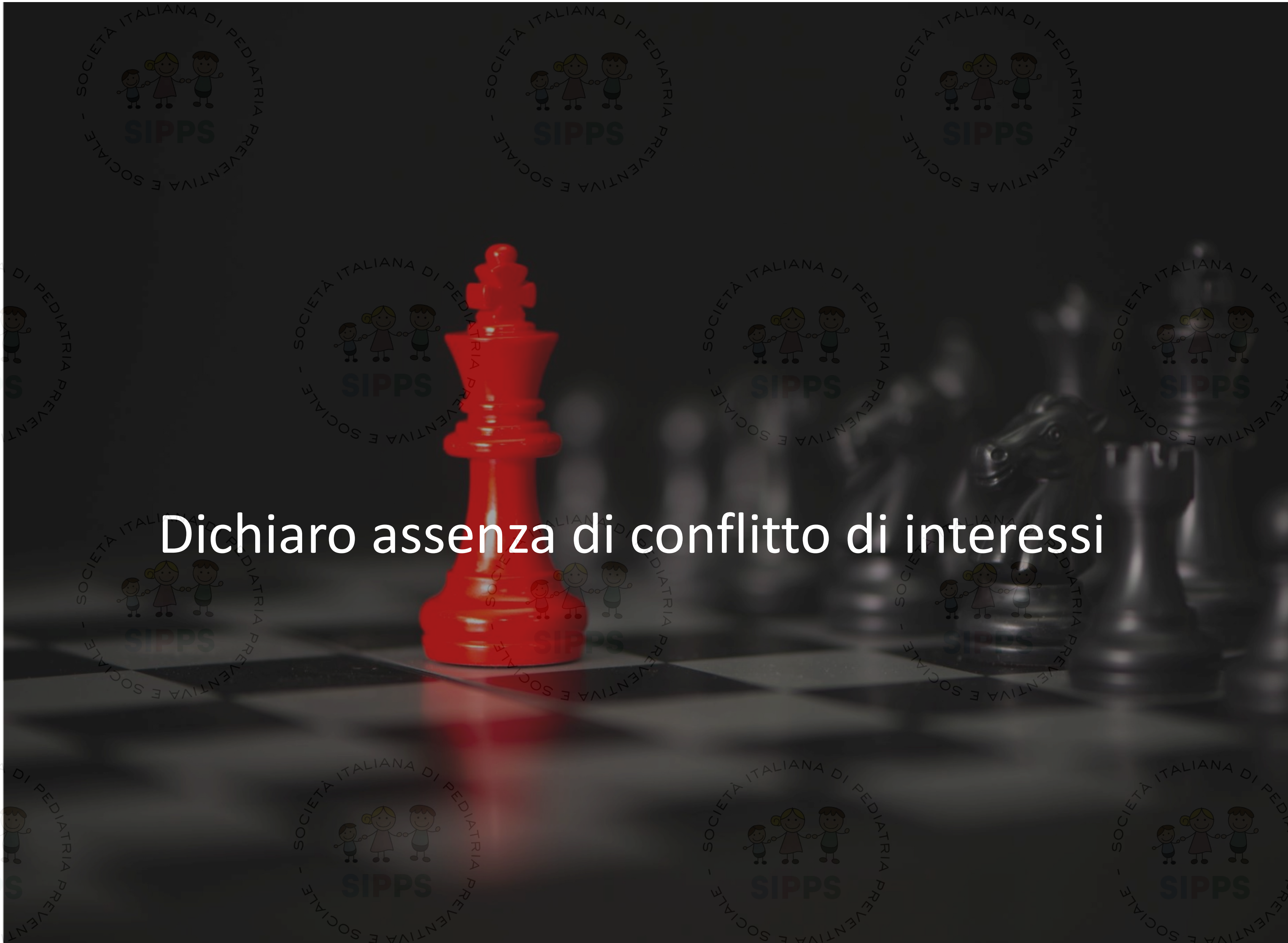
Il sonno nei disturbi del neurosviluppo: prospettive e ipotesi terapeutiche

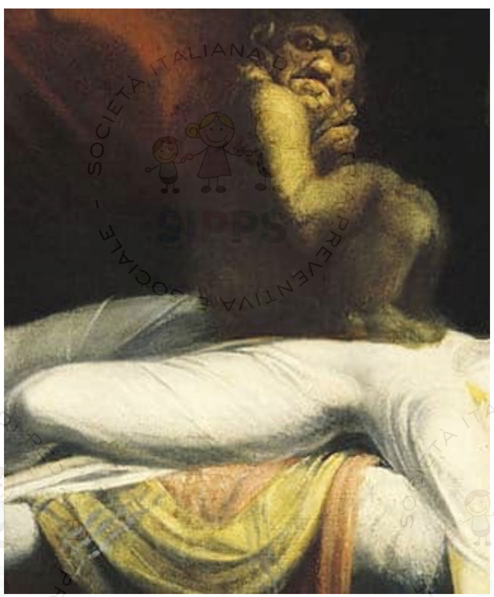
Prof. Marco Carotenuto

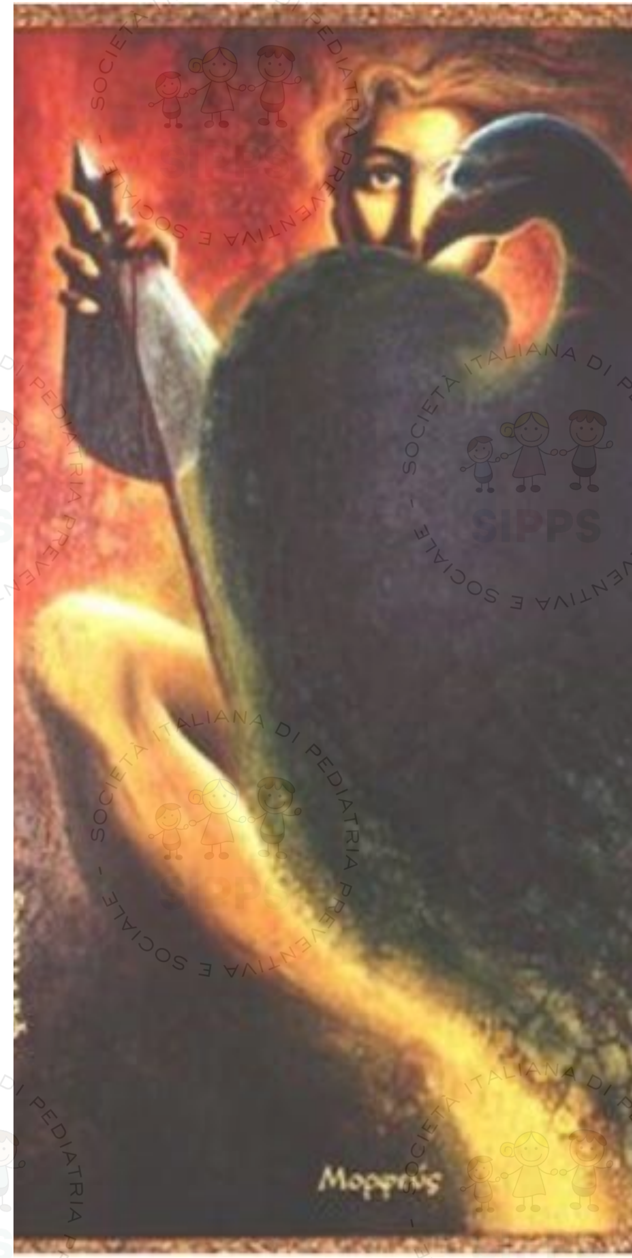
Università degli Studi della Campania *Luigi Vanvitelli*


Dichiaro assenza di conflitto di interessi

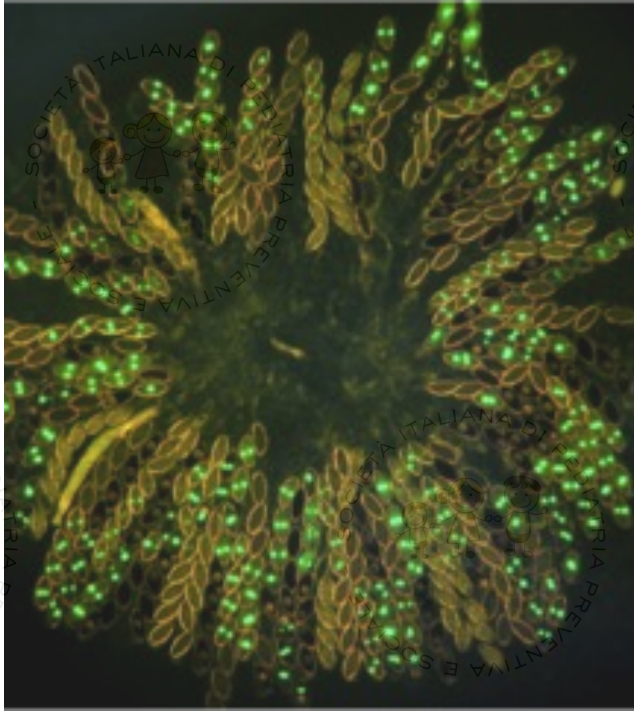
Overview

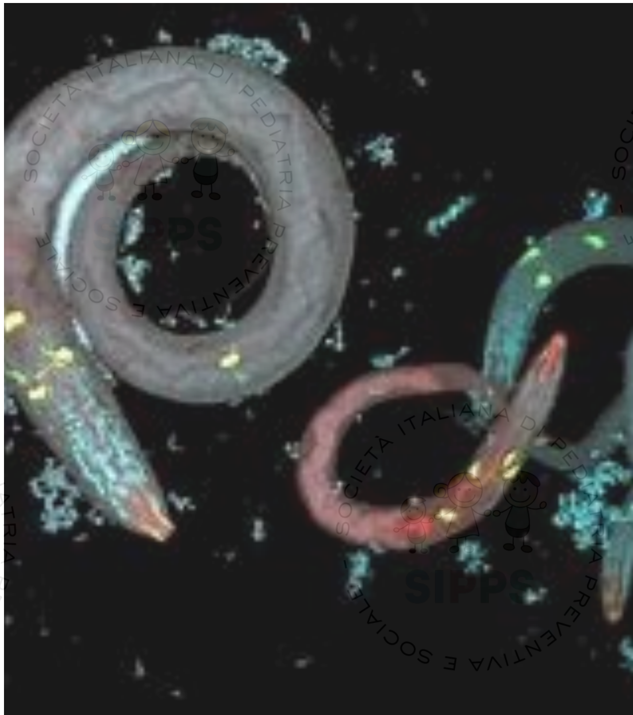
- Introduzione
- Neurochimica e regolazione del sonno
- Il sonno nei DNS
- Melatonina



