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ORIGINAL ARTICLE

Clinical Trials and Investigations

Exposure to a more unhealthy diet impacts sleep microstructure during normal sleep and recovery sleep: A randomized trial

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Abstract

Objective: Although intake of specific macronutrients has been associated with sleep parameters, interventional evidence is lacking. Therefore, this randomized trial was conducted to examine how a more unhealthy high-fat/high-sugar (HFHS) diet impacts sleep in humans.

Methods: In a crossover study, 15 healthy young men consumed two isocaloric diets in random order for a week: an HFHS and a low-fat/low-sugar diet. Following each diet, in-lab sleep was recorded using polysomnography during a full night of sleep and during recovery sleep after extended wakefulness. Sleep duration, macrostructure, and microstructure (oscillatory pattern and slow waves) were investigated using machine learning-based algorithms.

Results: Sleep duration did not differ across the diets based on actigraphy and the in-lab polysomnography. Sleep macrostructure was similar after 1 week on each diet. Compared with the low-fat/low-sugar diet, consumption of the HFHS diet resulted in reduced delta power, delta to beta ratio, and slow wave amplitude but increased alpha and theta power during deep sleep. During recovery sleep, similar sleep oscillatory changes were observed.

Conclusions: Short-term consumption of a more unhealthy diet alters sleep oscillatory features that regulate the restorative properties of sleep. Whether such changes can mediate adverse health outcomes associated with consumption of an unhealthier diet warrants investigation.

INTRODUCTION

Curtailed sleep has been associated with increased consumption of unhealthy foods and a greater long-term risk of adverse weight gain [1]. Conversely, primarily cross-sectional studies have studied how dietary factors may modulate sleep parameters [2], but studies on the direct impact of dietary intake patterns on human sleep are currently lacking.

Adherence to a more unhealthy and refined diet that is rich in sugar and saturated fat, a Western diet, is a contributing factor to the development and progression of metabolic disease. Dietary interventions can improve glucose metabolism in type 2 diabetes and reduce the risk of cardiovascular events [3, 4]. However, how different diets directly impact various neurobiological properties of sleep remains largely unknown. Such knowledge may provide insight into the neuroendocrine

mechanisms by which dietary factors impact sleep-modulated behavior and physiology. For instance, insulin sensitivity and secretion of growth hormone have been tied to slow wave sleep (SWS, sleep stage N3), which predominates in the early sleep period [5, 6].

Notably, slow wave activity (SWA), which represents the spectral power in the delta (1–4 Hz) and slow wave (SW) (<1.5 Hz) frequency range, can serve as a marker of the homeostatic buildup of sleep need and it may be tied to synaptic plasticity [7–9]. Importantly, SWS, SWA, and the ratio of delta to higher frequency bands (e.g., delta to beta) are impaired with increasing age and insomnia [10–13], and enhancing SWA could possibly help combat cognitive decline with aging [14]. It is therefore important to understand whether exogenous factors, such as dietary patterns, can alter sleep parameters that are impacted by aging.

Some prior evidence has indicated that dietary factors may modulate sleep quality and the amount of restorative sleep parameters such as SWS [15]. For example, greater intake of sugar and saturated fat has been correlated with less SWS, whereas fiber intake may exhibit the opposite relationship [16]. However, many such studies have been short-lasting, for example altering a single meal close to sleep onset [17, 18], and have mainly focused on macroscale sleep parameters (i.e., temporal dynamics and sleep stages). In addition, the homeostatic and restorative properties of sleep may also depend on its microstructural and oscillatory parameters such as delta power and SWA. Apart from a decline with aging, disruption in delta power during sleep has been associated with both sleep apnea and greater all-cause mortality risk [19, 20].

Our aim in the present study was to establish how consumption of two isocaloric but different diets in the short term modulate sleep at the macrostructure and microstructure level, focusing on restorative sleep parameters. Using a randomized crossover design, participants consumed both an unhealthier high-fat, high-sugar (HFHS) diet and a healthier low-fat, low-sugar (LFLS) diet, with sleep recordings under highly standardized in-lab conditions. To further validate our findings, participants subsequently also underwent an extended period of wakefulness, during which they were on an identical diet. This enabled us to study whether the diet-dependent changes in sleep parameters also carried over into recovery sleep, when there would also be a large buildup of homeostatic sleep pressure. Based on previous studies that have found diet-dependent changes to SWS following changes in the diet content of carbohydrates or sugar, fiber, and saturated fat [16, 17], our hypothesis in this exploratory study was that consumption of a refined unhealthier diet would disrupt the oscillatory pattern specifically during SWS.

Study Importance

What is already known?

- Consumption of high-fat/high-sugar (HFHS) diets has been associated with adverse metabolic outcomes and an increased risk of metabolic disease.
- Cross-sectional clinical studies and some interventional evidence have suggested that dietary factors can impact our sleep, but how exposure to an unhealthier diet directly impacts sleep parameters, and specifically its macrostructure, is currently unknown in humans.

What does this study add?

- In a randomized study, we found that a weeklong exposure to an HFHS diet, compared with a low-fat/low-sugar diet, did not impact the duration or macrostructure of sleep during regular sleep or during recovery sleep.
- During regular sleep, exposure to the HFHS diet reduced the relative power of delta frequencies and the amplitude of slow waves during deep sleep.
- The sleep oscillatory pattern was also impacted in a similar direction during recovery sleep.

How might these results change the direction of research or the focus of clinical practice?

- The observed diet-induced changes in sleep parameters are known to modulate numerous behavioral and physiological outcomes (such as memory consolidation, mood, attention, and glucose metabolism).
- Our findings thus warrant further investigation to determine the extent to which adverse outcomes of exposure to more unhealthy diets, which are rich in sugar and fat, are mediated through the dietary impact on the neurobiological properties of sleep.

METHODS

Participant recruitment

Inclusion criteria were self-reported good health, not taking any medication, having body mass index of 18 to 28 kg/m^2 and a normal waist circumference (<102 cm for men), and being weight stable (±5% body weight) over the past 6 months. Participants also had to report a regular sleep–wake pattern, with a sleep duration of 7 to 9.25 hours per night, and a regular daily meal pattern with three main meals.

Those on chronic medication or with any neurological or sleep disorder were excluded. For further exclusion criteria, please see the online Supporting Information Methods. All participants provided oral and written informed consent prior to study participation and received financial reimbursement. The Regional Ethical Review Board in Uppsala provided ethical approval for this study (EPN 2017/295/1).

