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Original Article

Sleep-stage transitions during polysomnographic recordings as diagnostic features of type 1 narcolepsy

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ABSTRACT

Objective: Type 1 narcolepsy/hypocretin deficiency is characterized by excessive daytime sleepiness, sleep fragmentation, and cataplexy. Short rapid eye movement (REM) latency (≤15 min) during nocturnal polysomnography (PSG) or during naps of the multiple sleep latency test (MSLT) defines a sleep-onset REM sleep period (SOREMP), a diagnostic hallmark. We hypothesized that abnormal sleep transitions other than SOREMPs can be identified in type 1 narcolepsy.

Methods: Sleep-stage transitions (one to 10 epochs to one to five epochs of any other stage) and bout length features (one to 10 epochs) were extracted from PSGs. The first 15 min of sleep were excluded when a nocturnal SOREMP was recorded. $F_{0.1}$ measures and receiver operating characteristic curves were used to identify specific (≥98%) features. A data set of 136 patients and 510 sex- and age-matched controls was used for the training. A data set of 19 cases and 708 sleep-clinic patients was used for the validation.

Results: (1) ≥5 transitions from ≥5 epochs of stage N1 or W to ≥2 epochs of REM sleep, (2) ≥22 transitions from ≥3 epochs of stage N2 or N3 to ≥2 epochs of N1 or W, and (3) ≥16 bouts of ≥6 epochs of N1 or W were found to be highly specific (≥98%). Sensitivity ranged from 16% to 30%, and it did not vary substantially with and without medication or a nocturnal SOREMP. In patients taking antidepressants, nocturnal SOREMPs occurred much less frequently (16% vs. 36%, $p < 0.001$).

Conclusions: Increased sleep-stage transitions notably from ≥2.5 min of W/N1 into REM are specifically diagnostic for narcolepsy independent of a nocturnal SOREMP.

1. Introduction

Current diagnostic criteria for type 1 narcolepsy (NC) include daytime sleepiness, cataplexy or low hypocretin-1 in the cerebrospinal fluid (CSF), and a positive multiple sleep latency test (MSLT). Polysomnographic (PSG) features include an instability of the sleep–wake cycle together with daytime sleepiness, short sleep latency, fragmented nocturnal sleep, and abnormal rapid eye movement (REM) sleep with a shortened REM sleep latency during nocturnal sleep and daytime naps, and events of dissociated REM sleep [1–3]. The disease is caused by the loss of approximately 50–70,000 hypocretin-producing neurons in the hypothalamus, resulting in negligible levels of hypocretin-1, a wake-promoting peptide, in the CSF [4–8]. The lack of hypocretin is causative to the disorder as animals mutated for hypocretin receptors or lacking the hypocretin ligand have narcolepsy [9,10]. Although this is not fully established, the cause of the hypocretin cell loss in humans is almost certainly of autoimmune origin. Indeed, the disease is strongly associated with human leukocyte antigen (HLA) DQB1*06:02 and other immune polymorphisms, and its onset is often triggered by upper airway infections such as influenza [11].

Historically, rapid transitions from sleep onset into REM sleep (so-called sleep-onset REM periods or SOREMPs, defined as REM sleep latency of ≤15 or 20 min) were first observed during nocturnal

Abbreviations: CSF, cerebrospinal fluid; FN, false negatives; FP, false positives; HLA, Human leukocyte antigen; ICSD, International Classification of Sleep Disorders; IH, idiopathic hypersomnia without long sleep time; MSL, mean sleep latency; MSLT, Multiple sleep latency test; NC, narcolepsy type 1; PSG, polysomnography; REM, rapid eye movement; ROC, receiver operating characteristic; SOREMP, sleep-onset REM period; TN, true negatives; TP, true positives.

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sleep in the 1960s [12,13]. Because of low sensitivity, however (~40–50%), it could not be used diagnostically, and the MSLT, a test where four to five daytime naps are administered, was used to give more SOREMP opportunities. The MSLT gained widespread acceptance as a diagnostic test, and it was shown to be ~95% specific and ~95% sensitive for type 1 narcolepsy when a mean sleep latency (MSL) of ≤8 min and ≥2 SOREMPs (REM latency ≤15 min) were observed during daytime naps, a criteria used in the International Classification of Sleep Disorder Second Edition (ICSD-2) [14]. More recently, because a nocturnal SOREMP was found to be highly specific (~99%) for narcolepsy [2,15] and a PSG is required before the MSLT to exclude sleep deprivation or other sleep disorders, nocturnal SOREMPs have been added back as a diagnostic criteria in the new International Classification of Sleep Disorders Third Edition, the ICSD-3 [16].

Considering the above, the diagnosis of type 1 narcolepsy is currently based on documenting two or more of the following: Clinical observation of cataplexy, low CSF hypocretin-1, or/and a diagnostic PSG-MSLT. A PSG-MSLT is considered to be diagnostic for narcolepsy when MSL is ≤8 min during the four to five daytime naps of the MSLT, and a REM sleep latency of ≤15 min is observed at least twice when falling asleep at night and during MSLT naps [16]. The PSG-MSLT must be performed in a sleep laboratory, most notably because a valid MSLT mandates that the subject does not sleep between daytime naps. In addition, the patient must have been shown to have regular, sufficient sleep during nighttime hours before testing (shift workers are particularly at risk of false positives) [17], and the patient has to have been free of any stimulant or antidepressant treatment for at least a week. Although the sensitivity and specificity of this revised ICSD-3 PSG-MSLT criteria have not been formally analyzed, they are likely to remain similar to those of the ICSD-2 MSLT alone. In a recent analysis of several thousand patients with type 1 narcolepsy, only three of over 1000 subjects had a SOREMP at night and only one SOREMP during the MSLT [18]. As specificity for a SOREMP alone is extremely high (99%), the overall specificity of the revised criteria is also unlikely to change significantly.