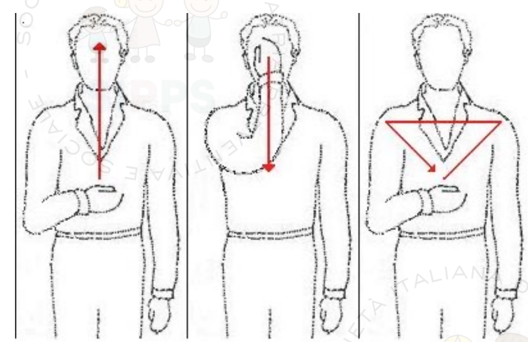

Μορφεύς

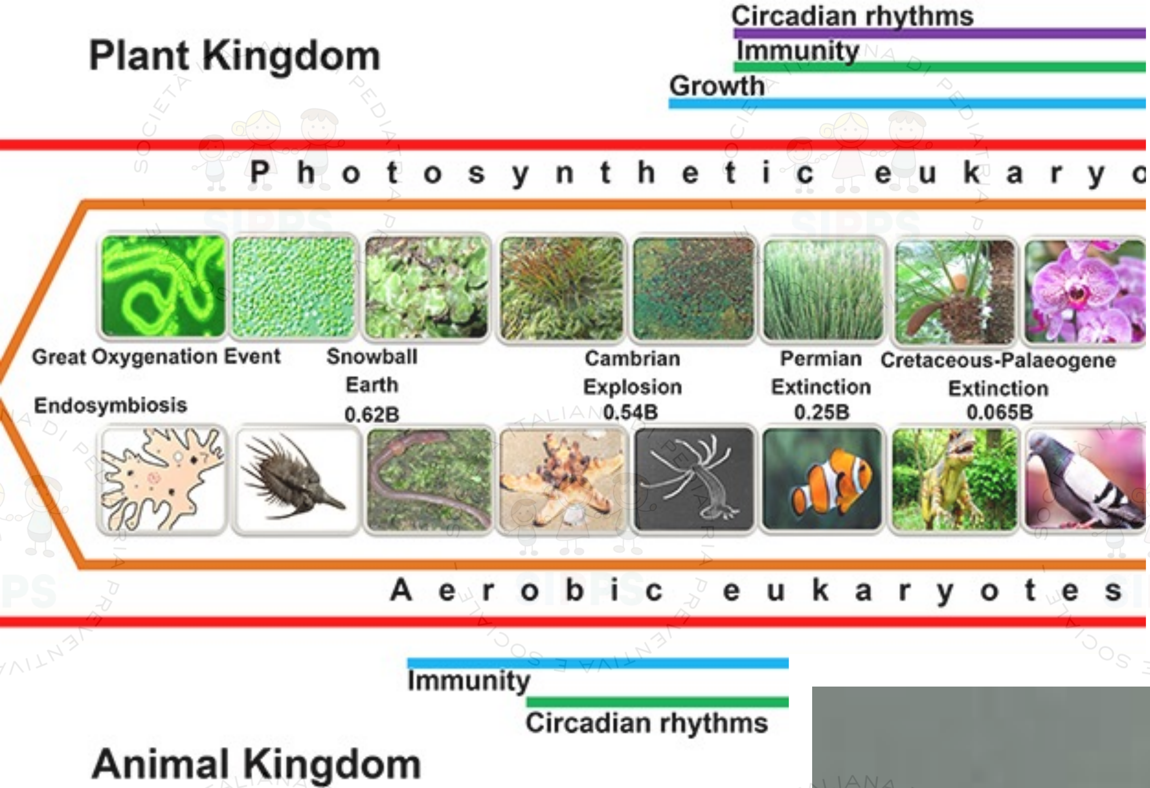


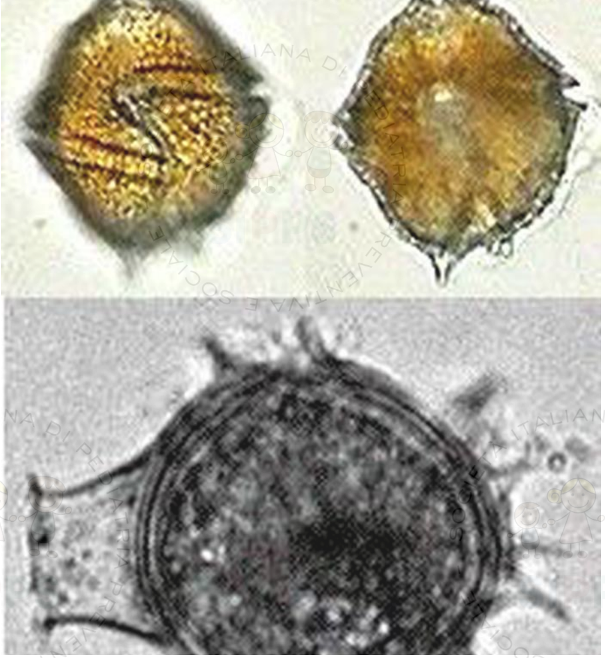


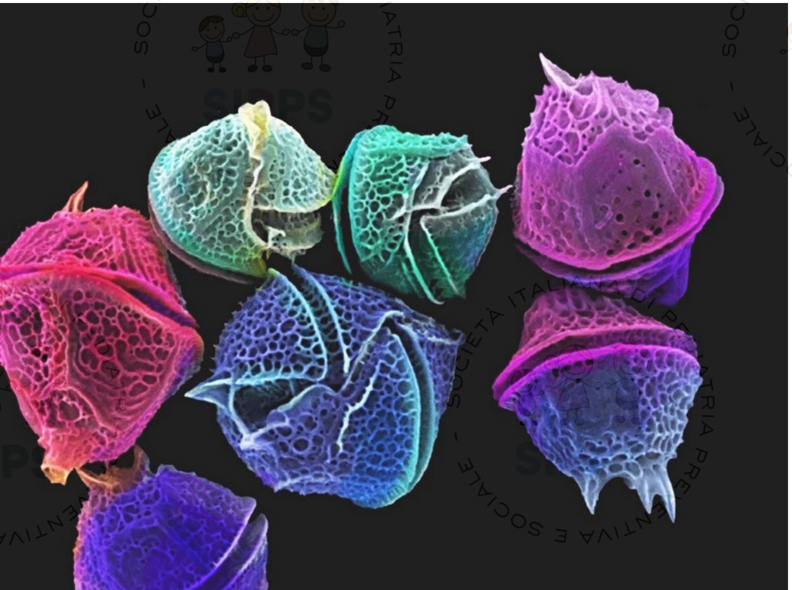



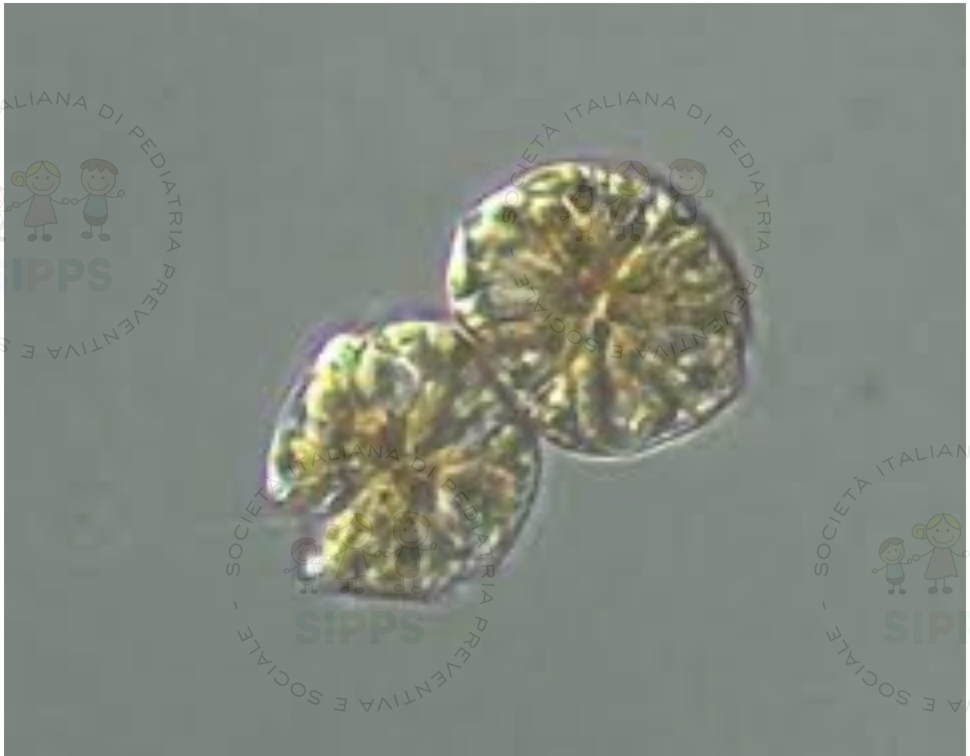

indiaglitz

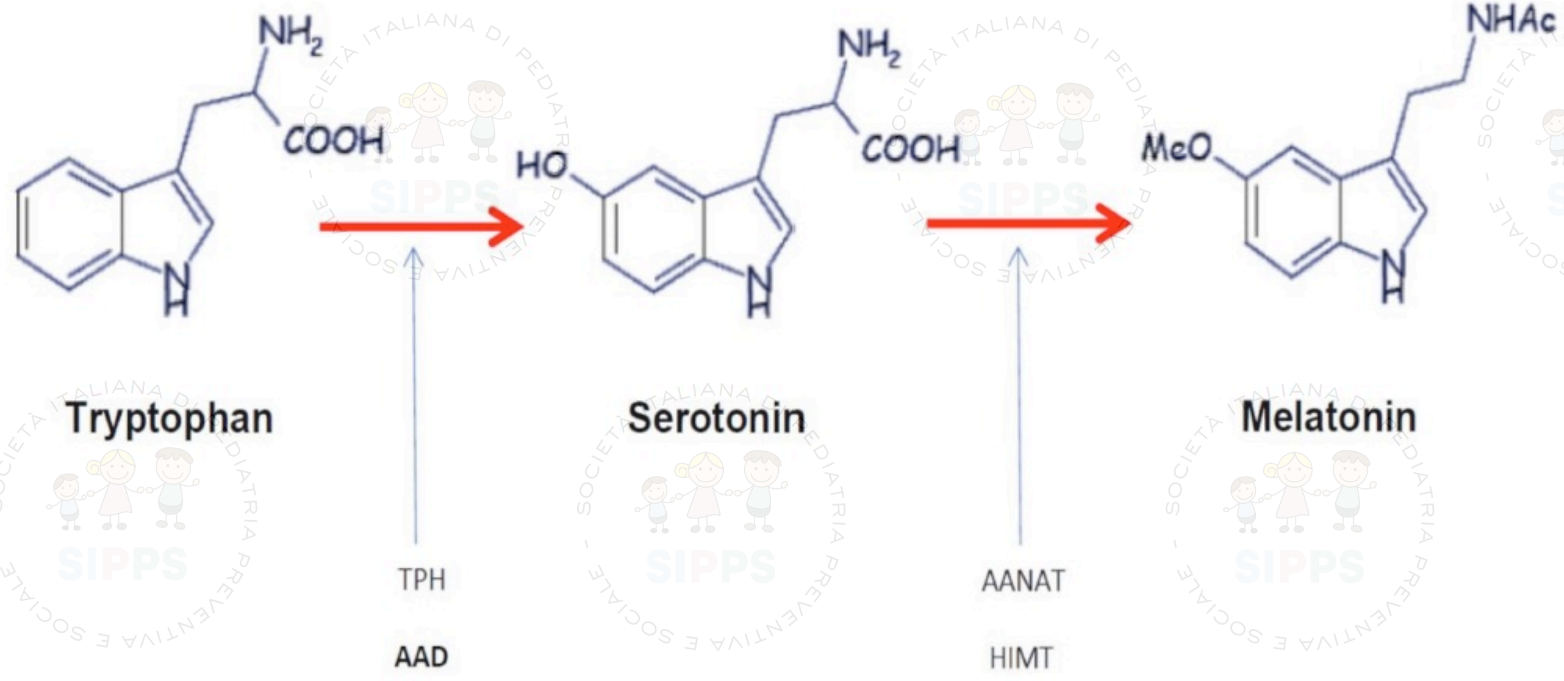


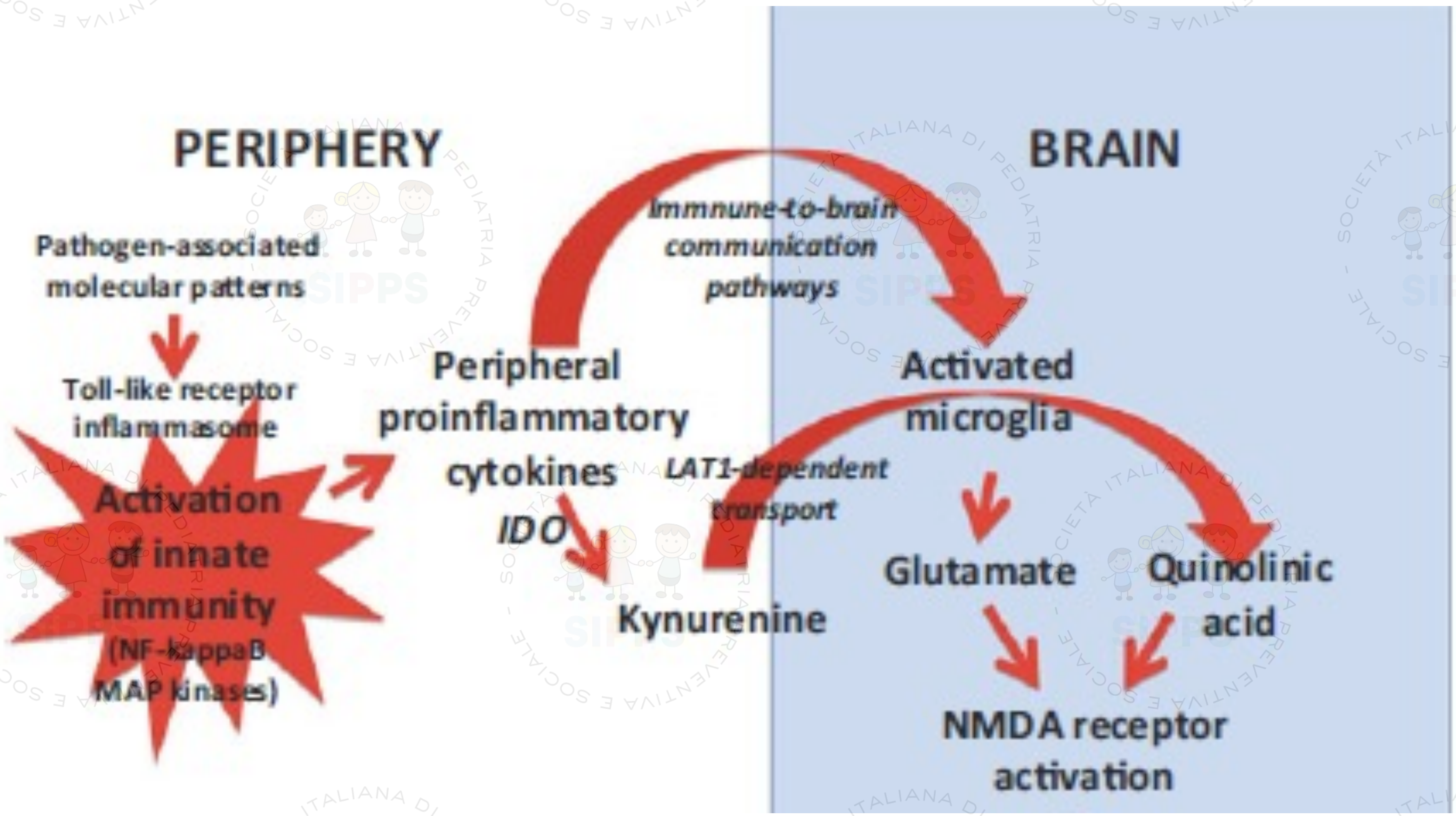

Plant Kingdom
Circadian rhythms
Immunity
Growth
P h o t o s y n t h e t i c e u k a r y o
Great Oxygenation Event
Endosymbiosis
Snowball Earth 0.62B
Cambrian Explosion 0.54B
Permian Extinction 0.25B
Cretaceous-Palaeogene Extinction 0.065B
A e r o b i c e u k a r y o t e s
Immunity
Circadian rhythms
Animal Kingdom

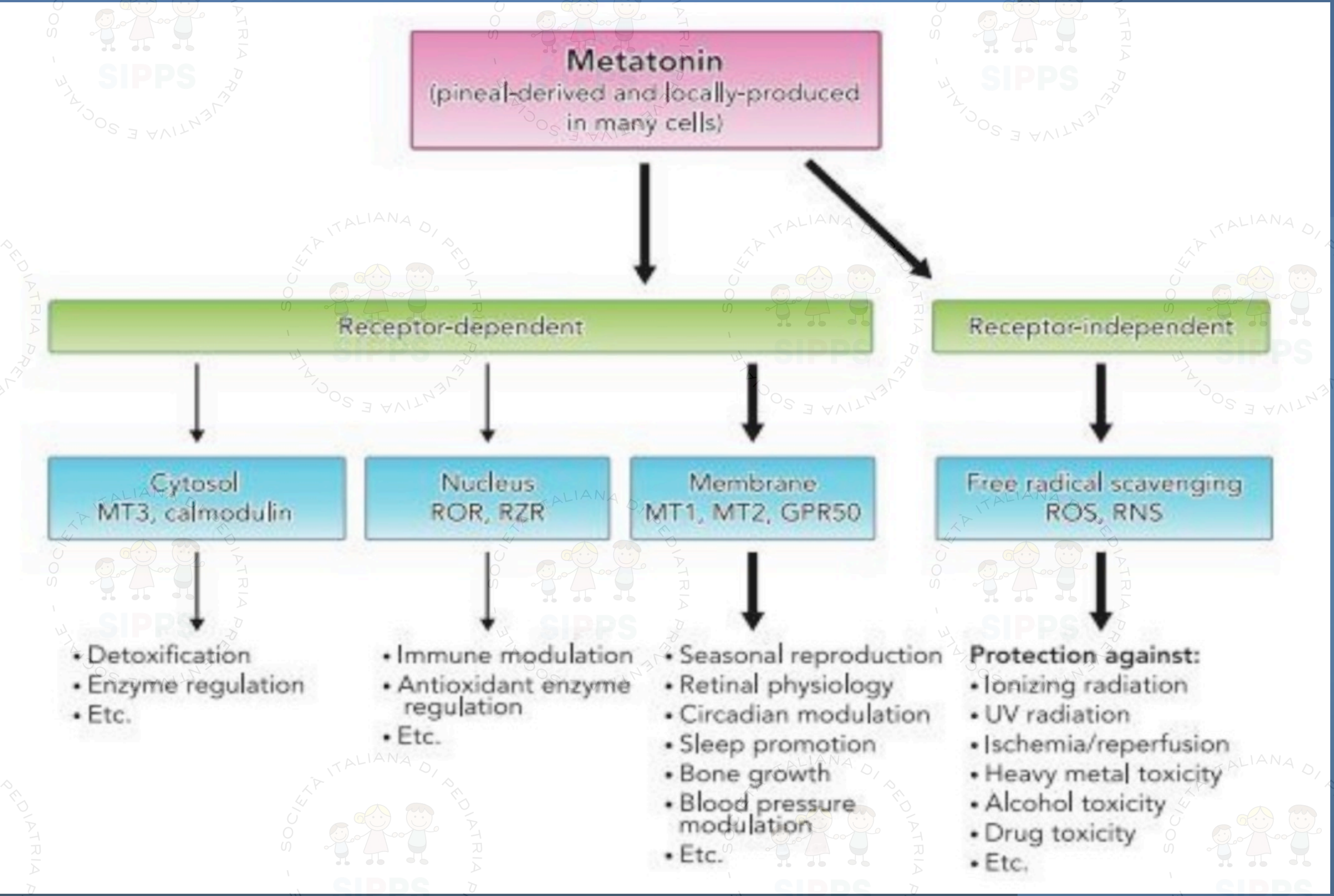




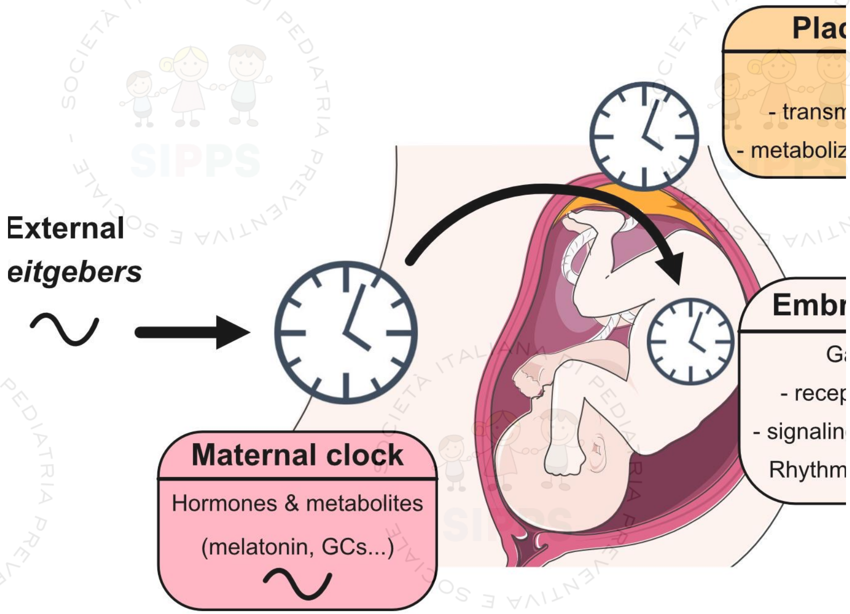


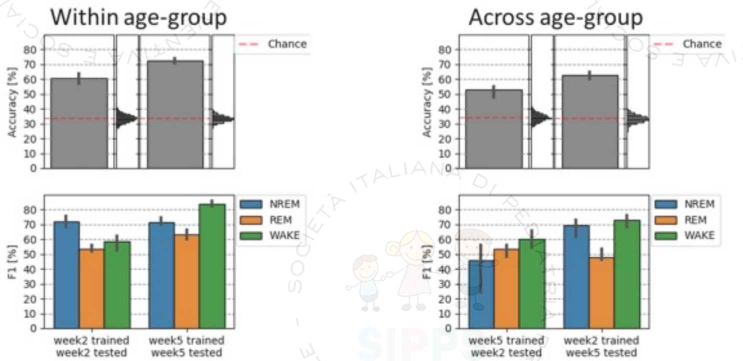

NH2
COOH
HO
NH2
COOH
MeO
NHAc
N
H
N
H
N
H
Tryptophan
Serotonin
Melatonin
TPH
AAD
AANAT
HIMT

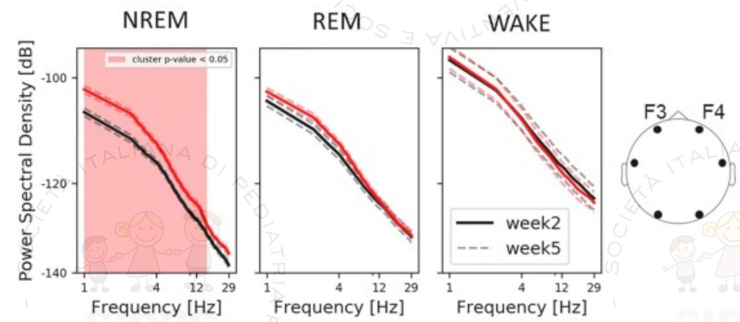

PERIPHERY
BRAIN
Pathogen-associated molecular patterns
Toll-like receptor inflammasome
Activation of innate immunity (NF-kappaB MAP kinases)
Peripheral proinflammatory cytokines
IDO
Kynurenine
Immnune-to-brain communication pathways
LAT1-dependent transport
Activated microglia
Glutamate
Quinolinic acid
NMDA receptor activation

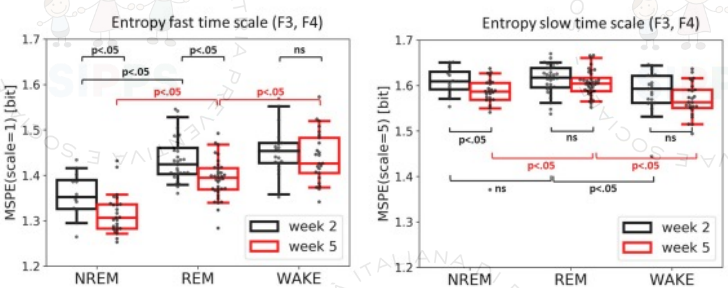


Metatonin
(pineal-derived and locally-produced in many cells)
Receptor-dependent
Receptor-independent
Cytosol
MT3, calmodulin
Nucleus
ROR, RZR
Membrane
MT1, MT2, GPR50
Free radical scavenging
ROS, RNS
• Detoxification
• Enzyme regulation
• Etc.
• Immune modulation
• Antioxidant enzyme regulation
• Etc.
• Seasonal reproduction
• Retinal physiology
• Circadian modulation
• Sleep promotion
• Bone growth
• Blood pressure modulation
• Etc.
Protection against:
• Ionizing radiation
• UV radiation
• Ischemia/reperfusion
• Heavy metal toxicity
• Alcohol toxicity
• Drug toxicity
• Etc.


External
eitgebers
Maternal clock
Hormones & metabolites
(melatonin, GCs...)
Plac
- transm
- metaboliz
Embr
Ga
- recep
- signalin
Rhythm