Dietary intervention

Participants were allocated randomly in a 1:1 ratio to start either with the HFHS or LFLS diet. Participants were not told in advance what diet they would be assigned to in each study arm. When they were

provided each diet, participants were furthermore not provided with any information regarding any expected or anticipated outcome. All food items were provided to the participants by the research staff, and the amount was set according to each participant's calculated daily caloric requirement (Harris-Benedict equation, factored individually for the estimated habitual physical activity level). The daily provided calories were adjusted according to body weight when entering each study arm and they did not differ significantly across the diets (LFLS: 2624 ± 85 kcal, HFHS: 2622 ± 86 kcal, $p = 0.88$). The meals comprised isocaloric breakfast, lunch, and dinner, with identical meals for each day of each diet arm. For the LFLS diet, the provided meal items were a low-fat, unsweetened, unflavored yogurt (0.5% fat content; 75.5% of breakfast calories) and an unsweetened muesli for breakfast; premade pasta (88% of lunch calories, identical to the pasta in the HFHS diet arm) and green peas for lunch; and a premade salmon-vegetable mix for dinner. For the HFHS diet, the food items comprised a more fat-rich unsweetened yogurt (3% fat, 28% of breakfast calories) with sweetened granola for breakfast; for lunch, a mix of premade pasta (25% of lunch calories), premade meatballs (69% of lunch calories), and sweetened ketchup; and for dinner, a premade pizza (~59% of dinner calories) and a chocolate wafer bar. Sugar contributed to 9.6% of the daily caloric content in the LFLS diet, versus 17.6% in the HFHS diet; for fat, the contributions were 23.0% and 44.4%, respectively (additional macronutrient composition in Supporting Information Table S1).

The participants were instructed to consume the meals at specific hours of the day, relative to the wake-up time: breakfast after 15 to 40 minutes; lunch after around 5.5 to 6 hours; and dinner around 11 hours (10 hours 45 minutes to 11 hours 15 minutes). Each meal was to be consumed in its entirety within 20 minutes, and no condiments or beverages other than water were allowed. To increase and verify compliance regarding meal timing, the participants sent deidentified photos (through encrypted messaging) depicting each meal prior to, as well as after, having consumed the meal. Furthermore, the timing of food intake was also logged in a daily food diary. Participants were instructed to strictly abstain from any alcohol or caffeine intake during each diet intervention week.

Regarding sleep, participants were instructed to maintain their habitual sleep timing and duration (aiming for 7–9 hours of sleep per night). A sleep diary was filled out daily by the participants on each diet arm. To increase compliance, the participants also sent the experimenters text messages (via encrypted messaging) each day when they got up in the morning, as well as when they were going to bed to sleep. Sleep timing was verified by actigraphy (Actiwatch, Philips Respironics), which was relied on whenever there was a mismatch for sleep diary versus actigraphy data. Further details regarding subjective data collection are described in the online Supporting Information Methods.

After each dietary intervention, a washout period of several weeks took place (on average 7 ± 2 weeks). As described in the online Supporting Information Methods, an experimenter instructed the participants to try to carefully match sleep/wake and activity levels across the two diet arms. This also entailed aiming to maintain identical daily food intake timing across the two diet study arms in relation to the daily sleep–wake schedule.

In-lab protocol

The participants arrived in the laboratory about an hour prior to their habitual dinnertime and they were thus in a fasted state since lunchtime. Dinner was provided according to each participant's designated diet study arm and dinnertime.

Bedtime (i.e., lights out to allow for sleep) for the full (first) in-lab sleep night (NS-night) was individually adjusted based on each participant's habitual and average bedtime and wake-up time

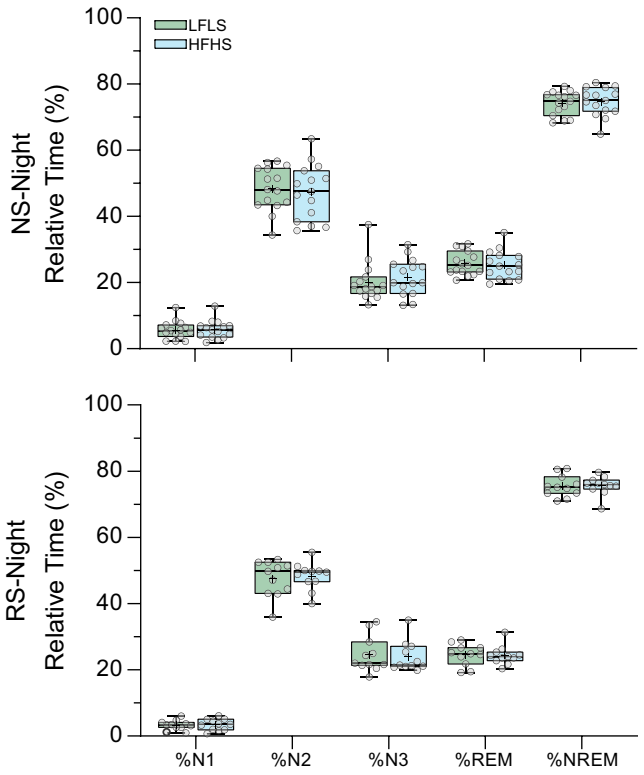

FIGURE 1 General sleep assessment and architecture of the first in-lab night (NS-night) and subsequent recovery sleep night (RS-night), following consumption of an isocaloric high-fat/high-sugar (HFHS) vs. low-fat/low-sugar (LFLS) diet. The NS-night took place after a week on an isocaloric LFLS or HFHS diet in randomized order (crossover design). The recovery sleep (RS-night) took place after 36 hours of wakefulness, during which time participants had been on an identical diet (i.e., after the main diet intervention) during the period of extended wakefulness (during a constant routine). (A) Box plots representing the percentage of time spent in the different sleep stages (i.e., rapid eye movement [REM] sleep and non-rapid eye movement [NREM] sleep phases) during the first in-lab night ($n = 15$ participants). (B) Box plots representing the percentage of time spent in distinct sleep stages during the recovery in-lab sleep night (RS-night) after 36 hours of wakefulness ($n = 11$ participants). The plus sign in each box plot indicates the mean value. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Macroscale sleep parameters for participants following a weeklong exposure to a low-fat/low-sugar diet vs. a high-fat/high-sugar diet