In continuation of the study by Andlauer et al. [2], this work aims at identifying sleep transition features in nocturnal sleep that could be an indicative of type 1 narcolepsy, with the ultimate goal of using nocturnal PSG alone to diagnose narcolepsy. Prior studies have shown abnormal sleep–wake transitions during nocturnal sleep in narcoleptics [1,19–23]. Specifically, Liu et al. [23] investigated the diagnostic value of transitions to REM sleep in nocturnal PSGs as well as in MSLT for narcolepsy types 1 and 2. This study not only investigates transitions to REM sleep but also performs an extensive search in various sleep transitions between all sleep stages and thresholds on the total number hereof to identify specific features, which can identify narcolepsy in a clinical setting. This study postulates that by extracting such features from the hypnogram of a nocturnal PSG and by combining those with the SOREMP feature, the sensitivity of identifying narcolepsy can be raised while maintaining the high specificity.

2. Materials and methods

2.1. Subjects and recordings

Two data sets were used in this study; a training data set that was used to identify potential diagnostic features, and a validation data set that was used to confirm findings in a clinical setting. Because our goal was to identify highly specific indices, the two data sets were oversampled in non-narcolepsy subjects. Patients who were diagnosed with type 1 narcolepsy met ICSD-3 criteria (narcolepsy with cataplexy/hypocretin-deficient narcolepsy) [16]. All had clear cataplexy, and they were HLA-DQB1*06:02 positive. In cases where CSF hypocretin had been measured, levels were below 110 pg/ml, consistent with hypocretin deficiency. All cases had a positive MSLT, defined as MSL of ≤8 min and ≥2 SOREMPs during naps or at nighttime sleep onset.

The training data set included 136 narcolepsy type 1 patients diagnosed at the Stanford Sleep Clinic as well as PSGs from two sodium oxybate drug trials (baseline sleep studies, SXB15 with 45 sites in Canada, USA, and Switzerland, and SXB22 with 44 sites in Canada, Europe, and the USA) conducted by Orphan Medical, now named Jazz Pharmaceuticals [24,25]. In SXB15, patients were allowed to be on a stable dose of stimulant [24], whereas in SXB22, both modafinil and anticataplectic antidepressants were allowed at stable doses [25]. In the combined drug trial baseline sample used in this study, which only included patients with clear cataplexy, 39% took antidepressants, whereas 79% took centrally acting stimulants. The training data set also included 510 sex- and age-matched control subjects obtained from the Wisconsin sleep cohort [26]. Samples were matched for age and sex using the nearest-neighbor-matching function from the MatchIt package for R, with a control/case ratio of 4, and a number of standard deviations of the distance measure within which to draw control units (caliper) set at 0.25 [27]. Thirty controls (5.8%) were working rotating or graveyard shifts. As for patients, controls were allowed to take usual medications such as over-the-counter antihistamine and pain-relieving medication. Antidepressants such as serotonin-specific reuptake inhibitors were taken by approximately 22%, whereas stimulants, mostly methylphenidate, were used in <2% of the control subjects. Although we noted that the use of therapy was different in cases versus controls, this was considered acceptable as doses were stable, and we also separately explored the effects of these medications on our results. The validation data set consisted of 727 patients evaluated at the Stanford Sleep Clinic. Nineteen were diagnosed with type 1 narcolepsy (untreated when tested), and the rest were non-narcolepsy patients, most notably patients with sleep apnea. This sample has been described elsewhere [2,28]. All evaluations included a comprehensive medical and medication history, nocturnal PSG, and, for narcolepsy cases, a PSG-MSLT. Demographic and PSG data for the two data sets are summarized in Table 1.

2.2. Extraction and definition of features under study

Features evaluated in this study were all extracted from manually scored hypnograms, as would be in a typical clinical sleep study. In older recordings, stage S4 was combined with S3, and it was defined as N3, according to the most recent scoring rules. Transitions between stages were computed and classified into eight feature groups: (1) transitions to REM sleep, (2) transitions to N3 sleep, (3) transitions to N2 sleep, (4) transitions to N1 sleep, (5) transitions to wakefulness, (6) transitions to N1 or wakefulness, (7) transitions to N2 or N3, and (8) number of sleep and wake bouts. Figure 1 illustrates the transition feature groups 1–7, where the total number of any of the specified transitions was counted for each subject. For feature group 1, for instance, the number of transitions from at least one to 10 epochs of any stage (N3, N2, N1, W, N2/N3, N1/W) to at least one to five epochs of REM sleep was computed, yielding 300 subfeatures; the first feature in this group is thus the total number of transitions from at least one epoch of N3 to at least one epoch of REM sleep; the next feature is the total number of at least two epochs of N3 to at least one epoch of REM sleep, and so forth. We wanted to do an exclusive search, and the maximum number of 10 epochs before and five epochs after the transition was chosen as none of the final features selected had numbers higher than these, and hence we had reached the boundary. For feature group 8, the total number of bouts of at least two to 10 epochs of N1 or

Table 1
Demographic and PSG data for the two data sets.

