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Caffeine-dependent changes of sleep-wake regulation: Evidence for adaptation after repeated intake

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ABSTRACT

Background: Circadian and sleep-homeostatic mechanisms regulate timing and quality of wakefulness. To enhance wakefulness, daily consumption of caffeine in the morning and afternoon is highly common. However, the effects of such a regular intake pattern on circadian sleep-wake regulation are unknown. Thus, we investigated if daily daytime caffeine intake and caffeine withdrawal affect circadian rhythms and wake-promotion in habitual consumers.

Methods: Twenty male young volunteers participated in a randomised, double-blind, within-subject study with three conditions: i) caffeine (150 mg 3 x daily for 10 days), ii) placebo (3 x daily for 10 days) and iii) withdrawal (150 mg caffeine 3 x daily for eight days, followed by a switch to placebo for two days). Starting on day nine of treatment, salivary melatonin and cortisol, evening nap sleep as well as sleepiness and vigilance performance throughout day and night were quantified during 43 h in an in-laboratory, light and posture-controlled protocol.

Results: Neither the time course of melatonin (i.e. onset, amplitude or area under the curve) nor the time course of cortisol was significantly affected by caffeine or withdrawal. During withdrawal, however, volunteers reported increased sleepiness, showed more attentional lapses as well as polysomnography-derived markers of elevated sleep propensity in the late evening compared to both the placebo and caffeine condition.

Conclusions: The typical pattern of caffeine intake with consumption in both the morning and afternoon hours may not necessarily result in a circadian phase shift in the evening nor lead to clear-cut benefits in alertness. The time-of-day independent effects of caffeine withdrawal on evening nap sleep, sleepiness and performance suggest an adaptation to the substance, presumably in the homeostatic aspect of sleep-wake regulation.

1. Introduction

Caffeine is the most commonly consumed psychoactive substance in the world (Fredholm et al., 1999). Around 80% of the worldwide population consume caffeine regularly on a daily basis (Heckman et al., 2010) and intake is increasing in terms of daily dosages and earlier age of regular substance intake (Roehrs and Roth, 2008). Caffeine containing aliments, e.g. coffee, tea, soda drinks and chocolate (Fredholm et al., 1999), are used since centuries to modulate sleep and wakefulness (Camandola et al., 2019).

Timing, quality and quantity of sleep and wakefulness are regulated by the interplay of a homeostatic and a circadian process (Borbély, 1982). Caffeine interferes with sleep homeostasis by antagonising adenosine (Landolt, 2008), a proposed mediator of the increase of homeostatic sleep pressure during time spent awake and its decrease during sleep (Porkka-Heiskanen, 2013). By blocking the A_1 and A_{2A} adenosine receptors (Fredholm et al., 1999), which are expressed in wide-spread areas of the human central nervous system (Elmenhorst

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et al., 2012; Naganawa et al., 2014), acute caffeine administration reduces the effects of sleep pressure, as mirrored in reduced sleepiness (James, 1998), improved behavioural performance (Einöther and Giesbrecht, 2013) and dampened sleep depth during nighttime sleep (Landolt, 2008), particularly when sleep pressure is high (Roehrs and Roth, 2008; Snel and Lorist, 2011).

Furthermore, evidence accumulates that caffeine also impacts on human circadian rhythms, as indexed by changes in salivary melatonin levels following administrations at a certain circadian phase. Acute caffeine intake in the evening and at night has been shown to delay the onset of melatonin secretion (Burke et al., 2015) and decrease nighttime melatonin levels (Wright Jr. et al., 1997; Wright Jr. et al., 2000). However, evening intake of caffeine is not common in the society nowadays (Martyn et al., 2018). Considering the average half-life of caffeine with a duration of around 4 h (Snel and Lorist, 2011), the question arises whether caffeine-induced circadian effects also occur when consumption is timed to morning and afternoon, as observed in habitual caffeine consumers (Martyn et al., 2018).

Besides the timing of caffeine intake, the duration of prior repeated daily use moderates the impact of caffeine-induced changes on sleep-wake regulation. There is evidence that consumers develop tolerance to the substance already after several days, such that effects of a particular dose of caffeine, for instance on sleep (Bonnet and Arand, 1992) or alertness (James, 1998) become weakened. However, in line with a recent study in animals (Panagiotou et al., 2018), it has also been shown that continuous hourly caffeine intake over four weeks strengthens circadian wake-promotion, as indicated by a reduced ability to sleep prior to habitual bedtime (Wyatt et al., 2004). Interestingly, timing of melatonin secretion was not shifted by the long-term treatment. An open question remains, whether the absence of phase shifts can be traced back to the continuous timing of caffeine administration around the entire circadian cycle or due to neuroadaptations in response to long-term treatment.

One of the typical indicators of neuronal and systemic alterations in response to long-term caffeine use is the occurrence of withdrawal symptoms when intake is ceased (Juliano and Griffiths, 2004). Caffeine withdrawal symptoms include decreased alertness (James, 1998; Rogers et al., 2005), impaired cognitive performance (James, 1998; Rogers et al., 2005) and changes in waking electroencephalogram (EEG) such as enhanced theta power (Sigmon et al., 2009), starting 12 to 24 h after last caffeine intake with peak intensity between 20 and 51 h and a maximal duration of nine days (Juliano and Griffiths, 2004). Based on changes in adenosine-signaling (Ferre, 2008), caffeine withdrawal thus constitutes a state of low arousal which may help triggering the maintenance of daily caffeine intake in habitual consumers (Juliano and Griffiths, 2004). However, to our best knowledge the impact of caffeine withdrawal on human circadian sleep-wake regulation has not yet been examined.

