The sleep-onset period in narcoleptics is typically differentiated from that of normal sleepers by using the multiple sleep latency test (MSLT) to assess latency to sleep onset and determine the presence of sleep-onset rapid-eye-movement (REM) periods. Narcoleptics fall asleep faster than normals do when placed in an environment conducive to sleep onset. Daytime MSLT polysomnography in narcoleptics typically reveals a reduced sleep-onset latency of less than 5 minutes in addition to the occurrence of REM sleep within 10-20 minutes of sleep onset on at least two nap attempts. Normal sleepers typically require 10-15 minutes to fall asleep on the MSLT, and rarely have sleep-onset REM periods. Furthermore, Broughton and Aguirre have documented that latency to sleep onset tends to be shorter prior to narcoleptic sleep-onset REM periods than narcoleptic NREM onsets, suggesting that sleepiness may differ qualitatively in narcoleptics, reflecting either selective pressure for REM sleep or pressure for NREM sleep.

By relying on visually scored sleep measures to distinguish normal sleepers from narcoleptics, differences within the microstructure of the normal and narcoleptic transition from wakefulness to sleep onset have been largely ignored. Electroencephalographic (EEG) spectral analysis provides a method of examining the microstructure of the process of sleep onset by tracking spectral changes in EEG activity throughout the entry into sleep. Although several

**Summary:** The sleep-onset period of 10 drug-free patients with narcolepsy-cataplexy and 10 normals matched for age and gender was investigated using the multiple sleep latency test to elicit episodes of intentional sleep onset. Spectral analyses were calculated for delta, theta, alpha, sigma, and beta frequencies using 5-second epochs beginning at lights-out and continuing until the first 2 minutes of stage 2 or REM sleep were reached, or until 20 minutes had elapsed. The sleep-onset period was divided into quartiles, and mean root mean square (RMS) amplitude within each quartile was calculated. Mean delta amplitude was significantly higher across the sleep-onset period of narcoleptic REM naps and narcoleptic stage 2 naps compared to the sleep-onset period of normal stage 2 naps or normal stage 1 naps. Mean theta amplitude was significantly higher for narcoleptic REM naps compared to normal stage 1 naps, and tended to be higher for narcoleptic stage 2 naps compared to normal stage 1 naps. Mean alpha amplitude was significantly lower for narcoleptic REM naps and narcoleptic stage 2 naps compared to normal naps containing just stage 1. Mean sigma amplitude was significantly lower for narcoleptic REM naps compared to normal stage 1 naps, and tended to be lower for narcoleptic REM naps compared to normal stage 2 naps. Mean beta amplitude did not differ between the narcoleptic and normal sleep-onset process. These findings support the existence of electrophysiologic differences within the microstructure of the process of sleep entry in narcoleptics and normals.

**Key words:** Narcolepsy; sleep onset; EEG spectral analysis

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studies have investigated spectral changes occurring during the normal sleep-onset process, to our knowledge not one study has used EEG spectral analysis to investigate the sleep-onset period in narcolepsy.

There is much debate about the precise point at which sleepiness ends and sleep begins. The physiologic onset of sleep has traditionally been characterized by decreases in fast, low-voltage EEG beta activity, decreases in the regularity and frequency of EEG alpha activity, and increases in slow delta and theta EEG activities. Spectral changes occurring in the EEG during the sleep-onset period have been investigated in normal sleepers by Ogilvie and colleagues. Participants were instructed to attempt to fall asleep while responding to a faint auditory tone. Fast Fourier transformation (FFT) power data were collected on the 5-second period prior to the tone onset, and were sorted into one of five bins on the basis of whether and how quickly the participant responded to the tone. Comparing the longest response time with the shortest response time, theta power increased, and alpha and beta power decreased. Significant increases in power were found across all frequency bands (delta, theta, alpha, sigma, and beta) at the transition into sleep (defined once the participant failed to respond to the tone). It was concluded that computer-based FFT analyses of 5-second EEG epochs detect transient fluctuations in arousal during the transition to sleep that remain unseen in visual scoring of 30-second EEG epochs. Ogilvie et al identified the sleep-onset period as consisting of “the lengthening of response times and intermittent response failure,” and defined sleep onset as “behavioral response cessation coupled with sharp increases in EEG synchronization.”

Badia, Wright, and Wauquier investigated spectral fluctuations of EEG during the transition from wakefulness to sleep in normal sleepers. Participants who demonstrated a ‘smooth transition’ into sleep, having at least three continuous 30-second epochs of wakefulness followed by three epochs of stage 1 sleep, were selected for analysis. Spectral EEG changes across an abbreviated wake-sleep transition period (ie, the last three epochs of wakefulness and the first three epochs of stage 1) were investigated for the broadbands 3-7 Hz (delta-theta), 8-12 Hz (alpha), and 13-25 Hz (sigma-beta) using 30-second epochs, and for single-hertz EEG (ie, from 3-4 Hz to 24-25 Hz) using both 30- and 5-second epochs. Power within the alpha broadband decreased, whereas power within the delta-theta broadband increased during the last epoch of wakefulness prior to stage 1. No changes were found in the sigma-beta broadband across the sleep-onset period. Single-hertz analyses of spectral changes occurring within the 30- and 5-second epochs across the transition into sleep revealed significant increases in the 3-4 Hz delta band and the 4-5 Hz theta band, and decreases in the 10-11 Hz alpha band. In a subsequent study, Wright, Badia, and Wauquier observed increases in theta power and decreases in alpha and beta power across the last minute of wakefulness and the first minute of stage 1 sleep.

Hori investigated the oscillatory nature or unsteadiness of EEG activity during the transition from wakefulness to sleep in normal young adults. Mean power and the coefficient of variation (ie, standard deviation/mean) were determined for 1-minute segments from 10 minutes before to 30 minutes after the onset of visually scored stage 1 sleep. Mean delta and theta power increased rapidly after the onset of stage 1. The coefficient of variation for delta, theta, and alpha frequency bands increased significantly just before or immediately after the onset of stage 1, and continued to increase significantly for about 10 minutes. Thus, an unsteadiness or oscillation of EEG activity was shown to be characteristic of the sleep onset period, as indicated by the increased coefficients of variation.

