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Transvenous phrenic nerve stimulation for treating central sleep apnea may regulate sleep microstructure

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ABSTRACT

Study objectives: To assess the impact of transvenous phrenic nerve stimulation (TPNS) on non-rapid eye movement sleep microstructure quantified by cyclic alternating pattern (CAP) in individuals with central sleep apnea (CSA).

Methods: We analyzed baseline and 6-month follow-up overnight polysomnograms (PSG) in 134 CSA patients enrolled in the remedē System Pivotal Trial implanted with TPNS randomized (1:1) to neurostimulation (treatment group) or no stimulation (control group). Differences in CAP rate, A1 index, and A2+A3 index between study arms at follow-up were assessed using Analysis of Covariance adjusted for baseline values.

Results: On follow-up PSG, the treatment group showed a decrease in the frequency of A2+A3 phases compared to controls (-5.86 ± 11.82 vs. 0.67 ± 15.25, $p = 0.006$), while the frequency of A1 phases increased more in the treatment group (2.57 ± 11.67 vs. -2.47 ± 10.60, $p = 0.011$). The change in CAP rate at follow-up was comparable between study arms.

Conclusions: TPNS treatment for central sleep apnea may affect sleep microstructure. Brief phases of rapid cortical activity appear to be replaced by short phases of slower cortical activity, which may promote sleep continuity. Further investigations are warranted to elucidate the mechanisms underlying the effect of TPNS on CAP.

1. Introduction

Sleep-disordered breathing has been associated with cardiovascular and cerebrovascular diseases, higher rates of depression, stress, suicidal thoughts, and a decline in cognitive functioning and memory [1]. Central sleep apnea (CSA) results from a temporary failure of the respiratory control centre to generate a breathing rhythm during sleep [2]. CSA is highly prevalent in patients with heart failure and is associated with significant morbidity and mortality [3].

CSA disrupts sleep, causing fragmentation and reducing its restorative properties. CSA is associated with cyclic alternating pattern (CAP), a sleep instability marker describing prolonged cyclic alternation of cerebral disturbance displayed by slow high-voltage waves or rapid, low-voltage rhythms intruding in low-voltage background electroencephalography (EEG) activity [4]. Central respiratory events tend to occur during phases of background activity whilst breathing is recovered during cerebral activation phases accompanied by hyperventilation [5]. Patients with obstructive sleep apnea (OSA) exhibit an increase in low-voltage, rapid EEG disturbances resulting in an increased slow-wave sleep (SWS) instability [6]. Compared to OSA, the cerebral activation phases in CSA do not appear to be triggered by mechanoreceptor stimulation and seem to last longer [5].

Treating OSA via positive airway pressure restores sleep microstructure and increases SWS stability and sleep continuity [7]. It is currently unknown whether CSA therapy improves sleep microstructure. The conventional treatment method for CSA is positive airway

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pressure therapy. Recently, transvenous phrenic nerve stimulation (TPNS) therapy has been introduced as a safe and effective treatment of CSA in adult patients.

This study aimed to assess the effect of TPNS on sleep microstructure in patients with CSA in an auxiliary study of the prospective, multicentre, randomized remedē System Pivotal Trial.

2. Material and methods

2.1. The remedē Pivotal Trial

The remedē System Pivotal Trial was a prospective, multicentre, randomized controlled trial at 31 hospital-based centres in Germany, Poland, and the USA [8]. The trial aimed to evaluate the safety and efficacy of the remedē System that uses TPNS for treating CSA. As the primary outcome, the proportion of patients in the treatment versus control groups achieving a reduction in apnea-hypopnea index (AHI) of 50 % or greater from baseline to 6 months was compared. The protocol was approved by local or central ethics or institutional review boards according to each centre's institutional procedures.

Eligibility required the following polysomnography (PSG) results on a qualifying overnight stay after completing the pre-screening: AHI of at least 20 events per h of sleep, central apneas at least 50 % or higher of all apneas, at least 30 central apneas throughout the night, and an obstructive apnea index of 20 % or lower of the total AHI. All patients provided written informed consent.