	Training data set			Validation data set			All data		
	Con	NC	*P*	Non-NC	NC	*P*	Non-NC	NC	*P*
No of subjects	510	136		708	19		1218	155	
Fraction of men	0.52	0.44	0.10	0.59	0.53	0.60	0.56	0.45	9.6×10^{-3}
Age (years, $\mu \pm \sigma$)	54.52 ± 8.03	53.36 ± 11.15	0.26	45.85 ± 13.86	28.12 ± 22.05	2.6×10^{-3}	49.48 ± 12.53	50.27 ± 15.32	0.54
BMI (kg/m^2, $\mu \pm \sigma$)	31.83 ± 7.49	29.29 ± 5.53	3.10×10^{-5}	27.15 ± 6.74	27.28 ± 5.33	0.95	29.14 ± 7.44	29.18 ± 5.52	0.93
Sleep efficiency (%, $\mu \pm \sigma$)	84.56 ± 10.45	75.86 ± 14.02	1.96×10^{-10}	82.58 ± 11.52	85.91 ± 11.16	0.21	83.41 ± 11.13	77.01 ± 14.06	2.26×10^{-7}
Fraction on antidepressants	0.22	0.39	5.30×10^{-5}	0.23	0.16	0.47	0.23	0.32	0.01
Fraction on stimulants	0.02	0.79	1.17×10^{-94}	0.08	0.37	1.20×10^{-5}	0.05	0.74	4.26×10^{-130}
REML (min, $\mu \pm \sigma$)	123.67 ± 74.34	118.56 ± 115.41	0.63	143.18 ± 84.86	85.50 ± 119.71	0.05	135.05 ± 81.18	114.45 ± 116.06	0.03
TST (hours, $\mu \pm \sigma$)	7.39 ± 0.82	8.02 ± 1.16	1.27×10^{-8}	7.40 ± 0.98	8.96 ± 0.91	5.10×10^{-7}	7.39 ± 0.91	8.14 ± 1.17	1.42×10^{-12}
W (%, $\mu \pm \sigma$)	15.44 ± 10.45	24.14 ± 14.02	1.96×10^{-10}	17.42 ± 11.52	14.09 ± 11.16	0.21	16.59 ± 11.13	22.91 ± 14.06	2.26×10^{-7}
REM (%, $\mu \pm \sigma$)	14.30 ± 5.81	12.31 ± 7.49	4.4×10^{-3}	13.71 ± 6.18	17.92 ± 6.99	0.02	13.96 ± 6.03	13.00 ± 7.63	0.13
N1 (%, $\mu \pm \sigma$)	8.20 ± 4.67	16.54 ± 8.45	2.01×10^{-21}	9.22 ± 7.10	7.09 ± 7.56	0.24	8.89 ± 6.22	15.38 ± 8.89	5.20×10^{-16}
N2 (%, $\mu \pm \sigma$)	58.22 ± 9.76	42.41 ± 12.35	3.40×10^{-30}	52.20 ± 12.09	44.63 ± 11.07	8.5×10^{-3}	54.72 ± 11.56	42.68 ± 12.19	4.9×10^{-24}
N3 (%, $\mu \pm \sigma$)	3.84 ± 5.26	4.60 ± 5.73	0.16	7.45 ± 7.74	16.28 ± 13.20	9.4×10^{-3}	5.94 ± 7.04	6.03 ± 7.99	0.89

Between-group comparisons for age, BMI, sleep efficiency, REML, TST, and distribution of sleep stages were performed using two-sampled *t*-tests with unknown or unequal variance. Between-group comparisons for fraction of men and fraction of medication (antidepressants and stimulants) were performed using χ^2 tests.
Abbreviations: BMI: body mass index; REML: REM sleep latency; TST: Total sleep time; NC: Patients with type 1 narcolepsy–cataplexy.

wakefulness, N2 or N3, and REM sleep was computed, yielding 27 features. We selected a minimum bout length of two epochs to exclude very short bouts and a maximum length of 10 epochs as none of the final features selected had a bout length of >10 epochs. Adding 300 features from group 1, 200 features/group in groups 2–5, 100 features/group in groups 6 and 7, and the 27 features in group 8, a grand total of 1327 features were tested, many of which were intercorrelated.

2.3. Selection of the most indicative features of each group

Using the training data set, we identified the most specific indices per group by computing an F_β-score for various thresholds for each of the features. Letting true positives (TP) be the number of correctly identified NC patients, true negatives (TN) be the number of correctly identified control subjects, false positives (FP) be the number of control subjects identified as NC patients, and false

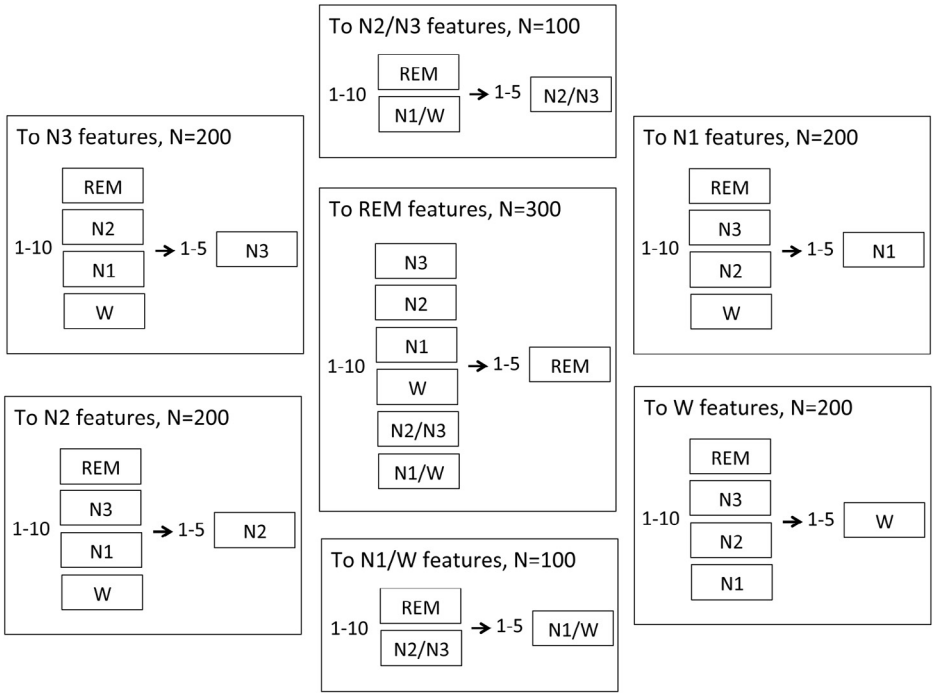

Fig. 1. Illustration of the transition feature groups. A total of eight feature groups were computed whereof seven of them hold the transition feature groups "To REM sleep," "To N3 sleep," "To N2 sleep," "To N1 sleep," "To wakefulness," "To N2/N3 sleep," and "To W/N1 sleep." Every transition from one to 10 epochs before the transition to one to five epochs after the transition was identified and summed. The first feature in the "To N3 sleep" feature group thus holds the total number of transitions defined as one epoch of REM sleep to one epoch of N3 sleep; the second feature holds the total number of transitions defined as two epochs of REM sleep to one epoch of N3 sleep, etc.

negatives (FN) be the number of NC patients identified as control subjects,the precision (P), also called positive-predictive value (PPV), and recall (R), also called sensitivity, can be computed as follows:

$$P = \frac{TP}{TP+FP} \text{ and } = \frac{TP}{TP+FN}, \text{respectively.}$$

F_β-score is then computed as

$$F_\beta = (1+\beta^2)\frac{P \cdot R}{(\beta^2 \cdot P)+R}$$

where β defines the relative importance of precision and recall in the calculation. When $\beta = 1$ the F_1-score obtained is the symmetric mean between recall and precision. As we wanted to find the most specific features, we aimed at attaching a higher relative importance to precision when compared with recall, therefore defining $\beta = 0.1$, which attach 10 times as much importance to precision than recall (sensitivity). This value was decided as it identified specific features that were still expressed in many patients.