Thus, we investigated the effects of daily daytime caffeine consumption and its withdrawal on human waking performance, circadian rhythms and wake-promotion. To establish both tolerance and withdrawal, and to enable a comparison to a withdrawal-free baseline, caffeine and placebo, respectively, were administered over 10 days in a crossover design with three conditions (caffeine, placebo and withdrawal). Starting at day nine of treatment, sleepiness and vigilance performance was assessed as well as salivary melatonin, cortisol and nap sleep during high circadian wake-promotion within a 43 h-laboratory protocol under controlled light, posture and meal intake.

2. Methods

The present study was approved by the Ethics Committee northwest/central Switzerland (EKNZ) and conducted in accordance with the declaration of Helsinki. All volunteers provided written informed consent and received a monetary compensation for study participation.

2.1. Volunteers

In total, 179 male healthy habitual caffeine consumers underwent a thorough screening procedure. Exclusion criteria comprised age < 18 or > 35 years, body mass index (BMI) < 18 or > 26, drug dependency, shiftwork within three months prior to study admission, transmeridian travels within one month prior to study, extreme chronotype (Morningness-Eveningness Questionnaire (Horne, 1976), score ≤ 30 and ≥ 70) and poor sleep quality (Pittsburgh Sleep Quality Index (Buysse et al., 1989), score > 5). Female volunteers were excluded in order to reduce variance in our data due to the menstrual cycle (Shechter and Boivin, 2010) and use of oral contraceptives (Balogh et al., 1995; Abernethy and Todd, 1985). Volunteers were included when habitual daily caffeine intake was between 300 and 600 mg, assessed with a survey tool based on (Bühler et al., 2013) and adapted to the caffeine content according to (Snel and Lorist, 2011). Twenty-nine volunteers were invited for a habituation night and a physical examination by a physician in charge to exclude poor sleep efficiency (SE $< 70\%$), clinical sleep disturbances (apnea index > 10, periodic leg movements > 15/h) and chronic or debilitating medical conditions. Demographic characteristics of the 20 participants who completed all three conditions can be found in the supplementary materials (Table S1).

2.2. Design and protocol

The protocol is illustrated in Fig. 1(a). A double-blind, crossover study comprising three conditions was conducted: a caffeine, a placebo and a withdrawal condition. This within-subject design was chosen to reduce variance in the data due to expectancies or inter-individual variability in caffeine metabolism. For calculation of sample size and pseudo-random allocation of volunteers to the order of the three conditions, see supplementary materials (Table S3). In each condition, participants ingested gelatin capsules over 10 days three times daily (45 min, 255 min and 475 min after wake-up), containing either placebo (mannitol, Hänseler AG, Herisau, Switzerland) or caffeine (150 mg, Hänseler AG, Herisau, Switzerland). Participants were instructed to refrain from caffeinated beverages and food. Compliance was verified by assessing caffeine metabolites from fingertip sweat collected prior to habitual bedtime (see supplementary materials). The length of the treatment of 10 days was based on the maximum duration of withdrawal symptoms (Juliano and Griffiths, 2004), occurring during placebo treatment in habitual consumers. Timing and dose were based on an earlier study investigating tolerance to caffeine and its withdrawal (James, 1998).

The caffeine and placebo conditions included one type of pill exclusively (caffeine or placebo, respectively). The withdrawal condition comprised a switch from caffeine to placebo pills in the late morning of day nine (255 min after wake-up). In scheduling the caffeine to placebo switch to the late morning, we aimed at a coincidence of the peak of withdrawal symptoms (after around 35 h after last caffeine intake) with a window of high circadian wake-promotion. Dim light melatonin onset (DLMOnset) was used as marker of circadian timing.

Each condition started with an ambulatory part of nine days during which participants ingested capsules according to the regimen described above. In addition, participants kept a fixed sleep-wake rhythm (within $\pm$ 30 min of self-selected bedtime, time in bed 8 h, no naps) verified by wrist actimetry (Actiwatch, Cambridge Neurotechnology, Cambridge, United Kingdom). The average deviation from the targeted bedtime was $\pm$ 21 min in the evening and $\pm$ 26 min in the morning with an average time in bed of 8 h and 3 min. The sleep-wake schedule was consistent across the conditions except for three volunteers (twice: $+30$ min in caffeine compared to placebo and withdrawal conditions; once: -30 min in placebo compared to caffeine and withdrawal conditions). Compliance to drug abstinence was checked prior to each laboratory part by a urinary toxicology screen (AccuBioTech Co., Ltd.,

