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Diagnostic value of sleep stage dissociation as visualized on a 2-dimensional sleep state space in human narcolepsy

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HIGHLIGHTS

- 2D space representing data modalities enables dissociation features to be extracted.
- By comparing a model in 2D with a subject narcolepsy can be identified.
- The accuracy is replicated from the training to the validation set.
- The results are negatively influenced when introducing medicine.
- Idiopathic hypersomnias are also harder to differentiate.

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ABSTRACT

Background: Type 1 narcolepsy (NT1) is characterized by symptoms believed to represent Rapid Eye Movement (REM) sleep stage dissociations, occurrences where features of wake and REM sleep are intermingled, resulting in a mixed state. We hypothesized that sleep stage dissociations can be objectively detected through the analysis of nocturnal Polysomnography (PSG) data, and that those affecting REM sleep can be used as a diagnostic feature for narcolepsy.
New method: A Linear Discriminant Analysis (LDA) model using 38 features extracted from EOG, EMG and EEG was used in control subjects to select features differentiating wake, stage N1, N2, N3 and REM sleep. Sleep stage differentiation was next represented in a 2D projection. Features characteristic of sleep stage differences were estimated from the residual sleep stage probability in the 2D space. Using this model we evaluated PSG data from NT1 and non-narcoleptic subjects. An LDA classifier was used to determine the best separation plane.
Comparison with existing methods: This method replicates the specificity/sensitivity from the training set to the validation set better than many other methods.
Results: Eight prominent features could differentiate narcolepsy and controls in the validation dataset. Using a composite measure and a specificity cut off 95% in the training dataset, sensitivity was 43%. Specificity/sensitivity was 94%/38% in the validation set. Using hypersomnia subjects, specificity/sensitivity was 84%/15%. Analyzing treated narcoleptics the specificity/sensitivity was 94%/10%.
Conclusion: Sleep stage dissociation can be used for the diagnosis of narcolepsy. However the use of some medications and presence of undiagnosed hypersomnolence patients impacts the result.

1. Introduction

Type 1 narcolepsy, a disorder caused by a loss of hypocretin neurons, is diagnosed based on the presence of daytime sleepiness, cataplexy, and a positive Multiple Sleep Latency Test (MSLT). The MSLT is a 4–5 daytime nap test opportunity where sleep latency

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and the occurrence of REM sleep within 15 min of onset is noted in each test, a feature called a Sleep Onset REM Period (SOREMP). The MSLT is performed following a night of nocturnal polysomnography (PSG), a procedure mostly performed to exclude confounding sleep disorders and note for the presence of a nocturnal SOREMP, a highly predictive diagnostic feature.

The cause of hypocretin cell loss in narcolepsy type 1 is likely of autoimmune origin. The disorder is strongly associated with HLA-DQB1*06:02, and has been shown to be triggered by upper airway infections such as streptococcus and influenza-A, notably 2009H1N1 (Andlauer et al., 2013; Sorensen et al., 2013). Documentation of low cerebrospinal fluid hypocretin 1 (csf-hcrt-1) below 110 pg/ml, is regarded as a definitive diagnostic test for diagnosing narcolepsy type 1 (Knudsen et al., 2010; Williams et al., 2008).

The MSLT gained popularity due to the fact that it is quite specific (≈97%) and sensitive (≈93%) in diagnosing Type 1 narcolepsy (Aldrich et al., 1997; Andlauer et al., 2013). Until recently, a mean sleep latency (MSL) 8 min, and 2 SOREMPs during the daytime naps were considered as diagnostic for narcolepsy. Based on recent findings that a nSOREMP is highly specific (≈99%) for type 1 narcolepsy, but has only moderate sensitivity (≈45%), the most recent classification of sleep disorders (ICSD3) revised the definition of a positive MSLT to include the nSOREMP as part of the 2 SOREMP requirement. At the practical level, this change is insignificant, as in our study of over 800 type 1 narcoleptic patients all subjects with a nSOREMP also had 2 SOREMPs during naps (Andlauer et al., 2013). For example, comparing 516 type 1 narcolepsy cases with a similar number of age matched controls, specificity for the ICSD3 defined PSG-MSLT was 98.6% and sensitivity 93.3% versus 98.6% and 92.9% for the older definition (Andlauer et al., 2013).

Because a nSOREMP is highly specific (≈99%) for narcolepsy but has only modest sensitivity (≈40 to 50%), it has been proposed that other diagnostic biomarkers should be sought within the PSG to add sensitivity, so that a nocturnal PSG alone could be used to diagnose narcolepsy without the need for a subsequent MSLT. Following on this hypothesis, sleep onset REM periods during nocturnal sleep, long periods of wakefulness within sleep, or the presence of specific EEG spectra abnormalities have been found to differentiate narcolepsy versus controls (Christensen et al., 2015, 2015). Unfortunately, however, none of these new biomarkers were sufficiently predictive alone, although combining them may be helpful and has not yet been systematically tested. The advantage of using a PSG alone for diagnosis is that widely used to diagnose sleep disordered breathing, and other sleep disorders, and could thus be used as a screening tool for type 1 narcolepsy.