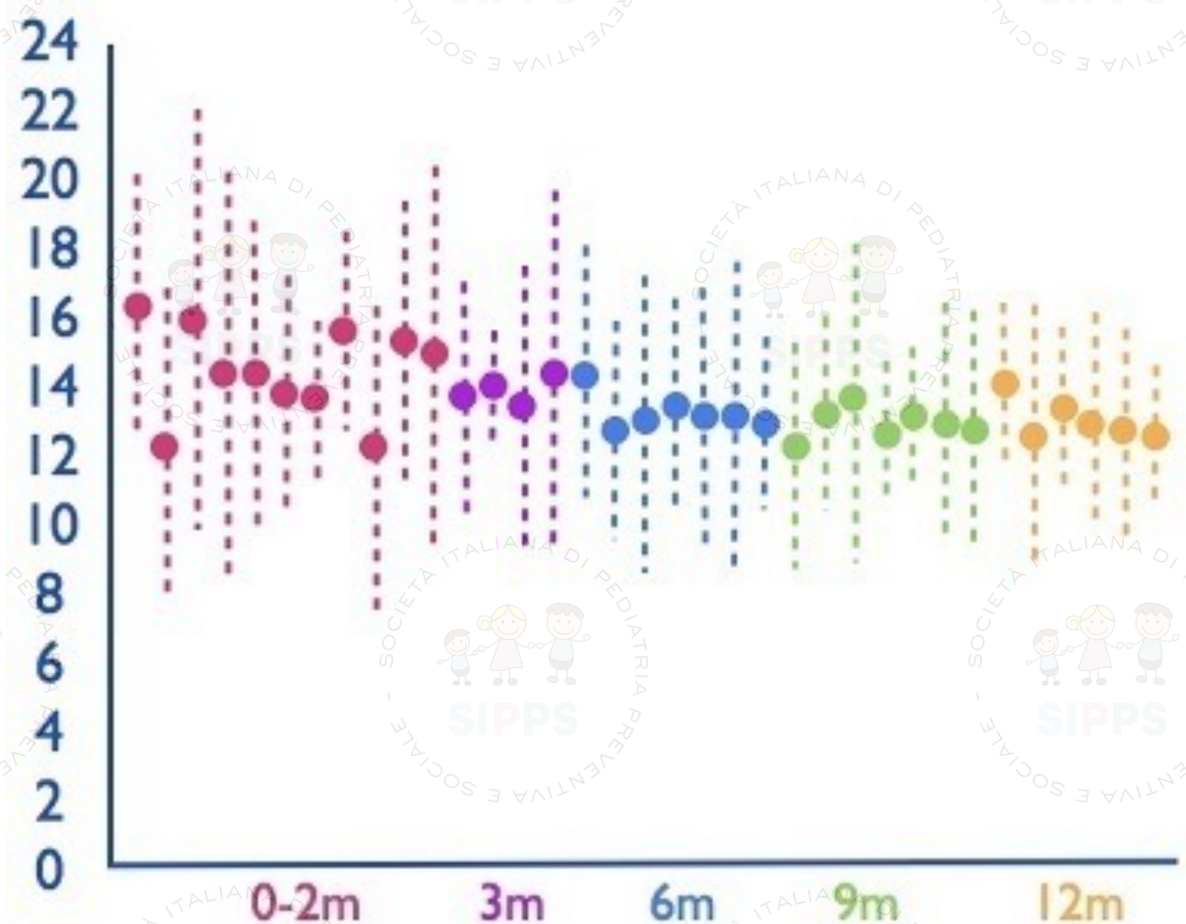


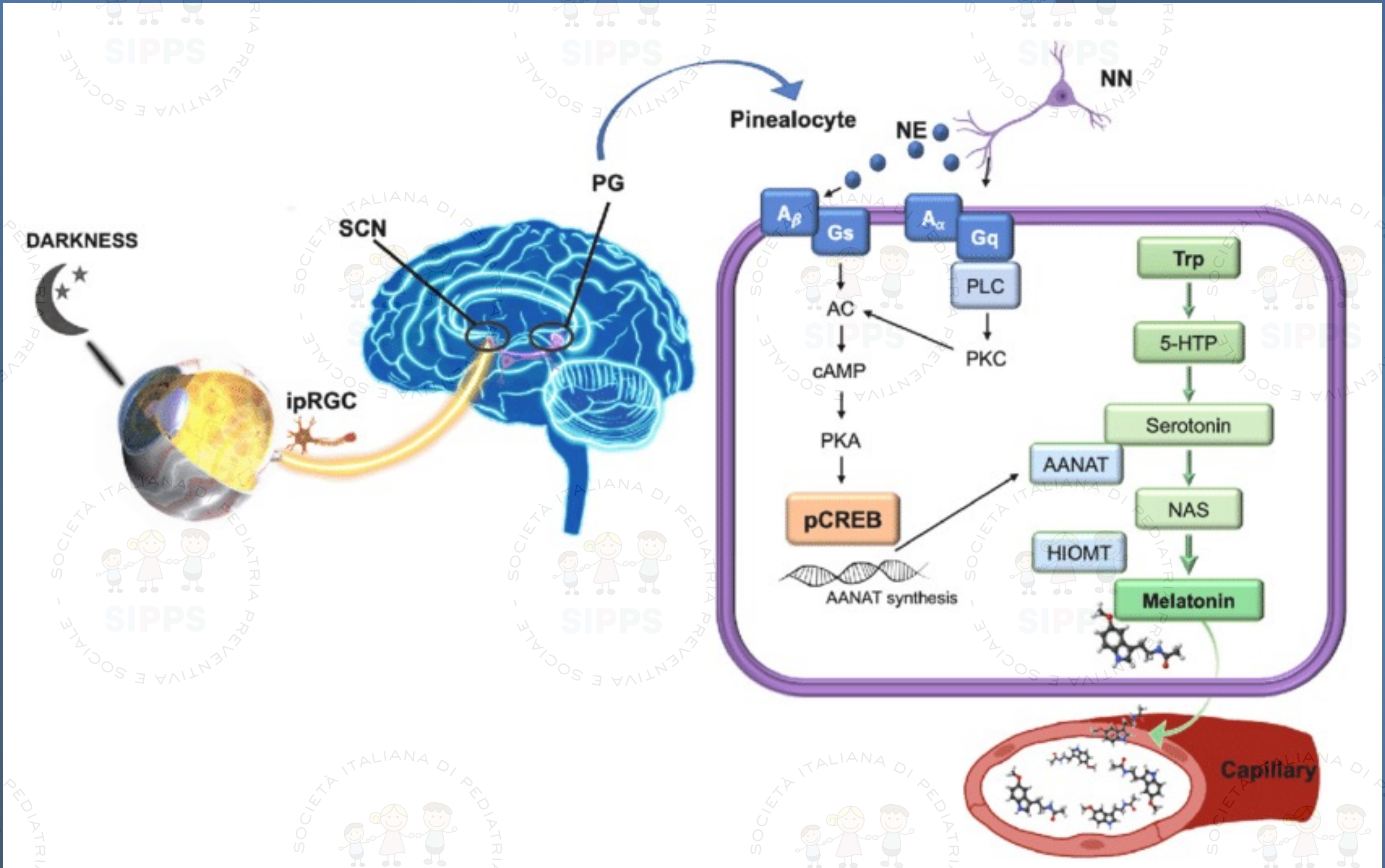


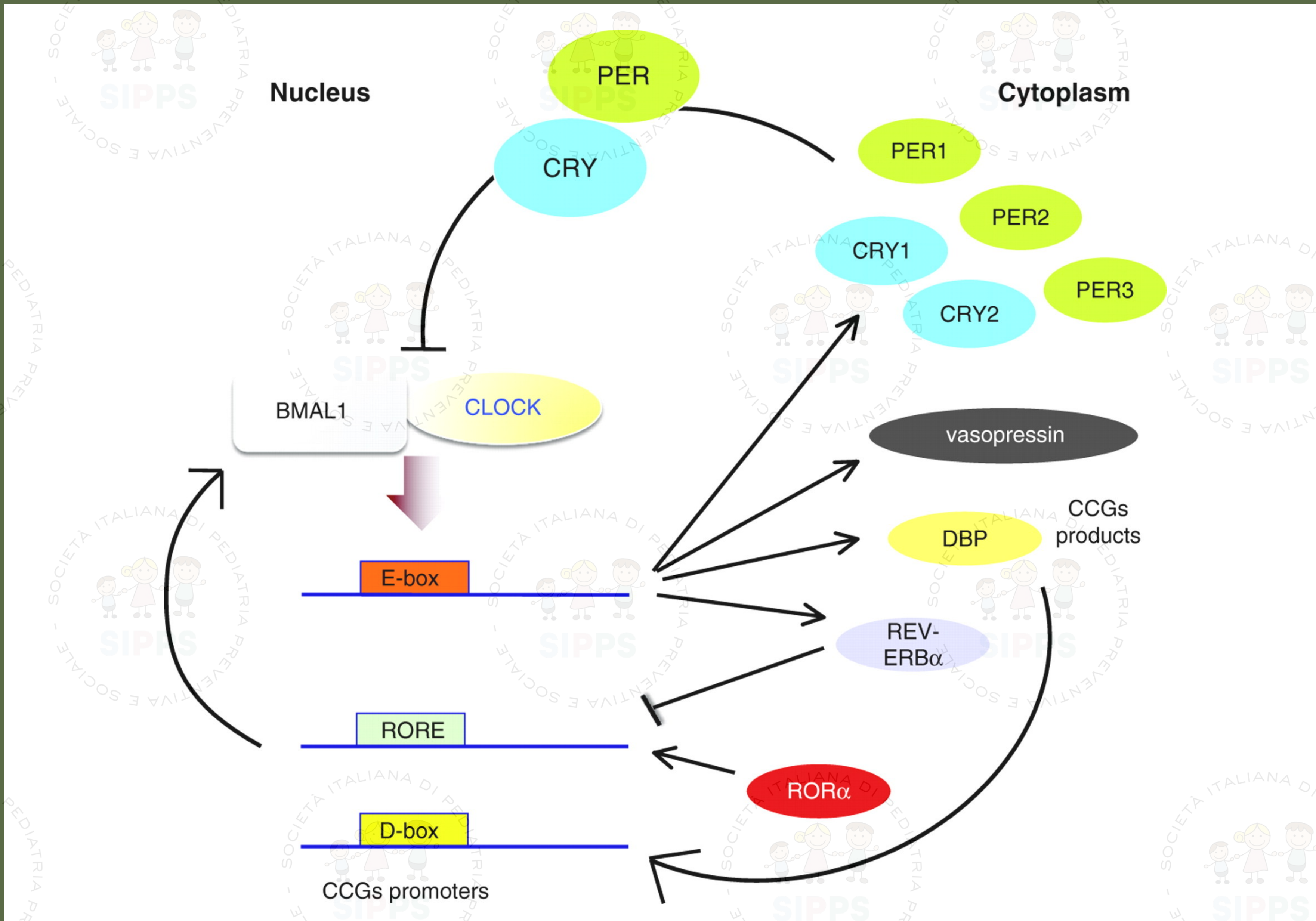
RESEARCH ARTICLE

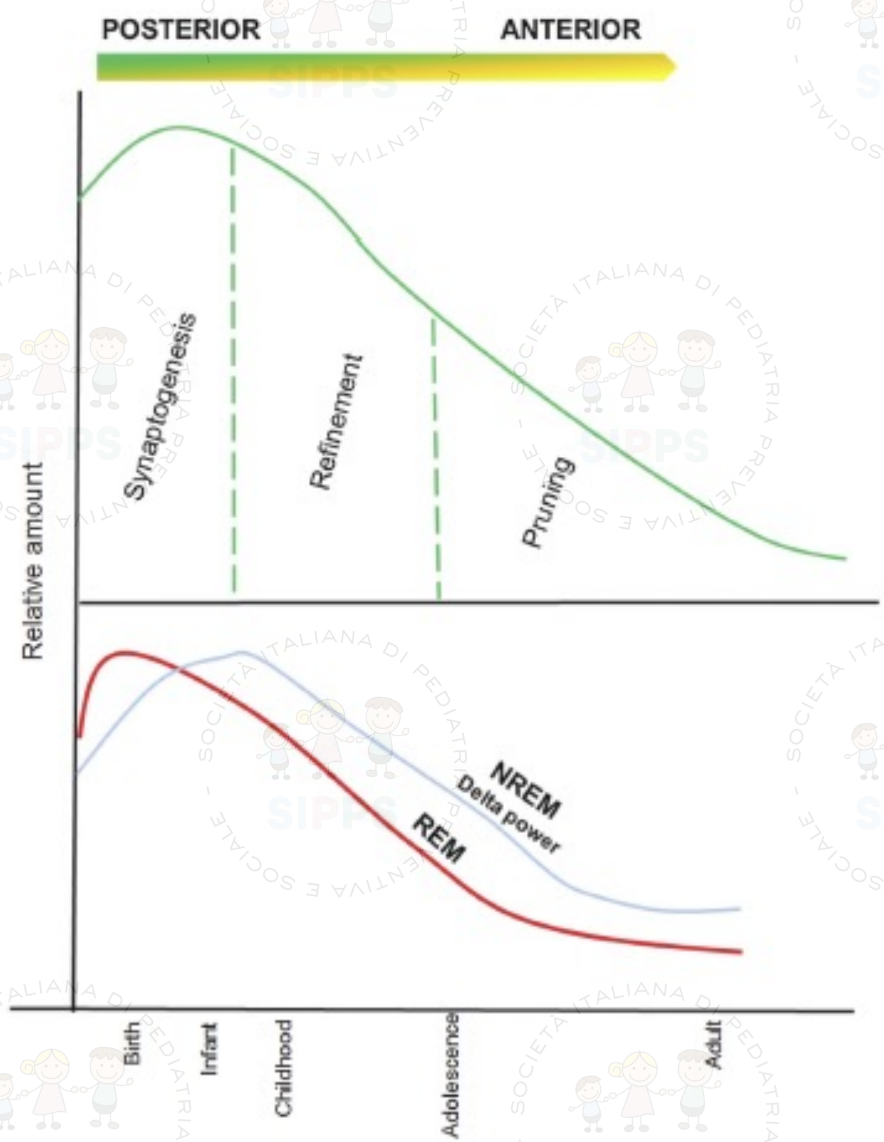
On the development of sleep states in the first weeks of life

Tomasz Wielek[1,2]*, Renata Del Giudice[3], Adelheid Lang[1,2], Malgorzata Wislowska[1,2], Peter Ott[4], Manuel Schabus[1,2]*

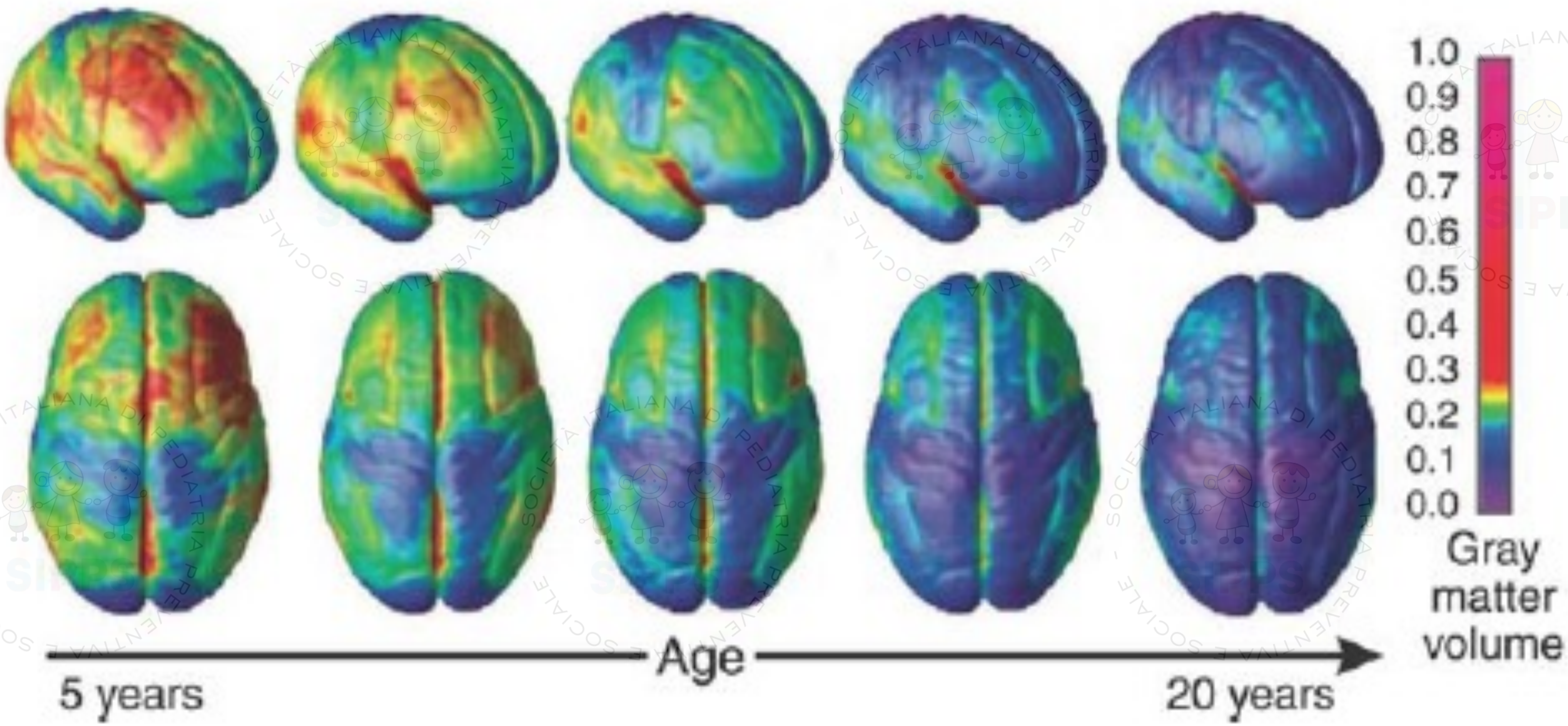

24
22
20
18
16
14
12
10
8
6
4
2
0
0-2m
3m
6m
9m
12m

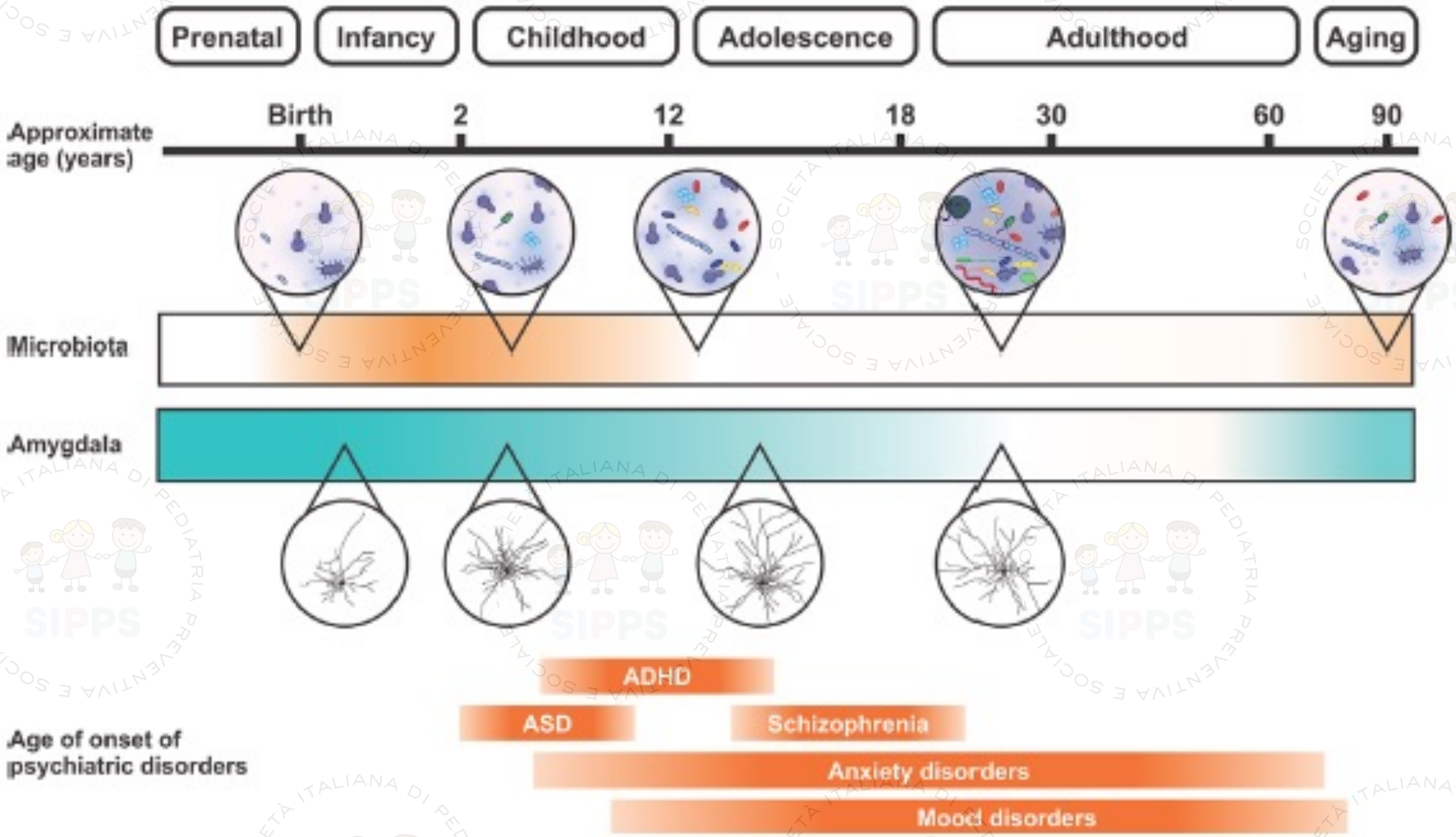

DARKNESS
ipRGC
SCN
PG
Pinealocyte
NE
NN
Gs
Gq
PLC
AC
PKC
cAMP
PKA
pCREB
AANAT synthesis
Trp
5-HTP
Serotonin
AANAT
NAS
HIOMT
Melatonin
Capillary


Nucleus
PER
CRY
Cytoplasm
PER1
PER2
CRY1
PER3
CRY2
BMAL1
CLOCK
vasopressin
CCGs
products
DBP
E-box
REV-
ERBα
RORE
RORα
D-box
CCGs promoters



POSTERIOR
ANTERIOR
Relative amount
Synaptogenesis
Refinement
Pruning
NREM
Delta power
REM
Birth
Infant
Childhood
Adolescence
Adult


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Gray matter volume
Age
5 years
20 years

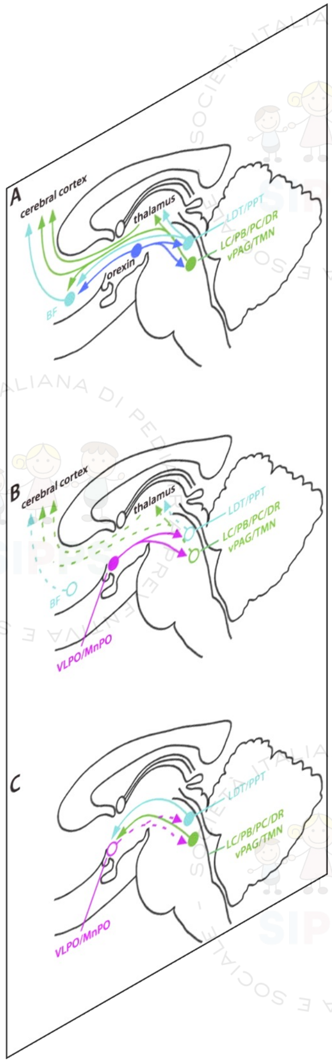

Prenatal
Infancy
Childhood
Adolescence
Adulthood
Aging
Approximate age (years)
Birth
2
12
18
30
60
90
Microbiota
Amygdala
Age of onset of psychiatric disorders
ADHD
ASD
Schizophrenia
Anxiety disorders
Mood disorders

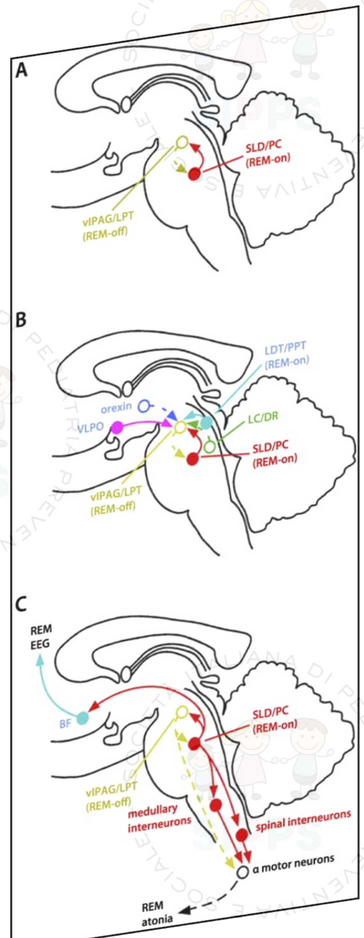
1-2 weeks	Fetal cycle loss
1-2 months	**Starting sleep structuring**
3-4 months	24 hrs cycle. Stable MLT endogenous production
6-9 months	**Prolonged diurnal waking periods; NAPS**
12 months	70-80% night sleeping.
3 years	**Stable nocturnal sleep** No NAPS
10 years	Stable circadian rhythms
12 years	DPS. Excessive diurnal somnolence

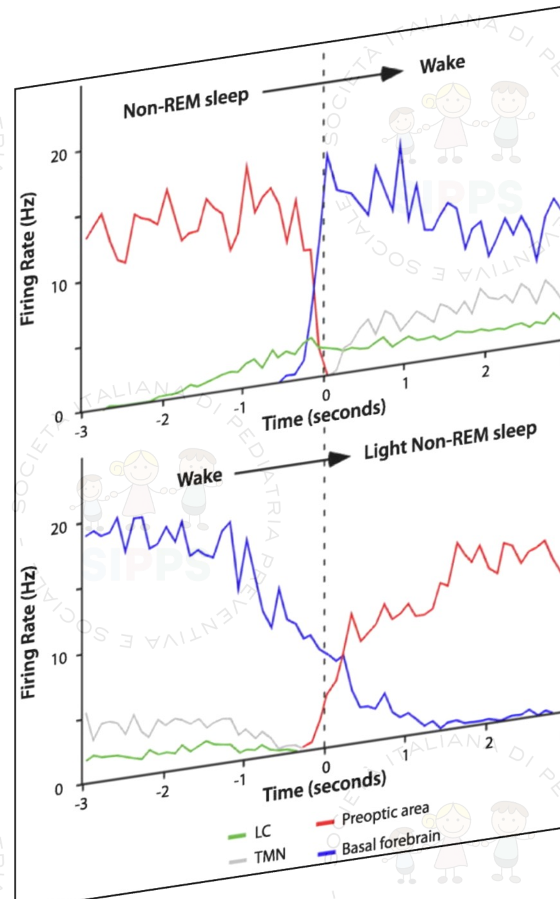
Arousal system

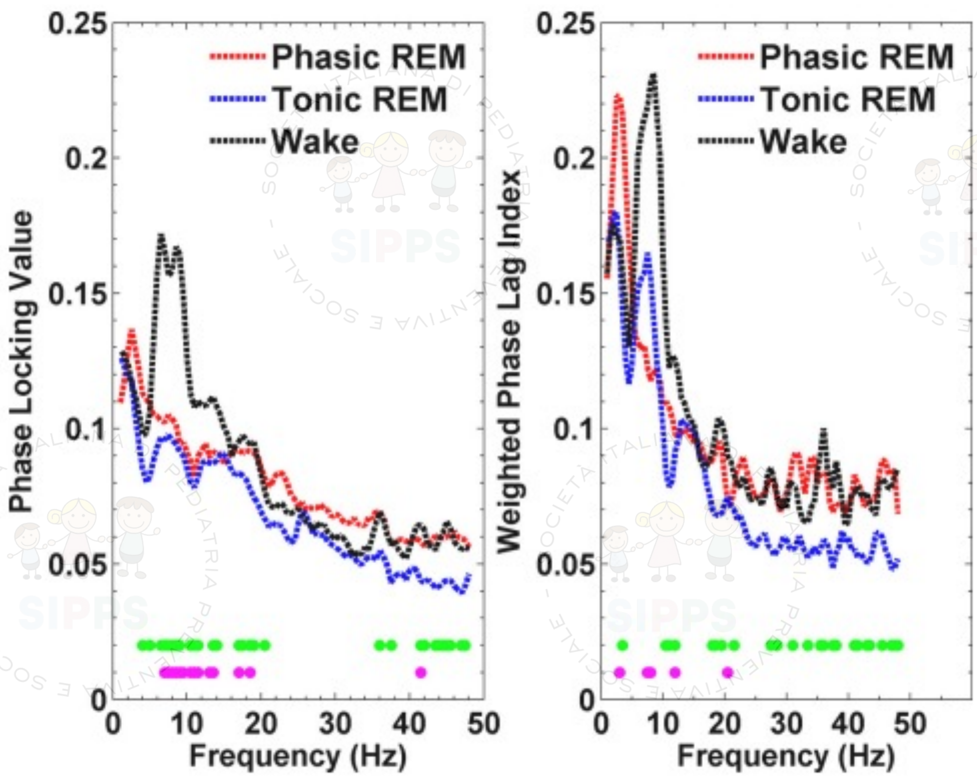
Sleep promoting system

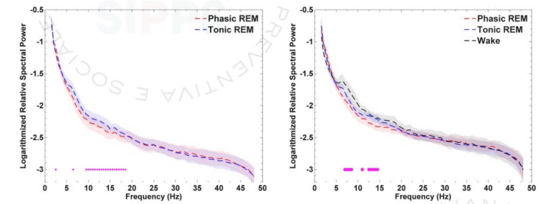
Interactions







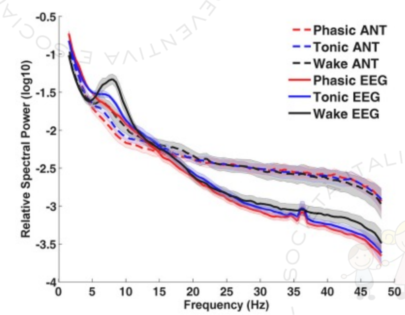




Behavioral/Cognitive

REM Sleep Microstates in the Human Anterior Thalamus

Péter Simor,[1,2,3] Orsolya Szalárdy,[2,4] Ferenc Gombos,[5] Péter Przemyslaw Ujma,[2,6] Zsófia Jordán,[6] László Halász,[6] Loránd Erőss,[6] Dániel Fabó,[6] and Róbert Bódizs[2,4]