A search of the literature for studies of the sleep-onset period in narcolepsy revealed an abstract that compared EEG power spectra during sleep-onset REM periods with those occurring during nocturnal periods of REM sleep in three narcoleptics. Sleep-onset REM periods and REM sleep did not differ in the amount of delta, theta, alpha, or beta power.

Borbély et al proposed that the prevalence of delta activity in the EEG of nocturnal sleep following sleep deprivation is indicative of the intensity of the sleep process. Specifically, they hypothesized that delta power is related to an endogenous sleep-enhancing factor which accumulates in the brain during the usual waking period, particularly during extended sleep deprivation, and is eliminated or inactivated during sleep. What is of relevance to the present study is whether a clinical population of excessively sleepy individuals (such as narcoleptics) would exhibit EEG power spectra similar to those observed in the recovery sleep of sleep-deprived normals—namely, increases in delta and theta power, and decreases in alpha and beta power. Besset and colleagues investigated EEG power in the delta frequency range during sleep in narcoleptics and controls under baseline conditions and conditions designed to increase prior wakefulness via sleep deprivation. Their purpose was to investigate the homeostatic regulation of sleep in narcoleptics. Nonetheless, it is noteworthy that following both 16 and 24 hours of sleep deprivation, delta power during subsequent sleep was significantly higher in narcoleptics compared to normal controls, and both groups exhibited a decrease in delta power throughout the sleep episode. The authors concluded that the homeostatic function of NREM sleep (ie, the progressive reduction of delta power for successive NREM/REM cycles) is maintained in narcolepsy. However, for the purpose of the present study, it was hypothesized that the increased physiologic sleepiness inherent to narcolepsy would be reflected in enhanced delta activity during the

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sleep-onset period of narcoleptics compared to normals.

Although studies using EEG spectral analysis have generally demonstrated that increases in delta and theta activity, and decreases in alpha and beta activity, occur during the normal transition from wakefulness to sleep onset, and that these frequencies are sensitive to variations in experimentally induced physiologic sleepiness, researchers have yet to apply the technique of EEG spectral analysis toward a comprehensive investigation of the sleep-onset period in a clinical population of excessively sleepy individuals, such as narcoleptics. Studies of visually scored latency to sleep onset have shown evidence for qualitatively different states of sleepiness, with sleepiness prior to REM onsets being greater than that prior to NREM onsets, resulting in shorter latencies to stage 1 sleep. The purpose of the present study was to quantify the daytime sleep-onset period and distinguish between normal sleepers and narcoleptics using EEG spectral analysis.

The present study investigated EEG spectra across the traditional frequency bands (delta, theta, alpha, sigma, and beta) during the transition from wakefulness to sleep in normals and narcoleptics. The MSLT paradigm was used to elicit a number of daytime opportunities for intentional sleep onset. To investigate the presence of qualitatively different states of sleepiness, the sleep-onset process was compared between narcoleptic naps containing REM sleep and narcoleptic naps containing NREM sleep. Spectral differences in the process of sleep onset were investigated by comparing normal naps containing NREM (stage 2) sleep with narcoleptic naps containing REM sleep and narcoleptic naps containing just NREM (stage 2) sleep. Because the EEG of REM sleep and stage 1 are nearly identical electrophysiologically, it was of interest to compare the sleep-onset process for normal naps containing just stage 1 and narcoleptic naps containing REM sleep. The normal process of entry into sleep was investigated by comparing normal naps containing NREM stage 2 with naps containing just stage 1 sleep. It was predicted that (a) compared to narcoleptic naps containing NREM sleep and normal naps containing NREM sleep, EEG activity for the narcoleptic naps containing REM sleep would be greater in the delta and theta frequency bands, and lower in the alpha, sigma, and beta frequencies; and (b) compared to normal controls, narcoleptics would exhibit greater delta and theta EEG activity and less alpha, sigma, and beta activity across the sleep-onset period.

METHODS

Participants

Five female and 5 male patients diagnosed with narcolepsy-cataplexy, and 10 normal sleepers matched for age and gender were studied. Narcoleptics were drug-free at the time of testing. Narcoleptics ranged in age from 29 to 62 years (mean=44.3 years, standard deviation [SD]=11.9 years), and controls ranged from 28 to 56 years (mean=42.7 years, SD=10.6 years). Each participant gave written informed consent and received an honorarium for participation in the study.

A screening process ensured that narcoleptics met the American Sleep Disorders Association’s diagnostic criteria for narcolepsy, and that normal controls did indeed report normal sleep habits (ie, the normals reported that they had no difficulty in falling or remaining asleep at night, typically slept between 6 and 8.5 hours a night, and were alert during the daytime). All narcoleptics complained of daytime sleepiness, and reported taking naps daily or several times weekly. Normals reported that they were generally alert during the day. All narcoleptics had a history of cataplexy, six reported experiencing sleep paralysis and hypnagogic hallucinations at least once a month, and two reported incidents of hypnagogic hallucinations one to five times during their lifetime. No normals reported a history of cataplexy, although two normals reported experiencing incidents of sleep paralysis and four reported incidents of hypnagogic hallucinations one to five times during their lifetimes. All narcoleptics reported multiple nocturnal awakenings. Four normals reported no nocturnal awakenings, and six reported awakening one to three times during the night.

Participants were also given sleep diaries in which they recorded their sleep and wake patterns for the 7 days preceding testing. A t-test showed that narcoleptics and normals did not differ with respect to the self-reported mean duration of nocturnal sleep. The self-reported mean duration of nocturnal sleep ranged from 4.7 to 10.8 hours for the narcoleptics (mean=7.9 hours, SD=2.1 hours), and from 6.2 to 8.6 hours for the normals (mean=7.4 hours, SD=0.9 hours).

Symptoms related to depression (which may elicit sleep-onset REM periods) were assessed with the Beck Depression Inventory (BDI), which consists of 21 statements related to depression. Participants rank each statement according to the degree to which it is experienced (ie, from neutral [0] to maximal severity [3]). BDI scores may range from 0 to 63. A t-test showed that narcoleptics and normals did not differ with respect to the number of depression-related symptoms they reported on the BDI. The scores obtained on the BDI for the narcoleptics ranged from 1.0 to 25.0 (mean=8.6, SD=7.47), and for the normals ranged from 1.0 to 16.0 (mean=4.5, SD=5.0).