		LFLS				HFHS					
Night and sleep parameter	*n*	Mean	SE	Median	IQR	Mean	SE	Median	IQR	*p* value	Effect size
NS-Night											
TIB (min)	15	499.3	4.2	495.0	22.5	499.5	4.0	496.0	25.5	0.943	$d = 0.02$
SPT (min)	15	486.5	4.2	487.5	22.2	487.1	3.3	484.5	20.2	0.898	$d = 0.03$
TST (min)	15	470.1	3.8	467.5	23.0	465.5	6.7	472.5	26.0	0.556	$d = 0.16$
SOL (min)	15	11.4	2.9	6.5	14.2	10.7	1.8	10.0	7.0	0.939	$r = 0.03$
WASO (min)	15	16.3	2.8	15.0	13.2	21.6	5.9	12.0	22.2	0.901	$r = 0.04$
N1 (min)	15	26.5	3.4	26.0	14.2	26.5	3.0	26.5	14.0	0.992	$d = 0.00$
N2 (min)	15	227.9	8.8	233.5	44.5	220.9	11.4	212.5	59.0	0.598	$d = 0.14$
N3 (min)	15	94.3	6.6	87.5	22.2	100.4	6.8	94.5	35.2	0.277	$r = 0.33$
NREM (min)	15	348.7	5.2	340.5	31.0	347.8	7.2	347.5	39.8	0.905	$d = 0.03$
REM (min)	15	121.5	4.6	116.5	29.2	117.7	5.6	112.5	23.0	0.679	$r = -0.13$
%N1	15	5.6	0.7	5.4	2.7	5.8	0.7	5.7	3.1	0.856	$d = 0.05$
%N2	15	48.4	1.7	48.1	10.6	47.3	2.2	47.5	12.9	0.648	$d = 0.12$
%N3	15	20.1	1.5	18.8	3.9	21.6	1.4	20.0	7.4	0.277	$r = 0.33$
%NREM	15	74.2	0.9	74.8	5.4	74.7	1.1	75.1	6.0	0.655	$d = 0.12$
%REM	15	25.8	0.9	25.2	5.4	25.3	1.1	24.9	6.0	0.655	$d = 0.12$
%SE	15	94.2	0.7	94.8	3.8	93.3	1.5	95.1	2.9	0.847	$r = -0.07$
RS-Night											
TIB (min)	11	711.1	6.0	719.0	17.8	716.8	2.9	719.0	12.2	0.592	$r = 0.20$
SPT (min)	11	695.9	6.0	705.0	30.5	701.7	4.2	706.5	14.8	0.637	$r = 0.18$
TST (min)	11	664.1	14.6	671.5	53.2	681.3	7.5	688.0	36.5	0.206	$d = 0.41$
SOL (min)	11	15.0	3.9	10.5	12.5	15.0	4.3	11.0	9.0	0.950	$r = 0.03$
WASO (min)	11	31.8	12.3	14.0	18.5	20.4	5.9	16.0	12.8	0.765	$r = -0.12$
N1 (min)	11	21.5	2.9	21.5	9.2	23.3	3.6	23.0	19.5	0.482	$d = 0.22$
N2 (min)	11	316.5	13.3	306.5	49.5	329.2	9.9	336.5	31.5	0.200	$d = 0.41$
N3 (min)	11	162.6	10.1	153.0	42.8	163.0	9.4	150.0	32.2	0.765	$r = 0.12$
NREM (min)	11	500.5	9.6	505.5	32.8	515.5	8.4	513.0	46.0	0.164	$d = 0.45$
REM (min)	11	163.6	8.7	171.0	41.2	165.8	6.2	167.0	15.5	0.811	$r = 0.09$
%N1	11	3.3	0.4	3.3	1.3	3.4	0.5	3.5	2.9	0.673	$d = 0.13$
%N2	11	47.6	1.6	49.7	8.2	48.3	1.2	49.5	3.2	0.582	$d = 0.17$
%N3	11	24.6	1.6	22.0	5.3	23.9	1.4	21.5	5.2	0.831	$r = -0.09$
%NREM	11	75.5	1.0	75.2	3.8	75.7	0.9	76.0	1.8	0.879	$d = 0.05$
%REM	11	24.5	1.0	24.8	3.8	24.3	0.9	24.0	1.8	0.879	$d = 0.05$
%SE	11	93.4	1.9	95.8	6.1	95.0	0.8	96.2	2.1	0.831	$r = 0.09$

Note: Macroscale sleep parameters, based on polysomnography, for the first in-lab night (NS-night) and subsequent recovery sleep night (RS-night). The NS-night took place after a week on an isocaloric LFLS vs. HFHS diet, in randomized order (crossover design). The recovery sleep (RS-night) took place after 36 hours of wakefulness, during which time participants had been on an identical diet (i.e., after the main LFLS vs. HFHS diet intervention) during the period of extended wakefulness (i.e., during a constant routine). Effect sizes were computed from nonparametric and parametric data as rank biserial correlation (*r*) or Cohen *d*, respectively.

Abbreviations: SE, sleep efficiency; HFHS, high-fat/high-sugar diet; LFLS, low-fat/low-sugar diet; NREM, non-rapid eye movement sleep; N1, NREM stage I; N2, NREM stage II; N3, NREM stage III; REM, rapid eye movement sleep; SOL, sleep onset latency; SPT, sleep period time; TIB, total duration of the hypnogram; TST, total sleep time; WASO, wake after sleep onset.

(adjusted for sleep onset latency), for the last days of each dietary intervention week (preceding each in-lab session). The aim was to enable the participants to sleep according to their habitual sleep/wake schedule. The timing of participants' bedtime, sleep onset, and wake-up time for the week during the dietary intervention was further validated prior to calculating the optimal bedtime and wake-up time for the first in-lab night by analyzing the participants' actigraphy data.

Three hours prior to bedtime on the first night of sleep (the "NS-night") in each session, light levels were lowered to <10 lux in the

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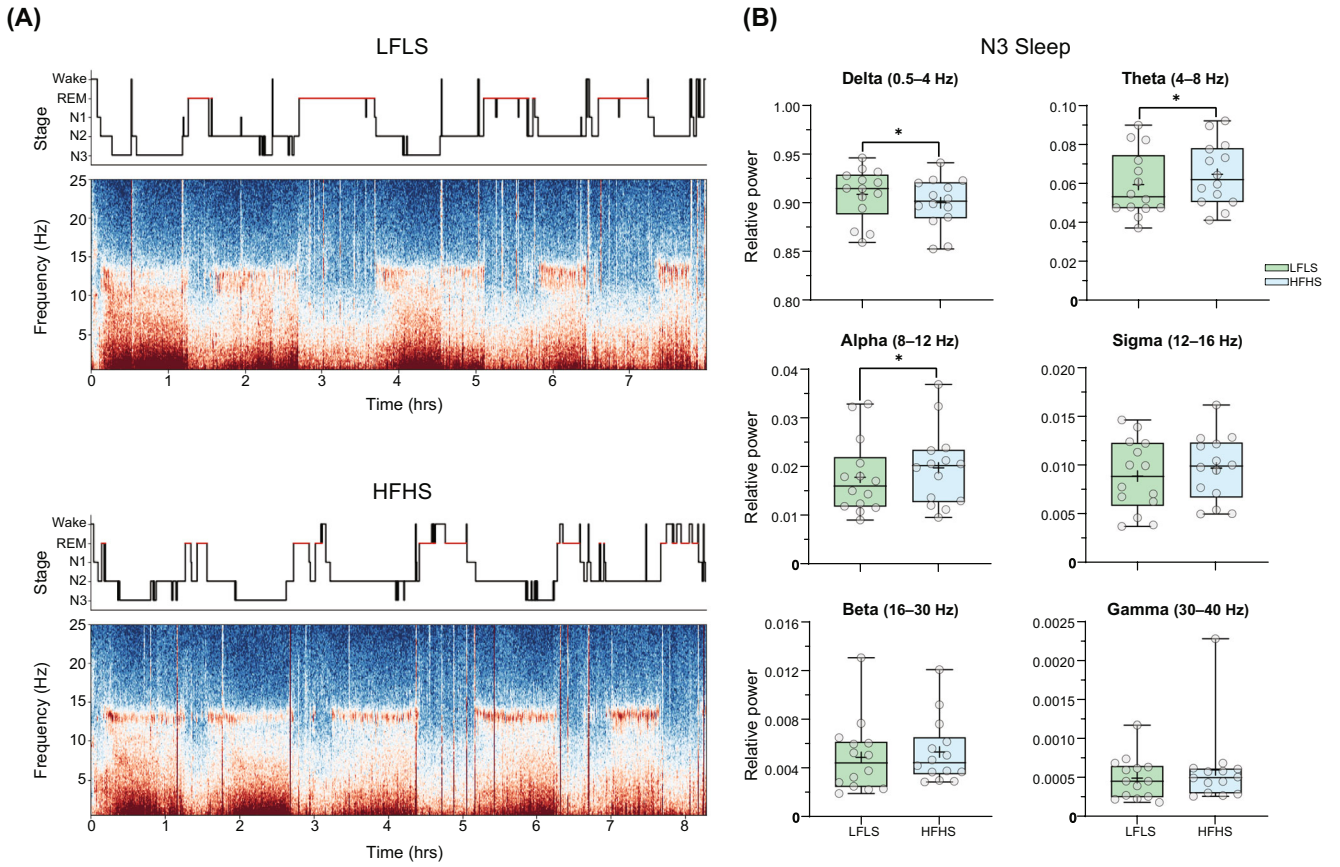

