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Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults

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The diagnosis of narcolepsy without documented cataplexy is based on the observation of two or more sleep-onset REM periods (SOREMPs) during the Multiple Sleep Latency Test (MSLT). We report on the prevalence and correlates of SOREMPs in the community-based Wisconsin Sleep Cohort Study. MSLTs were conducted following nocturnal polysomnography (NPSG) and daily sleep diaries in 289 males and 267 females (age 35–70, 97% Caucasians). Multiple SOREMPs were observed in 13.1% of males and 5.6% of females. An MSLT mean sleep latency ≤8 min and ≥2 SOREMPs (diagnostic of narcolepsy) was observed in 5.9% (males) and 1.1% (females), all without cataplexy. Because of significant sex interactions, analyses were stratified by sex. Increased prevalence of HLA-DQB1*0602, a marker of narcolepsy, was observed in males but not in females with ≥2 SOREMPs. Males with multiple SOREMPs compared with those with no SOREMPs had shorter rapid eye movement (REM) latency during NPSG, were sleepier on the MSLT and reported increased sleepiness, hypnagogic hallucinations and cataplexy-like symptoms, suggesting a narcolepsy-like phenotype. In males only, the occurrence of SOREMPs increased with shift work and some indirect markers of sleep restriction, such as shorter sleep a day before NPSG. SOREMPs were unrelated to age, body mass index, depression (Zung Scale), anxiety (State-Trait Anxiety Scale) and the number of apnea and hypopnea events per hour of sleep (AHI), but were associated with decreased mean lowest oxygen saturation in males. Finally, we found that both males and females with SOREMPs reported taking more antidepressants, but those were of the types known not to suppress REM sleep. These results suggest a high prevalence of narcolepsy without cataplexy, as defined by the International Classification of Sleep Disorders, and/or a large number of false-positives for the MSLT.

Keywords: HLA; DQB1*0602; sleep-onset REM period; MSLT; narcolepsy

Abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; EDS = excessive daytime sleepiness; EPW = Epworth sleepiness scale; HH = hypnagogic hallucinations; ICSD-2 = International Classification of Sleep Disorders (revised, 2005); MSL = mean sleep latency; MSLT = Multiple Sleep Latency Test; NPSG = nocturnal polysomnography; PLM = period leg movement; PSG = polysomnography; REM = rapid eye movement; SOREMPs = sleep-onset REM sleep periods; SP = sleep paralysis; SDB = sleep disordered breathing; TST = total sleep time; WSC = Wisconsin Sleep Cohort Study

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Introduction

Narcolepsy is classically separated into narcolepsy with and without cataplexy (Aldrich *et al.*, 1997; American Academy of Sleep Medicine, 2005). The diagnosis of narcolepsy–cataplexy is based on the existence of definite cataplexy [documented episodes of muscle weakness triggered by emotions, akin to rapid eye movement (REM) sleep atonia] (Anic-Labat *et al.*, 1999) and may be supported by the Multiple Sleep Latency Test (MSLT), with the observation of a mean sleep latency (MSL) ≤8.0 min and ≥2 sleep-onset REM periods (SOREMPs) (American Academy of Sleep Medicine, 2005).

Approximately 85% of patients with narcolepsy–cataplexy meet MSLT criteria (Aldrich *et al.*, 1997; Mignot *et al*, 2002; American Academy of Sleep Medicine, 2005). Many patients (40%) with narcolepsy–cataplexy also have sleep paralysis (SP) and hypnagogic hallucinations (HHs), two other symptoms of abnormal REM sleep, but these symptoms have a poor specificity (Aldrich *et al.*, 1997). A subset of patient also has insomnia and obesity (Overeem *et al.*, 2001; Dauvilliers *et al.*, 2003).

Narcolepsy–cataplexy typically starts in adolescence, with over 80% of cases fully developed before the age of 40 (Honda *et al.*, 1983; Dauvilliers *et al.*, 2001; Okun *et al.*, 2002). Cataplexy onset is in most cases within 5 years of onset of sleepiness (80% of cases who eventually develop cataplexy), although on rare occasions (4%) it may develop after 20 years or more (Honda *et al.*, 1983; Okun *et al.*, 2002). Prevalence-based studies have shown a prevalence of 0.02–0.07% for narcolepsy–cataplexy in Western Europe and North American adult populations (Mignot, 1998). The disorder affects both sexes, with a small male predominance reported by some (Honda *et al.*, 1983; Dauvilliers *et al.*, 2001, 2003), but not all authors (Honda *et al.*, 1983; Okun *et al.*, 2002). The pathophysiology of narcolepsy with cataplexy is well known. The disorder is tightly associated with HLA-DQB1*0602 (~90 versus 24% in the general Caucasian population) (Mignot *et al.*, 2001) and most cases are caused by the destruction of ~70 000 neurons producing the neuropeptide hypocretin (orexin) (Peyron *et al.*, 2000; Thannickal *et al.*, 2000). This abnormality is reflected in CSF (Nishino *et al.*, 2000; Dalal *et al.*, 2001; Hong *et al.*, 2002; Kanbayashi *et al.*, 2002; Krahn *et al.*, 2002; Mignot *et al.*, 2002; Dauvilliers *et al.*, 2003), with CSF hypocretin-1 levels below 110 pg/ml in most cases (Mignot *et al.*, 2002). The hypothesized cause of the disorder is an autoimmune destruction of hypocretin-containing neurons.

In contrast, little is known regarding narcolepsy without cataplexy. In the past, this diagnosis was reserved for patients with narcolepsy-like symptoms but no cataplexy, including children or recent onset cases who may later develop cataplexy (American Sleep Disorders Association, 1997). Patients with unexplained sleepiness, no cataplexy but SP or HH were also diagnosed as narcoleptic (American Sleep Disorders Association, 1997). MSLT abnormalities indicative of multiple REM sleep transitions were found to be supportive in these cases. In older case series, narcolepsy without cataplexy represented 20–40% of all diagnosed patients (Rosenthal *et al.*, 1990*a*,*b*; Moscovitch *et al.*, 1993; Aldrich *et al.*, 1997; Mignot *et al.*, 1997; Hong *et al.*, 2002; Silber *et al.*, 2002*a*), a figure also consistent with a recent prevalence study of diagnosed narcolepsy without cataplexy cases (Silber *et al.*, 2002*b*). More recently, however, with the observation that SP and HH are non-specific symptoms present in a large portion of the population (Ohayon *et al.*, 1996, 1999; Aldrich *et al.*, 1997; Szklo-Coxe *et al.*, 2005, 2006), the diagnosis of narcolepsy has been reserved for patients with unexplained daytime sleepiness and MSLT results consistent with narcolepsy. This last concept is reflected in the recently published revised International Classification of Sleep Disorders (ICSD-2) (American Academy of Sleep Medicine, 2005), which mostly focuses on the MSLT.

A problem in this approach is the lack of large-scale normative data and SOREMPs scoring reliability data for the MSLT. This data is badly needed considering the daily use of this test in the diagnosis of narcolepsy and idiopathic hypersomnia, and the increasing use of novel narcolepsy pharmacotherapies, most notably modafinil and sodium oxybate (gamma hydroxybutyric acid), in the treatment of these conditions. Limited, small-scale, studies in healthy volunteers had suggested that well-rested, normal volunteers without sleep complaints do not exhibit SOREMPs. In 1996, Bishop *et al.* (1996) found a high prevalence (17%) of $\geq$2 SOREMPs in 139 young healthy volunteers not complaining of sleep or psychiatric problems, a finding that led to considerable controversy (Rye and Bliwise, 1997). It was generally assumed that the young age of these volunteers (28 years of age in the $\geq$2 SOREMP group), chronic sleep deprivation and other factors, such as undiagnosed sleep apnea, may have led to this unusually high figure (Rye and Bliwise, 1997). Most recently, a study in patients with sleep disordered breathing (SDB) also found that 4.7% of subjects had two or more SOREMPs, although no relation with apnea severity was found (Aldrich *et al.*, 1997; Chervin and Aldrich, 2000).

Not only is information regarding SOREMPs in the general population lacking but little is known regarding the pathophysiology of narcolepsy without cataplexy. In diagnosed patients, HLA-DQB1*0602 frequency is slightly increased above the 24% population frequency, typically in the 35–40% range (Honda *et al.*, 1983; Mignot *et al.*, 1997; Lin *et al.*, 2006). CSF hypocretin-1 is low in 19% of cases reported to date (Kanbayashi *et al.*, 2002; Krahn *et al.*, 2002; Lin *et al.*, 2006); at least half of the cases with low CSF hypocretin-1 are adults with a long clinical history of daytime sleepiness (>10 years) and are thus unlikely to ever develop cataplexy. This, together with the observation of a moderately decreased hypocretin cell in the only post-mortem case examined to date (85 versus 90–95% in cases with cataplexy) (Thannickal *et al.*, 2000), indicate that some cases without cataplexy involve partial or complete hypocretin cell loss. The extent of the overlap in an unselected population sample of ICSD-2-defined narcolepsy without cataplexy cases is, however, unknown. It is likely that diagnosed cases without cataplexy represent a biased sample of more severe cases. As cataplexy is a more striking symptom than sleepiness, it is also possible that narcolepsy without cataplexy is frequently undiagnosed. Little is known about the health or social significance of such a condition.