For each group of features, the 20 most specific indices were first identified based on their maximum $F_{0.1}$-score when thresholding the feature values. In order to identify features for which most subjects had a value (ie, express the transition in question, value different from zero or absent), five of these 20 features with the least number of subjects having a feature value of zero were identified. In total, this yielded five features for each feature group, giving a total of 35 subfeatures. Lastly, as this study focused on identifying highly specific features (≥98%) at the expense of sensitivity, a threshold yielding a specificity of at least 98% on the training data set was identified for each feature. Receiver operating characteristic (ROC) curves for the features were obtained for both data sets, with performance measures computed for the thresholds found using the training data set.

2.4. Influence of medication and presence of a nocturnal SOREMP

To investigate whether medication influenced diagnostic predictability for the features discovered in this study, a sub-analysis was performed where we combined the two data sets and divided subjects into (1) those taking antidepressant versus not, (2) those taking stimulant versus not, and (3) those taking antidepressants and/or stimulants versus neither. We then first looked at sensitivity and specificity in each of the data subgroups. In addition, we used logistic regression to examine how these features were influenced by antidepressants or stimulant therapy. In this last analysis, odds ratios (OR) with 95% confidence intervals were computed to contrast the value of each diagnostic feature in the presence of specific treatments.

To investigate how well the features found will identify narcolepsy patients not expressing a nocturnal SOREMP, we computed sensitivity and specificity for patients expressing one of the new features or a nocturnal SOREMP. Finally, logistic regression was used to examine how the new indices were influences by a nocturnal SOREMP.

All computations, linear regression model, and statistics were carried out in Matlab (R2013b, MathWorks, Inc., Natick, MA, USA). Two-sided *t*-tests assuming unequal or unknown variance were performed for between-group comparisons on demographic data (Table 1). χ^2 tests were used to compare fractional measures (fraction of men and fraction of medication use).

3. Results

3.1. Selection of three useful diagnostic features

Using ROC curves and using the ≥98% specificity training data set threshold criteria, three of the 35 indices were chosen as the

Table 2
Performance measures of final features, when counts are for the entire night.

Data set	No. of subjects [NC/Con]	SOREMP ≤ 15	5N1W- > 2R ≥ 5	3N2N3- > 2N1W ≥ 22	N1Wbouts ≥ 6 epochs ≥ 16
All	155/1218	Sens: 29.7% Spec: 99.5% PPV: 88.5%	Sens: 16.8% Spec: 98.9% PPV: 65.0%	Sens: 16.1% Spec: 96.6% PPV: 37.9%	Sens: 29.0% Spec: 96.8% PPV: 53.6%
Training data set	136/510	Sens: 28.7% Spec: 99.6% PPV: 95.1%	Sens: 16.9% Spec: 99.8% PPV: 95.8%	Sens: 16.9% Spec: 99.0% PPV: 82.1%	Sens: 30.2% Spec: 99.0% PPV: 89.1%
Validation data set	19/708	Sens: 36.8% Spec: 99.4% PPV: 63.6%	Sens: 15.8% Spec: 98.2% PPV: 18.8%	Sens: 10.5% Spec: 94.9% PPV: 5.3%	Sens: 21.1% Spec: 95.2% PPV: 10.5%
Subjects taking antidepressants	49/279	Sens: 16.3% Spec: 99.3% PPV: 80.0%	Sens: 14.3% Spec: 98.6% PPV: 63.6%	Sens: 24.5% Spec: 95.3% PPV: 48.0%	Sens: 44.9% Spec: 96.8% PPV: 71.0%
Subjects not taking antidepressants	106/939	Sens: 35.9% Spec: 99.6% PPV: 90.4%	Sens: 17.9% Spec: 98.9% PPV: 65.5%	Sens: 12.3% Spec: 97.0% PPV: 31.7%	Sens: 21.7% Spec: 96.8% PPV: 43.4%
Subjects taking stimulants	115/66	Sens: 27.8% Spec: 97.0% PPV: 94.1%	Sens: 13.9% Spec: 100% PPV: 100.0%	Sens: 16.5% Spec: 92.4% PPV: 79.2%	Sens: 31.3% Spec: 95.5% PPV: 92.3%
Subjects not taking stimulants	40/1152	Sens: 35.0% Spec: 99.7% PPV: 77.8%	Sens: 25.0% Spec: 98.8% PPV: 41.7%	Sens: 15.0% Spec: 96.9% PPV: 14.3%	Sens: 22.5% Spec: 96.9% PPV: 20.0%
Subjects taking antidepressants or stimulants	120/306	Sens: 26.7% Spec: 99.0% PPV: 91.4%	Sens: 14.2% Spec: 98.7% PPV: 81.0%	Sens: 16.7% Spec: 95.1% PPV: 57.1%	Sens: 30.8% Spec: 96.4% PPV: 77.1%
Subjects not taking antidepressants or stimulants	35/912	Sens: 40.0% Spec: 99.7% PPV: 82.4%	Sens: 25.7% Spec: 98.9% PPV: 47.4%	Sens: 14.3% Spec: 97.2% PPV: 16.1%	Sens: 22.9% Spec: 96.9% PPV: 22.2%

5N1W- > 2R ≥ 5 indicate five or more transitions from at least five epochs of either N1 or W to at least two epochs of REM sleep. 3N2N3- > 2N1W ≥ 22 indicate 22 or more transitions from at least three epochs of either N2 or N3 to at least two epochs of either N1 or W. Lastly, N1Wbout ≥ 6 epochs ≥ 16 indicate 16 or more bouts of at least six epochs of either N1 or W.

