Lamezia, 3 luglio 2013

- I REM behavioural disorders

- Biancamaria Guarnieri
  - Centro di Medicina del Sonno
  - Riconosciuto AIMS
  - Casa di Cura accreditata “Villa Serena”, Città S. Angelo, Pescara
I vari disturbi comportamentali in sonno REM

- Disturbo del comportamento in sonno REM (RBD)
- Disturbo da incubi
- Paralisi ipnagogiche
“RBD is one of the more intriguing clinical curiosities in medicine and certainly in sleep medicine and neurology.”
RBD come contributo del sonno nell’esplorazione del funzionamento cerebrale

- Verso la possibile rilevazione di precoci markers di neurodegenerazione!
Schenk C, Manhowald M.

“REM sleep behavior disorder: clinical, developmental and neuroscience perspective 16 years after its formal identification in SLEEP”, Sleep 2002

Schenk C

”Paradox lost-Midnight in the battleground of sleep and dreams. violent moving nightmares, REM sleep behavior disorder.” Extreme nights, LLC, 2005
**REM SLEEP BEHAVIOR DISORDER (RBD)**

- **Parasonnia** formalmente identificata nel 1986 da Schenck e Mahowald
- **Comportamenti** motori vigorosi e spesso violenti, di solito associati a sogni spiacevoli e vividi ("dream enacting behaviors")
- **PSG**: perdita intermittente o completa dell’atonia muscolare del milo-ioideo e/o un incremento dell’attività muscolare fasica (milo ioideo e muscoli degli arti) durante sonno R, senza evidente attivazione vegetativa.
- **L’incubo tipico** dell’RBD: essere attaccati da animali o persone sconosciute e anche combattere per autodifesa o tentativo di fuggire
International Classification of Sleep Disorders: AASM 2005 - criteri diagnostici di RBD definito

- A-Presence of RSWA on PSG
- B- At least one of the following:
  - sleep-related, injurious, potentially injurious, or disruptive behaviors by history (i.e., dream enactment behavior), and/or
  - abnormal REM sleep behavior documented during polysomnographic monitoring,
- Absence of EEG epileptiform activity during REM sleep unless RBD can be clearly distinguished from any concurrent REM sleep related seizure disorder
- The sleep disorder is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder
RBD clinicamente probabile

- In assenza di polisonnografia o in chi non riesce a collaborare o in chi ha pochissimo o assente sonno REM in PSG, per la diagnosi:
- Anamnesi di eventi motorio-comportamentali tipici
- Risposte congrue a specifici questionari possibilmente validati
Mayo Sleep Questionnaire-Informant

Do you live with the patient? □ Yes □ No (If No, END FORM HERE)

Do you sleep in the same room as the patient? □ Yes □ No

If no, is it because of his/her sleep behaviors (i.e. snores too loud, acts out dreams, etc.)? □ Yes □ No

Please mark “Yes” if the described event has occurred at least 3 times.

1. Have you ever seen the patient appear to “act out his/her dreams” while sleeping? (punched or flailed arms in the air, shouted or screamed)

□ 0 no
□ 1 yes

- If Yes,
  a. How many months or years has this been going on?
     □□ year(s)
     □□ months
  b. Has the patient ever been injured from these behaviors (bruises, cuts, broken bones)?
     □ No
     □ Yes
  c. Has a bedpartner ever been injured from these behaviors (bruises, blows, pulled hair)?
     □ No
     □ Yes
     □ No bedpartner
  d. Has the patient told you about dreams of being chased, attacked or that involve defending himself/herself?
     □ No
     □ Yes
     □ Never told you about dreams

Mayo RBD questionnaire for PD and cognitive declined patients

2011 validato su 176 soggetti (normal, MCI, AD, LBD PD, PDD

98% Sensibilità
74% Specificità per RBD
A clinically probable RBD was diagnosed in patients presenting during sleep, about 1 h after falling asleep, rude movements and/or vocalizations as if they were enacting terrifying nightmares, sometimes provoking harm to self or to their bed partner: these episodes do not necessarily cause the complete awakening of the subject.
REM senza atonia (RSWA)

- RSWA is a requisite diagnostic feature of RBD, but may also be seen in patients without clinical symptoms or signs of dream enactment as an incidental finding in neurologically normal individuals, especially in patients receiving antidepressant therapy.

- RSWA non vuol dire RBD
RBD: decorso clinico

**RBD**

- **acuto**
  - alcohol (sospensione)
  - meprobamate (sospensione)
  - TCA, I-MAO, SSRI
  - cioccolata (intoxication)
  - RBD inserito nel delirium……?????

- **cronico**
  - idiopatico
  - sintomatico
    - (neurological diseases, mostly α-synucleinopathies)
RBD e malattie neurodegenerative

- Parkinson’s disease (PD) ++
- Lewy Body Dementia (LBD) +++
- Multiple System Atrophy (MSA) +++

\(\alpha\)-synucleiopathies
(Boeve et al., 2001)

\[
\text{RBD} = \text{Positive predicting value for } \alpha\text{-synucleinopathies} > 90\%
\]

- Progressive Supranuclear Palsy (PSP)
- Cortico-Basal degeneration (CBD)
- Alzheimer’s disease

Sporadically reported in tauopathies
(overlap LBD?)
REM Sleep Behavior Disorder
Associated with Neurodegenerative Disease

**Synucleinopathy**
- **Lewy body disease (LBD)**
- **Incidental LBD**
- **Parkinson’s disease (PD)**
- **PD with dementia (PDD)**
- **Dementia with Lewy bodies (DLB)**
- **Pure autonomic failure (PAF)**
- **Multiple system atrophy (MSA)**

**Trinucleotide Repeat Disorders**
- Spinocerebellar Atrophy-3 (SCA-3)
- Huntington’s Disease (HD)

**Prionopathy**
- Creutzfeldt-Jakob disease (CJD)
- Fatal familial insomnia (FFI)
- Gerstmann-Straussler-Scheinker (GSS)

**Amyloidopathy**
- Alzheimer’s disease (AD)

**Tauopathy**
- Pick’s disease
- Corticobasal degeneration (CBD)
- **Progressive supranuclear palsy (PSP)**
- Argyrophilic grain disease (AGD)
- Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17MAPT)
- Guadeloupean parkinsonism

**TDP-43opathy**
- Frontotemporal lobar degeneration (FTLD) with TDP-43-positive inclusions
- FTLD with motor neuron disease (FTLD-MND)
- Hippocampal sclerosis (HS)
- Amyotrophic lateral sclerosis (ALS)
- Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17PGRN)
REM sleep behavior disorder in a patient with frontotemporal dementia.

Lo Coco D, Cupidi C, Mattaliano A, Baiamonte V, Realmuto S, Cannizzaro E.
RBD idiopatico

- Non associato ad altre diagnosi neurologiche

- Prevalenza stimata con interviste telefoniche (soggetti 15-100 anni) ~ 0.5% (Ohayon 1997)

- Con PSG, in pz con età avanzata, spesso declino cognitivo che si rivolgono a Centro del sonno: 0.02% bias di selezione

- Prevalenza maschile (M/F: 9/1): in PD: 72%, in LBD: 72%, in MSA: 64%

- Età d’esordio: maggiore di 50 anni
RBD idiopatico al follow up

- Evoluzione verso malattie neurodegenerative nel 65% dei casi:
  - 38% of 29 iRBD pts developed parkinsonism and/or dementia after 12 yrs from onset (and 65% after 21 yrs from RBD onset) (Schenk 1996 and 2005)
  - 45% developed PD, MSA, DLB, MCI after a mean of 11.5 years from the RBD onset (Iranzo at al., 2006.)

Esiste realmente l’RBD idiopatico?
idiopathic RBD represents the prodromal phase of a Lewy body disorder and, with sufficient follow-up, most cases would eventually be diagnosed with a clinical defined Lewy body disorder, such as Parkinson's disease (PD) or dementia with Lewy bodies (DLB).
Patients from an IRBD cohort recruited between 1991 and 2003, and previously assessed in 2005, were followed up during an additional period of 7 years.

Of the 44 participants from the original cohort, 36 (82%) by the 2012 assessment:
- 16 patients were diagnosed with PD
- 14 with DLB
- 1 with multiple system atrophy
- 5 with mild cognitive impairment

Iranzo 2013
Follow-up of idiopathic RBD patients: Predicting value of PLMS?

- In the study of Schenck et al, 1996, the only variable that differentiated iRBD that eventually developed PD (38%) from those remaining idiopathic was the \( \uparrow \text{PLMS index} \) at the time of RBD diagnosis (85.2 vs 35.9)

- In a series of 100 patients with RBD diagnosed at the Sleep Disorders Center of San Raffaele H, the PLMS index was significantly higher in the symptomatic RBD compared to the idiopathic ones. (86% vs. 58% with a PLMS index>10) (Zucconi et al., 2003)
Periodic leg movements in patients with Parkinson’s disease are associated with reduced striatal dopamine transporter binding.

The reduced striatal $[^{123}]$I-β-CIT binding was significantly correlated with the number of PLMS. We propose that striatal dopaminergic nerve cell loss is involved in the increased number of PLMS in PD patients.

Fig. 1 Correlation of specific $[^{123}]$I-β-CIT binding ratio (mean of left and right) with number of periodic leg movements during sleep (PLMS) in patients with idiopathic Parkinson’s disease ($n = 11$).
Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder

Cohort of 93 IRBD (PSG) pts

Risk 5-year: 17.7%, 10-year: 40.6%, 12-year: 52.4%. (14PD i, 1MSA, 11 dementia-7LBD, 4 AD)
Probable rapid eye movement sleep behavior disorder increases risk for mild cognitive impairment and Parkinson disease: a population-based study.

Cognitively normal subjects aged 70 to 89 years in a population-based study of aging who screened positive for probable RBD using the Mayo Sleep Questionnaire were followed at 15-month intervals.