All patients undergoing an implant attempt were randomly assigned (1:1) to neurostimulation (treatment group; TPNS on) or no stimulation (control group; TPNS off). Although patients and physicians were aware of the treatment assignment, the polysomnography core laboratory remained masked throughout the study.

All patients underwent a baseline PSG within 40 days before implantation, an initiation study one month after implantation to activate the system in the treatment group with a full night PSG, and a whole night PSG at follow-up six months after the baseline visit. After completing the 6-month effectiveness assessment, control group patients' devices were activated. All PSG were scored by a central and blinded sleep core laboratory (Registered Sleepers, Winter Haven, Florida, USA).

2.2. Cyclic alternating pattern (CAP) analysis

CAP describes sequences of transient brain activity distinct from background activity [9] and is regarded as a measure of sleep microstructure. Sequences of transient brain activity consist of periodically recurring activation phases separated by a background phase. Activation phases can be categorized as either slow, high-voltage rhythms representing high EEG synchrony (A1), fast, low-voltage rhythms that characterize low EEG synchrony (A3), or a combination of both (A2). A1 phases are closely associated with the build-up and maintenance of sleep, whereas A3 phases represent muscle activation and autonomic functions during the breakdown of slow-wave sleep and the transition to REM sleep [5].

We deployed a fully automated CAP scoring system [10,11] to extract CAP measures from overnight PSG according to the atlas and rules for scoring CAP [9]. The scoring system consists of a multi-layer recurrent neural network that classifies each second of NREM sleep as non-activation or as part of one of the three A-phase subtypes (A1, A2, and A3) based on a time and frequency domain feature set including Hjorth activity, Shannon entropy, Teager Energy Operator, band power descriptor, and differential EEG variance. We updated our original scoring system by changing the system-internal sampling rate from 128 Hz to 200 Hz, adding a FIR bandpass filter (1–30 Hz) using Kaiser window, and adding the time between the current second and the last wake or REM stage as an additional feature. The new system version also incorporates a subject-level normalization method preceding the classification stage to reduce an individual's contribution to the feature dispersion. The system was trained with EEG recordings from 67 healthy children, 59 healthy adults, and 60 adults with sleep disorders such as insomnia, narcolepsy, nocturnal frontal lobe epilepsy, and periodic limb movement. Code for the automated CAP scoring system is available on https://github.com/sihartmann/CAPdetection-LSTM.

CAP rate was defined as the percentage of NREM sleep covered by CAP sequences. Activation subtypes were quantified as the number of A1 and A2+A3 events, respectively, per hour of NREM sleep. Subtypes A2 and A3 were merged into a single parameter (A2+A3) due to their congruent nature. Additionally, we included the average CAP sequence, CAP cycle, and B phase duration in our analysis. CAP cycle duration indicates the recurrence rate describing the frequency of CAP oscillations [9]. B phase duration indicates the period separating two A phases and is the dominant portion of a CAP cycle with 65–80 % of the entire CAP cycle length [5].

2.3. Spectral power analysis

EEG spectral power analysis during NREM sleep was conducted to account for changes in the spectral power bands. The power spectral density estimate across all NREM sleep epochs was calculated using Welch's method on a 2-s sliding window with 50 % overlap and Hamming windowing. Subsequently, the mean absolute power spectral density for the following EEG frequency bands was computed by averaging across each frequency range: Delta (1–4 Hz), Theta (4–8), Alpha (8–12 Hz), Sigma (12–15 Hz), and Beta (15–30 Hz).

2.4. Statistical methods

We used a generalized linear model including the baseline value of each variable as a covariate to compare differences in sleep microstructure between the treatment and control arms at six months, the primary endpoint visit per protocol. A nominal 2-sided $p < 0.05$ was considered statistically significant in this exploratory analysis. R 4.1.1 [12] and SAS version 9.4 (Cary, NC, USA) were used for all analyses.

3. Results

In total, 134 CSA patients had a PSG at baseline and 6-month follow-up. The recordings of 13 individuals were removed as they did not contain the required central channel (C4-A1) for automated CAP scoring, or the recording was not useable due to prolonged periods of noise or zero amplitude. Hence, the study included the PSGs of 121 individuals: 57 in the treatment arm and 64 in the control arm. Table 1 summarises the baseline patient characteristics for the control and treatment arms. The average age of study participants was 64 years, and the average BMI was 31 kg/m^2. Participants were predominately male and White. The baseline mean AHI and arousal index were 44–49 h^{-1} and 44-45 h^{-1}, respectively. Participants spent, on average, 11–12 % of their sleep in rapid eye movement sleep.