Mathematical Biosciences 355 (2023) 108929

Contents lists available at ScienceDirect

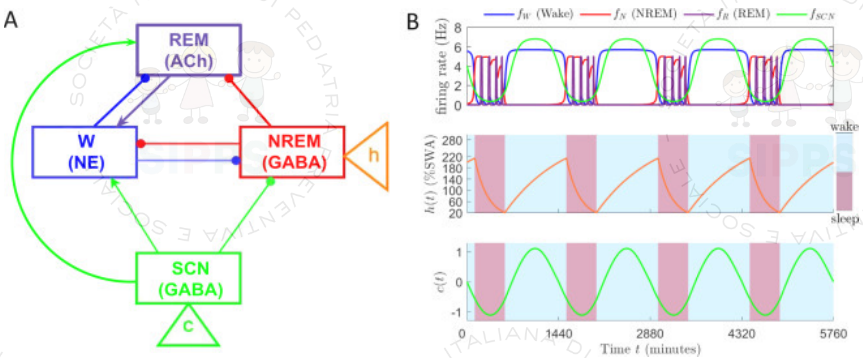
Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

ELSEVIER

Original Research Article

NREM–REM alternation complicates transitions from napping to non-napping behavior in a three-state model of sleep–wake regulation☆

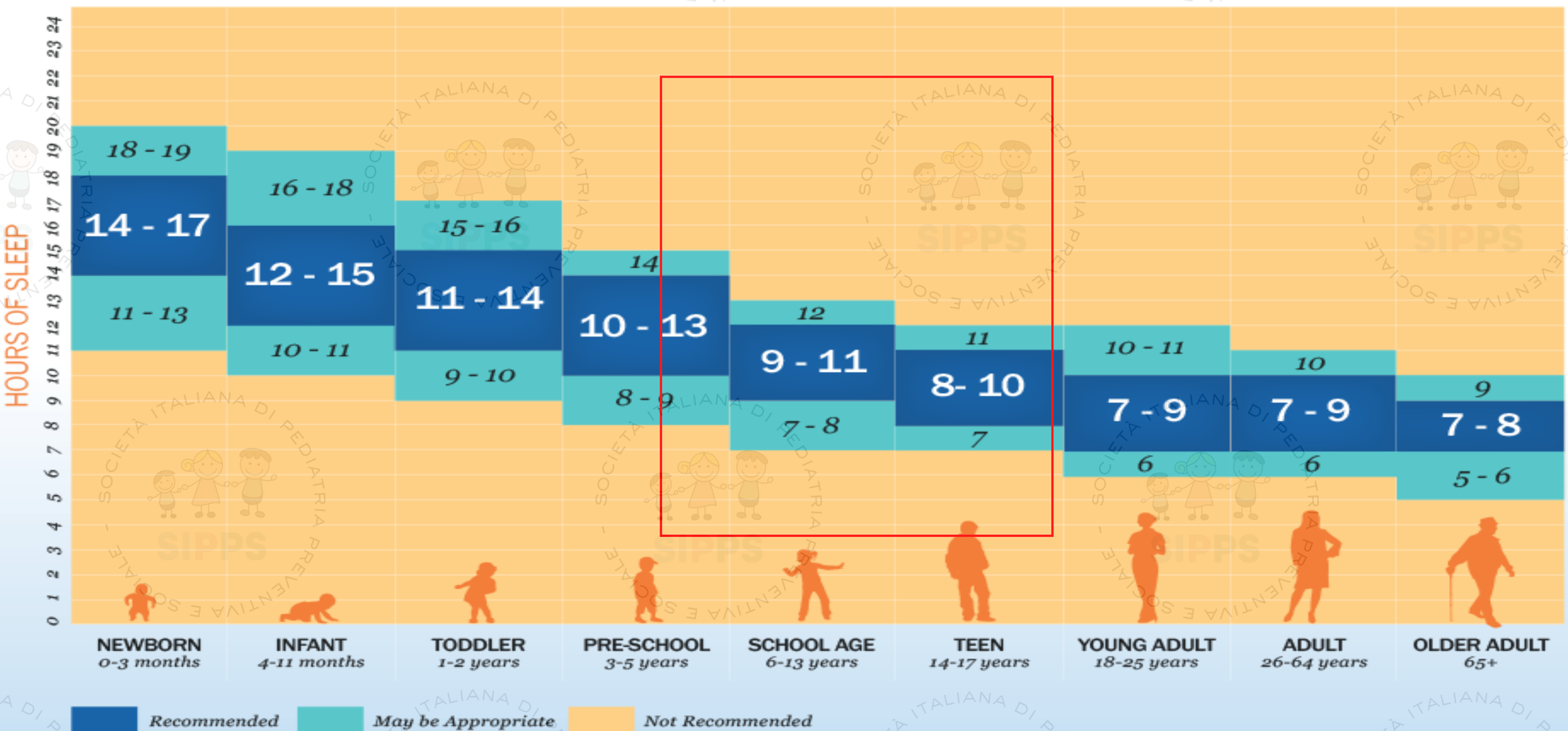


ABSTRACT

The temporal structure of human sleep changes across development as it consolidates from the polyphasic sleep of infants to the single nighttime sleep episode typical in adults. Experimental studies have shown that changes in the dynamics of sleep need may mediate this developmental transition in sleep patterning, however, it is unknown how sleep architecture interacts with these changes. We employ a physiologically-based mathematical model that generates wake, rapid eye movement (REM) and non-REM (NREM) sleep states to investigate how NREM–REM alternation affects the transition in sleep patterns as the dynamics of the homeostatic sleep drive are varied. To study the mechanisms producing these transitions, we analyze the bifurcations of numerically-computed circle maps that represent key dynamics of the full sleep–wake network model by tracking the evolution of sleep onsets across different circadian (~ 24 h) phases. The maps are non-monotonic and discontinuous, being composed of branches that correspond to sleep–wake cycles containing distinct numbers of REM bouts. As the rates of accumulation and decay of the homeostatic sleep drive are varied, we identify the bifurcations that disrupt a period-adding-like behavior of sleep patterns in the transition between biphasic and monophasic sleep. These bifurcations include border collision and saddle–node bifurcations that initiate new sleep patterns, period-doubling bifurcations leading to higher-order patterns of NREM–REM alternation, and intervals of bistability of sleep patterns with different NREM–REM alternations. Furthermore, patterns of NREM–REM alternation exhibit variable behaviors in different regimes of constant sleep–wake patterns. Overall, the sequence of sleep–wake behaviors, and underlying bifurcations, in the transition from biphasic to monophasic sleep in this three-state model is more complex than behavior observed in models of sleep–wake regulation that do not consider the dynamics of NREM–REM alternation. These results suggest that interactions between the dynamics of the homeostatic sleep drive and the dynamics of NREM–REM alternation may contribute to the wide interindividual variation observed when young children transition from napping to non-napping behavior.

NATIONAL SLEEP FOUNDATION

SLEEP DURATION RECOMMENDATIONS



SLEEPFOUNDATION.ORG | SLEEP.ORG

Hirshkowitz M, The National Sleep Foundation's sleep time duration recommendations: methodology and results summary, Sleep Health (2015), http://dx.doi.org/10.1016/j.sleh.2014.12.010

From: **Effects of Limiting Recreational Screen Media Use on Physical Activity and Sleep in Families With Children: A Cluster Randomized Clinical Trial**

JAMA Pediatr. 2022;176(8):741-749. doi:10.1001/jamapediatrics.2022.1519

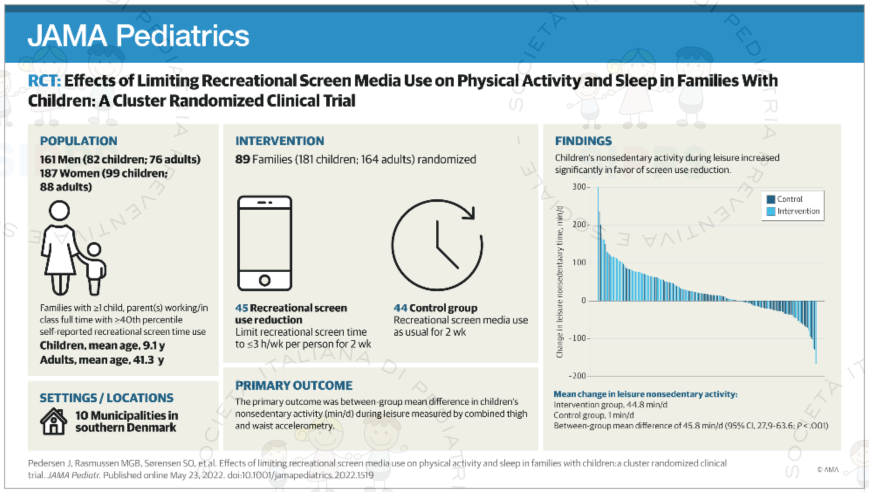
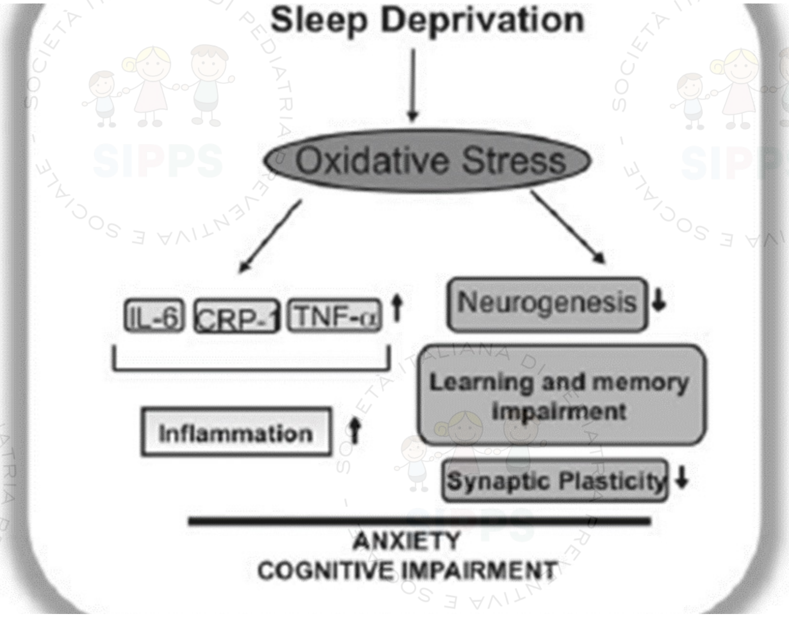


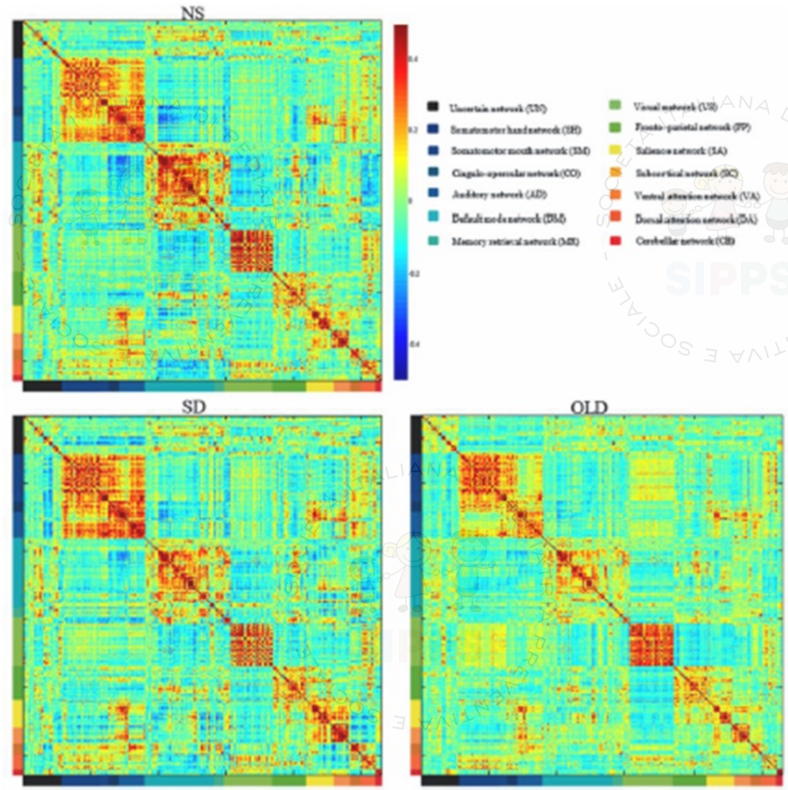
Figure Legend:

Effects of Limiting Recreational Screen Media Use on Physical Activity and Sleep in Families With Children: A Cluster Randomized Clinical Trial



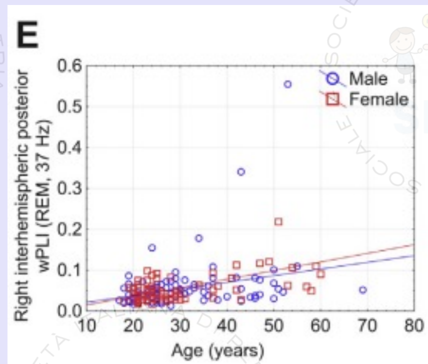
ts of SD and/or Regular Exercise, or Caffeine on the Basal Levels of Si
Expression

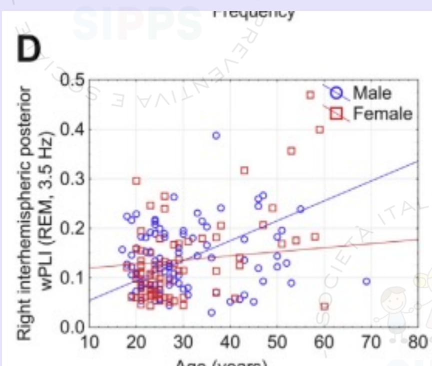
	Exercise	Exercise/SD	Caffeine
	No change	No change	No change
	No change	No change	Increase
	No change	No change	No change
	Increase	Increase	No change
	Increase	Increase	No change
	No change	No change	No change
	No change	No change	No change

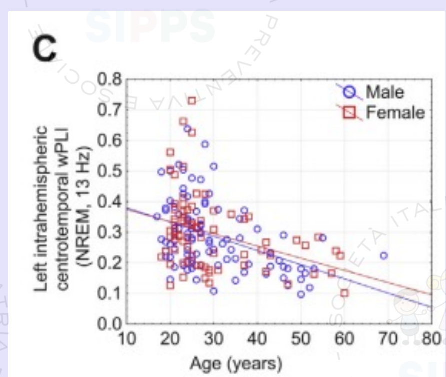


Sleep EEG functional connectivity varies with age and sex, but not general intelligence

Péter P. Ujma [a,b,*], Boris N. Konrad [c], Péter Simor [a,d], Ferenc Gombos [e,f], János Körmendi [g], Axel Steiger [h], Martin Dresler [c,h], Róbert Bódizs [a,b]







- Connectivity greater in females in the high sigma frequency range
- An opposite pattern in the alpha/low sigma and beta range
- General intelligence was not significantly associated with connectivity in either sex.
- Strong age effects on sleep spindle-frequency activity, which loses synchrony as a function of aging.

https://doi.org/10.5664/jcsm.9520

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Effect of sleep habits on academic performance in schoolchildren age 6 to 12 years: a cross-sectional observation study

Chithambara Thanu Sivakumar, MD; Mahalakshmi Rajan, MD; Umapathy Pasupathy, MD; Sathya Chidambaram, MBBS; Nithya Baskar, MD

Study Objectives: Sleep plays a vital role in the cognitive and neurodevelopmental outcome of children; therefore, adequate sleep is needed to improve academic performance. The primary objective of this study was determine the prevalence of sleep behaviors and their effect on academic performance in schoolchildren age 6–12 years and to translate the findings into greater opportunity for healthy development and academic success.

Methods: Our study included 791 healthy children between ages 6 and 12 years from schools that are parts of the Central Board of Secondary Education in the South Indian urban population. Pro forma and The Children's Sleep Habits Questionnaire (CSHQ in local language translation) was given to the parents, and any doubts regarding the questionnaire were clarified during parent-teacher meetings. The previous 2 cycles of academic grades for these children were collected and categorized into A, B, and C grades accordingly. Then a statistical analysis of the completed CSHQ questionnaires was performed.

Results: On analyzing the CSHQ questionnaire, 71.9% of the children studied had a score higher than 41, which is in the clinical range indicating a significant prevalence of altered sleep habits. Other risk factors included nocturnal enuresis (3.5%), snoring (10.6%), night terrors (8%), and teeth grinding (6.4%).

Conclusions: Altered sleep habits have a major effect on the academic performance of the school-age children. Assessment of sleep habits should be included in routine pediatric office visits.

Neuroscience Letters 485 (2010) 89–93

Contents lists available at ScienceDirect

Neuroscience Letters

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Borderline intellectual functioning and sleep: The role of cyclic alternating pattern

Maria Esposito, Marco Carotenuto*

Table 3
Spearman correlation analysis between sleep parameters (macrostructure and microstructure) and IQ (verbal IQ, VIQ; performance IQ, PIQ; total IQ, TIQ) both in BIF and control group children.

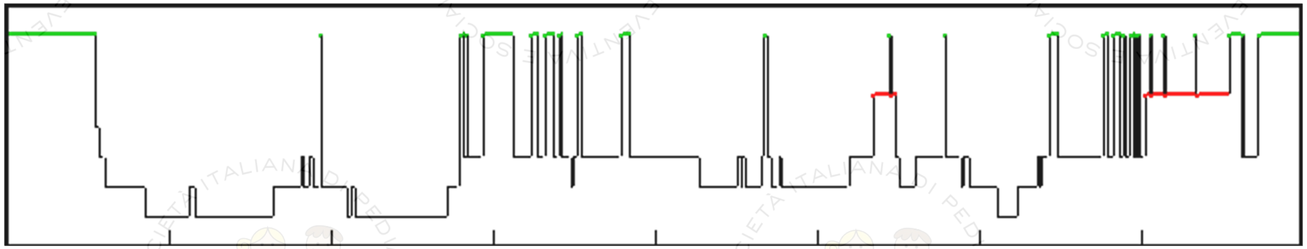
	VIQ	PIQ	TIQ
TIB, min	**0.51**	**0.48**	**0.58**
SPT, min	**0.52**	**0.60**	**0.68**
TST, min	**0.60**	**0.61**	**0.72**
SOL, min	0.28	0.35	0.30
FRL, min	**−0.45**	−0.09	−0.34
SS, h	**−0.63**	−0.46	−0.64
AWN, h	**−0.70**	**−0.53**	**−0.70**
SE%	0.36	0.31	0.43
WASO, spt	**−0.46**	**−0.42**	**−0.51**
S1, spt	**0.37**	0.12	0.25
S2, spt	**0.56**	**0.53**	**0.63**
SWS, spt	**−0.56**	**−0.47**	**−0.56**
REM, spt	**0.62**	**0.42**	**0.64**
CAP_tot_num	**0.67**	**0.76**	**0.79**
CAP rate%	0.29	**0.50**	**0.39**
CAP rate%S1	**0.57**	**0.71**	**0.72**
CAP rate%S2	**0.43**	**0.41**	**0.47**
CAP rate%SWS	0.17	**0.39**	0.24
Tot_num_A1%	**0.75**	0.26	**0.61**
Tot_num_A2%	**−0.74**	−0.32	**−0.64**
Tot_num_A3%	**−0.38**	−0.12	−0.29
A1_mean_dur	**−0.57**	**−0.50**	**−0.59**
A2_mean_dur	**−0.67**	**−0.65**	**−0.72**
A3_mean_dur	−0.05	−0.08	−0.10
A1 index	0.76	**0.65**	**0.82**
A2 index	−0.41	0.08	−0.25
A3 index	0.05	**0.38**	0.21
B_mean_dur	0.05	−0.33	−0.17
Cycle_mean_dur	**−0.55**	**−0.51**	**−0.63**
Seq_mean_dur	−0.09	0.06	−0.04
Num_of_seq	**0.75**	**0.67**	**0.81**
A1/A3 N TOT	**0.67**	0.21	**0.53**
A2/A3 N TOT	**−0.56**	−0.31	**−0.53**

	BIF		Control		M-W UTest
	Mean	SD	Mean	SD	p value*
TIB-min	495.500	26.668	540.118	48.399	NS
SPT-min	461.000	32.332	509.882	45.220	NS
TST-min	**387.417**	**80.730**	**496.677**	**45.513**	**0.010**
SOL-min	15.333	14.423	24.088	14.172	NS
FRL-min	152.792	70.318	111.353	35.552	NS
SS-h	**9.992**	**2.708**	**5.082**	**1.585**	**0.000**
AWN-h	**4.092**	**2.315**	**0.500**	**0.555**	**0.000**
SE%	78.117	14.985	92.088	5.302	NS
WASO %	**16.308**	**14.289**	**2.565**	**3.042**	**0.023**
S1 %	2.008	2.179	3.712	4.312	NS
S2 %	**32.875**	**10.238**	**46.841**	**5.551**	**0.007**
SWS %	**35.150**	**11.183**	**23.259**	**5.652**	**0.023**
REM %	**13.633**	**7.961**	**23.612**	**5.036**	**0.025**