FIGURE 2 Spectral analysis of the oscillatory components of the EEG signal obtained from central electrodes in the N3 sleep stage during the first in-lab sleep night, following consumption of the two different diets. (A) Representative hypnograms and spectrograms from the same participant after the two diet paradigms (low-fat/low-sugar [LFLS] diet in the upper half; high-fat/high-sugar [HFHS] diet in the bottom half). Rapid eye movement (REM) sleep is highlighted in red in both hypnograms. In the spectrograms, higher spectral power is represented by warmer colors, whereas lower power is represented by colder colors. (B) Box plots representing the relative power distribution of different oscillatory ranges (see *Methods* section for more details; corresponding N2 and REM sleep stage analyses are shown in Supporting Information Figure S3). *Denotes $p < 0.05$ when comparing the two diets. The plus sign in each box plot indicates the mean value. $n = 14$ participants [Color figure can be viewed at wileyonlinelibrary.com]

direction of gaze and were lowered to <5 lux in the direction of gaze starting at 2 hours prior to bedtime. Participants were not permitted to turn on any lights if they woke during the night and were provided with urine flasks to avoid any nighttime visit to the toilet.

In the morning after the first night in the lab, participants underwent a constant routine (CR; the results of which will be reported elsewhere). At all times throughout this 36-hour period, light was kept below 5 lux in the direction of gaze, and participants were not allowed to leave their designated stretchers, which they rested on in a semirecumbent position. Participants were provided hourly isocaloric liquid meals (a blended mix of cashew nuts, oats, banana, and a low-fat, unsweetened yogurt). These meals were designed to provide a proportion of calories from fat that was roughly intermediate (33.7%) to that consumed daily on the HFHS and LFLS diets. At the end of the CR paradigm, all participants were provided with a 12-hour overnight sleep opportunity ("RS-night").

For the second in-lab session, participants' bedtime for the first in-lab NS-night was adjusted to achieve the same sleep opportunity (in terms of duration) as for the first in-lab session, while once more anchoring its timing based on the timing of the preceding couple of nights' sleep (to minimize circadian phase shifts). This also meant that the timing of the subsequent second CR and the later 12-hour RS-night sleep opportunity was also adjusted accordingly.

Polysomnography recordings

During a separate habituation night, polysomnography (PSG) was also performed to habituate the participants to the equipment and sleep environment. Participants' sleep was then assessed by PSG at the end of each dietary intervention (NS-night), as well as during the recovery sleep opportunity (RS-night), which followed the CR. For more information regarding the PSG-based analysis, please see the online Supporting Information Methods.

Statistical analyses

Data preprocessing, sleep assessment, statistical analyses, and visualization were performed using R Statistical Software version 4.1.2

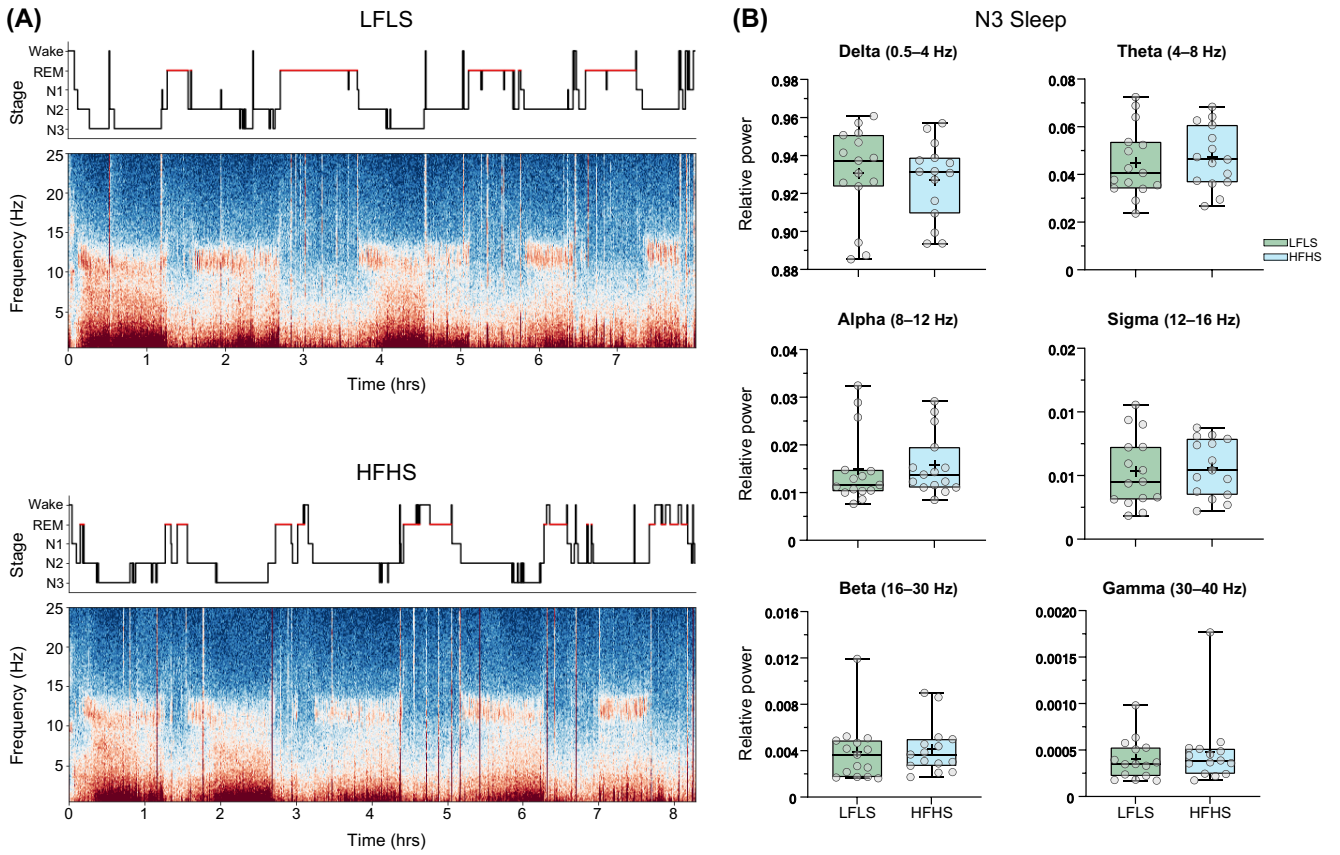

FIGURE 3 Spectral EEG analysis obtained from the frontal electrodes in the N3 sleep stage during the first in-lab sleep night, following consumption of the two different diets. (A) Representative hypnograms and spectrograms from the same participant after the two dietary paradigms (low-fat/low-sugar [LFLS] diet in the upper part; high-fat/high-sugar [HFHS] diet in the bottom part). Rapid eye movement (REM) sleep is highlighted in red in both hypnograms. In the spectrograms, higher spectral power is represented by warmer colors, whereas lower power is represented by colder colors. (B) Box plots representing the relative power distribution of different oscillatory ranges (see *Methods* section for more details; corresponding N2 and REM sleep stage analyses are shown in Supporting Information Figure S3). The plus sign in each box plot indicates the mean value. $n = 15$ participants [Color figure can be viewed at wileyonlinelibrary.com]

(R Core Team 2021), Python version 3.10.5, and GraphPad Prism version 9.4.0. Normality was assessed by the Shapiro–Wilk test.