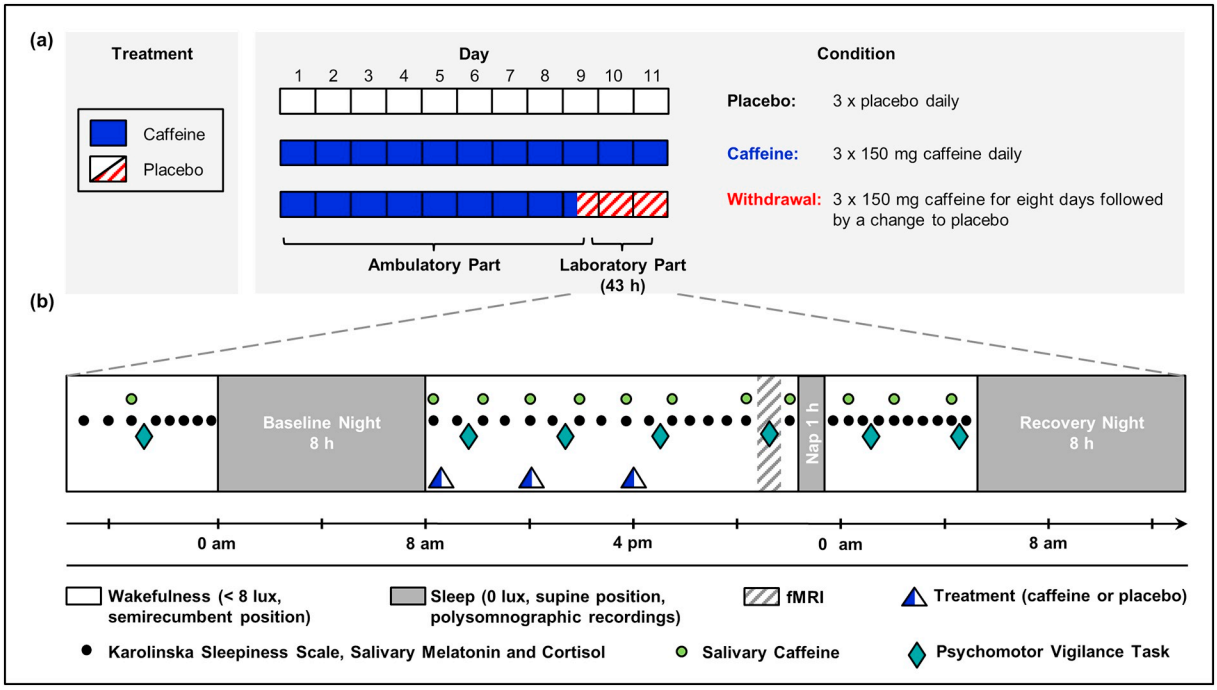

Fig. 1. Illustration of study protocol. (a) Each volunteer participated in a placebo, a caffeine and a withdrawal condition, each comprising a 43-h laboratory stay, preceded by an ambulatory part. In each condition either caffeine or placebo capsules were administered three times daily. (b) The laboratory stay started in the evening of day nine with assessments of subjective sleepiness, vigilance performance, salivary melatonin, cortisol and caffeine levels, which were continued on the next day after an 8-h baseline night. In the evening of day 10, 14.5 h after wake-up, a 1-h nap was scheduled during a time of high circadian wake-promotion (Dijk and Czeisler, 1994; Strogatz et al., 1987) followed by 5.75 h of scheduled wakefulness and an 8-h recovery night.

Beijing, China).

In the evening on day nine of treatment, 5.5 h before individual habitual bedtime, a 43-h laboratory part started, illustrated in Fig. 1(b). Volunteers were accommodated in single apartments, isolated from external time cues and communication was restricted to team members. Additionally, light conditions (< 8 lx), posture and meal intake was controlled.

2.3. Salivary caffeine

Caffeine levels were quantified in saliva samples collected in intervals of approximately 2 h during scheduled wakefulness during the laboratory stay. Subsequently, caffeine levels were analysed with liquid chromatography coupled to tandem mass spectrometry. One dataset was not included due to its non-availability.

2.4. Neurobehavioural assessments

Subjective sleepiness was assessed regularly with the Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg, 1990) every 30 to 60 min during scheduled wakefulness. For analyses, values were binned to 4-h intervals. Vigilance performance was measured by a visual 10-min psychomotor vigilance task (PVT) (Dinges and Powell, 1985), every 4 h during scheduled wakefulness. Volunteers were instructed to focus on a white cross displayed on a black screen and to respond as fast as possible by a key press as soon as a millisecond counter appeared. The inter-stimulus interval was randomised between 2 and 10 s. Here, we focus on the number of lapses (reaction time > 500 ms), the most sensitive measure for the interaction of caffeine with both sleep pressure and circadian phase (Wyatt et al., 2004). As one of the tests was conducted in a magnetic resonance scanner with a compatible button box, lapses were z-transformed before analyses according to this change in environment.

2.5. Salivary melatonin and cortisol

Saliva samples were collected regularly in intervals of 30 to 60 min. For handling, see supplementary materials. Melatonin and cortisol levels were detected using a direct double-antibody radio immunoassay (Weber et al., 1997) and an enzyme-linked immunosorbent assay (ALPCO, Salem, NH, USA), respectively. For analyses, data were collapsed into bins of 1.5 h.

Four datasets were excluded from melatonin analyses due to insufficient data quality (placebo condition: one; caffeine condition: two; withdrawal condition: one). For analyses of melatonin, data were resampled every minute by applying linear interpolation. Subsequently, a bimodal skewed baseline cosine function (BSBCF) curve (Van Someren and Nagtegaal, 2007) was fitted to the data based on (Kolodyazhniy et al., 2012) with the modified cost function proposed in (Gabel et al., 2017). Goodness of fit (R^2) was acceptable for all datasets ($R^2 > 0.6$) except for two volunteers (placebo condition: one; caffeine condition: one). DLMOnset and dim light melatonin offset (DLMOffset) were determined for the fitted BSBCF curve applying a threshold of 0.1 of its amplitude which was defined by the difference between peak to baseline levels (Van Someren and Nagtegaal, 2007). In order to estimate condition-specific changes in the melatonin profile, the amplitude and the area under the curve (AUC) were calculated including samples following wake-up at day 10 of treatment.

2.6. Polysomnography during nap sleep

To test caffeine-induced differences in circadian wake-promotion, EEG was recorded during a one hour nap episode in the evening, starting 14.5 h after wake-up. It has repeatedly been shown that the ability to sleep is lowest in the evening (Dijk and Czeisler, 1994; Strogatz et al., 1987), mirroring maximal wake-promoting strength at the end of the day. Recorded EEG data were visually scored according to (Berry et al., 2012) by scorers who were blind to the condition. Slow-wave sleep (SWS) was further classified into stages 3 and 4

(Rechtschaffen and Kales, 1968). For details on recording procedure and scoring, see supplementary materials.

Total sleep time (TST) was calculated as sum of sleep stages 1, 2, 3, 4 and rapid eye movement (REM) sleep. Sleep efficiency (SE) was calculated as TST divided by time in bed. SWS comprises the sum of sleep stages 3 and 4. Sleep latency 1 and 2 were defined as latency to the first occurrence of sleep stage 1 and 2, respectively. Non-REM (NREM) sleep was calculated as sum of stages 2, 3 and 4. Duration of REM sleep was not analysed as most participants (n = 16; corresponding to 93%) did not reach this sleep state. To test condition-specific differences in the time course of nap sleep, time spent asleep (stages 1, 2, 3, 4 and REM sleep) and SWS were collapsed into 5-min time bins.