Abbreviations: Sens: sensitivity; spec: Specificity; PPV: Positive Predictive Value; NC: Patients with type 1 narcolepsy–cataplexy; Con: Subjects without narcolepsy; SOREMP: Nocturnal Sleep Onset to REM sleep Period (REML ≤ 15 min).

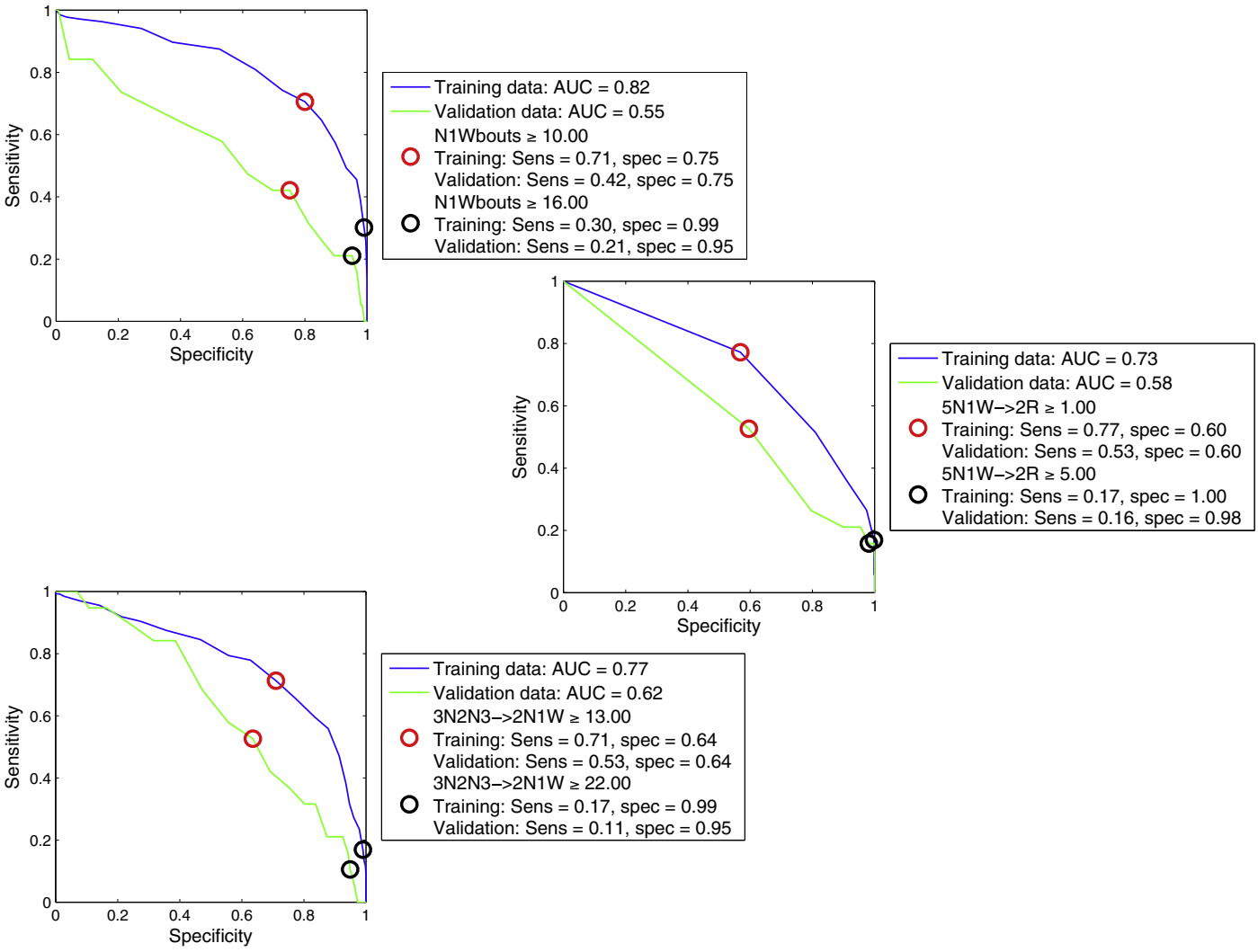

Fig. 2. ROC curves for the final chosen features, where the sleep-stage transition counts are for the entire night. The red dots indicate the performance measures where sensitivity and specificity are equally rated, and the black dots indicate the chosen thresholds for which the specificity measure yielded a minimum of 98% on the training data set. The blue curves represent the training data set and the green curves represent the validation data set.

final features (Table 2 and Fig. 2): (1) ≥5 transitions of ≥5 epochs of N1 or wake to ≥2 epochs of REM sleep. This feature gave a specificity of 100% and a sensitivity of 17% in the training data set, and a specificity of 98% and a sensitivity of 16% in the validation data set. (2) Transitions of ≥22 of ≥3 epochs of N2 or N3 to ≥2 epochs of either N1 or wake. This yielded a specificity of 99% and a sensitivity of 17% in the training data set, and a specificity of 95% and a sensitivity of 11% in the validation data set. (3) Bouts of ≥16 of ≥6 epochs of either N1 or W. This was found to give a specificity of 99% and a sensitivity of 30% in the training data set, and a specificity of 95% and a sensitivity of 21% in the validation data set. ROC curves for these three features are plotted in Fig. 2, and performance values are given for the optimal point rating sensitivity and specificity equally as well as for the point yielding a specificity of minimum 98% on the training data set. The same features were finally normalized by total sleep time (TST) amounts, and results were found to be similar (data not shown).

3.2. Influence of distribution across the night

As it is well known that the occurrence of REM sleep is strongly influenced by circadian timing, with higher amounts and shorter REM latency around the minimum of body temperature in the early morning hours, we investigated whether the nightly distribution of the three features had an influence on performance. To do so, features were computed for the first half of the night only and in the entire night minus the last 2 h (Supplementary Table S1). As for the total number of events, the optimal threshold of these revised features was optimized to yield a specificity of at least 98% on the training data set. ROC curves for these modified features are illustrated in Supplementary Figs. S1 and S2, respectively.