Prior to (but not during) testing, nine of the 10 narcoleptics were taking medications for their symptoms. Six narcoleptics were taking central nervous system stimulants (five took methylphenidate hydrochloride, one took dextroamphetamine sulfate) for their excessive daytime sleepi-
ness, three were taking sleeping pills (imovane) to improve their nocturnal sleep, and two were taking REM-sleep suppressants (clomipramine) to reduce their cataplexy. Two of the narcoleptics taking methylphenidate hydrochloride withdrew for 2 days prior to testing, and the seven remaining medicated narcoleptics withdrew from their medications for 7 days prior to testing.

All of the normal participants and nine narcoleptics reported consuming caffeinated beverages. On average, normals consumed 2.5 cups of tea/coffee/pop per day (SD=1.0). Narcoleptics consumed significantly more cups of tea/coffee/pop per day (mean=5.0, SD=3.7) [t(18)=2.13, p=.047]. Five normals and three narcoleptics reported consuming alcoholic beverages. On average, normals consumed 1.8 alcoholic drinks per week (SD=2.7). This did not differ from the average number of alcoholic drinks consumed by narcoleptics (mean=1.5 drinks weekly, SD=3.0). None of the normals reported smoking cigarettes or pipes, whereas four narcoleptics smoked an average of 29 cigarettes per day. During testing, these participants were permitted to smoke after each MSLT session. All participants agreed to refrain from alcohol, caffeine, and sleep-related medications during the 24 hours preceding testing.

PROCEDURE

Participants reported to the sleep lab at 2130 hours for orientation and electrode application. Electrodes were positioned to enable the monitoring of Cz (central) and O2 (right occipital) EEG (referred to A2 [right mastoid]), submental electromyogram (EMG), and outer canthi electrooculogram (EOG) activity. A 16-channel Neurofax polygraph (Nihon Kohden, Irvine, Calif) was used to amplify the polysomnographic recordings. Time constants were set at 0.3 for EEG and EOG recordings, and at 0.03 for EMG recordings. High frequency filters were set at 30 Hz for EEG and EOG, and at 70 Hz for EMG. Recording sensitivity was 7 V/mm for EEG and EOG, and 1-3 V/mm for EMG; the analog-to-digital EEG voltage gain was 30,000. To assess the system signal-to-noise ratio, an input signal of 5 V peak-to-peak at maximum sensitivity (1 V/mm) was used to calibrate the polygraph. On an oscilloscope, signal noise from 2 to 20 Hz averaged less than 0.5 V peak-to-peak, resulting in a signal-to-noise ratio of 1:1 to 2:1 at 1 V. Averaging during subsequent statistical analyses further improves this signal-to-noise ratio. Polysomnographic data from the polygraph were acquired on paper and on a 486 computer using the software program Microcomputer Quantitative Electrophysiology (MQE, Imaging Research Inc., Brock University, St. Catharines, Ontario, Canada). The analog-to-digital conversion was provided by 12-bit National Instruments A/D boards (model APX-5200), while signal processing was done via digital signal processor (DSP) boards from Communication Automation and Control (model DSP32C). The MQE software developed locally by Imaging Research for a Windows 3.1 environment controlled EEG data acquisition, scoring and spectral analyses. The EEG data were digitized using a sampling rate of 102.4 Hz, with a digitizer sensitivity of 12 bits for ±2.83 volts. The digitized EEG, EOG, and EMG activity was logged to the hard drive and copied in the morning to Panasonic re-writable optical disks (LM-D702W) using a Panasonic optical disk system (LF-7010).

Participants retired for the night at 2300 hours, and slept undisturbed until 0800 hours. Following nocturnal polysomnography, the MSLT was administered according to the guidelines for clinical use outlined in the report from the American Sleep Disorders Association.17 Nap opportunities were given at 1000, 1200, 1400, 1600, and 1800 hours. The 8-minute version of the alpha attenuation test18 was administered at 0900, 1100, 1300, 1500, and 1700 hours. The MSLT and AAT were scheduled 1 hour apart to reduce the likelihood that participating in one task would influence the other. Subjective sleepiness was assessed using the Stanford Sleepiness Scale (SSS)19 and the Visual Analogue Sleepiness Scale (VASS).20 The SSS and VASS were administered every half hour during the daytime testing, including immediately prior to and following each MSLT and AAT session. Detailed description of the AAT, SSS, and VASS administration and results may be found elsewhere.21

At the start of each session of the MSLT, participants were instructed to try to fall asleep while lying quietly with their eyes closed in a darkened room. During the MSLT session, EEG, EOG and EMG were recorded on paper and computer according to the parameters outlined above, and were scored in 30-second epochs using the criteria of Rechtschaffen and Kales.15 Sleep onset was defined as the beginning of the first 3 consecutive minutes of stage 1, 2, or REM sleep. Each MSLT session was terminated either 15 minutes following the initial onset of sleep, or after 20 minutes in bed with no sleep. Because the type of sleep obtained on each nap varied within participants and groups, the first nap to occur containing just NREM stages 1 and 2, and the first nap to occur containing REM sleep, were selected for analysis for each narcoleptic participant; the first nap to contain NREM stages 1 and 2, and the first nap to contain just NREM stage 1 were selected for analysis for each normal participant. Table 1 displays the distribution of REM, NREM (stage 1) and NREM (stages 1 and 2) naps selected for analysis in narcoleptics and normals.

