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## Moderate RBD symptoms in narcoleptic versus IRBD mice.

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► **To cite this version:**

Maxime Grenot, Alexis Roman, Sébastien Arthaud, Paul-Antoine Libourel, Christelle Peyron. Moderate RBD symptoms in narcoleptic versus IRBD mice.. 17th World Sleep Congress, Oct 2023, Rio de Janeiro, Brazil. pp.S200. hal-04788236

**HAL Id: hal-04788236**

**<https://hal.science/hal-04788236v1>**

Submitted on 18 Nov 2024

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evaluate the agreement, variability, and bias between the NTX-IMU algorithms and ground truth, based on the ability to estimate periodic leg movement index (PLMI) for each hour and ability to screen for pathological PLMS based on the diagnostic cutoff PLMI > 15 for each night. This work was supported by NIH/NINDS R44NS117294.

**Results:** For estimating PLMI for each hour (n=158 hours), NTX-Acc was strongly correlated with ground truth ( $r = 0.903$ ), showed minimal bias (mean  $\pm$  SD =  $0.80 \pm 14.05$ ), and had high accuracy (94.9%), sensitivity (0.882), and specificity (0.957). For classifying the potential presence/absence of pathological PLMS for each night, NTX100-Acc correctly classified 90.7% of nights, with a sensitivity of 0.750 and specificity of 0.943. NTX-Gyro had similar results on all metrics.

**Conclusions:** NTX-IMU showed strong agreement with PSG-based ground truth for detecting PLMS frequency and screening for the potential presence of pathological PLMS. This suggests that the NTX100 TOMAC system – a therapeutic platform – might also offer the possibility for long-term in-home PLMS monitoring.

**Acknowledgements:** We thank Viktoriia Kolotovska, Jatin Tekchandani, Massimiliano de Zambotti, Philip Strauss, and the research team.

### MODERATE RBD SYMPTOMS IN NARCOLEPTIC VERSUS IRBD MICE

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**Introduction:** Narcolepsy type 1 (NT1) is a rare neurological sleep disorder caused by the specific loss of the wake-promoting orexin/hypocretin neurons of the lateral hypothalamus. REM sleep behavior disorder (RBD) is frequently reported in NT1 patients including at young age, in men and women. However, in contrast to the isolated form of RBD (iRBD), RBD symptoms in NT1 (NT1-RBD) are less severe and not associated with a-synucleinopathy. In order to provide evidence for the physiopathology of NT1-RBD, we evaluated whether the lack of orexin would disturb REM sleep muscle atonia in prepro-hypocretin knockout mice (orexin-KO) and if the severity of these RBD-symptoms would be similar to RBD-symptoms in a mouse model of iRBD.

**Materials and Methods:** We carried out a compared analysis of EMG signal during REM sleep of orexin-KO mice (n=8), a group of WT mice (n=8), and an iRBD mice group (n=8). The iRBD phenotype on mice was induced by the specific invalidation of glutamatergic transmission of the sublaterodorsal nucleus (SLD), generator of muscle atonia during REM sleep, with a bilateral injection of AAV virus in SLD in orexin-KO mice.

**Results:** We found a significant alteration of muscle atonia during REM sleep in NT1 mice, with a higher number of REM sleep episodes without atonia (2.05% (WT) vs. 14.29% (NT1),  $p=0.029$ ), and an increase in the amount of phasic movements per minute of REM sleep (0.096 (WT) vs. 0.818 (NT1),  $p=0.04$ ) compared to WT mice. However, compared to iRBD mice, these movements were fewer (0.818 (NT1) vs. 4.904 (iRBD),  $p=0.032$ ), shorter and less complex in NT1 mice (number of movements per minute of REM sleep (mvt/min) of 1-5 sec duration: 0.502 (NT1) vs. 2.816 (iRBD),  $p=0.032$ ; mvt/min longer than 5 sec: 0.041 (NT1) vs. 0.636 (iRBD),  $p=0.012$ ). Interestingly, in contrast to the iRBD group, we observed a large variability of alterations within the NT1 group.