3.3. Influence of medication and relation to nocturnal SOREMPs

Table 2 and Supplementary Tables S1 and S2 reports on sensitivity, specificity, and positive PPV measures in the subgroups specified in the "Method" section with statistical analysis of the effects of therapy. As expected, nocturnal SOREMPs and the three new features reported here were highly significantly different between cases and controls (Supplementary Table S2). Strong interactions between narcolepsy status and treatment effects were also observed on most diagnostic features (Supplementary Table S2); thus, analyses were stratified by narcolepsy status. Stratified analysis

Table 3
P-values and odds ratios (OR) obtained following linear regression modeling.

Outcome	Age	Sex	*P*-value for SOREMP	*P*-value for antidep	*P*-value for stimulant	*P*-value for SOREMP*Antidep	*P*-value for Stimuli*SOREMP
SOREMP	OR = 0.99 (0.97–1.02) $p = 0.60$	OR = 1.06 (0.52–2.16) $p = 0.88$		OR = 0.37 (0.15–0.87) $p = 0.02$			
5N1W- > 2R ≥ 5	OR = 1.01 (0.98–1.05) $p = 0.37$	OR = 2.88 (1.15–7.20) $p = 0.02$	OR = 3.71 (1.51–9.09) $p = 4.12 \times 10^{-3}$				
3N2N3- > 2N1W ≥ 22	OR = 0.98 (0.95–1.01) $p = 0.27$	OR = 0.80 (0.32–1.98) $p = 0.63$	OR = 0.12 (0.01–0.96) $p = 4.56 \times 10^{-2}$	OR = 1.41 (0.52–3.80) $p = 0.49$		OR = 19.44 (1.36–277.18) $p = 0.03$	
N1W bouts ≥ 6 epochs ≥ 16	OR = 1.02 (0.99–1.05) $p = 0.13$	OR = 0.98 (0.47–2.04) $p = 0.96$		OR = 2.63 (1.25–5.53) $p = 0.01$			

Narcoleptics are stratified in all these models. Only final models are shown. An empty field indicates that the corresponding parameter was not included in the final model.

results are provided in Supplementary Table S3 (stratified on control subjects) and Table S3 (stratified on narcolepsy).

In controls, the only significant effects on these features were those of stimulants, which increased the probability of a SOREMP at night (OR = 10.38 (1.77–60.74), $p = 0.009$) (Supplementary Table S3). As these features are very rare in controls (≤2%), this result is to be taken with caution. In patients, stimulants did not have significant effects, but nocturnal SOREMPs were inhibited by antidepressant treatment (OR = 0.37 (0.15–0.87), $p = 0.02$) (Table 3). By contrast, the 5N1W- > 2R ≥ 5 sleep transition feature ("wake to REM transitions at night") was not influenced by therapy, but it was strongly correlated with the presence of a nocturnal SOREMP. Surprisingly, the N1W bouts of ≥6 epochs of ≥16 bout feature ("long bouts of wakefulness within sleep") were more likely to occur in patients treated with antidepressants (OR = 2.63 (1.25–5.53), $p = 0.01$). The 3N2N3- > 2N1W ≥ 22 ("sleep fragmentation feature") was inversely correlated with the presence of a SOREMP at night (OR = 0.12 (0.01–0.96), $p = 0.05$).

As can be seen in Table 4, adding any of the new features to the presence of a nocturnal SOREMP increased sensitivity at the expense of specificity, the most useful feature being transitions to REM sleep during the night (5N1W- > 2R ≥ 5) as it increased sensitivity by almost 10% with only a small drop of specificity of 0.9%. Results with the other features were more disappointing as specificity dropped to ~96%. It should be emphasized that adding any of the new features thus reduced the PPV. Using logistic regression models, we finally assessed if the presence of the three new features was significantly affected by the presence of a nocturnal SOREMP in patients with narcolepsy, and we found that the presence of a nocturnal SOREMP increased incidence of the 5N1W- > 2R ≥ 5 transition feature

Table 4
Performance values of features when adding SOREMP to the final features.

Data set (all counts)	No. of subjects [NC/Con]	SOREMP ≤ 15	SOREMP ≤ 15 OR 5N1W- > 2R ≥ 5	SOREMP ≤ 15 OR 3N2N3- > 2N1W ≥ 22	SOREMP ≤ 15 OR N1Wbouts ≥ 6 epochs ≥ 16	SOREMP ≤ 15 or anyone of the transitional features
All	155/1218	Sens: 29.7% Spec: 99.5% PPV: 88.5%	Sens: 37.4% Spec: 98.4% PPV: 74.4%	Sens: 43.2% Spec: 96.1% PPV: 58.8%	Sens: 49.7% Spec: 96.3% PPV: 63.1%	Sens: 60.0% Spec: 92.5% PPV: 50.3%
Training data set	136/510	Sens: 28.7% Spec: 99.6% PPV: 95.1%	Sens: 37.5% Spec: 99.4% PPV: 94.4%	Sens: 42.7% Spec: 98.6% PPV: 89.2%	Sens: 50.0% Spec: 98.6% PPV: 90.7%	Sens: 60.3% Spec: 97.5% PPV: 86.3%
Validation data set	19/708	Sens: 36.8% Spec: 99.4% PPV: 63.6%	Sens: 36.8% Spec: 97.6% PPV: 29.2%	Sens: 47.4% Spec: 94.4% PPV: 18.4%	Sens: 47.4% Spec: 94.6% PPV: 19.2%	Sens: 57.9% Spec: 88.8% PPV: 12.2%
Subjects taking antidepressants	49/279	Sens: 16.3% Spec: 99.3% PPV: 80.0%	Sens: 28.6% Spec: 97.8% PPV: 70.0%	Sens: 34.7% Spec: 94.6% PPV: 53.1%	Sens: 53.1% Spec: 96.0% PPV: 70.3%	Sens: 63.3% Spec: 91.0% PPV: 55.4%
Subjects not taking antidepressants	106/939	Sens: 35.9% Spec: 99.6% PPV: 90.4%	Sens: 41.5% Spec: 98.5% PPV: 75.9%	Sens: 47.2% Spec: 96.6% PPV: 61.0%	Sens: 48.1% Spec: 96.4% PPV: 60.0%	Sens: 58.5% Spec: 92.9% PPV: 48.1%
Subjects taking stimulants	115/66	Sens: 27.8% Spec: 97.0% PPV: 94.1%	Sens: 35.7% Spec: 97.0% PPV: 95.4%	Sens: 40.9% Spec: 89.4% PPV: 87.0%	Sens: 50.4% Spec: 92.4% PPV: 87.2%	Sens: 59.1% Spec: 84.9% PPV: 87.2%
Subjects not taking stimulants	40/1152	Sens: 35.0% Spec: 99.7% PPV: 77.8%	Sens: 42.5% Spec: 98.4% PPV: 48.6%	Sens: 50.0% Spec: 96.5% PPV: 33.3%	Sens: 47.5% Spec: 96.5% PPV: 32.2%	Sens: 62.5% Spec: 92.9% PPV: 23.4%
Subjects taking antidepressants or stimulants	120/306	Sens: 26.7% Spec: 99.0% PPV: 91.4%	Sens: 35.0% Spec: 97.7% PPV: 85.7%	Sens: 40.0% Spec: 94.1% PPV: 72.7%	Sens: 49.2% Spec: 95.4% PPV: 80.8%	Sens: 58.3% Spec: 90.2% PPV: 70.0%
Subjects not taking antidepressants or stimulants	35/912	Sens: 40.0% Spec: 99.7% PPV: 82.4%	Sens: 45.7% Spec: 98.6% PPV: 55.2%	Sens: 54.3% Spec: 96.8% PPV: 39.6%	Sens: 51.4% Spec: 96.6% PPV: 36.7%	Sens: 65.7% Spec: 93.2% PPV: 27.1%