Spectral analysis of NREM sleep was conducted using a fast Fourier transformation (FFT) on 4-s time windows (hamming, 0% overlapped) resulting in 0.25 Hz bins. Frequency bins from 0.5–32 Hz of NREM sleep, recorded from frontal derivations (F3, F4), were analysed. Data were collapsed into 1 Hz bins and log-transformed. Note that condition-specific analyses are based on a reduced number of datasets because 10 participants did not initiate NREM sleep in at least one of the three conditions (four participants in placebo, six participants in caffeine, none in the withdrawal condition).

2.7. Statistical analyses

Data analyses were conducted with the statistical analyses software (SAS Institute, Cary, NC, USA) version 9.4 using mixed model analysis of variance (PROC MIXED) with *subject* as a random factor and the two repeated factors *condition* (three levels: placebo, caffeine and withdrawal) and *time* (levels differ per variable). To account for correlations between adjacent points within *time*, we used AR(1) as covariance structure (i.e. autoregressive (1)). In analyses without the factor *time*, we assumed CS (i.e. compound symmetry) to model the covariance structure most properly. Degrees of freedom were adjusted based on Kenward-Roger (Kenward and Roger, 1997). *P*-levels of post-hoc comparisons, derived from the LSMEANS statement, were corrected for multiple comparisons with the Tukey-Kramer method. Data of one participant in the caffeine condition have been excluded from all analyses due to incompliance with the treatment.

3. Results

3.1. Caffeine levels

As expected, caffeine levels were higher in the caffeine condition compared to both the withdrawal and placebo condition (main effect of condition: $F_{2,121}$ = 185.16; p < .0001; post-hoc tests: p < .0001) while levels during withdrawal were increased compared to the placebo condition (post-hoc tests: p = .035; mean ± SD: placebo: 18.52 ± 84.80 ng/ml; caffeine: 3024.18 ± 2163.68 ng/ml; withdrawal: 296.81 ± 683.42 ng/ml). As illustrated in Fig. 2, this general pattern was modulated by time (interaction condition x time: $F_{22,237}$ = 2.76; p < .0001), mirroring both a decrease of caffeine levels during withdrawal condition and an increase in the caffeine condition after administration of treatment.

3.2. Subjective sleepiness and vigilance performance

The time course of subjective sleepiness values for each of the three conditions is illustrated in Fig. 3(a) and the number of lapses in the PVT in Fig. 3(b).

The results of the mixed model analysis of variance indicated higher subjective sleepiness in the withdrawal condition compared to the placebo and caffeine conditions (main effect of condition: $F_{2,58.2}$ = 9.71; p < .001, post-hoc tests: p < .01; mean ± SD: placebo: 4.72 ± 1.78; caffeine: 4.66 ± 1.91; withdrawal: 5.27 ± 1.81).

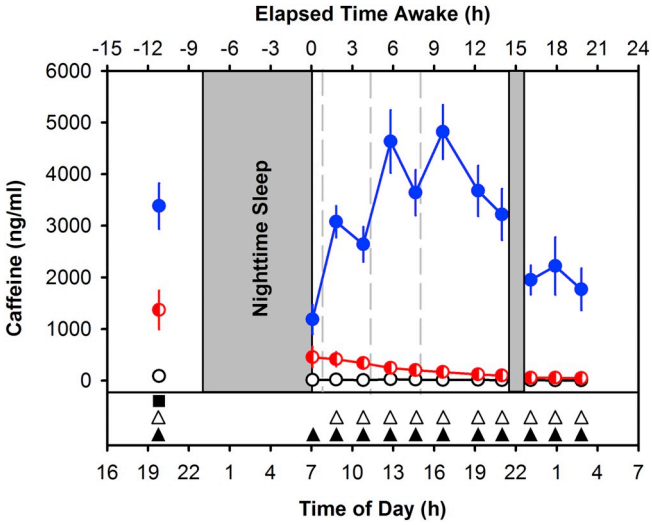

Fig. 2. Time course of caffeine levels across the 43 h under controlled laboratory conditions in the placebo (black open circles), caffeine (blue circles) and withdrawal (red semi-filled circles) condition. Pill administrations (caffeine or placebo) are depicted with dashed lines and the bottom x-axis indicates the mean time of day during which samples have been collected. Symbols mark significant (p < .05) post-hoc comparisons of the interaction effect condition x time, corrected according to (Curran-Everett, 2000) for multiple comparisons (black triangles: placebo compared to caffeine, open triangles: withdrawal compared to caffeine, black square: withdrawal compared to placebo). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

A significant main effect of time ($F_{7,127}$ = 54.62; p < .0001) confirmed a diurnal profile with higher sleepiness during the biological night compared to daytime.

The analysis of the number of lapses on the PVT yielded a significant main effect of condition ($F_{2,50.5}$ = 6.66; p = .0027; post-hoc tests: p < .01) revealing more lapses during the withdrawal condition compared to the placebo and caffeine conditions (mean ± SD: placebo: −0.18 ± 0.77; caffeine: −0.09 ± 1.04; withdrawal: 0.27 ± 1.11). A significant main effect of time ($F_{6,98.2}$ = 7.55; p < .0001) indicated more lapses during the night compared to daytime.

3.3. Melatonin and cortisol

In the analysis of melatonin levels, only the main effect of the factor time ($F_{17,290}$ = 33.44; p < .0001) was significant, confirming a diurnal profile of higher melatonin levels during the night compared to daytime (Fig. 4(a)). Neither DLMOnset ($F_{2,33.4}$ = 1.16; p = .325) nor DLMOffset ($F_{2,35.3}$ = 1.32; p = .280) significantly differed between conditions. Similarly, the effect of condition on amplitude ($F_{2,33.8}$ = 0.57; p = .573) and AUC ($F_{2,33.8}$ = 1.77; p = .185) on day 10 of treatment did not reach significance. For means and standard errors of the melatonin outcomes, see Table S4.

