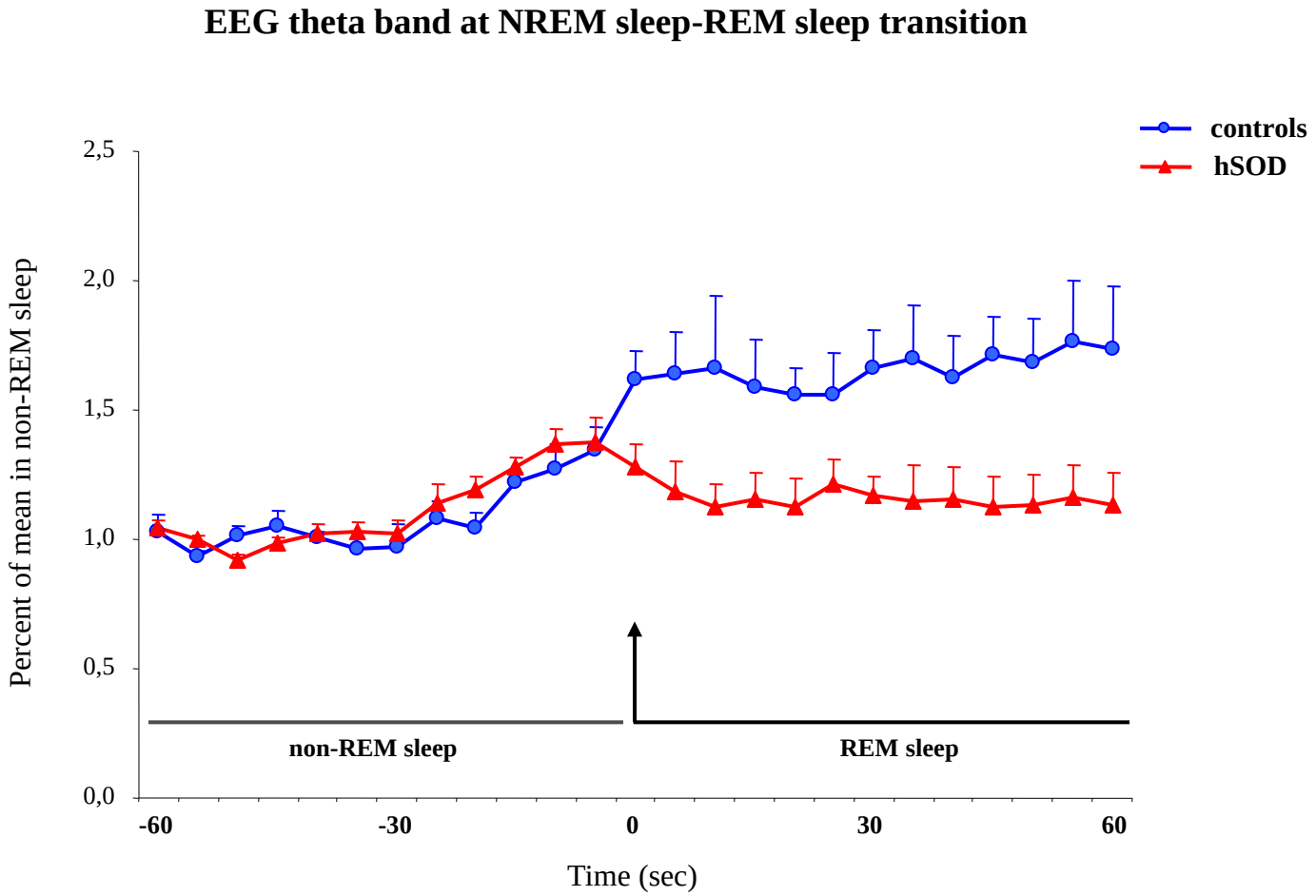
➢ **more fragmented sleep**

➢ no significant differences in the total amounts of wakefulness and non-REM sleep per 24 h