INTERPRETATION:

In this population-based cohort study RBD confers a 2.2-fold increased risk of developing MCI/PD over 4 years.
REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia

Table 2: Results of neuropsychological tests of patients with PD and control subjects

<table>
<thead>
<tr>
<th>Tests</th>
<th>A: PD-RBD, n = 18</th>
<th>B: PD-NRBD, n = 16</th>
<th>C: Controls, n = 25</th>
<th>A-B* p</th>
<th>A-C* p</th>
<th>B-C* p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia rating scale*</td>
<td>135.39 ± 6.77</td>
<td>139.56 ± 2.78</td>
<td>140.56 ± 2.26</td>
<td>0.03</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Trail A, sec*</td>
<td>60.78 ± 25.70</td>
<td>44.00 ± 16.37</td>
<td>37.84 ± 15.18</td>
<td>NS</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>Trail B, sec*</td>
<td>166.61 ± 85.33</td>
<td>91.88 ± 38.89</td>
<td>90.04 ± 30.66</td>
<td>0.002</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interference time, sec*</td>
<td>161.27 ± 59.01</td>
<td>117.06 ± 23.03</td>
<td>123.00 ± 48.25</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Interference errors†</td>
<td>5.22 ± 4.11</td>
<td>2.19 ± 1.83</td>
<td>1.68 ± 2.15</td>
<td>0.02</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic</td>
<td>27.00 ± 6.09</td>
<td>36.06 ± 5.38</td>
<td>36.71 ± 6.60</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Letter</td>
<td>30.16 ± 9.64</td>
<td>38.19 ± 8.22</td>
<td>37.63 ± 9.23</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>List of words (RAVLT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39.17 ± 8.73</td>
<td>47.25 ± 7.05</td>
<td>49.44 ± 8.70</td>
<td>0.006</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>6.94 ± 2.51</td>
<td>9.63 ± 2.36</td>
<td>10.48 ± 2.54</td>
<td>0.003</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>7.39 ± 2.75</td>
<td>9.94 ± 2.21</td>
<td>10.00 ± 3.34</td>
<td>0.01</td>
<td>0.005</td>
<td>NS</td>
</tr>
<tr>
<td>Recognition</td>
<td>13.41 ± 2.76</td>
<td>13.81 ± 1.22</td>
<td>14.33 ± 1.17</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rey-O figure, copy score</td>
<td>26.33 ± 7.14</td>
<td>30.00 ± 2.97</td>
<td>30.38 ± 3.27</td>
<td>0.03</td>
<td>0.008</td>
<td>NS</td>
</tr>
<tr>
<td>Block design, adjusted score†</td>
<td>8.11 ± 1.91</td>
<td>11.88 ± 2.36</td>
<td>12.56 ± 3.12</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>Bells test, omissions†</td>
<td>4.78 ± 3.15</td>
<td>1.94 ± 1.98</td>
<td>2.04 ± 2.42</td>
<td>0.005</td>
<td>0.002</td>
<td>NS</td>
</tr>
</tbody>
</table>
Rapid Eye Movement Sleep Behavior Disorder and Risk of Dementia in Parkinson’s Disease: A Prospective Study

Ronald B. Postuma, MD, MSc,1,2* Josie-Anne Bertrand, MPS,2,3 Jacques Montplaisir, MD, PhD,2,4 Catherine Desjardins, MPS,2 Mélanie Vendette, MSc,2,3 Silvia Rios Romenets, MD,1 Michel Panisset, MD,5 and Jean-François Gagnon, PhD2,6†

### TABLE 1. Patient Demographics and Outcomes According to Baseline RBD Status

<table>
<thead>
<tr>
<th>Demographics/Outcomes</th>
<th>No RBD (n = 15)</th>
<th>RBD (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.5 ± 10.6</td>
<td>70.5 ± 7.4</td>
<td>0.340</td>
</tr>
<tr>
<td>Sex (M/F) (%)</td>
<td>11/4 (73)</td>
<td>23/4 (85.2)</td>
<td>0.430</td>
</tr>
<tr>
<td>Disease duration (at follow-up)</td>
<td>9.5 ± 4.8</td>
<td>9.7 ± 4.3</td>
<td>0.920</td>
</tr>
<tr>
<td>Duration of follow-up (years)</td>
<td>4.1 ± 1.4</td>
<td>3.9 ± 1.4</td>
<td>0.530</td>
</tr>
<tr>
<td>Levodopa dose (mg)</td>
<td>633 ± 333</td>
<td>406 ± 331</td>
<td>0.083</td>
</tr>
<tr>
<td>Baseline % tonic REM</td>
<td>21.8 ± 26.3</td>
<td>67.0 ± 29.0</td>
<td>0.011</td>
</tr>
<tr>
<td>Baseline % phasic REM</td>
<td>13.9 ± 15.3</td>
<td>27.8 ± 19.0</td>
<td>0.038</td>
</tr>
<tr>
<td>Use of dopamine agonist (%)</td>
<td>6 (40)</td>
<td>8 (30)</td>
<td>0.620</td>
</tr>
<tr>
<td>UPDRS Part III</td>
<td>26.2 ± 16.2</td>
<td>34.1 ± 16.5</td>
<td>0.340</td>
</tr>
<tr>
<td>Dementia (%)</td>
<td>0 (0)</td>
<td>13 (48)</td>
<td>0.014</td>
</tr>
<tr>
<td>MCI (%)</td>
<td>4 (27)</td>
<td>7 (26)</td>
<td>0.870</td>
</tr>
<tr>
<td>Dementia or MCI (%)</td>
<td>4 (27)</td>
<td>20 (74)</td>
<td>0.025</td>
</tr>
<tr>
<td>MoCA</td>
<td>26.3 ± 2.3</td>
<td>20.1 ± 6.2</td>
<td>0.027</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 ± 1.8</td>
<td>24.4 ± 5.0</td>
<td>0.009</td>
</tr>
<tr>
<td>Visual hallucinations (%)</td>
<td>1 (7)</td>
<td>12 (44)</td>
<td>0.049</td>
</tr>
<tr>
<td>Mayo fluctuations score</td>
<td>0.20 ± 0.78</td>
<td>1.27 ± 1.43</td>
<td>0.012</td>
</tr>
<tr>
<td>Mayo score ≥3 (%)</td>
<td>0 (0)</td>
<td>6 (23)</td>
<td>0.390*</td>
</tr>
</tbody>
</table>

*P values are presented for regression analysis (adjusting for age, sex, disease duration at baseline, akinetic-rigid versus tremor-predominant subtype and follow-up duration). Except for % tonic REM and % phasic REM, all results are from the follow-up examination. Abbreviations: M, male; F, female.
*Because of 0 values, logistic regression could not be performed; results are presented using linear regression.
☐ REM sleep behaviour disorder: a marker of synucleinopathy.
☐ Mahowald MW, Schenck CH.

☐ Lancet Neurol 2013 May; 12 (5) :469-82
☐ Idiopathic RBD in the development of PD
☐ Boeve BF

☐ Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study.
Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies

T.J. Ferman, PhD, B.F. Boeve, MD et al.

- cohort of 234 autopsy-confirmed dementia patients followed longitudinally
- a history of definite or probable RBD was present in 76% of 98 autopsy-confirmed DLB, indicating it is a frequent feature of DLB.
- A history of RBD improves clinical diagnostic accuracy and increases the odds of autopsy-confirmed DLB by 6-fold.9

Neurology  2011;77:875–88
the presence of RBD may reflect a distinct subtype of DLB, suggestive of a bottom-up disease progression,

while DLB without RBD has additional features suggestive of a top-down progression.

Does RBD define clinicopathologic subtypes of DLB with distinct patterns of disease progression and treatment response? It could help the development of biomarkers that may assist in differential diagnosis, early detection and prognosis of DLB.................
Iniziali report hanno esaltato l’associazione tra RBD e allucinazioni visive (Pacchetti, Sinforianì, Onofrij).

Alcuni le hanno considerate intrusioni di sonno REM.

Studi più recenti non hanno trovato chiare associazioni (Postuma, …..)
La latenza di conversione da RBD idiopatico a RBD in malattia neurodegenerativa cambia negli anni

- Maggior attenzione e capacità diagnostica
- Studi non solo retrospettivi
- Studi non più limitati solo o prevalentemente ai centri del sonno
Idiopathic RBD

- Multiple subtle abnormalities:

  - **Slowing of waking EEG** *(Fantini, 2003)*
  - **Neuropsicological deficits** *(Ferini-Strambi et al, 2003; Vendette M, 2000, Fantini et al., 2011)*
  - **Subtle parkinsonism** *(motor and gait speed)* *(Postuma 2006)*
  - **Autonomic impairment** *(Ferini-Strambi 1996, Lanfranchi 2007, Postuma 2010)*
  - **Olfactory deficit** *(Fantini 2006, Postuma 2006)*
  - **Color vision impairment** *(Postuma 2006)*
  - **Neuroimaging**

**abilità visuospaziali, logiche non verbali, attenzione, funzioni esecutive**
Deficit olfattivo in iRBD

- Deficit olfattivo in un gruppo eterogeneo di pazienti con RBD, di cui 2 idiopatici. ([Stiasny-Kolster et al., 2004]

- Deficit della identificazione degli odori in un gruppo di 50 pazienti con RBD idiopatico. ([Fantini et al, 2005])
Olfatto e malattie neurodegenerative

- Deficit olfattivo simile a quello osservato nel PD.
  - L’odore del diluente (paint thinner): maggiore sensibilità, specificità e potere statistico di detezione sia nel PD che nell’iRBD.

- Deficit olfattivo in 70%-100% dei pazienti PD sin dagli stadi precoci (Doty, 1988; Tissingh, 2001; McSchane., 2001; Ponsen, 2004)

- Non presente in altre cause di parkinsonismo (PSP, CBD, parkinsonismo vascolare e PD associato a mutazione Parkin).

- Deficit olfattivo nella demenza: in DLB > AD (McShane et al., 2001)

- Deficit olfattivo= hallmark di Lewy body disease? (Hawkes C, 2003)
Deficit olfattivo e demenza a corpi di Lewy

- The olfactory deficit found in 61% of RBD patients suggests the presence of an underlying Lewy body disease in those patients and supports the notion of a continuum between RBD and LBD.