Owing to the crossover design of our study, comparisons between different sessions (LFLS or HFHS diet) were performed either by paired two-tailed *t* test or two-tailed Wilcoxon matched-pairs signed rank test, with α set to 5%. For repeated measures analysis, we used two-way repeated ANOVA, examining the effect of diet, time (days or nights), and their interaction. Outcomes were reported as mean ± standard error (SE) or median (interquartile range [IQR]). Effect sizes were also reported as Cohen *d* (*d*) for paired *t* tests or as a rank biserial correlation (*r*) for Wilcoxon tests [21].

PSG recordings for the first in-lab night were obtained for both conditions from 15 participants. For the sleep oscillatory parameters and microarchitecture analyses, because of poor signal quality, we had to exclude central electrode data from one participant (central = 14 paired recordings, frontal = 15). During the NS-night, technical reasons resulted in four PSG recordings (two from each diet condition) to terminate just prior to wakefulness, that is, the period far less rich in SWS or low band frequencies such as delta (truncated by 7, 8, and 30 minutes in comparison to the participant's actigraphy-derived wake time). We therefore conducted a sensitivity analysis, in which the duration of the longer recording (from the participant's other session) was also truncated to match the recording length for these four recording pairs.

For the RS-night, electrode detachment from four participants reduced our sleep macrostructure and oscillatory analyses to 11 paired recordings. We had to exclude data acquired from the central electrode from one participant because of poor signal quality (resulting in 10 paired recordings for the central data; 11 for the frontal). Moreover, SW events during N3 sleep stage were not detected in the central electrode from one participant (N3: central = 9 paired recordings, frontal = 11).

RESULTS

Sleep duration is not impacted by short-term consumption of a more unhealthy diet

We obtained electroencephalograms (EEGs) from both dietary conditions from a total of 15 participants (age 23.1 ± 0.8 years;

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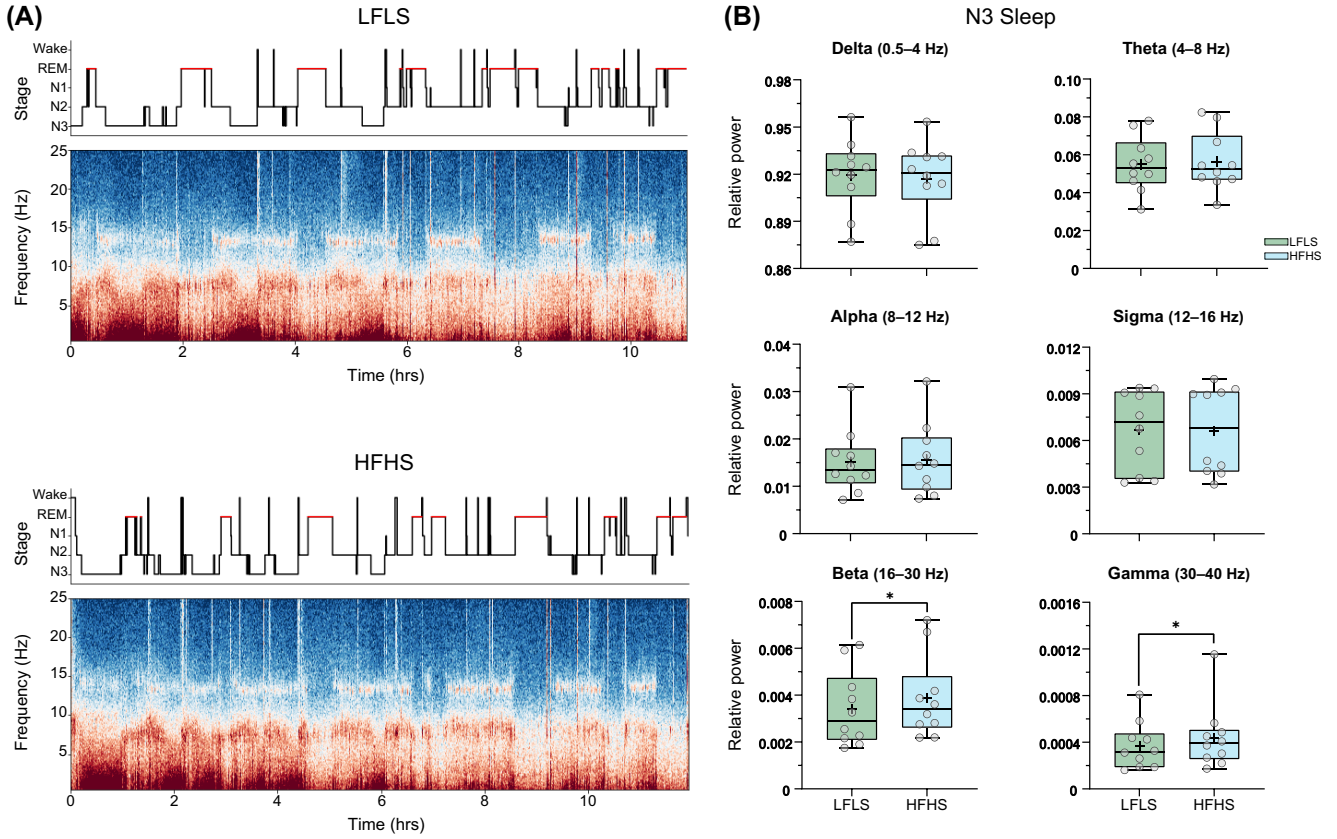

FIGURE 4 Spectral EEG analysis obtained from the central electrodes in the N3 sleep stage during the in-lab recovery sleep night, following consumption of the two different diets. The 12-hour recovery sleep opportunity took place after 36 hours of continued wakefulness, with preceding (crossover design) consumption of a low-fat/low-sugar (LFLS) or high-fat/high-sugar (HFHS) diet. (A) Representative hypnograms and spectrograms from the same participant after the two dietary conditions (LFLS diet in the upper part; HFHS diet in the bottom part). Rapid eye movement (REM) sleep is highlighted in red in both hypnograms. In the spectrograms, higher spectral power is represented by warmer colors, whereas lower power is represented by colder colors. (B) Box plots representing the relative power distribution of different oscillatory ranges (see *Methods* section for more details; corresponding N2 and REM sleep stage analyses are shown in Supporting Information Figure S5). *Denotes $p < 0.05$ when comparing the two diets. The plus sign in each box plot indicates the mean value. $n = 10$ participants [Color figure can be viewed at wileyonlinelibrary.com]

further characteristics in Supporting Information Table S2). Sleep duration during the in-field part of the study did not differ significantly between the two dietary conditions, as assessed by diaries and actigraphy (average LFLS: 7 hours 43 minutes ± 7 minutes, HFHS: 7 hours 47 minutes ± 7 minutes; ANOVA p values > 0.10 for night, diet, and interaction terms; Supporting Information Figure S1), and participants had a similar body weight across both study arms (LFLS: 76.0 ± 3.0 kg, HFHS: 76.2 ± 2.9 kg, $p = 0.50$). Furthermore, we found no significant diet-based differences regarding how participants perceived their night-to-night sleep quality, morning sleepiness, or morning and evening hunger ratings (Supporting Information Figure S1; ANOVA $p > 0.10$ for all day, diet, and interaction terms), and the average time interval from dinner to sleep onset was similar across conditions (Supporting Information Figure S1; $p = 0.61$).