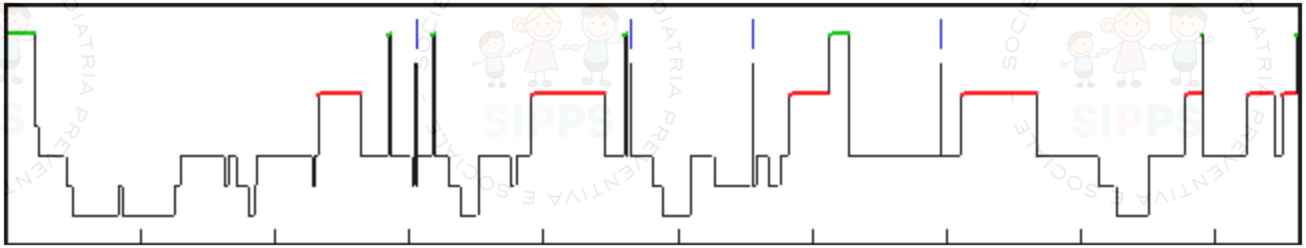
Esposito M, Carotenuto M. Neuroscience Letters 485 (2010) 89–93

	BIF		Control		Mann-Whitney Test
	Mean	SD	Mean	SD	p value*
CAP total number	**226.750**	**48.372**	**428.706**	**88.132**	**0.000**
CAP Rate%	30.375	15.700	37.241	6.874	NS
CAP Rate%S1	**7.490**	**21.169**	**32.706**	**21.846**	**0.024**
CAP Rate%S2	23.475	11.832	32.600	9.435	NS
CAP Rate%SWS	39.800	20.855	48.006	8.332	NS
Total number of A1%	**35.117**	**25.565**	**78.429**	**8.329**	**0.001**
Total number A2%	**48.467**	**24.077**	**12.253**	**6.870**	**0.001**
Total number A3%	16.433	10.447	9.324	3.107	NS
A1 mean duration, s	**13.858**	**4.475**	**4.765**	**0.339**	**0.000**
A2 mean duration, s	**19.167**	**5.010**	**7.924**	**1.762**	**0.001**
A3 mean duration, s	15.375	4.559	15.506	4.901	NS
A1 index, n/h	**11.967**	**10.234**	**46.300**	**10.594**	**0.000**
A2 index, n/h	17.175	13.627	8.094	6.028	NS
A3 index, n/h	5.192	4.912	5.318	3.168	NS
B phase mean duration	20.517	5.750	20.853	4.192	NS
Cycle mean duration	**37.300**	**6.711**	**26.659**	**4.254**	**0.006**
Sequences mean duration	232.775	123.823	193.482	43.412	NS
Number of sequences	**25.083**	**4.757**	**44.824**	**9.901**	**0.000**
A1/A3 total number	**3.194**	**3.311**	**9.732**	**4.587**	**0.003**
A2/A3 total number	4.202	3.758	1.381	0.682	NS

Esposito M, Carotenuto M. Neuroscience Letters 485 (2010) 89–93

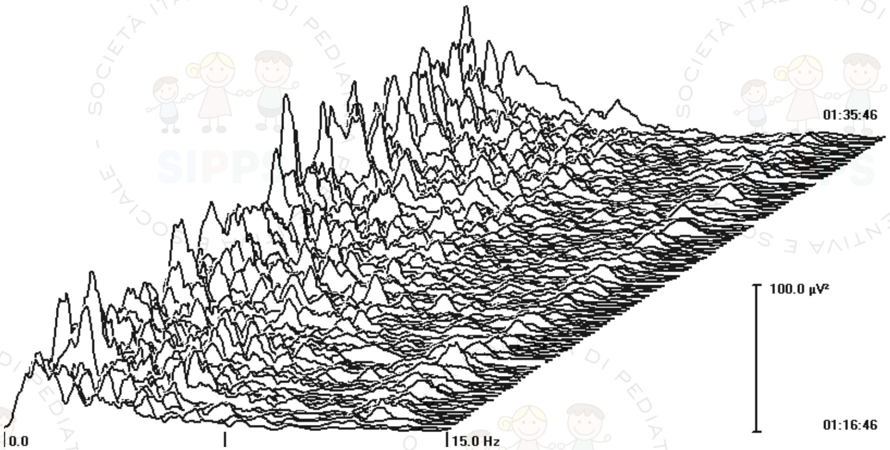


IQ 71-84



IQ 85-115

N2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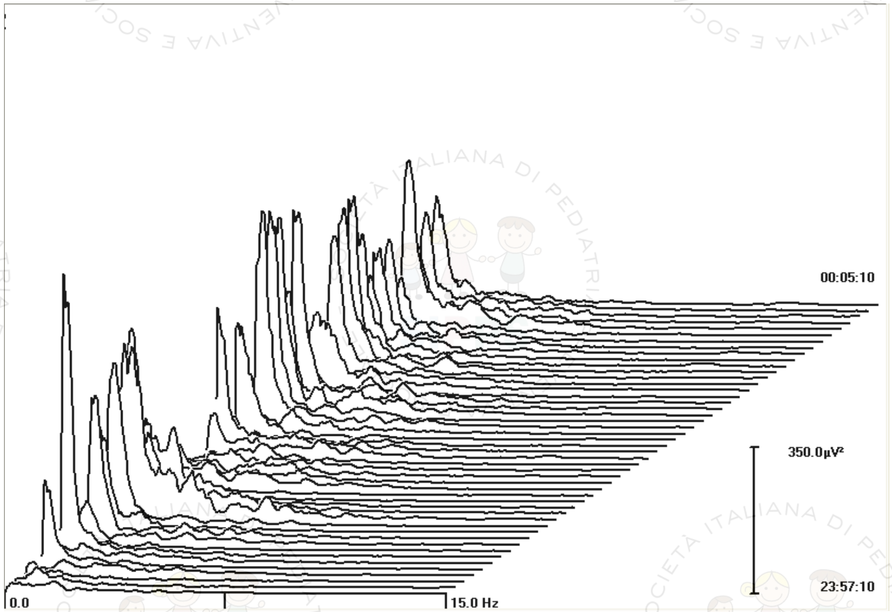
01:16:46
0.0
15.0 Hz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23:57:10
0.0
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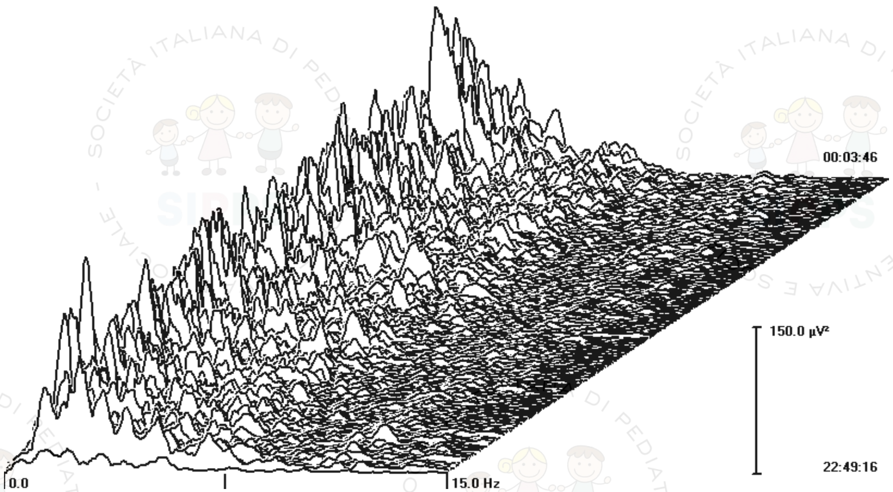
N3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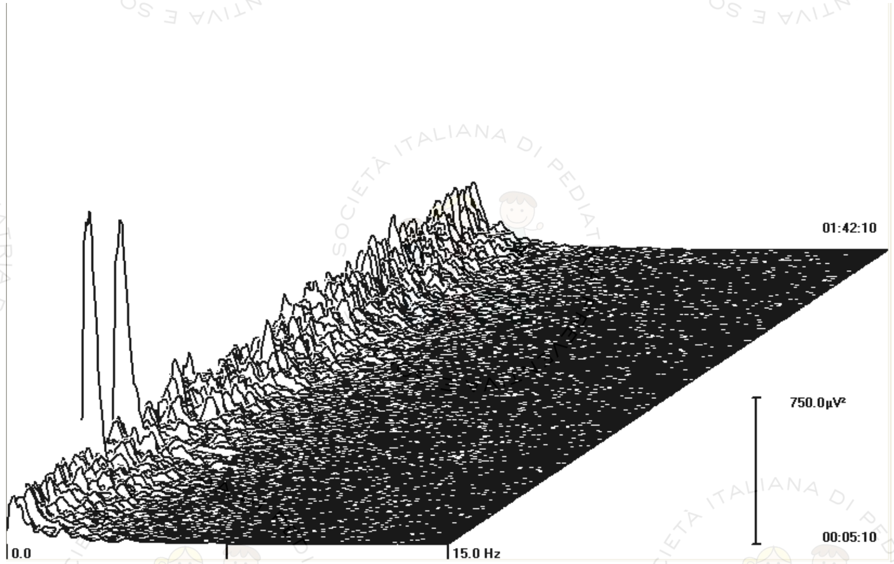
22:49:16
0.0
15.0 Hz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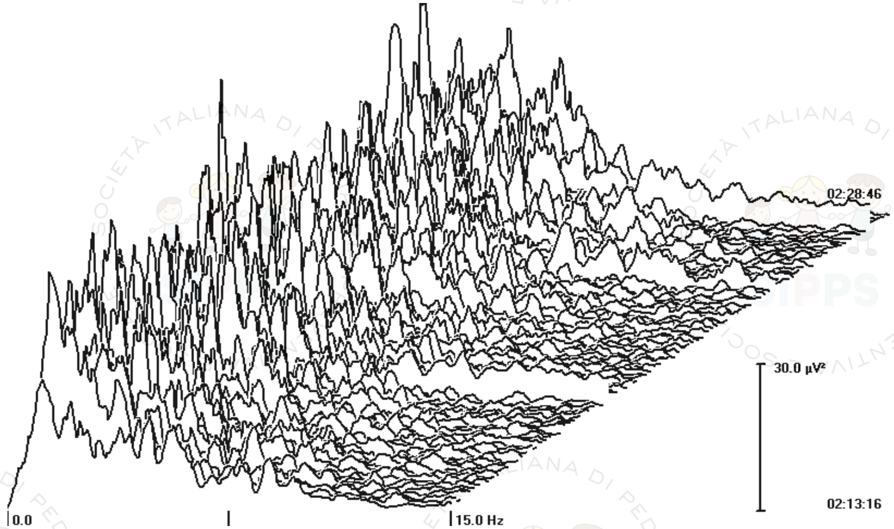
00:05:10
0.0
15.0 Hz

REM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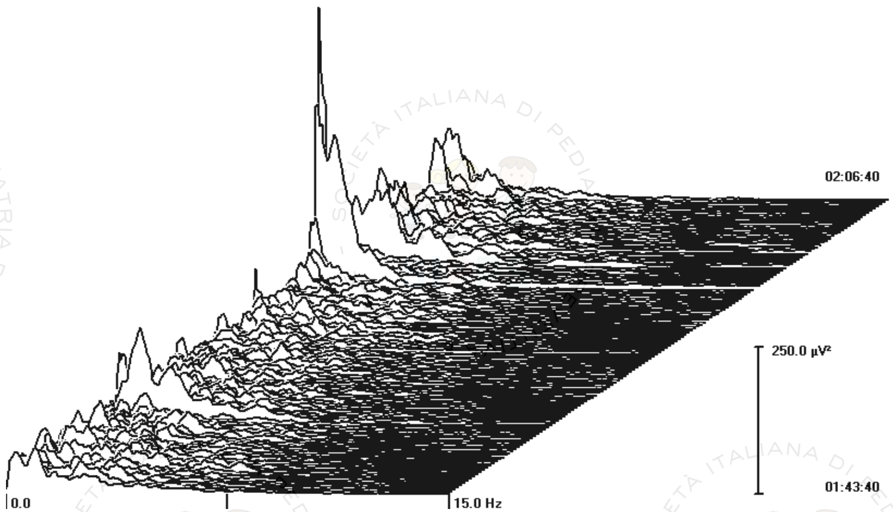
0.0
15.0 Hz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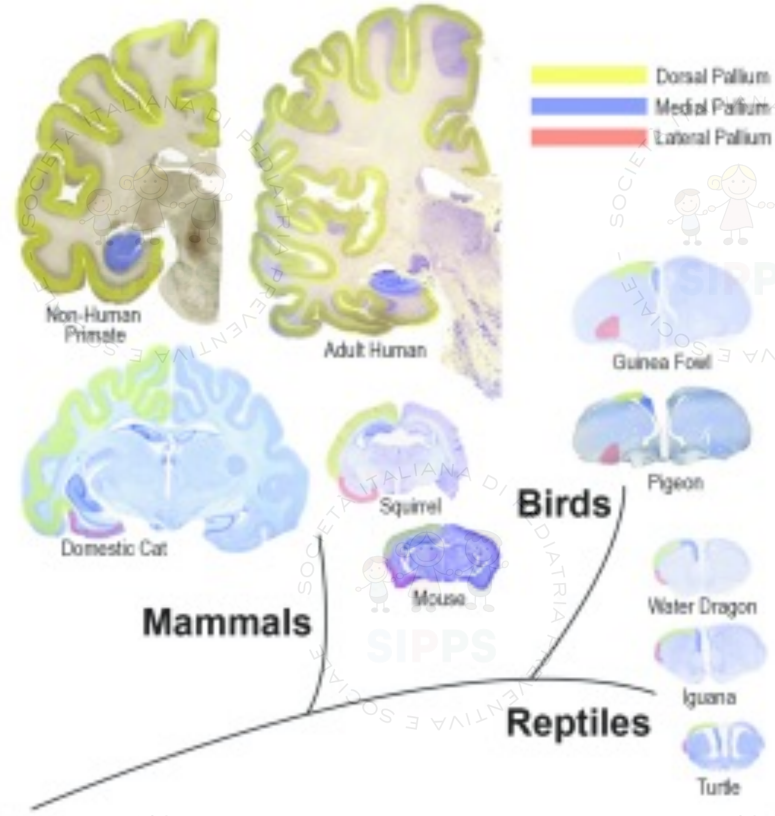
250.0 µV²
01:43:40
0.0
15.0 Hz


Safety, Connection and Problem-Solving
Survival State
BRAIN STEM
Emotional State
LIMBIC SYSTEM
Executive State
PREFRONTAL LOBES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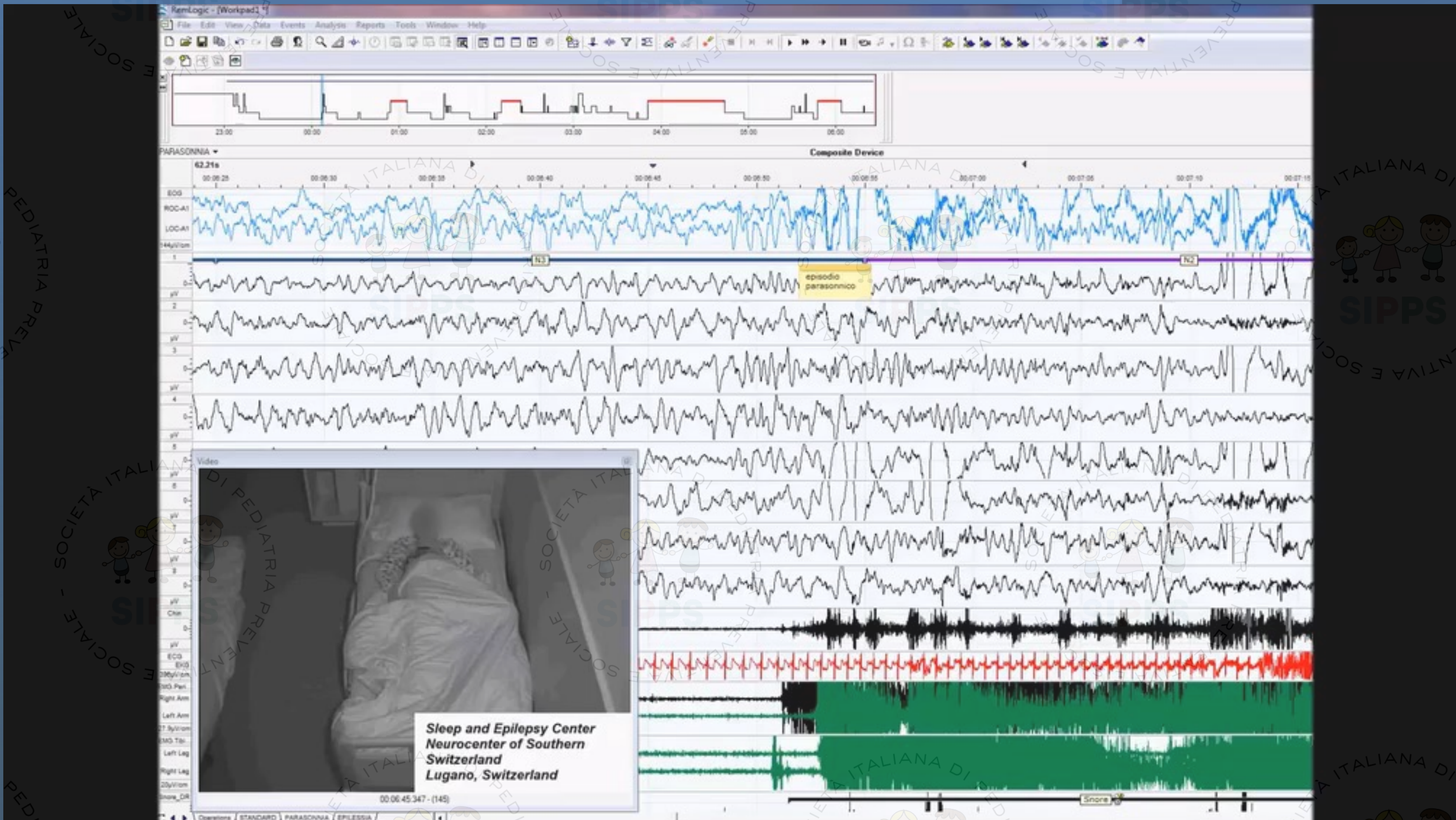
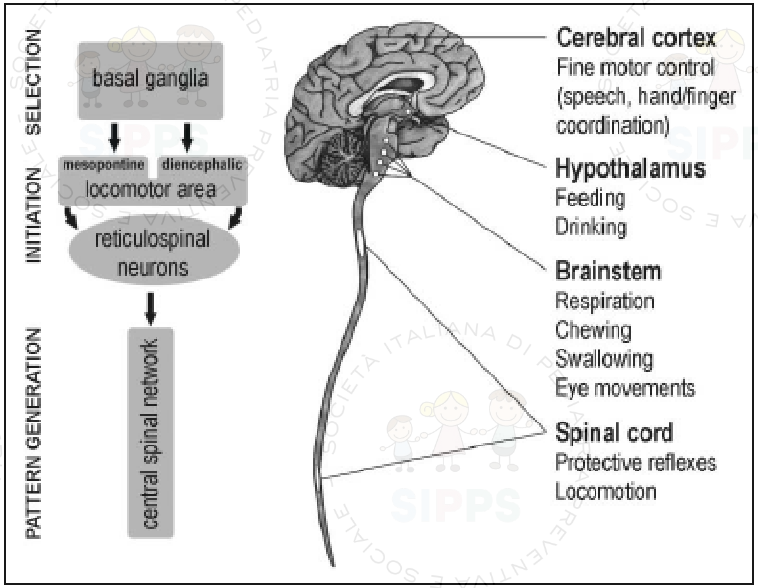
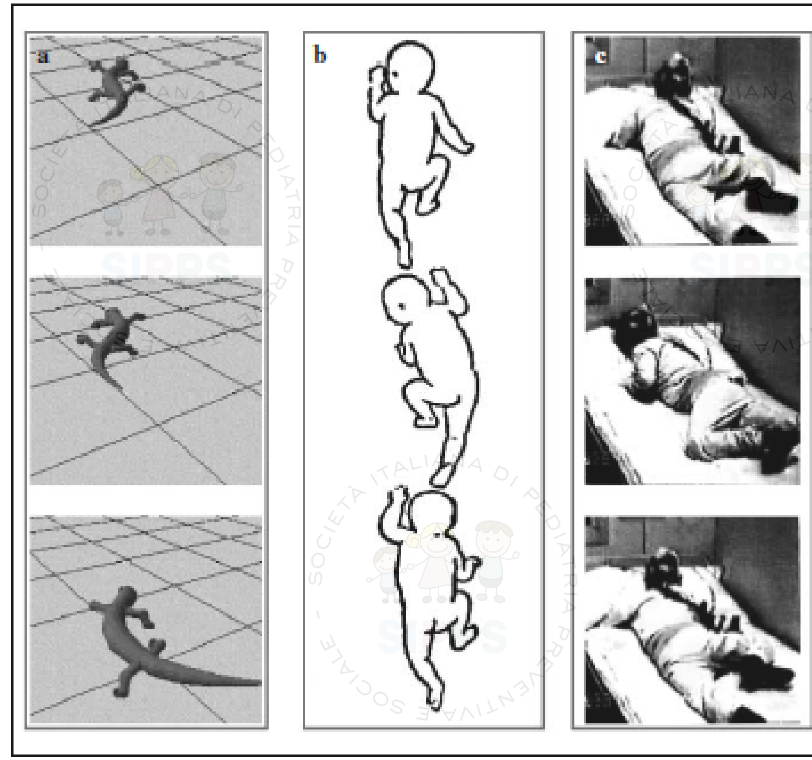
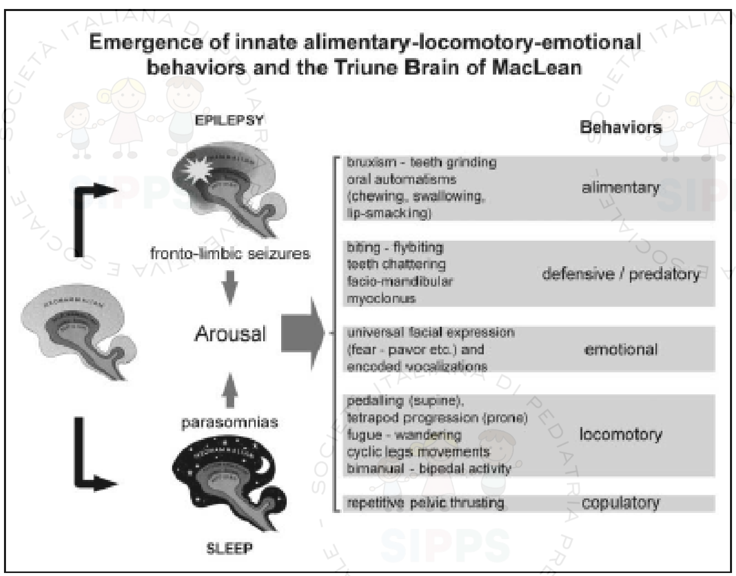
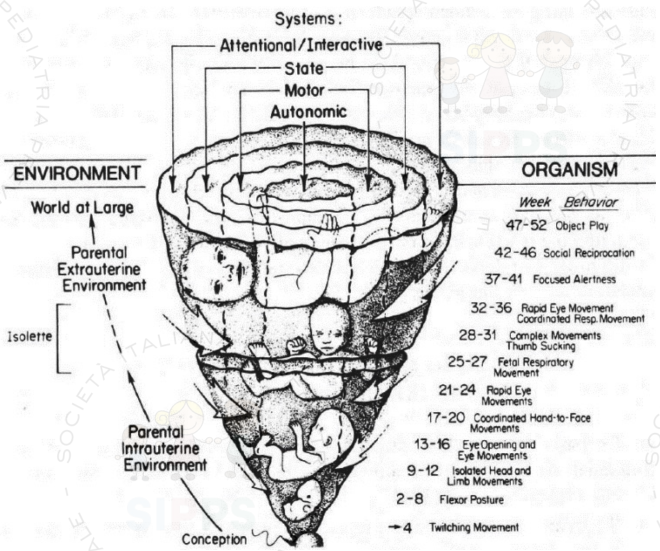
Medial Pallium
Lateral Pallium
Non-Human Primate
Adult Human
Guinea Fowl
Pigeon
Domestic Cat
Squirrel
Mouse
Birds
Mammals
Water Dragon
Iguana
Reptiles
Turtle