Spectral analyses of EEG were calculated using FFT on 5-second epochs with a bin size of 1 Hz within the delta (0.3-4 Hz), theta (4-8 Hz), sigma (12-15 Hz), and beta (15-30 Hz) frequencies at Cz-A2, and within the alpha (8-12 Hz)
Hz) frequency at O2–A1, beginning at lights-out and continuing until the first 2 minutes of stage 2 or REM sleep were reached, or until 20 minutes of wakefulness and stage 1 had passed since lights-out. Before being included in the spectral analysis, each 5-second epoch of EEG was first visually scanned for artifact due to muscle activity and eye movement. Epochs in which the EEG was obscured by artifact were not included in the spectral analysis. In order to maintain the chronology of the transition from wakefulness to sleep and to accommodate for unequal latencies to sleep onset, the sleep-onset period was then divided into quartiles, each quartile having an equal number of 5-second EEG epochs. Mean root mean square (RMS) amplitude within each frequency band was determined for each quartile of the sleep-onset period. RMS amplitude in (V) is the spectral measure calculated by our MQE EEG analysis system. RMS amplitude is to RMS power (V^2) as standard deviation is to variance.22

Data Analyses

Visually scored nocturnal polysomnography and MSLT data were analyzed using t tests and analyses of variance (ANOVAs). Four two-factor 2 × 5 (group-by-MSLT-session) ANOVAs were carried out to determine whether there were any differences between narcoleptics and normals in total RMS amplitude at Cz or O2 during wakefulness or stage 1, collapsing across MSLT session. A series of two-factor 2 × 4 (naptype by quartile) repeated-measures analyses of variance was calculated to compare spectral differences among narcoleptic naps containing REM sleep, narcoleptic naps containing stage 2 sleep, normal naps containing stage 2 sleep, and normal naps containing just stage 1 sleep. For brevity, main effects of quartile are noted only in Table 2. Main effects of naptype, and naptype-by-quartile interactions are reported in detail for mean amplitude within delta, theta, sigma, and beta bands at Cz and alpha at O2. In the presence of a significant main effect of naptype and the absence of a significant interaction, t tests were used to investigate hypotheses related to naptype differences at each quartile of the sleep onset period. Alpha level was maintained at the p=.05 level.

RESULTS

Visually Scored EEG

Nocturnal sleep.—Table 3 shows sleep architecture variables for the nocturnal sleep of narcoleptics and normals. Narcoleptics had a significantly shorter mean latency to stage 1 (mean=7.2 minutes) compared to normals (mean=17.2 minutes) [t(18)=2.29, p=.034], but latency to stage 2 sleep did not differ between narcoleptics (mean=24.6 minutes) and normals (mean=23.4 minutes). Seven of 10 narcoleptics, but none of the normals, had a sleep onset REM period during their nocturnal sleep onset. Mean latency to REM sleep from sleep onset (stage 1) was significantly shorter for narcoleptics (mean=26.4 minutes) than for normals (mean=86.1 minutes) [t(18)=4.24, p=.001]. Narcoleptics spent a greater percentage of their sleep time in stage 1 (mean=20.2 %) compared to normals (mean=11.2 %) [t(18)=2.37, p=.029]. However, percentage of time spent in stage 2, stage 3, stage 4, and REM sleep did not differ significantly between the groups. Total sleep time and sleep efficiency also did not differ significantly between groups.

MSLT.—Table 3 shows sleep architecture variables for the MSLT data of narcoleptics and normals. Mixed two-factor 2 × 5 (group by MSLT session) ANOVAs were conducted for data analyses (Table 2). Four two-factor 2 × 5 (naptype by quartile) repeated-measures ANOVAs were carried out to determine whether there were any differences between narcoleptics and normals in total RMS amplitude at Cz or O2 during wakefulness or stage 1, collapsing across MSLT session. A series of two-factor 2 × 4 (naptype by quartile) repeated-measures analyses of variance was calculated to compare spectral differences among narcoleptic naps containing REM sleep, narcoleptic naps containing stage 2 sleep, normal naps containing stage 2 sleep, and normal naps containing just stage 1 sleep.
performed to investigate main effects of group and time of day on the latency to stage 1 sleep, the percentage of time spent in sleep stages, and the total sleep time and wake time after sleep onset. Latency to stage 2 and REM sleep percentage were not investigated due to the fact that 8 narcoleptics and 6 normals had at least one nap opportunity that contained no stage 2 sleep, and 9 of the 10 normals had just NREM sleep. Significant group effects were found for stage 1 latency, total sleep time, and total wake time after sleep onset. As expected, mean latency to stage 1 sleep was significantly shorter in the narcoleptics (mean=3.5 minutes) compared to the normal sleepers (mean=10.4 minutes) \( F(1,18)=15.11, p=.001 \) (see Table 3). Narcoleptics spent significantly more time asleep (mean=15.2 minutes) than the normals (mean=12.2 minutes) \( F(1,18)=6.53, p=.02 \), and significantly less time awake after sleep onset (mean=0.2 minutes) compared to normals (mean=1.5 minutes) \( F(1,18)=14.53, p=.002 \). However, these main effects were mediated by an interaction with time of day \( F(4,72)=2.96, p=.025 \) for total sleep time, and \( F(4,72)=4.24, p=.005 \) for total wake time after sleep onset. While narcoleptics did not vary across MSLT sessions in the amount of sleep time or wake time after sleep onset, normals slept longer and had less wake time after sleep onset at the 1400-hours nap. No main effects of time of day were found.

The presence of qualitatively different states of sleepiness in the narcoleptics prior to naps containing REM sleep and naps containing just NREM sleep was investigated. For each narcoleptic, mean latency to stage 1 sleep for REM naps, and mean latency to stage 1 for NREM naps, were calculated and then compared using a paired t test. Although mean latency to stage 1 sleep for narcoleptics was shorter on average for naps containing REM sleep (mean=3.2 minutes) than for naps containing just NREM sleep (mean=4.3 minutes), contrary to expectations, the paired t test showed that this difference was not significant.

**EEG Spectral Analyses**

To determine whether normals and narcoleptics differed in total amplitude at Cz or O2 during wakefulness or stage 1, four two-factor 2 \( \times \) 5 (group by MSLT session) ANOVAs were performed. Collapsing across MSLT session, total amplitude at Cz and O2 during wakefulness did not differ between narcoleptics (11.46 V and 10.48 V respectively) and normals (10.29 V and 9.67 V respectively). Nor did total amplitude at Cz during stage 1 differ between narcoleptics (12.05 V) and normals (10.43 V). However, mean total amplitude at O2 during stage 1 was significantly higher in narcoleptics (9.20 V) compared to normals (7.71 V) \( F(1,18)=5.45, p=.031 \).

Table 2 presents a summary of significant main effects for naptype and quartile, and for naptype-by-quartile interactions across each of the frequency bands and naptype comparisons.