Results are expressed for the entire light-dark cycle (24 h)

mimick sleep alterations observed in children with Down syndrome

Electro-encephalographic alterations in homozygous hSOD1 mice



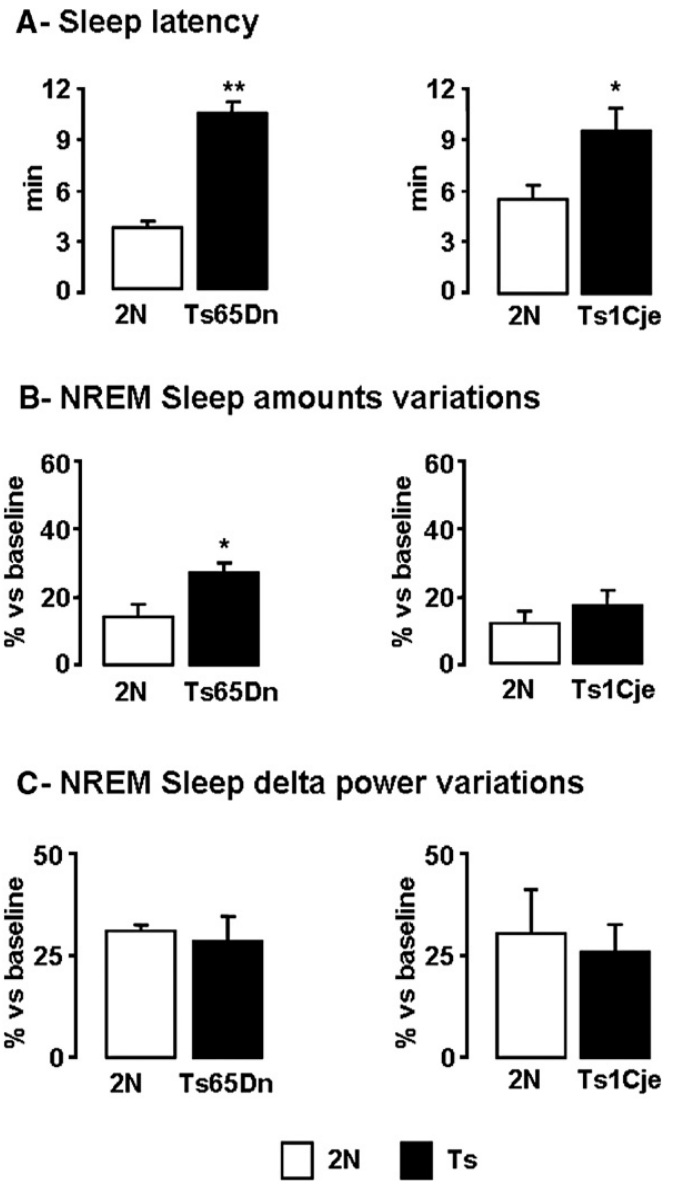
➢ **less intense REM sleep ?**

Work performed by Dr. D. Colas (USA)

- Work performed on Ts65Dn and Ts1Cje
- Only Ts65Dn exhibit some abnormalities
- Abnormalties are similar to those found in TgAPP mice and in murine models for AD
- These results first should be confirmed by others

Sleep and partial trisomic mice

(Colas et al. 2008)



CONCLUSION(I)

- Sleep characteristics can be studied in simple animal models for DS such as transgenic mice for a single gene and in more complex animals

- Biochemical and pharmacological studies can be performed on these animal models and thus provide clues for a better understanding of the altered neural circuits in Trisomy 21 and a medications finding based on scientific and reproducible results.

- **These works on sleep will help for a better functionning of our population of patients and also many other patients**

CONCLUSION(II)

- Before miracle solution??

- We need to pay better attention on the sleep of our kids

  a) when they are very young and try to improve their sleep quality

  b) when thy are older assay sleep in a special clinic when it is possible!

- **We need to find some therapie to help a better sleep**
- **I am sure it should be possible as for other early interventions!!**

How children with DS go to sleep

Recent study in UK
(*Carter M. et al 2008 Southampton)*

	DS 4-12 years	DS ≥ 13 years	Controls 4-12 years
Number of persons	**24**	**16**	**371**
Time to go to sleep	**9.75 ± 1.5**	**9.13 ± 1.6**	**7.06 ± 1.89**
Time of sleep	**3.88 ± 1.6**	**4.25 ± 1.8**	**3.41 ± 0.93**
Awake during night	**5.75 ± 1.9**	**4.44 ± 1.8**	**3.51 ± 0.85**
SDB	**5.75 ± 2.0**	**5.38 ± 2.0**	**3.24 ± 0,63**
Tendency to sleep during daytime	**15.2 ± 4.2**	**15.2 ± 3,4**	**9.64 ± 2.80**