Impact of Transcutaneous Electrical Nerve Stimulation (TENS) Therapy on Sleep Efficiency in Subjects with Chronic Pain

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BACKGROUND

There is a negative reciprocal relationship between chronic pain and sleep. As many as 80% of chronic pain patients report poor sleep quality and daytime fatigue. We have recently reported on the clinical benefits of fixed-site high-frequency transcutaneous electrical nerve stimulation (Quell®, NeuroMetrix, Inc.) in a chronic pain cohort. In addition to delivering therapeutic neurostimulation, this device collects health data including utilization and sleep measures. The latter is based on signals from an embedded tri-axial accelerometer. The data is communicated to the patient through a smartphone app and aggregated in a cloud server. This database presents a novel opportunity to study sleep in a large cohort of chronic pain sufferers.

Our long-term goal is to understand how neurostimulation impacts sleep in chronic pain patients. Specific aims of this study were to

1. Determine if neurostimulation dose directly influences sleep efficiency
2. Determine covariates of sleep efficiency in a chronic pain cohort using neurostimulation

METHOD

De-identified data from device users consenting to have their data uploaded to a cloud server was analyzed. Sleep parameters include:

- Total Bed Time (**TBT**, hours): Total time spent in bed each night, equals sleep latency plus total sleep period (TSP)
- Total Sleep Time (**TST**, hours): Portion of TSP with low activity level
- Sleep Efficiency (**SE**, %): Ratio in percentage between TST and TSP.
- Periodic Leg Movement Index (**PLMI**, events/hr): Periodic leg movements per hour of TSP
- Position Change Rate (**PCR**, events/hr): Body position change per hour of TSP
- Out of Bed Count (**OOB**, event count): Number of times going out of bed at night

Two therapy parameters

- **Total Dose** (hours): Total hours of therapy in a day
- **Night Dose** (hours): Total hours of therapy between 8PM and 8AM

<u>Relationship between Neurostimulation Dose and Sleep Efficiency</u>

For each user, average daily total dose was calculated. Sleep quality was quantified by averaging SE over the first and last ten available nights within first 90 days of the first night. Users were stratified into low (<5 hours), medium (5-9 hours), and high (>9 hours) dose groups. For each dose group, a paired t-test was used to test the hypothesis the group mean SE of the first ten nights was different from that of the last ten nights.

<u>Association between Sleep Efficiency and Sleep Parameters</u>

In this analysis, each night was considered as an independent sample. Correlations between SE and the other parameters were calculated. To explore covariates with significant influence on SE, multi-variate step-wise linear regression was repeated on bootstrapped datasets. Each bootstrapped dataset consisted of a single night of sleep and dose parameters associated with that night. TBT and TST were excluded from regression analysis to focus on non-duration parameters that might impact sleep quality. Parameters that were consistently (with frequency 95% or higher) in the final regression models were identified. The exact quantitative relationship between the consistent covariates and SE was specified by median values of the regression coefficients obtained from bootstrapped datasets.

The bootstrap method. A bootstrapped dataset consists of one randomly selected night from each subject. Based on each bootstrapped dataset, a linear regression model is developed by iteratively adding a covariate (if its coefficient is unlikely zero) or dropping a covariate (if zero-coefficient is unlikely to be rejected) at a time.

RESULTS

<u>Relationship between Neurostimulation Dose and Sleep Efficiency</u>

Data from 3,279 users were collected over 377 days, including 450,107 hours of therapy and 37,001 nights of sleep. 232 users had 30 or more nights with TBT between 4 and 12 hours. Of these users, 63 were in the low, 120 in the medium, and 49 in the high dose groups. The high dose group showed a statistically significant improvement in SE from 93.8%±3.3% to 94.6%±2.9% ($p < 0.01$).

<u>Association between Sleep Efficiency and Sleep Parameters</u>

Sleep data with the full complement of sleep parameters were collected for 9,015 nights from 776 users. Correlation between SE and sleep and dose parameters are summarized in Table 1. With the exception of total dose, SE correlates with all other parameters ($p<0.05$).