- A great heterogeneity in olfactory scores was observed in the RBD group.

- Follow up of iRBD patients with high and low olfactory identification score will allow to assess the predictive value of olfactory impairment for the development of α-synucleinopathy in idiopathic RBD.
Neuropsicologia in RBD idiopatico

- Deficit nelle abilità **costruttive visuo-spaziali** (43.7% dei pazienti) e nell’apprendimento **visuo-spaziale** (82.3%) \(\Rightarrow\) simile ai pazienti con DLB (*Ferini-Strambi et al., Neurology 2004*)

- Deficit nelle funzioni **visuo-spaziali** nell’RBD idiopatico (*Terzaghi et al, AIMS 2005*)
Cognitive dysfunction and REM sleep behavior disorder: Key findings in the literature and preliminary longitudinal findings.


It is unclear whether cognitive deficits in iRBD represent an associated feature or a marker predictive of subsequent development of a synucleinopathy.

Cross-sectional studies indicate that a proportion of iRBD patients show cognitive deficits similar to those typically found in patients with synucleinopathies.

The available longitudinal data suggest that cognitive dysfunction in iRBD tends to progress over time, with this progression probably being underpinned by a neurodegenerative process. RBD fattore di rischio per declino cognitivo fino alla demenza
Association between waking EEG slowing and REM sleep behavior disorder in PD without dementia

J.-F. Gagnon, M Ps; M.L. Fantini, MD, MSc; M.-A. Bédard, PhD; D. Petit, PhD; J. Carrier, PhD; S. Rompré, PSGT; A. Décart, PhD; M. Panisset, MD; and J. Montplaisir, MD, PhD, CRCPC

- EEG slowing only in PD with RBD
- RBD in PD: predictor of dementia? (v. EEG in LBD)

Neurology, 2003
Autonomic impairment in iRBD

- **Mild autonomic dysfunctions during both sleep and wakefulness** (e.g. abnormalities in sympathetic and parasympathetic tests) (*Ferini-Strambi et al.* 1996)

- **A reduced cardiac activation associated with periodic leg movements (PLMS)** (*Fantini et al.* 2002)
Reduced cardiac $^{123}$I-MIBG scintigraphy in idiopathic REM sleep behavior disorder

**Abstract**—Idiopathic REM sleep behavior disorder (RBD) may represent prodromal synucleinopathies. We report markedly reduced cardiac $^{123}$I-metaiodobenzylguanidine uptake, consistent with the loss of sympathetic terminals, in idiopathic RBD. We also demonstrate that this reduction is of the same magnitude as that found in patients with Parkinson disease. The results are consistent with the hypothesis that idiopathic RBD in older patients is a forme fruste of Lewy body disease.

NEUROLOGY 2006;67:2236–2238

T. Miyamoto, MD, PhD; M. Miyamoto, MD, PhD; Y. Inoue, MD, PhD; Y. Usui, MD; K. Suzuki, MD; and K. Hirata, MD, PhD

![Figure 2](image.png)

*Figure 2. Distribution of the heart-to-mediastium metaiodobenzylguanidine (H/M) uptake ratio in control subjects and patients with idiopathic REM behavior disorder (RBD) and Parkinson disease (PD). The horizontal lines indicate the median values.*
Disfunzioni autonomiche non correlate a parkinsonismo

- MIGB alterata sempre in RBD idiopatico (ma non in MSA...???)
- PD-nonRBD: non ci sono disfunzioni autonomiche
- Un paziente aveva 20 anni di storia di RBD, non sintomi parkinsoniani e captazione MIGB molto ridotta
- Un paziente aveva 4 anni di storia di RBD e anomalie alla MIGB al baseline. "anni dopo ha sviluppato un Parkinson ma la seconda scintigrafia MIGB era identica alla prima.

Forse differenti livelli di progressione attraverso gli stadi di Braak?

(Lang AE, The progression of PD: a hypothesis, Neurology 2007)
49 PD patients:

18 pts. = clinical RBD (36.7%),
8 pts. = subclinical RBD (16.3%),
23 pts. = normal REM sleep (46.9%)

“PD patients with clinical RBD might suffer from a wider a-synuclein pathology, including reduced cardiac sympathetic ganglia function as reflected by a lowered MIBG uptake”
Idiopathic RBD: Neuroimaging


- Multiple perfusion abnormalities (ECD-SPECT) (Mazza 2006, Vendette 2011)

- Gray and White Matter (Voxel-based MRI, DTI) (Scherfer 2011, Haniou 2011)

- Cardiac innervation (I-MGBI cardiac scintigraphy): precocious involvement (Myiamoto )

- **studi solo giapponesi…ridotta captazione in RBD, ma non in MSA( dove RBD è più frequente)
Parkinson and RBD: IPT SPECT study

Fig. 2 The $^{123}$I-IPT-SPECT of one patient with RBD, one patient with Parkinson’s disease (Hoehn and Yahr stage I) and one control subject. Binding ratios are given below the $^{123}$I-IPT-SPECTs. Note the bilaterally reduced IPT binding ratio in the RBD patient, whereas in the Parkinson’s disease patient the reduction is asymmetrical, being more pronounced contralateral to the symptomatic body side of the patient. RT = right; LT = left.

(Eisensehr et al., Brain 2000; 123:1155-1160)
PET STUDY: decrease of nigro-striatal DAergic innervation in idiopathic RBD

Aggressive dream content without daytime aggressiveness in REM sleep behavior disorder

M.L. Fantini, MD, MSc; A. Corona, MPS; S. Clerici, PhD; and L. Ferini-Strambi, MD

Abstract—Background: REM sleep behavior disorder (RBD) is characterized by vigorous sleep motor activity associated with dream mentation. Patients with RBD frequently report action-filled and violent dreams. Objective: To systematically assess dream characteristics and daytime aggressiveness in patients with RBD and controls. Methods: Forty-nine patients with polysomnographically confirmed RBD diagnosis and 71 age- and sex-matched controls were asked to recall the most recent dreams and to complete the Aggression Questionnaire (AQ). Forty-one patients with RBD (61.6%; 26 men, 15 women; mean age: 67.5 ± 7.5 years) and 35 controls (49.2%; 20 men, 15 women; mean age: 66.1 ± 5.9 years) were able to remember their dreams and a total of 98 (RBD) and 69 (controls) dreams were collected in the two groups. Verbatim dream descriptions were scored and analyzed according to the Hall and Van De Castle method. Results: Patients with RBD showed a higher percentage of dream with at least one aggressive episode (DWA) than controls (63% vs 15%; p < 0.00001), a higher aggression/friendliness interaction ratio (86% vs 44%; p < 0.0001), and a greater frequency of animal characters (19% vs 4%; p = 0.0001). In contrast to controls, no patient with RBD had dreams with elements of sexuality (0% vs 9%; p < 0.0001). The two groups did not differ in total AQ scores, except for a lower score on the physical aggressiveness subscale in patients with RBD compared to control subjects (16.5 ± 5.4 vs 20.4 ± 8.3; p = 0.024). No correlation was observed between dream aggressiveness and age, duration, or frequency of RBD symptoms. Conclusions: Dreams in patients with REM sleep behavior disorder were characterized by an elevated proportion of aggressive contents, despite normal levels of daytime aggressiveness. Dreams with aggressiveness and the known excessive phasic muscle activity during REM sleep may be related to the hyperactivity of a common neuronal generator.

NEUROLOGY 2000;54:1010–1015
CONTENUTO DEI SOGNI IN RBD

- Compared to control subjects, RBD showed:
  - **Dreams with at least one aggression** (66% vs. 15%; p<0.00001)
  - Ratio **Aggression/Friendliness interactions** (89% vs. 44%; p<0.0001)
  - Frequency of **Animal characters** (19% vs. 4%; p=0.0001)
  - **No Dreams with at least one element of sexuality** (0% vs. 9%; p<0.0001)

- A trend toward:
  - % of **Dreamer as aggressor** (29% vs. 0%; h = 1.14; p=0.002)
  - % of **Negative emotions** (82% vs. 61%; h = 0.46; p=0.003)
  - % of **Familiar characters** (52% vs. 65%; h=-0.26; p=0.065).
Aggressive dream content without increased daytime aggressiveness

- No between-group difference in overall daytime aggressiveness
- Patients with RBD showed lower score on “Physical Aggression” than controls

<table>
<thead>
<tr>
<th></th>
<th>RBD patients</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AQ total score</td>
<td>69.9 ± 16.1</td>
<td>73.8 ± 20.3</td>
<td>0.37</td>
</tr>
<tr>
<td>Physical Aggression</td>
<td>16.5 ± 6.4</td>
<td>20.4 ± 8.3</td>
<td>0.034</td>
</tr>
<tr>
<td>Verbal Aggression</td>
<td>15.0 ± 4.2</td>
<td>14.4 ± 4.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Anger</td>
<td>17.9 ± 6.5</td>
<td>17.3 ± 6.0</td>
<td>0.67</td>
</tr>
<tr>
<td>Hostility</td>
<td>20.4 ± 5.4</td>
<td>21.6 ± 6.2</td>
<td>0.38</td>
</tr>
</tbody>
</table>
Novità sul contenuto onirico durante RBD

Varia fenomenologia (riso, gesticolazione più quieta)

Diagnosi differenziale tra RBD e disturbo da incubi
Alterato contenuto dei sogni: un altro marker di neurodegenerazione?

- Increased frequency of both aggression and animals is reported also in children dreams (Domhoff, 1996).

- Developmental decrease in phasic muscle REM sleep activity, from birth to late childhood as an expression of maturation of the brainstem motor inhibitory systems (Kohyama et al., 1990, 1996 and 1999; Tachibana, WASM 2005).

- Chronic RBD, as a manifestation of a widespread neurodegenerative process, might lead to an impairment of brainstem inhibitory systems and to a release of ontogenetically early dream patterns.