3.1. Effect of transvenous phrenic nerve stimulation on CAP, sleep disturbance, and polysomnographic measures

Fig. 1 displays CAP rate, A1 index, and A2+A3 index at baseline and follow-up across both trial arms. All CAP variables were comparable at baseline, and no meaningful differences were detected (Table 2). CAP rate remained relatively steady in both groups from baseline to follow-up (change from baseline in treatment vs. control: -2.43 ± 10.26 vs. 0.06 ± 13.26, $p = 0.195$, see Table 2). The number of A2+A3 phases per hour of NREM sleep decreased on treatment compared to controls (-5.86 ± 11.82 vs. 0.67 ± 15.25, $p = 0.006$). On the contrary, treatment increased the number of A1 phases per hour of NREM sleep compared to the control group (2.57 ± 11.67 vs. -2.47 ± 10.60, $p = 0.011$). The average CAP cycle duration was shortened on treatment

Table 1
Patient characteristics at baseline.

	Treatment, N = 57	Control, N = 64
Age (years)	64 ± 12 (57)	64 ± 13 (64)
Male	88 % (50/57)	92 % (59/64)
Not Hispanic or Latino	98 % (56/57)	94 % (60/64)
White	98 % (56/57)	95 % (61/64)
Body mass index (kg/m^2)	30.5 ± 5.1 (57)	31.5 ± 6.6 (64)
Respiration rate (per minute)	17.4 ± 2.8 (57)	17.4 ± 2.7 (64)
Ejection Fraction≤40 %	41 % (23/56)	39 % (24/61)
Hypertension	72 % (41/57)	77 % (49/64)
Hyperlipidemia	81 % (46/57)	69 % (44/64)
Heart failure	60 % (34/57)	59 % (38/64)
NYHA Class I/II/III	15 %/38 %/47 %	29 %/47 %/24 %
Atrial fibrillation	39 % (22/57)	39 % (25/64)
Coronary Artery Disease	56 % (32/57)	55 % (35/64)
Myocardial Infarction	30 % (17/57)	28 % (18/64)
Stroke	5 % (3/57)	8 % (5/64)
Cardiac arrest	7 % (4/57)	8 % (5/64)
Chronic obstructive pulmonary disease	7 % (4/57)	9 % (6/64)
Cardiovascular implantable electronic stimulation device	39 % (22/57)	39 % (25/64)
Apnea hypopnea index (events/hour)	48.8 ± 17.7 (57)	43.6 ± 17.6 (64)
Central apnea index (events/hour)	31.3 ± 18.3 (57)	26.5 ± 16.6 (64)
Obstructive apnea index (events/hour)	1.9 ± 1.7 (57)	2.2 ± 2.8 (64)
Mixed apnea index (events/hour)	3.0 ± 3.9 (57)	1.9 ± 2.8 (64)
Hypopnea index[a] (events/hour)	12.6 ± 11.5 (57)	13.0 ± 10.8 (64)
Arousal Index (events/hour)	44.8 ± 18.7 (57)	43.7 ± 20.0 (64)
Rapid eye movement sleep (%)	10.6 ± 6.9 (57)	12.1 ± 7.2 (64)
Percent of sleep in Cheyne-Stokes Respiration	29.6 ± 26.5	31.5 ± 27.7
Epworth Sleepiness Scale (0–24, higher is worse)	10.3 ± 5.3 (57)	9.0 ± 5.6 (64)

Mean ± SD (n) for continuous variables and percent (n/N) for categorical variables.
Abbreviations: m = meters, kg = kilogram, NYHA=New York Heart Association.
[a] Hypopnea: 30 % reduction in airflow (or alternative hypopnea sensor) for ≥10 s over at least 90 % of the event's duration that was associated with a >4 % fall in oxygen saturation from baseline.

compared to controls (−0.72 ± 2.83 vs. 0.83 ± 2.68, p = 0.004) mostly due to a decrease in the average B phase duration on treatment compared to controls (−0.71 ± 2.80 vs. 0.76 ± 2.31, p = 0.004). However, the average CAP sequence duration was not significantly different at follow-up (−4.53 ± 94.53 vs. 9.06 ± 85.90, p = 0.173). The change in mean absolute power spectral density in each frequency band showed no differences between the treatment arms from baseline to 6-month follow-up.