**Comparisons within Narcoleptic Naptypes**

To investigate evidence for qualitatively different states of sleepiness within the microstructure of the narcoleptic sleep-onset period, EEG spectra were compared between narcoleptic naps containing REM sleep and narcoleptic naps containing NREM sleep. No significant main effects of naptype were found for mean amplitude within the delta, theta, alpha, sigma, or beta bands. However, significant naptype-by-quartile interactions were found for mean delta amplitude \( F(3,48)=3.90, p=.014 \) (see Fig. 1).
and mean sigma amplitude \([F(3,48)=5.71, p=.002]\) (see Fig. 2). For both the narcoleptic REM naps and the narcoleptic NREM naps, mean delta amplitude increased across the quartiles of the sleep-onset period. However, during the first quartile, mean delta amplitude did not differ between the REM and NREM naps, whereas by the third and fourth quartiles, mean delta amplitude was higher for the NREM naps than the REM naps. Mean sigma amplitude remained at a constant level across the quartiles of the sleep onset period of narcoleptic REM naps. During the first quartile, mean sigma amplitude did not differ between narcoleptic NREM and REM naps. However, by the fourth quartile, mean sigma amplitude was higher for the narcoleptic NREM naps.

Comparisons Between Normal and Narcoleptic Naptypes

EEG spectra across the quartiles of the sleep-onset period were compared between narcoleptic naps containing NREM sleep (stage 2) and normal naps containing NREM sleep (stage 2). A significant main effect of group was found for mean delta amplitude. No group-by-quartile interactions were found. Collapsing across quartiles, mean delta amplitude was significantly higher during narcoleptic naps consisting of NREM sleep stages 1 and 2 (mean=8.2 V) compared to normal naps containing NREM sleep stages 1 and 2 (mean=5.6 V) \([F(1,16)=9.36, p=.007]\) (see Fig. 1). Specifically, mean delta amplitude was greater in narcoleptics across each quartile of the sleep onset period \([t(16)=2.31, p=.035; t(16)=2.86, p=.011; t(16)=2.89, p=.011; t(16)=2.33, p=.033]\).
EEG spectra across the quartiles of the sleep onset period were compared between narcoleptic naps containing NREM sleep (stage 2) and normal naps containing just NREM stage 1. Significant main effects of group were found for mean delta and alpha amplitude, and a trend was observed for mean theta amplitude. Significant group-by-quartile interactions were found for mean delta, alpha, and sigma amplitude. Collapsing across quartiles, mean delta amplitude was significantly higher during narcoleptic naps consisting of NREM sleep stages 1 and 2 (mean=8.2 V) compared to normal naps containing just NREM stage 1 (mean=3.8 V) [F(1,12)=16.90, p=.001] (see Fig. 1). This effect was mediated by a significant group-by-quartile interaction [F(3,36)=11.54, p=.001]. In the narcoleptic NREM naps, mean delta amplitude increased across the quartiles of the sleep-onset period, whereas in the normal naps containing just stage 1, mean delta amplitude remained at a constant level. Collapsing across quartiles, mean alpha amplitude was significantly lower during narcoleptic NREM naps (mean=1.6 V) compared to normal naps containing just stage 1 (mean=3.5 V) [F(1,12)=9.10, p=.011] (see Fig. 3). Moreover, this effect was mediated by a significant group-by-quartile interaction [F(3,36)=6.30, p=.002]. In the narcoleptic NREM naps mean alpha amplitude decreased across the quartiles of the sleep-onset period, whereas in the normal naps containing just stage 1, mean alpha amplitude remained at a constant level. Collapsing across quartiles, mean alpha amplitude tended to be higher during narcoleptic NREM naps (mean=2.8 V) compared to normal naps containing just stage 1 (mean=1.8 V) [F(1,12)=4.61, p=.053] (see Fig. 4). Mean sigma amplitude was mediated by a group-by-quartile interaction [F(3,36)=3.83, p=.018] (see Fig. 2). During the first three quartiles of the sleep-onset period, mean sigma amplitude was lower for narcoleptic NREM naps compared to normal naps containing just stage 1. However, a crossover occurred such that during the fourth quartile mean sigma amplitude was higher in the narcoleptic NREM naps.

EEG spectra were compared between narcoleptic naps containing REM sleep and normal naps containing NREM sleep stage 2. Significant group main effects were found for mean delta amplitude, and a trend was observed for mean sigma amplitude. Significant naptype-by-quartile interactions were detected for mean delta, theta and sigma amplitude. Collapsing across quartiles, mean delta amplitude was significantly higher during the narcoleptic REM naps (mean=7.2 V) compared to the normal naps containing NREM stages 1 and 2 (mean=5.6 V) [F(1,18)=5.36, p=.029] (see Fig. 1). This effect was mediated by a group-by-quartile interaction [F(3,54)=3.27, p=.028]. During the first three quartiles of the sleep-onset period, mean delta amplitude was higher for narcoleptic REM naps than normal stage 2 naps. However, by the fourth quartile of the sleep-onset period, mean delta amplitude did not differ between the narcoleptic REM naps and normal stage 2 naps. Collapsing across quartiles, mean sigma amplitude tended to be lower in narcoleptic REM naps (mean=0.4 V) compared to normal naps containing stages 1 and 2 (mean=0.6 V) [F(1,18)=3.97, p=.062] (see Fig. 2). This effect was mediated by a group-by-quartile interaction [F(3,54)=3.83, p=.015]. Whereas mean sigma amplitude remained at a constant level across all four quartiles of the sleep-onset period in narcoleptic REM naps, in the normal stage 2 naps mean sigma amplitude remained at a constant level across the first three quartiles, and then increased in
the fourth quartile of the sleep-onset period. There was a significant naptype-by-quartile interaction for mean theta amplitude [F(3,54)=5.33, p=.003] (see Fig. 4). For both narcoleptic REM naps and normal stage 2 naps, mean theta amplitude tended to decrease across the quartiles of the sleep-onset period. However, during the first quartile, mean theta amplitude did not differ between narcoleptic REM naps and normal stage 2 naps, whereas by the fourth quartile, mean theta amplitude tended to be lower in narcoleptic REM naps than normal stage 2 naps.