  Fantini et al. Neurology 2005;65:1010-1015
Updated clinicopathologic experience at Mayo Clinic from January 1990 to April 2009 of REM sleep behavior disorder associated with dementia and/or Parkinsonism

<table>
<thead>
<tr>
<th>Primary pathologic diagnoses</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewy body disease</td>
<td>36</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>5</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>1</td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>43</strong></td>
</tr>
</tbody>
</table>

Synucleinopathy pathology associated with RBD in this series: 41/43 = 95%
RBD and Parkinson’s disease


N=33 PD PATIENTS

At the clinical interview only 5 patients (15%) reported RBD symptoms

At the PSG evaluation:

- 11 patients (33.3%): both PSG and behavioral manifestations of RBD
- 8 patients (24.2%): loss of atonia without behavioral manifestation (REM sleep without atonia = RSWA)
- A total of 19 patients (58%) with PD, had REM sleep without atonia.

RBD in PD: uno specifico sottotipo di PD?

- **Specific motor features** (akinetiic-rigid form, symmetrical onset, axial symptoms, L-dopa-induced dyskinesia ecc.)

- **More severe non motor signs:**
  - Autonomic deficits *(Postuma 2009 and 2011)*
  - EEG impairment *(Gagnon 2003)*
  - Cognitive deficits *(Vendette 2007, Postuma 2012)*
  - Colour vision impairment *(Postuma 2005)*
  - Visuoperceptive dysfunctions *(Marques, 2010)*
  - Hallucinations (controversial)

- **Different outcome to STN-DBS**

PD_RBD sembra avere una più estesa degenerazione nel sistema nervoso centrale rispetto al PD senza RBD
TEMPORAL PATTERN (Kumru et al., 2007)

- All tremor-dominant patients developed RBD following motor parkinsonism

- All patients whose RBD preceded parkinsonism belonged to the group of non-tremor dominant type

- RBD preceded parkinsonism only when parkinsonism started after the age of 50 years
Disfunzioni autonomiche

- Invariabilmente associate ad RBD
  - Stesso livello di compromissione in iRBD e in PD-RBD

- Non riscontrate in PD senza RBD
  - Sistolic blood pressure drop
  - Cardiac variability (R-R and Spectral analysis)
  - Cardiac innervation (MIGB)
  - Urinary symptoms
Table 1: Features in idiopathic RBD, Parkinson’s disease with RBD, Parkinson’s disease without RBD and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=36), A</th>
<th>Idiopathic RBD (n=68), B</th>
<th>PD-RBD (n=34), C</th>
<th>PD-NRBD (n=21), D</th>
<th>P</th>
<th>Post-hoc significance (LSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>65.8 (46–87)</td>
<td>68.0 (44–93)</td>
<td>68.8 (49–94)</td>
<td>69.8 (49–83)</td>
<td>0.511</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>28/8 (77.8%)</td>
<td>53/15 (78%)</td>
<td>28/6 (82%)</td>
<td>13/8 (62%)</td>
<td>0.365</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Special senses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olfaction (% normal)</td>
<td>99.3±2.8</td>
<td>69.7±3.1</td>
<td>48.1±3.3</td>
<td>51.1±3.5</td>
<td>&lt;0.001</td>
<td>A&gt;B***, A&gt;C***, A&gt;D***, B&gt;C***, B&gt;D***, C&gt;D*</td>
</tr>
<tr>
<td>Colour vision (FM-100)</td>
<td>94.5±11.6</td>
<td>174.6±12.5</td>
<td>193.1±4.9</td>
<td>124.9±4.6</td>
<td>&lt;0.001</td>
<td>A&lt;B***, A&lt;C***, C&gt;D*</td>
</tr>
<tr>
<td><strong>Motor function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS II</td>
<td>0.35±0.13</td>
<td>2.1±0.28</td>
<td>10.1±1.4</td>
<td>11.3±0.98</td>
<td>&lt;0.001</td>
<td>A&lt;B*, A&lt;C***, A&lt;D***, B&lt;C***, B&gt;D***, C&gt;D***</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>2.70±0.50</td>
<td>5.8±0.64</td>
<td>23.7±2.1</td>
<td>20.5±2.5</td>
<td>&lt;0.001</td>
<td>A&gt;C***, A&lt;D***, B&gt;C***, B&gt;D***</td>
</tr>
<tr>
<td>Timed 'Up and Go'</td>
<td>6.1±0.19</td>
<td>7.1±0.24</td>
<td>8.6±0.61</td>
<td>7.8±0.46</td>
<td>&lt;0.001</td>
<td>A&gt;B*, A&lt;C***, A&lt;D*, B&gt;C***</td>
</tr>
<tr>
<td>Alternate tap test</td>
<td>195.0±5.3</td>
<td>172.4±4.4</td>
<td>141.4±5.3</td>
<td>155.2±6.4</td>
<td>&lt;0.001</td>
<td>A&gt;B***, A&gt;C***, A&gt;D***, B&gt;C***, B&gt;D***</td>
</tr>
<tr>
<td>Purdue Peg Board</td>
<td>12.1±0.42</td>
<td>10.6±0.27</td>
<td>8.1±0.41</td>
<td>9.4±0.60</td>
<td>&lt;0.001</td>
<td>A&gt;B***, A&lt;C***, A&gt;D***, B&gt;C*, B&gt;D***</td>
</tr>
<tr>
<td><strong>Autonomic function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure drop</td>
<td>3.7±2.4</td>
<td>15.2±2.1</td>
<td>23.7±2.1</td>
<td>4.4±3.0</td>
<td>&lt;0.001</td>
<td>A&lt;B**, A&lt;C***, B&lt;C**, B&gt;D*, C&gt;D***</td>
</tr>
<tr>
<td>Orthostatic symptoms</td>
<td>0.17±0.098</td>
<td>0.26±0.058</td>
<td>0.88±0.13</td>
<td>0.52±0.20</td>
<td>0.005</td>
<td>A&lt;C***, B&lt;C***, C&gt;D*</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>0.04±0.042</td>
<td>0.36±0.073</td>
<td>0.71±0.18</td>
<td>0.40±0.14</td>
<td>0.001</td>
<td>A&lt;C***, B&lt;C***, C&gt;D*</td>
</tr>
<tr>
<td>Erectile symptoms</td>
<td>0.40±0.19</td>
<td>1.60±0.20</td>
<td>2.1±0.25</td>
<td>2.2±0.45</td>
<td>&lt;0.001</td>
<td>A&gt;B*, A&lt;C***, A&lt;D***, B&gt;C*</td>
</tr>
<tr>
<td>Constipation symptoms</td>
<td>0.13±0.092</td>
<td>0.73±0.11</td>
<td>1.1±0.15</td>
<td>1.1±0.22</td>
<td>&lt;0.001</td>
<td>A&gt;B*, A&lt;C***, A&lt;D***, B&gt;C*</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>29.2±0.30</td>
<td>28.0±0.26</td>
<td>28.4±0.24</td>
<td>29.1±0.22</td>
<td>0.014</td>
<td>A&gt;B**, B&lt;D**</td>
</tr>
<tr>
<td><strong>Personality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPQ novelty</td>
<td>97.3±3.9</td>
<td>92.7±2.0</td>
<td>N/A</td>
<td>N/A</td>
<td>0.25</td>
<td>N/A</td>
</tr>
<tr>
<td>TPQ harm avoidance</td>
<td>85.2±4.1</td>
<td>95.2±2.8</td>
<td>N/A</td>
<td>N/A</td>
<td>0.043</td>
<td>N/A</td>
</tr>
<tr>
<td>TPQ reward dependence</td>
<td>98.6±3.4</td>
<td>95.3±2.0</td>
<td>N/A</td>
<td>N/A</td>
<td>0.47</td>
<td>N/A</td>
</tr>
<tr>
<td>TPQ persistence</td>
<td>117.9±4.7</td>
<td>120.4±2.6</td>
<td>N/A</td>
<td>N/A</td>
<td>0.61</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Results are presented as mean±standard error. N/A = not applicable; PD-RBD = Parkinson’s disease with RBD; PD-NRBD = Parkinson’s disease without RBD; TPQ = Tridimensional Personality Questionnaire. Bold values indicate statistically significant values. *P<0.05, **P<0.01, ***P<0.001.
Cardiac Autonomic Denervation in Parkinson’s Disease Is Linked to REM Sleep Behavior Disorder

Ronald B. Postuma, MD, MSc, Jacques Montplaisir, MD, PhD, Paola Lanfranchi, MD, MSc, Hélène Blais, BSc, Sylvie Rompré, Roberto Colomba, BEng, and Jean-François Gagnon, PhD

Cardiac variability:

- **R-R standard deviation**
  - PD-RBD: severely impaired
  - PD-noRBD = controls
Restoration of normal motor control in Parkinson's disease during REM sleep

Valérie Cochen De Cock,1,3,4 Marie Vidailhet,1,4 Smaranda Leu,1 Antonio Texeira,1 Emmanuelle Apartis,2,7 Alexis Elbaz,1,5 Emmanuel Roze,1 Jean Claude Willer,3,6 Jean Philippe Derenne,3 Yves Agid4 and Isabelle Arnulf3

However, not been studied. We interviewed one hundred consecutive non-demented patients with Parkinson's disease and their bed partners using a structured questionnaire assessing the presence of RBD. They rated the quality of movements, voice and facial expression during RBD as being better, equal or worse than in awake ON levodopa condition. Night-time sleep and movements were video-monitored during polysomnography in 51 patients to evaluate the presence of bradykinesia, tremor and hypophonia during REM sleep. Fifty-nine patients had clinical RBD with 53/59 bed partners able to evaluate them. All 53 (100%) reported an improvement of at least one component of motor control during RBD. By history, movements were improved in 87% patients (faster, 87%; stronger, 87%; smoother, 51%), speech was better in 77% patients (more intelligible, 77%; louder, 38%; better articulated, 57%) and facial expression was normalized in 47% patients. Thirty-eight per cent of bed partners reported that movements were 'much better', even in the most disabled patients. The video-monitored purposeful movements in REM sleep were also surprisingly fast, ample, coordinated and symmetrical, without obvious sign of parkinsonism. The movements were, however, jerky, violent and often repetitive. While all patients had asymmetrical parkinsonism when awake, most of the time they used the more disabled arm, hand and leg during the RBD (P = 0.04). Movements involved six times as often the upper limbs and the face as the lower limbs (OR: 5.9, P = 0.004). The percentage of time containing tremor EMG activity decreased with sleep stages from 34.9 ± 15.5% during wakefulness, to 3.6 ± 5.7% during non-REM sleep stages 1–2, 1.4 ± 3.0% during non-REM sleep stages 3–4, and 0.06 ± 0.2% during REM sleep (in this last case, it was subclinical tremor). The restored motor control during REM sleep suggests a transient 'levodopa-like' reestablishment of the basal ganglia loop. Alternatively, parkinsonism may disappear by REM sleep-related disjunction between pyramidal and extrapyramidal systems. We suggest the following model: the movements during the RBD would be generated by the motor cortex and would follow the pyramidal tract bypassing the extrapyramidal system. These movements would eventually be transmitted to lower motor neurons because of brainstem lesions interrupting the pontomedullary pathways which mediate the REM sleep atonia.
Toward a Redefinition of Parkinson’s Disease