In brief, the percentage of sleep in stage 1 was reduced in the treatment group and increased in the control group (−3.08 ± 2.15 vs. 3.95 ± 2.03, p = 0.0190), while the percentage of stage 2 sleep increased in the treatment group and decreased in the control group (3.81 ± 1.80 vs. −2.03 ± 1.70, p = 0.0199). Additionally, there was no statistically significant improvement in REM for the treatment group compared to control (1.17 ± 0.96 vs −0.14 ± 0.90, p = 0.3217).

3.2. Association between sleep microstructure and sleep-disordered breathing

To assess the association between AHI improvement (i.e., the target variable for TPNS treatment) and change in sleep microstructure, we performed correlation analyses between changes from baseline to follow-up in AHI and the A1 index, A2+A3 index, and CAP rate, respectively, using Pearson's correlation coefficient. The reduction in AHI weakly correlated with a decrease in the A2+A3 index (ρ = 0.25), whereas the change in AHI did not correlate with the change in the A1 index and CAP rate, respectively. In a further analysis, we correlated the change in the A1 index with the change in the A2+A3 index showing a weak reciprocal association (ρ = −0.12).

In a cross-sectional analysis of baseline data, we further evaluated the relationship between Cheyne-Stokes respiration and CAP. The percentage of Cheyne-Stokes respiration (CSR) weakly correlated inversely with the A1 index (ρ = −0.21) and CAP rate (ρ = −0.10), respectively, and positively with the A2+A3 index (ρ = 0.17).

4. Discussion

This study shows the effect of TPNS for CSA treatment on sleep microstructure for the first time. Our results demonstrate a reduction in A2+A3 phases and an increase in A1 subtypes, while there was no evidence for a change in the overall CAP rate.

CAP scoring has evolved into a valuable source of information on an individual's sleep process. The primary metric, the CAP rate, describes the percentage of NREM sleep occupied by CAP sequences. In this study, TPNS stimulation did not affect the CAP rate but showed a significant shift in the activation types constituting CAP. The A2+A3 index was reduced in CSA patients receiving TPNS stimulation after six months compared to the control group. This finding suggests less fragmented sleep on treatment as subtypes A2 and A3 overlap largely with the AASM scoring criteria for arousals [13,14] and provoke a pronounced change in autonomic activity [15]. In parallel, we saw an increase in the frequency of A1 phases in the treatment group compared to the control

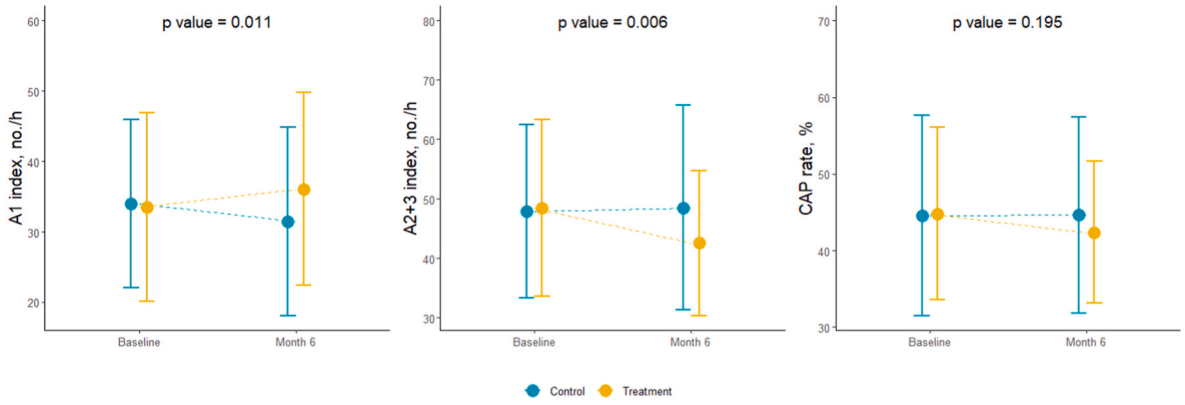

Fig. 1. Comparison of CAP measures in the treatment and control arms at baseline and the six-month visit.
Comparison of A1 index, A2+A3 index, and CAP rate in the treatment and control arms at baseline and the six-month visit. Data are presented as mean and standard deviation with the p value for treatment from analysis of covariance model including visit and baseline value.