The goal of the present study was to report on the frequency and correlates of SOREMPs during clinical MSLTs in a randomly selected sample of adults, and to use this information to estimate prevalence for narcolepsy without cataplexy.

Methods

Participants and overall design

Beginning in 2000, participants enrolled in the population-based Wisconsin Sleep Cohort Study (WSC) (Young *et al.*, 1993), an ongoing longitudinal study of sleep habits and disorders in the general population, were asked to complete an MSLT with full clinical protocol in addition to their overnight protocol. Participants completed a daily sleep diary for a week before an MSLT procedure. The procedure consists of a nocturnal polysomnography (NPSG) followed by a clinical MSLT (the MSLT sample). Of those invited, 86% completed the MSLT.

The MSLT sample includes 289 males and 267 females (Table 1). Mean age, body mass index (BMI), % Caucasian and % working shifts (working nights or a rotating schedule) are reported in Table 1. The presence of the DQB1*0602 genotype was determined as described (Mignot *et al.*, 1999). Parameters selected for comparison were either basic demographic information (e.g. BMI, age sex), parameters believed to influence the occurrence of SOREMPs (for example, HLA-DQB1*0602, shift work, past sleep history, sleep disorders, psychiatric disorders or psychotropic drugs) and narcolepsy symptoms, including measures of daytime sleepiness (objective and subjective), REM-related symptoms (cataplexy, SP, HHs) and NPSG parameters.

WSC sleep cohort sampling scheme

Details of the WSC overall study design have been described previously (Young *et al.*, 1993; Taheri *et al.*, 2004). Briefly, to construct a defined sampling frame, all employees aged 30–60 years of four state agencies in south central Wisconsin were mailed a survey on sleep habits, health and demographics in 1989. Mailed surveys were repeated at 5-year intervals. A stratified random sample of ~1500 respondents was then recruited for an extensive overnight protocol including NPSG at baseline. Recruitment for baseline studies was staggered to conduct seven studies/week; study entry and follow-up time thus vary within the cohort. Exclusion criteria included pregnancy, unstable cardiopulmonary disease, airway cancers and recent upper respiratory tract surgery. The baseline response rate was 51% with most refusals due to the inconvenience of sleeping away from home. Follow-up studies have been conducted at 4-year intervals, with up to three follow-up studies to date. Collection of morning fasted blood was added to the protocol in 1995 (Taheri *et al.*, 2004). Extensive survey and other data available from the sampling frame have been used to evaluate the potential for response and drop-out biases.

NPSG

Overnight sleep studies are conducted at the University of Wisconsin General Clinical Research Center in rooms resembling typical bedrooms. Participants arrive in the early evening. Informed consent is obtained, medication history is documented (most notably intake of psychotropic compounds such as antidepressants) and blood pressure is recorded. Health-history, lifestyle and sleep questionnaires are administered. Height and weight are measured for BMI calculation.

A 16-channel polysomnographic recording system (Telefactor Heritage digital polysomnography systems, Grass Instruments, Quincy, MA, USA) is used to assess sleep states, respiratory, leg movements and cardiac variables. Sleep is studied using EEG, electrooculography and chin EMG. Leg movements are recorded using leg EMG leads. Oxyhaemoglobin saturation is continuously recorded by pulse oximetry (model 3900, Datex-Ohmeda, Louisville, CO, USA). PTAF-2 Nasal pressure transducer (Pro-Tech, Mukilteo, WA, USA) and Dymedix PVDF (polyvinylidene fluoride film) detect oral and nasal airflow. Respiratory inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY) records rib cage and abdominal excursions. It was calibrated in the evening before the sleep study.

Sleep stage and respiratory events are assessed by trained sleep technicians. Several sleep variables were obtained from the overnight study: total sleep time (TST) was defined as the total hours of polysomnographically defined sleep. Sleep efficiency was TST divided by time from lights out until arising in the morning. Sleep onset is defined as the interval between light off and the first three consecutive epochs of stage 1 sleep or one epoch of stage 2, 3, 4 or REM. REM sleep latency is defined as the interval between sleep onset and the first epoch of REM sleep.

Each 30 s interval of the polysomnographic record is inspected visually for episodes of abnormal breathing. Cessation of airflow for at least 10 s is defined as an episode of apnea. A discernible reduction in the sum amplitude of the rib cage plus the abdominal excursions on respiratory inductance plethysmography that last at least 10 s and that is associated with a reduction in the oxyhaemoglobin saturation of at least 4% is defined as an episode of hypopnea. The apnea–hypopnea index (AHI), defined as the average number of episodes of apnea and hypopnea per hour of objectively measured sleep, is the key summary measurement of the occurrence of SDB. Commonly used cut-off for SDB severity, such as AHI $\geq$1, 5, 15 or 30, were also used. The lowest oxygen saturation during sleep was also computed. The number of leg movement per hour of sleep (PLM index) was also recorded.

MSLT subsample protocol

The procedure consisted of a night of NPSG followed by a clinical MSLT, as described in Carskadon *et al.* (1986). The night of the NPSG, conducted as described below to record sleep, SDB and leg movements, participants were free to go to bed at their habitual bedtime. A few modifications, described below, were performed for convenience purpose and to reflect a more naturalistic approach. These modifications included (i) conducting the MSLT even if TST during the NPSG was short, for example, <6 h, and (ii) continuation of typical regimen of psychotropic and any other drugs during the procedure. As there is a lot of variability in the way MSLT is conducted in clinical sleep laboratories, these modifications may be common when diagnosing narcolepsy using the ICSD-2 classification. To use such a flexible approach also allowed us to study the potential effect of these variables on the occurrence of SOREMPs.

As in the Carskadon's original protocol (Carskadon *et al.*, 1986) and subsequent American Academy of Sleep Medicine task-force-approved modifications (Littner *et al.*, 2005), naps were scheduled at 2 h intervals starting 1.5 h after awakening. Four naps were conducted in all cases, and a fifth nap was added if REM was detected in the first four naps. If no sleep occurs in 20 min, the nap trial is ended and sleep latency recorded as 20 min. If sleep occurs within 20 min, onset is defined as the time from lights out to the first epoch of sleep (including stage 1). In order to assess for the presence of REM sleep, the test continues for at least 15 min after sleep onset. If present, latency to REM sleep is noted. After scoring and for analysis purpose, the fifth nap was analysed only in cases where REM sleep

Table 1 Baseline characteristics of the sample, stratified by sex and by number of SOREMP on the MSLT