Matthew B. Stern, MD,1* Anthony Lang, MD,2 and Wemer Poewe, MD3

PD: a 3-phase disease

<table>
<thead>
<tr>
<th>PHASE 1</th>
<th>PRECLINICAL PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD-specific pathology assumed to be present, supported by molecular or imaging markers, no clinical signs and symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHASE 2</th>
<th>PREMOTOR PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Presence of early non-motor signs and symptoms due to extranigral PD pathology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHASE 3</th>
<th>MOTOR PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD pathology involves substantia nigra leading to nigrostriatal dopamine deficiency sufficient to cause classic motor manifestations followed by later nonmotor features due to extension of the pathology</td>
</tr>
</tbody>
</table>

A multisystem synucleinopathy with pathology extending beyond the confines of the central nervous system and clinical manifestations extending beyond dopamine cell loss in the SNc.

Mov Dis, 2012
Prevalence of Sleep Disturbances in Mild Cognitive Impairment and Dementing Disorders: A Multicenter Italian Clinical Cross-Sectional Study on 431 Patients


*Center of Sleep Medicine, Villa Serena Hospital, Città S. Angelo, *Italian National Research Center (ITB-CNR), and *Neuroscience Department, S. Gerardo Hospital Monza, Bicocca University, Milan, *Neuroscience Department, University of Rome "Tor Vergata", Rome, *Institute of Neurology, University of Verona, *Department of Neurology, University of L'Aquila, *Neurology Department, University of Urbino, *Neurological Clinic, University of Cagliari, *Department of Neurology, University of Padua, *Neurology Department, University of Ferrara, *Department of Neurology, University of Naples, *Neurology Department, University of Messina, and *Neurology Department, University of Udine.
Table 3. Prevalence and risk of sleep disorders for MCI, VaD, FTD, LBD/PDD relative to AD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AD*</th>
<th>MCI</th>
<th>VaD</th>
<th>FTD</th>
<th>LBD/PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>110 (53.9)</td>
<td>81 (58.7)</td>
<td>32 (74.4)</td>
<td>17 (68.0)</td>
<td>16 (76.2)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.1; 0.6-2.0</td>
<td>2.5*; 1.1-5.7</td>
<td>1.3; 0.5-3.3</td>
<td>1.7; 0.6-5.2</td>
</tr>
<tr>
<td></td>
<td>98 (48.5)</td>
<td>60 (44.4)</td>
<td>28 (66.7)</td>
<td>12 (48.0)</td>
<td>14 (66.7)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.0; 0.5-1.7</td>
<td>2.4*; 1.1-5.2</td>
<td>0.9; 0.3-2.1</td>
<td>1.4; 0.4-4.1</td>
</tr>
<tr>
<td>RBD</td>
<td>43 (21.6)</td>
<td>26 (19.3)</td>
<td>11 (25.6)</td>
<td>6 (24.0)</td>
<td>10 (47.6)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.9; 0.5-2.7</td>
<td>1.2; 0.7-3.1</td>
<td>0.8; 0.3-2.4</td>
<td>2.6*; 1.0-7.1</td>
</tr>
<tr>
<td>RLS</td>
<td>13 (6.4)</td>
<td>9 (6.7)</td>
<td>2 (4.8)</td>
<td>2 (8.0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.2; 0.4-4.1</td>
<td>0.8; 0.2-3.7</td>
<td>1.0; 0.2-5.4</td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>89 (44.5)</td>
<td>68 (50.4)</td>
<td>25 (58.1)</td>
<td>16 (64.0)</td>
<td>15 (71.4)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.4; 0.8-2.4</td>
<td>1.5; 0.8-3.1</td>
<td>2.0; 0.8-5.0</td>
<td>2.8; 0.9-8.1</td>
</tr>
<tr>
<td>Any sleep disturbance</td>
<td>134 (65.7)</td>
<td>90 (65.2)</td>
<td>35 (81.4)</td>
<td>19 (76.0)</td>
<td>19 (90.0)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.0; 0.6-2.0</td>
<td>2.1; 0.9-5.3</td>
<td>1.2; 0.4-3.6</td>
<td>2.6; 0.5-12.3</td>
</tr>
</tbody>
</table>

Numbers in round parentheses are percentage with the disturbance within the diagnostic group. Numbers in squared parentheses are relative risks estimated as odds ratios and 95% CI. The estimates are adjusted for age, sex, MMSE and BDI-II score. MCI = Mild cognitive impairment; AD = Alzheimer's disease; VaD = vascular dementia; FTD = frontotemporal dementia; LBD = Lewy body dementia; PDD = Parkinson's disease dementia; SDB = sleep-disordered breathing; RBD = REM behavior disorder; RLS = restless legs syndrome; EDS = excessive daytime sleepiness; MMSE = Mini-Mental State Examination; BDI-II = Beck Depression Inventory-II. * Reference category.
RBD distingue DLB e PD demenza dalla VaD e dall’AD e sottolinea la necessità di ricercare altri disturbi del sonno particolarmente frequenti nella VaD (v. apnee morfeiche)

Guarnieri et al, 2012
Table 2. Associations among different sleep disturbances

<table>
<thead>
<tr>
<th></th>
<th>Insomnia</th>
<th>SDB</th>
<th>RBD</th>
<th>RLS</th>
<th>EDS</th>
<th>Isolated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>190 (89.6)</td>
<td>68 (32.1)</td>
<td>22 (10.4)</td>
<td>140 (66.4)</td>
<td>22 (10.4)</td>
<td>212</td>
<td></td>
</tr>
<tr>
<td>SDB</td>
<td>190 (74.5)</td>
<td>94 (36.9)</td>
<td>26 (10.2)</td>
<td>196 (76.9)</td>
<td>3 (1.2)</td>
<td>255</td>
<td></td>
</tr>
<tr>
<td>RBD</td>
<td>68 (32.1)</td>
<td>94 (21.8)</td>
<td>19 (19.8)</td>
<td>70 (72.8)</td>
<td>2 (2.1)</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>RLS</td>
<td>22 (84.6)</td>
<td>26 (100)</td>
<td>19 (73.1)</td>
<td>20 (76.9)</td>
<td>0</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>EDS</td>
<td>140 (74.5)</td>
<td>196 (92.0)</td>
<td>70 (32.9)</td>
<td>20 (9.4)</td>
<td>17 (8.0)</td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>212 (49.1)</td>
<td>255 (59.2)</td>
<td>96 (22.3)</td>
<td>26 (6.0)</td>
<td>44 (10.2)</td>
<td>431</td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses are row percentages. SDB = Sleep-disordered breathing; RBD = REM behavior disorder; RLS = restless legs syndrome; EDS = excessive daytime sleepiness.

Table 3. Prevalence and risk of sleep disorders for MCI, VaD, FTD, LBD/PDD relative to AD

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AD*</th>
<th>MCI</th>
<th>VaD</th>
<th>FTD</th>
<th>LBD/PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>98 (48.5)</td>
<td>60 (44.4)</td>
<td>28 (66.7)</td>
<td>12 (48.0)</td>
<td>14 (66.7)</td>
</tr>
</tbody>
</table>
La presenza di RBD nella malattia di Parkinson e nella demenza a corpi di Lewy va dal 38% all’ 83%

RBD spesso precede l’insorgenza dei parkinsonismi e della demenza di molti anni, fino a 20

Nelle diagnosi cliniche di AD ed RBD in altre malattie neurodegenerative, non sinucleinopatie, RBD insorge quasi contemporaneamente o dopo i deficit cognitivi e/o motori.
# SNC lesions associated to RBD

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Localisation</th>
<th>Auteurs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Left upper pons</td>
<td>Kimura et al. 2000</td>
</tr>
<tr>
<td>Lacunar ischemic</td>
<td>Right pontine tegmentum</td>
<td>Li et al, 2009</td>
</tr>
<tr>
<td>Demyelinating in R-R MS,</td>
<td>Pontine white matter</td>
<td>Plazzi et al., 2002</td>
</tr>
<tr>
<td>Neurinoma</td>
<td>Brainstem</td>
<td>Zambelis et al, 2002</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>Ponto-mesencephalic tegmentum</td>
<td>Provini et al., 2004</td>
</tr>
<tr>
<td>Demyelinating in MS</td>
<td>Dorsal pontine tegmentum</td>
<td>Tippmann et al., 2006</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Brainstem (pontine tegmentum?)</td>
<td>Limousin et al., 2009</td>
</tr>
<tr>
<td>Inflammatory (VGKC-Ab limbic encephalitis)</td>
<td>Amygdala (brainstem spared)</td>
<td>Iranzo et al, 2006</td>
</tr>
<tr>
<td>Inflammatory (acute aseptic LE)</td>
<td>Amygdala</td>
<td>Lin et al, 2009</td>
</tr>
<tr>
<td>Inflammatory (Guillain-Barré sdr.)</td>
<td>Hypothalamus ? (↓ level of hypocretin)</td>
<td>Cohen V, 2005</td>
</tr>
<tr>
<td>? (Narcolepsy)</td>
<td>Hypothalamus</td>
<td>Nightingale et al, 2001</td>
</tr>
<tr>
<td>Degenerative (Fatal Familiar Insomnia)</td>
<td>Anterior and dorsomedian Thalamus</td>
<td>Lugaresi et al, 2001</td>
</tr>
<tr>
<td>Post-surgery (after electrode implantation for STN-DBS)</td>
<td>Upper part of SN pars compacta ? (interruption of descending inputs)</td>
<td>Piette et al, 2007</td>
</tr>
</tbody>
</table>
Proposed Nuclei Involved in REM Sleep Control as Shown on Human Brainstem Templates