Features are counts for the entire night. 5N1W- > 2R ≥ 5 indicate five or more transitions from at least five epochs of either N1 or W to at least two epochs of REM sleep. 3N2N3- > 2N1W ≥ 22 indicate 22 or more transitions from at least three epochs of either N2 or N3 to at least two epochs of either N1 or W. Lastly, N1Wbout ≥ 6 epochs ≥ 16 indicate 16 or more bouts of at least six epochs of either N1 or W.
Abbreviations: Sens: sensitivity; spec: Specificity; PPV: Positive predictive value; NC: Patients with NC; Con: Subjects without narcolepsy; SOREMP: Nocturnal sleep Onset to REM sleep Period (REML ≤ 15 min).

(OR = 3.71 (1.51–9.09), $p = 0.004$), but decreased the probability of the 3N2/N3- > 2N1/W ≥ 22 transition feature (OR = 0.12 (0.01–0.96), $p = 0.05$). No significant effects were found for the N1/W bout feature. Overall, the data confirmed that these new features offer additional diagnostic information to the presence of a nocturnal SOREMP.

4. Discussion

The diagnostic value of various sleep-stage transition features was systematically computed using manually scored hypnograms of NC patients and controls. We searched for highly specific features, which in combination with the presence of a SOREMP at night (REML, ≤15 min) could enhance sensitivity while maintaining high specificity, with the goal of identifying NC patients from a nocturnal PSG alone. We found that the presence of at least (1) five transitions from five epochs of either N1 or W to two epochs of REM sleep, (2) 22 transitions from three epochs of either N2 or N3 to two epochs of N1 or wakefulness, and (3) 16 bouts of six or more epochs of N1 or wakefulness were all characteristics of NC. The presence of either of these features or SOREMP was found to increase the sensitivity without lowering the specificity significantly compared with the measures obtained by the presence of SOREMP alone.

Of note, we found that merging stage 1 with wake as a "mixed" W and N1 state seemed to produce more features that were more predictive of narcolepsy. In previously published nocturnal PSG studies of narcolepsy patients, increased stage 1 is a constant and highly significant finding for the disorder [29]. Increased stage 1 sleep at the expense of stage 2 was also found in our data set (Table 1). Although strikingly different, however, this finding is not specific when narcolepsy is compared with other sleep disorders such as insomnia or sleep-disordered breathing, limiting its diagnostic value [30]. Stage 1 is a transitory state where the alpha activity of wake disappears, a phenomenon believed to reflect sleep onset. Other studies have, however, found that the loss of consciousness and reduced arousal threshold occur progressively during sleep onset, and they become complete only after a few minutes of stage 2, although this may also vary with scalp topography [31–34]. For other authors, stage 1 may be closer to normal hypnagogic experience – a phenomenon named "reverie" – a state of intermediate consciousness that precedes sleep, and it is somewhat similar to REM sleep (reviewed by Yang et al. [32]). The fact that merging stage 1 and stage W in our data set yielded more predictive features in narcolepsy may suggest that stage 1 is an unusual stage in narcolepsy, and that it could reflect a core abnormality of the disorder. It may be worth noting that the electroencephalogram (EEG) of stage 1, with its theta dominance, is similar to that of REM sleep in the absence of saw tooth waves and REMs, and that thus it may be difficult to distinguish from the EEG of sleep paralysis [35,36]. Stage 1 in narcolepsy may therefore represent a more complex mix of dissociated stages of consciousness that is distinct from controls.

The first of these features, increased transitions from five epochs of either N1 or W to two epochs of REM sleep, was notable and expected, as it represents "SOREMPs within the night" (with a least 1 min of sustained REM sleep following at least 2.5 min of wake/N1 sleep, a prolonged arousal). Many studies have found that in narcolepsy, REM latency from sleep onset is reduced; thus, it is not surprising that SOREMP-like features are found not only at sleep onset but also when patients wake up at night and fall asleep again. SOREMPs have been shown to be predictive of narcolepsy in 24-h continuous sleep recording studies, and this test has been proposed as a valid alternative to the MSLT [37,38]. One possible confounding factor for this feature could have been that REM sleep propensity is strongly regulated by the circadian clock, peaking in the early morning hours (including in narcolepsy). Carskadon et al. [39], for example, using a "90-min day" schedule, found that even control subjects can experience SOREMPs throughout their body temperature cycle, whereas in narcoleptic patients, these occur all through the day. Our control samples, for example, contain a small number of shift workers (5.8%), and this could have a shifted REM sleep propensity toward the daytime, although this should reduce SOREMPs at night and thus not create false positives. To address this issue, we also excluded the second part of the night, or the last few hours of nocturnal sleep for the evaluation of SOREMPs at night, but we found that this only marginally improved performance (Supplementary Table S1).