	Males								Females							
	0 SOREMP		≥1 SOREMP			≥2 SOREMPs			0 SOREMP		≥1 SOREMP			≥2 SOREMPs		
	n	Mean ± SE	*n*	Mean ± SE	*P*-value	*n*	Mean ± SE	*P*-value	*n*	Mean ± SE	*n*	Mean ± SE	*P*-value	*n*	Mean ± SE	*P*-value
Age (years)	231	58.90 ± 0.50	58	59.50 ± 0.93	0.59	38	59.35 ± 1.07	0.73	239	56.46 ± 0.50	28	56.07 ± 1.57	0.80	15	52.70 ± 1.88	0.07
Body mass index (kg/m^2)	231	31.26 ± 0.38	58	32.94 ± 1.03	0.07	38	31.49 ± 0.90	0.82	239	33.65 ± 0.57	28	33.83 ± 1.49	0.92	15	31.52 ± 1.59	0.37
Caucasian	231	96.54%	58	93.10%	0.24	38	92.11%	0.20	239	96.23%	28	100.00%	0.30	15	100.00%	0.44
Shift worker	221	0.90%	56	8.90%	0.0006	38	13.20%	0.0001	227	4.00%	28	0.00%	0.28	15	0.00%	0.43
Nocturnal polysomnography (NPSG)																
Total sleep time (h)	231	354.29 ± 4.41	58	359.65 ± 8.48	0.58	38	361.84 ± 11.14	0.52	239	382.76 ± 4.02	28	377.50 ± 11.90	0.67	15	383.43 ± 18.27	0.97
Sleep efficiency (%)	231	77.87 ± 0.86	58	81.14 ± 1.63	0.086	38	82.09 ± 2.10	0.07	239	81.90 ± 0.69	28	82.70 ± 2.05	0.71	15	83.71 ± 2.99	0.52
Sleep latency (min)	231	11.16 ± 0.77	58	10.53 ± 1.18	0.71	38	9.63 ± 1.48	0.44	239	13.87 ± 0.92	28	14.14 ± 2.90	0.92	15	18.00 ± 4.75	0.29
REM sleep latency (min)	226	122.26 ± 5.07	58	105.12 ± 8.32	0.12	38	89.47 ± 8.56	0.0114	234	137.25 ± 1.25	28	126.18 ± 16.39	0.50	15	135.17 ± 25.34	0.93
Time spent in NREM sleep (%)	231	84.82 ± 0.41	58	83.31 ± 0.89	0.11	38	82.27 ± 1.08	0.0223	239	83.51 ± 0.42	28	84.92 ± 1.13	0.27	15	82.99 ± 1.63	0.76
Time spent in REM sleep (%)	226	15.52 ± 0.39	58	16.69 ± 0.90	0.19	38	17.75 ± 1.08	0.036	234	16.85 ± 0.39	28	15.08 ± 1.13	0.14	15	17.02 ± 1.62	0.92
Total sleep time ≤ 6 h	231	51.08%	58	46.55%	0.54	38	44.74%	0.47	239	31.80%	28	35.71%	0.67	15	33.33%	0.90
Apnea–hypopnea index (events/h)	218	9.89 ± 0.93	54	10.17 ± 1.65	0.89	34	10.16 ± 2.17	0.92	227	5.74 ± 0.59	26	5.93 ± 1.57	0.92	14	2.33 ± 0.63	0.16
Apnea–hypopnea index ≥ 15	218	20.18%	54	24.07%	0.53	34	26.47%	0.40	227	11.01	26	7.69	0.60	14	0.00	0.19
Lowest oxygen saturation (%)	218	85.10 ± 0.52	54	82.84 ± 1.43	0.08	34	83.09 ± 2.06	0.20	227	86.15 ± 0.58	26	85.45 ± 1.00	0.69	14	87.54 ± 0.75	0.56
Positive airway pressure therapy use	231	1.73%	58	5.17%	0.13	38	7.89%	0.03	239	3.77%	28	7.14%	0.39	15	6.67%	0.58
Non-CPAP use in habitual users	231	11.69%	58	6.90%	0.29	38	5.26%	0.24	239	5.86%	28	0.00%	0.19	15	0.00%	0.33
Limb movement index (events/h)	231	30.56 ± 1.92	58	39.67 ± 4.58	0.042	38	37.09 ± 5.88	0.22	239	20.41 ± 1.24	28	17.92 ± 3.21	0.51	15	13.20 ± 2.35	0.15
Subjective symptoms																
Feelings of excessive daytime sleepiness	223	18.83%	57	36.84%	0.0037	38	39.47%	0.0044	238	21.43%	28	28.57%	0.39	15	33.33%	0.28
Epworth sleepiness scale	222	8.59 ± 0.29	56	10.35 ± 0.73	0.0099	38	10.54 ± 0.90	0.014	225	8.81 ± 0.32	28	9.12 ± 0.80	0.74	15	8.87 ± 0.92	0.96
Epworth sleepiness scale ≥ 11	222	30.63%	56	50.00%	0.0064	38	52.63%	0.0081	225	36.44%	28	42.86%	0.51	15	40.00%	0.78
Automatic behaviour	220	12.73%	56	8.93%	0.43	38	7.89%	0.40	224	21.88%	28	17.86%	0.63	15	13.33%	0.43
Sleep paralysis	220	3.18%	56	1.79%	0.58	38	2.63%	0.857	223	4.04%	28	0.00%	0.28	15	0.00%	0.43
Hypnagogic hallucinations	221	3.62%	56	10.71%	0.0304	38	13.16%	0.0129	227	7.93%	28	7.14%	0.88	15	0.00%	0.26
Cataplexy-like symptoms	221	0.90%	56	3.57%	0.14	38	5.26%	0.0442	224	2.23%	28	0.00%	0.43	15	0.00%	0.56
Snoring	212	60.85%	55	65.45%	0.53	37	67.57%	0.44	210	53.33%	25	40.00%	0.21	13	38.46%	0.30

Insomnia	220	17.30%	56	26.80%	0.11	38	23.70%	0.34	225	26.20%	28	14.30%	0.17	15	13.30%	0.27
Habitual sleep (h)	208	7.17 ± 0.06	52	6.96 ± 0.12	0.12	36	7.08 ± 0.15	0.58	220	7.32 ± 0.07	25	7.15 ± 0.21	0.42	15	7.45 ± 0.27	0.63
Diary sleep one day before lab study (min)	228	433.95 ± 4.64	57	414.09 ± 9.24	0.057	38	415.05 ± 11.19	0.12	238	442.97 ± 3.99	28	432.86 ± 11.39	0.41	15	433.00 ± 18.32	0.55
Diary sleep two days before lab study (min)	227	442.94 ± 4.41	53	434.23 ± 9.94	0.40	34	431.18 ± 12.02	0.34	236	443.78 ± 5.49	27	450.07 ± 12.95	0.71	14	450.36 ± 19.58	0.78
Psychiatric symptoms																
Anxiety trait score	231	31.18 ± 0.51	58	29.45 ± 0.94	0.12	38	30.50 ± 1.29	0.62	239	33.24 ± 0.60	28	32.57 ± 1.44	0.72	15	32.53 ± 1.96	0.77
Zung score	231	31.24 ± 0.41	58	30.17 ± 0.92	0.25	38	30.97 ± 1.28	0.81	238	33.07 ± 0.46	28	32.82 ± 1.38	0.86	15	33.40 ± 2.02	0.86
Zung ≥50	231	11.26%	58	12.07%	0.86	38	18.42%	0.21	238	18.07%	28	21.43%	0.66	15	26.67%	0.41
Psychotropic drugs																
On antidepressants	231	10.82%	58	22.41%	0.0195	38	23.68%	0.03	238	34.45%	28	32.14%	0.81	15	40.00%	0.66
REM-suppressing antidepressants	231	8.70%	58	17.20%	0.06	38	15.80%	0.17	238	31.50%	28	21.40%	0.27	15	26.70%	0.69
Non-REM-suppressing antidepressants	231	2.20%	58	6.90%	0.06	38	7.90%	0.05	238	5.50%	28	17.90%	0.01	15	26.70%	0.00
Stimulants	231	0.43%	58	1.72%	0.29	38	2.63%	0.14	238	2.52%	28	0.00%	0.40	15	0.00%	0.53
All psychotropic compounds	231	17.75%	58	24.14%	0.27	38	23.68%	0.38	238	38.66%	28	32.14%	0.50	15	40.00%	0.92
Multiple Sleep Latency Test (MSLT)																
Mean sleep latency (all) (min)	231	11.91 ± 0.30	58	9.90 ± 0.58	0.0025	38	8.98 ± 0.67	0.0002	239	12.30 ± 0.30	28	11.37 ± 0.63	0.30	15	11.38 ± 0.92	0.45
Mean sleep latency (SOREMP excluded) (min)	231	12.19 ± 0.29	56	10.95 ± 0.67	0.07	36	10.30 ± 0.86	0.0212	239	12.56 ± 0.29	28	12.44 ± 0.77	0.89	15	12.88 ± 1.21	0.79
Mean sleep latency ≤5	231	5.63%	58	12.07%	0.08	38	15.79%	0.0235	239	5.86%	28	7.14%	0.79	15	6.67%	0.90
Mean sleep latency ≤8	231	23.38%	58	39.66%	0.0122	38	44.74%	0.0056	239	22.18%	28	14.29%	0.34	15	20.00%	0.84
REM in nap 1(no. of subjects)	231	–	58	31.0% (18)		38	42.1 % (16)		239	–	28	25.0 % (7)		15	33.3% (5)	
REM in nap 2 (no. of subjects)	231	–	58	39.7% (23)		38	44.7 % (17)		239	–	28	50.0 % (14)		15	66.7% (10)	
REM in nap 3 (no. of subjects)	231	–	58	48.3 % (28)		38	57.9 % (22)		239	–	28	32.1% (9)		15	53.6% (8)	
REM in nap 4 (no. of subjects)	231	–	58	48.3% (28)		38	57.9 % (22)		239	–	28	53.6 % (15)		15	60.0% (9)	
REM in nap 5 (no. of subjects)*	–	–	58	29.3% (17)		38	44.7% (17)		–	–	28	7.1 % (2)		15	13.3% (2)	
HLA-DQB1*0602	224	24.11%	58	32.76%	0.18	38	39.47%	0.0467	231	22.08%	27	29.63%	0.38	14	7.14%	0.18

Data are reported as means ± SEM or as %, when appropriate. Comparisons are univariate analyses of variance or χ^2-tests. Non-CPAP use in habitual users: habitual users of CPAP who did not use it the day of the study; for exact definitions for these parameters, see Methods. *Only reported for subjects who had at least one SOREMP in the first four naps.

was actually confirmed in the subsequent scoring of the first four naps.