Table 1. Correlation between SE and sleep and dose parameters

TBT	TST	PLMI	PCR	OOB	Total Dose	Night Dose
0.064	0.253	-0.540	-0.290	-0.469	-0.014*	0.060

* Correlation value is not statistically significant from zero (p=0.189)

Based on 50,000 bootstrapped datasets, PLMI, PCR, and OOB were identified as the consistent covariates for predicting SE. The quantitative relationship between these covariates and SE is summarized in Table 2. The expected SE was reduced by 3.3% with each unit increase of OOB. Similarly, each PCR unit increase reduced SE by 1.6% and each PLMI increase reduces SE by 0.37%. The predictive model in Table 2 was able to explain 49% of SE variance. Scatter plot of the predicted and actual SE are shown in the figure on the left.

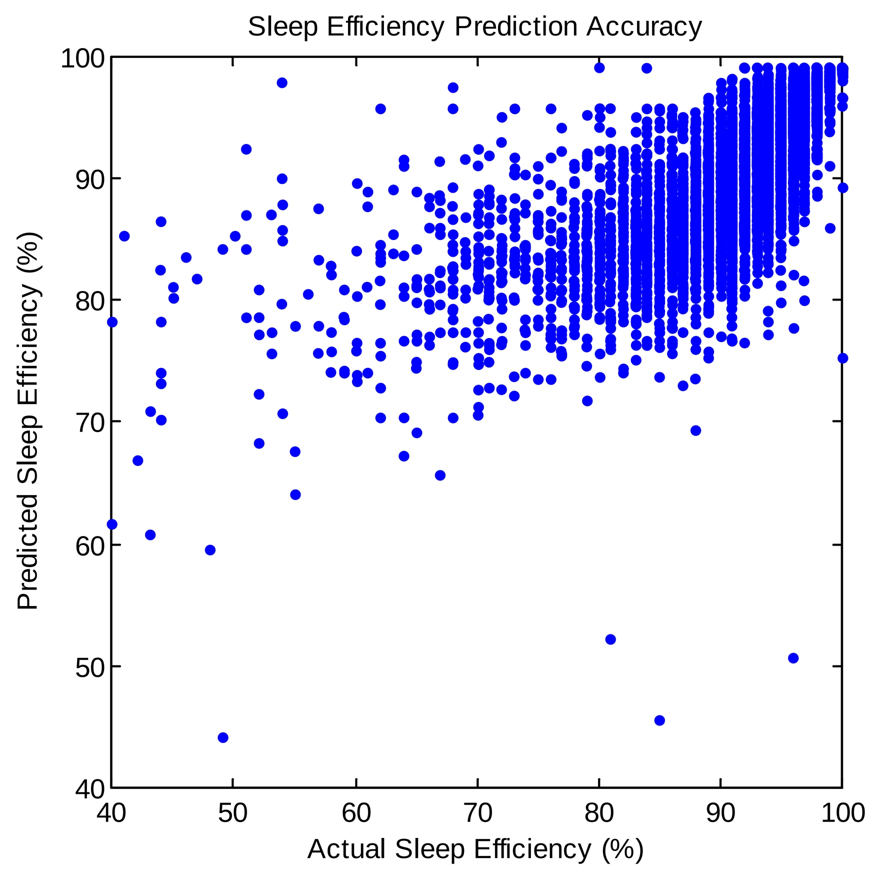

Table 2. Quantitative relationship between SE and consistent covariates

Constant	PLMI	PCR	OOB
99.30	-0.37	-1.60	-3.30

CONCLUSIONS

Preliminary analysis of sleep metrics collected from a cohort of chronic pain patients using a wearable neurostimulator showed that SE had a small but statistically significant improvement for high dose users. This increase is not clinically significant and therefore its relevance is unclear at this time. Negative associations were found between SE and three sleep parameters that were known to be elevated in chronic pain sufferers: periodic leg movements, body position changes, and out of bed events. Future studies should evaluate how sleep quality is impacted by wearable neurostimulation through modifications of covariates that are found to be strongly associated with SE.

A Poster Presented at SLEEP 2016, A Joint Meeting of *American Academy of Sleep Medicine* and the *Sleep Research Society*, Denver, CO, June 11—15, 2016. Abstract ID 0722.
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