The analysis of cortisol levels did not show significant differences between conditions ($F_{2,129}$ = 0.43; p = .653). However, a significant main effect of the factor time ($F_{17,303}$ = 31.66; p < .0001) demonstrated a normal diurnal pattern with higher cortisol levels in the morning and lower levels during the night. The time course of salivary cortisol levels is illustrated in Fig. 4(b).

3.4. Evening nap sleep

A summary of sleep variables per condition and results of the statistical analyses are presented in Table 1. TST and SWS were longer, and SE was higher during withdrawal compared to placebo and caffeine conditions (post-hoc tests: p < .05). Furthermore, sleep latency to

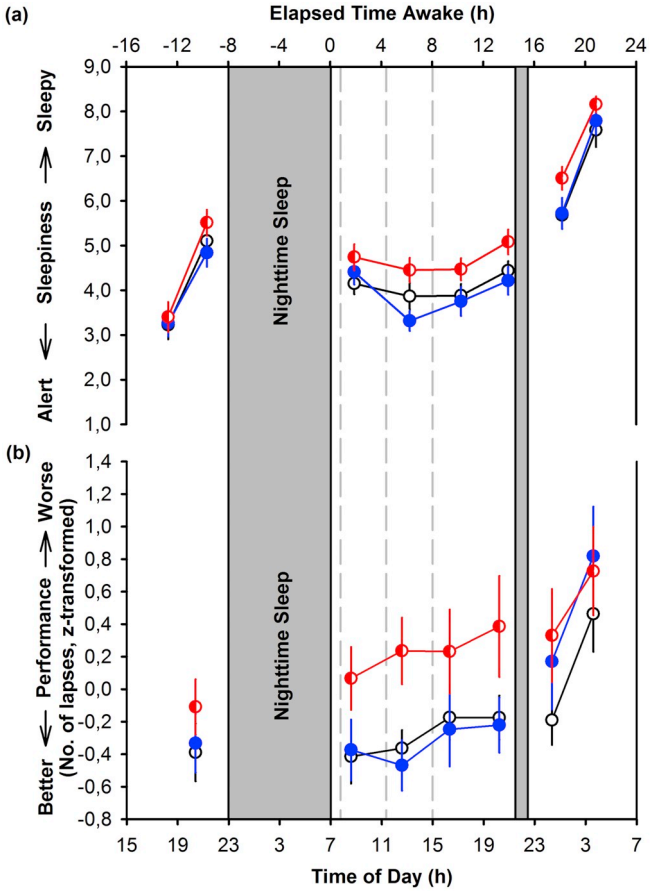

Fig. 3. Time course of subjective sleepiness (a) and attentional lapses assessed during PVT (b) in the placebo (black open circles), caffeine (blue circles) and withdrawal (red semi-filled circles) condition across 43-h (means ± standard errors). Pill administrations (caffeine or placebo) are depicted with dashed lines and the bottom x-axis indicates the mean time of day during which samples have been collected. Both subjective sleepiness and vigilance performance were impaired during withdrawal compared to placebo and caffeine. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

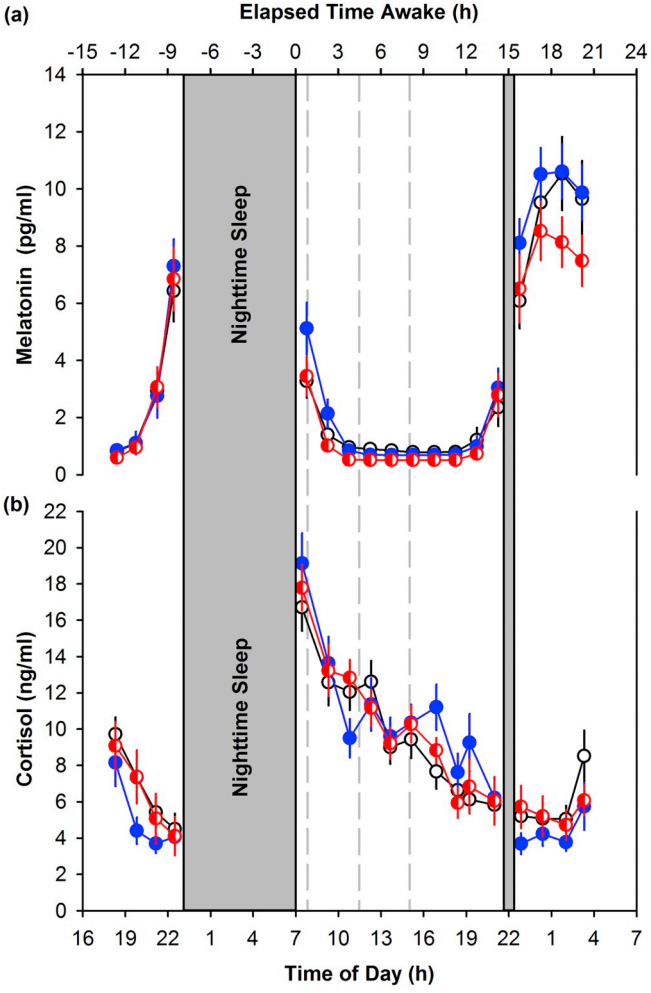

Fig. 4. Time course of salivary melatonin (a) and cortisol (b) across the 43-h laboratory stay. The means ± standard errors are depicted for placebo (black open circles), caffeine (blue circles) and withdrawal (red semi-filled circles) conditions and pill administrations (caffeine or placebo) are indicated with dashed lines. The melatonin profile depicts the fitted data and the bottom x-axis indicates the mean time of day during which samples have been collected. The typical course of both melatonin and cortisol across a day is clearly visible, however being independent of the treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sleep stage 1 and stage 2 were shorter during withdrawal compared to placebo and caffeine conditions (post-hoc tests: $p < .05$). Generally, initiation of NREM sleep was less frequent in the caffeine and placebo conditions compared to withdrawal (no NREM sleep in placebo: $n = 4$, caffeine: $n = 6$, and withdrawal condition: $n = 0$, Cochrans Q-test: $p < .05$).