Scoring reliability and further analysis of REM sleep in naps

Sleep latency, REM latency and the presence of REM in naps were scored twice at the WSC site by two experienced technicians. Recorded parameters included sleep latency, presence/absence of REM sleep and, if applicable, nap REM latency. Any difference was resolved by local consensus discussion. To calculate reliability, EEG and EMG data on 122 MSLTs were sent blindly to Stanford University and scored independently a third time by a sleep specialist. These 122 MSLTs (589 naps) were 90 naps with at least one SOREMP and 32 without SOREMP, as detected at the WSC site after the first scoring. The Stanford site further recorded sleep latency and the presence/absence of REM sleep and, if applicable, REM latency. These data were used to calculate reliability. Any disagreement between the WSC and Stanford sites were next re-evaluated by the Stanford site and, if still considered valid, by the WSC site. A final consensus was obtained for the very few naps where disagreement still existed, and used for data analysis.

Once a final consensus was reached, a more detailed analysis of every SOREMP positive nap was conducted. Parameters computed for each SOREMP positive nap included sleep-onset latency, REM latency, duration of REM sleep in the remaining sleep recorded and the number of eye movements (bilateral) per minute of REM sleep recorded. A subjective assessment on the presence or absence of twitches, atonia and/or sawtooth waves (yes or no) was also performed. This data was used to compare REM sleep in HLA-DQB1*0602 positive and negative subjects with SOREMPs.

Questionnaire evaluations

A questionnaire detailing symptoms of snoring, insomnia, daytime sleepiness, SP, HHs, automatic behaviour and cataplexy-like symptoms was administrated at the time of the MSLT. Other questionnaire variable collected included the Anxiety State Anxiety Scale (Spielberger *et al.*, 1983) and the Zung Self-Rating Depression scale (Zung, 1965). Habitual snoring was defined as history of snoring on several nights per week or more. Insomnia was defined as difficulties getting to sleep, waking up during the night and having a hard time falling back to sleep, waking up repeatedly during the night or/and waking up too early in the morning without being able to go back to sleep, with a frequency of almost always, 16–30 times/month) for any one of these items. An insomnia score adding frequency value on these four items was also analysed but did not show any difference across SOREMP groups and is not reported. Subjective sleepiness was evaluated either on the basis of how often participants experienced 'feeling of excessive daytime sleepiness' (presence = often or almost always) or using the Epworth Sleepiness Scale (EPW) (Johns, 1991). An EPW score cut-off value of $\geq$11 was selected to define clinically significant sleepiness as 92% of 1074 narcolepsy cases with and without cataplexy in the Stanford database have an EPW $\geq$11 (data not shown). Automatic behaviour, a symptom reflecting sleep attacks, was defined as reports of suddenly going blank, with no memory of that period of time when driving and/or working at a desk. To be present, this symptom had to occur at least once a month or more. SP was defined as being unable to move and feeling paralysed upon awakening in the morning. HH, also referred as sleep hallucinations, was defined as hearing/seeing strange things/people when falling asleep and/or upon awakening in the morning and/or when drowsy. Cataplexy-like episodes were defined as having episodes of muscle weakness in the legs or buckling of the knees with more than one of the following emotions: (i) laughter, (ii) anger and/or (iii) telling or hearing a joke. To be present, cataplexy, SP, HH had to occur at least once a month or more.

Self-reported sleep-duration data included responses from the following in-lab questions: how many hours of sleep do you usually get in (i) a workday night? (ii) a weekend or non-work night? Habitual sleep was calculated as (5 workday sleep + 2 weekend sleep)/7. Sleep-duration data immediately before the MSLT was also obtained from a sleep diary, which subjects kept for 6 days before the daytime protocol. These two variables are highly correlated (Taheri *et al.*, 2004) and were used to study the potential effect of sleep history before the MSLT. In sleep diaries, subjects recorded the time they went to bed, the time they arose each day and the duration of any naps. The amount of sleep reported 2 days before the NPSG night was used in the analysis.

Medications

Participants were instructed to take their usual medication during the overnight and daytime protocol. While in the General Clinical Research Center for the NPSG and MSLT, drug intake was verified and recorded. We analysed, most specifically, psychotropic agents, with special emphasis on antidepressant treatments. Stimulants included modafinil, methylphenidate and amphetamine. Antidepressants were analysed as combined and separated into two categories, REM suppressant antidepressant (all tricyclic medications, serotonin reuptake inhibitors and dual serotonin/norepinephrine reuptake inhibitors) and non-REM suppressant antidepressants (nefazodone, mirtazapine and bupropion). Of note, in our categorization, trazodone was not considered as an antidepressant; rather, it was included in 'other psychotropic agents', together with hypnotics because of its prescription primarily as a sleep inducer.

Statistical analysis

Reliability measures analysis included (i) % mismatches and Kappa statistics for binary variables such as the presence of REM sleep; and (ii) mean differences $\pm$ standard error between scorers and correlation coefficients for continuous variables such as sleep latencies and REM latencies. These reliability measures were calculated per nap and per subject. Bivariate analyses were conducted to examine associations between SOREMPs and variables of clinical interest. Two variables for SOREMPs were created, $\geq$1 SOREMPs versus 0 SOREMPs and $\geq$2 SOREMPs versus 0 SOREMPs. χ^2-tests were used for categorical variables and *t*-tests for continuous data. Strong gender differences were observed in prevalence estimates and gender was a clear interaction factor for correlations of interest. Thus, all analyses are stratified by gender.

Prevalence of HLA and associated risk for diagnostic definitions of narcolepsy

The prevalence of multiple SOREMPs during MSLT testing (without and with an MSL $\leq$8 min, the latter corresponding to a positive diagnostic finding for narcolepsy), with and without self-reported sleepiness (based on reported feeling of excessive daytime sleepiness or EPW score $\geq$11) was next estimated in both sexes, with 95% CI. These estimates roughly correspond to ICSD-2-defined narcolepsy

(with and without cataplexy) (Medicine AaoS, 2005). Logistic regression was used to obtain estimates of the association of these definitions of narcolepsy and the presence of HLA-DQB1*0602, both overall and stratified for gender. The outcome variable was always defined as no SOREMPs as the comparison group.

Associations with multiple SOREMPs

Logistic models in SAS (Procedure Logistic, SAS Institute In, Cary, NC) were used to estimate associations with variables of interest and multiple SOREMPs. Two primary models were run within each gender: ≥1 SOREMPs versus 0 SOREMPs and ≥2 SOREMPs versus 0 SOREMPs. The potential effects of age, sex, BMI and variables that have been suggested by others to influence SOREMPs (past sleep-duration history, lowest oxygen saturation, HLA-DQB1*0602, occurrence of sleep or psychiatric disorders, drugs) were investigated. Final models were chosen after examining changes in magnitude and statistical significance (Wald chi-squares, $P < 0.05$) in beta coefficients with confounding variables. The variables included in the final models were selected because of their clinical relevance or if significant associations were observed in Table 1. Associations were expressed as odds ratios and 95% CI.

Association of the presence of a SOREMP in each nap

To further investigate the relationship of the variables of interest with SOREMPs, each nap (up to five/person) was analysed with the presence or absence of a SOREMP as the outcome. All variables of interest were examined in logistic regression models stratified by gender using Proc Genmod in SAS. This procedure estimates the variance/covariance structure of the repeated measures data and adjusts the standard errors of the estimates, providing robust estimates for hypothesis testing.

Comparison of HLA positive and negative subjects in SOREMP only naps

We compared HLA positive versus HLA negative subjects in only those naps where a SOREMP occurred. To explore if HLA could have an effect on REM sleep itself, we compared sleep latency, REM latency, duration of REM sleep (calculated over the entire nap), the number of REMs/minute of REM sleep, the number of twitches per minute of REM sleep, the presence of atonia (yes/no) and the presence of saw tooth wave (yes/no) in HLA positive versus negative subjects. In these models, outcome variables were both of continuous and binary nature. For example, the presence of sawtooth wave pattern was a binary outcome and was modelled with logistic regression and REM latency was a continuous variable modelled with linear regression. In these analyses, it was also necessary to adjust for repeated measures as described above. For the continuous data, Proc mixed was used in SAS. Because of the small numbers, these data were modelled both overall and stratified by gender.

Results

The scoring of the MSLT is highly reliable across sites

A total of 589 naps in 122 people were re-scored blindly at Stanford University (90 with ≥1 SOREMPs) after initial scoring at the Wisconsin centre. Reliability was first calculated by nap. A 93% agreement was obtained on the presence of REM sleep in 589 naps ($\kappa = 0.827$, $P < 0.0001$). Sleep latency in all naps was also highly correlated ($r^2 = 0.67$, $P < 0.0001$), with the Stanford site reporting longer sleep latencies (MSL difference was 0.41 ± 0.20 min, $P = 0.04$). In the 144 naps where REM sleep was observed by both scorers, REM latency was also highly correlated ($r^2 = 0.63$, $P < 0.0001$), with REM latency scored somewhat longer at the WSC site (mean REM sleep latency difference was 1.17 ± 0.28 min, $P < 0.001$).