EEG spectra were compared between narcoleptic naps containing REM sleep and normal naps containing just NREM sleep stage 1. Significant main effects of group were found for mean delta, theta, alpha, and sigma amplitude. Collapsing across quartiles, mean delta amplitude was significantly higher during the narcoleptic REM naps (mean=7.2 V) compared to the normal naps containing just NREM stage 1 (mean=3.8 V) F(1,14)=16.68, p=.001) (see Fig. 1). Specifically, mean delta amplitude was higher for narcoleptic REM naps across all four quartiles of the sleep-onset period [t(14)=1.98, p=.067; t(14)=3.71, p=.002; t(14)=5.25, p=.001; t(14)=2.93, p=.011]. Collapsing across quartiles, mean theta amplitude was significantly higher during the narcoleptic REM naps (mean=2.6 V) compared to the normal naps containing just NREM stage 1 (mean=1.8 V) F(1,14)=4.82, p=.046] (see Fig. 4). This effect was mediated by a significant group-by-quartile interaction [F(3,42)=3.47, p=.024]. Mean theta amplitude tended to decrease across the quartiles of the sleep-onset period in narcoleptic REM naps, but increase in normal stage 1 naps. Collapsing across quartiles, mean alpha amplitude was significantly lower during the narcoleptic REM naps (mean=1.7 V) compared to the normal naps containing just NREM stage 1 (mean=3.5 V) [F(1,14)=9.09, p=.009] (see Fig. 4). This effect was mediated by a significant group-by-quartile interaction [F(3,42)=4.72, p=.006]. Mean alpha amplitude deceased across the quartiles of the sleep-onset period in narcoleptic REM naps, but remained at a constant level in normal stage 1 naps. Collapsing across quartiles, mean sigma amplitude was significantly lower during the narcoleptic REM naps (mean=0.4 V) compared to the normal naps containing just NREM stage 1 (mean=0.7 V) [F(1,14)=5.44, p=.035] (see Fig. 2). Specifically, mean sigma amplitude was significantly lower in the narcoleptic REM naps for the first [t(14)=2.44, p=.028], and second [t(14)=3.28, p=.005] quartiles, but not the third or fourth quartiles of the sleep-onset period.

Comparisons within Normal Naptypes

To investigate the chronological microstructure of the normal transition from wakefulness to sleep, EEG spectra during the quartiles of the sleep-onset period were compared between normal naps containing stage 2 and normal naps containing just stage 1 sleep. Significant main effects of naptype were found for mean delta and alpha amplitude. Collapsing across quartiles, mean delta amplitude was significantly higher during the normal naps containing stage 2 sleep (mean=5.6 V) compared to the normal naps containing just stage 1 (mean=3.8 V) [F(1,14)=20.38, p=.001] (see Fig. 1). This effect was mediated by a significant naptype-by-quartile interaction [F(3,42)=12.79, p=.001]. During the first quartile of the sleep-onset period, mean delta amplitude did not differ between normal naps containing stage 2 and normal naps containing just stage 1. However, by the third and fourth quartile, mean delta amplitude had increased for the normal naps containing stage 2, but remained at a constant level for the naps containing just stage 1. Collapsing across quartiles, mean alpha amplitude was significantly lower during the normal naps containing stage 2 sleep (mean=2.1 V) compared to the normal naps containing just stage 1 (mean=3.5 V) [F(1,14)=4.73, p=.047] (see Fig. 3). This effect was mediated by a significant naptype-by quartile interaction [F(3,42)=7.32, p=.001]. During the first quartile of the sleep-onset period, mean alpha amplitude did not differ between normal naps containing stage 2 and normal naps containing just stage 1. However, mean alpha amplitude decreased across the quartiles of the sleep-onset period for stage 2 naps, whereas mean alpha amplitude remained at a constant high level for stage 1 naps. A significant naptype-by-quartile interaction was found for mean sigma amplitude [F(3,42)=5.42, p=.003] (see Fig. 2). Across the first three quartiles of the sleep-onset period, mean sigma amplitude was higher for normal naps containing just stage 1. However, by the fourth quartile, a crossover occurred, and mean sigma amplitude was higher for the normal naps containing stage 2.

DISCUSSION

The present study demonstrates that a wide range of EEG spectral differences exist within the sleep-onset period of narcoleptics and normal sleepers. These findings have theoretical implications for the understanding of the microstructure of the processes of narcoleptic and normal sleep onset.

Visually Scored EEG

As expected, mean latency to sleep onset on MSLT was significantly shorter for narcoleptics than normals, confirming that narcoleptics were physiologically sleepier than normals. This finding has been widely demonstrated (eg, ref. 23). Based on research by Broughton and Aguirre, it was also expected that within narcoleptics, the pressure for REM sleep would be greater than the pressure for NREM sleep onset.
sleep, resulting in shorter sleep-onset latencies for REM naps compared to NREM naps. When mean latency to stage 1 for REM naps and for NREM was calculated within each narcoleptic and then compared using a paired *t* test, mean latency to stage 1 sleep for REM naps (mean=3.2 minutes) was not significantly shorter than that for NREM naps (mean=4.3 minutes). However, it bears noting that Broughton and Aguirre's findings were replicated in the present study. Nevertheless, although the proposal that REM and NREM sleepiness reflect qualitatively different states of sleepiness, varying delta amplitude did not reflect qualitatively different states of sleepiness. However, when the individual latencies obtained from each narcoleptic nap opportunity in the present study were analyzed using a between-groups *t* test as per Broughton and Aguirre, mean latency to stage 1 for REM naps (mean=2.4 minutes) was significantly shorter than mean latency to stage 1 for NREM-only naps (mean=4.8 minutes, *t*(48)=2.64, *p*=.011). Statistical considerations aside, these findings replicate the direction of difference reported by Broughton and Aguirre, and are consistent with their finding that REM sleepiness was objectively greater than NREM sleepiness, supporting their proposal that REM and NREM sleepiness reflect qualitatively different states of sleepiness. However, although the present study replicated Broughton and Aguirre’s findings using inflated degrees of freedom, it must be noted that the effect size is very small. Indeed, further confirmation of these findings involving a larger sample of narcoleptics appears warranted before the existence of qualitatively different states of sleepiness can be verified.