In a next step, we were interested whether time spent asleep and SWS accumulate differently depending on the treatment. As depicted in Fig. 5, particularly in the beginning of the nap, time spent asleep and SWS accumulated faster during the withdrawal condition compared to caffeine and placebo conditions (interaction condition x time for time spent asleep: $F_{22,354} = 5.40$; $p < .0001$; and SWS: $F_{22,354} = 3.82$; $p < .0001$).

In a final step, differences in spectral power density between conditions were analysed. There were no significant differences in spectral power density between caffeine and placebo. However, spectral power density was reduced in the sigma range during withdrawal compared to placebo condition (15 Hz: $F_{2,27.4} = 3.48$; $p = .045$; 16 Hz: $F_{2,27.6} = 3.15$; $p = .059$).

4. Discussion

The aim of the present study was to examine the effects of daily caffeine intake and its cessation on circadian timing, wake-promotion and the course of neurobehavioural indices in habitual consumers under entrained conditions. Making use of a carefully controlled within-subject design, we focused on the effects of repeated daily consumption in the morning and afternoon, as this is the typical pattern in the society nowadays. Under these conditions, neither caffeine consumption nor its cessation affected the diurnal profile of melatonin or cortisol secretion. However, for > 20 h, cessation of intake induced a state of withdrawal, characterised by higher subjective sleepiness, impaired vigilance performance and a higher drive to sleep even at a phase of high circadian wake-promotion. It is concluded that daily daytime intake of caffeine throughout the morning and afternoon does not strongly affect human circadian rhythms under entrained conditions. Still, it induces adaptations, potentially at the level of the adenosine receptors, which come to light as a state of reduced arousal and alertness as soon as caffeine intake is ceased.

In animal studies, long-term treatment with caffeine leads to a different timing of circadian rest-activity rhythms, specifically to a lengthening of circadian period under constant lighting conditions (Oike et al., 2011; van Diepen et al., 2014). Similar observations in

Table 1
Sleep parameters derived from visual scoring assessed during evening nap sleep.

Sleep parameter	Placebo	Caffeine	Withdrawal	Factor condition
TST (min)	31.63 ± 3.90	24.26 ± 4.55	43.88 ± 2.83[a]	$F(2,37.3) = 9.64$, $p < .001$
SE (%)	52.71 ± 6.50	40.44 ± 7.58	73.12 ± 4.72[a]	$F(2,37.3) = 9.64$, $p < .001$
Stage 1 (min)	4.95 ± 0.73	4.66 ± 0.83	5.80 ± 0.85	$F(2,37.6) = 0.67$, $p = .519$
Stage 2 (min)	12.10 ± 1.97	9.82 ± 2.22	15.30 ± 1.57[b]	$F(2,37.2) = 3.85$, $p = .030$
Stage 3 (min)	6.53 ± 1.48	5.74 ± 1.73	10.20 ± 1.96[b]	$F(2,37.4) = 4.09$, $p = .025$
Stage 4 (min)	6.80 ± 2.16	3.74 ± 2.01	11.48 ± 2.69[b]	$F(2,37.2) = 6.06$, $p = .005$
SWS (min)	13.33 ± 2.82	9.47 ± 2.70	21.68 ± 3.00[a]	$F(2,37.3) = 8.22$, $p = .001$
NREM (min)	25.43 ± 4.01	19.29 ± 4.27	36.98 ± 3.34[a]	$F(2,37.1) = 8.87$, $p < .001$
SL1 (min)	25.70 ± 3.94	28.51 ± 4.57	12.09 ± 2.11[a]	$F(2,37.4) = 7.59$, $p = .002$
SL2 (min)	31.16 ± 4.11	37.94 ± 4.51	18.39 ± 2.87[a]	$F(2,37.3) = 9.80$, $p < .001$

Values are for means ± standard errors. TST: total sleep time; SE: sleep efficiency; SWS: slow-wave sleep (stage 3 + 4); NREM: non-rapid eye movement sleep; SL1: sleep latency to sleep stage 1; SL2: sleep latency to sleep stage 2.
[a] $p < .05$ compared to placebo and caffeine conditions.
[b] $p < .05$ compared to caffeine condition.