Overall MSLT reliability analyses were also conducted. Both sites reported the same number of SOREMP in 81% of 122 MSLTs ($\kappa = 0.746$, $P < 0.0001$; weighted $\kappa = 0.806$, $P < 0.0001$). The MSLT MSL was also highly correlated ($r^2 = 0.875$, $P < 0.0001$), with the Stanford site reporting slightly longer sleep latencies (MSL difference was 0.42 ± 0.20 min, $P = 0.04$). These results indicate that the scoring of REM sleep in clinical MSLTs is reliable. The mismatches described above were resolved by reexamination and consensus, leading to 86 subjects ≥1 SOREMPs and 36 with no SOREMP.

The occurrence of SOREMP is strongly sex-dependent

The effects of demographic variables such as age, BMI and sex on the occurrence of SOREMPs in the MSLT was first examined in the overall sample. Whereas BMI and age had no effect, a strong effect of male sex was found in all models of SOREMPs, with evidence of interactions when the effects of other parameters such as DQB1*0602 was studied. The OR of ≥2 SOREMPS in male versus female was 2.62 (CI, 1.40–4.90; $P = 0.0025$).

Characteristics of participants with and without SOREMPs

Sample characteristics are reported in Table 1, stratified by sex and number of SOREMPs. In females, the only significant finding was that of an increased intake of non-REM suppressant antidepressants in volunteers with ≥1 and ≥2 SOREMPs. This finding was notable as a similar increase in non-REM suppressant antidepressant intake was also found in males with ≥2 SOREMPs. The absence of effect for many parameters in females may reflect both sex-specific effects and a significantly smaller sample size for females with SOREMPs.

In males, subjects with ≥2 SOREMPs versus no SOREMPS were more likely to be HLA-DQB1*0602 positive, had a significantly shorter REM latency and a slightly higher % REM sleep during NPSG. Males with ≥1 or ≥2 SOREMPs were also more likely to report shift work and reported more HHs. They also reported slightly less sleep the night preceding polysomnography but slept an equivalent amount of time the day before that and the day of the nocturnal

polysomnography (NPSG). They were sleepier both subjectively (EPW, problem EDS) and objectively (MSLT MSL). As the occurrence of a SOREMP requires a short sleep latency on the corresponding nap, we also calculated the MSL derived from the naps without SOREMPs in subjects with ≥1 and ≥2 SOREMPs. This parameter, the MSL of naps without SOREMPs, was also significantly shorter in subjects with ≥1 and ≥2 SOREMPs, confirming the existence of objectively measured sleepiness in males with SOREMP.

Males with ≥2 SOREMP versus no SOREMPS also reported slightly more cataplexy-like symptoms (Table 1). Importantly, however, this symptom was only reported in 2 of 38 subjects and was not clinically confirmed (Table 1). Additionally, none of the subjects with 1 SOREMP reported cataplexy-like symptoms, and these two subjects had an MSL > 8 min inconsistent with a narcolepsy-like MSLT (see below). Other cut-off values for HH, SP and cataplexy, such as rarely, that is, more than 'a few time ever', were also analysed but did not show any significant difference and are not reported.

Prevalence of narcolepsy-like MSLT abnormalities

Prevalence estimates for various MSLT findings and potential narcolepsy definitions are reported in Table 2, together with % HLA-DQB1*0602 positivity. Multiple SOREMPs were observed in 13.1% of males and 5.6% of females. An MSLT MSL ≤8 min and ≥2 SOREMPs (diagnostic of narcolepsy) was observed in 5.9% of males and 1.1% of females. As the ICSD-2 criteria for narcolepsy includes a clinical complaint of excessive daytime sleepiness, we also estimated prevalence for males and females with a subjective complaint of sleepiness plus an MSLT positive for narcolepsy. To define subjective sleepiness in this sample, we used a cut-off EPW score of ≥11 based on our experience with narcolepsy patients (92% of 1074 narcolepsy patients in our database have an EPW ≥11) and/or the report of feelings of excessive daytime sleepiness 'often' or 'almost always'. Using these criteria, 12 males (4.15%) and one female (0.37%) may have narcolepsy (Table 2). None reported cataplexy.

Predictors for SOREMPs

The lack of effect of SDB and past sleep history on the occurrence of SOREMP, together with the fact that males with SOREMP more frequently took antidepressant (Table 1), was examined further with multivariable modelling (Tables 3 and 4). In naps and using SOREMP as the outcome and a repeated measure logistic analysis, we found that DQB1*0602 had a positive effect in males but no effect in females (Table 3). A similar effect was obtained when the outcome was the occurrence of two or more SOREMPs (Table 4). We also found that sleep the day before NPSG (but not diary sleep 2 days before, data not shown) had a small but significant effect on ≥1 and 2 SOREMP occurrence

Table 2 HLA association with narcolepsy as defined by sleepiness and SOREMPs

Variable	Total (n = 556)				Males (n = 289)				Females (n = 267)			
	n	% (CI)	% HLA +	HLA association OR (CI)	n	% (CI)	% HLA +	HLA association OR (CI)	n	% (CI)	% HLA +	HLA association OR (CI)
0 SOREMP	470	84.5 (82–88)	23.08		231	79.9 (75–85)	24.11		239	89.5 (86–93)	22.08	
≥1 SOREMP	86	15.5 (12–18)	31.74	1.53 (0.93–2.54)	58	20.1 (15–25)	32.76	1.53 (0.82–2.87)	28	10.5 (7–14)	29.63	1.49 (0.62–3.59)
≥2 SOREMPs	53	9.5 (8–14)	30.32	1.45 (0.78–2.71)	38	13.1 (9–17)	39.47	2.05 (1.00–4.21)	15	5.6 (3–8)	7.14	0.27 (0.04–2.13)
≥2 SOREMPs, MSL ≤8	20	3.6 (8–12)	35.00	1.80 (0.70–4.64)	17	5.9 (2–10)	41.18	2.20 (0.80–6.07)	3	1.1 (0–2)	0	Non-estimable*
≥2 SOREMPs, MSL ≤8, EDS Y or/and EPW ≥11	13	2.3 (1–3)	38.46	2.09 (0.67–6.54)	12	4.2 (2–6)	41.67	2.25 (0.69–7.38)	1	0.4 (0–10)	0	Non-estimable*

MSL = mean sleep latency; EDS Y = feelings of excessive daytime sleepiness, often or almost always; EPW = Epworth sleepiness scale. *Non-estimable owing to absence of subjects in some categories and small sample sizes.

Table 3 Multivariate modelling with repeated measures predicting SOREMP in naps

		Males		Females	
		OR (CI)	*P*-value	OR (CI)	*P*-value
DQB1*0602	Positive versus negative	1.98 (1.06–3.70)	0.032	1.01 (0.43–2.37)	0.99
NPSG total sleep time	<6 h versus ≥6	0.94 (0.45–1.91)	0.85	1.13 (0.44–2.90)	0.80
Apnea–hypopnea index	Increase of 10 events/h	0.90 (0.71–1.14)	0.37	0.78 (0.45–1.34)	0.36
Mean % oxygen saturation	Decrease of 15%	1.81 (1.14–2.87)	0.012	1.06 (0.74–1.52)	0.75
Diary sleep before lab study	Decrease of 1 h	1.29 (0.98–1.72)	0.07	1.15 (0.68–1.95)	0.61
Habitual sleep	Decrease of 1 h	1.06 (0.77–1.45)	0.72	1.00 (0.71–1.41)	0.99
Shift work	Yes versus no	5.98 (2.35–15.20)	0.0002	Non-estimable*	
REM suppressant antidepressants	Taking versus not taking	1.81 (0.75–4.39)	0.19	0.35 (0.13–0.97)	0.044
Non-REM suppressant antidepressants	Taking versus not taking	10.24 (2.86–36.62)	0.0003	28.37 (1.70–10.73)	0.002

NPSG = nocturnal polysomnography. *Non-estimable owing to absence of subjects in some categories and small sample sizes.