**Conclusions:** Taken together, our results show that the lack of orexinergic transmission is sufficient to cause an alteration of REM sleep muscle atonia with the expression of abnormal movements in NT1 mice although with a lower density and a lower duration than observed in iRBD mice when glutamatergic neurotransmission is also altered. Our experimental results provide new evidence for the physiopathology of RBD in NT1.

**Acknowledgements:** MG received a doctoral fellowship from the French Ministry of Research. The work is supported by the ANR#22-C17- and the SFRMS.

### MODIFICATION AND VALIDATION OF A DIAGNOSTIC QUESTIONNAIRE FOR RESTLESS LEGS SYNDROME: MODIFIED- RESTLESS LEGS SYNDROME DIAGNOSTIC QUESTIONNAIRE (M-RLS-DQ)

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**Introduction:** Diagnosis of RLS using questionnaires is challenging as most of the questionnaires do not eliminate RLS mimics, thus lead to inclusion of false positive cases. This study was aimed at modification of RLS-Diagnostic Questionnaire and its validation.

**Materials and Methods:** Additional items including RLS mimics were identified, and were subjected to evaluation and content validation by experts. Based on their responses, content validity indices (item, scale average and scale universal agreement) were calculated. This was followed by translation of modified questionnaire in Hindi and validation in clinical population. Patients reporting RLS, somatic symptoms disorder, anxiety, other RLS mimics and osteoarthritis were requested to complete modified questionnaire and clinical diagnosis of RLS was ascertained. Additionally, a group of healthy controls was also included. Face, concurrent, and discriminant validities were calculated for the modified RLS diagnostic questionnaire.

**Results:** Among 209 subjects, nearly 40 subjects had clinical diagnosis of RLS, osteoarthritis, somatic-symptoms-disorder and anxiety disorder, each. In addition, 16 patients had other RLS mimics (akathisia, varicose veins, BFS, leg-cramps, chronic insomnia) and 30 were healthy controls. After three revisions, content validity indices achieved score of 1 for m-RLS-DQ. Sensitivity and specificity of m-RLS-DQ for the diagnosis of RLS were 94.9% and 94.1%, respectively. For the diagnosis of RLS, PPV was 78.7% and NPV was 98.7% with accuracy of 94.3%.

Concurrent validity with clinical diagnosis of RLS was 0.83 ( $P<0.001$ ). Discriminant validity with somatic symptoms disorder was -0.14 ( $P=0.03$ ) and with osteoarthritis was -0.24 ( $P<0.001$ ).

**Conclusions:** m-RLS-DQ is a valid instrument with acceptable psychometric properties which can be used for the screening as well as diagnosis of RLS in clinical practice and research studies.

### NEUROTRANSMITTER REGULATION AS COMMON PATHWAYS BETWEEN SLEEP PHENOTYPES, RESTLESS LEG SYNDROME AND TOURETTE SYNDROME

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**Introduction:** Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics. Sleep disorders, including restless leg syndrome (RLS), have been frequently reported among TS patients. Additionally, RLS has been associated with TS by studies that describe pathophysiological similarities among both. However, the convergent pathogenetic mechanisms between these comorbidities are largely unknown.

**Materials and Methods:** We aim to (1) test if there is a shared genetic architecture between TS and RLS (TS/RLS); (2) address the shared genetic architecture between TS and a broader list of sleep traits (TS/SLEEP); (3) determine molecular pathways enriched among these shared genes. We manually curated 3 sets of genes. The first list mainly encompassed discoveries driven by recent large-scale genome-wide association studies and included genes that code known circadian cycle regulators and genes associated to sleep phenotypes (e.g. insomnia, narcolepsy, sleep apnea, chronotype, sleep latency, sleep efficiency, sleep duration, and daytime sleepiness). The second list focused specifically on genes related to RLS and was a result of hits from linkage analysis, meta-analysis, mutational load analysis and transcriptome-wide association study. The third one was