During the in-lab night of sleep (NS-night), sleep duration remained similar between the two dietary conditions, as assessed by PSG (Figure 1 and Table 1). During the 12-hour recovery sleep opportunity (the RS-night) after the 36 hours of extended wakefulness, the participants accrued a PSG-assessed sleep duration that slightly exceeded 11 hours in each condition, but without any diet-specific differences (Figure 1 and Table 1).

Short-term consumption of a more unhealthy diet does not alter sleep macrostructure

We next assessed general and stage-specific sleep parameters (%N1, %N2, %N3, % non-rapid eye movement [NREM], % rapid eye movement [REM], and total time in minutes), which were similar and within normal range (e.g., ~20% in N3) across the two study arms during the NS-night (Table 1). Similarly, sleep onset or efficiency, or stage latencies, were not different between the diet arms (Table 1 and Supporting Information Table S3). These findings were not altered in a sensitivity analysis controlling for the subset of truncated NS-night recordings (Supporting Information Table S4). During the RS-night, we

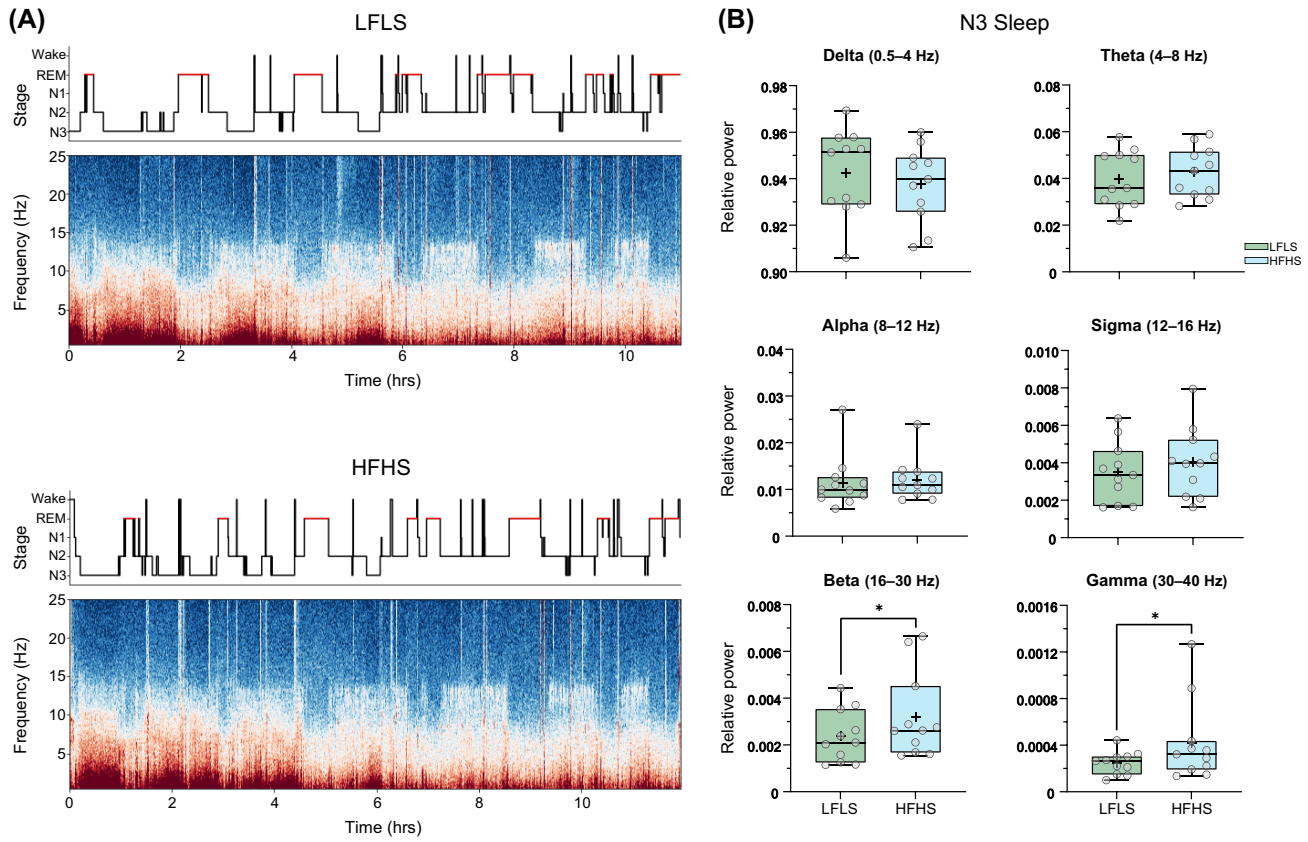

FIGURE 5 Spectral analysis of the oscillatory components of the EEG signal obtained from the frontal electrodes in the N3 sleep stage during the in-lab recovery sleep night. In both dietary conditions, sleep occurred after 36 hours of wakefulness, during which time participants were on an identical diet (in each condition having been preceded by a week's consumption of either the low-fat/low-sugar [LFLS] or the high-fat/high-sugar [HFHS] diet). (A) Representative hypnograms and spectrograms from the same participant after the two dietary conditions (LFLS diet in the upper half; HFHS diet in the bottom half). Rapid eye movement (REM) sleep is highlighted in red in both hypnograms. In the spectrograms, higher spectral power is represented by warmer colors, whereas lower power is represented by colder colors. (B) Box plots representing the relative power distribution of different oscillatory ranges (see *Methods* section for more details; corresponding N2 and REM sleep stage analyses shown in Supporting Information Figure S5). *Denotes $p < 0.05$ when comparing the two diets. The plus sign in each box plot indicates the mean value. $n = 11$ participants [Color figure can be viewed at wileyonlinelibrary.com]

also observed no significant diet-dependent differences in terms of sleep duration, latencies, or proportional sleep parameters (Table 1 and Supporting Information Table S3).

The first and second halves of sleep provide unique restorative properties: for example, growth hormone release primarily occurs during the early sleep period. Therefore, we analyzed sleep macrostructure in these halves separately in sensitivity analyses. However, this did not reveal any significant differences for sleep macrostructure between the two dietary conditions for the NS- or RS-night (Supporting Information Figure S2).