Table 4 Multivariate analysis predicting ≥1 and ≥2 SOREMP during the MSLT

		Males				Females			
		≥1 SOREMP		≥2 SOREMPs		≥1 SOREMP		≥2 SOREMPs	
		OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value
DQB1*0602	Positive versus negative	1.71 (0.81–3.61)	0.16	2.56 (1.07–6.13)	0.035	1.45 (0.51–4.10)	0.48	0.27 (0.03–2.58)	0.26
NSPG total sleep time	<6 h versus ≥6	0.72 (0.31–1.65)	0.44	1.11 (0.41–3.03)	0.84	1.08 (0.36–3.29)	0.89	1.36 (0.31–6.04)	0.69
Apnea–hypopnea index	Increase of 10 events/h	0.90 (0.65–1.24)	0.52	0.84 (0.56–1.23)	0.36	1.16 (0.69–1.95)	0.57	0.21 (0.03–1.61)	0.14
Mean % oxygen saturation	Decrease of 15%	2.10 (1.12–3.95)	0.021	2.09 (1.03–4.21)	0.04	1.12 (0.58–2.18)	0.73	1.36 (0.56–3.32)	0.50
Diary sleep before lab study	Decrease of 1 h	1.68 (1.13–2.46)	0.009	1.61 (1.00–2.57)	0.049	1.24 (0.75–2.07)	0.41	1.22 (0.62–2.42)	0.57
Habitual sleep	Decrease of 1 h	0.96 (0.62–1.48)	0.86	1.40 (0.82–2.39)	0.22	1.18 (0.72–1.94)	0.50	0.96 (0.51–1.79)	0.90
Shift work	Yes versus no	10.19 (1.68–61.97)	0.012	29.37 (3.96–217.02)	0.001	Non-estimable*		Non-estimable*	
REM-suppressing antidepressants	Taking versus not taking	2.16 (0.77–6.04)	0.14	2.01 (0.55–7.36)	0.29	0.40 (0.12–1.34)	0.14	0.30 (0.05–1.63)	0.16
Non-REM-suppressing antidepressants	Taking versus not taking	3.90 (0.77–19.71)	0.10	8.24 (1.50–45.24)	0.015	5.92 (1.52–23.00)	0.010	11.19 (2.34–53.52)	0.003

*Non-estimable owing to absence of subjects in some categories and small sample sizes; NPSG: nocturnal polysomnography.

in males (Table 4). TST before the MSLT, whether treated as a continuous variable or as TST ≥ or <6 h (a typical cut-off used as a guideline for correct interpretation of the MSLT), had no effect in all models.

We also found that AHI, whether treated as a continuous variable or as a categorical variable (AHI ≥15 and 30), did not influence SOREMPs (Tables 3 and 4), but decreased lowest oxygen saturation had a small but significant and consistent effect on SOREMP occurrence (Tables 3 and 4), as previously reported in a study of subjects with SDB (Chervin and Aldrich, 2000). A 15% drop in lowest oxygen saturation during the night, a parameter selected to be comparable with the study of Chervin and Aldrich (2000), increased the risk of ≥2 SOREMPs by 1.3. This effect was difficult to explain as it also occurred with a similar effect-size in subjects without SDB (AHI ≤1 or AHI ≤5), or with SDB at various AHI cut-offs, without being statistically significant because of smaller sample sizes in these subgroups.

Similarly, against expectation, we found that males with SOREMPs were more likely to take antidepressants than males without SOREMPs (Tables 3 and 4). This was surprising, as antidepressants such as SSRI are known to be strong REM sleep suppressants. A possible explanation for this finding could have been depression itself. This was, however, unlikely as Zung ≥50, a marker of depression (Zung, 1965), had no effect on this association and by itself. Further, in males (and females) not taking antidepressants, Zung ≥50 had no effect on the occurrence of SOREMPs. We therefore next separated antidepressant into two classes, those with known REM suppressant effects and those without (mostly bupropion, nefazodone and mirtazapine). Surprisingly, we found that most of the subjects with multiple SOREMPs

on antidepressants were taking non-REM suppressant antidepressant such as mirtazapine, bupropion and nefazodone. REM suppressant antidepressants were also increased in males, but not females. Using multivariate analysis, a large increase in the risk of SOREMP was observed in subjects taking non-REM suppressant antidepressants (Tables 3 and 4).

We next explored if the strong male/female difference in SOREMP occurrence was due to a sex difference in the ability of males to fall asleep more easily in naps. To do so, repeated measure models predicting REM sleep were also estimated only using naps where sleep onset actually occurred and with control of nap sleep latency. These new models showed significant effects for sleep latency in all cases and did not change beta coefficients or significant effects in males and females; these models are thus not presented. We also explored if the effects of parameters with reported effects on SOREMP occurrence (Tables 3 and 4) varied by naps. The occurrence of REM sleep in the various naps was 4.5% (25 out of 556) in nap 1, 6.7% (37 out of 556) in naps 2 and 3, and 7.7% (43 out of 556) in nap 4. For nap 5, a sample enriched in subjects having had SOREMPs in the previous 4 naps, 8.3% (22 out of 266) occurrences were observed (including two subjects with no SOREMPs in the first four naps and one SOREMP in the fifth nap). The effects of the identified predictors were also generally similar in the various naps, with DQB1*0602 having significant effects in naps 1, 2 and 4; lowest oxygen saturation having significant effects in naps 3 and 4 and mean sleep the night before the NPSG having significant effects on nap 3 and 4 in most models. Nap 5 was also analysed separately, but data were not significant because of lower sample size.

The other potential confounders listed in Table 1 were finally added to these models. The only other significant parameters were subjective sleepiness parameters (EPW, feelings of EDS), REM latency and nap latency (individual nap latency in the repeated measure models; MSL in the logistic model predicting $\geq$1 or $\geq$2 SOREMPs). As expected, MSLT sleep latencies, NPSG, REM latency and parameters significant in Table 1 were significantly associated (data not shown). Adding these parameters did not greatly change beta coefficient estimates for predictors listed in Tables 3 and 4 but did reduce statistical significance; depending on the final list of parameters included, differences in these other parameters reflecting sleepiness are not likely to cause SOREMP, but rather be associated with it, for example, in the context of the narcolepsy phenotype. We therefore decided not to present models including these parameters, but to rather focus on potential predictors.

HLA positive and negative subjects with multiple SOREMPs

We explored if HLA positive and negative subjects with SOREMPs were significantly different at the symptomatic level, and if HLA-DQB1*0602 positivity had any influence on REM sleep itself in naps. Males (114 naps in 37 subjects) and females (47 naps in 28 subjects) were studied together and separately (Table 5). Sleep latency and REM latencies were similar in HLA positive versus negative subjects in all cases. More twitches and more atonia were observed in HLA positive versus negative males. The length of REM was also slightly longer in HLA positive versus negative subjects overall and in females only. These effects were not altered when adjusted for intake of REM suppressant and non-REM suppressant antidepressants. These results suggest that in subjects with DQB1*0602, REM sleep was more evident both quantitatively (duration) and qualitatively (atonia and twitches, but not REMs or sawtooth wave).

For exploratory purposes, all parameters described in Table 1 were compared in HLA positive versus negative males with $\geq$2 SOREMPs and no SOREMP. No significant differences were found, but sample size for HLA positive males with $\geq$2 SOREMP was small (n = 19).

Discussion

Our results demonstrate a surprisingly high prevalence of MSLT abnormalities compatible with narcolepsy in a randomly selected sample of community adults, independent of SDB and prior history of sleep deprivation. These cases did not report cataplexy. A strong but complex association with antidepressant therapy was also found. The high prevalence of SOREMPs was mostly notable in males. These results challenge generally accepted knowledge regarding the prevalence of narcolepsy without cataplexy and MSLT SOREMPs. We found our results to be compatible with previously published studies, extending data collected in clinical samples to the normal population. Our results suggest the need for further studies in the area of narcolepsy without cataplexy, and the need for re-evaluating the MSLT as a diagnostic tool for narcolepsy.

Initial studies had suggested that the appearance of REM sleep during daytime sleep was rare in healthy controls without daytime sleepiness, yet the number of subjects involved were small. Vogel (1960) was the first to report SOREMPs in narcoleptic patients (Vogel, 1960). Rechtschaffen *et al.* (1963) and others (Hishikawa *et al.* 1968) suggested that short REM latency may be diagnostic for narcolepsy. In his study, Rechstchaffen *et al.* noted the appearance of REM onset in a daytime nap in only one of 23 healthy volunteers (Rechtschaffen *et al.*, 1963). Dement *et al.* (1966), found that 20 out of 24 of narcoleptic patients with cataplexy entered REM sleep within a few minutes in a daytime nap, whereas only 1 out of 10 patients with isolated daytime sleepiness did so. This led to the development of the clinical MSLT as we use it today (Carskadon *et al.*, 1986; Littner *et al*, 2005).