Using various components of the EEG, EOG and EMG that are known to differentiate sleep stages, it is possible to artificially project a multi component difference on a 2-D plane that display a clear clustering of the various sleep stage, a procedure called sleep state space analysis. In essence, a sleep state space analysis displays for any subject how distinct various sleep stages are from each other. Sleep state space abnormalities has been proposed as a new possible narcolepsy biomarker based on EEG studies in narcoleptic mice (Diniz Behn et al., 2010). In this study, Diniz Behn et al. (Diniz Behn et al., 2010) used a sleep stage space projection analysis to cluster sleep and wake and shows that narcoleptic mice have less distinct and more labile states of sleep and wakefulness. Similar work (Imbach et al., 2012) has shown that it is possible to separate human sleep stages and look at their dynamics in a 2-D space, although these projections did not include stage 1 and did not attempt to study narcoleptics. Stage 1 may be particularly important to analyze as increased stage 1 is the most consistent difference in sleep architecture found in patients with narcolepsy (Roth et al., 2013). Further, stage 1, REM sleep and wake are the most similar states at the electrophysiological level. In this study, we expanded on this idea, creating sleep state space projections in controls and narcolepsy, demonstrating that sleep stage dissociation in patients with narcolepsy (i.e. reduced distance between sleep stages) can be used to discriminate Type 1 patients from controls and other patients.

2. Population samples used in the study

This section applies the original number of patients in the datasets used in this study. It is important to note that these dataset have been analyzed by technicians and if the validity of the data were questioned by the technician, the subject has been removed from the dataset. This section reflects the original dataset numbers before removal.

2.1. Stanford sleep cohort (SSC)

This sample is a naturalistic sample of 862 successive patients that were seen at the Stanford Sleep Clinic between October 1999 and March 2007 at the Stanford Sleep Clinic (Moore et al., 2014, 2015). Data from the sample only includes 25 patients with type 1 narcolepsy (none taking sodium oxybate) and other patients with Delayed Sleep Phase (DSP) $n = 14$, Insomnias $n = 141$, REM Behavior disorders (RBD) $n = 4$, Restless Leg Syndrome (RLS), $n = 23$, Sleep Disordered Breathing (SDB) $n = 607$ plus 39 subjects suffering from others disorders. Summary statistics for these subjects are provided in Table 1.

PSGs were all recorded using the Sandman Elite digital sleep software and Sandman SD32+ amplifiers. The recording was done using the Stanford Sleep Disorder clinic protocol, which is an extension of the AASMs clinical guidelines in the fact that it records additional respiratory signals with increased precision and processing. It best corresponds to updated AASM 2012 scoring rule criteria. In total 18 channels of information are recorded: EEG (using 10/20 electrode placement), EOG, EMG (measured on the submentalis muscle but also on the anterior tibialis muscles of each leg combined into a single EMG channel for both legs), ECG, vibration snoring, breathing effort, airflow, nasal pressure and oxygen saturation (SpO_2). EEG is recorded using the international 10–20 system with a sampling frequency of 256 Hz. EMG, ECG and snoring signals are recorded using a sampling rate of 512 Hz, breathing effort and airflow recorded with a sampling rate of 64 Hz and SpO_2 recorded at 4 Hz. Filtering is done on electrophysiological signal channels by bandpass filtering in the range of 0.1 Hz and 0.45 times the sample rate. EMG channels are further high pass filtered at 10 Hz. Sleep stage scoring is performed by trained Registered Polysomnographic technicians under the supervision of board certified sleep disorder specialists at the Stanford Sleep Clinic.

2.2. Wisconsin sleep cohort (WSC)

This sample includes 1522 PSGs from the Wisconsin Sleep Cohort, a longitudinal study of sleep habits and disorders in the general population (Goldbart et al., 2014). The cohort was established in 1988 from a sample of employees of 4 state agencies in south central Wisconsin, aged 30–60 years. Beginning in 2000, approximately 800 participants enrolled in the Wisconsin Sleep Cohort were recruited for an MSLT following a PSG study. Summary statistics for the sample are provided in Table 1. PSGs were all recorded using a Grass model 78 polysomnography machine and scoring performed using standard criteria at the time based on AASM guidelines. In total 18 channels were recorded including EEG (using 10/20 electrode placement), EOG and EMG. Breathing was measured using respiratory inductance plethysmography, nasal and oral airflow using thermocouples and SpO_2 using pulse