Published cases with RBD associated with brainstem lesions shown as approximate lesions on human brainstem templates
“Pseudo-RBD”

dream enactment during Sindrome delle apnee ostruttive in sonno (OSAS)
OSAS RBD: una diagnosi differenziale da considerare sempre sia nell’ RBD isdiopatico che nelle malattie neurodegenerative

RBD-OSAS con caduta

OSA-RBD

RBD in ventilazione

RLS-OSAS
The AASM Manual
for the Scoring of Sleep
and Associated Events

Rules, Terminology and Technical Specifications

CONRAD IBER, MD, SONIA ANCOLI-ISRAEL, PhD, ANDREW L. CHESSON JR., MD AND
STUART F. QUAN, MD FOR THE AMERICAN ACADEMY OF SLEEP MEDICINE

AMERICAN ACADEMY OF SLEEP MEDICINE, WESTCHESTER, IL
Visual rules for adults

1. TECHNICAL SPECIFICATIONS

A. Electroencephalogram (EEG)

1) The recommended derivations are:

[RACOMMENDED]

a. F₄-M₁
b. C₄-M₁
c. O₂-M₁

Backup electrodes should be placed at F₃, C₃,O₁ and M₂ to allow display of F₃-M₂, C₃-M₂ and O₁-M₂ if electrodes malfunction during the study.

B; EMG chin
3) EEG electrode position is determined by International 10-20 System

Note:
1. A minimum of 3 EEG derivations are required in order to sample activity from the frontal, central, and occipital regions.
2. $M_1$ and $M_2$ refer to the left and right mastoid processes.

B. Electrooculogram (EOG)

1) The recommended EOG derivations are:
   a. $E_1-M_2$ ($E_1$ is placed 1 cm below the left outer canthus)
   b. $E_2-M_2$ ($E_2$ is placed 1 cm above the right outer canthus)

2) Alternative acceptable derivations are:
   a. $E_1-F_{pz}$ ($E_1$ is placed 1 cm below and 1 cm lateral to the outer canthus of the left eye)
   b. $E_2-F_{pz}$ ($E_2$ is placed 1 cm below and 1 cm lateral to the outer canthus of the right eye)

Note: The alternative derivations record the direction of eye movements, i.e. vertical movements will show in-phase deflections, eye movements out-of-phase deflections.
L’IPNOGRAMMA
Rapid Eye Movements (REM) sleep

**Tonic phenomena**
- Desynchronized fast EEG activity
- Suppression of muscle tone = ATONIA (paradoxical)

**Phasic phenomena**
- Rapid Eye Movements (REMs)
- Muscle twitch (face, extremities)
- Erratic respiration and heart rate
REM sleep in four different patients, showing definitely normal EMG atonia (A), definitely increased EMG tone and hence definite REM sleep without atonia (B), and equivocally increased EMG tone (C and D).
REM SENZA ATONIA

1) sustained muscle activity in REM sleep with 50% of the epoch having increased chin EMG amplitude, and/or

2) excessive transient muscle activity, defined by the presence of 5 or more mini-epochs (a 30 second epoch is divided into 10 3-second mini-epochs) in an epoch having transient muscle activity lasting at least 0.5 seconds.

no minimum number of epochs showing abnormal muscle activity required for the RSWA designation – this was purposefully not stated as there is little good normative data

AASM 2007
 Mov Disord. 2013 Jun.

Analysis of video-polysomnographic sleep findings in dementia with Lewy bodies.


Video-PSG findings in 29 consecutive subjects diagnosed with DLB.

29 nondemented patients with Parkinson's disease (PD)

Complex mix of overlapping sleep alterations: impaired sleep structure, sleep comorbidities, and various motor-behavioral events (not restricted to RBD).

Clinicians should be aware of the possibility of misleading symptoms and of the risk of overlooking sleep comorbidities, and consider performing polysomnographic sleep investigations in selected cases.
Per l’espressività clinica di RBD:

- Perdita dell’inibizione muscolare in REM
- Aumento del drive motorio
REM sleep in cats

Fig. 1 Control of REM sleep based on studies in cat. See text for details. Excitatory projections represented by encircled plus sign, inhibitory projections represented by encircled minus sign, with the size of these symbols representing the relative effect of each projection on the synapsing nuclei. Normally populated nuclei are represented by coloured circles or ovals. EMG = electromyographic, REM = rapid eye movement. Adapted from Boeve et al. (2003b). Reprinted with permission from Human Press, Inc.
RBD model in cats

Fig. 2 Pathophysiology of REM sleep without atonia based on studies in cat. See text for details. Excitatory projections represented by incircled plus sign, inhibitory projections represented by encircled minus sign, with the size of these symbols representing the relative effect of each projection on the synapsing nuclei. Nuclei are represented by circles or ovals, with solid covered circles and ovals reflecting those with normal populations of neurons, and speckled circles and ovals reflecting those with significantly reduced populations of neurons. A cross sign reflects ablation of a nucleus. The relative tonic influences of each projection are represented by line thickness, with thicker lines depicting stronger influences, thinner lines depicting weaker influences and dashed lines depicting weak influences due to damaged neurons in the respective nuclei. Questionable or unproven effects of lesions represented by ‘?’. EMG = electromyographic, REM = rapid eye movement. Adapted from Boeve et al. (2003b). Reprinted with permission from Human Press, Inc.
Neurobiology of Disease

Impaired GABA and Glycine Transmission Triggers Cardinal Features of Rapid Eye Movement Sleep Behavior Disorder in Mice

Patricia L. Brooks¹ and John H. Peever¹,²
¹Systems Neurobiology Laboratory, Department of Cell and Systems Biology, and ²Department of Physiology, University of Toronto, Toronto, Ontario M5S 3G5, Canada

Rapid eye movement (REM) sleep behavior disorder (RBD) is a neurological disease characterized by loss of normal REM motor inhibition and subsequent dream enactment. RBD is clinically relevant because it predicts neurodegenerative disease onset (e.g., Parkinson’s disease) and is clinically problematic because it disrupts sleep and results in patient injuries and hospitalization. Even though the cause of RBD is unknown, multiple lines of evidence indicate that abnormal inhibitory transmission underlies the disorder. Here, we show that transgenic mice with deficient glycine and GABA transmission have a behavioral, motor, and sleep phenotype that recapitulates the cardinal features of RBD. Specifically, we show that mice with impaired glycine and GABA_\text{A}_ receptors exhibit REM motor behaviors, non-REM muscle twitches, sleep disruption, and EEG slowing—the defining disease features. Importantly, the RBD phenotype is rescued by drugs (e.g., clonazepam and melatonin) that are routinely used to treat human disease symptoms. Our findings are the first to identify a potential mechanism for RBD—we show that deficits in glycine- and GABA_\text{A}_-mediated inhibition trigger the full spectrum of RBD symptoms. We propose that these mice are a useful resource for investigating in vivo disease mechanisms and developing potential therapeutics for RBD.
RBD patophysiology in humans

(From: Boeve BF et al., Brain, 2007)
RBD pathophysiology in PD (according to Braak staging)

(From: Boeve BF et al., Brain, 2007)
Staging brain pathology in PD
(Braak et al, 2003)

- Lewy Body pathology progresses in a stereotyped fashion:
  - Stage 1: anterior olfactory and dorsal motor nucleus of IX/X n.
  - Stage 2: upper brainstem nuclei (PPN and LC) (RBD)
  - Stage 3: Substantia Nigra (motor PD)
  - Stage 4-5: Cerebral cortex. (DLB)
ALTERNANZANZA NonREM-REM
MODELLO DI INTERAZIONE RECIPROCA
(Mc Carley & Hobson, 1975)

REM-off
Locus Coeruleus
(Noradrenalina)
N Dorsale del Rafe
(Serotonina)

REM-on
Nuclei Peduncolopontino
(PPN) e Dorsolaterale
(DLT)
(Acetilcolina)

NA 5-HT

Ach

+ 

NA 5-HT

- 

Ach

+ 

Ach

-
The sleep-wake switch

“Flip-Flop”
Neuropathological analysis of brainstem cholinergic and catecholaminergic nuclei in relation to rapid eye movement (REM) sleep behaviour disorder

B. N. Dugger*, M. E. Murray*, B. F. Boeve‡, J. E. Parisi‡, E. E. Benarroch‡, T. J. Fermant† and D. W. Dickson*

Departments of *Pathology and Neuroscience, and ‡Psychology, Mayo Clinic, Jacksonville, FL, and †Department of Neurology, Mayo Clinic, Rochester, MN, USA

Locus coeruleus (LC), nucleo pedunculopontino (PPN)/ tegmento laterodorsale (LDT)
Neuropathological studies

Idiopathic RBD (2 cases)

1. **Incidental Lewy bodies disease** with severe neuronal loss and gliosis in the substantia nigra (SN) and coeruleus/subcoeruleus (LC) (*Uchiyama et al.*, 1995)

2. **Incidental Lewy body disease** (brainstem-predominant, dorsal motor nucleus and medullary tegmentum), but **no significant degeneration of SN, LC and raphe nuclei** (*Boeve BF*, 2007)

Degeneration of the monoaminergic SN and LC is really the primary cause of idiopathic RBD?
Neuropathological studies
Symptomatic RBD (a total of 17 cases)

- In 1 pt RBD-dementia (combined Lewy bodies + Alzheimer pathology): marked neuronal loss within the LC but higher density of cholinergic mesopontine neurons ➔ possible disinhibition of cholinergic neurons by reduced number of LC neurons leading to increased REM sleep drive and RBD? (Schenck et al, 1996-1997)

- In 1 pt RBD-PD: severe neuronal loss of subcoeruleus nucleus, with no changes in PPT/LDT nuclei (Arnulf et al., 2000)

- In 4 RBD-MSA patients, depletion of the cholinergic neurons in PPT/LDT (Benarroch and Schmeichel, 2002)

- In 11 pt with DLB-RBD: same degree of depletion in PPN-LDT as in patients DLB-non RBD (Dugger et al., 2012)

Alterations in PPN and LDT do not fully account for RBD pathogenesis
Neuropathological analysis of brainstem cholinergic and catecholaminergic nuclei in relation to rapid eye movement (REM) sleep behaviour disorder.