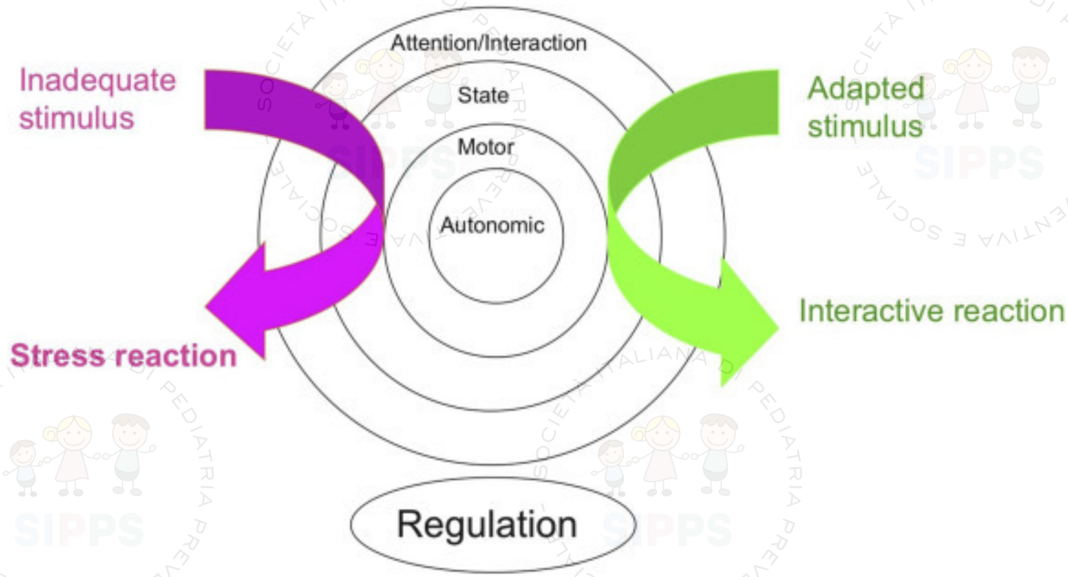

RemLogic - [Workpad1 *]
PARASONNIA
Composite Device
episodio parasonnico
Video
Sleep and Epilepsy Center
Neurocenter of Southern
Switzerland
Lugano, Switzerland
Operations
STANDARD
PARASONNIA
EPILESSIA


SELECTION
INITIATION
PATTERN GENERATION
basal ganglia
mesopontine
diencephalic
locomotor area
reticulospinal neurons
central spinal network
Cerebral cortex
Fine motor control (speech, hand/finger coordination)
Hypothalamus
Feeding
Drinking
Brainstem
Respiration
Chewing
Swallowing
Eye movements
Spinal cord
Protective reflexes
Locomotion


a
b
c

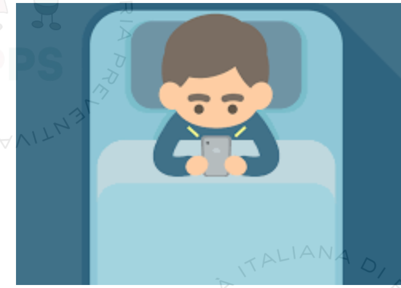

Emergence of innate alimentary-locomotory-emotional behaviors and the Triune Brain of MacLean
EPILEPSY
fronto-limbic seizures
Arousal
parasomnias
SLEEP
Behaviors
bruxism - teeth grinding
oral automatisms
(chewing, swallowing, lip-smacking)
alimentary
biting - flybiting
teeth chattering
facio-mandibular myoclonus
defensive / predatory
universal facial expression (fear - pavor etc.) and encoded vocalizations
emotional
pedaling (supine), tetrapod progression (prone)
fugue - wandering
cyclic legs movements
bimanual - bipedal activity
locomotory
repetitive pelvic thrusting
copulatory

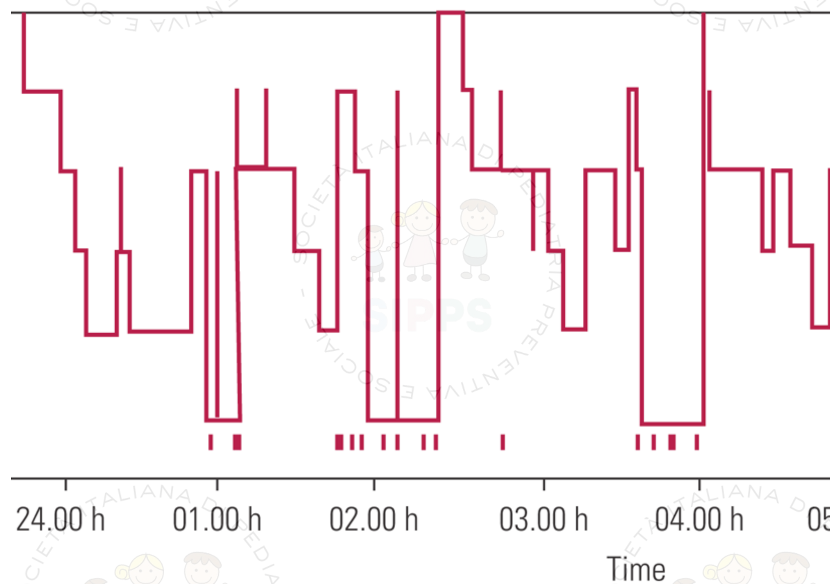

Systems:
Attentional/Interactive
State
Motor
Autonomic
ENVIRONMENT
World at Large
Parental Extrauterine Environment
Isolette
Parental Intrauterine Environment
Conception
ORGANISM
Week Behavior
47-52 Object Play
42-46 Social Reciprocation
37-41 Focused Alertness
32-36 Rapid Eye Movement Coordinated Resp. Movement
28-31 Complex Movements Thumb Sucking
25-27 Fetal Respiratory Movement
21-24 Rapid Eye Movements
17-20 Coordinated Hand-to-Face Movements
13-16 Eye Opening and Eye Movements
9-12 Isolated Head and Limb Movements
2-8 Flexor Posture
→4 Twitching Movement


Inadequate stimulus
Stress reaction
Attention/Interaction
State
Motor
Autonomic
Regulation
Adapted stimulus
Interactive reaction

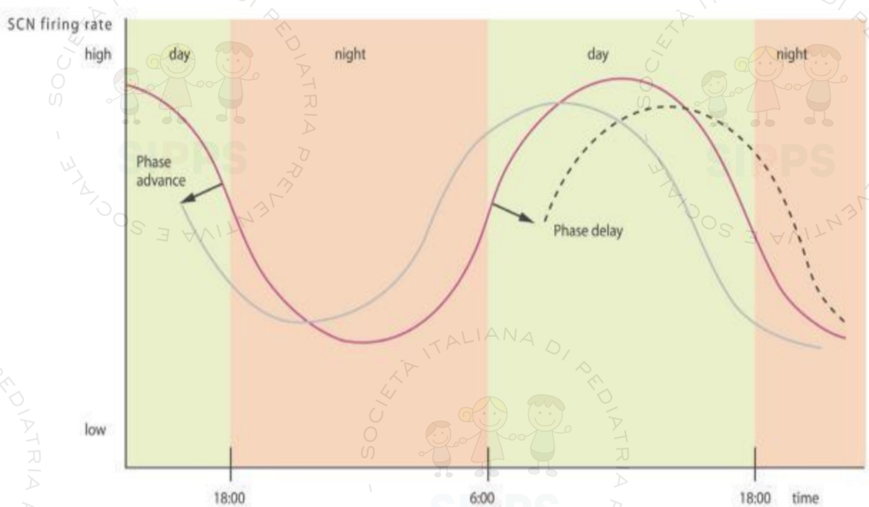
ADHD

- Bedtime resistance
- Sleep onset difficulties
- Night awakenings
- Difficulties with morning awakenings
- Sleep disordered breathing
- Daytime sleepiness
- No established consensus on how to treat sleep disorders in ADHD
- Melatonin may be an option
- Abnormal melatonin genetic pathways
- Five trials of melatonin in doses ranging from 3 to 6 mg/night) significantly reduced sleep onset delay and increased total sleep duration
- **No impact on daytime ADHD core symptoms**



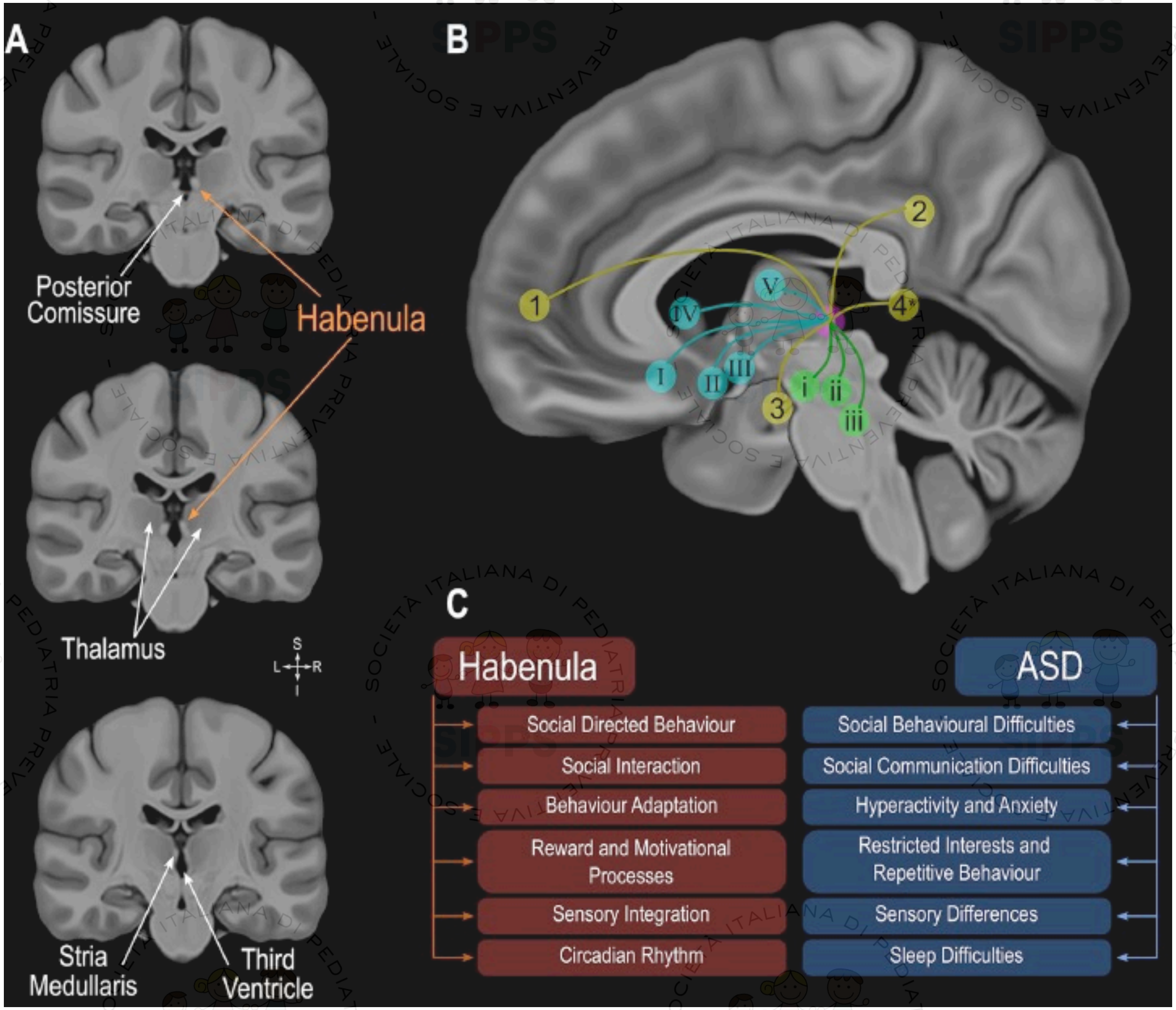


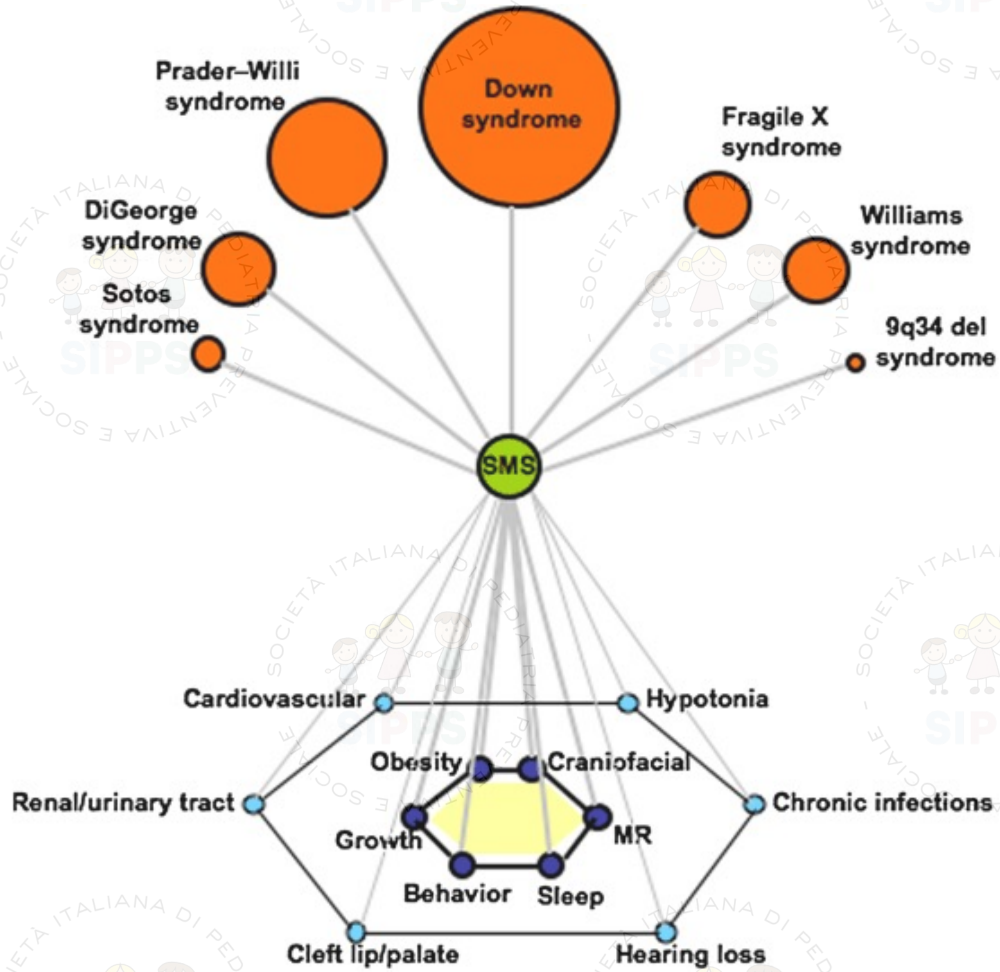
ASD



Tab. I. Differenze percentuali e OR tra le due popolazioni per le singole categorie di disturbi del sonno: DIMS, disturbi di inizio e mantenimento del sonno; DRS, disturbi respiratori del sonno; DA, disordini dell'"arousal; DTVS, disturbi della transizione veglia-sonno; DES, disordini da eccessiva sonnolenza; IPN, iperidrosi notturna

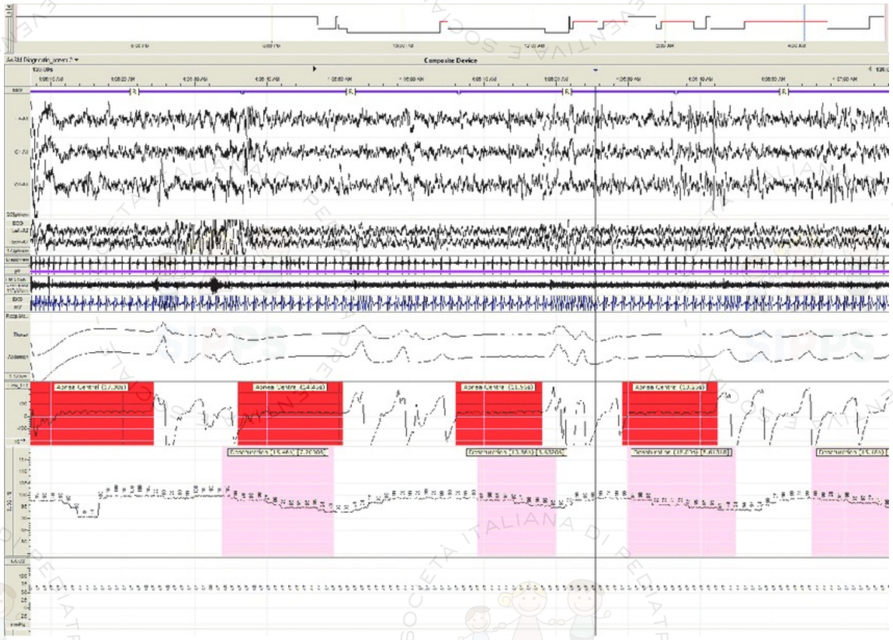
	ASD (n = 65) (%)	Controlli (n = 114) (%)	OR	95% IC	Z	p
DIMS	30.77	2.63	16.44	4.655 - 58.088	4.349	< 0.0001
DRS	53.85	10.53	9.92	4.583 - 21.455	5.827	< 0.0001
DA	36.92	8.77	6.09	2.677 - 13.843	4.310	< 0.0001
DTVS	49.23	10.53	8.24	3.813- 17.817	5.363	< 0.0001
DES	29.23	7.89	4.82	2.027- 11.45	3.561	0.0004
IPN	23.08	4.39	6.54	2.252 - 18.991	3.453	0.0006
TOT	18.46	3.51	4.82	1.916- 20.224	3.043	0.0023

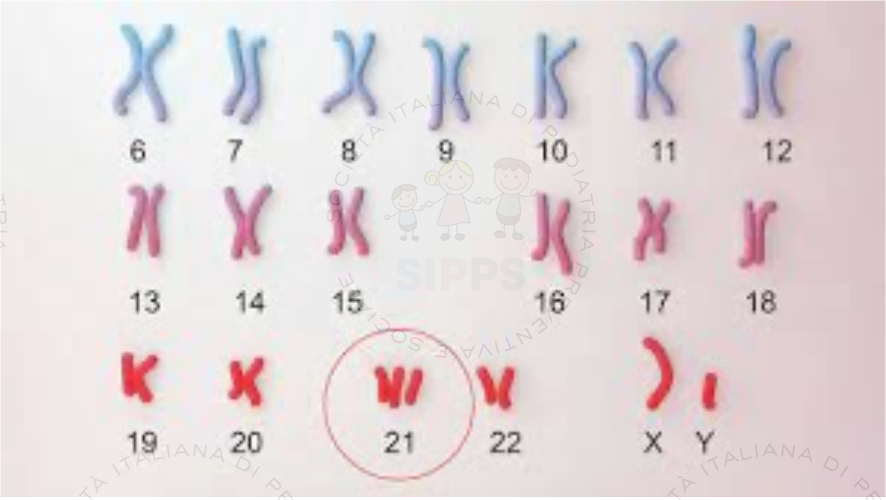

A
Posterior Comissure
Habenula
Thalamus
Stria Medullaris
Third Ventricle
S
L
R
I
B
1
2
3
4
I
II
III
IV
V
i
ii
iii
C
Habenula
ASD
Social Directed Behaviour
Social Interaction
Behaviour Adaptation
Reward and Motivational Processes
Sensory Integration
Circadian Rhythm
Social Behavioural Difficulties
Social Communication Difficulties
Hyperactivity and Anxiety
Restricted Interests and Repetitive Behaviour
Sensory Differences
Sleep Difficulties