Whereas the finding of multiple SOREMPs in narcolepsy was quickly established, very few healthy controls were studied to address the specificity of this finding

Table 5 Repeated measure comparison of REM parameters in HLA-DQB1*0602 positive and negative in naps

	Total			Males			Females		
	DQB1*0602		*P*-value	DQB1*0602		*P*-value	DQB1*0602		*P*-value
	Positive	Negative		Positive	Negative		Positive	Negative	
N	65			37			28		
Nap no.	159			112			47		
Sleep latency	8.5 ± 0.8	8.7 ± 0.6	0.82	8.3 ± 1.0	8.0 ± 0.7	0.78	8.3 ± 1.3	9.6 ± 0.9	0.39
REM latency	7.1 ± 0.6	7.1 ± 0.4	0.93	7.3 ± 0.6	7.6 ± 0.5	0.71	7.6 ± 1.1	6.6 ± 0.7	0.44
REM length	7.1 ± 0.7	5.2 ± 0.5	0.0188	7.8 ± 0.7	6.4 ± 0.6	0.10	7.2 ± 1.4	3.7 ± 1.0	0.0486
REM sleep twitch no./min	35%	20%	0.06	39%	20%	0.06	28%	20%	0.62
Atonia % (yes/no)	93%	88%	0.38	97%	88%	0.05	90%	88%	0.84
Sawtooth	95%	99%	0.18	91%	98%	0.19	100%	100%	–
REM index	2.5 ± 0.3	2.5 ± 0.2	0.85	2.5 ± 0.3	2.4 ± 0.2	0.80	2.5 ± 0.5	2.5 ± 0.3	1.00
REM no.	16.5 ± 3.1	13.7 ± 2.2	0.43	19.5 ± 3.9	16.6 ± 3.0	0.50	13.1 ± 3.0	10.7 ± 1.7	0.50

(Richardson *et al.*, 1978; Mitler *et al.*, 1979). Mitler *et al.* (1979) demonstrated that the presence of ≥2 SOREMPs discriminated 40 narcoleptic patients from 13 control subjects without daytime sleepiness (Mitler, 1982). Folkerts similarly found that ≥2 SOREMPs were found in 28 of 30 narcolepsy patients (27 with cataplexy), but in none of 30 age-matched control subjects (Folkerts *et al.*, 1996). Further studies compared narcoleptic patients with other patients with daytime sleepiness in a clinical setting (Van den Hoed *et al.*, 1981; Mitler, 1982; Zorick *et al.*, 1982; Reynolds *et al.*, 1982; Amira *et al.*, 1985; Moscovitch *et al.*, 1993; Aldrich *et al.*, 1997; Dauvilliers *et al.*, 2004). Healthy controls were not studied and false-positives in a clinical setting were suggested to reflect sleep deprivation, 'narcolepsy without cataplexy' or other sleep disorders.

As early as 1982, Walsh *et al.* (1982) found that 4 out of 14 (28%) patients with the sleep apnea syndrome had ≥2 SOREMPs, suggesting the need to exclude other sleep disorders before diagnosing narcolepsy. In 1997, Aldrich *et al.* noted a high prevalence of ≥2 SOREMPs (14%) in patients evaluated at a sleep clinic, a minority of which (8.2%) were later diagnosed as narcoleptic (Aldrich *et al.*, 1997). Most strikingly, 7% of subjects with SDB and sleep disorders other than narcolepsy (662 subjects) also had ≥2 SOREMPs. A follow-up analysis of the same sample by Chervin and Aldrich (2000) also found that in patients with a final diagnosis of SDB, ≥2 SOREMPs occurred in 4.7% of cases and were best predicted by male sex and decreased lowest oxygen saturation, but not AHI (Chervin and Aldrich, 2000). Reduced MSLT MSL and NPSG REM latency also predicted SOREMPs during the MSLT, as we found in our study. The conclusion of these studies was that the presence of other sleep disorders, most notably sleep apnea, may confound the MSLT. It is, however, notable that the predictors identified in the Chervin and Aldrich study (Chervin and Aldrich, 2000) are strikingly similar to ours in a normal population sample, largely without sleep apnea.

Our finding of high SOREMP prevalence in a representative sample also agrees with more recent, largely unpublished data in healthy individuals. Bishop *et al.* (1996) studied 139 healthy, drug-free volunteers without sleep-related symptoms, medical or psychiatric conditions. These volunteers were young (mean age = 33) subjects without habitual napping habits wanting to enter pharmacological protocols. NPSG indicated no sleep apnea and adequate TST. A surprisingly high prevalence of ≥2 SOREMPs (24 subjects, 17%) was observed. As in our study, subjects with multiple SOREMP were mostly male (75 versus 47%). Multiple SOREMP was found to be related to MSL during the MSLT but not to subjective reports of daytime sleepiness, as evaluated using the EPW scale. This report generated a considerable amount of controversy (Rye and Bliwise, 1997) and was largely ignored. Since then, however, two studies, published as abstracts, have also suggested a high prevalence of SOREMPs in normal individuals. In the first, Geisler *et al.* (1998) studied 100 normal volunteers aged 20–69 years old selected on the basis of an absence of any sleep problems and excessive daytime sleepiness, and found 11% with ≥1 SOREMPs and 3% with ≥2 SOREMPs. Most recently, Singh *et al.* (2005) studied 539 subjects, 333 of whom were randomly selected and 206 subjectively sleepy, and found that 3.9% had ≥2 SOREMPs. In this study, short sleep latency on the MSLT but not NPSG TST or EPW predicted ≥2 SOREMPs. Together with the present study, these preliminary reports indicate that the high prevalence of ≥2 SOREMP is not limited to patients with sleep disorders (e.g. sleep apnea), but extend to the general population.

Our study not only demonstrated a high prevalence of narcolepsy-like MSLT findings in a randomly selected sample of adults but it also challenged widely held notions on what could be confounding the interpretation of the MSLT. Intake of antidepressant for example, a treatment well known to decrease REM sleep during nocturnal sleep after acute administration (Mayers and Baldwin, 2005; Wilson and Argyropoulos, 2005), was associated with unexpectedly complex effects on SOREMPs. Further analysis suggested that this effect was dependent upon the type of antidepressants used. Indeed, in males and females with multiple SOREMPs

increased antidepressant use was most evident for non-REM suppressant compounds (bupropion, mirtazapine and nefazodone) (Mayers and Baldwin, 2005; Wilson and Argyropoulos, 2005). Even for REM suppressant antidepressants such as SSRI (Wilson and Argyropoulos, 2005), however, either increased (males) or decreased (females) antidepressant intake was observed in volunteers with SOREMPs. This last finding may reflect the fact that these subjects were chronically treated with antidepressant therapy and/or different dosages (Wilson and Argyropoulos, 2005). REM suppressant effects are known to decrease during long-term therapy and to be associated with increased phasic activity (Reynolds *et al.*, 1997; Wilson and Argyropoulos, 2005). A recent study in the WSC cohort found only a slightly prolonged nocturnal REM latency in subjects treated with antidepressants (Szklo-Coxe *et al.*, 2005).

Another possibility could have been that antidepressant intake in these subjects reflected depression, a condition that has also been linked to reduced REM latency (Giles *et al.*, 1998; Argyropoulos and Wilson, 2005). Importantly, however, our study did not find an association between SOREMPs and depression, as reflected with Zung $\geq$50. This was the case even in subjects without antidepressant treatment. Nocturnal REM sleep latency was also found to be unaltered in WSC subjects with Zung $\geq$50 (Szklo-Coxe *et al.*, 2005). It may thus be that some antidepressant treatment, when taken chronically, actually increased the occurrence of REM sleep during naps. Stopping antidepressant 2–3 weeks before the MSLT, as currently recommended, may thus be needed not only to avoid false-negative but also to decrease false-positives. Against expectation, it may be most important to control antidepressant therapy in the case of non-REM suppressant antidepressants such as bupropion, nefazodone and mirtazapine. Additional studies would be needed to evaluate every antidepressant separately and to identify the washout period needed.

As mentioned above, we also found that AHI (linear or various cut-off values) had no effect on the occurrence of SOREMPs. The finding that a decrease in the lowest nocturnal oxygen saturation increases the risk of multiple SOREMPs in males, also found in the Chervin and Aldrich study (Chervin and Aldrich, 2000), is of unknown significance. Decreased lowest nocturnal oxygen saturation may be linked to sleep apnea, obesity, hypoventilation, asthma or other factors. In our sample, the effect of decreased lowest oxygen saturation on SOREMP was not altered when AHI was added as a cofactor in our multivariate models. An analysis in subjects with AHI $\leq$1 and AHI $\leq$5 also detected a similar association, suggesting that not all could be accounted by SDB. We also hypothesized that mild versus severe levels of sleep apnea would have opposite effects on SOREMP occurrence (for example, severe sleep apnea would delay the onset of REM sleep, while mild SDB would reduce REM latency). This hypothesis was, however, also not supported by our analysis with various AHI cut-offs. These results are reminiscent of studies in sleep apnea populations, where both hypoxemia and sleep fragmentation contribute to daytime sleepiness, as measured using the MSLT (Punjabi *et al.*, 2002). AHI is well known to only capture a portion of the severity and nature of SDB. Additional studies will be needed to further examine AHI in combination with various oxygen saturation levels. Whether or not the association between lowest oxygen saturation and SOREMP found in this study reflect mild SDB, it was a small effect; a 15% drop in mean O_2 saturation only increased the probability of $\geq$2 SOREMP by 30%, an effect similar to that reported in the Chervin and Aldrich study (Chervin and Aldrich, 2000).