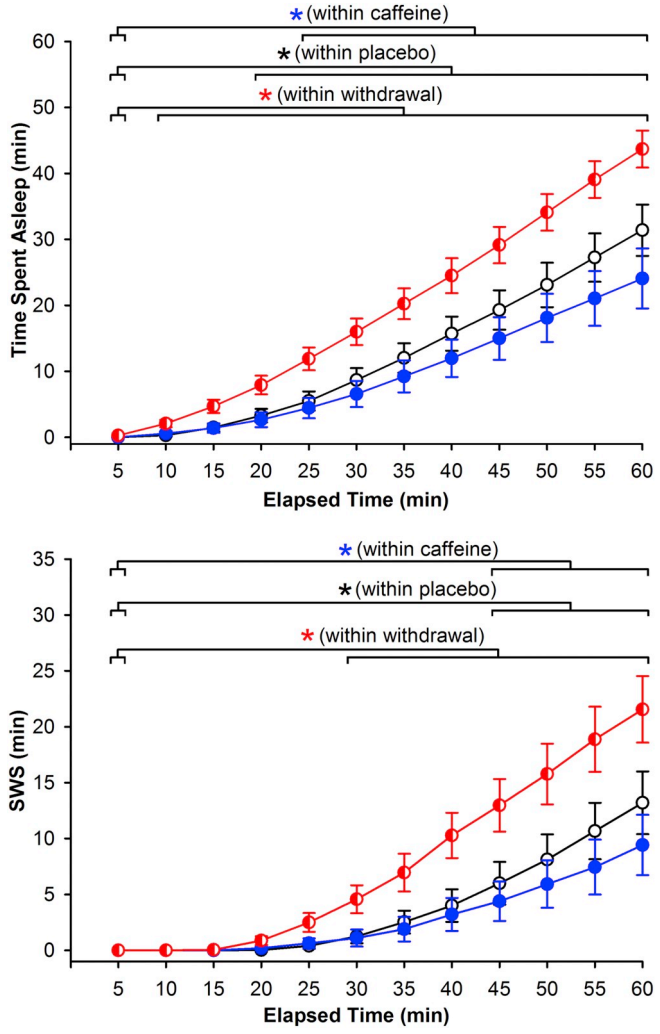

Fig. 5. Accumulation curves of time spent asleep and SWS during evening nap sleep. Data were collapsed into bins of 5 min and accumulated across the 1 h. Means and standard errors are represented for placebo (black open circles), caffeine (blue circles) and withdrawal (red semi-filled circles). Asterisks mark significant differences to the first bin within the same condition ($p_{all} < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

unmasked human rest-activity cycles are missing so far. However, under conditions of forced desynchronisation between the timing of circadian rhythms and sleep-wake cycles, circadian plasma melatonin rhythms were not altered in response to hourly administration of caffeine over four weeks (Wyatt et al., 2004). The results of the present study add that – under entrained conditions – the timing of both melatonin and cortisol does not necessarily change by daily caffeine consumption in the morning, midday and afternoon, a temporal pattern which is commonly observed in habitual consumers (Martyn et al., 2018). Importantly, based on the absence of a clear-cut shift in circadian timing in the withdrawal condition, it seems unlikely that the participants might have developed tolerance to the phase-shifting effects of the drug. Please note, however, that apart from statistics on the group's average, visual inspection revealed a delay in DLMOffset during caffeine in more than half of the volunteers ($n = 13$, see supplementary materials). Thus, interindividual differences in response to the stimulant (Fulton et al., 2018) as well as the small sample size might have hampered statistical condition-specific differences at $p < .05$. Interestingly, one (Panagiotou et al., 2018) of three (Panagiotou et al., 2018; Oike et al., 2011; Narishige et al., 2014) animal studies on the effects of repeated caffeine intake suggests a slight delay in activity onset of mice under normal light-dark cycles. However, in naïve animals no phase-shift in locomotor activity pattern has been found if caffeine was administered at activity onset (Jha et al., 2017). In humans, a one-time treatment before regular wake-up time could have the potential to prevent dim-light induced phase delays (Burke and Wright, personal communication (Burke et al., 2018)). Together, the effects of caffeine intake on circadian timing in the morning hours might thus differ according to treatment continuity (i.e. acute vs chronic). Moreover, the available evidence indicates that the effects of repeated daytime caffeine intake on human circadian timing when consumed in the morning, midday and afternoon under entrained conditions seem to be small.

Most likely, however, the effects of caffeine on circadian rhythms depend on the time of intake. While there is evidence that morning caffeine intake prevents dim-light induced phase delays (Burke and Wright, personal communication (Burke et al., 2018)), caffeine administration in the evening delays circadian phase (Burke et al., 2015). As a consequence caffeine taken throughout the day as in the present study may have cancelled out any potential phase shifting effects. So far, a delay (Burke et al., 2015) or reduction in melatonin (Wright Jr. et al., 1997) in humans, either abstinent (Burke et al., 2015) or potentially under withdrawal (Wright Jr. et al., 1997), was specifically induced after a caffeine treatment in the evening or at night. In contrast, repeated caffeine intake in the morning did not successfully entrain three blind patients (St Hilaire and Lockley, 2015). Furthermore, a recent animal study under constant conditions suggests that caffeine treatment does only potentiate light-induced phase shifts when given at the end of the active phase or during rest, but not at the start of the active phase (Jha et al., 2017). Together with the present results, the evidence suggests that the circadian system seems to be particularly

sensitive to caffeine when given at the end of the biological day. Future studies might disentangle circadian and sleep-homeostatic contributions to this effect.

Independent of time-of-day, we observed clear-cut effects induced by caffeine withdrawal. In line with earlier studies (Juliano and Griffiths, 2004), the acute challenge of cessation from caffeine was associated with signs of increased sleep pressure, such as increased subjective sleepiness and worse vigilance performance during day and nighttime as well as a faster initiation of NREM sleep even at a time of high circadian wake-promotion. Thus, the preceding repeated presence of caffeine might have induced compensatory adaptations at the neuronal level (Ferre, 2008), which modulate the stimulatory effects of caffeine and underlie the effects of withdrawal as soon as consumption is stopped. Several changes have been associated with long-term caffeine intake, e.g. upregulation of adenosine receptors (Varani et al., 1999; Johansson et al., 1997; Fredholm, 1982; Shi et al., 1993), increased plasma adenosine concentrations (Conlay et al., 1997) or modulations in the function of adenosine heteromers (Ciruela et al., 2006). These neuronal changes in the adenosinergic system might alter the homeostatic sleep need. In the present study, an increased sleep pressure experienced during caffeine withdrawal might have overruled the circadian drive for wake-promotion in the evening, a phenomenon which has already been shown after sleep restriction in humans (Sargent et al., 2012).