Dugger BN, Murray ME, Boeve BF, Parisi JE, Benarroch EE, Ferman TJ, Dickson DW.

- human brain banked tissues of
- 11 Lewy body disease (LBD) cases with RBD,
- 10 LBD without RBD,
- 19 Alzheimer's disease (AD)
- 10 neurologically normal controls.

Tissues were stained with choline acetyl transferase immunohistochemistry to label neurones of PPN/LDT and tyrosine hydroxylase for the LC. The burden of tau and α-synuclein pathology was measured in the same regions with immunohistochemistry.
Whether decreases in brainstem cholinergic neurones in LBD contribute to RBD is uncertain, but our findings indicate these neurones are highly vulnerable to α-synuclein pathology in LBD and tau pathology in AD. The mechanism of selective α-synuclein-mediated neuronal loss in these nuclei remains to be determined.
Figure 1. Cholinergic neuronal loss in PPN/LDT in LBD. (a) Choline acetyl transferase (ChAT) staining in the pedunculopontine/laterodorsal tegmental nucleus (PPN/LDT) of normal, Alzheimer's disease (AD), and Lewy body disease (LBD) cases without rapid eye movement sleep behaviour disorder (RBD) (LBD NRBD) and with RBD (LBD RBD). Photos taken at x 20. (b) Quantification of percentages of ChAT-positive neurones out of total neurones in the PPN/LDT. *LBD RBD contained significantly less ChAT-positive neurones than normals and AD.
Sulla genetica ancora non c'è niente di sostanziale, c'è un lavoro sulla aumentata storia familiare nei paz con RBD, ma questo lavoro ha dei limiti poiché il dato è ottenuto con la single question di Postuma (RBD1Q) di cui però non si conosce bene la sensibilità e specificità.

In ogni caso la familiarità nel complesso non è frequente: uno studio genetico è in corso a Montreal ma i risultati non sono noti.

Ipotizzata da alcuni trasmissione genetica possibile, a scarsa penetranza.
Family history of idiopathic REM behavior disorder: A multicenter case-control study.


- 316 PSG-confirmed iRBD
- 316 controls.

A positive family history of dream enactment was reported in 13.8% of iRBD cases compared to 4.8% of controls.

CONCLUSION:

increased odds of proxy-reported family history of presumed RBD among individuals with confirmed iRBD. This suggests the possibility of a genetic contribution to RBD.
NUOVE PROSPETTIVE DI INDAGINE
Ventricular orexin-A (hypocretin-1) levels correlate with rapid-eye-movement sleep without atonia in Parkinson's disease


The orexin-A (hypocretin-1) hypothalamic system plays a central role in controlling REM sleep. Loss of orexin neurons results in narcolepsy-cataplexy, a condition characterized by diurnal sleepiness and REM sleep without atonia.

high levels of orexin-A in Parkinson's disease may be associated with loss of REM muscle atonia.
Psychiatric symptoms and compulsive behaviors in RBD pazienti con RBD: maggiore compulsività
TABLE 4. Psychiatric manifestations and special sensory dysfunction

<table>
<thead>
<tr>
<th>Psychiatric manifestations</th>
<th>RBD (n = 21)</th>
<th>No RBD (n = 15)</th>
<th>Regression RBD main effect (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallucinations (awake), y:n</td>
<td>5:16 (24%)</td>
<td>2:13 (13%)</td>
<td>0.89 (1.08)</td>
<td>0.41</td>
</tr>
<tr>
<td>UPDRS Part I hallucinations (score = 1 not included)</td>
<td>0.71 (0.94)</td>
<td>0.37 (0.77)</td>
<td>0.40 (0.32)</td>
<td>0.23</td>
</tr>
<tr>
<td>UPDRS Part I, depression</td>
<td>0.71 (0.90)</td>
<td>0.53 (0.64)</td>
<td>0.36 (0.28)</td>
<td>0.22</td>
</tr>
<tr>
<td>UPDRS Part I, apathy</td>
<td>0.64 (0.96)</td>
<td>0.87 (1.13)</td>
<td>-0.12 (0.37)</td>
<td>0.76</td>
</tr>
<tr>
<td>Paranoia, y:n</td>
<td>3:18 (14%)</td>
<td>0:15 (0%)</td>
<td>—</td>
<td>0.25*</td>
</tr>
<tr>
<td>Increased gambling, y:n</td>
<td>2:19 (9.5%)</td>
<td>1:14 (6.7%)</td>
<td>0.46 (1.40)</td>
<td>0.74</td>
</tr>
<tr>
<td>Change in spending, y:n</td>
<td>2:19 (9.5%)</td>
<td>2:13 (13%)</td>
<td>0.66 (1.34)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypersexuality, y:n</td>
<td>0:21 (0%)</td>
<td>0:15 (0%)</td>
<td>—</td>
<td>1.0*</td>
</tr>
<tr>
<td>Punding, y:n</td>
<td>1:20 (4.8%)</td>
<td>0:15 (0%)</td>
<td>—</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special Senses</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfaction, UPSIT score/40</td>
<td>16.5 (4.7)</td>
<td>17.3 (5.8)</td>
<td>0.26 (1.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Color vision, “off” FM-100</td>
<td>187.6 (85.9)</td>
<td>142.0 (54.2)</td>
<td>44.4 (31.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Color vision, “on” FM-100</td>
<td>175.8 (66.6)</td>
<td>132.3 (47.8)</td>
<td>52.5 (22.5)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Data for continuous variables are presented as mean (SD).

*Indicates the P-value from an unadjusted analyses (Fischer exact test) due to lack of fit of the regression model.

RBD, REM sleep behavior disorder; UPSIT, University of Pennsylvania Smell Identification Test; FM, Farnsworth-Munsell; y:n, yes:no.
Tra l'altro, l'ultimissimo dato che abbiamo appena osservato è che i PD-RBD hanno un rischio almeno doppio di sviluppare un disturbo del controllo degli impulsi, rischio che diventa triplo per alcuni ICDs, dopo avere controllato per età, sesso, durata e severità del PD e soprattutto per dose levodopa equivalente.

Considerato che dei fattori di rischio per ICDs non si sa granché (a parte un'associazione con giovane età, esordio giovanile e lieve prevalenza di sesso maschile), è un dato credo interessante che può anche orientare il clinico nel trattamento soprattutto con i dopaminoagonisti.
TRATTAMENTO
The goals of therapy are to minimize the three cardinal features of the disorder – decrease the frequency and severity of the abnormal vocalizations (thereby reducing the embarrassing nature of screams and swearing with guests in the home, when traveling and sleeping in hotels, and when fishing/hunting/camping and sleeping in tents), decrease the frequency and severity of the abnormal behaviors (thereby reducing the risk of injury to the patient and bedpartner), and decrease the unpleasant dreams
trattamento FARMACOLOGICO

- Clonazepam (0.5-2 mg bedtime), ~90% of success (Schenck, 1990)
- Melatonina (3-12 mg at bedtime) (Kuntz 1999)
- Pramipexole (Fantini, 2003)
- Carbamazepine
- Donepezil (10-15 mg bedtime) (Simmonds 2000)
- Levodopa
- Quetiapina, Clozapina....
Five out of 8 patients: sustained reduction in frequency or intensity of sleep motor behaviors, confirmed by video-recording.

No change for % of phasic EMG activity during REM sleep.

Surprisingly, a decrease in the % of REM sleep muscle atonia was observed.

The treatment did not modify the indexes of periodic leg movements.
**Trattamento**

- **Agenti che riducono la frequenza e/o severità di RBD**
  - Clonazepam
  - Melatonina

- **Agenti che tendono a aumentare la frequenza e/o severità di RBD**
  - Antidepressivi tetraciclici (in particolare amitriptilina)
  - Cioccolato
  - Inibitori selettivi della riasorbizione della serotonina e norepinefrina (in particolare venlafaxina e mirtazapina)

- **Effetti controversi su RBD**
  - Anticolinergici (donepezil, rivastigmina)
  - Neurodopaminergici (Levodopa, pramipexole)
Nuove opzioni terapeutiche

- **Sodium Oxybate**: forme resistenti (3g prima del sonno notturno e 3g tre ore più tardi). Un paziente non rispondere a 4 mg clonazepam, 12 mg melatonina, 100mg quetiapina….ha risposto a Sodium Oxybate…..

- **Agomelatina** ????
# Effects of cholinergic drugs

<table>
<thead>
<tr>
<th>Anticholinesterase</th>
<th>Effect on RBD</th>
<th>Diagnosis</th>
<th>Type of study</th>
<th>PSG</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental comp.</td>
<td>Induced</td>
<td>AD (n=1)</td>
<td>Case report</td>
<td>No</td>
<td>Carlander, 1996 (Abstract).</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Reduced</td>
<td>Idiopathic RBD (n=3)</td>
<td>Case report</td>
<td>No</td>
<td>Ringman, 2000</td>
</tr>
<tr>
<td></td>
<td>Reduced</td>
<td>DLB (n=1)</td>
<td>Case report</td>
<td>No</td>
<td>Massironi, 2010</td>
</tr>
<tr>
<td></td>
<td>No change</td>
<td>DLB (n=9)</td>
<td>Case report</td>
<td>No</td>
<td>Boeve, 2003</td>
</tr>
<tr>
<td>Donepezil or Rivastigmine</td>
<td>Reduced</td>
<td>Idiopathic RBD (n=10)</td>
<td>Case report</td>
<td>No</td>
<td>Simmonds et al, 2009 (Abstract)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Induced after</td>
<td>DLB (n=1)</td>
<td>Case report</td>
<td>No</td>
<td>Yeh et al, 2010</td>
</tr>
<tr>
<td></td>
<td>increasing dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>from 1.5 to 3 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of STN-DBS in RBD

- 7 studies on sleep after STN-DBS
  - 4 with PGS measures
  - 4 with only subjective measures of Sleep (PSQI etc.)