Consumption of a more unhealthy diet alters the oscillatory properties during deep sleep

The spectral component analysis of the NS-night revealed that compared with the LFLS diet, the unhealthier HFHS diet led to a reduced relative power of delta frequencies (0.91 ± 0.01 vs. 0.90 ± 0.01, $t_{[13]} = 2.518$, $p < 0.05$, $d = 0.67$) and increased relative power of theta (0.059 ± 0.004 vs. 0.065 ± 0.004, $t_{[13]} = 2.487$, $p < 0.05$, $d = 0.66$) and alpha (0.016 [0.010] vs. 0.020 [0.011], $W = 73$, $p < 0.05$, $r = 0.70$) frequencies during the N3 but not N2 or REM sleep stages (Figure 2 and Supporting Information Figure S3). This effect was quite consistent (e.g., reduced delta in 11/14 participants) and observed in the central EEG region. This region also exhibited a lower delta to beta ratio after the HFHS diet (248.2 ± 34.8 vs. 202.9 ± 21.5, $t_{[13]} = 2.259$, $p < 0.05$, $d = 0.60$; Supporting Information Figure S4), but in contrast, no diet-induced spectral changes were detected in the frontal EEG regions (Figure 3 and Supporting Information Figure S3). The oscillatory changes remained significant when controlling for the subset of somewhat truncated PSG recordings (Supporting Information Tables S5 and S6).

During the RS-night, we observed that the HFHS diet resulted in an increase in the relative power of beta and gamma frequencies during N3 sleep across both the frontal and central EEG regions (N3,

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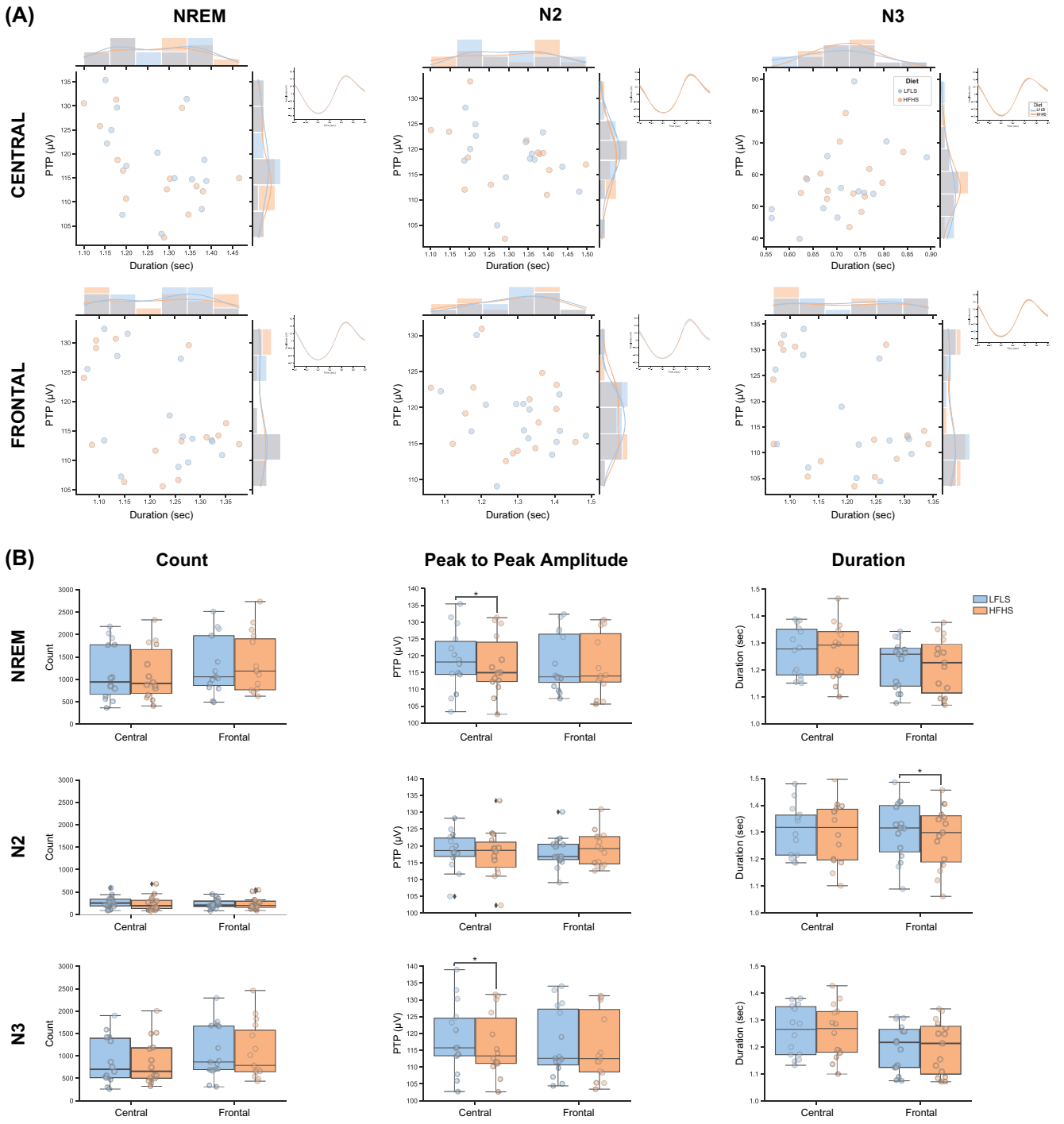

FIGURE 6 Analysis of slow waves detected during non-rapid eye movement sleep (NREM) sleep of the EEG signals obtained from central and frontal electrodes during the first in-lab sleep night, following consumption of each diet. (A) Scatterplots accompanied by marginal histograms representing the duration (x-axis) and peak-to-peak amplitude (y-axis) of all detected slow waves (frequencies 0.3–1.5 Hz) from each participant, after the low-fat/low-sugar (LFLS) diet and the high-fat/high-sugar (HFHS) diet. The average shape of these events is represented at the side of each plot. (B) Box plots representing the total count (left column), peak-to-peak amplitude (middle column), and duration (right column) of the slow waves detected during NREM (N2 + N3 – upper row), N2 (middle row), and N3 (bottom row) sleep stages. *Denotes $p < 0.05$ when comparing the two diets. Outliers are represented by diamond shape symbols, ◆. $n = 15$ participants [Color figure can be viewed at wileyonlinelibrary.com]

Central-Beta: 0.0030[0.0026] vs. 0.0034[0.0022], $W = 43$, $p < 0.05$, $r = 0.82$; Central-Gamma: 0.00032[0.00029] vs. 0.00039[0.00025], $W = 45$, $p < 0.05$, $r = 0.82$; Frontal-Beta: 0.0021[0.0023] vs. 0.0026 [0.0028], $W = 64$, $p < 0.005$, $r = 0.97$; Frontal-Gamma: 0.00026 [0.00015] vs. 0.00032[0.00024], $W = 53$, $p < 0.005$, $r = 0.97$; Figures 4 and 5 and Supporting Information Figure S5). Concomitantly,

both regions exhibited a lower delta to beta ratio in N3 after the HFHS compared with the LFLS diet (Central: 325.3 ± 44.2 vs. 276.8 ± 33.2, $t_{[9]} = 3.147$, $p < 0.05$, $d = 1.00$; Frontal: 491.2 ± 69.8 vs. 371.3 ± 50.9, $t_{[10]} = 4.882$, $p < 0.001$, $d = 1.47$; Supporting Information Figure S4). These latter effects were quite consistently observed, as 10 of 11 participants exhibited a decrease in the frontal, and 9 of 10 for the central, delta to beta ratios.