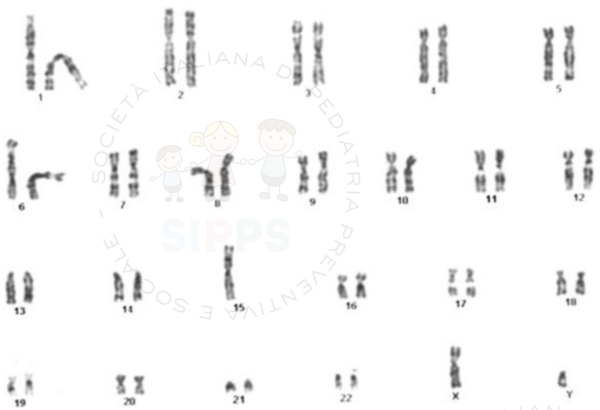
Prader–Willi syndrome
Down syndrome
Fragile X syndrome
DiGeorge syndrome
Williams syndrome
Sotos syndrome
9q34 del syndrome
SMS
Cardiovascular
Hypotonia
Obesity
Craniofacial
Renal/urinary tract
Chronic infections
Growth
MR
Behavior
Sleep
Cleft lip/palate
Hearing loss

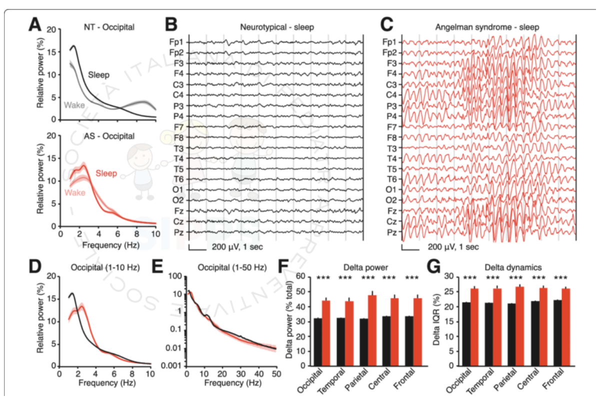
Down syndrome

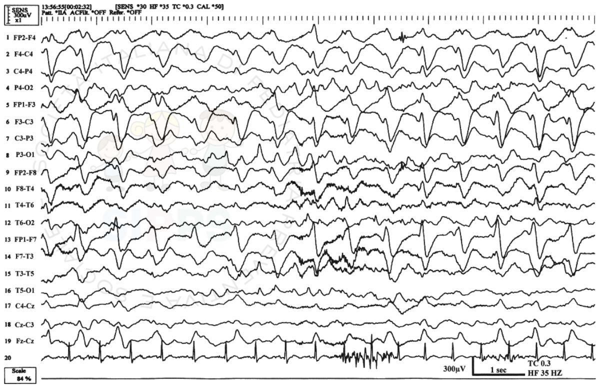




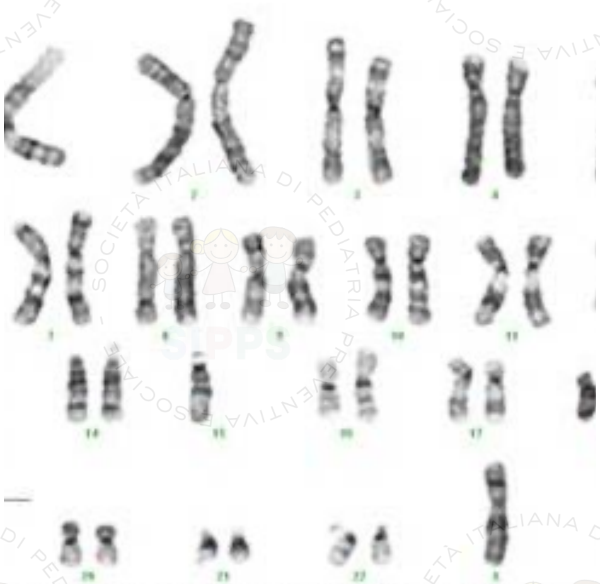
Angelman syndrome



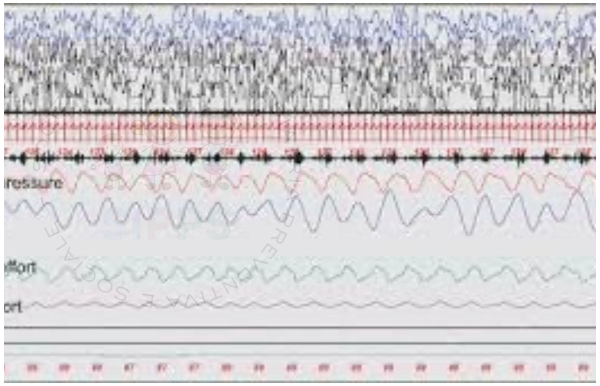




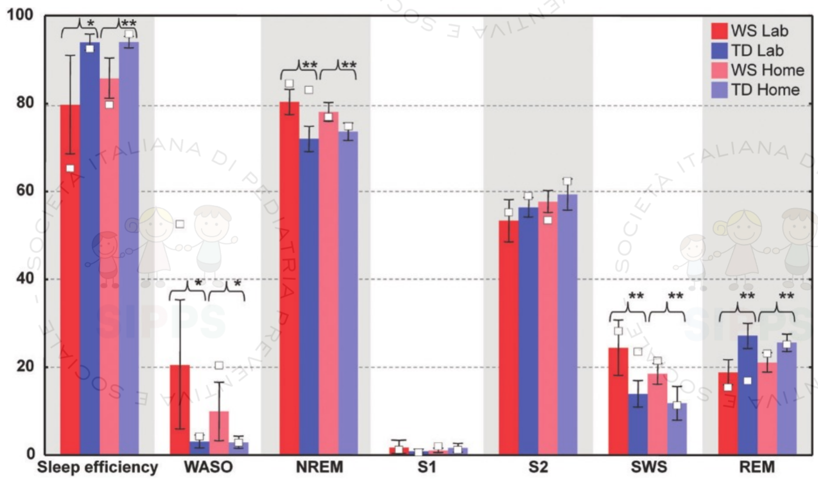
Prader-Willi syndrome



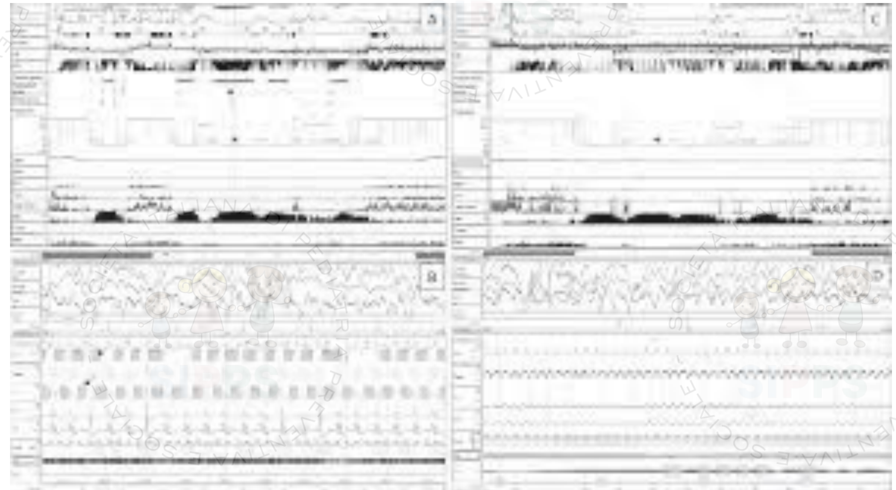
45,XY,-15,der(19)t(15;19)(q13;p13.3)

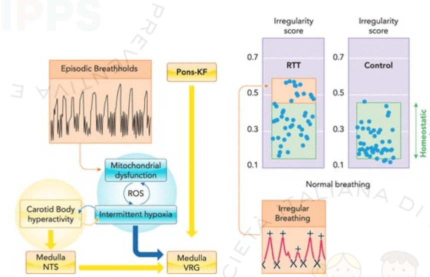


Williams syndrome

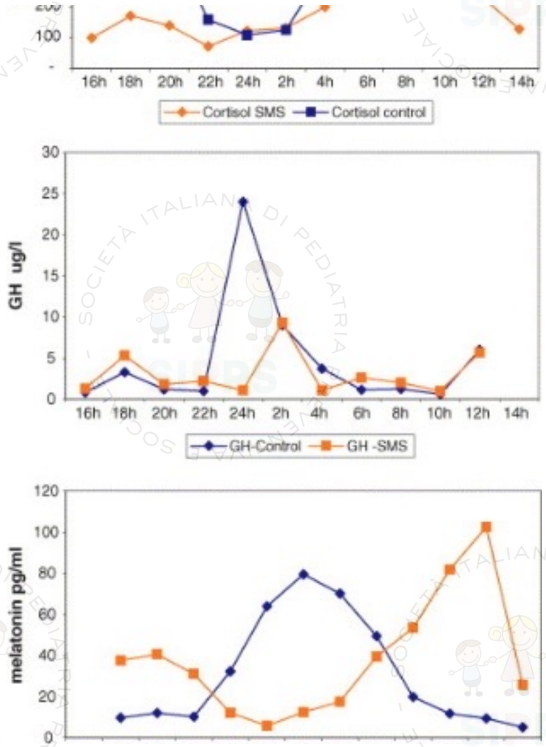


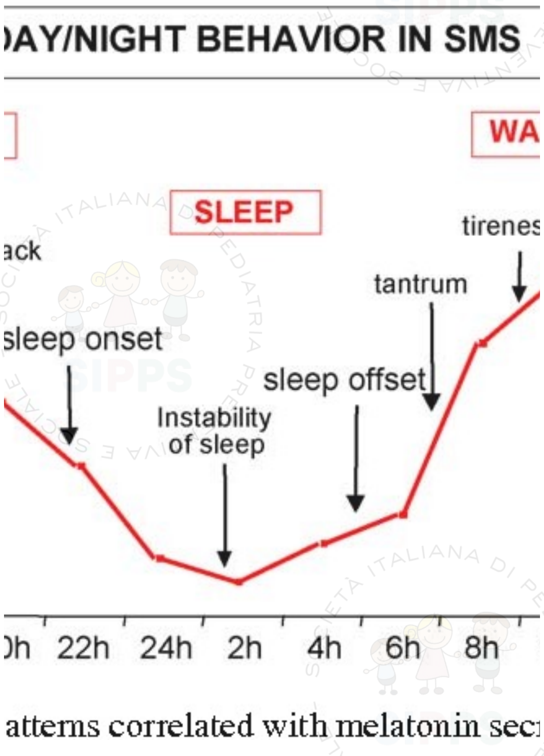
Rett syndrome





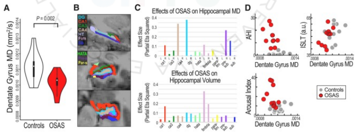
Smith-Magenis syndrome





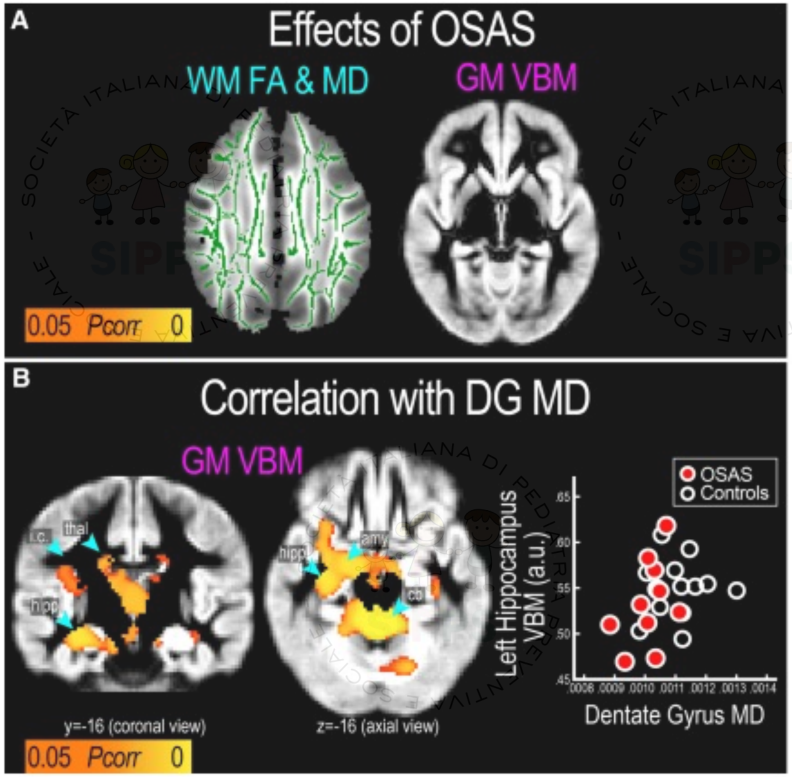
The Effects of Obstructive Sleep Apnea Syndrome on the Dentate Gyrus and Learning and Memory in Children

Jiook Cha,[1]* Johanna A. Zea-Hernandez,[2]* Sanghun Sin,[2] Katharina Graw-Panzer,[2] Keivan Shifteh,[3] Carmen R. Isasi,[4] Mark E. Wagshul,[6] Eileen E. Moran,[5] Jonathan Posner,[1] Molly E. Zimmerman,[5] and Raanan Arens[2]



Significance Statement

In this study we investigate the relationships between dentate gyrus structure, hippocampus-dependent cognition, and obstructive sleep apnea syndrome (OSAS). We demonstrate lower mean diffusivity of the dentate gyrus in children with OSAS, which correlates with a lower verbal learning and memory score. This study provides new evidence of disrupted microstructure of the dentate gyrus in children with OSAS that may help explain some of the neurocognitive deficits described in these children.

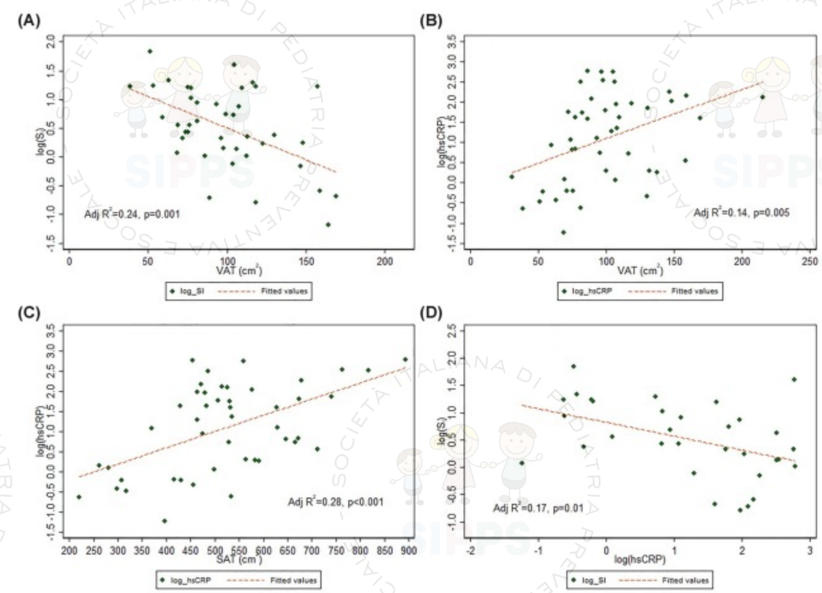


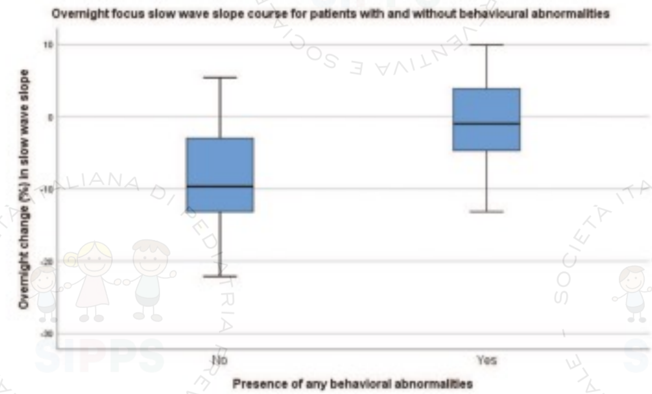
DE GRUYTER

J Pediatr Endocrinol Metab 2022; 35(8): 1069–1077

Mary Ellen Vajravelu*, Joseph M. Kindler, Babette S. Zemel, Abbas Jawad, Dorit Koren, Preneet Brar, Lee J. Brooks, Jessica Reiner and Lorraine E. Levitt Katz

Visceral adiposity is related to insulin sensitivity and inflammation in adolescents with obesity and mild sleep disordered breathing





Sleep slow-wave homeostasis and cognitive functioning in children with electrical status epilepticus in sleep

van den Munckhof, Bart ; Gefferie, Silvano R ; van Noort, Suus A M ; van Teeseling, Heleen C ; Schijvens, Mischa P ; Smit, William ; Teunissen, Nico W ; Plate, Joost D J ; Huiskamp, Geert Jan M ; Leijten, Frans S S ; Braun, Kees P J ; Jansen, Floor E ; Bölsterli, Bigna K

Sleep architecture and epileptic characteristics of drug naïve patients in childhood absence epilepsy spectrum. A prospective study

Argirios Dinopoulos[a], Maria A. Tsirouda[a,*], Anastasios Bonakis[b], Roser Pons[c], Ioanna D. Pavlopoulou[d], Konstantinos Tsoumakas[d]

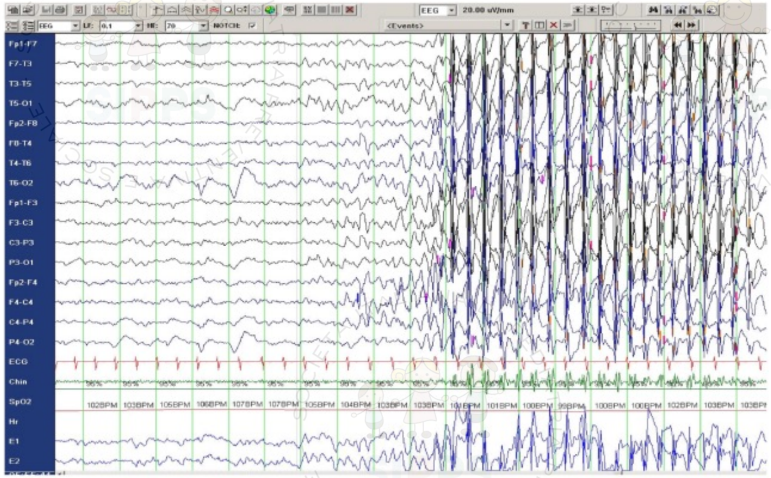
A B S T R A C T

Purpose: Childhood absence epilepsy (CAE) is an epileptic syndrome presenting between 2nd–10th years. The spells are elicited with hyperventilation (HV) while sleep seems to exacerbate the electrical activity. Our aim is to describe sleep architecture and its relationship with epileptic discharges (EDs) in patients with CAE, before treatment and one year later.

Methods: Twenty-eight, drug-naive children were recruited (21 girls), mean age 90.1 ± 32.6 months. Routine-EEG and overnight EEG-polygraphy were conducted upon diagnosis and one year later. Patients were separated in two groups of similar mean age, according to their clinical response at the second recording: group A: children with absolute control of absences and group B: children with partial control. Sleep parameters, EDs and arousals were measured. The effect of medication on sleep parameters was examined, according to 2 groups: valproic-treated and non valproic-treated.

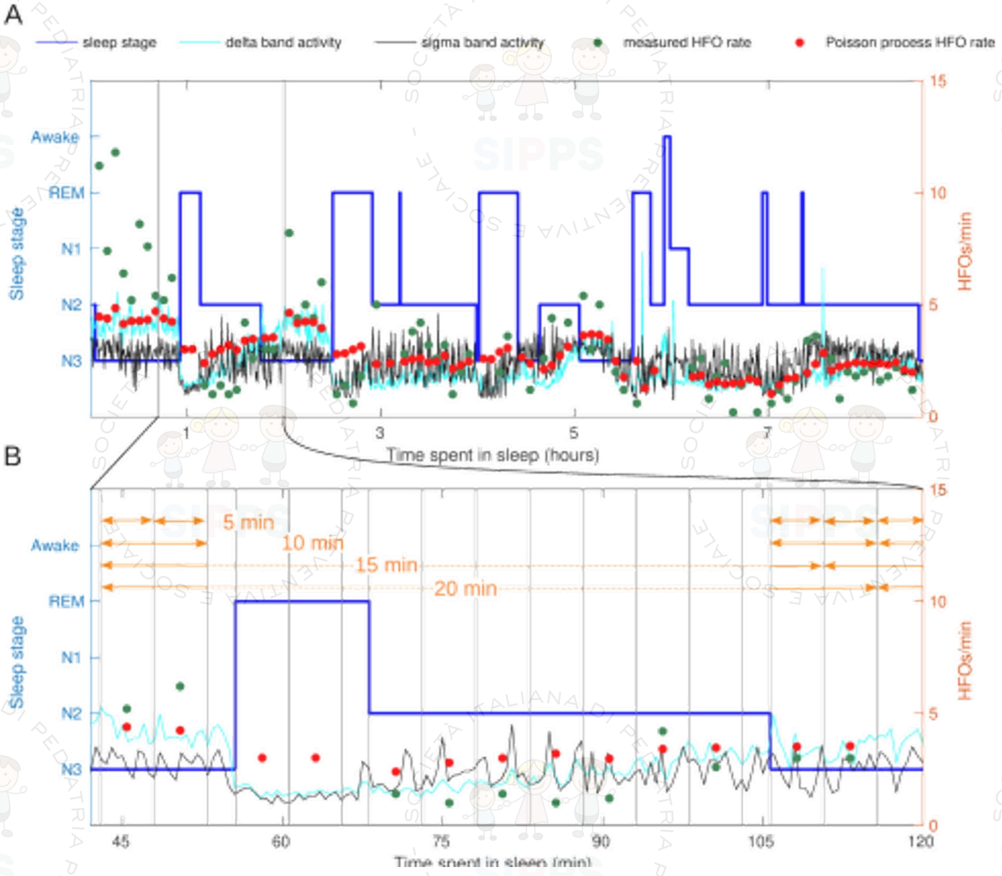
Results: Group A showed significant improvement in total sleep time, REM-sleep latency, REM-sleep, arousals-number/hour and arousals-duration/hour between the two recordings. Comparing the two groups for each recording separately, group A initially demonstrated greater epileptic activity and worse sleep parameters, whereas in the second recording exhibited total elimination of the EDs and significantly less arousals. Group B demonstrated persisting EDs and slight deterioration in some sleep parameters during the second recording, despite the lower epileptic load initially. No significant difference was identified between valproic and non-valproic treated patients, regarding the effect on sleep parameters.