In contrast to the clear-cut symptoms of caffeine withdrawal in behaviour, we do not have any indication for a significant difference in either of the measured variables during daily caffeine consumption compared to placebo. Importantly our study was designed to focus on the effects of caffeine after a certain period of repeated intake under normal sleep-wake conditions. In earlier studies that showed a caffeine-induced sleep disruption during circadian wake-promotion after continuous daily intake, measurements were taken under relatively high levels of sleep pressure (i.e. after 25 h (Carrier et al., 2009) or 28 h (Wyatt et al., 2004) of wakefulness). Interestingly, reviews indeed suggest that the stimulating properties of caffeine are most prominent under high sleep pressure such as after sleep deprivation or sleep restriction (Roehrs and Roth, 2008; Snel and Lorist, 2011). Therefore, we may not exclude that caffeine intake would have induced sleep disruption and alertness under a longer duration of wakefulness as was applied in the present study. However, studies controlling for withdrawal reversal, similarly applied in our study, failed to show a caffeine-induced improvement in performance in sleep-restricted subjects (Keane and James, 2008; James et al., 2005), indicating that improvements by caffeine cannot solely be explained by sleep-wake-history but probably also depend on preceding caffeine intake. Applying repeated caffeine administrations and an ambulatory period of nine days prior to each assessment phase, potential effects in the caffeine condition deriving from withdrawal reversal and carry-over effects can likely be excluded.

Moreover, one might argue that the lack of improvement in subjective alertness and performance during caffeine intake compared to placebo condition is due to a floor effect. In other words, the low sleepiness and high performance level occurring during the placebo condition did not leave much room for additional improvement by caffeine. However, our measurements took place also during the biological night, in which we observed the typical nighttime decrease in alertness and performance. As we did not observe a significant caffeine-induced improvement under these conditions, our results suggest that the effects of daytime caffeine intake on alertness and performance are either short-lasting, small or not present under conditions of habitual daily caffeine intake.

Finally, the development of tolerance could have been induced by regular daily caffeine consumption. There are convincing indicators for tolerance to occur after 3–5 days of habitual caffeine intake (James, 2014) during both wakefulness and sleep with the potential of complete (Evans and Griffiths, 1992) or partial tolerance (Bonnet and Arand, 1992; Watson et al., 2002). Moreover, the current results in subjective sleepiness and vigilance performance during caffeine cessation provide evidence for an adaptation to the daily exposure of caffeine, however, circadian timing and amplitude remain mainly unaffected. Within this context, it is important to note that the present study design does not include a condition assessing the effects of acute caffeine intake after long-term abstinence. Thus, we cannot provide a strict measure of tolerance by comparing acute effects of caffeine with the effects after daily treatment in the same individuals. This is of particular interest, as the habitual consumption level in the present sample might be an indicator for a reduced sensitivity to react to caffeine (Retey et al., 2007). Nevertheless, doses of 400 mg have been shown to induce certain performance benefits in habitual consumers (Brunye et al., 2010a) and it is still debatable whether there is a dose-dependent saturation of caffeine-induced performance benefits at 200 mg as suggested by (Brunye et al., 2010b) (but see (Brunye et al., 2010b; Childs and de Wit, 2006)).

We are aware that this study may have several limitations which have to be taken into careful consideration. First, no washout phase was scheduled between the conditions. However, we implemented an ambulatory part with a fixed sleep-wake schedule and a constant treatment during nine days preceding data collection in the lab. Thus, circadian and sleep-wake systems might have returned to a normal state and recovered from previous conditions. Second, the exclusion of female volunteers clearly limits the generalisability of the present results. We studied male participants only in order to avoid potential confounding by the menstrual cycle on caffeine elimination (Lane et al., 1992) and sleep-wake regulation and thus on our main outcome variables melatonin, cortisol and sleep (Shechter and Boivin, 2010). Moreover, we aimed at reducing variance in the data due to the potential use of oral contraceptives which have been shown to change caffeine clearance (Balogh et al., 1995; Abernethy and Todd, 1985) and its effect depending on the duration of oral contraceptive use (Rietveld et al., 1984). Third, we studied volunteers with an age range of 18–35 years. As evidence suggests an age-related modulation of caffeine-effects on cognition (Jarvis, 1993; Hogervorst et al., 1998) and sleep (Drapeau et al., 2006; Robillard et al., 2015) our results are not necessarily transferable to other age groups such as teenagers or adults older than 40 years. Fourth, in the present study regular caffeine consumers were studied of which some reported habitual caffeine consumption in the evening (see supplementary materials). However, evening caffeine intake is not common (Martyn et al., 2018) presumably due to potential sleep-disruption (Landolt, 2008) and thus might be an indicator of a certain insensitivity to the effects of caffeine. While the observed clear-cut withdrawal-induced effects make it unlikely that our sample was entirely unresponsive to the stimulant, the impact of caffeine might be stronger as compared to our sample in more sensitive individuals. Last, no genetic information including variations in the adenosine A_{2A} receptor gene (ADORA2A) were collected, which have been previously associated with habitual caffeine intake and insensitivity to the effects of the stimulant (Retey et al., 2007). However, based on the clear-cut changes in performance and sleepiness when caffeine was ceased, it is unlikely that volunteers were insensitive to the effects of caffeine but rather developed tolerance due to the repeated intake of the stimulant.

Taken together, this is the first study investigating the impact of habitual caffeine consumption on human circadian rhythms under entrained conditions. The study was designed to focus on the effects of a typical pattern of caffeine consumption with daily intake in the morning, midday and afternoon. We provide first evidence that this type of exposure to the stimulant does not considerably shift circadian markers such as melatonin and cortisol nor does it lead to an increased wake-promotion in the evening. However, the acute challenge of cessation from caffeine was associated with signs of increased sleep pressure. Together, our data point to an adaptation of waking-performance to habitual exposure to the stimulant while circadian markers remain fairly stable. These mechanisms of both adaptation and robustness

might enable normal sleep-wake states during constant supply of a stimulating agent in the central nervous system.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2019.109851.

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