- 3 studies RBD after STN-DBS (tot of 14 RBD?)
  - Arnulf 2000: no change
  - Iranzo 2000: no change
  - Cicolin 2004: no change
% of Phasic EMG during REM sleep

<table>
<thead>
<tr>
<th></th>
<th>Stim OFF</th>
<th>Stim ON</th>
<th>Δ Phasic EMG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 1</td>
<td>7</td>
<td>15</td>
<td>+ 8</td>
</tr>
<tr>
<td>Pt 2</td>
<td>18</td>
<td>23</td>
<td>+ 5</td>
</tr>
<tr>
<td>Pt 3</td>
<td>27</td>
<td>72</td>
<td>+ 45</td>
</tr>
<tr>
<td>Pt 4</td>
<td>66</td>
<td>100</td>
<td>+ 34</td>
</tr>
<tr>
<td>Pt 5</td>
<td>10</td>
<td>8</td>
<td>-2</td>
</tr>
<tr>
<td>Mean</td>
<td>25.6</td>
<td>43.6</td>
<td>+ 18</td>
</tr>
</tbody>
</table>

PLMS index (tot n/h of sleep)

<table>
<thead>
<tr>
<th></th>
<th>Stim OFF</th>
<th>Stim ON</th>
<th>Δ PLMS index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 1</td>
<td>2</td>
<td>33.2</td>
<td>+ 31.2</td>
</tr>
<tr>
<td>Pt 2</td>
<td>0</td>
<td>52.7</td>
<td>+ 52.7</td>
</tr>
<tr>
<td>Pt 3</td>
<td>5</td>
<td>12.2</td>
<td>+ 7.2</td>
</tr>
</tbody>
</table>

Study 1 (Arnulf et al. 2000)
RBD and STN-DBS
Study 2 (Iranzo et al. 2000)

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes of body position (n)</td>
<td>0.9 (1.3)</td>
<td>3.7 (3.6)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>405.8 (120.2)</td>
<td>447.1 (20.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>303.6 (64.0)</td>
<td>253.4 (115.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>68.6 (12.6)</td>
<td>62.5 (17.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Sleep onset latency (min)</td>
<td>44 (59)</td>
<td>21.4 (19.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>Longest continuous sleep period (min)</td>
<td>33.4 (15.5)</td>
<td>51.3 (33.5)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Wake time after sleep onset (min)</td>
<td>110.6 (54.6)</td>
<td>98.8 (78.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>Awakenings (n)</td>
<td>17.6 (12)</td>
<td>12.8 (10.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Arousal index</td>
<td>18.0 (11.3)</td>
<td>11.2 (12.4)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Stage I (%)</td>
<td>10.1 (10.2)</td>
<td>12.3 (11.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Stage II (%)</td>
<td>54.9 (16.8)</td>
<td>45.7 (18.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Stage III–IV (%)</td>
<td>15.5 (9.6)</td>
<td>22.2 (11.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>REM (%)</td>
<td>19.4 (9.8)</td>
<td>19.6 (12.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>Phasic REM submental density (%)</td>
<td>38 (63.6)</td>
<td>17.4 (15.6)</td>
<td>0.54</td>
</tr>
<tr>
<td>PLMS index</td>
<td>6.8 (9.7)</td>
<td>13.7 (16.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Spindles stage II (+)</td>
<td>35.2 (30.0)</td>
<td>31.1 (24.0)</td>
<td>0.23</td>
</tr>
<tr>
<td>Spindles stage III–IV (+)</td>
<td>16.0 (14.0)</td>
<td>22.2 (30.3)</td>
<td>0.62</td>
</tr>
<tr>
<td>Apnoea–hypopnoea index</td>
<td>4.2 (3.9)</td>
<td>4.8 (4.3)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Values are mean (SD).
*P<0.05.
PLMS, periodic limb movement during sleep; REM, rapid eye movements; (+), total number of spindles per 20 minutes.
In effetti, nel campo dell'RBD idiopatico le novità più grandi negli ultimi anni sono state nella definizione della patogenesi con il modello animale di RBD ottenuto con topi knockout per la trasmissione glicinergica e gabaergica che deriva anche dalla ridefinizione del meccanismo del sonno REM e il modello flip-flop e il dato di Iranzo e di Schenck sull'80% di conversione.

Per il resto in questi anni si sono accumulati molti dati sul fatto che, nell'ambito delle mal neurodegenerative, la presenza di RBD spesso si associa a un quadro neurodegenerativo più esteso e più severo, soprattutto nel PD.
Prospettive future

♦ Necessità di biomarkers precoci di neurodegenerazione

♦ RBD idiopatico, da solo o in associazione con altre anomalie elettrofisiologiche può essere un marker importante di neurodegenerazione ad uno stadio preclinico.

• Studi longitudinali per affermare il valore predittivo di questi markers

♦ Futuri trials farmacologici con terapie «disease-modifying » per pazienti con RBD idiopatico, ad alto rischio
Progression in the Parkinson’s Disease-Predominant Phenotype

Motor Functioning

- RBD

Mild parkinsonian signs (MPS)

Parkinson’s disease (PD)

PD with mild cognitive impairment (PD+MCI)

PD with dementia (PDD)

Brainstem, limbic +/- neocortical Lewy body disease

Age
Progression in the Dementia With Lewy Bodies-Predominant Phenotype

- RBD
- Mild cognitive impairment (MCI)
- Probable dementia with Lewy bodies (DLB)
- Obvious parkinsonism
- Brainstem, limbic +/- neocortical Lewy body disease

Age
Potential Effects of a Synucleinopathy-Active Therapy in Patients With Appropriately Identified “Idiopathic” RBD
DOPAMINERGIC SYSTEM and RBD

- Association with PD
- Decreased striatal innervation in I-RBD (Eisensher 2000, Albin 2000)
- Reduced size of putamen in I-RBD (Ellmore et al., 2010)

but

- Absence of RBD in pts. with pallidopontonigral degeneration (Boeve 2006)
- No correlation between EMG activities and DAT densities in idiopathic RBD
- Controversial effects of DA
2012- LBD con e senza RBD

- Confronto tra LBD, AD, soggetti di controllo
- Patologia: tau ed alfa sinucleina
- LC, PPN /LDT: vulnerabili ad alfa syn in LBD ed AD, ma perdita neuronale significativa solo in LBD
- Perché questa perdita neuronale alfa synucleino mediata in questi nuclei ????
LBD meno neuroni colinergici in PPN/LDT, ma non differenze con e senza RBD..eppure tali nuclei sono coinvolti nell’atonia REM …forse i LBD sono diversi…

Tale perdita neuronale, però, correlerebbe con andatura e controllo posturale..

Allora sono coinvolti altri nuclei nel determinismo dell’ RBD… oppure

DIVERSI NODI DI UNO STESSO NETWORK COINVOLTI INDIVERSI INDIVIDUI , GENERANDO LO STESSO FENOTIPO RBD
PLMS and sleep disorders

- Restless Legs syndrome +++
- Narcolepsy ++
- REM sleep behavior disorder (RBD) +++
- Insomnia +
- Hypersomnia +

Sleep Disorder with involvement of the DA system

<table>
<thead>
<tr>
<th></th>
<th>N of subjects</th>
<th>Age</th>
<th>Gender</th>
<th>PLMS index</th>
<th>PLMS index &gt; 5(\text{f})</th>
<th>PLMS index &gt; 10(\text{f})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>20</td>
<td>47.5 ± 8.2</td>
<td>10M;10F</td>
<td>6.9 ± 6.9</td>
<td>55%</td>
<td>20%</td>
</tr>
<tr>
<td>Insomniacs</td>
<td>20</td>
<td>47.7 ± 9.4</td>
<td>9M;11F</td>
<td>4.9 ± 7.4</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypersomniacs</td>
<td>20</td>
<td>47.8 ± 7.1</td>
<td>10M;10F</td>
<td>5.1 ± 7.3</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Narcoleptics</td>
<td>20</td>
<td>47.5 ± 9.2</td>
<td>10M;10F</td>
<td>18.6 ± 16.0</td>
<td>80%</td>
<td>65%</td>
</tr>
<tr>
<td>RLS patients</td>
<td>20</td>
<td>47.2 ± 8.0</td>
<td>10M;10F</td>
<td>34.1 ± 33.7</td>
<td>85%</td>
<td>80%</td>
</tr>
<tr>
<td>RBD patients</td>
<td>40</td>
<td>64.9 ± 1.0</td>
<td>10M ;5F</td>
<td>26.9 ± 26.7</td>
<td>80%</td>
<td>70%</td>
</tr>
</tbody>
</table>

\(\text{f}\)Percentage of subjects with a PLMS index > 5 and >10

Modified from: Montplaisir et al., Sleep Medicine 2000
Prevalence of PLMS in the general population increases with age (6% subjects aged 30 – 50 yrs, 30% after 50 yrs) (Hening, 1999, Coleman, 1983; Ancoli-Israeli 1985)

Prevalence in PD > MSA > controls (Coccagna, 1985; Plazzi 1997; Vetrugno 2004; Wetter 2002)

Frequently associated to RBD

Evidence of an involvement of the DA system (diencephalo-spinal DAergic system)

- Pharmacological (DA agonists=potent suppressors of PLM)
- Metabolic (Cohrs, 2004)
- Neuroimaging (↓ binding with striatal postsynaptic D2 receptor with SPECT or PET studies (Staedt, 1995; Turianski, 1999; Michaud 2002))
“Comparison between the polysomnography studies of those with AD compared to frontotemporal dementia showed greater REM sleep disruption in AD, again suggesting that sleep in frontotemporal dementia may be better preserved.”