Table 2
Sleep disturbance, CAP, and polysomnographic measures at baseline PSG as well as change at 6-month follow-up PSG from baseline PSG adjusted for baseline differences.

	Visit	Treatment, N = 57	Control, N = 64	ANCOVA[1]
Sleep microstructure				
A1 index, no./h	Baseline	33.50 ± 13.36	33.97 ± 11.98	
	Change from baseline	2.57 ± 11.67	−2.47 ± 10.60	0.011
A2+A3 index, no./h	Baseline	48.46 ± 14.82	47.87 ± 14.54	
	Change from baseline	−5.86 ± 11.82	0.67 ± 15.25	0.006
CAP rate, %	Baseline	44.82 ± 11.22	44.57 ± 13.03	
	Change from baseline	−2.43 ± 10.26	0.06 ± 13.26	0.195
Average CAP sequence duration, seconds	Baseline	213.21 ± 72.88	223.91 ± 76.69	
	Change from baseline	−4.53 ± 94.53	9.06 ± 85.90	0.173
Average CAP cycle duration, seconds	Baseline	26.16 ± 2.55	25.66 ± 2.54	
	Change from baseline	−0.72 ± 2.83	0.83 ± 2.68	0.004
Average B phase duration, seconds	Baseline	20.61 ± 2.37	19.99 ± 2.18	
	Change from baseline	−0.71 ± 2.80	0.76 ± 2.31	0.004
Spectral power				
Delta, μV^2	Baseline	27.07 ± 14.94	24.80 ± 12.12	
	Change from baseline	−0.74 ± 8.33	1.64 ± 11.96	0.381
Theta, μV^2	Baseline	7.75 ± 5.79	7.39 ± 4.80	
	Change from baseline	−0.52 ± 2.74	1.12 ± 8.01	0.156
Alpha, μV^2	Baseline	4.48 ± 2.69	4.28 ± 2.19	
	Change from baseline	0.10 ± 2.79	0.61 ± 2.92	0.366
Sigma, μV^2	Baseline	2.61 ± 1.74	2.26 ± 1.30	
	Change from baseline	0.03 ± 1.13	0.62 ± 2.39	0.128
Beta, μV^2	Baseline	1.22 ± 0.88	1.16 ± 1.26	
	Change from baseline	0.45 ± 2.05	1.58 ± 9.04	0.388
Sleep architecture				
Total sleep time, minutes	Baseline	351.80 ± 9.95	330.00 ± 9.39	
	Change from baseline	−41.30 ± 10.05	1.57 ± 9.48	0.0025
Percentage of sleep in REM, %	Baseline	10.56 ± 0.94	12.05 ± 0.89	
	Change from baseline	1.17 ± 0.96	−0.14 ± 0.90	0.3217
Percentage of sleep in NREM, %	Baseline	89.44 ± 0.94	87.95 ± 0.89	
	Change from baseline	−1.17 ± 0.96	0.143 ± 0.90	0.3217
Percentage of sleep in stage 1, %	Baseline	33.19 ± 2.55	30.93 ± 2.41	
	Change from baseline	−3.08 ± 2.15	3.95 ± 2.03	0.0190
Percentage of sleep in stage 2, %	Baseline	49.83 ± 2.03	48.11 ± 1.92	
	Change from baseline	3.81 ± 1.80	−2.03 ± 1.70	0.0199
Percentage of sleep in stage 3, %	Baseline	6.44 ± 1.35	8.91 ± 1.27	
	Change from baseline	−1.46 ± 0.75	−2.16 ± 0.71	0.4986

All values are presented as mean ± SD. Nominal 2-sided p-value from Wilcoxon test for baseline values and from ANCOVA for changes from baseline to follow-up with baseline value as a covariate. Abbreviations: CAP = cyclic alternating pattern, h = hour, REM = rapid eye movement, NREM = non-rapid eye movement. [1]Significance level for ANCOVA: $p < 0.05$.

group. Furthermore, the recurrence rate of periodic EEG activity determined by the average CAP cycle duration was increased in CSA patients receiving TPNS stimulation compared to the control group, although the change was minimal. The change in average CAP cycle duration was mostly due to a simultaneous reduction in average B phase duration, indicating an effect of TPNS on the duration of B phases.