Conclusion: Absolute control of absences and normalization of the electroencephalogram are accompanied by more continuous, stable and efficacious sleep in children with CAE.

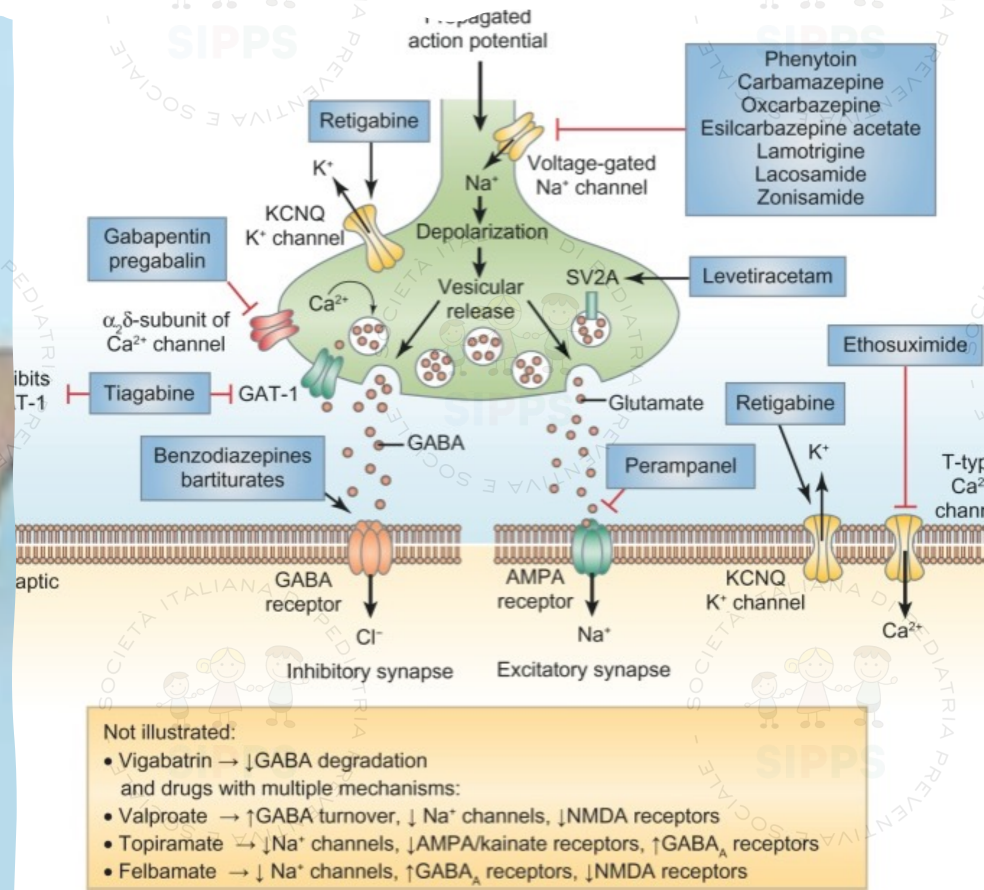


Variation of scalp EEG high frequency oscillation rate with sleep stage and time spent in sleep in patients with pediatric epilepsy

Dorottya Cserpan [a,b], Richard Rosch [a], Santo Pietro Lo Biundo [a], Johannes Sarnthein [b,c,d], Georgia Ramantani [a,c,e,*]

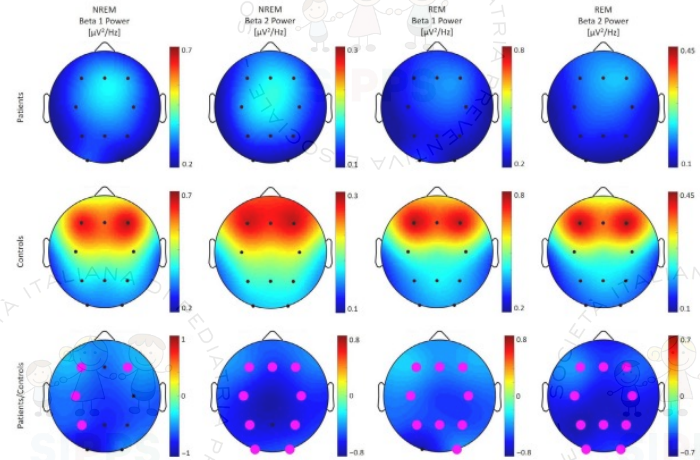


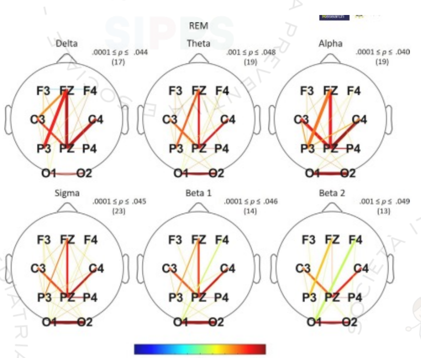
- AEDs could contribute to sleep disruption such as in the presence of cerebral lesions
- About 42% of patients with epilepsy have SRBD
- High rate of sleep problems regarding the qualitative aspects, the macrostructural organization, and the NREM sleep instability

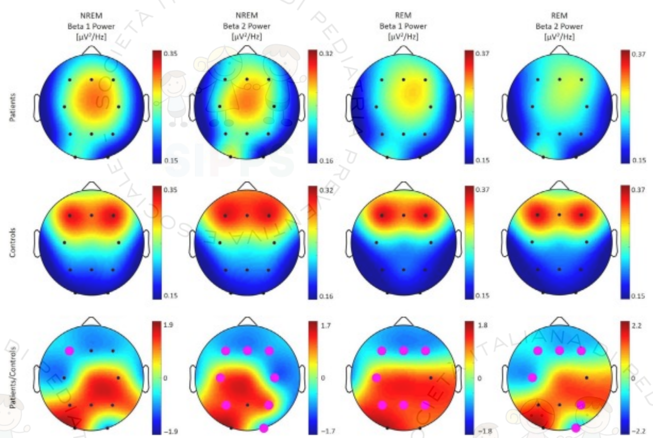


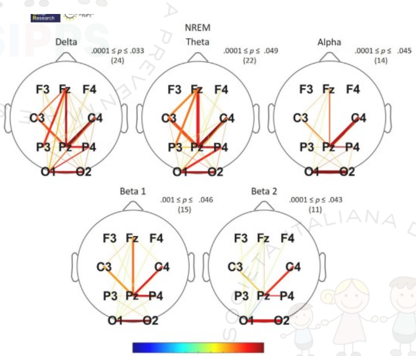
Sleep neurophysiology in childhood onset schizophrenia

Andjela Markovic[1,2] | Ashura Buckley[3] | David I. Driver[4] | Diane Dillard-Broadnax[4] | Peter A. Gochman[4] | Kerstin Hoedlmoser[5] | Judith L. Rapoport[4*] | Leila Tarokh[1*]









EXPERT OPINION ON PHARMACOTHERAPY
2019, VOL. 20, NO. 18, 2257–2271
https://doi.org/10.1080/14656566.2019.1674283

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REVIEW

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Pharmacotherapeutic management of sleep disorders in children with neurodevelopmental disorders

Oliviero Bruni[a], Marco Angriman[b], Maria Grazia Melegari[a] and Raffaele Ferri[c]

Article highlights

- Sleep disturbances are associated with NDDs in as many as 70% of cases.
- Both subjective (i.e., detected with questionnaires) and objective (i.e., revealed by actigraphy or neurophysiologic tools) sleep alterations have been found to be significantly more frequent in individuals with NDDs, compared to controls.
- Clinicians should screen for sleep disturbances in patients with NDDs at each visit.
- There is a paucity of empirical evidence to guide treatment of sleep disturbances in NDDs.
- Melatonin and other pharmacological treatments, such as gabapentin, clonidine, trazodone, and mirtazapine, can constitute a valid option in the case of inefficacy of behavioral treatment.
- More rigorous evaluations of therapeutic strategies for sleep disorders are needed in individuals with NDDs. RCTs of pharmacological and non-pharmacological interventions will be valuable to support the clinician in making evidence-based decisions in daily clinical practice.

The pathophysiology of sleep disorders in children with NDDs is multifactorial: in some patients, problematic sleep is a phenotypic characteristic of a particular disorder or genetic condition (as an example, inverted melatonin secretion in SMS), and knowledge of the distinctive features of sleep disorders in patients with NDDs is crucial for their effective treatment [11].

In other cases, sleep disorders represent one of the most important comorbidities, such as insomnia in Angelman syndrome, sleep disordered breathing in Down's Syndrome, excessive daytime sleepiness or narcolepsy in Prader Willi syndrome, and low levels of melatonin in ASD [1]. Sleep difficulties may also be related to unrecognized behavioral insomnia in childhood, which can be difficult to identify in children with NDDs due to their reduced communication skills, or factors related to poor sleep hygiene or, finally, to co-occurring medical conditions (e.g., epilepsy or gastroesophageal reflux). Moreover, sleep disorders might be aggravated by common issues linked to NDDs (such as sensory and motor deficits, psychopathological disturbances, respiratory disorders, epilepsy, and mental retardation), which can contribute to developmental delay.

Melatonin for sleep problems in children with neurodevelopmental disorders

Children with neurodevelopmental disorders are at risk of sleep problems, typically difficulty getting to sleep, sleep/wake rhythm disturbances and reduced duration of sleep (insomnia).[1,2] This may be associated with abnormally timed or inadequate secretion of melatonin, a naturally-occurring hormone involved in coordinating the body's sleep-wake cycle.[1,3] Previously, we reviewed the use of a melatonin product licensed for primary insomnia in adults aged over 55 years.[4] Here we review off-label and unlicensed use of melatonin in children with attention-deficit hyperactivity disorder (ADHD) or autism spectrum disorder or related neurodevelopmental disorders.

Conclusion

Sleep problems are common in children with neurodevelopmental disorders and may be associated with abnormalities in the metabolism of melatonin, a hormone involved in the sleep-wake cycle. The child's history should be carefully assessed as there may be features amenable to management (e.g. adjusting concomitant medication). Sleep hygiene and behavioural interventions are also sometimes helpful and should be tried before drug treatment is introduced. Based on a limited number of small, short-term clinical trials, melatonin has been shown to reduce the delay before sleep onset and increase the total duration of sleep. However, the absolute size of such changes is quite small. Little is known about melatonin's long-term effects in children.

Melatonin is available as a modified-release tablet licensed for short-term use in adults aged over 55 years and also as unlicensed formulations. Off-label use of the licensed product provides reassurance about manufacturing quality. If melatonin is to be used, the prescriber should provide sufficient information to allow parents and children to make an informed decision on the unlicensed use of melatonin. Prescribing should be initiated by a specialist and the arrangement for providing further supplies of melatonin clearly documented. An agreed treatment plan should be in place to ensure that children are followed up regularly to assess response to therapy, unwanted effects and the need for long-term treatment.

CURRENT MEDICAL RESEARCH AND OPINION
2022, VOL. 38, NO. 2, 211–227
https://doi.org/10.1080/03007995.2021.2000714
Article ST-0362.R2/2000714

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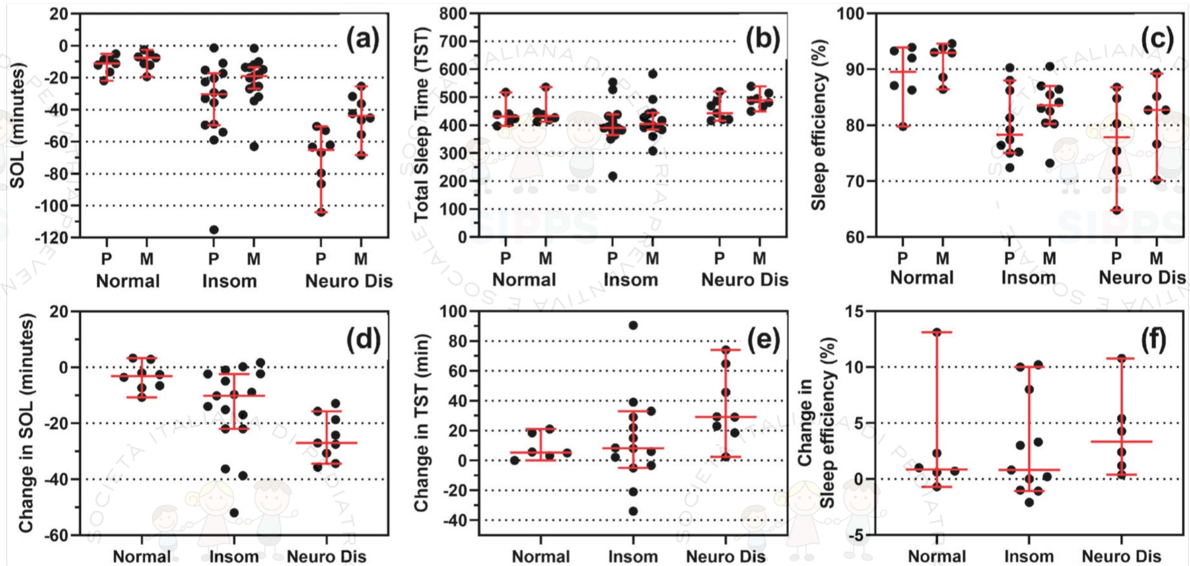
REVIEW ARTICLE

What do we really know about the safety and efficacy of melatonin for sleep disorders?

David J. Kennaway



ABSTRACT

Melatonin is a hormonal product of the pineal gland, a fact that is often forgotten. Instead it is promoted as a dietary supplement that will overcome insomnia, as an antioxidant and as a prescription only drug in most countries outside the United States of America and Canada. The aim of this review is to step back and highlight what we know about melatonin following its discovery 60 years ago. What is the role of endogenous melatonin; what does melatonin do to sleep, body temperature, circadian rhythms, the cardiovascular system, reproductive system, endocrine system and metabolism when administered to healthy subjects? When used as a drug/dietary supplement, what safety studies have been conducted? Can we really say melatonin is safe when it has not been systematically studied and many studies show interactions with a wide range of physiological processes? Finally the results of studies investigating the efficacy of melatonin as a drug to alleviate insomnia are critically evaluated. In summary, melatonin is an endogenous pineal gland hormone with specific physiological functions in animals and humans, with its primary role in humans to maintain synchrony of sleep with the day/night cycle. When administered as a drug it affects a wide range of physiological systems and has clinically important drug interactions. With respect to efficacy for treating sleep disorders, melatonin can advance the time of sleep onset but the effect is modest and variable. In children with neurodevelopmental disabilities melatonin appears to have the greatest impact on sleep onset but little effect on sleep efficiency.

Increase MLT bioavailability

- Fluvoxamine
- IMAO
- Tricyclic antidepressant
- VIP
- PACAP
- Opiates

Decrease MLT bioavailability

- Beta1-blockers
- a2-blockers
- Neuropeptide Y
- Dopamine
- Glutamate

- No hangover
- No tollerance
- No physical dependence
- Few ADR

BIAS prescription

MLT long-term effects not surely safe for puberty onset

Lack of controlled data on TDC

No differences among children for sleeping

No necessity to schedule MLT administration

No dose

nutrients

MDPI

Article

Adherence to the Mediterranean Diet is Associated with Better Sleep Quality in Italian Adults

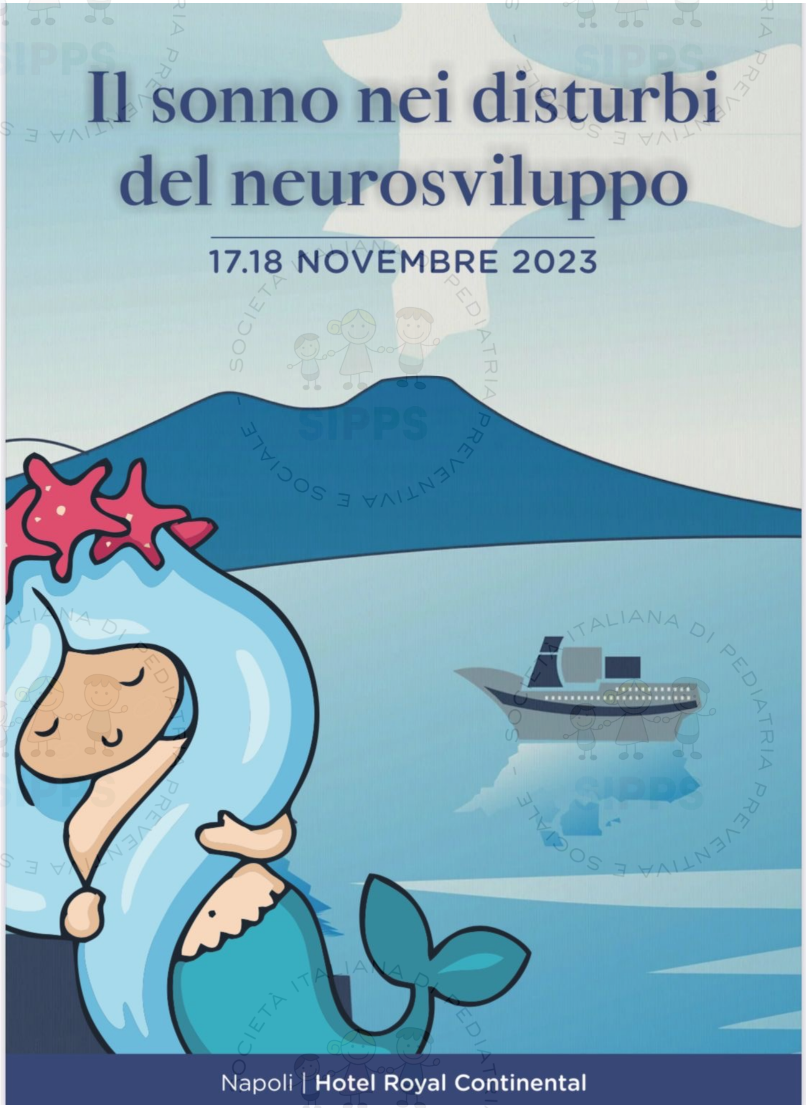
Justyna Godos [1], Raffaele Ferri [2], Filippo Caraci [2,3], Filomena Irene Ilaria Cosentino [2], Sabrina Castellano [4], Fabio Galvano [1,†] and Giuseppe Grosso [1,*,†]

	Mediterranean Diet Adherence Score *				
	Q1	Q2	Q3	Q4	*p*-Value
Overall sleep quality, *n* (%)					<0.001
Adequate	272 (58.9)	403 (68.0)	440 (72.6)	199 (72.4)	
Inadequate	190 (41.1)	190 (32.0)	166 (27.4)	76 (27.6)	
Sleep duration, *n* (%)					<0.001
>7 h	246 (53.2)	371 (62.6)	376 (62.0)	171 (62.2)	
6–7 h	111 (24.0)	130 (21.9)	137 (22.6)	57 (20.7)	
5–6 h	65 (14.1)	58 (9.8)	74 (12.2)	33 (12.0)	
<5 h	40 (8.7)	34 (5.7)	19 (3.1)	14 (5.1)	
Sleep disturbance, *n* (%)					0.311
None	53 (11.5)	54 (9.1)	74 (12.2)	35 (12.7)	
Low	335 (72.5)	444 (74.9)	451 (74.4)	207 (75.3)	
Medium	74 (16.0)	95 (16.0)	81 (13.4)	33 (12.0)	
High	0	0	0	0	
Sleep latency, *n* (%)					0.003
Very short	172 (37.2)	253 (42.7)	298 (49.2)	135 (49.1)	
Short	153 (33.1)	210 (35.4)	181 (29.9)	85 (30.9)	
Medium	101 (21.9)	94 (15.9)	97 (16.0)	41 (14.9)	
Long	36 (7.8)	36 (6.1)	30 (5.0)	14 (5.1)	
Day dysfunction, *n* (%)					<0.001
None	296 (64.1)	433 (73.0)	440 (72.6)	201 (73.1)	
Low	75 (16.2)	91 (15.3)	93 (15.3)	30 (10.9)	
Medium	35 (7.6)	28 (4.7)	27 (4.5)	23 (8.4)	
High	56 (12.1)	41 (6.9)	46 (7.6)	21 (7.6)	

Conclusions: High adherence to a Mediterranean diet is associated with better sleep quality either toward direct effect on health or indirect effects through improvement of weight status

Mediterranean product	Melatonin	Reference
Grape products		
Red wines	< 0.5 ng mL^{-1}	Mercolini et al., 2008; Stege et al., 2010; Vitalini et al., 2013
White wines	< 0.5 ng mL^{-1}	Mercolini et al., 2008; Stege et al., 2010; Vitalini et al., 2013
Dessert wines	< 0.5 ng mL^{-1}	Vitalini et al., 2013
Grape juice (undisclosed cultivar)	< 0.5 ng mL^{-1}	Mercolini et al., 2012
Albana grappa	0.3 ng mL^{-1}	Mercolini et al., 2012
Modena balsamic vinegar (DO*)	~ 0.1 ng mL^{-1}	Vitalini et al., 2013
Olive oil		
Extra virgin (DO)	71-119 pg mL^{-1}	de la Puerta et al., 2007
Refined	53-75 pg mL^{-1}	de la Puerta et al., 2007

*DO, Designation of Origin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