A third factor widely believed to increase MSLT SOREMP is shift work (Santos *et al.*, 2004) and sleep deprivation (Dinges *et al.*, 1997). We found a strong increase in shift workers in males with SOREMPs, but no difference in females. This was in spite of the fact that females in our group are more frequently shift workers (Table 1). Current guidelines for the clinical MSLT suggest that the use of the MSLT to diagnose narcolepsy is suspect if TST before the MSLT day is shorter than 6 h (Medicine AaoS, 2005). In this study, MSLT SOREMPs were unrelated to NPSG TST, whether assessed continuously or as a categorical variable ($\geq$6 or <6 h) (American Academy of Sleep Medicine, 2005). We also studied the potential effect of short sleep two nights before the NPSG/MSLT and of habitual sleep amounts, and found only a small effect of decreased sleep the night before the NPSG. We suggest that the need for TST $\geq$6 h before the MSLT may not be justified by existing data, but that sleeping at home well at least one night before the entire procedure may be important.

The absence of expected associations raised the question of what the meaning of SOREMP is in the general population. Like another group (Drake *et al.*, 2000), we found that the scoring of SOREMPs during the MSLT was highly reliable, and likely to measure a genuine biological trait. SOREMPs during the MSLT also correlated with NPSG REM latency, a parameter independently scored by different technicians (see Table 1, data not shown for multivariate models). A very short REM latency during NPSG is also predictive of narcolepsy in clinical samples (Rechtschaffen *et al.*, 1963; van den Hoed *et al.*, 1981; Rosenthal *et al.*, 1990*a*, *b*; Folkerts *et al.*, 1996; Aldrich *et al.*, 1997; Overeem *et al.*, 2001; Dauvilliers *et al.*, 2003*a*). As in other studies (Bishop *et al.*, 1996; Chervin and Aldrich, 2000; Singh *et al.*, 2005), we found that the occurrence of SOREMP was strongly associated with short sleep latencies during the MSLT naps (Table 1, data not shown for multivariate models). SOREMP occurred with the same frequency at every nap opportunity, although it was slightly less frequent in the first nap. As SOREMP can only occur when sleep onset has been realized in a given nap, we also studied sleep latencies in naps where REM has not occurred and still found significant shorter sleep latency in subjects with SOREMPs, indicating a genuine association with objectively measured sleepiness. In line with other studies (Bishop *et al.*, 1996; Singh *et al.*, 2005), we also found that males with SOREMPs versus those

without SOREMPs were subjectively sleepier, as reported by questionnaire items, but that the difference was only small. This result is in line with multiple reports indicating weak to moderate correlations between objective measures (e.g. MSL) and subjective (e.g. EPW) reports of sleepiness in community samples (Punjabi *et al.*, 2003; Kim and Young, 2005) and patients (Olson *et al.*, 1998; Sangal *et al.*, 1999). Similarly, we also found that some REM-related symptoms (cataplexy-like symptoms and HH) but not others (SP) were increased in males with multiple SOREMPs. This last finding corroborates increasing evidence suggesting that these parameters are not very specific for narcolepsy but correlate with excessive daytime sleepiness (Ohayon *et al.*, 1996, 1999; Szklo-Coxe *et al.*, 2005, 2006). Recent studies in the WSC sample (Szklo-Coxe *et al.*, 2005) and other samples (Ohayon *et al.*, 1996, 1999) indicated statistical correlation with these symptoms and depression/anxiety ratings, with a possible partial mediation through excessive daytime sleepiness (Szklo-Coxe *et al.*, 2005).

The low frequency of SOREMP in females led us to hypothesize that a previously reported lower frequency to sleep onset in MSLT naps in females (Punjabi *et al.*, 2003) may reduce SOREMP opportunities. To address this issue, multivariate analysis was conducted only in naps where sleep onset had actually occurred. This analysis still indicated a strong predisposition to SOREMP in males even after further control of sleep latency, suggesting a difference unrelated to sleep-onset tendencies. This, together with the fact that none of the parameters found to be significant in males with SOREMP predicted SOREMPs in females, suggests fundamental differences in REM sleep regulation between the sexes. Additional studies with increased sample size in females will be needed to address these issues.

In consideration of the above, could SOREMPs in the population reflect a mild narcolepsy phenotype, especially in males? The only prevalence study available for narcolepsy without cataplexy found a strong male predisposition (Silber *et al.*, 2002), but much lower prevalence estimates (Silber *et al.*, 2002) than found here. This study examined all medical records to identify diagnosed cases, leading to a prevalence estimate for narcolepsy without cataplexy of 0.032% in males and 0.012% in females (~36% of all narcolepsy cases). Large case series for narcolepsy without cataplexy are rare, but a male predisposition was found in most cases (Hong *et al.*, 2002; Mignot *et al.*, 2002; Dauvilliers *et al.*, 2003*b*). Several subjects have also suggested a male predisposition for narcolepsy–cataplexy (Honda *et al.*, 1983; Dauvilliers *et al*, 2001, 2003*a*). The higher prevalence in our sample may reflect the fact that narcolepsy without cataplexy is a milder phenotype that does not come to the attention of the medical communities. If so, some of these subjects may be more frequently shift workers and antidepressant takers in an attempt to compensate their mild and undiagnosed/misdiagnosed narcolepsy symptoms.

The possibility of a disease continuum between our subjects with multiple SOREMPs and narcolepsy–cataplexy was studied through the study of HLA-DQB1*0602 in the population. HLA-DQB1*0602 is tightly associated with narcolepsy and hypocretin deficiency (95–100% HLA positivity versus 25% in the general population) (Nishino *et al.*, 2000; Dalal *et al.*, 2001; Hong *et al.*, 2002; Kanbayashi *et al.*, 2002; Krahn *et al.*, 2002; Mignot *et al.*, 2002; Dauvilliers *et al.*, 2003*b*; Lin *et al.*, 2006). Interestingly, increased HLA-DQB1*0602 positivity was also observed in our SOREMP sample (30–40%, Table 2). This result only reached significance in males, where larger sample sizes were reached, and was independent of confounding variables (Tables 3 and 4). The increased HLA frequency in subjects with multiple SOREMPs in our sample also corroborate an earlier study in the same population where shorter NPSG REM latency was observed in DQB1*0602 positive participants (Mignot *et al.*, 1999). That DQB1*0602 has an effect on REM sleep in at least a subset of volunteers was also substantiated by our observation that REM sleep may be more evident in HLA positive subjects in terms of short REM latency, duration of REM sleep and atonia in naps with REM sleep (Table 5).

A 30–40% HLA positivity in volunteers with multiple SOREMPs is in line with HLA typing results in case series of patients with narcolepsy without cataplexy. Approximately 25% of such cases are hypocretin-deficient, a result that may explain the slight increase in HLA positivity from the 25% population frequency to 30–40% (Honda *et al.*, 1983; Mignot *et al.*, 1997; Lin *et al.*, 2006). These results may indicate that a fraction (e.g. 10–15%) of the subjects with multiple SOREMPs may actually have genuine HLA-associated hypocretin deficiency. If so, narcolepsy–cataplexy may be the extreme expression of a larger, biochemically defined, disease prevalence (up to a few per cent of the population), but with limited symptomatic complaints in most cases. This result would be reminiscent of similar findings in other HLA-associated autoimmune diseases such as Type I diabetes (Naik and Palmer, 2003), thyroiditis (Vanderpump *et al.*, 2002) and coeliac disease (Hovdenak *et al.*, 1999) where mild, silent or late-onset cases are increasingly recognized.

In summary, we found that a significant portion of randomly selected adults has MSLT findings consistent with narcolepsy, but without definite cataplexy. These cases were mostly male and would meet ICSD-2 diagnostic criteria for narcolepsy without cataplexy. Further analysis indicated that antidepressant therapy (mostly with newer, non-REM suppressant antidepressant) and shift work may contribute to multiple SOREMPs; these parameters may need to be considered when interpreting MSLT results. Male volunteers with $\geq$2 SOREMPs were more frequently HLA-DQB1*0602 positive, suggesting some degree of aetiological overlap with narcolepsy–cataplexy and hypocretin deficiency. Increased sample size and careful medical evaluation of SOREMP positive subjects by a sleep disorder specialist (with re-testing after adequate withdrawal of psychotropic compounds and SDB treatment in some cases) and possibly biochemical evaluation (CSF hypocretin-1 measurements) will be needed to confirm and extend these findings.

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