Modulations of phase A subtypes with no change in CAP rate have been previously described in sleep bruxism [16,17]. Bruxers presented with more subtypes A3 and fewer subtypes A1 compared to healthy controls, indicating that a hierarchical modulation of phase A subtypes precedes the onset of significant alterations of CAP rate, as seen in our study. Our results show that the drop in subtypes A2+A3 on TPNS treatment is partially compensated by a shift in favor of more A1 subtypes, indicating a change in A phase composition to balance the internal forces of REM-off and REM-on mechanisms [18]. Fig. 2 displays the A phase distribution superimposed on the hypnogram at baseline and the six-month visit for a CSA patient randomized to neurostimulation with the remedē System as an example of the shift in A phase subtype composition.

Indeed, the reduction in the A2+A3 index was inversely correlated with the increase in the A1 index, albeit the association was weak. The reciprocal distribution of phase A subtypes may find further support in sleep macrostructure. Treatment is associated with the decrease in phase A subtypes that typically occur closer to awakening (A2 and A3) and prolongation of N2 sleep.

While the detailed physiological mechanisms facilitating the change in CAP composition are unclear, the shift from A2+3 to A1 phases was paralleled by an improvement in sleep apnea. The more AHI was reduced, the more the A1 index increased, and the more the A2+A3 index declined. According to a recent study by Gnoni et al. [19], subtypes A1 prevail in milder obstructive sleep apnea phenotype, whilst subtypes A2 and A3 become dominant among moderate-to-severe obstructive sleep apnea patients. Whether these findings may be extended to CSA remains to be confirmed. However, it is interesting that CSA appears almost exclusively during NREM sleep [20], where CAP occurs. Our cross-sectional correlation analysis of baseline measures adds additional evidence to the association between CAP and CSA, showing a weak negative association between CSR and the A1 index and a weak positive association between the CSR percentage and the A2+A3 index as A2+A3 phases largely overlap with arousals which play a key role in sustaining ventilatory overshoot during cyclic hyperpnea and a