**EEG Spectral Analysis**

The microstructure of the sleep-onset process in narcoleptics and normals was investigated using EEG spectral analysis (RMS amplitude) on the nap opportunities elicited by the MSLT. Because individuals may fluctuate between wakefulness and stage 1 throughout the entry into sleep, the sleep-onset period was divided into quartiles based on the length of the sleep-onset period. This strategy (four time-based quartiles) enabled the chronological development of the sleep-onset process to be studied.

**Evidence for Qualitatively Different States of Sleepiness**

Contrary to predictions, EEG spectral analyses did not provide evidence in support of Broughton and Aguirre’s findings that within narcoleptics, the pressure for REM sleep is greater than the pressure for NREM sleep. Mean delta, theta, alpha, sigma, and beta amplitude did not differ significantly between the sleep-onset periods of narcoleptic REM naps and narcoleptic NREM naps. More interestingly, there was evidence to suggest that spectral differences exist within the sleep-onset period of narcoleptic naps containing REM sleep and normal naps containing NREM sleep. Although the EEG of REM sleep and stage 1 sleep appears nearly indistinguishable when assessed using visually based sleep scoring techniques, EEG spectral analysis revealed enhanced delta and theta amplitude, and decreased alpha and sigma amplitude throughout the sleep-onset period of narcoleptic REM naps compared to normal stage 1 naps. In addition, delta amplitude was higher during the sleep-onset period of narcoleptic REM naps compared to normal stage 2 naps. These findings suggest the existence of physiologic differences within the microstructure of the narcoleptic sleep onset during REM naps and the normal process of sleep onset during stage 1 naps and stage 2 naps.

**Narcoleptic vs Normal Sleep-onset Process**

**Delta activity.**—The most robust finding was the enhancement of delta activity during the narcoleptic transition from wakefulness to sleep. As predicted, EEG spectral analyses demonstrated that delta amplitude was higher for narcoleptics than normals across quartiles of the sleep-onset period, regardless of whether the narcoleptic NREM naps or REM naps were compared with the normal stage 2 naps or normal stage 1 naps. Elevated delta activity has been noted in the nocturnal sleep of narcoleptics following 16 hours and 24 hours without sleep, in the recovery sleep of sleep-deprived normals, and in wakefulness prior to sleep onset in insomniacs. However, it must be stressed that in the present study, no evidence was found to suggest that the narcoleptics were sleep deprived. Mean nocturnal sleep length did not differ significantly between normals and narcoleptics for either the sleep diary completed for 7 days prior testing, or the nocturnal polysomnography carried out immediately preceding daytime testing. Nocturnal polysomnography did not yield significant differences between narcoleptics and normals in sleep efficiency, and percent stage 2, 3, 4, and REM did not differ in narcoleptics and normals. The only differences found between narcoleptics and normal sleepers during nocturnal polysomnography was that latency to stage 1 and REM sleep was shorter and percentage of time spent in stage 1 was higher for narcoleptics. Thus, there is no evidence to suggest that the enhanced delta activity observed during the daytime process of sleep entry in narcoleptics could be accounted for by the effects of experimentally induced nocturnal sleep deprivation.

The process of entering sleep was compressed in narcoleptics, as indicated by the significantly shorter mean latency to sleep onset observed in narcoleptics on the MSLT compared to normals. The compressed sleep-onset period in the presence of enhanced delta activity observed in narcoleptics mimics the effects of sleep deprivation in normals. However, it is proposed that the increased delta amplitude observed throughout the sleep-onset period in

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the narcoleptics may indicate the presence of an enhanced physiologic need for sleep in the absence of sleep deprivation, and when considered in light of the rapid sleep-onset data, may reflect a fundamental difference in the process of entering sleep in narcoleptics compared to normals. According to Borbély et al., the prevalence of delta activity in the EEG of nocturnal sleep in normals following sleep deprivation is indicative of the intensity of the sleep process: Delta power is related to an endogenous sleep-enhancing factor which accumulates in the brain during the usual waking period, particularly during extended sleep deprivation, and is eliminated or inactivated during sleep. The present findings of enhanced delta activity in the absence of sleep deprivation in narcoleptics may suggest the presence of an overaccumulation of Borbély’s proposed endogenous sleep-enhancing factor. Moreover, given that delta activity is mediated by the incidence and amplitude of synchronized EEG rhythms induced by the coactivation of large groups of cortical pyramidal cells with connections to thalamic and hypothalamic basal forebrain systems, the enhanced delta activity observed in the narcoleptics may also reflect an overactivation within this neuronal system. It is useful to note that the present study’s use of RMS amplitude as a measure of EEG spectral activity yields results consistent with power spectral analysis.

**Theta activity.**—Support was obtained for the prediction that theta activity would be higher during the sleep-onset period of narcoleptics compared to normals. Theta amplitude across quartiles of the sleep-onset period was significantly higher for narcoleptic REM naps compared to normal stage 1 naps, and tended to be higher for narcoleptic NREM (stage 2) naps compared to normal stage 1 naps. When narcoleptic REM naps were compared with normal NREM (stage 2) naps, a group-by-quartile interaction was observed, such that during the first three quartiles but not the final quartile of the sleep-onset period, theta amplitude was higher for narcoleptic REM naps. These findings are consistent with studies showing that elevated theta activity is present in sleepy normals working a nightshift, and in normals deprived of sleep. It is proposed that the elevated theta activity present during the sleep-onset period of narcoleptics compared to that of normals is in keeping with the narcoleptic complaint of excessive daytime sleepiness, and reflects a fundamental difference in the process of sleep entry. Contrary to predictions, theta activity did not differ between the sleep-onset period of narcoleptic REM naps and narcoleptic NREM naps.

**Alpha activity.**—As expected, alpha activity was lower for narcoleptics during the quartiles of the sleep-onset period when narcoleptic NREM (stage 2) naps and narcoleptic REM naps were compared with normal naps containing just NREM (stage 1). It is possible that the greater alpha amplitude present during normal stage 1 naps compared to narcoleptic naps may simply reflect the visual sleep-stage scoring criteria (wherein stage 1 sleep may contain up to 50% alpha activity). However, these findings may also indicate greater physiologic sleepiness in narcoleptics compared to normals, as the decreased (eyes-closed) alpha amplitude observed throughout the sleep-onset period for the narcoleptics is consistent with studies of sleep-deprived normals that have demonstrated that decreased (eyes-closed) alpha power during wakefulness is indicative of increased physiologic sleepiness. Contrary to predictions, alpha activity did not differ during the sleep-onset period of narcoleptic REM naps and narcoleptic NREM naps.