Sleep microstructure is altered by exposure to a diet higher in fat and sugar

SW events were detected during the N2 and N3 phases of NREM sleep (Figure 6). During the NS-night, the peak-to-peak amplitude of SW events detected in the central region decreased during N3 sleep in the HFHS compared with the LFLS diet condition (119 ± 3 vs. 117 ± 3 μV, $t_{[13]} = 2.305$, $p < 0.05$, $d = 0.187$). When all NREM epochs were evaluated together (i.e., N2 + N3 epochs), the amplitude of SW events was also significantly lower in the HFHS diet condition (NREM: 119 ± 3 vs. 117 ± 2 μV, $t_{[13]} = 2.218$, $p < 0.05$, $d = 0.174$; Figure 6B, middle panels). Additionally, we observed that the HFHS diet resulted in a shortened duration of SWs during N2 sleep (1.31 ± 0.03 vs. 1.28 ± 0.03 s, $t_{[14]} = 2.222$, $p < 0.05$, $d = 0.215$) in the frontal EEG regions (Figure 6B, right panels).

During the RS-night, no diet-dependent differences were observed for SW parameters vis-à-vis the amplitude, duration, or total count (Supporting Information Figure S6).

DISCUSSION

Here we provide the first direct evidence, to our knowledge, to demonstrate that oscillatory patterns of sleep can be altered in healthy humans through exposure to a diet with a greater fat and sugar content, as assessed in a randomized crossover trial. Furthermore, we demonstrate that, although macrostructure changes in sleep were not different across the two short-term dietary exposures, the diet-dependent oscillatory changes carried over into a recovery night following extended wakefulness. Given the myriad functions of sleep, our findings provide insight into a potential mechanism through which consumption of an unhealthier diet may modulate sleep-regulated health parameters, such as cognition and hormone secretion.

Our findings suggest that consumption of an unhealthier HFHS diet results in changes to the oscillatory pattern of sleep that mirror a less restorative or less youthful state, encompassing less relative power in delta frequencies during deep sleep and a lower delta to beta ratio [13, 22, 23]. A similar observation was observed for SWs, the amplitude of which was found to be reduced following consumption of the unhealthier diet. The fact that we observed some changes primarily in the central electrodes could suggest that the changes reflect more global changes following consumption of the unhealthier diet. Our findings were overall quite consistent in directionality, for example, regarding the proportion of individuals (91%) exhibiting an HFHS diet-induced change in cortical hyperarousability (lower delta to beta ratio). Of note, the magnitude of some of our spectral changes were similar in magnitude but opposite of those observed following sleep restriction therapy in insomnia [24], highlighting the potential sleep health-related relevance of our findings.

Overall, diets rich in fiber seem to be associated with more high-quality sleep, such as more SWS, whereas this may be impaired by saturated fat and sugar [16]. A diet that contains more fiber but less saturated fat than a typical Western diet is the Mediterranean diet. Greater adherence to the Mediterranean diet has been associated with better sleep quality [25]. The less restorative EEG pattern that we observed following the HFHS diet may therefore possibly have been caused by the combined greater daily proportion of dietary sugar and saturated fat and the lower proportion of dietary fiber.

The unhealthier HFHS diet that we used herein indeed provided almost twice the percentage of calories from fat and sugar and almost five times the percentage of calories from saturated fat, compared with the LFLS diet. On the HFHS diet, the percentage of calories that participants obtained from fat (∼44%) and saturated fat (18.6%) slightly exceeded the average reported (∼36% and ∼12%, respectively) and the recommended daily intake proportions (20%–35% and <10%, respectively) for US citizens [26] (The 2015-2020 Dietary Guidelines for Americans). The percentage of calories from sugar was, however, less than the average daily intake across US age groups (17.6% vs. 19%–23%). It is possible that an even unhealthier diet (e.g., higher in sugar) may have resulted in even greater diet-induced differences in, for example, sleep delta power [16]. At the same time, our findings suggest that more typical dietary intake patterns common to many adults, and possibly week-to-week changes in macronutrient intake, may potentially impact the restorative features of sleep.

Importantly, the robustness of our findings is strengthened by several aspects, one of which is the randomized crossover design. Furthermore, sleep and its quality preceding the in-lab PSG assessment did not differ between the two conditions. Finally, some dietary effects on sleep seemed to carry over even after participants were switched to the same diet. Nevertheless, our findings require validation in a larger study, as well as in women and children. Older individuals will also be of interest: boosting SWs can improve functions that decline with aging, such as memory and immune function, and potentially also aging-associated harmful waste accumulation in the brain [27, 28]. Consumption of an unhealthy Western diet has instead been linked to impaired memory and impaired immunity, as well as to neurodegeneration [29–32]. Whether these observations at least in part are mediated through dietary effects on sleep remains unknown.

Our findings are subject to several limitations. Our study cannot establish night-to-night temporal dynamics in the onset of the observed diet-dependent changes. Most participants were habitually quite physically active, and their training status may potentially have masked some diet-dependent effects on sleep [33]. Larger studies are warranted to explore potential interindividual mediation by, for example, weight status, dietary and physical activity habits, genetics, and potential interactions with gut microbiome-induced signaling [25, 34, 35]. Furthermore, the present study was exploratory, and

even though the study size was larger than many similar studies [15–17], we may have been underpowered to detect changes in, for example, sleep macrostructure.

Within each dietary intervention, we did not match macro- or micronutrient content across the three daily meals. Although the HFHS diet included some milk chocolate, the caffeine content in such items is generally low [36] and was provided several hours prior to sleep. Importantly, after the dietary interventions, the participants consumed an identical in-lab diet for 36 hours. Subsequent exposure to this diet may have possibly contributed to the region-specificity of the changes observed between the normal sleep night versus the recovery sleep, which likely were also impacted by the homeostatic buildup from the extended wakefulness. Even so, similar diet-dependent changes in sleep oscillations were observed across the two nights. This suggests that the diet-dependent changes to sleep dynamics did not depend on the timing of dietary factors consumed nearest to bedtime, but rather the overall differences in the two intervention diets.

In conclusion, we herein provide novel evidence to indicate that exposure to a more unhealthy diet, higher in the proportion of daily calories from sugar and fat, can impact several sleep parameters that are known to be associated with the restorative properties of sleep in humans. As we also observed similar changes in sleep parameters during recovery sleep, which occurred after cessation of the two different diets, our findings raise the possibility that even a short-term dietary exposure can continue to impact the neurobiology of sleep over several days.

AUTHOR CONTRIBUTIONS

Jonathan Cedernaes came up with the study idea, designed the study, and wrote the protocol. Alexandru Popa, Erasmus Cedernaes, Christopher Cedernaes, Lauri Lampola, and Jonathan Cedernaes conducted the experiments and collected the data; Luiz Eduardo Mateus Brandão and Jonathan Cedernaes conducted the analyses and interpreted the data; Jonathan Cedernaes wrote the original manuscript draft. All authors contributed to review and editing and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

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