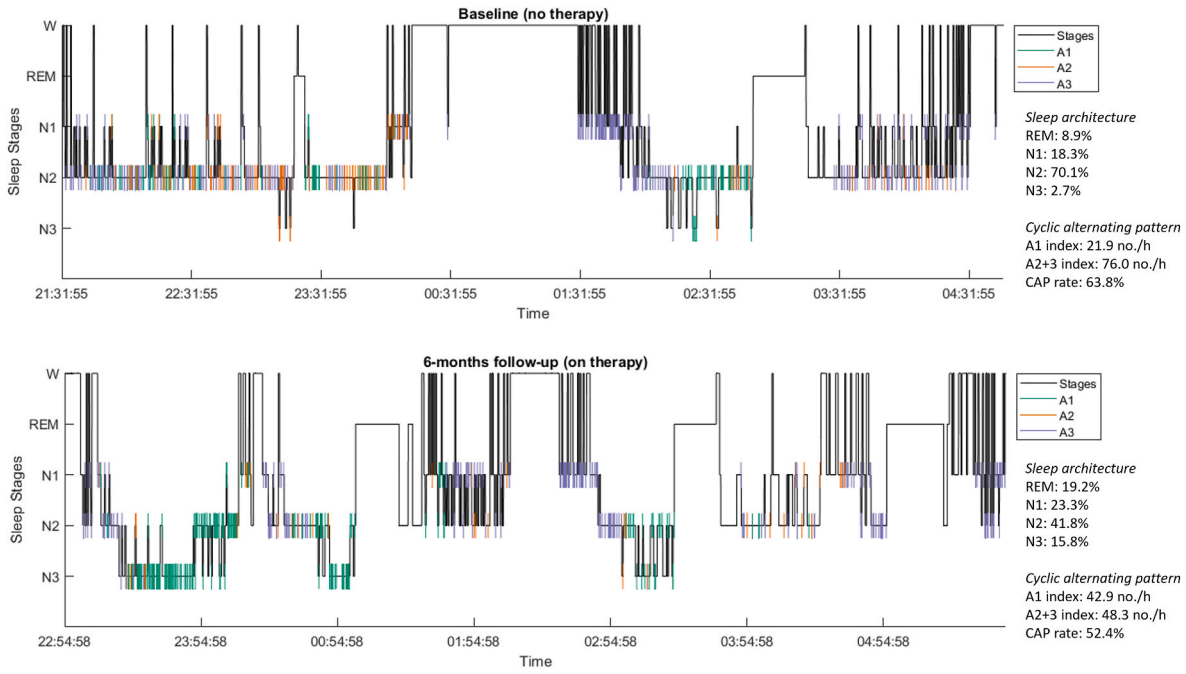

Fig. 2. Comparison of A phase distribution throughout sleep on baseline PSG and the six-month visit of a CSA patient randomized to neurostimulation with the remedē system.
Each hypnogram displays the sleep stages over time, and the small vertical lines superimposed on the hypnogram indicate the onset of an isolated A phase or an A-phase part of a cyclic alternating pattern (CAP) sequence during non-rapid eye movement sleep. Sleep staging was performed at the sleep core laboratory, and an automated system scored CAP. Summary statistics are listed next to each hypnogram, showing increased deep sleep and A1 phases on the follow-up PSG.

consequent greater hypocapnia propagating CSR-CSA [21,22]. As shown in a previous study, the majority of arousals during CSR-CSA tend to occur at hyperpnea onset or within the first half of the hyperpneic phase most likely caused by a concurrent increase in chemoreceptor stimulation [22].To further analyse the relationship between CSR and CAP in CSA patients, computer-assisted technologies could help detect arousals, their onset, and termination, as well as the interaction between A phases and ventilation [22,23].

The effects of central sleep apnea treatment on sleep microstructure are unknown; however, previous studies have investigated the effects of OSA treatment on sleep microstructure. Nasal continuous positive airway pressure therapy decreased CAP in OSA patients [7]. Rapid maxillary expansion for treating children with OSA syndrome was shown not to lower the CAP rate in slow-wave sleep but to increase the A1 index, which somewhat resembles our observation [24].

Our study has several limitations. Automated sleep scoring systems have shown promising performance in large datasets but may not always concur with manual labelling in individual cases [25]. In the case of CAP scoring, the classification of A phase subtypes has shown to be challenging [26]. This may have introduced measurement noise and artificially weakened the observed effect sizes. Moreover, EEG signal variability due to individual differences, such as underlying sleep disorders or different study sites with varying recording equipment, can result in a model's performance overestimation when not accounting for inter-subject variability in EEG and measurement setup aspects within cross-subject models. Hence, subject-level normalization, as implemented in the model deployed in this study, appears to lessen these issues [27]. Additionally, the system has shown high reproducibility [14] and utility for analyzing clinical trials [28,29].

5. Conclusion

In conclusion, TPNS for treating central sleep apnea may affect sleep microstructure. On treatment with TPNS, the composition of periodically recurring EEG activation phases that organize sleep microstructure appears to shift towards less rapid EEG rhythms and more slow, synchronized EEG activation phases. Such a rearrangement may facilitate sleep continuity.

Author statement

Simon Hartmann: Conceptualization, Methodology, Software, Formal analysis, Writing – Original Draft. Sarah Immanuel: Data curation, Writing- Reviewing and Editing. Scott McKane: Formal analysis, Investigation, Data Curation, Writing – Review & Editing. Dominik Linz: Writing – Review & Editing. Liborio Parrino: Writing – Review & Editing. Mathias Baumert: Conceptualization, Methodology, Writing-Reviewing and Editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Mathias Baumert reports financial support was provided by ZOLL Respicardia Inc. Scott McKane reports a relationship with ZOLL Respicardia Inc that includes: employment.

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