**Sigma activity.**—As predicted, sigma activity was significantly lower across the quartiles of the sleep-onset period when narcoleptic REM naps were compared with normal stage 1 naps, and sigma activity tended to be lower when narcoleptic REM naps were compared with normal NREM (stage 2) naps. When narcoleptic NREM (stage 2) naps were compared with normal naps containing just NREM stage 1, a significant interaction was observed: during the first three quartiles of the sleep-onset period, sigma amplitude was lower for narcoleptics, but during the fourth quartile, sigma amplitude was higher for narcoleptics. The lower levels of sigma activity observed in narcoleptics may be due to the relatively greater activity in the lower frequencies (although absolute amplitude measures were calculated, spectral estimates are influenced by activity in other frequencies). A significant interaction was observed when narcoleptic REM naps were compared with narcoleptic NREM naps. During REM naps, sigma amplitude remained at a constant level across the quartiles of the sleep-onset period, whereas during NREM naps, sigma amplitude increased from the third to fourth quartile, presumably reflecting the imminent onset of sleep spindles and stage 2 sleep (sigma frequency).

**Beta activity.**—Contrary to predictions, beta activity did not differ between the narcoleptic and normal sleep-onset process. Nor were there differences between narcoleptic REM and NREM naps.

**Normal Sleep-onset Process**

The present study provided information on the normal process of entry into sleep by comparing normal naps containing NREM stage 2 with naps containing just stage 1 sleep. As expected, mean delta activity was higher for normal stage 2 naps than normal stage 1 naps. Moreover, interaction effects revealed that during the first two quartiles of the sleep-onset period, delta amplitude did not differ between normal stage 2 naps and normal stage 1 naps. During the third and fourth quartiles, delta amplitude was higher for normal stage 2 naps than the normal stage 1 naps. The fact that—early on in the sleep-onset process—
delta amplitude did not differ between normal stage 1 naps and normal stage 2 naps suggests that physiologic sleepiness did not differ at the onset of the nap opportunity. However, an increase in delta amplitude occurred later in the sleep-onset period of naps, which progressed to include the development of stage 2 sleep. This finding is consistent with those of Badia et al and Ogilvie et al, and suggests that delta activity is sensitive to variations within the microstructure of the normal sleep-onset process according to whether the development of stage 2 sleep is imminent.

Information about changes in alpha activity across the normal sleep-onset period was also obtained. As expected, alpha amplitude was lower for normal stage 2 naps than normal stage 1 naps. Interaction effects revealed that alpha amplitude remained at a consistently high level across quartiles for the normal stage 1 naps, suggesting that alertness/sleepiness levels did not vary much throughout this time. During the first quartile of the sleep-onset period, alpha amplitude did not differ between stage 1 and stage 2 naps, suggesting that initial alertness/sleepiness levels following lights-out were identical and could not predict whether stage 2 would develop. The decrease in alpha activity across the quartiles of the sleep-onset period for stage 2 naps may indicate that sleepiness increased as the entry into sleep stage 2 unfolded, and is consistent with findings from Badia et al. Alternately, these changes in alpha activity may reflect the differences in visual sleep stage scoring criteria for stage 1 and stage 2 sleep. In any case, it appears that alpha activity is sensitive to variations within the microstructure of the normal sleep-onset process according to whether the development of stage 2 sleep is imminent.

It is important to mention that significant main effects of quartile were found for delta, alpha, sigma, and beta amplitude by averaging across naptype. No matter whether normal stage 2 naps were compared with normal stage 1 naps, or normal naps were compared with narcoleptic REM naps or narcoleptic NREM naps, the same significant findings were found, suggesting that the main effects for spectral changes across the quartiles of the sleep-onset period were consistent and inherent to the process of sleep onset in general both for normals and narcoleptics. Mean delta amplitude increased whereas mean alpha and beta amplitude decreased across the quartiles of the sleep-onset period. These findings substantiate those of Ogilvie et al, who observed decreases in alpha and beta power during the progression toward the onset of sleep when the longest reaction times to auditory stimuli were compared with the shortest reaction times. Also supported are the findings of Hori and Badia et al, who observed increases in delta power across the sleep-onset period. Similarly, Wright et al noted temporal differences in theta, alpha, and beta power across the sleep-onset period. Our findings are consistent with their finding that alpha and beta amplitude decreased from the first minute of wakefulness to the last minute of wakefulness, the first minute of stage 1, and the last minute of stage 1. Contrary to Wright et al and Hori, mean theta activity did not differ across the quartiles of the sleep-onset period.

**MSLT Data-selection Process**

Because the type of sleep to occur (ie, REM, stage 2, or stage 1) on each nap opportunity varied within and between subjects, the decision was made to select for analysis the first NREM nap and REM nap to occur in narcoleptics, and the first stage 2 nap and stage 1 nap to occur in normals. It is possible that different results may have been obtained had a different system of nap selection been implemented. However, the method was chosen because it increased the likelihood that all variations in sleep stages (ie, REM sleep, stage 1 and stage 2) would be obtained, sometimes at the cost of eliminating data from later MSLT naps.

**CONCLUSIONS**

This study documents spectral differences among normal sleepers and narcoleptics within the sleep-onset period of daytime nap opportunities in the absence of experimentally induced sleep deprivation. These findings have theoretical implications for the understanding of the microstructure of the processes of both normal and narcoleptic sleep onset. Given that the technique of EEG spectral analysis is now readily available to researchers and clinicians alike, it is suggested that by investigating, in particular, the magnitude of delta activity during the sleep-onset period induced by the MSLT, rather than focusing exclusively on visually scored latency to sleep onset, a more valid estimate of physiologic sleepiness may be obtained. Future research is warranted in order to assess the usefulness of a protocol utilizing a spectral-based MSLT in the measurement of physiologic sleepiness. We predict that delta activity during intentional sleep onset would differ reliably among normal populations and a number of sleep-disordered populations (ie, ref. 29), and would be sensitive to variations in physiologic sleepiness produced by both pharmacologic and behavioral treatment strategies.

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