In non-narcolepsy subjects, REM sleep is often preceded by a brief transition into stage 2, and this was not found as often in narcolepsy. A decreased N2 to REM sleep transition feature was also found to be specific for narcolepsy (data not shown), but as it inversely correlated with the SOREMPs at night transition feature and was less predictive, it was not pursued. This is in accordance with the findings of Liu et al. [23] who found altered transition from N2/N3 sleep to REM sleep in narcolepsy types 1 and 2 compared with unaffected relatives and controls. By combining sleep variables in a decision tree, they enhanced the sensitivity and specificity of diagnosing narcolepsy types 1 and 2, but they found that the transition measures computed from MSLT were more indicative than those computed from nocturnal PSGs [23]. However, they did not include a confirmation sample, and it is therefore unclear how their decision tree would perform in a clinical setting. In narcolepsy, REM sleep transitions rather occurred from wake or stage 1, as several recent studies suggested also finding that N1 to REM transitions can differentiate narcolepsy from idiopathic hypersomnia (IH) and behavior-induced inadequate sleep syndrome [1,19,20,40]. Based on the fact that similar features have been consistently found by multiple investigators, the ≥5 occurrences of ≥5 epochs of either N1 or W to ≥2 epochs of REM sleep is likely one of the most useful indicators of narcolepsy [1,19,20,40]. A limitation may, however, be that this feature strongly correlated with a SOREMP at night (Table 3), so that when added to a nocturnal SOREMPs it only modestly increased sensitivity (Table 4). Unlike nocturnal SOREMPs, it was, however, not strongly modulated by antidepressant therapy (Table 3).

The second feature, the presence of at least 22 transitions from three epochs of either N2 or N3 to two epochs of N1 or wakefulness, was also expected based on the fact that narcolepsy has been reported to have less deep sleep and significant sleep fragmentation. Sleep fragmentation and sleep-state instability have also been found in animal models of narcolepsy [41]. As noted in Table 4, however, specificity was not as high, not surprisingly considering that many other sleep disorders are associated with sleep fragmentation. Most interesting was the third feature, ≥16 bouts of ≥6 epochs of N1 or wakefulness, which reflect not simply sleep fragmentation with microarousals but the presence of multiple long (≥3 min) periods of wakefulness or semi-wakefulness, which are typically associated with daytime recall in normal subjects [42]. As multiple long awakenings may be less frequent in disorders such as sleep-disordered breathing, the feature is more likely to be useful (Table 4). Pizza et al. [29] investigated various micro- and macro-sleep structures (eg, cyclic alternating pattern, power spectra in clinical bands in 2-s mini-epochs, quantification of submentalis EMG, leg movements, and percentage of different sleep stages) in nocturnal PSGs from 19 patients with IH without long sleep time, 17 patients with narcolepsy–cataplexy, and 13 control subjects. Relevant to the present study, they found that patients with narcolepsy–cataplexy have significantly more stage shifts per hour compared with control subjects, but less compared with IH patients. Narcolepsy patients were also found to have significantly fewer awakenings per hour compared with IH patients, whereas no significant differences were found for awakening numbers per hour between type 1 narcolepsy and controls.

By investigating the total number of transitions instead of the frequency of transitions (ie, per hour), TST was not taken into

account, which could be a limitation for this study as Table 1 reports that NC patients had a significantly longer TST compared with controls. Intuitively, longer TST could lead to more transitions simply because the patients slept longer. However, as the final features involve rare transitions that are constrained by high threshold number values (5, 22, and 16 times, respectively), it is unlikely that control subjects or non-NC patients would express the features found if they slept half an hour longer. Furthermore, we believe that expressing these features as raw number makes them more accessible in a clinical setting.

Another limitation of this study is the fact that the features are based on manually single-scored hypnograms from various clinics. Notably, controls as well as patients belong to different cohorts that were scored by different laboratories. As the observed transitions are rare and limited by rather high thresholds of occurrence, we, however, believe that this effect is likely limited. We have not investigated the inter-rater variability of the narcoleptics nor the controls from any of the clinics. Sleep-stage dissociation in narcoleptics could lead to a higher inter-rater variability, which could flatten out indicative features for narcolepsy. In future exploration of transitions between wake and sleep states, the indicative measures could be more objective by making them independent of manually scored hypnogram.

5. Conclusions

In summary, we found that by combining a nocturnal SOREMP with specific transitions extracted from typically manually scored hypnograms of nocturnal PSGs, we could enhance the sensitivity from ~30% to nearly 50% while maintaining a high specificity compared with using nocturnal SOREMP alone. PPV values, however, decreased, most likely reflecting the small number of NC patients compared with controls, as well as the heterogeneity of the control group when combining healthy controls and non-NC sleep-disorder patients. We also found that antidepressants have a significant suppressing effect on SOREMP in type 1 narcolepsy patients, no effect on nocturnal transitions to REM and bouts of nocturnal N1 or wakefulness, and a significant enhancing effect on nocturnal transitions to nocturnal N1 or wakefulness. We suggest that when evaluating subjects in a clinic, the features in combination with a nocturnal SOREMP could be used to screen for type 1 narcolepsy based on the results of a nocturnal PSG alone. Combined with other PSG features as well, such as state-space analysis [43] or analysis of REM sleep atonia [44] in narcolepsy, these features could lead to new diagnostic procedures for type 1 narcolepsy.

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Conflict of interest

Julie A. E. Christensen, Eileen B. Leary, Paul E. Peppard, Terry Young, Helge B. D. Sorensen, and Poul Jennum state no conflicts of interest. Oscar Carrillo is an occasional consultant for Jazz Pharmaceuticals. Dr. Emmanuel Mignot receives funding and occasional consulting income from Jazz Pharmaceuticals, which funded part of the study.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.06.007.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2015.06.007.

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